Lisa A. Eaton · Seth C. Kalichman
Editors

Biomedical Advances in HIV Prevention

Social and Behavioral Perspectives

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Preface

HIV prevention has turned a critical corner. Years of research have yielded an arsenal of new biomedical technologies that, if put into practice, could alter the course of HIV epidemics. However, numerous challenges face the shifting tide of HIV prevention that, if ignored, will squander the opportunities before us. *Biomedical Advances in HIV Prevention: Social and Behavioral Perspectives* was written to shed light on and address the challenges that face increasing access and use of biomedical HIV prevention technologies. Randomized clinical trials that have tested prevention technologies have understandably focused on determining their efficacy. However, there is a vast gap between determining efficacy of a prevention tool and optimal use in communities most affected by HIV. Nearly three decades of behavioral research in HIV prevention has produced numerous interventions that have mostly gone unused. Our hope is that this same fate does not fall on these promising new biomedical advances. Understanding the gap between efficacy and use is critical if we are to realize the true benefits of new HIV prevention technologies. This sentiment was the impetus for editing and contributing to this book. Our goal was to highlight the social and behavioral realities that can stymie biomedical advances in HIV prevention. We therefore sought the contribution of true experts in the most essential aspects of biomedical HIV prevention. Our charge to these authors was for them to offer their guidance on how best to address the challenges facing emerging HIV prevention technologies.

Currently, there are numerous advances in HIV prevention to be excited about. We have observed remarkable prevention intervention efficacy associated with male circumcision, microbicides, and antiretroviral therapy-based prevention; albeit, with some setbacks along the way. All of us working in HIV prevention recognize the tremendous potential of biomedical prevention. At the same time we must acknowledge the considerable effort it will take to make wide-scale availability and optimal use a reality. On the whole, recent years have brought a renewed energy and focus regarding the potential to end the HIV/AIDS epidemic. However, our progress is vulnerable to being held back by behavioral and social aspects of prevention technologies. The current landscape of HIV prevention includes numerous studies investigating multiple combinations of prevention tools and it is very likely that biomedical prevention technologies will continue to evolve at a rapid pace. Yet, it

is imperative to underscore that issues relating to behavioral and social components are enduring and, therefore, have the potential to enhance or undermine the ultimate impact of these critically important advances.

In developing this volume, all the authors were asked to consider the social and behavioral issues they believe are most vital to address for the successful implementation of biomedical HIV prevention technologies. Our contributors have considerable expertise in their respective areas and have been working extensively with populations affected by HIV. We are quite fortunate to have collaborated with such a remarkable group of scientists, scholars, and prevention advocates in formulating this book. Our goals for each chapter were to elaborate on how the field can make the tools of HIV prevention work effectively in diverse settings across multiple groups. This thinking led us to consider how aspects of behavior, particularly adherence, risk compensation, substance use, and mental health will affect one's ability to access and take advantage of HIV prevention technologies. We also aimed to present diverse perspectives on various cultural factors important in the uptake of prevention technologies, including the unique challenges faced in some of the most pressing HIV epidemics of southern Africa, Asia, Australia, Europe, South America, and North America. Our approach was to find the best possible authors and give them creative license to structure their chapters as they wanted, with the only caveat being that they focus on areas that they saw as most critical. Our hope was that the authors would convey their enthusiasm in their respective areas of study by putting forth interesting and stimulating content; the authors delivered above and beyond our expectations.

This book is organized in three separate yet complementary sections. *Advances in HIV Prevention Technologies* offers perspectives on where we are in terms of developing technologies for HIV prevention and also highlights specific areas of interest including how biomedical prevention fits within President Obama's US National HIV/AIDS Strategic Plan as well as priorities set by the World Health Organization. We have also included views on the progress being made in producing an effective rectal microbicide. *Behavioral Challenges and Opportunities* covers psychosocial factors that undermine implementation of advances in HIV prevention. Given the, at-times, conflicting results of biomedical trials, we devote considerable attention to reviewing individual-level factors that we believe are most important to effectively address in order to maximize the benefits of existing and emerging prevention tools. In the final section, *Global Perspectives*, we sought to provide chapters that would give the reader a sense of the practicality of making prevention tools available in various cultural settings. Producing effective biomedical technologies for HIV prevention is not sufficient for ending the HIV/AIDS epidemic; we must simultaneously address barriers relating to accessibility, uptake, and sustained use. We therefore asked contributors to consider how well equipped their respective country was for providing biomedical prevention, including what strategies work and what changes would have to be made.

Together the content offers a wide-range of perspectives on many of the most pressing issues in current HIV prevention research, practice, and policy. We nevertheless recognize that that no single book can cover every critical issue facing a field as large and fast moving as HIV prevention. We are quite sure that the types

of biomedical technologies discussed will require updating. However, the social, behavioral, and contextual factors that ultimately determine the success and failure of any biomedical prevention technology, from condoms to vaccines, are far more enduring. Our hope is that this book will offer a framework for optimizing the impact of all biomedical advances in HV prevention, those currently available as well as those not yet even imagined.

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Part I
Advances in HIV Prevention Technologies

Chapter 1
Advances, Promises, and Challenges in HIV Prevention

Douglas Krakower and Kenneth H. Mayer

As there are over two million new HIV infections worldwide each year [1], including approximately 50,000 new infections in the United States [2], the development of effective HIV prevention strategies remains a critical public health priority. The incidence of HIV infection in the United States and many international settings [1] has remained at these levels for the past decade despite the increasingly widespread availability of effective treatment for HIV infection with antiretroviral therapy (ART) and intensive efforts to develop preventive interventions [3]. For every two persons who start ART each year, there are five more who become HIV infected [1], creating a cycle that would inexorably lead to unending growth in the global burden of HIV-related disease if it were to remain unbroken. However, over the past several years, groundbreaking advances in biomedical HIV prevention have been achieved, providing a newfound optimism about the potential to implement effective HIV prevention strategies on a broad scale and potentially curtail the HIV epidemic [4].

These novel biomedical strategies center on the concept that early initiation of ART by individuals who are living with HIV infection can reduce their infectiousness to others and administering antiretroviral medications to persons who are HIV-uninfected but at high risk for becoming infected can protect them from HIV acquisition. Since 2010, both observational and prospective randomized multinational studies have demonstrated that treating HIV-infected individuals with ART can reduce the likelihood that they will transmit HIV to their sexual partners [5], known as "Treatment as Prevention," and that administration of oral or topical antiretroviral medications to high-risk persons prior to HIV exposure can reduce their risk of viral acquisition, known as preexposure prophylaxis (PrEP) " [6–9]. An additional approach to reducing the risk of HIV acquisition among susceptible individuals that can be implemented in parallel to antiretroviral-based approaches involves voluntary medical male circumcision (VMMC) [10, 11].

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Importantly, the human trials that have studied the efficacy of these biomedical interventions have tested these interventions in conjunction with intensive behavioral counseling, treatment of sexually transmitted coinfections, and promotion and provision of condoms [5–9, 11]. This underscores the critical notion that biomedical and behavioral strategies are most likely to be effective, and perhaps even synergistic, when studied [12] and implemented together as part of a combination biomedical and behavioral approach to HIV prevention [13].

Primary HIV Prevention

Efforts to develop biomedical interventions for primary prevention among persons with high-risk exposures to HIV have been ongoing for two decades. These efforts have been punctuated with unequivocal successes and numerous disappointments along the way, from the remarkable discovery in 1994 that administering peripartum antiretroviral medications is highly effective at preventing transmission of HIV from pregnant mothers to their babies [14], to a series of over ten early vaginal microbicide studies that were unable to demonstrate efficacy [15]. Fortunately, major breakthroughs in primary biomedical HIV prevention have occurred in the past several years, including large human studies that have demonstrated the efficacy of topical [9] and oral PrEP [6–8] and VMMC [10, 11]. However, some of the completed oral and topical PrEP studies were unable to demonstrate efficacy among at-risk women in Africa [16, 17] as a result of low adherence and possibly additional reasons that are not yet fully elucidated (related to tissue pharmacology and efficacy in the setting of genital tract inflammation), but are undergoing vigorous study. Therefore, the excitement that has accompanied the advent of PrEP has been tempered by concerns about its efficacy in critical populations, and numerous questions about the optimal approaches to utilizing PrEP in clinical settings merit further investigation.

Topical Microbicides: Early Disappointments, Recent Successes

Topical microbicides encompass a range of products that can be applied directly to mucosal tissues for the purpose of preventing the establishment of HIV infection. Microbicides can be classified according to whether they contain antiretroviral medications as part of their formulation (antiretroviral-based) or other compounds designed to block the establishment of infection by various methods, such as destroying HIV viral particles or preventing viral binding and entry into host cells (nonantiretroviral-based).

Nonantiretroviral-Based Microbicides

Early microbicide studies of nonantiretroviral-based microbicides showed disappointing results. The first microbicide studies tested whether the spermicide

nonoxynol-9, which has in vitro activity against HIV [18], could prevent HIV acquisition among high-risk women, including female sex workers. These studies did not demonstrate that this microbicide was efficacious at decreasing HIV incidence [19, 20]. In contrast, these studies found that use of nonoxynol-9 was associated with increased genital inflammation as compared to placebo [19], which could potentially increase the risk of acquiring HIV [21]. Low concentrations of nonoxynol-9 are still used in some contraceptive gels, so it is important to educate consumers that they are not protective against HIV, and could potentiate HIV transmission, especially in settings of increased use (e.g., among sex workers).

Several additional nonantiretroviral-based microbicides showed promise in early clinical studies, including polyanionic compounds that used electrostatic charge to prevent HIV proteins from binding to host cells [22]. One such compound, known as PRO2000 gel, demonstrated a modest (30 %) but statistically nonsignificant relative risk reduction in HIV incidence among at-risk women in one study [23], but was shown to be ineffective in another large, multinational study [24]. Other compounds in this class, such as cellulose sulfate, were also found to be ineffective [25]. Although an acidic pH (maintained by vaginal lactobacilli) has been shown to be protective against HIV in vitro, a compound designed to maintain an acidic vaginal pH in spite of seminal base buffering, known as BufferGel, was not shown to be protective [23].

Tenofovir Gel for Women

An era of disappointment was supplanted by a sense of promise in 2010, when investigators from the Centre for the AIDS Programme of Research in South Africa 004 (CAPRISA-004) study reported that pericoital administration of an intravaginal gel containing the antiretroviral medication tenofovir reduced the incidence of HIV infection by 39 % as compared to a placebo gel among 889 at-risk women [9]. This landmark result represented the first demonstration in humans that a microbicide could protect against HIV acquisition; it also represented the first human study to demonstrate the efficacy of antiretroviral PrEP. The findings of CAPRISA-004 were announced initially at the International AIDS Society meeting in Vienna during July 2010, and these results garnered "cheers, applause, and a standing ovation" among scientists, advocates, and others in attendance after numerous prior studies had failed to show that microbicides could protect against HIV acquisition [26].

In CAPRISA-004, a direct relationship was found between adherence to the study medication and its degree of protective efficacy [9]. Study participants were advised to apply the intravaginal gel during the 12-h period before intercourse with a male partner and again during the 12-h period after intercourse, with no more than two doses in any 24-h period. Among women who used the study drug as directed for at least 80 % of coital episodes, use of the tenofovir gel decreased HIV incidence by 54 % as compared to placebo. This analysis illustrates that the benefit of microbicides will likely be dependent on achieving sufficient levels of adherence, a critical and recurring theme among studies that have tested the efficacy of antiretroviral chemoprophylaxis.

Although the gel was extremely well-tolerated by the vast majority of the participants, those who were randomized to use the tenofovir gel in CAPRISA-004 experienced increased rates of diarrhea and gastrointestinal infections as compared to women who were randomized to use a placebo gel, but there were no serious safety concerns with use of the tenofovir gel [9]. It is not clear why use of the intravaginal gel was associated with these gastrointestinal symptoms, although vaginal dosing is associated with measurable drug levels in the rectum, which could cause colonic symptoms [9, 27]. Nearly all (97 %) of the women who were subjects in CAPRISA-004 stated that they would be interested in using the gel after the conclusion of the study, suggesting that the microbicide was well-tolerated and that women may find the gel to be acceptable for use outside of study settings [9].

Conflicting Efficacy Results with Tenofovir Gel

In contrast to CAPRISA-004, the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study was unable to demonstrate efficacy with use of the same intravaginal tenofovir gel [17, 28]. This study enrolled approximately 5,000 African women and randomized them to receive either a gel (tenofovir versus placebo) or a pill (tenofovir or a fixed-dose combination tablet containing tenofovir plus the antiretroviral medication emtricitabine, versus placebo) to be used once daily. In VOICE, women were instructed to apply the gel once per day regardless of whether or not they were engaging in coital activity. The gel arms of the study were stopped early because an independent data, safety, and monitoring board determined that the trial was unlikely to demonstrate efficacy of the tenofovir gel, although there were no serious safety concerns with its use [28].

Several hypotheses have been proposed to explain the discrepant results between CAPRISA-004 and VOICE. Participants in VOICE may have had lower rates of adherence to study drug than participants in CAPRISA-004, as a case-cohort study within VOICE found that only 22 % of women randomized to use tenofovir gel had detectable drug levels in quarterly blood samples [17]. Participants in VOICE may also have overcome a modest protective benefit of tenofovir gel applied vaginally by engaging in vaginal intercourse more than once a day, engaging in anal sex, or having more partners with higher-level viral concentrations (e.g., acute viremia), which could have overwhelmed the degree of protection provided by the microbicide gel. As concomitant sexually transmitted infections (STI) and genital tract inflammation may facilitate HIV acquisition [29], women in the VOICE study could possibly have had increased rates of STI or genital tract inflammation that could have increased the incidence of HIV infection. It is also feasible that the daily dosing of tenofovir gel, as required in the VOICE protocol, decreased mucosal host defenses against HIV, compared to the less frequent pericoital dosing protocol in CAPRISA 004. When detailed results of the VOICE study become available, analysis of tissue drug concentrations, rates of STI, and sociobehavioral factors will help to address these hypotheses.

A third study of tenofovir gel, the Follow-on African Consortium for Tenofovir Studies 001 (FACTS-001) study, started enrolling in 2011 to confirm the positive results of CAPRISA-004 before potential licensure and any large-scale roll out of tenofovir intravaginal gel. FACTS-001 will test the same pericoital dosing regimen as was tested in CAPRISA-004 in 2,200 at-risk South African women, and it is expected to shed light on the discordant results of CAPRISA-004 and the VOICE study [30]. In South Africa, a national survey of antenatal care clinics revealed HIV prevalence rates of 14 % in women ages 15–19 and 43 % in women ages 30–34, illustrating the dramatically high rate of new infections among young women [31]. Given the urgent need for effective interventions in this population, additional studies to assess the safety and acceptability of tenofovir gel among 16- and 17-year-old South African women are already undergoing planning [30].

Rectal Microbicides

The efficacy of tenofovir gel among young South African women is proof-of-concept that antiretroviral-based microbicides can "work" in humans. This result has energized the field of microbicide research, and early phase studies of tenofovir gel in additional at-risk populations are underway. Globally, a greatly disproportionate burden of new HIV infections occurs among men who have sex with men (MSM) [32–34]. This disparity clearly exists in the United States with 61 % of new HIV infections occurring among MSM [2]. Therefore, studies are testing the safety and acceptability of tenofovir gel for rectal use, given that anal sex remains the predominant mode of HIV transmission in this population.

Preclinical studies in nonhuman primates (rhesus macaques) found that rectal application of tenofovir gel prior to local challenge with a retrovirus (simian immunodeficiency virus) can protect against retroviral infection [35]. An initial safety study in humans found that rectal application of the tenofovir gel was safe but was associated with GI side effects [36], likely owing to the glycerin in its formulation, which can increase peristalsis. A reduced-glycerin formulation was developed to address this concern [37] and was found to be safe and well-tolerated with rectal application in a phase I study. A phase II expanded safety study with this formulation is underway, recruiting MSM in the United States, Peru, South Africa, and Thailand [38]. Additional studies to test the utility of rectal microbicides that would contain combinations of antiretroviral medications are being planned, including a study that will evaluate a microbicide that contains tenofovir plus maraviroc, an antiretroviral medication that prevents HIV entry into host cells [38].

Novel Delivery Mechanisms for Topical Microbicides

Novel approaches to delivering antiretroviral medications to mucosal sites are also being explored, including the use of drug-eluting intravaginal rings. The use of intravaginal rings that remain in place for an extended period of time

could allow for sustained local concentrations of drug and may increase adherence as compared to gels that require more frequent application, both of which could enhance product effectiveness. A 90-day tenofovir reservoir intravaginal ring was found to be safe in an animal model [39]. Studies of intravaginal rings containing other classes of antiretroviral medications, including nonnucleoside reverse-transcriptase inhibitors, have been shown to be safe in humans (e.g., dapivirine [40] or maraviroc) and have appeared efficacious against retroviral challenge in nonhuman primates (e.g., MIV-150) [41]. Efficacy trials of an intravaginal ring containing maraviroc are now underway in Africa. Another approach under study is the use of injectable antiretrovirals with very long half lives. A formulation of the NNRTI, rilpivirine, has been found to be safe and well-tolerated in humans, and preclinical studies of long-acting integrase inhibitors are underway [42].

Oral PrEP: Promising Results, New Questions

The concept of oral preexposure chemoprophylaxis— the use of a medication before the onset of an undesirable medical outcome to prevent that outcome—has numerous precedents in medicine and public health. Many women use oral contraceptives to prevent unintended pregnancy. Persons at high risk for having heart disease may benefit from daily use of aspirin to reduce their risk of a heart attack (myocardial infarction). Within the field of infectious diseases, people who travel from areas of the world where malaria is rare or absent, such as the United States or Western Europe, to areas where malaria is endemic, such as sub-Saharan Africa, commonly utilize antimalarial chemoprophylaxis to protect themselves against infection and subsequent illness for finite periods of exposure. Although the administration of chemoprophylaxis within these areas of medicine has represented standard care for several decades and guidelines for postexposure prophylaxis (PEP) after HIV exposures have been available for more than 15 years [43], the paradigm of oral chemoprophylaxis has only been tested recently within the field of HIV prevention. Yet, despite its relatively recent application to this field, the safety and efficacy of oral antiretroviral PrEP has already been tested in several large-scale, multinational studies. Some of these studies have demonstrated that PrEP can reduce HIV incidence in high-risk populations [6–8], but others have failed to do so [16, 28], thereby generating pivotal questions about how best to utilize PrEP in real-world settings.

Preclinical Studies of PrEP

PrEP studies have been informed by animal studies demonstrating that antiretroviral medications can decrease HIV transmission when administered before retroviral challenge. Numerous studies with nonhuman primates or humanized mice have demonstrated that administering one or more antiretroviral medications prior to retroviral challenge in oral, parenteral, or topical formulations can protect against viral

infection [44–46]. Several of these animal studies tested the safety and efficacy of tenofovir with or without emtricitabine, an antiretroviral medication from the same class as tenofovir (nucleoside/nucleotide reverse-transcriptase inhibitors) that is commonly used with tenofovir as part of HIV treatment regimens.

Tenofovir is attractive as a potential PrEP medication because it has been generally well-tolerated when used as part of HIV treatment regimens, and it achieves sustained concentrations in the serum and in genital tissues, which could provide a continuous barrier against viral infection [47]. Tenofovir also maintains antiviral activity against HIV quasi-species that have developed several common drug-resistant mutations (i.e., the drug has a high genetic barrier to drug resistance), which could allow for protection against drug-resistant viral strains that circulate in some communities. Emtricitabine is also well-tolerated with minimal side effects when used as part of HIV treatment regimens, although this drug does not maintain antiviral activity against one of the more common drug-resistant mutations [48]. Given the favorable characteristics of these two medications and the encouraging results from animal studies in which they were tested, the first studies to test the safety and efficacy of PrEP in humans also utilized tenofovir with or without emtricitabine [8, 49, 50].

Antiretroviral Postexposure Prophylaxis

In addition to promising animal studies, PrEP trials have been informed by human studies that have suggested a decreased risk of viral acquisition among individuals who utilize antiretroviral medications after HIV exposure. An observational study in humans showed that healthcare workers who utilized the antiretroviral medication zidovudine (AZT) for 28 days after high-risk occupational exposures to HIV were at lower odds of acquiring HIV infection than healthcare workers who did not utilize this medication [51]. This was the first human study to report that antiretroviral PEP could protect individuals against HIV acquisition after high-risk exposure. Although the efficacy of PEP has not been tested in randomized, placebo-controlled studies, numerous observational and uncontrolled studies have supported that PEP is safe [52–54], and its use has been associated with decreased HIV acquisition among MSM [55]. However, studies with MSM in the United States [53] and Australia [56] have suggested that some individuals may not accurately estimate their personal risk, leading to HIV acquisition despite the availability of PEP. Given the limitations of PEP and evidence from nonhuman primate studies that administration of antiretroviral medications before retroviral challenge may result in a greater degree of protection than administration after exposure [46], investigators hypothesized that PrEP could offer a promising way forward for oral chemoprophylaxis.

Safety Studies with PrEP

The first study to assess the safety of PrEP randomized 936 high-risk women in several nations in West Africa to receive either daily oral tenofovir or a placebo

tablet. No differences in safety outcomes or adverse effects were detected between the two groups of women [49]. Another safety study of PrEP that randomized 400 MSM in the United States to receive daily tenofovir or placebo found that serious adverse effects were uncommon and not different between the two groups of men [57]. As tenofovir has been associated with loss of bone mineral density when used as part of HIV treatment regimens [58], this study measured bone mineral density in a subset of participants at baseline and periodically thereafter. The men who were randomized to receive tenofovir as PrEP experienced small (approximately 1 %), but statistically significant decreases in bone mineral density as compared to men randomized to placebo. However, no difference in fracture rates was observed during the trial [50], and this degree of bone density loss is of uncertain clinical significance. Tenofovir has also been associated with nephrotoxicity [59] when used for treating HIV infection, but in both these initial safety studies, no significant difference in renal function was found between participants randomized to tenofovir or placebo [50, 57].

The iPrEx Study: The First Efficacy Study with Daily Oral PrEP

In November 2010, The PrEP Initiative (iPrEx) study enrolled 2,499 high-risk MSM and transgender women in six countries and demonstrated that daily administration of a fixed-dose combination tablet containing tenofovir and emtricitabine (tenofovir-emtricitabine) decreased HIV incidence by 44 % as compared with a placebo tablet over a median of 1.2 years of follow-up [8]. This groundbreaking result was the first study to demonstrate the efficacy of daily oral PrEP and represented a sentinel moment in the field of biomedical HIV prevention. The PrEP tablet was generally well-tolerated, although men in the tenofovir-emtricitabine arm of the study reported increased rates of mild GI symptoms and decreased weight gain, both of which tended to resolve after several weeks of use [8].

This study also found that PrEP was generally safe, with no difference in serious adverse events among men randomized to use tenofovir-emtricitabine or placebo. In iPrEx, men randomized to use tenofovir-emtricitabine had higher rates of elevated creatinine (2 % of men), a marker of kidney toxicity, as compared to men who were randomized to use the placebo tablet (1 % of men). However, this difference was not statistically significant, and nearly all participants who were directed to stop using the study drugs owing to elevated creatinine were able to restart the drugs safely [8]. Similar to the safety study of daily oral tenofovir among MSM, iPrEx also reported a small decrease in bone mineral density among participants who were randomized to receive tenofovir-emtricitabine as compared to those randomized to receive placebo [60]. Given these findings, collecting longer-term data on the possible bone and renal toxicities from using tenofovir as PrEP will be essential.

Potential Unintended Consequences That Could Be Associated with PrEP Use

An important theoretical concern is that persons who utilize PrEP will engage in risk compensation, whereby individuals increase their high-risk behaviors while using a

protective intervention to achieve a stable overall level of personal risk. In a survey of MSM in New York conducted prior to iPrEx, some men reported intentions to decrease condom use while using PrEP, if it were available [61]. However, participants in iPrEx reported increased levels of condom use and decreased numbers of sexual partners over the course of the trial [8], although this is likely owing at least in part to the intensive behavioral counseling and free access to condoms that were provided to participants as part of the study. An open label extension to iPrEx is underway (the iPrEx OLE study), where all HIV-uninfected participants from the original iPrEx cohort, whether they had received active drug or placebo, are being offered tenofovir-emtricitabine for an extended period of time. This study will follow participants for 72 weeks and will accrue data on adherence, changes in sexual risk behaviors, and adverse drug effects, which will provide longer-term data about the possible unintended consequences of using tenofovir-emtricitabine as PrEP [62].

Another potential concern is that HIV acquisition during PrEP use could select for drug-resistant viral strains, which could potentially compromise treatment regimens for those individuals and could increase the frequency of drug-resistant strains that circulate in the community [63]. In iPrEx, none of the participants who became HIV-infected after the start of the study had acquired viral strains with detectable drug resistance when analyzed with highly sensitive genotyping assays [64]. Yet, a substudy within the larger trial found that many of the men who acquired HIV during the study did not have detectable levels of study drug in their serum or blood cells [8] despite high self-reported adherence levels [65]. This suggests that there may not have been sufficient levels of drug present to select for resistant viral strains in many individuals who became infected. Importantly, viral strains with drug resistance to emtricitabine were detected in 3 of 10 men who were already HIV–infected at the start of the study but had not yet developed detectable levels of HIV antibodies (i.e., who were in the "window period" of acute HIV infection at study entry). Two of these three men were in the active arm of the study [8], and the discovery of drug-resistant virus in these participants could represent the evolution of drug-resistant viral strains as a result of PrEP use, although it is also possible that these participants had already been infected with drug-resistant viral strains before they entered the study. The finding of drug-resistant HIV among these recently infected participants underscores that it will be critical to assess for signs and symptoms of acute HIV infection before starting PrEP in individuals who may have had recent high-risk exposures, and to test for acute HIV infection with assays that are sensitive at diagnosing early infection, such as HIV RNA tests.

Efficacy Studies of PrEP for Heterosexual Men and Women: Mixed Results

Additional studies have tested the efficacy of daily oral PrEP among at-risk heterosexual populations in sub-Saharan Africa. The Partners PrEP study enrolled 4,758 HIV serodiscordant African couples in which the HIV-infected partner was not receiving antiretroviral treatment and randomized the uninfected partner to receive tenofovir, tenofovir-emtricitabine, or a placebo tablet to be used once daily [6]. This study demonstrated that HIV acquisition by the uninfected partner of these couples was decreased by 62 % with tenofovir and 73 % with tenofovir-emtricitabine as compared

to placebo. The TDF2 study demonstrated that daily tenofovir-emtricitabine reduced HIV incidence among 1,219 at-risk heterosexual men and women with concurrent or sequential sexual partners in Botswana by 62 % as compared to placebo [7].

However, despite the robust levels of protection associated with PrEP use in the Partners PrEP and TDF2 studies, two other studies were unable to demonstrate the efficacy of PrEP among at-risk African women. The FEM-PrEP study enrolled 2,120 high-risk women in Kenya, South Africa, and Tanzania to received daily tenofovir-emtricitabine or placebo. The study was terminated early, as an independent data safety and monitoring board determined that this study would be highly unlikely to detect a protective benefit associated with PrEP use given similar rates of HIV acquisition among women assigned to use PrEP versus placebo [16]. Similarly, the arms of the VOICE study that randomized women to receive tenofovir or tenofovir-emtricitabine did not demonstrate efficacy, though low levels of adherence may have precluded any definitive conclusions about efficacy [17].

Although completed PrEP trials have reported mixed results in terms of the efficacy of this novel intervention, these studies have generally aligned in demonstrating that PrEP is safe and well-tolerated. No difference in the rate of serious adverse effects was detected among groups of participants randomized to receive active drug versus placebo in any of these studies, including rates of creatinine abnormalities [6, 7, 66]. Detailed safety data are not yet available for VOICE, but preliminary reports indicate that no safety concerns were identified [17]. In TDF2, the group of participants receiving active medication had decreased bone mineral density as compared to the group receiving placebo. Similar to iPrEx and a safety study of tenofovir as PrEP among MSM, the decrease in bone mineral density was small and was of unclear long-term clinical consequence [7]. In terms of tolerability, active study medications were associated with modestly increased rates of gastrointestinal symptoms for the first few weeks of use in Partners PrEP and TDF2, as well as fatigue in Partners PrEP and dizziness in TDF2 [6, 7].

Risk compensation was not evident in these studies as measured by increases in risky sexual behaviors (e.g., rates of unprotected sex or number of sexual partners) over the duration of the studies [6, 7, 16], presumably owing to the intensive risk reduction counseling provided to participants at study visits, although behavioral data from VOICE are also pending. Drug resistance was detected among a few persons with unrecognized acute HIV infection before receipt of PrEP medications and among 3 of 33 women in FEM-PrEP who were in the active drug arm and had access to study drugs around the time of infection. However, all three of these women seroconverted within 12 weeks of study entry, so it is possible that some or all of them had already been infected prior to study enrollment [16]. Studies to assess for the development of drug-resistant viral strains among PrEP users who acquire HIV in clinical settings will be essential.

Possible Explanations for Conflicting Efficacy Results

Several hypotheses have emerged to explain the discrepant efficacy results among oral and topical PrEP studies. These potential explanations build on those that have been proposed to explain the conflicting efficacy results between the two studies of

topical PrEP with tenofovir (i.e., CAPRISA-004 and VOICE), including differences in adherence, risky sexual behaviors, and rates of sexually transmitted coinfections and/or genital tract inflammation among women enrolled in different trials. Analyses of serum drug levels in subsets of study participants strongly suggest that adherence was far lower among participants in FEM-PrEP and VOICE than in Partners PrEP or TDF2, offering a plausible explanation for the failure to demonstrate the efficacy of PrEP in the studies with low adherence. Notably, participants in FEM-PrEP self-reported high rates of adherence [16], highlighting the need for accurate and feasible measures of adherence in PrEP studies [67].

Pharmacokinetic properties of the antiretroviral medications tested in PrEP studies could also lead to different levels of protection in various at-risk populations. Topical tenofovir achieves greater concentrations in vaginal compartment tissues than does oral tenofovir [68], which would presumably provide a greater degree of protection against viral infection. Oral dosing of tenofovir achieves greater concentrations in rectal tissues than in vaginal tissues and secretions, whereas the opposite is true for emtricitabine [27]. These differences could contribute to different levels of protection among MSM than among heterosexual men and women, given that the predominant mode of transmission among MSM involves anal intercourse. The pharmacological data could suggest that for women to achieve optimal protection using oral tenofovir-based chemoprophylaxis, high levels of medication adherence may be necessary. In terms of participant preferences for these two routes of delivering the medications, a cross-over study that assessed the acceptability of topical versus oral PrEP in 144 women found that 72 % of women in the United States preferred tablets, whereas 42 % of African women preferred gel and 40 % preferred tablets [69]. Given different pharmacokinetic properties and acceptability of these topical and oral PrEP formulations, further studies to understand how best to deliver topical and/or oral PrEP among populations with different sexual risk behaviors and cultural preferences are warranted.

The Future of PrEP: New Populations and Novel Medications

Ongoing and future studies will test the feasibility of implementing PrEP in additional at-risk populations. As injection drug use remains the predominant mode of HIV transmission in some microepidemics, results from an ongoing study of daily oral tenofovir among persons who use injection drugs in Thailand will provide important information about the utility of PrEP for this high-risk population [70]. The Adolescent Trial Network is studying the acceptability of PrEP in combination with culturally tailored behavioral interventions among at-risk young MSM in the United States given very high rates of new infections in this population [71]. Interventions for HIV serodiscordant couples wishing to conceive children that combine periconception PrEP with behavioral risk reduction strategies, such as ART for the HIV-infected partner and intercourse timed to coincide with peak fertility, are promising [72] and merit further study, particularly in areas where couples may not be able to access resource-intensive methods of assisted reproduction [73, 74].

Other studies will examine the safety, acceptability, and efficacy of additional antiretroviral agents. Maraviroc, which binds to host cell receptors to prevent HIV entry into host cells, is attractive as a PrEP medication, as it achieves high concentrations in vaginal and rectal tissues, can be administered with once-daily dosing, and has been safe and well-tolerated when used for HIV treatment [75–77]. The NEXT-PrEP study (HPTN 069) is evaluating the safety and tolerability of maraviroc as PrEP for at-risk MSM by comparing four regimens: maraviroc, maraviroc combined with emtricitabine or tenofovir, and tenofovir-emtricitabine [70]. Studies of topical maraviroc and non-nucleoside reverse-transcriptase drugs (e.g., dapivirine) delivered as gels or intravaginal rings are also being studied by the Microbicide Trials Network (www.mtnstophiv.org) and the International Partnership for Microbicides (www.ipm.org). Updates on the status of different clinical trials are available online from the AIDS Vaccine Advocacy Coalition (www.avac.org).

Intermittent PrEP

Studies are testing whether intermittent dosing of PrEP is feasible and efficacious, as intermittent dosing could potentially increase adherence while decreasing costs and the amount of overall drug exposure as compared to daily dosing. A study to examine the feasibility of an intermittent PrEP regimen among 72 MSM and sex workers in Kenya and Uganda compared daily dosing of tenofovir-emtricitabine to a dosing regimen that combined two fixed doses weekly plus an additional dose around the time of intercourse. This study found that many participants did not adhere to the postcoital dose [78], suggesting that intermittent dosing strategies may still present adherence challenges. Qualitative interviews with participants suggested that adherence to pericoital dosing was challenging due to alcohol use around the time of sex, transactional sex, and the mobility of study populations [79]. The Adapt Study (HPTN 067) has enrolled high-risk MSM in Bangkok and New York and high-risk women in Cape Town (www.hptn.org), and is comparing different approaches to intermittent PrEP dosing, i.e., fixed interval versus pericoital dosing. Another study to test the efficacy of intermittent PrEP (the Ipergay study) will randomize 300 MSM and transgender women to receive either tenofovir-emtricitabine or placebo to be used as two daily doses before sex and another single dose after sex (www.ipergay.fr).

Optimizing Adherence

The efficacy of PrEP has correlated strongly with adherence levels in all completed studies to date [6–8, 16]. Therefore, strategies to assess and optimize adherence in clinical settings will be essential. A novel intervention known as Integrated Next Steps Counseling was developed to assess and support adherence among participants in the iPrEx study and was found to be feasible and acceptable [80]. This intervention incorporated neutral assessment (i.e., supporting a comfortable environment for participants to report nonadherence) to increase the accuracy of self-reported adherence

as well as patient-centered adherence counseling, based on motivational interviewing techniques, to support adherence. In the Partners PrEP study, a couples-based counseling intervention that utilized elements of cognitive behavioral therapy and motivational interviewing was feasible and acceptable, and its efficacy at improving adherence among members of serodiscordant couples with suboptimal adherence to PrEP medications will be tested in future studies [81]. Enhancing PrEP in Community Settings (EPIC) is a community-based study that will assess correlates of adherence to PrEP in real-world settings and then test whether a multicomponent behavioral intervention can optimize adherence. The EPIC intervention will utilize an educational "starter kit" for persons utilizing PrEP, interactive text message reminders, and brief client-centered counseling [82]. Analyses of serum and intracellular drug levels from participants in PrEP efficacy studies suggest that they have tended to overestimate their degree of adherence [6–8, 16], perhaps due to social desirability bias. Understanding ways to accurately and efficiently assess adherence to PrEP will be essential to gauge the effectiveness of adherence support interventions. Creative and efficient approaches to measuring adherence in real-world settings, such as analyzing hair samples for the presence of antiretroviral medications [82, 83], are undergoing study.

Implementing PrEP in Clinical Settings

In July 2012, the FDA approved tenofovir-emtricitabine for use as daily oral PrEP among MSM and heterosexuals at high risk for HIV acquisition [84]. This approval could facilitate PrEP prescribing by healthcare providers in clinical practice and could therefore open the door to broader implementation. Community readiness to utilize PrEP is likely to be a critical determinant of actual uptake by at-risk individuals. Survey-based studies have demonstrated that many high-risk individuals, such as MSM who are members of online social networks in the United States [85] and sex workers, young women, members of serodiscordant couples, and persons using injection drugs in several nations, report high interest in using PrEP [86], although other studies have found lower levels of interest [87]. Several studies of at-risk MSM [85, 87] and healthcare providers [88, 89] suggest that PrEP utilization has been uncommon since the release of efficacy data [85], and additional studies to understand facilitators and barriers to PrEP utilization in community settings are warranted. PrEP demonstration projects are starting in San Francisco, Miami, Washington, DC, several cities in southern California, and other locations. These projects will provide PrEP to several hundred at-risk MSM who present to STD clinics and other clinical settings and then assess safety parameters, adherence, and changes in sexual risk behaviors over the course of the following year [90]. This work will provide important data on the safety and feasibility of implementing PrEP in these clinical settings.

HIV Prevention Focusing on People Living with HIV

In addition to the promising advances in primary HIV prevention, including microbicides, oral PrEP, as well as VMMC, recent studies have demonstrated both disappointing and groundbreaking biomedical approaches to secondary HIV prevention. As the presence of sexually transmitted coinfections has been shown to increase transmission of HIV, studies have examined whether treatment of coinfections in HIV-infected persons can decrease HIV transmission to their uninfected partners, but these studies have generally been unable to demonstrate the effectiveness of this approach [91]. However, observational and controlled studies have demonstrated that treating HIV-infected persons with ART can greatly decrease their infectivity, thereby reducing the risk that they will transmit HIV to their sexual partners [5, 92]. These findings have rapidly influenced HIV treatment guidelines in some resource-rich settings [93]. If sufficient public and political will exists to scale up antiretroviral treatment for HIV-infected persons on a global scale, secondary biomedical HIV prevention has great potential to impact the HIV epidemic.

Treatment of STIs

Epidemiological studies have suggested that STIs increase HIV susceptibility and infectiousness [94–97], which is biologically plausible, given their propensity to cause genital tract inflammation and ulceration. However, of seven randomized, controlled trials that used an STI intervention, only one was associated with a decrease in HIV incidence. The Mwanza Study was launched in an area of low HIV prevalence, and included diagnosis and treatment of a range of bacterial and protozoal STIs [98]. It has not thought to be scalable on a public health basis in resource-constrained environments, particularly those with generalized HIV epidemics. Moreover, the high coprevalence of other viral STIs, like Herpes simplex virus type 2 (HSV-2), raised questions about whether addressing this pathogen could lead to more successful STI interventions (see below). Nonetheless, regular bacterial and protozoal STI screening and treatment of high-risk and HIV-infected persons is beneficial in decreasing the global STI burden, and can be an adjunctive part of more efficacious prevention interventions.

Recently more attention has focused on the role of HSV-2 control in HIV prevention. HSV-2 is one of the coinfections that is most strongly associated with HIV transmission [99]. Administration of antiviral medications with activity against HSV-2, specifically acyclovir, has been shown to decrease HIV levels in the plasma, genital, and rectal compartments of HSV-2-/HIV-coinfected individuals [100–103]. However, a multinational, randomized, placebo-controlled study of the administration of acyclovir to HSV-2-/HIV-coinfected persons did not detect a decrease in HIV transmission to their HIV-uninfected sexual partners (the Partners in Prevention HSV/HIV study) [104].

The HIV Prevention Trials Network 039 Study tested whether antiviral treatment of HSV-2 in HIV-uninfected females and MSM could decrease their susceptibility to HIV acquisition, which would represent a primary prevention strategy for HIV. This study was also unable to demonstrate decreased HIV acquisition [105]. Some have argued that HSV-2 control could still be an effective way to decrease HIV transmission, either by greater control of HSV-2 reactivation with higher doses of antiviral therapy than were utilized in these two studies (i.e., greater than 400 mg of acyclovir twice daily) [106], or by prevention of HSV-2 acquisition with an effective vaccine. If future studies can demonstrate the efficacy of anti-HSV-2 interventions at preventing HIV transmission, they could be a useful component as part of a combination HIV prevention strategy.

Treatment as Prevention

Over a decade ago, studies of HIV serodiscordant couples in Uganda (the Rakai Project) determined that HIV plasma viral load was the strongest predictor of the likelihood of sexual transmission between partners. Moreover, these studies showed that the risk of transmission was very low when the HIV-infected partner of serodiscordant couples had low levels of viremia [99, 107]. These results suggested that therapies to reduce the HIV viral load among infected persons might be able to decrease their infectiousness. In 2011, the HIV Prevention Trials Network 052 Study (HPTN 052) demonstrated that early initiation of antiretroviral treatment to the HIV-infected members of 1,763 HIV serodiscordant couples at CD4 cell counts between 350–550 cells/ml could decrease the likelihood of viral transmission to their uninfected partners by 96 %, as compared to delayed initiation of treatment [5]. Named the "Scientific Breakthrough of the Year 2011" by the prestigious journal *Science*, this study has been widely acknowledged to be a "game-changer" in secondary HIV prevention. As the study demonstrated that early ART was also associated with individual health benefits among HIV-infected persons, largely owing to decreased rates of tuberculosis-related complications [5], this study has influenced HIV treatment guidelines in the United States to recommend universal antiretroviral treatment for all HIV-infected persons owing to the potential personal and prevention benefits of this strategy [93].

Challenges to Implementing Treatment as Prevention

Early administration of ART to HIV-infected persons to prevent the spread of HIV, known as "Treatment as Prevention," has moved to the forefront of the HIV prevention agenda after HPTN 052. However, numerous barriers could impede successful implementation of Treatment as Prevention on a broader scale. In HPTN 052, genetic studies demonstrated that more than one-fifth of persons who became HIV-infected during the study acquired viral strains that were genetically distinct from those of

their long-term partner, suggesting that they had sexual partnerships outside of their primary relationship [5, 108]. For at-risk individuals with multiple sexual partnerships, additional primary prevention strategies, like PrEP, may be required to prevent viral acquisition. As nearly all the serodiscordant couples in HPTN 052 were heterosexual, it is not known if early initiation of treatment will decrease the spread of HIV among persons whose primary risk factors for HIV acquisition include anal sex or injection drug use. Although, it is biologically plausible that earlier initiation of treatment would decrease transmission in these situations, additional studies among MSM and injection drug users are needed to delineate whether a comparable level of protection can be expected. Moreover, individuals with acute HIV may be highly infectious but asymptomatic and therefore undiagnosed and not using ART, which suggests that additional prevention strategies will be needed to interrupt the spread of HIV in this context.

Programs to scale up antiretroviral treatment in resource-limited settings may not have sufficient resources to provide medications to all HIV-infected persons. These programs may need to prioritize treatment for individuals with advanced disease, which could limit the availability of antiretroviral medications for other persons. Treatment as Prevention faces implementation challenges in resource-rich areas as well. Many persons who are HIV-infected may be unaware of their status, or they may not be linked to HIV care or retained in care such that they can receive antiretroviral treatment and achieve long-term virologic suppression. These gaps along the spectrum of engagement in HIV care, also known as the "HIV treatment cascade," represent formidable obstacles for implementing Treatment as Prevention. In the United States, for example, approximately one-fifth of HIV-infected persons are unaware of their status, half are engaged in care, and only 20–30 % of HIV-infected persons have achieved virologic suppression overall [109, 110]. Policymakers are attempting to address gaps along the treatment cascade, but without allocating more resources toward these efforts, these gaps are likely to persist into the foreseeable future [111].

Population-Level Impact of Early Antiretroviral Treatment

Several geographic regions have instituted policies that encourage early treatment of persons infected with HIV, before immunologic decline, thereby allowing insights into the population-level impact of this strategy. In Vancouver, British Columbia, where a majority of new HIV infections occur among persons who use injection drugs, observational data from 1996 to 2009 suggest a relationship between increasing coverage with ART, increasing rates of virologic suppression, and decreasing HIV incidence [112]. In San Francisco, decreases in HIV incidence from 2004 to 2008 have correlated with decreases in "community viral load," the sum of all reported viral loads in a community, and the decreasing community viral load may be attributable to increasing coverage with ART [113]. In 2010, public health authorities in San Francisco began to recommend universal treatment for all HIV-infected persons, and rates of virologic suppression among individuals presenting to care

with CD4 cell counts >500 cells/ml at one clinic increased from 14 % before the new recommendation to 53 % after this recommendation [114], an illustration that treating individuals before immunologic decline can be feasible, at least on a local scale. Observational data suggest that increasing coverage with ART in African nations is correlated with decreasing HIV incidence [115] and HIV-related mortality [116, 117].

Scaling Up Treatment as Prevention

Effective scale-up of Treatment as Prevention will require provider training and enhanced HIV testing uptake. Although few studies have assessed HIV provider attitudes toward early ART, a qualitative study of HIV providers in Boston suggests that providers have positive attitudes toward this strategy but cite numerous barriers to treating all their HIV-infected patients in clinical practice, including patient readiness to initiate life-long treatment and perceived adherence challenges [118]. Increasing HIV testing rates among key populations is a critical first step toward scaling up Treatment as Prevention. Programs to increase testing among couples could identify greater numbers of serodiscordant couples, whereas testing programs tailored toward MSM, injection drug users, and sex workers could increase diagnoses among these at-risk populations. Community-wide testing campaigns have been associated with increased testing rates in the Bronx, New York [119], and programs to train primary care physicians to increase HIV testing among their patients hold promise [120].

Community Mobilization to Scale Up HIV Testing

Project Accept (HPTN 043) randomized communities in Africa and Thailand to receive resources to scale up community-based voluntary counseling and testing through community mobilization, including the training of key opinion leaders, the use of mobile testing units in remote areas, and public messaging campaigns, versus standard clinic-based voluntary counseling and testing. This study demonstrated that the community-based approach was associated with a 14 % reduction in HIV incidence in the intervention communities compared to the standard clinic-based approach, though this decrease was not statistically significant ($p = 0.08$) [121]. The modest decrease in incidence associated with community-based testing suggests that increased testing at the community level could be an important component of a combination prevention strategy, but that it is not sufficiently effective to be delivered as a stand-alone intervention without increased uptake of antiretroviral treatment on a population level.

Newer HIV tests, including combined antibody-antigen tests (fourth-generation assays), may allow for earlier diagnosis than current antibody tests that are used for screening, which could increase identification of individuals with acute HIV infection who are in the “window period” (i.e., having acquired HIV infection but not yet produced detectable levels of HIV antibody). However, a programmatic study

in the United Kingdom found that this test offered marginal benefit over standard assays in a low-prevalence setting [122], and further studies are needed to understand optimal uses of antigen-based tests. Over-the-counter, home testing with rapid HIV tests, the first of which received FDA approval in July 2012 [123], could also facilitate testing among persons who are not engaged with the healthcare system, though the actual benefit of home testing requires further study [124]. A recent study found that MSM who were given home tests for partner testing found this practice to be highly acceptable and associated with decreased risk taking behavior [125].

Other Approaches to Biomedical HIV Prevention

Voluntary Medical Male Circumcision Numerous observational studies and several randomized, controlled trials have demonstrated that VMMC can decrease HIV acquisition by heterosexual men in high-prevalence settings. A meta-analysis of three large, controlled studies in Kenya, Uganda, and South Africa found that VMMC decreased HIV incidence among adult heterosexual men between 38 and 66 % after 2 years of follow-up with minimal safety concerns [10]. Observational studies involving large numbers of neonates have also found VMMC to be safe among this population [126]. Scaling up VMMC to enhance community efficacy in nations with generalized epidemics remains a priority. Over one million men have already undergone this procedure as part of HIV prevention programs. As the United States has committed funds from the President's Emergency Plan for AIDS Relief (PEPFAR) to support VMMC of an additional 4.7 million men by 2014 [127], VMMC could play a substantial role in curbing the HIV epidemic over the next few years.

HIV Vaccines An HIV vaccine would likely provide a tremendous new tool in preventing new HIV infections, but the development of an effective vaccine has remained elusive despite decades of intensive research. In 2009, the RV144 study demonstrated that a two-vaccine approach achieved 31 % efficacy in decreasing HIV incidence among 14,000 at-risk individuals in Thailand, the most promising HIV vaccine efficacy study, to date [128]. The vaccines tested in RV144 were designed to elicit cellular and humoral (i.e., antibody-based) immune responses, and the finding that the vaccine conferred a modest degree of protection has generated great interest in identifying correlates of protection with this vaccine, to inform the development of next-generation vaccine candidates [129]. Despite the renewed optimism in HIV vaccine research after RV144, the most recent HIV vaccine efficacy trial (HVTN 505) was recently terminated early because of an independent data safety and monitoring board's recognition that efficacy could not be demonstrated (www.hvtn.org). Thus, the development of a vaccine that is sufficiently effective to merit widespread use is likely years away, underscoring the need to optimize other biomedical prevention strategies at the present time.

Conclusion

With promising recent developments in primary and secondary HIV prevention, including microbicides, PrEP, VMMC, and decreasing HIV transmission with early ART, there are considerable reasons for optimism that the epidemic can be arrested. However, it is important to note that each of these interventions requires careful attention to psychosocial and structural issues. The trust of at-risk and infected communities is needed to scale up these interventions, and medication-based prevention can only work if individuals are adherent to their regimen. Poor adherence and increased risk compensation because of optimism about the potency of these interventions could mitigate any benefit. Moreover, none of these interventions is likely to be completely effective if instituted alone given numerous challenges to implementing each of them in clinical settings (ranging from resources to purchase medications or to perform surgery, to training the health care work force). Therefore, the optimal way forward is likely to involve a "Combination Prevention" approach, whereby prevention interventions are adapted to local epidemic dynamics and personal preferences to yield the greatest reductions in HIV incidence with the available resources. As all the promising biomedical prevention strategies have been tested in conjunction with behavioral counseling, future studies should address ways to synergistically combine biomedical and behavioral interventions and implement them in the community. If this can be successfully achieved, there is renewed hope to curb the HIV epidemic and achieve an "AIDS-free generation" [130].

References

1. UNAIDS Report on the Global AIDS Epidemic 2010. Joint United Nations Programme on HIV/AIDS (UNAIDS). http://www.unaids.org/GlobalReport/default.htm. Accessed 1 June 2012.
2. Prejean J, Song R, Hernandez A, Ziebell R, Green T, Walker F, et al. Estimated HIV Incidence in the United States, 2006–2009. PLoS One. 2011;6(8):e17502.
3. Dieffenbach CW, Fauci AS. Thirty years of HIV and AIDS: future challenges and opportunities. Ann Intern Med. 2011;154(11):766–71.
4. Karim SS, Karim QA. Antiretroviral prophylaxis: a defining moment in HIV control. Lancet. 2011;378(9809):e23–5.
5. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6):493–505.
6. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367(5):399–410.
7. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012;367(5):423–34.
8. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363(27):2587–99.

9. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010;329(5996):1168–74.
10. Siegfried N, Muller M, Deeks JJ, Volmink J. Male circumcision for prevention of heterosexual acquisition of HIV in men. Cochrane Database Syst Rev 2009(2):CD003362.
11. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med. 2005;2(11):e298.
12. Montgomery CM, Pool R. Critically engaging: integrating the social and the biomedical in international microbicides research. J Int AIDS Soc. 2011;14(Suppl 2):S4.
13. Kurth AE, Celum C, Baeten JM, Vermund SH, Wasserheit JN. Combination HIV prevention: significance, challenges, and opportunities. Curr HIV/AIDS Rep. 2010;8(1):62–72.
14. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med. 1994;331(18):1173–80.
15. Obiero J, Mwethera PG, Hussey GD, Wiysonge CS. Vaginal microbicides for reducing the risk of sexual acquisition of HIV infection in women: systematic review and meta-analysis. BMC Infect Dis. 2012;12(1):289.
16. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012;367(5):411–22.
17. Marrazzo JM, Ramjee G, Nair GB, Palanee T, Mkhiza B, Nakabiito C et al Pre-exposure Prophylaxis for HIV in Women: Daily Oral Tenofovir, Oral Tenofovir/Emtricitabine, or Vaginal Tenofovir Gel in the VOICE Study (MTN 003). Conference on Retroviruses and Opportunistic Infections. Atlanta; 3–6 March 2013. http://www.retroconference.org/2013b/Abstracts/47951.htm. Accessed 12 April 2013.
18. Polsky B, Baron PA, Gold JW, Smith JL, Jensen RH, Armstrong D. In vitro inactivation of HIV-1 by contraceptive sponge containing nonoxynol-9. Lancet. 1988;1(8600):1456.
19. Kreiss J, Ngugi E, Holmes K, Ndinya-Achola J, Waiyaki P, Roberts PL, et al. Efficacy of nonoxynol 9 contraceptive sponge use in preventing heterosexual acquisition of HIV in Nairobi prostitutes. J Am Med Assoc. 1992;268(4):477–82.
20. Roddy RE, Zekeng L, Ryan KA, Tamoufe U, Weir SS, Wong EL. A controlled trial of nonoxynol 9 film to reduce male-to-female transmission of sexually transmitted diseases. N Engl J Med. 1998;339(8):504–10.
21. Van Damme L, Ramjee G, Alary M, Vuylsteke B, Chandeying V, Rees H, et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. Lancet. 2002;360(9338):971–7.
22. Pirrone V, Wigdahl B, Krebs FC. The rise and fall of polyanionic inhibitors of the human immunodeficiency virus type 1. Antiviral Res. 2011;90(3):168–82.
23. Abdool Karim SS, Richardson BA, Ramjee G, Hoffman IF, Chirenje ZM, Taha T, et al. Safety and effectiveness of BufferGel and 0.5 % PRO2000 gel for the prevention of HIV infection in women. AIDS. 2011;25(7):957–66.
24. McCormack S, Ramjee G, Kamali A, Rees H, Crook AM, Gafos M, et al. PRO2000 vaginal gel for prevention of HIV-1 infection (Microbicides Development Programme 301): a phase 3, randomised, double-blind, parallel-group trial. Lancet. 2010;376(9749):1329–37.
25. Van Damme L, Govinden R, Mirembe FM, Guedou F, Solomon S, Becker ML, et al. Lack of effectiveness of cellulose sulfate gel for the prevention of vaginal HIV transmission. N Engl J Med. 2008;359(5):463–72.
26. Meeting Report: Next Steps with 1 % Tenofovir Gel. World Health Organization and Joint United National Programme on HIV/AIDS. 13 January 2011. http://www.who.int/reproductivehealth/topics/rtis/WHO_UNAIDS_Next_steps_tenofovir_gel_Ex_sum.pdf. Accessed 13 December 2011.
27. Hendrix CW. The clinical pharmacology of antiretrovirals for HIV prevention. Curr Opin HIV AIDS. 2012;7(6):498–504.

28. Press Release: MTN Statement on Decision to Discontinue Use of Tenofovir Gel in VOICE, a Major HIV Prevention Study in Women. Microbicides Trial Network. 28 November 2011. http://www.mtnstopshiv.org/node/3909. Accessed 1 June 2012.
29. Mayer KH, Venkatesh KK. Interactions of HIV, other sexually transmitted diseases, and genital tract inflammation facilitating local pathogen transmission and acquisition. Am J Reprod Immunol. 2011;65(3):308–16.
30. Follow-on African Consortium for Tenofovir Studies (FACTS) [website]. http://www.facts-consortium.co.za/?page_id=83. Accessed 1 June 2012.
31. National Antenatal Sentinal HIV and Syphilis Prevalence Survey in South Africa, 2010. National Department of Health, South Africa. http://www.doh.gov.za/docs/reports/2011/hiv_aids_survey.pdf. Accessed 13 Dec 2011.
32. Beyrer C. Global prevention of HIV infection for neglected populations: men who have sex with men. Clin Infect Dis. 2010;50(Suppl 3):S108–13.
33. Baral S, Sifakis F, Cleghorn F, Beyrer C. Elevated risk for HIV infection among men who have sex with men in low- and middle-income countries 2000–2006: a systematic review. PLoS Med. 2007;4(12):e339.
34. Beyrer C, Baral SD, Griensven F van, Goodreau SM, Chariyalertsak S, Wirtz AL, et al. Global epidemiology of HIV infection in men who have sex with men. Lancet. 2012;380(9839):367–77.
35. Cranage M, Sharpe S, Herrera C, Cope A, Dennis M, Berry N, et al. Prevention of SIV rectal transmission and priming of T cell responses in macaques after local pre-exposure application of tenofovir gel. PLoS Med. 2008;5(8):e157.
36. Anton PA, Cranston RD, Kashuba A, Hendrix CW, Bumpus NN, Richardson-Harman N, et al. RMP-02/MTN-006: a phase 1 rectal safety, acceptability, pharmacokinetic, and pharmacodynamic study of tenofovir 1 % gel compared with oral tenofovir disoproxil fumarate. AIDS Res Hum Retroviruses. 2012;28(11):1412–21.
37. Dezzutti CS, Rohan LC, Wang L, Uranker K, Shetler C, Cost M, et al. Reformulated tenofovir gel for use as a dual compartment microbicide. J Antimicrob Chemother. 2012;67(9):2139–42.
38. McGowan I. Rectal microbicide development. Curr Opin HIV AIDS. 2012;7(6):526–33.
39. Johnson TJ, Clark MR, Albright TH, Nebeker JS, Tuitupou AL, Clark JT, et al. A 90-day tenofovir reservoir intravaginal ring for mucosal HIV prophylaxis. Antimicrob Agents Chemother. 2012;56(12):6272–83.
40. Romano J, Variano B, Coplan P, Van Roey J, Douville K, Rosenberg Z, et al. Safety and availability of dapivirine (TMC120) delivered from an intravaginal ring. AIDS Res Hum Retroviruses. 2009;25(5):483–8.
41. Singer R, Mawson P, Derby N, Rodriguez A, Kizima L, Menon R, et al. An intravaginal ring that releases the NNRTI MIV-150 reduces SHIV transmission in macaques. Sci Transl Med. 2012;4(150):150ra123.
42. Kobayashi K, Seki T, Kawasuji T, Taishi T, Sato A, Fujiwara T et al Antiviral Characteristics Of S/GSK1265744, An HIV Integrase Inhibitor (INI) dosed by oral or long-acting parenteral injection. 52nd Interscience Conference on antimicrobial agents and chemotherapy. San Francisco; Sept 9–12, 2012. http://conference-cast.com/ICAAC/Common/presentation.aspx?ConfId=6&TrackId=11&SessionId=845. Accessed 31 Jan 2012.
43. Panlilio AL, Cardo DM, Grohskopf LA, Heneine W, Ross CS. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. MMWR Recomm Rep. 2005;54(RR-9):1–17.
44. Garcia-Lerma JG, Heneine W. Animal models of antiretroviral prophylaxis for HIV prevention. Curr Opin HIV AIDS. 2012;7(6):505–13.
45. García-Lerma J, Otten R, Qari S, Jackson E, Cong M, Masciotra S, et al. Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. PLoS Med. 2008;5(2):e28.
46. Garcia-Lerma JG, Cong ME, Mitchell J, Youngpairoj AS, Zheng Q, Masciotra S, et al. Intermittent prophylaxis with oral truvada protects macaques from rectal SHIV infection. Sci Transl Med. 2010;2(14):14ra4.

47. Kwara A, DeLong A, Rezk N, Hogan J, Burtwell H, Chapman S, et al. Antiretroviral drug concentrations and HIV RNA in the genital tract of HIV-infected women receiving long-term highly active antiretroviral therapy. Clin Infect Dis. 2008;46(5):719–25.
48. Hamers RL, Sigaloff KC, Wensing AM, Wallis CL, Kityo C, Siwale M, et al. Patterns of HIV-1 drug resistance after first-line antiretroviral therapy (ART) failure in 6 sub-Saharan African countries: implications for second-line ART strategies. Clin Infect Dis. 2012;54(11):1660–9.
49. Peterson L, Taylor D, Roddy R, Belai G, Phillips P, Nanda K, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. PLoS Clin Trials. 2007;2(5):e27.
50. Liu AY, Vittinghoff E, Sellmeyer DE, Irvin R, Mulligan K, Mayer K, et al. Bone mineral density in HIV-negative men participating in a Tenofovir pre-exposure prophylaxis randomized clinical trial in San Francisco. PLoS One. 2011;6(8):e23688.
51. Cardo DM, Culver DH, Ciesielski CA, Srivastava PU, Marcus R, Abiteboul D, et al. A Case-control study of HIV seroconversion in health care workers after percutaneous exposure. N Engl J Med. 1997;337(21):1485–90.
52. Mayer KH, Mimiaga MJ, Cohen D, Grasso C, Bill R, Van Derwarker R, et al. Tenofovir DF plus lamivudine or emtricitabine for nonoccupational postexposure prophylaxis (NPEP) in a Boston Community Health Center. J Acquir Immune Defic Syndr. 2008;47(4):494–9.
53. Roland ME, Neilands TB, Krone MR, Katz MH, Franses K, Grant RM, et al. Seroconversion following nonoccupational postexposure prophylaxis against HIV. Clin Infect Dis. 2005;41(10):1507–13.
54. Mayer KH, Mimiaga MJ, Gelman M, Grasso C. Raltegravir, tenofovir DF, and emtricitabine for postexposure prophylaxis to prevent the sexual transmission of HIV: safety, tolerability, and adherence. J Acquir Immune Defic Syndr. 2012;59(4):354–9.
55. Schechter M, do Lago RF, Mendelsohn AB, Moreira RI, Moulton LH, Harrison LH. Behavioral impact, acceptability, and HIV incidence among homosexual men with access to postexposure chemoprophylaxis for HIV. J Acquir Immune Defic Syndr. 2004;35(5):519–25.
56. Poynten IM, Jin F, Mao L, Prestage GP, Kippax SC, Kaldor JM, et al. Nonoccupational post-exposure prophylaxis, subsequent risk behaviour and HIV incidence in a cohort of Australian homosexual men. AIDS. 2009;23(9):1119–26.
57. Grohskopf L, Gvetadze R, Pathak S, O'Hara B, Mayer K, Liu A, et al. Preliminary analysis of biomedical data from the phase II clinical safety trial of tenofovir disoproxil fumarate (TDF) for HIV-1 pre-exposure prophylaxis (PrEP) among U.S. men who have sex with men (MSM) [Abstract FRLBC102]. XVIII International AIDS Conference. Vienna, Austria; 18–23 July 2010. http://pag.aids2010.org/Abstracts.aspx?AID=17777. Accessed 1 June 2012.
58. Jacobson DL, Spiegelman D, Knox TK, Wilson IB. Evolution and predictors of change in total bone mineral density over time in HIV-infected men and women in the nutrition for healthy living study. J Acquir Immune Defic Syndr. 2008;49(3):298–308.
59. Szczech LA. Renal dysfunction and tenofovir toxicity in HIV-infected patients. Top HIV Med. 2008;16(4):122–6.
60. Mulligan K, Glidden DV, Gonzales P, Ramirez-Cardich ME, Liu A, Namwongprom S, et al. Effects of FTC/TDF on bone mineral density in seronegative men from 4 continents: DEXA results of the global iPrEx study [Abstract #94LB]. 18th Conference on retroviruses and opportunistic infections. Boston: 27 February–2 March 2011. http://www.retroconference.org/2011/Abstracts/42550.htm. Accessed 1 June 2012.
61. Golub SA, Kowalczyk W, Weinberger CL, Parsons JT. Preexposure prophylaxis and predicted condom use among high-risk men who have sex with men. J Acquir Immune Defic Syndr. 2010;54(5):548–55.
62. iPrEx Fact Sheet: Rollover Study and Next Steps. 2010. http://www.iprexnews.com/studyresults/pdfembargo/englishversion/iPrEx%20Fact%20Sheet%20Rollover%20Study%20and%20Next%20Steps%20PE.pdf. Accessed 20 Nov 2012.
63. Hurt CB, Eron JJ Jr, Cohen MS. Pre-exposure prophylaxis and antiretroviral resistance: HIV prevention at a cost? Clin Infect Dis. 2011;53(12):1265–70.

64. Liegler T, Abdel-Mohsen M, Atchison R, Mehotra M, Schmidt T, Eden C, et al. Drug resistance and minor drug resistant variants in iPrEx [Abstract #97LB]. 18th Conference on Retroviruses and Opportunistic Infections. Boston: 27 February–2 March 2011. http://www.retroconference.org/2011/Abstracts/42553.htm. Accessed 13 Dec 2011.
65. Amico KR, Liu A, McMahan V, Anderson P, Lama JR, Guanira J, et al. Adherence indicators and PrEP drug levels in the iPrEx study [Abstract #95LB]. 18th Conference on Retroviruses and Opportunistic Infections. Boston; 27 February-2 March 2011. http://www.retroconference.org/2011/Abstracts/42627.htm. Accesssed on: 1 June 2012.
66. Guedou FA, Van Damme L, Mirembe F, Solomon S, Becker M, Deese J, et al. Intermediate vaginal flora is associated with HIV prevalence as strongly as bacterial vaginosis in a cross-sectional study of participants screened for a randomised controlled trial. Sex Transm Infect. 2012;88(7):545–51.
67. Muchomba FM, Gearing RE, Simoni JM, El-Bassel N. State of the science of adherence in pre-exposure prophylaxis and microbicide trials. J Acquir Immune Defic Syndr. 2012;61(4): 490–8.
68. Hendrix C, Minnis A, Guddera V, Riddler S, Salata R, Nakabiito C, et al. MTN-001: A phase 2 cross-over study of daily oral and vaginal tfv in healthy, sexually active women results in significantly different product acceptability and vaginal tissue drug concentrations [Abstract #34LB]. 18th Conference on Retroviruses and Opportunistic Infections. Boston; 27 February-2 March, 2011. http://www.retroconference.org/2011/Abstracts/42418.htm. Accessed 13 Dec 2011.
69. Minnis AM, Gandham S, Richardson BA, Guddera V, Chen BA, Salata R, et al. Adherence and acceptability in MTN 001: a randomized cross-over trial of daily oral and topical tenofovir for HIV prevention in women. AIDS Behav. 2013;17(2):737–47.
70. AIDS vaccine advocacy coalition [website]. http://avac.org/. Accessed 1 June 2012.
71. ClincalTrials.gov: pre-exposure prophylaxis in YMSM [website]. http://clinicaltrials.gov/show/NCT01033942. Accessed 23 Nov 2012.
72. Vernazza PL, Graf I, Sonnenberg-Schwan U, Geit M, Meurer A. Preexposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child. AIDS. 2011;25(16):2005–8.
73. Matthews LT, Crankshaw T, Giddy J, Kaida A, Smit JA, Ware NC, et al. Reproductive decision-making and periconception practices among HIV-positive men and women attending HIV services in Durban, South Africa. AIDS Behav. 2013;17(2):461–70.
74. Matthews LT, Baeten JM, Celum C, Bangsberg DR. Periconception pre-exposure prophylaxis to prevent HIV transmission: benefits, risks, and challenges to implementation. AIDS. 2010;24(13):1975–82.
75. Brown KC, Patterson KB, Malone SA, Shaheen NJ, Prince HM, Dumond JB, et al. Single and multiple dose pharmacokinetics of maraviroc in saliva, semen, and rectal tissue of healthy HIV-negative men. J Infect Dis. 2011;203(10):1484–90.
76. Abraham BK, Gulick R. Next-generation oral preexposure prophylaxis: beyond tenofovir. Curr Opin HIV AIDS. 2012;7(6):600–6.
77. Dumond JB, Patterson KB, Pecha AL, Werner RE, Andrews E, Damle B, et al. Maraviroc concentrates in the cervicovaginal fluid and vaginal tissue of HIV-negative women. J Acquir Immune Defic Syndr. 2009;51(5):546–53.
78. Mutua G, Sanders E, Mugo P, Anzala O, Haberer JE, Bangsberg D, et al. Safety and adherence to intermittent pre-exposure prophylaxis (PrEP) for HIV-1 in African men who have sex with men and female sex workers. PLoS One. 2012;7(4):e33103.
79. Van der Elst EM,M, Mugo P, et al. High acceptability of HIV pre-exposure prophylaxis but challenges in adherence and use: qualitative insights from a Phase I trial of intermittent and daily PrEP in at-risk populations in Kenya. AIDS Behav. 2013;17(6):2162–72.
80. RA K, McMahan V, Goicochea P, Vargas L, Marcus JL, Grant RM, et al. Supporting study product use and accuracy in self-report in the iPrEx study: next step counseling and neutral assessment. AIDS Behav. 2012;16(5):1243–59.

81. Psaros C. Evaluation and process outcomes from an adherence intervention to support HIV pre-exposure prophylaxis (PrEP) adherence in HIV serodiscordant couples in Uganda [Abstract 80031]. 7th International Conference on HIV Treatment and Prevention Adherence. Miami Beach; June 5–7, 2012. http://www.iapac.org/AdherenceConference/presentations/ADH7_80031.pdf. Accessed 31 Jan 2013.
82. Liu A. Implementing PrEP in the Real World: Key issues and challenges for MSM populations. Presentation at the 6th National Scientific Meeting of the Social and Behavioral Sciences Research Network. http://www.cfarsbsrn2012.com/wp-content/uploads/2012/04/Liu-Al.pdf. Accessed 23 Nov 2012.
83. Amico KR. Adherence to preexposure chemoprophylaxis: the behavioral bridge from efficacy to effectiveness. Curr Opin HIV AIDS. 2012;7(6):542–8.
84. Truvada approved to reduce the risk of sexually transmitted HIV in people who are not infected with the virus. U.S. Food and Drug Administration. 16 July 2012. http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm312264.htm. Accessed 17 July 2012.
85. Krakower DS, Mimiaga MJ, Rosenberger JG, Novak DS, Mitty JA, White JM, et al. Limited awareness and low immediate uptake of pre-exposure prophylaxis among men who have sex with men using an internet social networking site. PLoS One. 2012;7(3):e33119.
86. Eisingerich AB, Wheelock A, Gomez GB, Garnett GP, Dybul MR, Piot PK. Attitudes and acceptance of oral and parenteral HIV preexposure prophylaxis among potential user groups: a multinational study. PLoS One. 2012;7(1):e28238.
87. Holt M, Murphy DA, Callander D, Ellard J, Rosengarten M, Kippax SC, et al. Willingness to use HIV pre-exposure prophylaxis and the likelihood of decreased condom use are both associated with unprotected anal intercourse and the perceived likelihood of becoming HIV positive among Australian gay and bisexual men. Sex Transm Infect. 2012;88(4):258–63.
88. White JM, Mimiaga MJ, Krakower DS, Mayer KH. Evolution of massachusetts physician attitudes, knowledge, and experience regarding the use of antiretrovirals for HIV prevention. AIDS Patient Care STDS. 2012;26(7):395–405.
89. Maznavi K, Hardy D, Bredeek F. Pre-exposure prophylaxis (PrEP) for HIV: An online survey of HIV healthcare providers evaluating their knowledge, perception, and prescription of PrEP. 49th Annual Meeting of the Infectious Diseases Society of America. Boston, MA; 2011.
90. SFDPH to Launch PrEP Demonstration Project for HIV Prevention [press release]. 17 September 2012. http://www.sfdph.org/dph/files/newsMediadocs/2012PR/DemoProjectFINAL.pdf. Accessed 23 Nov 2012.
91. Hayes R, Watson-Jones D, Celum C, Wijgert J van de, Wasserheit J. Treatment of sexually transmitted infections for HIV prevention: end of the road or new beginning? AIDS. 2010;24(Suppl 4):S15–26.
92. Donnell D, Baeten JM, Kiarie J, Thomas KK, Stevens W, Cohen CR, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. The Lancet. 2010;375(9731):2092–8.
93. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. In: March 27, 2012. p. 1–161. Accessed 24 Nov 2012.
94. Laga M, Manoka A, Kivuvu M, Malele B, Tuliza M, Nzila N, et al. Non-ulcerative sexually transmitted diseases as risk factors for HIV-1 transmission in women: results from a cohort study. AIDS. 1993;7(1):95–102.
95. Vincenzi I de. A longitudinal study of human immunodeficiency virus transmission by heterosexual partners. European Study Group on Heterosexual Transmission of HIV. N Engl J Med. 1994;331(6):341–6.
96. Cameron DW, Simonsen JN, D'Costa LJ, Ronald AR, Maitha GM, Gakinya MN, et al. Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. Lancet. 1989;2(8660):403–7.

97. Plummer FA, Simonsen JN, Cameron DW, Ndinya-Achola JO, Kreiss JK, Gakinya MN, et al. Cofactors in male-female sexual transmission of human immunodeficiency virus type 1. J Infect Dis. 1991;163(2):233–9.
98. Grosskurth H, Mosha F, Todd J, Mwijarubi E, Klokke A, Senkoro K, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. Lancet. 1995;346(8974):530–6.
99. Gray RH, Wawer MJ, Brookmeyer R, Sewankambo NK, Serwadda D, Wabwire-Mangen F, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. Lancet. 2001;357(9263):1149–53.
100. Baeten JM, Strick LB, Lucchetti A, Whittington WL, Sanchez J, Coombs RW, et al. Herpes simplex virus (HSV)-suppressive therapy decreases plasma and genital HIV-1 levels in HSV-2/HIV-1 coinfected women: a randomized, placebo-controlled, cross-over trial. J Infect Dis. 2008;198(12):1804–8.
101. Zuckerman RA, Lucchetti A, Whittington WL, Sanchez J, Coombs RW, Magaret A, et al. HSV suppression reduces seminal HIV-1 levels in HIV-1/HSV-2 co-infected men who have sex with men. AIDS. 2009;23(4):479–83.
102. Zuckerman RA, Lucchetti A, Whittington WL, Sanchez J, Coombs RW, Zuniga R, et al. Herpes simplex virus (HSV) suppression with valacyclovir reduces rectal and blood plasma HIV-1 levels in HIV-1/HSV-2-seropositive men: a randomized, double-blind, placebo-controlled crossover trial. J Infect Dis. 2007;196(10):1500–8.
103. Nagot N, Ouedraogo A, Foulongne V, Konate I, Weiss HA, Vergne L, et al. Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus. N Engl J Med. 2007;356(8):790–9.
104. Celum C, Wald A, Lingappa JR, Magaret AS, Wang RS, Mugo N, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. N Engl J Med. 2010;362(5):427–39.
105. Celum C, Wald A, Hughes J, Sanchez J, Reid S, Delany-Moretlwe S, et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. Lancet. 2008;371(9630):2109–19.
106. Tanton C, Abu-Raddad LJ, Weiss HA. Time to refocus on HSV interventions for HIV prevention? J Infect Dis. 2011;204(12):1822–6.
107. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med. 2000;342(13):921–9.
108. Eshleman SH, Hudelson SE, Redd AD, Wang L, Debes R, Chen YQ, et al. Analysis of genetic linkage of HIV from couples enrolled in the HIV Prevention Trials Network 052 trial. J Infect Dis. 2011;204(12):1918–26.
109. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis. 2011;52(6):793–800.
110. Marks G, Gardner LI, Craw J, Giordano TP, Mugavero MJ, Keruly JC, et al. The spectrum of engagement in HIV care: do more than 19 % of HIV-infected persons in the US have undetectable viral load? Clin Infect Dis. 2011;53(11):1168–9. (Author's reply 1169–70).
111. Forsyth AD, Valdiserri RO. Reaping the prevention benefits of highly active antiretroviral treatment: policy implications of HIV Prevention Trials Network 052. Curr Opin HIV AIDS. 2012;7(2):111–6.
112. Montaner JS, Lima VD, Barrios R, Yip B, Wood E, Kerr T, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. Lancet. 2010;376(9740):532–9.
113. Das M, Chu PL, Santos GM, Scheer S, Vittinghoff E, McFarland W, et al. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. PLoS One. 2010;5(6):e11068.
114. Geng EH, Hare CB, Kahn JO, Jain V, Van Nunnery T, Christopoulos KA, et al. The effect of a "Universal Antiretroviral Therapy" recommendation on HIV RNA levels among HIV-infected

patients entering care with a CD4 count greater than 500/muL in a public health setting. Clin Infect Dis. 2012;55(12):1690–7.
115. Tanser F, Barnighausen T, Graspa E, Newell ML. Effect of ART Coverage on rate of new HIV Infections in a hyper-endemic, rural population: South Africa [#136LB]. 19th Conference on Retroviruses and Opportunistic Infections. Seattle; Mar 5–8, 2012. http://www.retroconference.org/2012b/Abstracts/45379.htm. Accessed 31 Jan 2013.
116. Floyd S, Marston M, Baisley K, Wringe A, Herbst K, Chihana M, et al. The effect of antiretroviral therapy provision on all-cause, AIDS and non-AIDS mortality at the population level–a comparative analysis of data from four settings in Southern and East Africa. Trop Med Int Health. 2012;17(8):e84–93.
117. Herbst AJ, Cooke GS, Barnighausen T, KanyKany A, Tanser F, Newell ML. Adult mortality and antiretroviral treatment roll-out in rural KwaZulu-Natal, South Africa. Bull World Health Organ. 2009;87(10):754–62.
118. Krakower D, Mitty JA, Trinidad J, Mayer KH. HIV Providers' Perceived barriers and facilitators to implementing treatment as prevention in clinical practice: a qualitative study [Abstract 101]. Forum for Collaborative HIV Research. Washington, D.C.: 26–28 November 2012.
119. Myers JE, Braunstein SL, Shepard CW, Cutler BH, Mantsios AR, Sweeney MM, et al. Assessing the impact of a community-wide HIV testing scale-up initiative in a major urban epidemic. J Acquir Immune Defic Syndr. 2012;61(1):23–31.
120. Myers JJ, Bradley-Springer L, Kang Dufour MS, Koester KA, Beane S, Warren N, et al. Supporting the integration of HIV testing into primary care settings. Am J Public Health. 2012;102(6):e25–32.
121. Coates T, Eshleman S, Chariyalertsak S, Chingono A, Gray G, Mbwambo J, et al. 3–6 March 2013. http://www.retroconference.org/2013b/Abstracts/47715.htm. Accessed 12 April 2013. Conference on retroviruses and opportunistic infections. Atlanta.
122. Taegtmeyer M, MacPherson P, Jones K, Hopkins M, Moorcroft J, Lalloo DG, et al. Programmatic evaluation of a combined antigen and antibody test for rapid HIV diagnosis in a community and sexual health clinic screening programme. PLoS One. 2011;6(11):e28019.
123. FDA approves first over-the-counter home-use rapid HIV test. 3 July 2012. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310542.htm. Accessed 24 Nov 2012.
124. Paltiel AD, Walensky RP. Home HIV testing: good news but not a game changer. Ann Intern Med. 2012;157(10):744–6.
125. Carballo-Dieguez A, Frasca T, Balan I, Ibitoye M, Dolezal C. Use of a rapid HIV home test prevents HIV exposure in a high risk sample of men who have sex with men. AIDS Behav. 2012;16(7):1753–60.
126. Young MR, Bailey RC, Odoyo-June E, Irwin TE, Obiero W, Ongong'a DO, et al. Safety of over twelve hundred infant male circumcisions using the mogen clamp in Kenya. PLoS One. 2012;7(10):e47395.
127. Reed JB, Njeuhmeli E, Thomas AG, Bacon MC, Bailey R, Cherutich P, et al. Voluntary medical male circumcision: an HIV prevention priority for PEPFAR. J Acquir Immune Defic Syndr. 2012;60(Suppl 3):S88–95.
128. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med. 2009;361(23):2209–20.
129. Rolland M, Gilbert P. Evaluating immune correlates in HIV type 1 vaccine efficacy trials: what RV144 may provide. AIDS Res Hum Retroviruses. 2012;28(4):400–4.
130. Fauci AS, Folkers GK. Toward an AIDS-free generation. J Am Med Assoc. 2012;308(4):343–4.

Chapter 2
Translating Pre-Exposure Prophylaxis Evidence into Practice and Public Health Impact

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For the first 29 years of the HIV epidemic, there were only five randomized controlled trials that demonstrated an impact on reducing HIV incidence. They were studies of medical male circumcision in South Africa [1], Kenya [2], and Uganda [3], a trial on treating sexually transmitted infections in Tanzania [4], and the RV144 HIV vaccine trial conducted in Thailand [5]. However, over the past 2 years, results from five randomized trials have provided compelling evidence that antiretrovirals (ARVs) can prevent sexual transmission of HIV. The first in a series of trials showing that ARVs can reduce HIV acquisition was the CAPRISA 004 tenofovir gel trial. This trial, conducted among 889 rural and urban South African women, showed that tenofovir gel used before and after sex reduced acquisition of HIV infection in women by 39 % (95 % confidence interval (CI): 6;60) overall, thereby providing the proof-of-concept that ARVs can prevent sexual transmission of HIV [6]. Soon thereafter, the results of the iPREX trial were announced, which showed that the daily oral tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) combination (Truvada) reduced HIV incidence by 44 % (95 % CI 15;63) among 2,499 men or transgender women who have sex with men [7] (Fig. 2.1).

Further evidence for the effectiveness of daily oral pre-exposure prophylaxis (PrEP) in heterosexual men and women comes from results of the Partners PrEP

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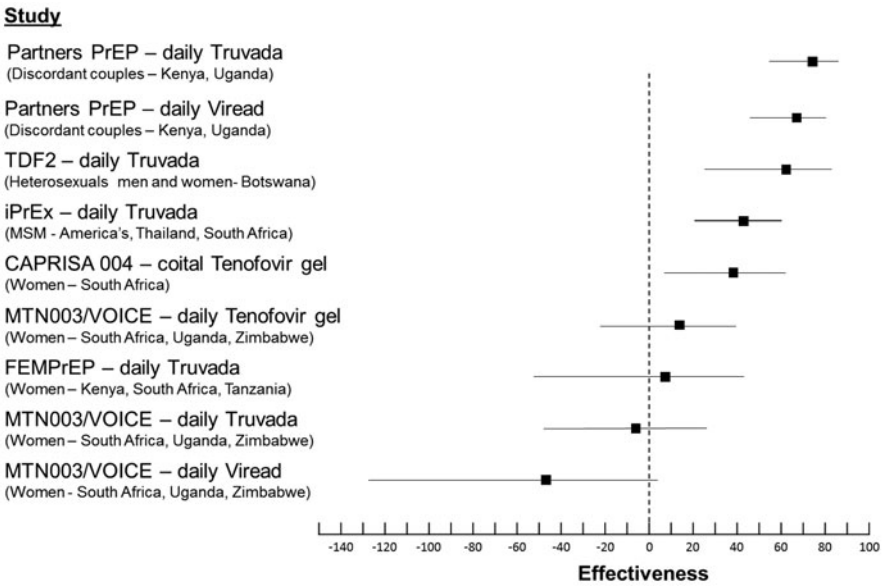

Fig. 2.1 Results of pre-exposure prophylaxis effectiveness trials

trial [8] and the Botswana TDF2 trial [9]. The Partners PrEP trial, which included 4,758 HIV-discordant couples from Kenya and Uganda showed that daily oral TDF and TDF/FTC reduced HIV incidence by 67 % (95 % CI 44;81) and 75 % (95 % CI 55;87), respectively, whereas the Botswana TDF2 trial, conducted among 1,200 heterosexual men and women from the general population, found that daily oral TDF-FTC reduced HIV incidence by 62 % (95 % CI 22;83; Fig. 2.1).

The use of ARVs for treatment of HIV-infected patients has also recently been shown in a randomized clinical trial to prevent onward transmission of HIV to their uninfected partners (Treatment as Prevention—TasP). The HPTN 052 trial, conducted among 1,763 HIV-discordant couples from nine countries, showed that HIV transmission was reduced by 96 % (95 % CI, 73;99.5) when ART was initiated in patients with CD4 counts between 350 and 550 cells/mm^3 [10].

This series of scientific breakthroughs in HIV prevention, combined with the recent approval of the first antiretroviral drug (Truvada) for reducing the risk of sexually acquired HIV infection by the US Food and Drug Administration (FDA) [11], has made the use of antiretroviral drugs as part of a comprehensive HIV prevention package, a reality and has created newfound hope that the epidemic can be stopped. This unprecedented opportunity to alter the course of this disease will depend on the extent to which regulators, health service providers, funders, and researchers are able to translate this new evidence into effective large-scale treatment and ARV prophylaxis programs.

Implementation of Biomedical HIV Prevention Technologies: Potential Impact

Significant prevention benefits have been shown to be possible with the implementation of the "test and treat" strategy, where all individuals who test HIV positive are immediately initiated on antiretroviral therapy, irrespective of CD4 count [12]. Several mathematical models have produced impressive estimates of the potential prevention impact of universal testing and immediate antiretroviral treatment. In rural KwaZulu-Natal in South Africa, scale-up of the routine AIDS treatment program has shown an impact on HIV incidence at community level. A population-based prospective cohort study, which included 16,667 individuals who were HIV-uninfected at baseline, showed that the risk of HIV acquisition between 2004 and 2011 was 38 % lower in communities where 30–40 % of HIV-infected individuals were on ART compared with communities where less than 10 % of the HIV-infected population were on ART [13].

The provision of PrEP to avert new HIV infections needs to be weighed against the potential costs of providing life-long ARVs for individuals who may become infected with HIV. Several mathematical models have illustrated the potential impact of oral and topical PrEP on the epidemic trajectory. Up to 3.2 million new HIV infections could be averted in southern sub-Saharan Africa over 10 years by targeting PrEP (having 90 % effectiveness) to those at highest behavioral risk [14]. Similarly, mathematical modelling has shown that in South Africa alone, over the next two decades, tenofovir gel could avert 1.3 million new HIV infections and over 800,000 deaths [15]. Mathematical models have also shown that oral and topical PrEP is cost effective [15–17].

Although medical male circumcision took some time to be incorporated in the HIV prevention package, widespread implementation of this HIV prevention technology is already having a population-level impact. In Orange Farm, South Africa, the male circumcision rate has increased from 16 % in 2007 to 50 % in 2010 and has been shown to be associated with reductions of 55 % in HIV prevalence and 76 % in HIV incidence [18].

Regulatory Obstacles Restricting Access to Biomedical Technologies Such As ARVs for HIV Prevention

Despite the potential impact of PrEP, only the US FDA has officially approved Truvada as an HIV prevention option. This led to the development of guidelines for its use in men who have sex with men [19] and in heterosexuals [20]. Since Truvada has not been approved by medicines regulators in any other countries, country-specific individual patient guidelines and programmatic public health guidelines on implementation of PrEP cannot be developed.

Challenges in the Implementation of PrEP

Besides the regulatory hurdles and lack of country-specific guidelines, several other challenges could impact on the rapid implementation of PrEP. Although mostly unwarranted, the main criticisms and concerns about PrEP implementation include the following.

Data on the Effectiveness of PrEP, Especially in Women, Are Inconsistent

It is sometimes argued that the evidence that oral prophylaxis is effective in women is inconsistent. This is not true. The Partners PreP and TDF2 studies have shown that daily ARVs can be taken with high adherence and thereby reduce the risk of HIV acquisition in women by up to 60 %. The lack of protective effect observed in the FEM-PrEP [21] and the VOICE trials [22] can partially be explained by suboptimal adherence. In the FEM-PREP trial [23], only 24 % of the women allocated to the daily oral TDF/FTC group had detectable drug levels. Similarly, in the VOICE trial, only 23, 28, and 29 % of women allocated to the daily tenofovir gel, daily oral TDF and daily oral TDF/FTC groups, respectively, had detectable drug levels [22].

The Challenges of Long-Term Adherence

Adherence is the Achilles' heel for PrEP and long-term, high adherence is essential for its success. The strong correlation between effectiveness and adherence is clearly evident when we compare levels of effectiveness observed in PrEP trials with an objective measure of adherence, i.e. the presence of drug (Fig. 2.2; Pearson correlation = 0.86; $p = 0.003$). Poor adherence may lead not only to suboptimal protection but may also impact on drug resistance. This highlights the need for integration of behavioral interventions as integral to implementation of biomedical interventions.

Although clinical trials may achieve high adherence, the same may not pertain to "real-world" settings where PrEP may be implemented in underdeveloped public healthcare facilities without adequate attention to adherence support.

However, it is worth noting that drug adherence was also one of the key concerns raised when ART first became available as treatment. Concern about poor adherence was actually used as an argument against the implementation of these life-saving drugs in Africa. Experiences from implementing ART treatment has shown that high levels of adherence are achievable in a real-world setting, even in developing countries [24–26]. Although high adherence to treatment of HIV-positive people is encouraging, this may not be readily applicable to adherence in healthy asymptomatic people. On the other hand, adherence may not turn out to be an issue as the product's effectiveness may serve as strong motivation for adherence. Regardless, adherence is likely to be a challenge that will require a concerted effort to overcome and PrEP programs will need to include practical and proven adherence support programs.

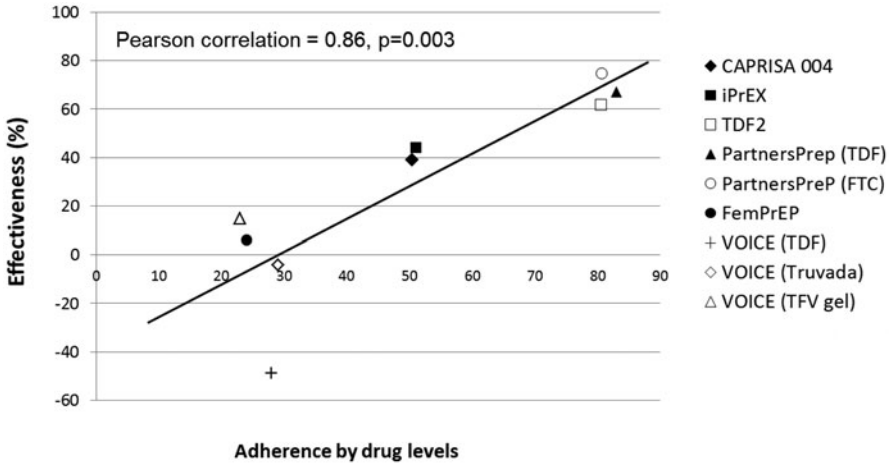

Fig. 2.2 Correlation between PrEP effectiveness trials and adherence as measured using detectable drug levels

Varying Adherence Leading to Varying Efficacy

Both the CAPRISA 004 and iPrEX trials showed that effectiveness was closely linked to levels of adherence and presence of drug. In the CAPRISA 004 trial, the effectiveness of tenofovir gel increased to 54 % when women used the gel according to the dosing strategy in more than 80 % of all sexual encounters but was only 28 % when the gel was used less than 50 % of the time [6]. A case-control study of the iPrEX trial showed that effectiveness was increased to 90 % (95 % CI 71 %–98 %, $p < 0.001$) in those with detectable drug [27]. Clearly, adherence and effectiveness are closely linked and it will be important to convey this message to potential PrEP users to ensure the highest possible adherence in the real world.

PrEP May Undermine Future AIDS Treatment by Causing Drug Resistance

The risk of drug resistance from PrEP is markedly different from that observed when, for example, nevirapine is given to HIV-positive pregnant women, as those taking PrEP generally do not have circulating virus which can become drug-resistant. However, the possibility of resistance is present in instances where PrEP is taken for several weeks inadvertently by those with unidentified HIV infection; as was the case in the iPrEX trial where two men assigned to the TDF/FTC arm, whose HIV infection was not detected at enrolment, developed resistance to FTC [28].

A model based on the South African epidemic has shown that after 10 years of ART and PrEP rollout, the number of new infections would have decreased by 38 %

and the drug resistance prevalence would have increased to 11.4 %. This compares with levels of between 10 and 17 % observed in high-income countries. Importantly, most of the resistance is predicted to be a consequence of ART rather than from PrEP [29]. The main issue regarding resistance, however, is whether the use of PrEP will compromise an individual's ARV treatment options in several years' time when they may require ART. At present, there are no data to answer this question.

A separate concern about resistance is the use of the same drugs (e.g., Tenofovir) in therapy and prevention. Therapy failure is associated with the development of resistance and thereby the spread of resistant viruses, which in turn may compromise the efficacy of the same drugs (or occasionally, the same class of drugs) used for prophylaxis. Currently, there are over 30 licensed drugs to treat HIV, including several cost-effective non-tenofovir containing first-line regimens. Some consideration about setting aside a class (or classes) of ARVs for use in prevention only is warranted.

PrEP Users May Reduce Their Use of Higher-Efficacy HIV Prevention Strategies Like Condoms

The current oral and topical PrEP strategies are only partially effective, ranging from 39 to 73 %. Risk compensation is a potential concern when implementing any new suboptimal HIV prevention strategy [30] and is not specific to PrEP. Risk compensation could potentially undermine and even reverse the beneficial effects of PrEP, as shown by mathematical models on HIV epidemics in Botswana, Kenya, and southern India [31]. Although a low-efficacy intervention may be reversed by risk compensation, current evidence from medical male circumcision implementation has found this concern to be baseless. An assessment of the real-world effect of the rollout of medical male circumcision in a community in South Africa has shown no evidence of risk compensation after 3 years [18]. A more important consideration is that some of the PrEP strategies specifically empower women, who have no other alternative HIV protection strategies. Even a low-efficacy product would be critically important to large numbers of young women in South Africa who are unable to ensure their partner's fidelity or condom use. Indeed, PrEP is most appropriate for the target populations where condom use is low or nonexistent.

ARVs Should Be Prioritized for AIDS Treatment

Some have argued that it would be unethical to divert ARVs that would have been used for treatment for prevention [32], especially since only 54 % of those in need of ART were receiving it in 2011 [33]. Although it is a legitimate concern that eligible HIV-positive patients should be prioritized for ART for their own health and to save their lives, it is spurious to trade off treatment and prevention as if these drugs are being taken away from sick and dying patients to be given to healthy people.

Treatment and prevention strategies are a continuum in their use of ARVs—both are needed in conjunction with each other to ensure that ART provision is sustainable in the long term and to realize the quest to end the HIV epidemic.

One of the main reasons why so many people who are in need of treatment have not yet accessed it is because many do not know their HIV status. Based on ten recent national population-based surveys in sub-Saharan Africa, less than 40 % of people living with HIV know their HIV status [34]. In the 2008 South African National HIV survey, 74 % of those most at risk of acquiring HIV infection were unaware of their HIV status [35]. If self-denial, a common reason for not testing, is not overcome it will severely limit the potential impact of these new HIV prevention approaches [36]. Initiation of PrEP will require an assessment of HIV status and could therefore be used as an opportunity for not only scaling up PrEP to HIV-uninfected at-risk individuals but could also be used for identifying those who need ART for treatment.

Is It Safe to Give ARV Drugs to Healthy Asymptomatic People?

Tenofovir has an excellent safety profile and low rates of adverse effects. Less than 1 % of patients with HIV taking tenofovir in clinical trials had serious drug-related adverse events [37]. However, tenofovir may reduce bone density, exacerbate existing renal impairment, and has been associated with hepatic flares in chronic hepatitis B-infected individuals when the treatment is stopped [38]. Emtricitabine has a similar safety profile as tenofovir and adverse events occurring in clinical trials were generally of mild or moderate severity [39]. Although mild side effects are readily tolerated when medication is taken for therapeutic reasons, the same is not necessarily true when medication is taken by healthy asymptomatic individuals where even mild side effects may compromise adherence. Ongoing drug safety surveillance will need to be a component of plans for large-scale rollout of ARVs for PrEP. Hepatitis B testing and vaccinations for susceptible individuals at high risk may also need to be considered.

Who Would Benefit Most and Criteria for Initiating and Terminating PrEP

When resources are scarce, it is necessary to rationalize and prioritize certain high-risk groups for access to interventions over others. Determining who would benefit most will vary from country to country and although some groups, like MSMs and injection drug users (IDUs) are easily identifiable, identifying who should be prioritized in generalized epidemics is more complex. Nevertheless, before PrEP can be initiated, it will be important to establish the HIV status of the individuals and ongoing HIV testing would be an important component of any PrEP rollout program.

The Efficacy–Effectiveness Gap: Implications for Implementation Programs and the Implementation Science Agenda

At present, there are no data available on the extent to which the outcomes achieved in the PrEP trials described earlier can be translated into real-world effectiveness. This leap from trials to implementation, generally referred to as the efficacy–effectiveness gap, can be substantial, as seen in implementation of prevention of mother-to-child transmission (PMTCT) programs. For example, a PMTCT program in Cote d' Voire showed that 40 % of HIV-positive pregnant women did not benefit from zidovudine to reduce mother-to-child transmission as only 60 % returned to the clinic for their HIV test results [40].

Some of the biggest contributors to the efficacy–effectiveness gap anticipated in the PrEP field will be willingness to know and monitor HIV status, suboptimal adherence levels, the extent to which people continue with the other proven prevention interventions (risk compensation), and the extent to which the existing public sector health services can facilitate uptake and maintain clients in long-term follow-up. The extent to which health services in countries most affected are sufficiently well managed to absorb the implementation of ARVs for prevention, in a manner that provides high uptake, adherence, and follow-up, will determine its success or failure. One approach to maximize the chance of success is to integrate PrEP as a component of existing comprehensive HIV prevention programs and services.

The implementation of PrEP faces substantial financial challenges. Besides the drug costs, the programmatic and laboratory monitoring costs, including HIV testing, hepatitis B virus testing, renal function assessment prior to tenofovir-containing PrEP initiation and then at regular intervals, of yet unknown duration, are likely to be substantial. Unfortunately, HIV prevention programs in regions with the highest HIV burden are already substantially underfunded and many highly effective prevention options such as condoms, are not being used at the scale and intensity needed [41]. A recent analysis shows that the per capita spending on health in high-HIV-burden countries like Kenya and Uganda is US$ 17 and US$ 16, respectively, with 60.7 and 50.2 % of the health expenditure being dedicated towards HIV [42]. The efficiency of health spending will need to be dramatically improved in these countries if PrEP is to be successfully implemented.

Although funds for Treatment for Prevention or PrEP may not be readily available at this point, it would be short-sighted to consider this in isolation. For PrEP, the long-term consequences of not implementing PrEP need to be considered, especially in women who may have no other effective options. Although the unmet need to provide antiretroviral treatment to all those in need is large, the opportunity to prevent new HIV infections cannot be passed over. Additional funding resources will need to be raised to implement PrEP as part of combination HIV prevention programs to avoid an unsustainable future with ever increasing numbers of people requiring life-long antiretroviral therapy.

Consequences of Not Implementing Biomedical HIV Prevention Interventions

The challenges of implementing treatment for prevention or PrEP should not detract from the potential importance of these interventions. The realization of these strategies as part of an overall prevention plan is essential. The emphasis should be both on treating patients who require the ARVs for their own needs and also for those who need it for prevention. As was the case in MTCT, most of the concerns about scale-up can only be addressed in scale-up programs and not in relatively small phase I and II trials.

The regulatory approval of Truvada for PrEP by the FDA provides an opportunity to undertake scale-up programs but critically, these programs can be used as an opportunity to generate the evidence on how best to address the concerns and shortcomings of PrEP.

Initially, implementation programs should focus on providing PrEP to individuals at highest risk, e.g., MSM and young women in Africa and progressively scale up PrEP as part of a comprehensive HIV prevention package. To address the issue of the partial efficacy of PrEP, the impact of PrEP implementation should be monitored. Monitoring should include, at minimum, an assessment of HIV incidence rates, PrEP uptake levels, adherence levels, and the impact of PrEP uptake on condom use. Given the importance of adherence, programmatic implementation needs to carefully assess the factors impacting on adherence. In particular, the gender power imbalances and impact on power relations in acquiring HIV needs special attention. Resistance will also need to be closely monitored, both from use of Truvada as part of treatment and prevention. Long-term safety will need to be monitored, with special attention to kidney, bone mineral, and hepatitis B-related safety concerns. Implementation of PrEP will enable us to answer the questions about who to prioritize, when to initiate, and when to terminate by monitoring who benefits maximally and the period of highest risk that benefits most from PrEP.

Other clinical trial research should also continue in parallel, with some consideration being given to the assessment of different dosing strategies (daily vs. intermittent), as well as a range of formulations. Studies on alternative delivery mechanisms for PrEP such as gels and rings should also be pursued simultaneously.

Conclusion

Treatment for prevention and PrEP have created newfound optimism in HIV prevention. ARVs increase options for HIV prevention, especially for specific high-risk populations such as young women in Africa. Despite the inherent challenges that lie ahead, implementation of ARVs for prevention is imperative and will be part of the solution to realizing the goal of finally turning the tide on the HIV epidemic.

References

1. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med. 2005;2:e298.
2. Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, Williams CF, Campbell RT, Ndinya-Achola JO. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet. 2007;369:643–56.
3. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, Kiwanuka N, Moulton LH, Chaudhary MA, Chen MZ, Sewankambo NK, Wabwire-Mangen F, Bacon MC, Williams CF, Opendi P, Reynolds SJ, Laeyendecker O, Quinn TC, Wawer MJ. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007;369:657–66.
4. Grosskurth H, Mosha F, Todd J, Mwijarubi E, Klokke A, Senkoro K, Mayaud P, Changalucha J, Nicoll A, ka-Gina G, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. Lancet. 1995;346:530–6.
5. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, Premsri N, Namwat C, de Souza M, Adams E, Benenson M, Gurunathan S, Tartaglia J, McNeil JG, Francis DP, Stablein D, Birx DL, Chunsuttiwat S, Khamboonruang C, Thongcharoen P, Robb ML, Michael NL, Kunasol P, Kim JH. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med. 2009;361:2209–20.
6. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, Kharsany ABM, Sibeko S, Mlisana KP, Omar Z, Gengiah TN, Maarschalk S, Arulappan N, Mlotshwa M, Morris L, Taylor D, on behalf of the CAPRISA 004 Trial Group. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010;329:1168–74.
7. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, Goicochea P, Casapia M, Guanira-Carranza JV, Ramirez-Cardich ME, Montoya-Herrera O, Fernandez T, Veloso VG, Buchbinder SP, Chariyalertsak S, Schechter M, Bekker LG, Mayer KH, Kallas EG, Amico KR, Mulligan K, Bushman LR, Hance RJ, Ganoza C, Defechereux P, Postle B, Wang F, McConnell JJ, Zheng JH, Lee J, Rooney JF, Jaffe HS, Martinez AI, Burns DN, Glidden DV. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363:2587–99.
8. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, Tappero JW, Bukusi EA, Cohen CR, Katabira E, Ronald A, Tumwesigye E, Were E, Fife KH, Kiarie J, Farquhar C, John-Stewart G, Kakia A, Odoyo J, Mucunguzi A, Nakku-Joloba E, Twesigye R, Ngure K, Apaka C, Tamooh H, Gabona F, Mujugira A, Panteleeff D, Thomas KK, Kidoguchi L, Krows M, Revall J, Morrison S, Haugen H, Emmanuel-Ogier M, Ondrejcek L, Coombs RW, Frenkel L, Hendrix C, Bumpus NN, Bangsberg D, Haberer JE, Stevens WS, Lingappa JR, Celum C. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367(5):399–410.
9. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, Henderson FL, Pathak SR, Soud FA, Chillag KL, Mutanhaurwa R, Chirwa LI, Kasonde M, Abebe D, Buliva E, Gvetadze RJ, Johnson S, Sukalac T, Thomas VT, Hart C, Johnson JA, Malotte CK, Hendrix CW, Brooks JT. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012;367:423–34.
10. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH, Godbole SV, Mehendale S, Chariyalertsak S, Santos BR, Mayer KH, Hoffman IF, Eshleman SH, Piwowar-Manning E, Wang L, Makhema J, Mills LA, de Bruyn G, Sanne I, Eron J, Gallant J, Havlir D, Swindells S, Ribaudo H, Elharrar V, Burns D, Taha TE, Nielsen-Saines K, Celentano D, Essex M, Fleming TR. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6):493–505.
11. U.S. Food and Drug Administration. FDA approves first drug for reducing the risk of sexually acquired HIV infection. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.html. In: Silver Spring, MD 2012. Accessed 19 July 2012.

12. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009;373:48–57.
13. Tanser F, Barnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. Science. 2013;339:966–71.
14. Abbas UL, Anderson RM, Mellors JW. Potential impact of antiretroviral chemoprophylaxis on HIV-1 transmission in resource-limited settings. PLoS ONE. 2007;2:e875.
15. Williams BG, Abdool Karim SS, Gouws E, Abdool Karim Q. Epidemiological impact of tenofovir gel on the HIV epidemic in South Africa. J Acquir Immune Defic Syndr. 2011;58: 207–10.
16. Pretorius C, Stover J, Bollinger L, Bacaer N, Williams B. Evaluating the cost-effectiveness of pre-exposure prophylaxis (PrEP) and its impact on HIV-1 transmission in South Africa. PLoS ONE. 2010;5:e13646.
17. Walensky RP, Park JE, Wood R, Freedberg KA, Scott CA, Bekker LG, Losina E, Mayer KH, Seage GR 3rd, Paltiel AD. The cost-effectiveness of pre-exposure prophylaxis for HIV infection in South African women. Clin Infect Dis. 2012;54:1504–13.
18. Auvert B, Taljaard D, Rech D, Lissouba P, Singh B, Shabangu D, Nhlapo C, Otchere-Darko J, Mashigo T, Phatedi G, Taljaard R, Tsepe M, Chakela M, Mkhwanazi A, Ntshangase P, Billy S, Lewis D. Effect of the Orange Farm (South Africa) male circumcision roll-out (ANRS-12126) on the spread of HIV [abstract WELBC02]. In: Sixth International AIDS Society Conference. Rome; 2011.
19. Centers for Disease Control and Prevention. Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. MMWR Morb Mortal Wkly Rep. 2011;60:65–8.
20. Centers for Disease Control and Prevention. Interim guidance for clinicians considering the use of preexposure prophylaxis for the prevention of HIV infection in heterosexually active adults. MMWR Morb Mortal Wkly Rep. 2012;61:586–9.
21. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, Malahleha M, Owino F, Manongi R, Onyango J, Temu L, Monedi MC, Mak'Oketch P, Makanda M, Reblin I, Makatu SE, Saylor L, Kiernan H, Kirkendale S, Wong C, Grant R, Kashuba A, Nanda K, Mandala J, Fransen K, Deese J, Crucitti T, Mastro TD, Taylor D, for the FEM-PrEP Study Group. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012;367:411–22.
22. Microbicide Trials Network. Press release: daily HIV prevention approaches didn't work for African women in the VOICE Study. 2013.
23. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, Grant R, Kashuba A, Taylor D, FEM-PrEPS Study Group. The FEM-PrEP Trial of Emtricitabine/Tenofovir Disoproxil Fumarate (Truvada) among African Women [Abstract 32LB]. In: Conference of Retroviruses and Opportunistic Infections. Seattle; 2012.
24. van Oosterhout JJ, Bodasing N, Kumwenda JJ, Nyirenda C, Mallewa J, Cleary PR, de Baar MP, Schuurman R, Burger DM, Zijlstra EE. Evaluation of antiretroviral therapy results in a resource-poor setting in Blantyre, Malawi. Trop Med Int Health 2005;10:464–70.
25. Nachega JB, Stein DM, Lehman DA, Hlatshwayo D, Mothopeng R, Chaisson RE, Karstaedt AS. Adherence to antiretroviral therapy in HIV-infected adults in Soweto, South Africa. AIDS Res Hum Retroviruses. 2004;20:1053–6.
26. Byakika-Tusiime J, Oyugi JH, Tumwikirize WA, Katabira ET, Mugyenyi PN, B DR. Adherence to HIV antiretroviral therapy in HIV+ Ugandan patients purchasing therapy. Int J STD AIDS. 2005;16:38–41.
27. Anderson PL, Lama JR, Buchbinder S, Guanira J, Montoya O, Casapia M, Liu A, Bushman LR, McMahan V, Amico KR, Glidden DV, Grant RM, iPrEx Study Team. Expanded case-control analysis of drug detection in the global iPrEx trial [abstractMOLBPE034]. In: 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention. Rome, Italy; 2011.
28. Aurigemma M, Goicochea P. iPrEx Fact Sheet: Drug Resistance. In: Global iPrEX; 2011.

29. Abbas U, Glaubius R, Mubayi A, Hood G, Mellors J. Predicting the Impact of ART and PrEP with Overlapping Regimens on HIV Transmission and Drug Resistance in South Africa [abstract no 98LB]. In: 18th Conference on Retroviruses and Opportunistic Infections. Boston, Massachusetts; 2011.
30. Cassell MM, Halperin DT, Shelton JD, Stanton D. Risk compensation: the Achilles' heel of innovations in HIV prevention? Br Med J. 2006;332:605–7.
31. Vissers DC, Voeten HA, Nagelkerke NJ, Habbema JD, de Vlas SJ. The impact of pre-exposure prophylaxis (PrEP) on HIV epidemics in Africa and India: a simulation study. PLoS ONE. 2008;3:e2077.
32. Macklin R, Cowan E, Rutherford G. Given financial constraints, it would be unethical to divert antiretroviral drugs from treatment to prevention. Health Aff. 2012;31:1537–44.
33. World Health Organisation. The strategic use of antiretrovirals to help end the HIV epidemic. Geneva, Switzerland: World Health Organisation; 2012.
34. WHO, UNAIDS, UNICEF. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector. Geneva, Switzerland: World Health Organisation; 2010.
35. Shisana O, Rehle T, Simbayi LC, Zuma K, Jooste S, Pillay-van-Wyk V, Mbelle N, Van Zyl J, Parker W,., Zungu NP, Pezi S, the SABSSM III Implementation Team. South African national HIV prevalence, incidence, behaviour and communication survey 2008: a turning tide among teenagers? Cape Town: HSRC Press; 2009.
36. Abdool Karim SS. Stigma impedes AIDS prevention. Nature. 2011;474:29–31.
37. Gilead Sciences Inc. Investigators Brochure: Tenofovir Gel (GS-1278). In: Foster City, California Gilead Sciences, Inc; Second Edition, 31 March 2005.
38. Nuesch R, Ananworanich J, Srasuebkul P, Chetchotisakd P, Prasithsirikul W, Klinbuayam W, Mahanontharit A, Jupimai T, Ruxrungtham K, Hirschel B. Interruptions of tenofovir/emtricitabine-based antiretroviral therapy in patients with HIV/hepatitis B virus co-infection. AIDS. 2008;22:152–4.
39. Gilead Sciences Inc. Emtriva package insert. July 2003.
40. Msellati P, Hingst G, Kaba F, Viho I, Welffens-Ekra C, Dabis F. Operational issues in preventing mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire, 1998–99. Bull World Health Organ. 2001;79:641–7.
41. World Health Organisation. Coverage of selected health services for HIV/AIDS prevention and care in less developed countries in 2001. http://whqlibdoc.who.int/publications/9241590319.pdf. In: Geneva, Switzerland: World Health Organisation; 2002.
42. Amico P, Aran C, Avila C. HIV spending as a share of total health expenditure: an analysis of regional variation in a multi-country study. PLoS ONE. 2010;5:e12997. doi:12910.11371/journal.pone.0012997.

Chapter 3
Prevention Services with Persons Living with HIV

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In July 2010, the administration released the National HIV/AIDS Strategy (NHAS) for the United States. This was the first time that the United States released a national strategic plan for HIV prevention and President Obama referred to the development and implementation of the NHAS as one of the administration's top HIV/AIDS policy priorities. The ambitious plan sets forth a vision, that:

> The United States will become a place where new HIV infections are rare and when they do occur, every person, regardless of age, gender, race/ethnicity, sexual orientation, gender identity or socio-economic circumstance, will have unfettered access to high quality, life-extending care, free from stigma and discrimination [1].

Guided by this vision, the Strategy outlines three primary goals: "(1) reducing the number of people who become infected with HIV; (2) increasing access to care and improving health outcomes for people living with HIV (PLWH); and, (3) reducing HIV-related health disparities" [1]. While the Strategy acknowledges the momentous accomplishments that have been made in the fight against the HIV epidemic so far, it also notes the need to "take bold actions" in this new era of infections. The Strategy seeks to achieve multiple results by 2015 including: to reduce HIV incidence by 25 %, to reduce the HIV transmission rate by 30 %, to increase linkage to care for PLWH to 85 %, to increase housing for homeless PLWH receiving Ryan White Care Act services to 86 %, to reduce health disparities, and to improve service coordination. The NHAS states that the achievement of these ambitious goals depends upon a more coordinated and collaborative national approach. Governmental agencies at

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all levels must work with each other and with organizations from varied sectors to ensure success.

To *reduce new HIV infections*, the Strategy introduces three action steps. First, there is a need to intensify HIV prevention efforts in communities where HIV is most heavily concentrated. Given the disproportionate burden of HIV among gay and bisexual men of all racial/ethnic backgrounds, Black Americans, Latino Americans, and substance users, there is a need to re-focus HIV prevention efforts to target these high-risk populations. Public funding should be reallocated to reflect the disease burden. Second, it is important to expand the efforts to prevent HIV infection using a combination of behavioral and biomedical evidence-based approaches that operate across various levels, including the individual level, community level, and societal level. All PLWH should know of their status and be linked to and retained in high-quality care in a timely manner. In addition, those persons, both HIV-negative and positive, who engage in behaviors that may put them at high risk for HIV transmission (such as unprotected sexual relationships) should be regularly tested for sexually transmitted infections. There is a need to conduct more research to determine which behavioral interventions are scalable and able to produce sustainable outcomes. Third, it is critical to educate all Americans about the threat of HIV and its prevention measures. It is an unfortunate reality that many Americans still hold misconceptions about HIV. Schools, in partnership with parents, should provide current and accurate information about sexual health.

In order to *increase access to care and improve health outcomes for PLWH*, the second primary goal, the Strategy recommends three action steps. First, a system that links people to quality care upon diagnosis must be established. Linkage coordinators are essential to help overcome barriers to obtaining care and should be made available where health and social services are received. Medical and social service providers must better collaborate to link and retain people in HIV care. Second, there is a need to increase the availability of clinical care providers for PLWH and also the *number* of HIV care providers. Efforts should be made to ensure that care is culturally appropriate. Third, support must be provided to assist PLWH with their co-occurring conditions, basic needs (such as housing and food security), and barriers to care. Case management, clinical services, and nonmedical supportive services must all become critical elements of an HIV care system.

Lastly, in order to achieve its third primary goal *to reduce HIV-related disparities and health inequities*, the Strategy also outlines three action steps. First, noting the significant racial disparities in HIV infection in the United States, the Strategy emphasizes the need to reduce HIV-related mortality in communities that are at high risk for HIV infection. Second, it stresses that community-level approaches must be adopted, promoting a more holistic approach to health to shift the focus beyond the individual. Third, the stigma and discrimination faced by PLWH must be remedied to ensure success in the fight against HIV. Policies and laws must be in place to support this endeavor.

Costs and Consequences of the National HIV/AIDS Strategy

In 2010, Holtgrave [2] estimated that it would cost approximately US $ 15.2 billion to implement the NHAS across all years through 2015. Given new developments since then, such as the advances in the field of HIV treatment as prevention (TasP), revised incidence and prevalence estimates, and observed funding patterns, Holtgrave et al. revisited the costs, consequences, and feasibility of achieving the NHAS in 2012 [3]. The authors pose three policy questions:

1. "Is it still epidemiologically feasible to attain the incidence and transmission rate reduction goals of NHAS by 2015?
2. If so, what costs will be incurred in necessary program expansion, and will the investment be cost-effective?
3. Would substantial expansion of prevention services for PLWH augment the other strategies outline in the NHAS in terms of effectiveness and cost-effectiveness?"

The authors examine two of the central goals of the NHAS: reduction of HIV incidence by 25 % by 2015, and reduction of the HIV transmission rate by 30 % by 2015 (the NHAS goal of 85 % linkage to care by 2015 was assumed to be met in this model). Although the NHAS does specifically mention the importance of services that help PLWH to avoid transmission to seronegative partners, it does not specify a quantifiable goal or funding measures [1].

Standard methods of economic evaluation and epidemiologic modeling were used to construct eight policy scenarios. Each scenario was developed on three factors (two levels per factor): (1) whether HIV testing services are expanded to meet the NHAS's 90 % awareness goal by 2015 (yes or no), (2) whether prevention services are provided only for PLWH who are new to care or also for PLWH who are not currently linked to care and/or not receiving prevention counseling in care ("minimal coverage" and "fully scaled up," respectively), and (3) assumptions regarding levels of effectiveness of HIV treatment in achieving suppressed viral load (either 69.4 or 80.7 % at the population level). These eight scenario definitions are summarized in Table 3.1. For all scenarios, it was assumed that the 2015 goal of 85 % engagement in care for diagnosed PLWH is achieved.

Results from each of the eight scenarios were compared with a flat transmission rate. The resulting analysis indicates that the NHAS incidence and transmission rate reduction goals are met in the scenarios in which the 90 % awareness goal is met and prevention efforts among PLWH are expanded, irrespective of viral load suppression assumptions. The goals are also met in the scenario in which the higher viral load suppression assumption is made and prevention efforts are scaled up, but the awareness goal is not met. In all other scenarios, the goals are not met by 2015. In addition to these findings, the analysis reveals that the most cost-effective scenarios are those in which the awareness goal is met and prevention efforts among PLWH are scaled up. Notably, the single *most* cost-effective scenario is that in which the higher viral load suppression is assumed, the awareness goal is met, and prevention efforts among PLWH are scaled up. The single *least* cost-effective scenario is that

Table 3.1 Definition of intervention scenarios for HIV service implementation strategies [3]

Assumed percentage of clients in care achieving suppressed viral load, year 2015 and beyond (%)	Meet NHAS diagnosis goal of 90 % by 2015?	Level of coverage of risk behavior change services for PLWH
69.4	Yes	Minimal coverage
69.4	Yes	Fully scaled up coverage
69.4	No	Minimal coverage
69.4	No	Fully scaled up coverage
80.7	Yes	Minimal coverage
80.7	Yes	Fully scaled up coverage
80.7	No	Minimal coverage
80.7	No	Fully scaled up coverage

NHAS National HIV/AIDS Strategy, *PLWH* people living with HIV

in which the lower viral load suppression is assumed, the awareness goal is not met, and prevention efforts among PLWH are not scaled up [3].

Even recognizing the limitations inherent in any modeling exercise, it seems clear that immediate expansion of prevention efforts among the population of PLWH is critical to bending the incidence curve of HIV in the United States. Holtgrave et al. note that while NHAS goals to reduce incidence by 25 % and transmission by 30 % may still be achieved by 2015, time is of the essence. There is "a closing window for success" [3].

With this background in mind, it is the intent of this chapter to provide a definition of "Prevention with Positives" (PwP) and highlight how this approach is important for achieving the goals of the NHAS. The chapter will also focus on behavioral risk reduction PwP services by examining the scope and costs of unmet needs, and the possible benefit of meeting these needs. In conclusion, some areas which require further exploration and research necessary to achieve NHAS goals will be highlighted.

Further Definition of "Prevention with Positives" Services

The Centers for Disease Control and Prevention (CDC)'s Division of HIV/AIDS Prevention (DHAP)'s Strategic Plan 2011–2015 echoed the priorities of the NHAS [4]. The DHAP Plan includes four goals: (1) HIV incidence—prevent new infections; (2) prevention and care—increase linkage to, and impact of prevention and care services with PLWH; (3) health disparities—reduce HIV-related disparities; and (4) organizational excellence—promote a skilled and engaged workforce and effective and efficient operations to ensure the successful delivery of CDC's HIV prevention science, program, and policies [4].

CDC and Health Resources and Service Administration (HRSA) have placed an increased emphasis on prevention services for PLWH (also known as "Prevention with Positives" services). PwP services can be defined as on-going care and treatment, education, and risk-reduction counseling for PLWH in order to reduce the

spread of HIV to others and individual re-infection [5]. Examples of PwP services include screening and identification to increase individuals' awareness of their infection, linkage to care once diagnosed, on-going counseling and support services for managing stigma and barriers to care, increasing access to antiretroviral (ARV) treatment (in part to lower viral load and reduce probability of transmission), education on health risks of HIV and its co-morbidities, as well as general education about HIV and behavioral risk reduction counseling. These services can range from various counseling techniques on managing medications and disclosure of status, distribution of condoms and dental dams, public health campaigns that are aimed at reducing stigma, and coaching partners on how to negotiate safer sexual and drug use behaviors. They also include sexually transmitted disease treatment, substance use treatment, mental health services, and reproductive health services (including services designed to prevent perinatal transmission).

It is important that PwP services be client-centered to comprehensively address the individual needs and life circumstances of each client. CDC's online PwP resources highlight the importance of confidentiality and privacy, given the potential HIV-related stigma, discrimination, and interpersonal violence [6]. Further, CDC provides strategies for assessing clients' PWP service needs, and creating a climate of shared responsibility for addressing these needs. Beyond the medical, behavioral, and social services at the client level, there is also a need to address the social, legal, policy, and programmatic issues at the community and societal levels [6].

Since PwP can consist of a variety of interventions, some detailed examples of particular services maybe in order. One PwP intervention, "Anti-Retroviral Treatment and Access to Services" (ARTAS), is an initiative to increase the number of patients accessing care after their initial diagnosis [7]. The goal of ARTAS is to use brief interventions to help build self-efficacy of individuals to connect with a primary care physician and enroll in AIDS Drugs Assistance Programs and other necessary health insurance coverage. It also addresses the gap in language proficiency and cultural competency in service delivery to better connect newly diagnosed people into care.

TasP is another PwP service initiative that utilizes ARV medication to reduce viral load and reduce the risk of transmission in combination with other prevention strategies [8]. Examples of TasP initiatives include initiating treatment at diagnosis, at postexposure (PEP), or prior to exposure (PrEP) [9, 10].

CDC offers on its website a summary of a variety of HIV prevention interventions that have been reviewed carefully for the strength of their empirical basis [11]. They list ten prevention interventions specifically developed for PLWH; 70 % of these rise to the level of "best" scientific evidence as judged by CDC in its review (the other 30 % achieve a rating of "good" level of scientific support). The seven "best" evidence HIV prevention risk reduction interventions for PLWH include the following: (a) "Choosing Life: Empowerment, Action, Results, (CLEAR)" (an 18 session, community-based, individual level intervention for young PLWH facing substance abuse challenges found to be effective at changing risk behavior) [12]; (b) Healthy Living Project (a 15-session, community-based, individual level intervention targeting PLWH, found effective at changing risky sexual behavior) [13]; (c) Healthy Relationships (a 5-session, skills-based small group intervention, found

effective at reducing risky sexual behavior) [14, 15]; (d) "Living in the Face of Trauma (LIFT)" (a 15-session, group level intervention targeting HIV-positive adults with history of childhood sexual abuse, found effective at reducing risky sexual behavior) [16, 17]; (e) Positive Choice: Interactive Video Doctor (a single individual-level, computer-based session targeting clinic patients, found effective at reducing risky sexual behavior) [18]; (f) "Seropositive Urban Men's Intervention Trial (SUMIT)" (a 6-session, group level intervention targeting men who have sex with men, found effective at reducing risky sexual behavior) [19, 20]; and (g) "Women Involved in Life Learning from Other Women (WILLOW)" (a 4-session, group level intervention targeting sexually active female clinic patients living with HIV, found effective at reducing risky sexual behavior and incident sexually transmitted infections (STIs)) [21]. The three "good" level HIV prevention interventions for PLWH include: (a) Options/Opciones Project (a brief 5–10 min session repeated at each clinic visit, targeting HIV-positive clinic patients, found effective at reducing risky sexual behavior) [22, 23]; (b) Partnership for Life (a brief 3–5 min session repeated at each clinic visit, targeting HIV-positive clinic patients, found effective at reducing risky sexual behavior) [24]; and (c) "Together Learning Choices (TLC)" (a 12-session, group level intervention targeting HIV-positive adolescents and young adults who are clinic patients, found effective at reducing risky sexual behavior) [25, 26]. Some of these prevention interventions, such as "Healthy Living Project" and "TLC," have also been shown to be cost-saving or cost-effective [27, 28].

Economic Issues of Prevention with Positives Services

A recent analysis examining the costs and consequences of the NHAS is summarized earlier on in this chapter [3]. The goals of the NHAS can be met by 2015 only with urgent and proper levels of investment. The services that must be provided to achieve the NHAS goals include targeted HIV testing and screening, care and treatment (including TasP), housing, and comprehensive prevention services for PLWH. Under the very broad definition of PwP used by CDC and HRSA (discussed in the preceding section), all of these interventions could technically be labeled PwP services. One of these services, however, behavioral PwP interventions for PLWH at behavioral risk of transmission to HIV-seronegative partners, has received less attention in economic analyses and this section discusses the topic in further detail.

Number of PLWH at risk of behaviorally transmitting HIV: CDC has estimated that slightly less than one in five PLWH do not know that they are living with the virus [3, 4, 29, 30]. Therefore, about one in five PLWH may be at increased risk for transmitting HIV due to lack of awareness of their serostatus (of course, all PLWH, diagnosed or not, were by definition infected via some instance of behavioral risk, but not all persons who are undiagnosed are currently engaged in risk behavior). At the time of our previous analysis, the number of unaware PLWH was about 236,400 persons [3, 31]. Of PLWH who are diagnosed, it was previously estimated that

roughly 16 % are engaged in any risk behavior that might result in transmission [3, 31]. In a study of PLWH in care, the 2009 cycle of CDC's Medical Monitoring Project found that of those who are not virally suppressed, 11 % of men who have sex with women, 17 % of women who have sex with men, and 16 % of men who have sex with men, engaged in unprotected risk behavior with unknown serostatus or HIV-seronegative partners [32]. This would therefore imply that approximately 150,700 PLWH are engaged in transmission relevant risk behaviors (while over 790,000 PLWH are not engaged in such unprotected risk behaviors). It has been estimated that these approximately 150,700 persons account for roughly one-half of the new HIV transmissions in the USA each year [31]. Therefore, providing risk reduction services, while working to also link and retain this population of persons in high quality care, could substantially impact HIV transmission in the USA, and are critical public health priorities. However, it is important to emphasize that such services must be client-centered and mindful of discrimination, stigma, and legal issues that surround HIV disclosure [31].

An important challenge is understanding who the 150,700 persons who need behavioral PwP services are. One strategy for reaching these persons would be a much more widespread use of risk behavior screening strategies in HIV care. There are some recommended best practices for such behavioral screening, including those studied by Golden et al. [33], but uptake of these strategies has been low. Indeed, CDC found that only 55 % of PLWH in care were receiving risk reduction counseling services [29].

Another strategy is the potential "over-provision" of behavioral risk reduction services with cessation when the services are not needed by clients [3]. It was this approach that was explored in the aforementioned paper that provided an economic evaluation of the NHAS goals [3]. Under this full-scale coverage approach, all persons newly diagnosed should be offered behavioral PwP services, as should persons newly receiving HIV care and treatment, in addition to all diagnosed PLWH not in care, and persons now in care but not receiving any counseling services. This serves more than the 16 % of PLWH who are diagnosed but continue to engage in transmission relevant risk behavior should clearly receive such services. This strategy is likely assuming too much coverage, however, it ensures that even if the 16 % of PLWH requiring these services are not readily identifiable, they will receive services if this comprehensive approach to service provision is taken.

CDC has previously estimated the cost of behavioral PwP services to be $ 680 per client [34]. The economic evaluation of the NHAS utilizes this per-client cost estimate, but also doubled it for clients who are not in care and who engage in risk behavior, as these clients would be especially challenging to identify and reach. For the scenario with the most optimistic assumption about treatment effectiveness, full scale up of diagnostic services, and full scale up of behavioral PwP services, it is seen that the PwP services would cost the following:

> . . . the 2-year total spent on risk-reduction services for PLWH in 2014 and 2015 combined [in the most comprehensive scenario examined] is $ 85,008,132 (for PLWH newly diagnosed) + $ 353,827,341 (for PLWH receiving the newly expanded care services) + $ 227,382,495 (for the 15 % of diagnosed PLWH who would still not be in care in 2015) + $ 222,607,463

(for the 55 % of PLWH who are in care even before expansion but were not yet receiving prevention counseling services [3], (pp. 1396).

Of course, this is substantially higher than the cost of simply providing the services for the 150,700 or so persons who most clearly need them, but this approach of possible "over-offering" of services substantially increases the likelihood that clients who need the services will get them. Even with this "over-offering" approach—and even considering the uncertainty in the cost analysis and modeling exercise—the cost-utility analyses indicate that the medical care costs saved by averting HIV transmissions to seronegative partners will clearly outweigh the costs of the PwP services provided. This is important as it indicates that while the investment in PwP services may appear high, the return on that investment will outweigh the costs. In other words, it is actually more expensive to *not* provide the PwP services, given the higher transmission and higher downstream medical care costs for persons newly infected. From an economic perspective, the provision of PwP services is therefore a very attractive option [3].

Unresolved Program, Evaluation, and Research Questions

The NHAS includes indicators and benchmarks to monitor progress and set standards for interventions to address HIV in the United States [1]. Many of these indicators can be evaluated with current data systems, such as CDC's National HIV Surveillance System or Medical Monitoring Project or data reported to the HRSA [29, 35–39]. These indicators can be assessed on the national and local level and can also evaluate programs implemented in target areas. However, there are some limitations in the data available to evaluate programs and NHAS goals. There are also gaps in research to address what programs work to reach these goals.

The Institute of Medicine reviewed public and private data systems for monitoring HIV care [39]. Currently, there is limited information on gender identity, sexual orientation, income or poverty, and insurance status in the data system. There is also a lack of information on substance abuse, housing, food security, transportation, data representative of persons living with HIV, and interoperability of data systems. Full implementation of reporting of all CD4 and viral load test results to HIV surveillance is particularly critical to monitor care and treatment outcomes.

With the reporting of CD4 and viral load test results to HIV surveillance, it is now possible to use these data to determine whether people diagnosed with HIV are promptly linked to care and whether PLWH are in regular care. This allows follow-up intervention to assure people with HIV receive the services they need [40, 41]. However, operational research is needed to determine best practices in the use of data from surveillance systems for client-level intervention. There is a need to further explore best contact tracing, models for provider and health department patient contact, success rates, and cost effectiveness. Operational research is also needed to determine the feasibility of implementing a test and treat strategy on the community level [42]. TasP, in particular, is considered an integral part of a strategy

to address HIV in the United States [4]. However, additional research is needed to determine whether treatment effectiveness in reducing HIV transmission as shown among heterosexual couples would also apply to men who have sex with men, who comprise the majority of persons infected with HIV in the United States [43].

Currently, less than half of the PLWH are in regular care [36]. Scaling up retention in care is necessary to deliver risk counseling and offer treatment to all according to the new treatment guidelines [44, 45]. While some promising approaches using outreach to improve retention in care have been implemented [46, 47], additional research is required to develop optimal strategies and proven interventions for retention in care and overcoming barriers such as stigma, lack of health insurance, substance use, and other socio-economic factors. Studies must also determine better tools to measure retention in care measures that can be predictive of viral suppression [48].

It is the intent of this chapter to assert that in order to fully realize high-impact prevention, effective interventions need to be prioritized and administered at a scale to reach key populations [4]. The "Prevention with Positives" approach and the behavioral PwP interventions targeted for PLWH to reduce behavioral risk of transmission to HIV seronegative partners are important components in realizing the ambitious goals outlined in the NHAS [1]. However, as the last section of the chapter attests, there are questions that remain inadequately addressed [31]. These questions include better measurement of the prevalence of transmission risk behaviors; addressing unmet needs in access to high-quality, client-centered HIV care; achievement of viral suppression; identifying better ways to reduce health disparities; and measuring and addressing costs of unmet needs.

An emerging area of study worthy of further research is better determining what fraction of the roughly 150,000 PLWH who are engaged in any unprotected serodiscordant risk behavior in which the index partner living with HIV has unsuppressed virus. Recently, it has been estimated that fewer than 96,000 diagnosed PLWH are engaged in unprotected serodiscordant risk behavior in which virus is not suppressed [49]. Continually monitoring and refining this estimate is an area of important future investigation. While addressing these limitations and uncertainties will be important in the future, the fundamental conclusion remains the same: prevention services for PLWH are a critical part of any highly impactful HIV prevention program, which appear to substantially influence onward HIV transmission, and seem to have an excellent return on economic investment.

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References

1. The White House Office of National AIDS Policy. National HIV/AIDS Strategy for the United States. Washington, DC: White House; 2010.
2. Holtgrave DR. On the epidemiologic and economic importance of the National AIDS Strategy for the United States. J Acquir Immune Defic Syndr. 2010;55(2):139–42.
3. Holtgrave DR, Hall HI, Wehrmeyer L, Maulsby C. Costs, consequences, and feasibility of strategies for achieving the goals of the National HIV/AIDS strategy in the United States: a closing window for success? AIDS Behav. 2012;16(6):1365–72.
4. CDC. High-Impact HIV Prevention CDC's Approach to reducing HIV infections in the United States. 2011. Available from: http://www.cdc.gov/hiv/strategy/dhap/pdf/nhas_booklet.pdf. Accessed 12 Oct 2012.
5. Patt M. Prevention is treatment: prevention with positives in clinical care. HRSA Careaction. 2003;1–8.
6. CDC. Incorporating HIV prevention into the medical care of persons living with HIV. Mortal Wkly Rep. 2003;52:1–24.
7. Gardner LI, Marks G, Craw J, Metsch L, Strathdee S, Anderson-Mahoney P, del Rio C, Antiretroviral Treatment Access Study Group. Demographic, psychological, and behavioral modifiers of the Antiretroviral Treatment Access Study (ARTAS) intervention. AIDS Patient Care and STDS. 2009;23(9):735–42.
8. Cohen MS, Chen YQ, McCauley M. Prevention of HIV-1 infection with early antiretroviral therapy. New Engl J Med. 2011;365(6):493–505.
9. Smith DK, Grohskopf LA, Black RJ, et al. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States. Mortal Wkly Rep. 2005;54:1–20.
10. Smith DK, Grant RM, Weidle PJ, Lansky A, Mermin J, Fenton KA. Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. Mortal Wkly Rep. 2011;60:65–8.
11. CDC. Listing of all risk reduction interventions, by characteristic. Available from: http://www.cdc.gov/hiv/topics/research/prs/subset-best-evidence-interventions.htm#link2.6. (2012). Accessed 30 Nov 2012.
12. Rotheram-Borus M, Swendeman D, Comulada S, Weiss RE, Lee M, Lightfoot M. Prevention for substance-using HIV positive young people: telephone and in-person delivery. J Acquir Immune Defic Syndr. 2004;37(2):S68–S77.
13. Healthy Living Project Team. Effects of a behavioral intervention to reduce risk of transmission among people living with HIV: the Healthy Living Project randomized controlled study. J Acquir Immune Defic Syndr. 2007;44:213–21.
14. Kalichman SC, Rompa D, Cage M, et al. Effectiveness of an intervention to reduce HIV transmission risk in HIV-positive people. Am J Prev Med. 2001;21(2):84–92.
15. Kalichman SC, Rompa D, Cage M. Group intervention to reduce HIV transmission risk behavior among persons living with HIV-AIDS. Behav Modif. 2005;29(2):256–85.
16. Sikkema KJ, Hansen NB, Kochman A, et al. Outcomes from a group intervention for coping with HIV/AIDS and childhood sexual abuse: reductions in traumatic stress. AIDS Behav. 2007;11:49–60.
17. Sikkema KJ, Wilson PA, Hansen NB, et al. Effects of a coping intervention on transmission risk behavior among people living with HIV/AIDS and a history of childhood sexual abuse. J Acquir Immune Defic Syndr. 2008;47:506–13.
18. Gilbert P, Ciccarone D, Gansky SA, et al. Interactive "Video Doctor" counseling reduces drug and sexual risk behaviors among HIV-positive patients in diverse outpatient settings. PLoS ONE. 2008;3(4):1–10.
19. Wolitski RJ, Gomez CA, Parsons JT. Effects of a peer-led behavioral intervention to reduce HIV transmission and promote serostatus disclosure among HIV-seropositive gay and bisexual men. AIDS. 2005;19(Suppl 1):S99–110.

20. Wolitski RJ, Parsons JT, Gomez CA. Prevention with gay and bisexual men living with HIV: rationale and methods of the Seropositive Urban Men's Intervention Trial (SUMIT). AIDS. 2005;19(Suppl 1):S1–11.
21. Wingood GM, DiClemente RJ, Mikhail I, et al. A randomized controlled trial to reduce HIV transmission risk behaviors and sexually transmitted diseases among women living with HIV: the WiLLOW program. J Acquir Immune Defic Syndr. 2004;37:S58–67.
22. Fisher JD, Fisher WA, Cornman DH, Amico KR, Bryan A, Friedland GH. Clinician-delivered intervention during routine clinical care reduces unprotected sexual behavior among HIV-infected patients. J Acquir Immune Defic Syndr. 2006;41(1):44–52.
23. Fisher JD, Cornman DH, Osborn CY, Amico KR, Fisher WA, Friedland GH. Clinician-initiated HIV risk reduction intervention for HIV-positive persons: formative research, acceptability, and fidelity of the Options Project. J Acquir Immune Defic Syndr. 2004;37(Suppl 2):S78–87.
24. Richardson JL, Milam J, McCutchan A, et al. Effect of brief safer-sex counseling by medical providers to HIV-1 seropositive patients: a multi-clinic assessment. AIDS. 2004;18:1179–86.
25. Rotheram-Borus MJ, Lee MB, Murphy DA, et al. Efficacy of a preventive intervention for youths living with HIV. Am J Pub Health. 2001;91:400–5.
26. Rotheram-Borus M, Murphy DA, Coleman C, Swendeman D. Counseling adolescents: designing interventions to target routines, relationships, roles, and stages of adaptation. In: Chesney MA, Antoni MH, Editors. Innovative approaches to health psychology: prevention and treatment lessons from AIDS. Washington, DC: American Psychology Association; 2002. pp. 15–44.
27. Soorapanth S, Chick SE. Cost-utility analysis of behavioral interventions for HIV-infected persons to reduce HIV transmission in the USA. Proceedings of the 2010 Winter Simulation Conference. B. Johansson, S. Jain, J. Montoya-Torres, J. Huga, and E. Yucesan, Editors. Baltimore, MD. USA, 2010.
28. Lee MB, Leibowitz A, Rotheram–Borus MJ. Cost-effectiveness of a behavioral intervention for seropositive youth. AIDS Educ Prev. 2005;17(2):105–18.
29. CDC. Vital signs: HIV prevention through care and treatment—United States. Morb Mortal Wkly Rep. 2001;60:1618–23.
30. CDC. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 U.S. dependent areas—2010. HIV Surveillance Supplemental Report. 2012;17(3), part A. Available from: http://www.cdc.gov/hiv/topics/surveillance/resources/reports/.
31. Holtgrave DR, Maulsby C, Wehrmeyer L, Hall HI. Behavioral factors in assessing impact of HIV treatment as prevention. AIDS Behav. 2012;16:1085–91.
32. Freedman M, Mattson C, Johnson C, et al. Medical monitoring project, 2009 to 2010. National representative estimates of sexual risk behaviors among HIV? Adults receiving medical care: U.S. 19th conference on retroviruses and opportunistic infections, Seattle, 2012 (abstract 1090).
33. Golden MR, Brewer DD, Kurth A, Holmes KK, Handsfield HH. Importance of sex partner HIV status in HIV risk assessment among men who have sex with men. J Acquir Immune Defic Syndr. 2004;36:734–42.
34. Lasry A, Sansom SL, Hicks KA, Uzunangelov V. A model for allocating CDC's HIV prevention resources in the United States. Health Care Manage Sci. 2011;14(1):115–24.
35. Mahle K, Tang T, Satcher Johnson A, Shouse L, Li J, Hall HI. Using HIV surveillance-based indicators to monitor the National HIV/AIDS Strategy. 2011 National HIV Prevention Conference, Atlanta, Georgia, USA 14–17 Sept 2011.
36. Hall HI, Gray Mahle K, Tang T, Li J, Shouse L, Mermin J. Retention in care of adults and adolescents living with HIV in 13 U.S. areas. J Acquir Immune Defic Syndr. 2012;60:77–82.
37. Prejean J, Song R, Hernandez A, et al. for the HIV Incidence Surveillance Group. Estimated HIV Incidence in the United States, 2006–2009. PLoS ONE. 2011;6(8):e17502.
38. Holtgrave DR, Hall HI, Prejean J. HIV transmission rates in the United States, 2006–2008. Open AIDS J. 2012;6:20–2.
39. Institute of Medicine (IOM). Monitoring HIV care in the United States: indicators and data systems. Washington, DC: The National Academies Press; 2012.

40. Louisiana Office of Public Health. Louisiana Public Health Information Exchange 2012, 2012. Available from: http://www.lsms.org/site/images/stories/LaPhie-Non-techincal%20Guide.pdf. Accessed: 11 Nov 2012.
41. Fairchild AL, Bayer R. HIV Surveillance, public health, and clinical medicine—will the walls come tumbling down? New Engl J Med. 2011;365(8):685–7.
42. Donnell DJ, Hall HI, Gamble T, et al. Use of HIV case surveillance system to design and evaluate site-randomized interventions in an HIV prevention study: HPTN 065. Open AIDS J. 2012;6(Suppl 1: M9):122–30.
43. Fallon SJ, Forrest DW. Unexamined challenges to applying the treatment as prevention model among men who have sex with men in the United States: a community public health perspective. AIDS Behav. 2012;16:1739–42.
44. Department of Health and Human Services (HHS), Panel on Antiretroviral Guidelines for Adults and Adolescents, 2012. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Available from: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed 12 Oct 2012.
45. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA Panel. J Am Med Assoc. 2012;308(4):387–402.
46. Bradford JB. The promise of outreach for engaging and retaining out-of-care persons in HIV medical care. AIDS Patient Care STDS. 2007;21(Suppl 1):S85–91.
47. Horstmann E, Brown J, Islam F, Buck J, Agins BD. Retaining HIV-infected patients in care: where are we? Where do we go from here? Clin Infect Dis. 2010;50:752–61.
48. Mugavero MJ, Westfall AO, Zinski A, et al. Measuring retention in HIV care: the elusive gold standard. J Acquir Immune Defic Syndr. 2012;61(5):574–80.
49. Hall HI, Holtgrave DR, Tang T, Rhodes P. HIV transmission in the United States: considerations of viral load, risk behavior, and health disparities. AIDS Behav. 2013;17(5):1632–6.

Chapter 4
Advocating for Rectal Microbicides and Safe Lubricants

Marc-André LeBlanc and Jim Pickett

> I would love a microbicide gel. But right now, even cheap water-based lubes are simply NOT available in many settings. So what would be the case with a specially formulated gel? Of course, something to consider is that in some of our countries, something that "promotes homosexuality" like a rectal microbicide for anal sex, God forbid, might be banned before it is even actually produced! But, the biggest advantage with a rectal microbicide is that most of us need a lubricant for anal sex. Even if we despise condoms, we just can't do without lubrication. We love the pleasure of sex, not pain. So combining a microbicide and lubrication in the same product in our pockets or bedside table is a no-brainer. We would use it. It would be fun. We would even forget that it is a medicine—it's just a lube, and lube is good with sex.
> –Dr. Paul Semugoma, HIV and LGBT activist, IRMA member, Uganda

What will it take to develop safe, effective, acceptable, accessible, and affordable rectal microbicides (RMs)? What will it take to create such products for the men, women, and transgender individuals the world over who engage in anal intercourse (AI) and need/want options beyond male and female condoms to protect themselves from HIV infection? What will it take to ensure that condom-compatible lubricants are safe and widely available? What will it take to put such products on nightstands, in pockets, backpacks, and purses; in pharmacy shelves and next to the bowls of condoms in community-based organizations (CBOs); in national strategic plans and the portfolios of prevention programmers and funders? This is an enormous question, or more accurately, an enormous series of questions. We will not attempt to answer them all here.

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Making Rectal Microbicides a Reality: Overcoming Scientific and Sociocultural Challenges

We will not tackle the science of protecting the rectum from HIV, although it is absolutely critical for us to understand. After all, unprotected AI is 10–20 times more likely to result in HIV infection compared to unprotected vaginal intercourse, mostly owing to the fragile mucosa of the rectum and the hordes of T cells waiting on the other side—"ideal" conditions for HIV infection to take hold. Inhibiting HIV in that fragile, fertile environment while also causing no harm is no small feat, and we are thankful to the scientists, particularly those connected to the Microbicide Trials Network (MTN), who have made RM research a priority. Their commitment to this field of inquiry requires an advocacy mindset and a sense of fearlessness that is not necessarily common in much more "mainstream" and "respectable" pursuits.

When microbicides were first imagined, they were "vagina-centric." While many embraced the notion of creating vaginal products women could control, the majority of the HIV/AIDS community—scientists and advocates alike—dismissed the possibility of developing RMs for use during AI as an HIV prevention method. It was not considered feasible and the pursuit was seen as hopeless, even laughable. At best, the RM field would consist of testing vaginal microbicides for rectal safety, because these products would undoubtedly end up in the rectum despite their intended destination. But rectal efficacy? No way.

Biological challenges certainly played a role in the widespread lack of enthusiasm for RM research. Additionally, the political and sociocultural context reinforced the dismissal of RMs. Pervasive homophobia across the globe has resulted in a lack of adequate attention and resources devoted to gay men and other men who have sex with men (MSM) despite the disproportionate HIV burden borne by this population. And few knew, or acknowledged, that AI is a common practice among heterosexuals, not just gay men. Thus, homophobia and evidence-free assumptions relegated the rectal portion of the microbicide field to a small, dark corner.

Despite this array of challenges, including only a small fraction of total microbicide funding specifically directed to RM research and development, the field has moved from simply being an adjunct to vaginal studies to a force in its own right. This is owing to passionate and dogged scientists and advocates, and critical support from the United States National Institutes of Health (NIH) the funder responsible for nearly the entire array of past and present RM studies.

Making Rectal Microbicides a Reality: Overcoming Challenging Contexts and Barriers to Eventual Access

Addressing political, sociocultural, human/civil rights considerations are vital to creating enabling environments. In much of the world, the act of AI is ignored, denied, stigmatized, demonized, and criminalized. According to ILGA (International

Lesbian, Gay, Bisexual, Trans, and Intersex Association), 78 countries and six entities call for the imprisonment of individuals for same-sex activities; five countries and parts of Nigeria and Somalia call for the death penalty. As of this writing, Uganda is once again taking up their infamous "kill the gays" legislation, inspired by Christian fundamentalists from the United States that would call for the death penalty for gay and lesbian Ugandans. The speaker of the Parliament is actually calling it a "Christmas gift" to Uganda. At the same time, politicians in Nigeria are also looking to enact harsher anti-gay laws. In the United States, only 21 states and the District of Columbia prohibit discrimination based on sexual orientation; one can be fired from their job simply for being gay in more than half the country. Most places in the world criminalize sex work.

If you can't be who you are wherever you are, if your very being puts you in harm's way, you won't be able to access RMs. If your sexual behaviors are ignored or shamed or grounds for criminal prosecution, it's not likely you will have a bottle of RMs next to your bed. It's not likely you will ask for them at the pharmacy, or that your local CBO will distribute them. We can have a fantastic RM product that is safe, super effective, and highly acceptable and it won't matter one bit if the people who need this intervention are unable to get their hands on it because of a hostile environment.

Poverty, food and housing insecurity, unemployment, poor healthcare access, lack of education, failed criminal justice systems, sexism, and racism are equally significant structural challenges that must be addressed in the fight against HIV. These enormous, seemingly intractable issues also will contribute to whether RMs actually make it into the hands—and bodies—of those who need them.

While we recognize the importance of addressing the challenging contexts and barriers we mention above, our remit here is less broad, less overwhelming, and more narrowly focused. What we would like to do first is share our perspectives and provide some examples of international advocacy specific to RMs. Next, we will discuss the need for substantive scientific engagement with impacted communities in the global north and south, and finally we will lay out the interconnected and vexing issues of lube safety and lube access. Pursuing these activities and issues are as essential as maintaining a robust, adequately funded scientific agenda and reducing, or eliminating, the array of structural barriers. We feel they are critical to realizing the day when safe and effective RMs are affordable and within reach of anyone, anywhere.

International Rectal Microbicide Advocates—Who We Are

We represent IRMA (International Rectal Microbicide Advocates— "the bottom line in HIV prevention"—www.rectalmicrobicides.org), a global network of advocates, scientists, health educators, policy makers, and funders housed at AIDS Foundation of Chicago (AFC) and dedicated to the research and development of RMs. Founded in 2005 by a small handful of individuals from AFC, the Canadian AIDS Society,

Community HIV/AIDS Mobilization Project, and the Global Campaign for Microbicides, the group now boasts a dynamic membership of more than 1,200 people from over 100 countries.

IRMA is the first and only network in the world to focus on RM advocacy. The story of RM advocacy is the story of IRMA. Central to its efforts, IRMA nourishes multiple platforms, including a highly active, moderated listserv, by which the stakeholders involved in RM research and advocacy and other new prevention technologies can regularly discuss and debate the issues of the day.

In addition to a host of education, awareness, and advocacy activities, with special initiatives in South America and Africa, IRMA produces a variety of printed, video, and web-based materials and reports to further understanding and discussion of RMs and AI. IRMA has brought attention to past and current scientific endeavors, noted the inadequate funding devoted to RM research, forecasted funding needs for the field up to 2020, characterized data on the frequency of AI (heterosexual and homosexual) and its underreported role in the AIDS epidemic, called for an African-specific RM research and advocacy strategy, analyzed the impact of homophobia and criminalization on the field, described global patterns of lubricant use for AI, called attention to issues of lube safety and access, and pushed for a more coordinated RM research agenda. While IRMA's focus is RM research and issues related to AI and lubricant safety and access, the group also actively supports the development and implementation of other forms of prevention, including new strategies such as PrEP (pre-exposure prophylaxis) as well as underutilized tools like female condoms.

International Rectal Microbicide Advocacy—South America

Following the Microbicides 2008 conference in Delhi, India, Peruvian investigators, advocates, and allies, led by IRMA member Jerome T. Galea, decided to form an IRMA chapter that concentrated on South and Latin America. Dubbed IRMA-ALC (América Latina y el Caribe), IRMA's Spanish-speaking sister is based at a gay men's community health center in Lima called Epicentro (founded by Galea) that provides a host of services for gay men and transgender individuals modeled on the successful Magnet health center in San Francisco, California. Galea has also researched and published on RM acceptability, lubricant use, and rectal douche behaviors among gay men and other MSM from Peru, Ecuador, and Brazil.

In collaboration with IRMA and AVAC, IRMA-ALC translates existing materials into Spanish, produces new ones, and conducts education and advocacy efforts to increase the awareness of RM research and its relevance to communities in the region. Other biomedical strategies such as PrEP and improved treatment access are included in these efforts. In fact the group is currently advocating for access to the ARV drug Truvada in Peru, which is not yet available in the country. Truvada is the drug which was tested in the iPrEx PrEP trial among gay men and transgendered women, showing high levels of efficacy when used consistently and correctly. The vast majority of iPrEx participants were from Peru, and these individuals as well as

their communities should be able to access Truvada for PrEP, as well as treatment for that matter.

IRMA-ALC also works to reduce the stigma and silence around AI. A trait that distinguishes IRMA-ALC is the fun and sense of humor with which it imbues its efforts. In 2012, the group created an animated character named Tia IRMA (Auntie IRMA) who shares her knowledge of AI, RMs, and HIV on YouTube in a sassy, colloquial, rapid-fire manner that is both hilarious and informative. She not only appears on YouTube, but exists in the physical world as well. In larger-than-life costume, Tia IRMA shows up at community events to spread awareness—and pose for photo opportunities—in person. IRMA-ALC members and allies are there with her, proudly wearing pink "Pasivista" t-shirts, a witty reference to those who take on the passive role (are penetrated) during AI.

Tia IRMA and her "Pasivistas" help to reduce the shame, stigma, and "ick factor" felt by many of us when the discussion includes anuses and rectums. Laughter breaks the tension and the silence and allows us to better understand that AI is a normal part of the human sexual repertoire.

International Rectal Microbicide Advocacy—Africa

For far too long the operating principle concerning the HIV epidemic in Africa has been that it is solely heterosexual, and that sexual transmission is entirely driven by unprotected vaginal intercourse between men and women. But an increasing body of evidence tells us quite clearly that unprotected AI is happening all across the continent—among heterosexuals as well as gay men, other MSM, and transgender individuals. Therefore, RM research and advocacy efforts must not neglect Africa. "Our diverse sexualities in Africa shouldn't be defined only by the prevention tools we have available. HIV prevention tools must be adapted to our sexualities" states Alliance Nikuze, IRMA member from Rwanda.

In advance of the 2011 International Conference on AIDS and STIs in Africa, held in Addis Ababa, Ethiopia, IRMA convened a two-day consultation as part of its Project ARM initiative (Africa for Rectal Microbicides). Over 40 African advocates and allies met to develop strategies to ensure substantive African involvement in RM research and advocacy. The results were published in a report called "On the Map: Ensuring Africa's Place in Rectal Microbicide Research and Advocacy" released at the Microbicides 2012 conference. The report calls for a set of activities related to research and community mobilization designed to fully engage Africans, including a Knowledge, Attitudes, and Behaviors study on anal sex, advocacy for increased condom-compatible lubricant access, and communication and education activities. "Africans need rectal microbicides and they need to be part of the advocacy, research and development processes that are essential to creating products that are not only safe and effective but acceptable and accessible too," said Dr. Ian McGowan (United States), MTN co-principal investigator and IRMA Scientific Vice Chair.

"We still face significant hurdles regarding human rights for gay men, MSM, and transgender individuals in Africa, but the collective, long-term efforts of advocates and scientists are indeed lifting the denial around anal sex in the African context," said Morenike Ukpong, New HIV Vaccines and Microbicides Advocacy Society in Nigeria, IRMA member, and one of the chief architects of the Project ARM strategy. "Great efforts have long been underway to develop safe and effective vaginal microbicides for African women. We need the same level of commitment and resources for the development of safe, effective, acceptable and accessible rectal microbicides for Africans regardless of gender identity or sexual orientation."

International Rectal Microbicide Advocacy—Material Development

As the RM field expands from small Phase I safety studies to larger Phase II safety studies, and eventually efficacy trials, appealing materials are needed to accurately explain RM clinical trial participation and engage interested community members in RM development. In December 2012, IRMA, the MTN, and the Population Council released a jointly produced video called "The Rectal Revolution is Here: An Introduction to Rectal Microbicide Clinical Trials." While explaining the basics of RM clinical research, the 13-min video is designed to facilitate clinical trial recruitment, ensure consistency and accuracy of messages, and educate clinic staff and communities on RM development. It includes information on concepts such as voluntary participation, risks and benefits, and participant protections.

The video was developed through an intensive process that involved the participation of an international video advisory committee comprising individuals from RM trial sites and other IRMA members. A "rough cut" was viewed by over 80 participants at the Microbicides 2012 conference who provided feedback, and was subsequently tested in 13 focus group discussions of gay men and transgendered women in the United States, Peru, South Africa, and Thailand. The collective feedback obtained was critical in shaping the final video, now available in English, Spanish, and Thai on YouTube.

International Rectal Microbicide Advocacy—The Bottom Line

Anal intercourse is a common human behavior practiced the world over. Gay men and others who engage in AI in Boston, Bangkok, Cape Town, and Lima—and all points in between—need RMs, but advocacy and educational efforts to engage these disparate communities need to be unique and informed by the communities themselves. They must be tailored, contextually relevant, and culturally resonant. The science of RM development should be made appealing and accessible, and accurate information on AI and anal health should underpin these efforts. Materials developed should be in multiple formats and available on multiple platforms.

Scientific Engagement with Communities

The MTN's MTN-017 trial, set to launch in 2013, represents a major milestone: it is the first-ever phase II expanded safety and acceptability study of an RM and is the first RM trial to include clinical research sites outside of the United States. The 186 gay men, other MSM, and transgender women who will be recruited into MTN-017 will more than double the total number of human beings who have participated in RM clinical trials to date. This landmark study—taking place in the United States, Puerto Rico, Peru, South Africa, and Thailand—will investigate the safety and acceptability of reduced glycerin tenofovir gel, and will directly compare acceptability and adherence to daily oral Truvada.

To prepare for the MTN-017 trial, the MTN and IRMA, in conjunction with trial sites and local HIV and LGBT organizations in each city held in-person consultations with community members to obtain feedback on the draft protocol as well as AI and RM research in general.

"The MTN strongly believes that effective communications and meaningful community engagement are essential for the successful and ethical conduct of HIV prevention trials," said Clare Collins, MTN's Associate Director of Communications and External Relations who organized and implemented the MTN's consultation efforts. "Although MTN-017 is a relatively small trial, engagement with civil society and advocates occurred during the design phase of the study and prior to study implementation to address questions and concerns about rectal microbicides and the study protocol. Given that MTN-017 is the first-ever phase II trial of a rectal microbicide and will take place in multiple countries, we believed it was especially important to conduct consultations with key stakeholders and advocates at each trial site to address cultural differences and the sites' unique and specific needs."

Collins explained that MTN was looking for insight from community members about social norms, practices, and perceptions related to AI and biomedical approaches to HIV prevention that could affect the way MTN-017 was designed and implemented. Consultations were conducted while the protocol was still in the design phase to allow changes to be made before the protocol was submitted for final approval.

"MTN-017 also represented the first time the MTN was conducting clinical research in Thailand and Peru, which made it important to introduce key community members to the network by explaining our process of conducting clinical research and giving needed background on our approach to rectal microbicides research," she explained.

In addition to seeking general comments and questions about RMs and MTN-017, some of the specific questions posed to consultation attendees included: Should MTN-017 include transgender women as well as gay men and other MSM? What are the biggest challenges to conducting MTN-017 in your community? How can these challenges be addressed? Do you foresee any concerns about confidentiality and privacy related to people enrolling and participating in MTN-017? Are there any factors you think could negatively impact adherence to the study regimens? How

can we best address these concerns? What are the biggest challenges recruiting and retaining volunteers in MTN-017?

"The feedback MTN received from the consultations directly resulted in changes to the design of the study and its eligibility requirements," said Collins. "It also gave study investigators and site staff important feedback on challenges related to conducting the study." Collins shared the specifics of what was learned from the series of consultations: (1) the initial study design was confusing and difficult to follow; (2) transgender women should be included in the study; (3) the eligibility criteria needed to be revised to exclude couples from participating in the study at the same time; (4) informed consent and study compensation needed to be carefully considered on a site-by-site basis; (5) study materials needed to be as simple as possible and appropriately translated; (6) there could be acceptability challenges to the use of the rectal microbicide applicator; (7) sites that required more invasive procedures such as sigmiodoscopy and biopsy may find it difficult to recruit; and, (8) it may be challenging to recruit young gay and other MSM in the United States since the perception for many is that HIV is seemingly irrelevant to their lives.

"The feedback MTN received from the face-to-face consultations was extremely valuable to the protocol development team. It provided community input that we may not have otherwise obtained and gave us an opportunity to learn from community members and vice versa," Collins said. "Provided funding is available to support additional consultations for rectal microbicide studies, the approach is certainly something MTN is committed to continuing into the future." Collins emphasized that "conducting face-to-face consultations before a protocol has been submitted for approval provides an opportunity for the research team to address any concerns about the study early-on in the protocol development process. It allows the team to learn more about a particular community's social norms and practices that could impact the way the study is perceived and conducted. Holding consultations at an early stage in the research process also helps to create trust and promote collaboration among community members and the research team well before the study launches, setting the stage for future engagement."

MTN's co-principal investigator Dr. Ian McGowan is considered the leading RM researcher in the world. The community consultations for MTN-017 were conducted under his guidance and direction. He and his colleagues have heard from advocates and community members alike that using an applicator to deliver an RM may be a "deal breaker." It is one thing to acquiesce to using an applicator in a trial; it is quite another to ask men and women who have AI to use an applicator in their real lives. After all, people who use lube most commonly use their fingers to apply it, utilizing the "dab will do ya method." And if more lube is needed, "another dab will do ya." In the MTN's recompete application to the NIH, McGowan reported that the network put in a placeholder for a very novel Phase I RM safety, acceptability, and pharmacokinetics (PK) study. Participants will be asked to apply product to the insertive partner's penis and the perianal area/anal canal of the receptive partner. They will then have anal sex. "We want to see if the tissue PK exposure is similar to when product is applied with an applicator. Obviously this would be a challenging study and will need significant development including discussion with advocacy/community

representatives," McGowan said. "However," he continued, "the fact that the study is in the recompetition underscores our commitment to doing this type of research and our responsiveness to community feedback on how these products might be used."

Scientific Engagement with Communities—The Bottom Line

If we are to have RM products that real people are going to use in their real lives, scientists and impacted communities must continue to engage with one another. Tapping community wisdom before, during, and after trials is not a luxury, or something nice to do—it is absolutely essential. And this sort of engagement should not be "trial-centric" but more expansive.

In an ideal world, there will be safe and effective microbicides that work against HIV as well as other sexually transmitted infections (STIs) in both the vagina and the rectum. Having products that work in both "compartments" can effectively reduce the stigma associated with something designed specifically for the rectum. It will also avoid the fumbling for various tubes and lubes by women who are engaging in AI and vaginal intercourse as well. These microbicides will be easily applied, delivered in multiple manners, and available in contraceptive and noncontraceptive versions. Additionally, non-ARV microbicides will be developed so people living with HIV are able to take advantage of this prevention strategy as well.

We recognize we are in the "car phone" phase of microbicides—vaginal and rectal. Early products will be similar to the brick-like car phones of decades ago—perhaps a bit clunky and not as effective as we would like. But it will be what we have, and we will need to make the best of it while keeping our eyes on the prize. Said prize will be products that are like the smart phones of today—efficacious, sleek, strongly desired, and accessible/affordable. Like the evolution of all technologies, this will take time. One only need recall the early years of highly active antiretroviral therapy, with the high pill burdens, complicated dosing regimens and plethora of side effects and compare that to the current array of HIV drugs which are much easier to take, and in some instances, consist of only one pill a day.

Lubricant Safety and Access

As shocking as it may seem, we do not know much about the safety of sexual lubricants and whether or not they contribute to the spread of HIV. More than 30 years into the HIV pandemic, we do not know whether sexual lubricants (lubes) increase, decrease, or have no impact on the risk of acquiring HIV and STIs. In fact, it is only quite recently that most advocates, HIV prevention workers, researchers, and policy makers have even realized that we do not know the answer to this fundamental question.

For years there was very little attention paid to lube safety. Before 2010, researchers and advocates who worked on this issue were voices in the wilderness.

Researchers in Belgium tested lubes on slugs; at the Population Council they tested lubes in mice; at the University of Texas Medical Branch they tested lubes in the laboratory; and, at Johns Hopkins they conducted what still remains the only study testing lubes in humans. Meanwhile, IRMA began advocating for more research on lube safety.

Now a few more studies have been conducted or are underway. Researchers at the Population Council and the University of Pittsburgh have tested many lubes in the laboratory; at UCLA they have explored links between lube use and rectal STIs; and, at the U.S. Centers for Disease Control (CDC) they are testing lubes in the laboratory and in monkeys.

Equally shocking is the deplorable level of access to condom-compatible lubes around the globe, particularly in low-income and middle-income countries. For people at high risk through sexual transmission, including women, men, and transgender people who engage in AI, and sex workers, the situation is even worse. This is despite the fact that we know that condom-compatible lubricants help reduce the risk of condoms breaking or slipping. And as we know, using male or female condoms is considered a very effective way to prevent acquiring both HIV and STIs during intercourse. There is one thing that is clear: we will not get an answer to the lube safety question, nor will we improve lube access without advocacy. We need advocates to urge researchers, manufacturers, funders, donors, and policy makers to make this a priority.

Many men, women, and transgender individuals use lubes during sexual intercourse, and there are hundreds of products on the global market. Sexual lubricants used for intercourse, anal or vaginal, have generally not been tested for safety in humans. Regulatory bodies such as the Food and Drug Administration (FDA) in the United States do not require safety data from testing in humans. At most, the FDA requires manufacturers to demonstrate that lubes are safe in the vaginas of rabbits or guinea pigs. Meanwhile, a number of studies have revealed that some lubricants cause cell inflammation and damage, and another study identified an association between lube use and acquisition of rectal STIs.

It is unclear what laboratory tests should be used to assess lube safety. Furthermore, even when a study shows that a lube causes damage in the laboratory, we do not know how that finding transfers to the real world. We do not know to what extent—if any—using such a lubricant might lead to a higher risk of acquiring HIV or other STIs. Based on current evidence, we do know that lubes with higher osmolarity (a measure of the concentration of soluble components—or solutes—present in a solution) are associated with higher levels of inflammation and cell damage.

IRMA has prioritized the issue of lubricant safety for several years, and we work on a number of fronts. We coordinate a global Lube Safety Working Group comprising researchers, advocates, educators, and policy makers from 12 countries—including all researchers who have worked on rectal safety of lubes, as far as we know. We conducted a global survey on rectal use of lube in 2007. The survey provided valuable information on lube use, preferences, and acceptability among nearly 9,000 men and women from over 100 countries, establishing a list of the most widely used lubes. We disseminate information on lube safety through key documents available in seven

languages and through regular global teleconferences. We gather information on how lubes are regulated in various countries. So far that includes the United States, Canada, the United Kingdom, Nigeria, South Africa, and Australia. We have reached out to a number of manufacturers to get their perspective on lube safety, and to identify ways of working together. We are developing a research agenda to articulate key research objectives that could ultimately help us answer the question of lube safety.

We need to determine whether lubes increase, decrease, or have no impact on the risk of acquiring HIV and/or STIs. Even when microbicides that have been shown to be safe and effective and are widely available, potentially in the next decade, they will still be competing with hundreds of other lubricants that will remain on the market. We need a lube safety research agenda that provides a roadmap toward answering the question of lube safety. This requires more studies and more research funding. It requires the involvement of manufacturers, researchers, and funders. It requires ongoing monitoring of regulatory oversight and adjustments to regulatory requirements. All of this necessitates sustained advocacy to ensure that lube safety remains on the HIV prevention research agenda and on the radar of funders, policy makers, regulators, researchers, and manufacturers.

Another concern is lubricant availability; for many people around the world, sexual lubricants are not accessible in the first place. Although the science has not been able to tell us much about lube safety yet, we do know that condom-compatible lubes help reduce the risk of condoms breaking or slipping. Condom-compatible lubes should be part of any HIV prevention campaign or program that distributes condoms, especially to individuals who engage in AI. Sadly, on a global level, this is the exception, not the rule. This must change, and it is unlikely to do so without advocacy.

That is why IRMA, through its Project ARM initiative, recently unveiled a new campaign called GLAM—Global Lube Access Mobilization. The GLAM campaign is focused on increasing access to condom-compatible lubes. Because it was developed through Project ARM, the initial focus is on Africa where lube access is especially poor. A number of analyses in various settings indicate the use of oil-based products is the most common form of lubrication—and is known to significantly reduce condom effectiveness. Faced with the lack of condom-compatible lubricants, people often resort to such products as body lotion, soap, cooking oil, spit, precum, antibiotic creams, and even motor oil to provide lubrication during AI. This lack of appropriate lubricant products for people who practice AI is unacceptable.

IRMA collaborated with its cadre of Project ARM members as well as amfAR and AVAC to develop a "toolkit" to help improve lube access. The toolkit, launched in December 2012, contains a list of proposed action steps, African case studies, and other resources that advocates can use to ramp up their lube access advocacy efforts in African contexts. Along with a set of three microgrants, recently awarded to organizations in Liberia, Nigeria, and Zambia through a competitive process, it is hoped that advocates utilizing the toolkit are successful in getting governments, funders, and CBOs to include condom-compatible lubes in their policy and programmatic priorities and their prevention budgets.

All men, women, and transgender individuals across the globe deserve the right to have safer sex and protect themselves and their partners from HIV and other STIs. Safe, condom-compatible lubricant must be a priority, positioned as an absolute necessity, along with male and female condoms. Advocates should work together through coalitions of natural allies on this issue—HIV prevention advocates, sexual and reproductive health organizations, advocates for LGBT rights, and advocates for sex workers' rights. Policy makers, donors and funders, public health officials, Ministries of Health, UN agencies, and other development partners must be engaged as well.

Advocacy for lube safety and lube access is gaining momentum. In 2013, we are poised to realize significant progress on both lube safety and lube access.

Some of the more recent research, as well as the increased level of advocacy from IRMA in favor of both lube safety and lube access, have caught the attention of critically important players. This includes several lubricant manufacturers, regulators such as the FDA, funders such as the NIH, policy makers and donors such as the U.S. Office of the Global AIDS Coordinator (OGAC), which administers the President's Emergency Plan for AIDS Relief (PEPFAR), normative bodies and multilateral agencies such as the World Health Organization (WHO) and the United Nations Population Fund (UNFPA), and major distributors of sexual and reproductive health commodities such as Population Services International (PSI). At the time of this writing, PEPFAR has drafted its own Lube Safety Research Agenda to focus on the need for answers to the fundamental questions about lube safety and HIV risk. When finalized and released, this document is expected to provide both direction and much-needed global energy on the issue of lube safety.

Lubricant Safety and Access—The Bottom Line

IRMA believes that the advocacy momentum generated by its dual efforts on lube safety and lube access will lead to a world where men, women, and transgender people from around the globe who engage in vaginal intercourse or AI have access to safe, condom-compatible sexual lubricants. Rectal microbicides are in the future; the need for safe lube is now. It is as urgent and "of the moment" as you can get. If we cannot ensure access to safe, condom-compatible lube for people who need it today, how in the world do we think we are going to be successful in distributing RMs? Developing new pathways for lube distribution, and improving current ones, will have a direct impact on RM accessibility. It bears repeating that the best, most effective, wildly acceptable RM will be for naught if it is inaccessible.

Final Thoughts

It may be a blessing for the RM field to be behind (pun intended) the development of vaginal microbicides and PrEP. Rectal microbicide researchers have been able to

learn valuable lessons from the outcomes of vaginal microbicide and PrEP trials, such as recently reported results from the VOICE trial which revealed most trial participants were not using study products, and adjust accordingly. Advocates have learned how to better engage communities around complicated science and products that are not yet available, and perhaps not seen as a priority in comparison to voluntary counseling and testing, linkage to care, and expanded treatment.

Currently, Truvada as PrEP has been proven to work among gay men, other MSM and transgender women, and among heterosexual men and women, and among persons who inject drugs. While this is an incredible scientific achievement that could be of significant benefit to individuals of all stripes across the world, many policy makers, funders, program implementers, community stakeholders—and most importantly, people at high risk of HIV infection—are just confronting this new strategy now. Consequently, there is a fair amount of resistance, confusion, and misinformation among all these groups. A strong PrEP-specific advocacy movement has never really existed until after the iPrEx trial reported its results, and could explain some of the current challenges in implementing PrEP programs.

The RM advocacy movement, in contrast, has been in place since the early days of rectal studies. It will be up to advocates, scientists, policy makers, funders, and impacted communities to continue preparing the ground so the first day an RM is introduced on the market is not seen as a surprise or an unwelcome diversion.

Part II
Behavioral Challenges and Opportunities

Chapter 5
Adherence to HIV Treatment as Prevention and Preexposure Prophylaxis

K. Rivet Amico

Advances in the pharmacotherapeutic treatment of HIV have transformed what was a definitively fatal disease to a manageable chronic disease, provided availability of antiretroviral therapy (ART) medication and high rates of adherence are achieved and maintained (80–95 % depending on regimen) [1]. Presently, among the estimated near 15 million people living with HIV (PLWH) worldwide in need of ART, only 54 % have access to ART [2]. Who is "in need," however, is increasingly expanding as many countries are now adjusting guidelines for when to start ART to increasingly less restrictive criteria in response to recent findings supporting treating HIV early to reduce odds of onward HIV transmission [3–5]. Whereas availability is clearly a necessary condition for individual or public health benefits of ART, the past 15 years of research and practice in this area identify that a sizable proportion of PLWH with access to ART do not take it consistently enough to increase longevity or maintain suppressed viral load that would thwart transmission. For example, in the United States, where ART is generally widely available, there were 17,000 AIDS-related deaths in 2010, and onward transmission has been fairly stable at 50,000 new HIV infections per year. Global estimates suggest that while the majority of PLWH prescribed ART do achieve and potentially maintain high rates of adherence (about 60 % of those on ART), a substantial minority (40 %) do not [6].

For over a decade, reasons for ART nonadherence and strategies to promote adequate adherence have been under evaluation. Behavioral science has contributed actively to the identification of correlates and determinants of adherence producing numerous models of ART adherence [7] and a host of intervention approaches evaluated in diverse populations [8–10]. Recent international guidelines for monitoring and supporting both retention in HIV care and ART adherence have been offered that recommend providing some level of monitoring and support for ART adherence [11]. This amassed body of literature is of relevance to "treatment as prevention" (TasP)

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approaches as well as the recent innovations in the use of ARV drugs in noninfected individuals for the prevention of HIV infection, PreExposure Prophylaxis (PrEP).

Common to TasP and PrEP success, self-administered drug requires specific rates of adherence or patterns of dosing to provide the intended benefit. A number of commonalities between TasP and PrEP adherence are clear—use of same ARV agent and thus associated experience of start-up syndrome or side effects, daily dosing with some degree of forgiveness for occasional nonadherence, role of medication management skills (e.g., planning, memory, scheduling, organization), and potentially a number of motivators (e.g., social support, positive attitudes toward ARV(s) and positive feelings toward adherence). However, whereas ARVs for treatment draw on beliefs and attitudes toward one's own longevity and health in the context of a known, diagnosed illness, and, more recently, motivation to prevent onward transmission, PrEP likely draws more heavily on beliefs about the extent to which one is "at risk" for HIV infection and one's sense of agency in being able to avoid it. ART treats a known condition and PrEP aims to prevent a possible infection typically in situations where actual exposure is uncertain.

In this chapter, behavioral pathways underlying successful TasP and PrEP are highlighted, which include discrete correlates as well as more complex social behavioral models, potential strategies for support drawn from available evidence gathered to date are identified, and notes of caution provided. Ongoing research and recommendations for future research as well as practice are offered throughout. In providing this kind of overview, it is important for readers to remain aware of the rapid and dynamic nature of this evidence base; new directions and data emerge daily. Websites and other resources that provide excellent avenues for remaining abreast of emerging issues are provided. Additionally, rather than providing an exhaustive summary, the focus of this chapter is on current major issues and strategies to be considered in the construction of scientific and practice agendas from a social behavioral science perspective. Issues not addressed here include the policy implications and needs for either prevention strategy to achieve high community penetration, consistent (uninterrupted) supply, cost/benefit analyses, or the pharmacokinetic nuances of effective ART or PrEP. In short, the social behavioral factors considered here are those that would influence self-administration of an available treatment and/or proven prevention tool. As PrEP continues to be evaluated in blinded randomized control trials (RCT) as well as open-label projects, strategies used to promote blinded study product use are also noted.

Treatment as Prevention (TasP)

With worldwide attention and accolades, HPTN052 reported a 96 % reduction in transmission of HIV in serodiscordant couples where the person living with HIV started ART immediately (at diagnosis generally with CD4 counts $<=500$ cells/mm^3) rather than waiting until their CD4 count or experience of opportunistic infections met far lower country-specific criteria for ART initiation [4]. The idea

that effective, durable suppression of viral load in PLWH can prevent onward HIV transmission is not new. The Swiss statement of 2008 concluded that PLWH who were virally suppressed and free of STDs had a negligible risk on transmitted HIV [12]. The evidence provided by a large RCT is new and the evidence in favor of starting ART early [5] has prompted countries around the world to reconsider ART-start criteria. The World Health Organization (WHO) in a June 2012 programmatic update [13] identified 1 of 79 countries evaluated in 2011 with ART-start guidelines recommending ART irrespective of CD4 values (USA), 3 with criteria of $<=500$ cells/mm^3, 43 at $<=350$ cells/mm^3, 5 at $<=200$ cells/mm^3, 5 at $<=250$ cells/mm^3, and 15 at $<=200$ cells/mm^3, with varying alterations of these if coinfected with TB and higher HIV staging. Countries are also actively considering adding in status of main partners (e.g., serodiscordant partnership status) into formularies. It is difficult to identify another study in this decade that had as much policy impact as HPTN052.

Although cost-effectiveness of adopting TasP approaches of starting ART early appear quite economical in the long term [14], mustering the finances and structural resources for implementation on a large scale is formidable. Furthermore, for TasP to substantially impact the epidemic, the identification of PLWH who are unaware of their HIV status presents a remarkable barrier that must be overcome [15]. Making substantial headway in addressing remarkable barriers that appeared at one time impossible to tackle is not uncommon in HIV treatment; note the progress in providing ART to people in need of it over the last decade (c.f., [16, 17]). The daunting task of making ART available and increasing the number of individuals who know their HIV status is being aggressively addressed in a number of ongoing projects and research (mentioned later in this chapter). In this work and the work that follows in the next decade, the role of social behavioral factors in the potential success of TasP needs definitive positioning on the research agenda as an essential element of success.

Success of the TasP approach relies on achievement of durably suppressed viral load among those who would otherwise transmit HIV. Two critical biobehavioral components emerge from this assumption—the first concerns the identification of those who contribute most to new HIV cases and the second concerns the actual use of ART at sufficient levels or constancy to produce rapid and sustained suppressed viral load. Condomless sex and/or sharing of needles or drug paraphernalia are the main routes of transmission; the odds transmission increase during times when PLWH are highly viremic (acute infection [AHI] or existing infection that has reached levels of high viral load). Many PLWH substantially reduce risk of HIV transmission once they are diagnosed and sustain these changes [18], thus knowledge of HIV status not only provides the opportunity to link individuals into HIV care but also has the added benefit of self-directed changes in potential transmission behaviors. AHI continues to be a challenge to identify and may appear as a common cold or flu. Presently, commonly used HIV-testing formulas do not identify those acutely infected. Second-generation and third-generation tests are available that do identify AHI but are cost prohibitive in many settings. With acute infection, particularly in combination with STI coinfections, creating "hyperinfectious" events [3], yet largely undiagnosed by current commonly used HIV tests, the scientific community is aggressively pursuing strategies to identify acutely infected. However, some models of HIV infection in men-who-have-sex-with-men (MSM) communities suggest that acute infection

drives new HIV cases less than chronic-stage HIV [19]. Innovations in increasing knowledge of HIV status also include the use of home-based testing [20] and oral testing kits that can be used in privacy and as couples [21]. Increasing uptake of testing and sophistication of tests offered is an active area of research and practice, with excellent summaries of state of the science available (c.f. recent reviews, [22–29]). Ongoing clinical trials addressing aspects of TasP include continuation of HPTN 052, the Strategic Timing of ART study (START), and Agence Nationale de Recherche sur le Sida (National Agency for AIDS Research) TasP Study, all with results expected in 2015. TasP approaches rely heavily on early identification of HIV status and can benefit extensively from increasing feasibility, acceptability, sophistication, and uptake of HIV testing as opportunities to link into care (HIV positive) or offer prevention packages potentially including PrEP (HIV negative). Large-scale trials in progress investigating strategies to promote the test and link portion of this formula include HPTN 065 (TLC-Plus) and HIV VCT and Linkage to Care in Uganda. The remainder of this chapter is allocated toward the second social behavioral factor driving TasP success—adherence to available, effective ART.

TasP Adherence

Shortly after the introduction of effective combination therapy for HIV in 1996 in the United States, discrepancies between efficacy (health benefits realized in clinical trials) and effectiveness (health benefits realized by PLWH on ART in clinical care) emerged [30]. Over a decade of targeted attention has identified ART adherence as one of the strongest determinants of viral suppression, and nonadherence as one of the main factors decreasing ART effectiveness in practice. ART adherence as a construct has changed considerably over this period of time, with dramatic advances in available agents and regimens offering less toxic and simplified regimens producing higher rates of adherence [31]. Currently, coformulated once or twice daily regimens are recommended, however, whether such regimens are available depends heavily on the resources available to add these more expensive drugs into formularies [32]. While simplified regimens offer marked advantages [33], nonadherence to these regimens still occurs. Research identifying rates of adherence required for rapid durable viral suppression suggests that high adherence to dosing intervals is critical across all regimens currently available [34].

As indicated in Fig. 5.1, adherence can be defined in terms of initiation (starting a prescribed regimen), execution (doses taken of doses recommended to be taken), and persistence (duration of being “on” therapy) [31, 35]. Inconsistent or erratic use of ART (imperfect or suboptimal execution of a regimen) can produce resistant strains of HIV that are no longer responsive to a given agent or class of agents and may exacerbate toxicity as drug builds and depletes in one’s system. Nonuse (nonpersistence) would not be expected to create the suboptimal drug pressure needed for HIV to develop resistant strains, but would lead to viral rebound and associated depletion of immune functioning. For durable suppression of viral load to occur and last over time, high execution and persistence are needed. Reviews of persistence

have suggested that 23–78 % PLWH in clinical care may discontinue medication for 48 h or more (see [34]). Estimates for loss from HIV care once initiated ranges from 16 % (based on estimates from South Africa of PLWH who started care but were lost from care before ART start [36]) to as high as 22 % failing to return for second HIV care appointment and 57.4 % subsequently drop from care over the first year (based on data from 12 different clinics in the HIV Research Network [37]). Reviews of ART execution suggest that about 40 % of PLWH on ART fail to adhere to regimens at levels of 90 % or greater [6], and depending on area and country, percent with viral suppression among those offered/on ART range from 64 to 72 % [14, 38, 40] to 90 % [41] 73 % [39].

From a "logic driven" or rational decision-making perspective, nonadherence and certainly complete cessation of available ART is counterintuitive. The drive for self-preservation and the certainty of death without ART would position adherence as of considerable benefit, nonadherence of unacceptable cost, and ART of high value. Indeed, this profile of valuation is not uncommon in early adopters of ART in settings where ART is newly made available. But history has demonstrated repeatedly that over time in a community and in individuals adherence appeared to deteriorate producing the discrepancy between clinical trial and "real world" estimates of adequate adherence. A sizable number of discrete (univariable) correlates of poor execution, poor persistence, loss to care, and ultimately the failure to suppress viral load have been identified in attempts to better understand what and how ART failures occur (Table 5.1). Correlates identified in Table 5.1 are not intended to be all inclusive, but do highlight common findings across many studies in terms of demography and other variables that often are related to outcomes of interest. From an intervention development perspective, however, these correlates vary considerably in terms of malleability (e.g., gender and age are not targets for interventions, whereas treatment beliefs can be targeted for change).

Correlates of adherence and viral suppression are valuable to establish as potential targets of intervention efforts or factors to use in targeting intervention approaches or programs. However, correlates can be misleading or obscure more meaningful understanding of ART adherence or TasP success. Moreover, several studies find no reliable predictor of sample-level viral failure (e.g., [42]), suggesting that conceptualizing adherence metrics on an individual and community level may be preferable. For intervention planning and comprehensive support strategies for consistent and adequate use of ART once prescribed, use of behavioral models of ART adherence is preferable to correlates.

Models of TasP Adherence

A number of behavioral models identifying critical determinants of ART adherence have been proposed and favorably evaluated, although none have yet to incorporate TasP fully. It is likely that knowledge of prevention benefits of ART if viral suppression is achieved and sustained would influence motivation toward adherence for many. The presence of such beliefs in the MSM community in the United States has been recognized since as early as 2002, where 53 % of HIV-negative and 43 % of

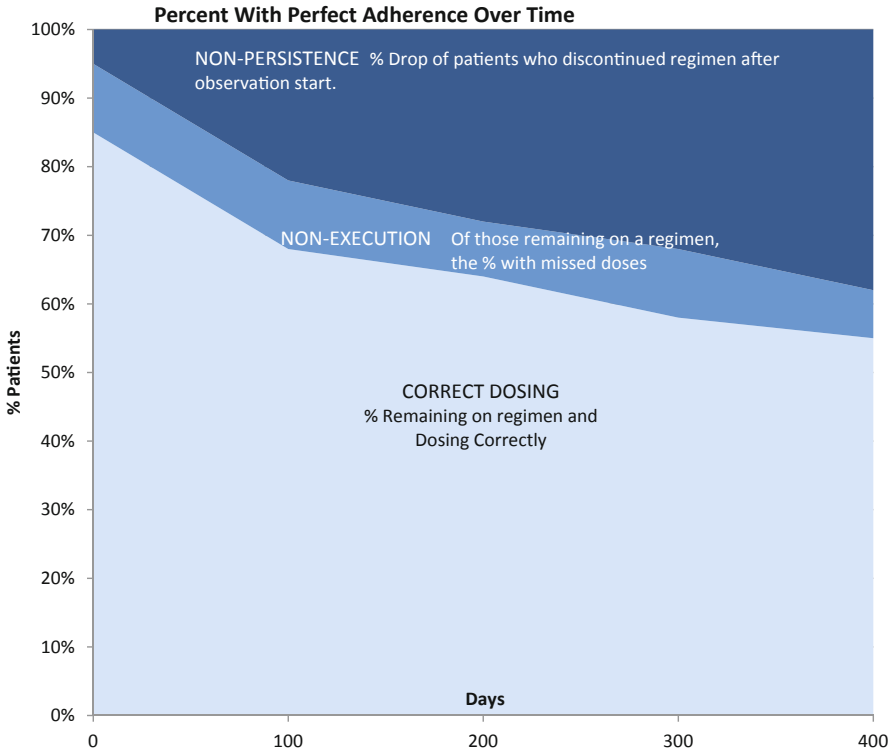

Fig. 5.1 Adherence: Initiation, execution and persistence. (Adapted from [34], available at http://arjournals.annualreviews.org/article/suppl/10.1146/annurev-pharmtox-011711-113247?file=pa-52-blaschke-fig1.pps)

HIV-positive MSM surveyed in San Francisco reported believing that chances for HIV transmission decreased when viral load was suppressed [43], however in the absence of definitive data, it was unclear if this belief would be considered accurate information about transmission or inaccurate. Rather, much of the data gathered early on about TasP beliefs and how they would translate into behavior focused on potential increases in HIV risk because of misplaced belief in no to low likelihood that those on ART could transmit HIV. The emerging evidence suggests that leveraging information about lower likelihood of onward HIV transmission with durable viral suppression to promote adherence may be an added strategy for ART adherence support that had to this point been largely avoided. Some caution, given that HPTN052 enrolled heterosexual couples and there is still debate about viral reservoirs that may be untreated by ART and underestimated by circulating viral load [44], is still warranted.

Of the models developed to characterize the main drivers of ART adherence, the Information Motivation Behavioral Skills (IMB) model [45, 46], Social Cognitive Theory (SCT) model [47], and the Cognitive Behavioral Therapy (CBT) model [48]

Table 5.1 Correlates of factors influencing TasP (execution, persistence, engagement in care, and viral suppression)

Poor execution (insufficient adherence) [109–112]
Younger age
Resource/food limitations
Time on ART (longer)
Disorganization (nonuse of pill boxes, reminders)
Low health literacy/low numeracy
Higher pill burden
Treatment beliefs
Negative ART-related feelings/fears
Nonpersistence [34]
Female
High VL
Substance abuse or d/o
Depression
Younger age
Shorter duration on ART
Lack of medication coverage/consistency of access
Experience of adverse medication events or toxicity
Higher medication dose or pill burden
Loss to care [36, 37, 39, 113, 114]
ART ineligibility
Male (sub-Saharan Africa)/Female (US)
Lower SES
Unemployment
Low entry CD4 count
Black (US)
Substance abuse or d/o
Detectable VL (VL failure) [38–41]
Public (vs private) insurance
Substance abuse or d/o
Female (US)
Black (US)
Lower entry CD4
Gaps in HIV care
Recent incarceration
Year ART prescribed (earlier lines of ART vs later)
HIV care at village/township clinic vs county-level hospital (China)

have received considerable attention (c.f. [7]). Models of health behavior that focus on motives, incentives, and values (e.g., return on investment), such as the Behavioral Learning Model (BLM) and applications of behavioral economics concepts, have also received increasing interest in research communities [49]. While these and other emerging models have unique assumptions, most recognize and define: (1) the influence of *beliefs* about the positive and negative consequences of adopting, and not adopting, a given behavior, (2) *perceived* vulnerability to a *risk* or threat, (3) estimated *self-efficacy* or confidence in one's abilities to enact behaviors or coping to avoid a threat or adopt a given health behavior, and (4) the specific *skills* sets

available to an individual that are requisite for implementing the health behavior across diverse personally relevant circumstances. Of these, motivation and skills are critical factors that permeate throughout literatures in health psychology and decision making, and motivation specifically (e.g., motivation to consistently use a given treatment or product) is an essential part of behavioral economics formularies and marketing approaches applied to health behavior. How one values ART (their access to it, their use of it, the costs of being on ART, side effects, disclosure, and so on) is a core factor in most, if not all, models of what characterizes uptake and sustained use of ART. Individual, societal, and structural influencers vary across models and disciplines, with most models assuming that the more difficult it is to implement behaviors needed to achieve and sustain suppressed viral load (e.g., linking to care, accessing ART, adherence to care, and ART) because of limited resources, limited service, or considerable HIV stigma, the higher one's motivation and skills need to be to succeed. Thus, the valuation of ART in the context of one's lived experiences with HIV and taking ART in the social fabric of life is fundamental to understanding ART adherence and sustained viral suppression. Establishing which of the many proposed factors are most influential of high valuation (or more comprehensively, high levels of motivation) and how people "act" on these beliefs continues to be an area of debate with no model of ART adherence proving far superior to others across diverse populations (c.f., [10]). Arguably, however, a one-size-fits-all model may be as infeasible as a one-size-fits-all intervention approach. Several well-supported models are available, each emphasizing different facets of motivation, social support, self-efficacy, affect and arousal, health literacy, belief structures, cost/benefit valuations, skill sets, and other components of decision making around self-care that offer researchers and clinicians a valuable opportunity to consider which models best represent adherence in their particular sample or cohort. The recommendation is to use a model, not necessarily one particular model, but a model that is articulated so that outcomes of interest, proximal ones like positive beliefs, HIV knowledge, use of reminder strategies, or disclosure to significant others and more distal ones like sustained adherence and suppressed viral load, can be targeted and monitored.

Recently, social behavioral models have expanded to include a relatively neglected but highly influential set of behaviors now known to impact rapid and durable viral suppression—retention in HIV care. Because viral suppression requires access to ART and access to ART requires attendance in HIV care, models identify factors promoting (or hindering) linkage and ongoing engagement in HIV care have recently been proposed. One such model is an adaptation of Anderson's Behavioral model [50] and positions viral suppression as the result of factors in the environment (e.g., the contextual environment [rural/urban, local community] and health care environment [clinic (wait times), system (available support services) and provider (trust) factors]) and characteristics of the patient (e.g., predisposing factors (demography), enabling factors (social support), and perceived need for treatment) leading to health promoting behaviors (care use, adherence) [51]. Another model recently proposed adapts the IMB model (the situated Information Motivation Behavioral Skills Model of Care Initiation and Maintenance-sIMB-RIC) [52], such that retention in HIV care

is proposed to be the result of accurate information, personal and social motivation and a specific set of behavioral skills all situated to the cultural, structural, and affective-cognitive context in which HIV care is negotiated for a given individual. To date, the sIMB model has received preliminary support [53]. Where the Behavioral model provides a comprehensive characterization of the dynamics of entry into and retention in HIV care and suggests areas which should be targeted for improvement, the sIMB-RIC model provides detailed direction on specific factors to target when working with a given individual in a given community or system of care. A number of ongoing studies examining the determinants of linkage and retention in HIV care are in the field and testing novel, theory-based intervention approaches. Presently, both the theory and intervention approaches for linking and retaining individuals in HIV care are in their naissance. However, this evidence base is expected to grow substantially over the next several years.

One of the critical roles of theory is in directing the targets of intervention efforts to support or improve these behaviors. Any effective strategy used to support adherence presumably "works" for systematic reasons and behavioral and psychosocial models offer insights into what those reasons may be. Intervention mapping [54] and other strategies to identify quality metrics for improving adherence or viral suppressing rely on a clear articulation of the pathways through which adherence (or viral suppression) is achieved. Moreover, using a guiding theory to develop intervention approaches has been in association with stronger intervention outcome effects (e.g., [55]).

In short, there is no one correct model and models share many core constructs. Articulating which factors are relevant to one's population and how they interrelate is a critical exercise that can readily identify factors essential to adherence that have no clinic or community-level support (suggesting intervention targets) or those that are available but are not well situated within the model of adherence (suggesting misallocation of resources). Process approaches are available that offer systematic steps to evaluating services, developing improvements on current services and support strategies, and evaluating them for effectiveness allow researchers and clinicians alike to use a scientific method in providing best practice services [56]. Readers are strongly encouraged to sketch out their working models of adherence and engagement in HIV care more globally for their populations and position the support services and strategies available within that model. Even informal evaluation of where intervention efforts "hit" or "miss" critical adherence facilitators or deterrents can provide substantial guidance.

Strategies to Promote TasP Adherence

Recently, international recommendations for retention and ART adherence monitoring and support were issued [32]. Summarized in Table 5.2, these recommendations are strongly in favor of basic monitoring, navigational support, providing education

Table 5.2 Recommendations for monitoring and support of HIV care utilization and adherence [32]

Entry into and retention in HIV medical care
Systematic monitoring of successful entry into HIV care is recommended for all individuals diagnosed with HIV (II A)
Systematic monitoring of retention in HIV care is recommended for all patients (II A)
Brief, strengths-based case management for individuals with a new diagnosis is recommended (II B)
Intensive outreach for individuals not engaged in medical care within 6 months of a new HIV diagnosis may be considered (III C)
Use of peer or paraprofessional patient navigators may be considered (III C)
Monitoring ART adherence
Self-reported adherence should be obtained routinely in all patients (II A)
Pharmacy refill data are recommended for adherence monitoring when medication refills are not automatically sent to patients (II B)
Drug concentrations in biological samples are not routinely recommended (III C)
Pill counts performed by staff or patients are not routinely recommended (III C)
EDMs are not routinely recommended for clinical use (I C)
ART strategies
Among regimens of similar efficacy and tolerability, once-daily regimens are recommended for treatment-naïve patients beginning ART (II B)
Switching treatment-experienced patients receiving complex or poorly tolerated regimens to once-daily regimens is recommended, given regimens with equivalent efficacy (III B)
Among regimens of equal efficacy and safety, fixed-dose combinations are recommended to decrease pill burden (III B)
Adherence tools for patients
Reminder devices and use of communication technologies with an interactive component are recommended (I B)
Education and counseling using specific adherence-related tools is recommended (I A)
Education and counseling interventions
Individual one-on-one ART education is recommended (II A)
Providing one-on-one adherence support to patients through one or more adherence counseling approaches is recommended (II A)
Group education and group counseling are recommended; however, the type of group format, content, and implementation cannot be specified on the basis of currently available evidence (II C)
Multidisciplinary education and counseling intervention approaches are recommended (III B)
Offering peer support may be considered (III C)
Health system and service delivery interventions
Using nurse- or community-based care has adherence and biological outcomes similar to those of doctor- or clinic counselor-based care and is recommended in underresourced settings (II B)
Interventions providing case management services and resources to address food insecurity, housing, and transportation needs are recommended (III B)
Integration of medication management services into pharmacy systems may be considered (III C)
DAART is not recommended for routine clinical care settings (I A)
Pregnant women
Targeting PMTCT treatment (including HIV testing and serostatus awareness) improves adherence to ART for PMTCT and is recommended compared with an untargeted approach (treatment without HIV testing) in high HIV prevalence settings (III B)
Labor ward-based PMTCT adherence services are recommended for women who are not receiving ART before labor (II B)

Table 5.2 (continued)

Substance use disorders
Offering buprenorphine or methadone to opioid-dependent patients is recommended (II A)
DAART is recommended for individuals with substance use disorders (I B)
Integration of DAART into methadone maintenance treatment for opioid-dependent patients is recommended (II B)
Mental health
Screening, management, and treatment for depression and other mental illnesses in combination with adherence counseling are recommended (II A)
Incarceration
DAART is recommended during incarceration (III B) and may be considered upon research to the community (II C)
Homeless and marginally housed individuals
Case management is recommended to mitigate multiple adherence barriers in the homeless (III B)
Pillbox organizers are recommended for persons who are homeless (II A)
Children and adolescents
Intensive youth-focused case management is recommended for adolescents and young adults living with HIV to improve entry into and retention in care (IV B)
Pediatric- and adolescent-focused therapeutic support interventions using problem-solving approaches and addressing psychosocial context are recommended (III B)
Pill-swallowing training is recommended and may be particularly helpful for younger patients (IV B)
DAART improves short-term treatment outcomes and may be considered in pediatric and adolescent patients (IV C)

and counseling, and access to adherence tools. The specific kinds of education and counseling strategies most effective, however, remain difficult to discern from the available evidence base.

What is clear, is that adherence support is likely best positioned when tailored to be responsive to issues specific to an individual in a specific context (community and system of care) [42, 57, 59]. This is reflected as will in the ever increasing number of diverse interventions demonstrating efficacy in improving adherence and/or rapid and durable viral suppression. Similar to the compendium of effective behavioral interventions (EBIs) for HIV prevention, CDC added effective (evidence-based) adherence support interventions to their compendium of intervention packages (http://www.cdc.gov/hiv/topics/research/prs/ma-chapter.htm). This resource provides packaged intervention approaches found effective under rigorous criteria in the United States, as well as the kind of material and assistance required for implementing one of these intervention approaches. A number of different kinds of approaches (individual discussion based, technology delivered, group discussion based) have been effective, and a number of metaanalyses highlight discrete aspects of interventions that provide significant impact on adherence [8–10]. As noted in the adherence guidelines in Table 5.2, in order to promote adherence, retention in HIV care must also be supported. The evidence base is only just emerging in terms of strategies for promoting linkage and retention in HIV -care.

While CDC provides complete intervention packages, a number of discrete strategies can be extracted from published guidelines, meta analyses, and the literature

base more broadly for consideration. Table 5.3 presents the main findings of a recent comprehensive review [56] that compiled discrete recommendations for adherence support strategies that could be implemented in practice and as part of research protocols or designs. Readers will note that some are highly specific (use of education material) and others are general (support self-efficacy). The recommendations are provided to stimulate thought around standard of care practices (eg., which recommendations are already being addressed, which are not), as well as protocol-defined practices in research (which aspects are addressed in research protocols or design, which are not). Implementation of any of these recommendations requires additional development to identify how a given facilitator or barrier would be addressed, based on available resources and relevance of issue in one's population or community. Importantly, monitoring impact of any implemented strategy is recommended.

Cautions

Clearly, the advances in our understanding of and confidence in treatment offering potential for prevention of HIV transmission are remarkable and deserving of the reinvigoration of efforts to make ART access truly universal and available to all PLWH. However, it is arguably not so much "Treatment as Prevention" as it is "Suppression for Prevention" that is the key to using treatment with ART as an effective HIV-prevention strategy, operationalized as rapid durable viral suppression. As slight as this shift in terminology may appear, the foci differ substantially in terms of where to place aggressive efforts. Treatment emphasizes the prerequisite of needing to have widespread, uninterrupted availability of effective ART. As a behavioral scientist, there is an implied over simplicity to "TasP" that leaves certain discomfort. Which is not to say that TasP is simple by any means—making ART available to all individuals diagnosed HIV positive is formidable and intensely complex. Rather, the discomfort centers on potential prematurity in defining success with TasP. It is not enough to treat. For each individual gaining access to ART, they may or may not initiate ART and if initiated there is variability in rapidly securing or sustaining viral suppression. The odds of viral suppression are decreased with delays in initiation of ART, in the presence of even slightly below-perfect execution, inconsistent execution, nonpersistence, and loss from or sporadic use of care. The intent to treat findings from HPTN052 strongly support the added benefit of offering ART, but likely present an optimistic picture of effects given the intensive adherence support offered that may not replicate in real-work ART offering. Intent to treat will be insufficient to produce the desired AIDS-free generation. Promoting linkage to care, retention in care, and adherence to ART will produce the desired effect of viral suppression and it is that combination package (biobehavioral) that should be targeted for roll-out (c.f., [60, 61]). Too often the focus of discussions concerning TasP focus on the criteria for ART-start and availability with little reference to the realities of the psychosocial factors (used here to reflect factors that rest in community, culture, and networks and not just a single individual) that will ultimately play a critical role

Table 5.3 Areas and strategies for ART adherence support and practice. (From and See [56] for sources)

Area	Recommendation
General	Assess factors that influence adherence/assess barriers and suggest strategies to overcome them
General	Implement targeted interventions (address barriers; problem-solving support)
General	Support development and use of discrete specific skills (over general messaging on importance of or need for perfect adherence)
General	Provide one-on-one adherence support through one or more counseling approaches
General	Provide group education/group counseling support in a format and to cover content relevant to a specific patient population
General	Target and enhance self-efficacy for adherence
General	Assess and address common misconceptions and cultural beliefs regarding ART
General	Review and adopt an evidence-based intervention package (e.g., CDC's EBI)
General	Mobilize community support
Engagement	Invite patients to actively contribute to care and treatment planning
Engagement	Facilitate positive interactions at point of care (positive patient–provider relationships)
Access	Ensure consistent access to ART medications
Monitor	Monitor levels of adherence
Monitor	Presence of adverse events when starting ART and over time
Monitor	Collect self-report data and medication refill data routinely [pill counts, drug concentration, and electronic drug monitoring not recommended for routine use in practice]
Monitor	Ask about adherence at each clinical visit using open-ended questions (Please tell me how you took your medications over the last 3 days)
Monitor	Identify type of nonadherence (prescription refill, timing/quantity, or food requirement/special instructions nonadherence)
Monitor with feedback	Collect adherence data and use to provide targeted feedback
Monitor with feedback	Collect and feedback CD4 and viral load
Regimen	Simplify regimen-effective once-daily or coformulated regimens are preferred
Education	Explain the regimen
Education	Use of material (figures, pictures, so on) to promote transfer of information and promote memory and understanding
Education	Explain role of adherence, consequences on nonadherence and resistance
Education	Provide brochure or written information (general and specific to one's regimen for when to take what)
Education/Skills	Discuss side effects and management
Navigation	Link to services; treat concomitant conditions
Navigation for unmet needs	Offer case management and resources for food insecurity, housing, and transportation
Patient-centered care	Adopt regimens that are tailored to patient's lifestyle and as "simple" as possible

Table 5.3 (continued)

Area	Recommendation
Patient-centered care	Establish readiness for ART before prescribing
Patient-centered care	Use multidisciplinary treatment team approaches to consolidate treatment of multiple conditions and use of combined services
Patient-centered care	Avoid judgmental or punishing interactions in discussing and reacting to nonadherence
Patient-centered care	Adopt neutral stance in discussion of adherence (avoid overly enthusiastic or overly negative reactions to reported adherence)
Patient-centered care	Support maintenance of high rates of adherence
Patient-centered care	Encourage patient accessing clinic if and when questions arise via phone contact
Patient-centered care	Ask about experiences with taking ART and refrain from "solving" or fixing reported barriers. Allow patients to tell you their strategies
Patient-centered care	Avoid leading and closed questions about adherence ("You are taking all you meds right?")
Patient-centered care	Follow-up with adherence plans or difficulties with adherence between appointments (e.g., via phone)
Patient-centered care	Deliver medications to home
Patient-centered care	Increase resources at care through task shifting so that more ART prescribers are available
Patient-centered care	Establish a care team that is accessible and is perceived as trusted (establish trusting relationships with patients)
Social	Support development of social support/enlist support of those in social networks
Social	Facilitate connections with peers who are on ART
Social	Facilitate sharing among long-term ART users about their experiences (enlist collaborations with CBOs and the community)
Social (persuasion)	Encourage adherence (communication and messages delivered to support adherence)
Tools	Reminder devices
Tools	Communication technologies (interactive text messaging)
Tools	Encourage use of pillboxes, diaries, cell phone alarms as needed and as adjuncts to other adherence support strategies
Skills	Plan ahead for changes in routine, weekends, and holidays
Skills	Establish a routine; plan dose taking around routine, daily events, and cues; develop medication-taking schedules
Skills	Recommend storing/carrying extra dose/doses
Targeted intervention	Increase intensity of intervention and follow-up for those struggling with adherence
Targeted intervention	Tailor intervention approaches to stage of ART use (prior to initiation, initiation, and long-term use)
Targeted intervention	Incorporate routine HIV testing among expecting mothers and provision of ART for PTMTCT
Targeted intervention	Treat comorbid conditions—opiod-dependent patients on ART should be offered methadone or buprenorphine as part of comprehensive care; screen and treat for mental health conditions such as depression as part of routine care
Targeted intervention	Offer directly observed therapy for substance using populations (independently or in conjunction with methadone maintenance and for incarcerated individuals); DAART is not recommended for general population

in successful prevention of onward HIV transmission. Psychosocial, cultural, and behavioral factors would likely be better recognized if we referred to this prevention approach as "Suppression for Prevention" as the role of a number of essential self-care behaviors in viral suppression is well established.

Preexposure Prophylaxis (PrEP)

The remarkable discoveries supporting the safety and efficacy of oral PrEP for HIV prevention have generated both enthusiasm and caution in research, practice, and public forums. Results from several trials provide clear support for TDF/FTC daily oral PrEP [62–64]. However, concerns over the viability of this approach in producing individual and community levels of protection consistently identify adherence [65, 66] as a critical component that can promote or dilute potential efficacy. A number of demonstration projects are underway in the United States and international projects are also ongoing (discussed later). Based on data available and lessons learned to date in PrEP trials and neighboring areas of research, potential approaches to conceptualizing and providing support for as-recommended PrEP use are provided. As previously mentioned, PrEP use presented in this review is specific to situations where PrEP is available to potential users at manageable costs and with consistent access.

PrEP Adherence

Guidance for use of oral PrEP with MSM and heterosexual individuals at risk for HIV infection prioritize monitoring and supporting adherence [67]. In the major PrEP trials recently analyzed (Table 5.4), self-report of product use (blinded study drug), as well as clinic-based product counts, suggested high rates of adherence to study product, while drug exposure based on evaluation of drug levels ranged from lower than 26 % (e.g., FEM PrEP [68]) to upward of 70 % (e.g., Parnters PrEP [62]). Thus, there is variability in rates of product use in different trials, dramatically so in some cases. Variability in rates of drug detection has also been observed by research site; in the iPrEx RCT where the vast majority of samples from US participants had drug detected whereas participants from other locations, on average, did not [69, 70]. As can be seen in Table 5.4, efficacy is strongly tied to rates of drug exposure estimated by drug levels, and that self-report-based estimates of adherence grossly overestimated use of study product in most trials. For a number of reasons, this profile of findings has generated concern over how accurate these estimates of blinded study product use (in a context where participants appeared reluctant or unable to report product nonuse) may be in estimated actual PrEP use (uptake or adherence to a known active agent with known efficacy in preventing HIV infection). From a social behavioral perspective, nonuse of study product may have suggested an overall distrust of study products

Table 5.4 Recently completed PrEP double-blinded randomized control efficacy trials

Trial name	Locations	Population	Intervention arms	Efficacy results	Adherence results
CAPRISA 004 [115]	South Africa	899 women	1 % tenofovir gel taken pre and post sex	39 % overall 54 % among those estimated as adherent based on product returns	38 % with > = 80 % product return based adherence 98 % with drug levels in case controls sampled
FEM-PrEP [68]	Kenya, South Africa, and Tanzania	2,120 women	Daily oral TDF/FTC	6 %/Undetermined owing to low rates of product use	95 % self-reported usually or always using product ~26 % with drug levels detected 44–51 % with drug levels in case controls
iPrEx [63]	Brazil, Ecuador, Peru, South Africa, Thailand, United States	2,499 MSM and transgender women	Daily oral TDF/FTC	42 % overall efficacy 73 % among those with > = 90 % estimated adherence 92 % among those with drug detected	47–65 % self-reported perfect adherence, average 91–96 % adherence rates ~51 % with drug levels detected in matched case controls Dramatically higher drug levels in US cohort (~97 % of participants had drug levels detected) [70]
Partners n PrEP [62]	Kenya, Uganda	4,758 couples with one person HIV-negative and one person HIV-positive	Daily oral TDF Daily oral TDF/FTC	67 % TDF overall 86 % TDF among those with drug detected 75 % TDF/FTC overall 90 % TDF/FTC among those with drug detected	97 % on unannounced pill counts~67 % with TDF drug levels detected in case controls ~75 % with TDF/FTC drug levels

Table 5.4 (continued)

Trial name	Locations	Population	Intervention arms	Efficacy results	Adherence results
TDF2 Botswana [64]	Botswana	1,200 men and women	Daily oral TDF/FTC	62 % overall 78 % among those with no drug supply interruptions	84 % adherence based on pill counts 79 % with drug levels detected
VOICE [116]	South Africa, Uganda, Zimbabwe	5,029 women	Daily oral TDF Daily oral TDF/FTC Daily 1 % tenofovir gel	−49 % TDF −4.2 TDF/FTC 14.7 % gel	~90 % rates of adherence reported across arms by self-report 28 % samples with recent TDF use (in past 2 days) via drug levels detected 29 % samples with recent TDF/FTC use (in past 2 days) via drug levels detected 22 % samples with tenofovir gel use via drug levels detected

Blinded RCT participants assigned to active drug or placebo without knowledge (by participant or staff) of which they are getting*TDF/FTC* coformulated tenofovir disoproxil fumarate/emtricitabine (single tablet)

and a negative valuation of adhering to them (e.g., low value, high cost). Individuals adopting PrEP as a prevention strategy may have a more positive relationship with PrEP and adherence. Conversely, adherence estimated in the treatment literature or in other oral and topical prevention medications would suggest that adherence may prove to be difficult for a sizable portion of individuals [71]. Simply stated, rates of PrEP adherence among those who adopt it as a prevention strategy are unknown, but the field has considerable reason to be both worried and cautiously optimistic.

Because data concerning open-label PrEP adherence is only now being collected, we similarly do not yet have a profile of potential correlates of PrEP adherence identified. However, correlates of adherence to blinded study product identified in PrEP RCTs have included age (older), recent potential risk exposure (e.g., recent report of condomless sex), and low/no binge drinking or methamphetamine use [72, 73]. These are similar to the discrete correlates for ART adherence discussed earlier.

PrEP adherence may share similarities with ART adherence, but increasingly the field is producing data that differentiate the operationalization of adequate adherence (how much and how often do you need to use the drug to get the benefit) between these two uses of ARVs. ART adherence is well understood as requiring high to near perfect daily use to avoid negative outcomes (e.g., viral rebound, resistance). PrEP adherence needs to provide "enough" drug to thwart infection "if" exposure does occur in order to avoid negative outcomes (e.g., HIV infection). Whereas initiation, execution, and persistence are the hallmarks of ART adherence, PrEP use is increasingly defined by sufficient (e.g., taken to some criteria but perhaps not daily) oral PrEP dosing to provide "coverage" at the time of potential exposure. The basis for CAPRISA 004's (Table 5.4) BAT24 (one gel application before sex, one gel application after sex, and no more than two per 24-h period) rests on the balance between drug coverage per potential exposure. Recent work with oral PrEP suggests that for MSM, 4 days a week of PrEP dosing may provide protection that is essentially equivalent to daily dosing [74], however, additional support for these findings is needed before adoption of nondaily regimens can be confidently implemented. Emerging concepts in PrEP are under evaluation (see ongoing studies in Table 5.5). For example, "coverage" is an emerging concept that is distinct from adherence and has been variously defined as taking a PrEP dose within the 4 days prior to a condomless sex event and 24 h post the event (HPTN067 [75]) or the day before, of, and post the condomless event (HPTN 069 [76]). Other variants have been proposed but the idea of nondaily dosing has considerable appeal and is under evaluation for feasibility in HPTN067 and tolerability in iPrERGAY [77]. As data emerge in this area, models of and strategies to support nondaily oral PrEP use may be needed, as daily PrEP and intermittent PrEP will certainly pose unique challenges. Similarly, working models of sex-dependent gel use, nonremoval of slow release vaginal rings, and use of rectal micribicides will need articulation.

Table 5.5 Common and promising strategies for promoting PrEP use

Information messaging	
Goal—Enhance knowledge and literacy concerning health behavior and presence of threat/risk	
Examples	Standardized or media-delivered information Tailored messaging One-way informational texts
Pros	Basic information must be provided as standard of care Information about efficacy and risks can influence motivation to use PrEP Messages that contain the right amount of threat and clear strategies to manage it can be effective in decision making Information can be standardized and disseminated through media or texts with minimal costs or resources Accurate information/low misinformation may be influential of PrEP uptake and use
Cons	Information is likely insufficient to promote behavior change or adoption when motivation or "readiness" in not also high Information intended to heighten perceived risk to HIV or negative consequences to inadequate PrEP use can "backfire" leading instead to the messages being ignored The same information repeated at each visit can become stale, predictable, and noninfluential "Canned" or standardized information may lack the personal relevance required to have an impact on behavior Approaches heavily based on information may undervalue other critical determinants of health behavior adoption (e.g., motivation, efficacy, skills, social and structural support, and so on)
Recommendations	Whereas being well informed about PrEP is likely to be an important factor in uptake and use, it is not expected to be the main influencer of consistent or adequate rates of adherence for most users. Conversely, misinformation about requirements of use (e.g., cannot be taken when drinking alcohol) can seriously limit one's adherence Information about how PrEP works to prevent infection, recommended dosing regimen to produce protection and the meaning and limits of protection, should be provided Optimizing information and its delivery requires careful attention to cultural and community-based beliefs about PrEP and ongoing monitoring of changes in common knowledge and media presentations of PrEP as new results and findings are released Using information that maximizes personal relevance and utility is recommended.
Reinforcement and contingency	
Goal—behavior promotion through external provision of positive outcomes to its adoption and negative outcomes to its nonadoption	
Examples	Praising or rewards for adherence Cash incentives for objectively measured adherence Negative (or positive) social consequences of nonuse/use (shaming, moralizing, or reprimanding)
Pros	Reasonable evidence base for use of reinforcement to promote a behavior, particularly if immediate and in response to an observed behavior May heighten threat perception or internalization of positive praise from others into internal reinforces Recognizes role of social context and influence of important "others" Common practice—a natural part of social interactions involves influencing behavior through approval and disapproval responses—easy to implement (difficult to avoid)

Table 5.5 (continued)

Cons	Those providing reinforcement typically are not able to observe and respond to a self-directed behavior occurring outside of the clinic or program—thus what gets reinforced is often self-report and not actual behavior
	Reinforcement runs the risk of degrading internal attributions for performing a behavior (limiting rather than enhancing internal motivation)
	Perceived disappointment or acceptance from providers or team members on the basis of use or nonuse can create a prescriptive atmosphere, where one may become reluctant to discuss potential difficulties
Recommendations	Implementation of negative social consequences based on real or perceived nonuse should be either avoided or implemented only in the context of well-developed strong interpersonal relationships
	Use of positive social interactions (praise) in response to reported PrEP use should carefully consider whether reported or actual adherence is being promoted
	Carefully monitor the kinds of social and structural reinforcement and contingencies overtly adopted or implied in demonstration trials, and consider both their viability and intended and unintended impact on participants/PrEP users
Theory-based approaches	
Goals—Mixed—dictated by assumptions of the model (typically some constellation of motivation, self-efficacy, and skills) as well as the delivery model used to address these "drivers" of health behavior adoption	
Examples	Strategies targeting factors identified by social behavioral models targeted through counseling, community or structural models delivered in individual one-on-one discussions, groups based education or counseling, or technology (phone, text, websites) by diverse deliverers (health care team, peer, media).
Pros	Across diverse health behaviors, theory-based interventions have numerous advantages over a-theoretical approaches, including higher efficacy in some cases
	Use of health behavior models to identify the proximal factors that lead to and support as-recommended PrEP use leverages decades of social science research and provides clear markers for monitoring and evaluating success
	Models for communication and counseling have similarly extensive practice and research profiles, and provide guidance for promising approaches for PrEP use support
	Promotes a tailored, individualized approach
Cons	Requires adequate training in the explanatory or delivery model for interveners, which may be extensive depending on the particular approach
	Evidence-based models and model-based interventions for PrEP use are not presently available
	Adoption of delivery approaches that are based on MI or applications of it require that some other strategies, such as heavy threat messaging or persuasion through social reinforcement (negative or punishment), *not* be used (they would be expected to counteract benefits of person-based or strengths-based approaches)
	Potential for "over kill" (intervention intensity exceeding PrEP user's needs) if counseling or group-based approaches are excessively time consuming or otherwise burdensome to PrEP users

Table 5.5 (continued)

Recommendations	At minimum, programs and projects providing PrEP should be aware of the social behavioral models of health behavior adoption and seek to identify or adapt a model that can guide promotion of PrEP use in their communities
	Efforts to streamline and create brief, feasible, low-cost applications of theory-based PrEP use support strategies are needed
	Theory-based approaches that require basic training for approach implementation by individuals with diverse backgrounds (e.g., peers, lay counselors, or available staff) are preferable to ones that require high levels of training or specific backgrounds
	Given the availability of and support for a number of person-centered approaches, these kinds of models of interaction should be considered for adoption
Community campaigns	
Goal—Promote social acceptance and approval of an innovation for uptake in targeted population through dissemination of accurate information, building of positive perceptions and developing alliance between prescribing programs and surrounding communities	
Examples	Community events/campaigns targeting awareness and promoting social support
	Community events/campaigns to decrease stigma
	Media spots, special events, talks/presentations in local venues
Pros	Innovations require community support for adoption
	Events and awareness building are likely essential factors for PrEP uptake and normalize PrEP as a prevention strategy *not* indicative of being a "high-risk" individual
	Efforts to reduce HIV and MSM stigma may decrease privacy concerns that may negatively impact PrEP use
Cons	Can be costly
	Requires monitoring and reinvigoration over time and in light of new results and findings
	Does not ensure that individual PrEP users will benefit directly from these strategies
	Requires careful preparatory work to determine best venues for activities and to identify community-level concerns
Recommendations	It is not clear what community reactions will be the programs that offer PrEP launching in their communities. Considerable diversity in opinions about the benefits of ARVs for prevention is already mainstream in the United States
	Community-based strategies to raise awareness of PrEP for prevention and disseminate accurate information about it would be worthwhile and likely a necessity for the ultimate success of PrEP
Technology	
Goals—Mixed—Reminder prompts provide cues for dosing, motivation messaging targets enhanced motivation through appeals to vulnerability, efficacy, and positive beliefs, and interactive text messaging and web-based applications target the provision of tailored, as needed, self-directed support	
Examples	Reminder text messaging
	Interactive text messaging
	Websites or interactive computer programs
	Media (social media, audio-visual)

Table 5.5 (continued)

Pros	Once developed, audio-visual and other media-based strategies for information dissemination can be implemented at low cost
	Texts and web-accessed support can be delivered when and as-needed, outside of the clinical care appointment
	Interactive messaging may foster a sense of collaboration with prescribing program and health facilities
	Interactive, communications and social media are common in the United States and may offer methods to work with PrEP users that are ubiquitous in the daily life of many PrEP users
Cons	High development costs for high-end media or websites, and interactive programs require confidentiality measures
	Texts as reminders or one-way persuasion may be considered intrusive by recipients or otherwise lose effects as people get used to receiving them
	Persuasion that is not tailored to one's risk thresholds and efficacy can "back fire"
	Interactive messaging requires trained staff to respond to texted requests for assistance, which may be costly
	Communication and internet devices can be lost or stolen.
Recommendations	Leveraging technology to support health behavior is clearly an emerging area of interest across a number of domains. Simple strategies including texting reminders for upcoming care visits and need for renewal of prescriptions seems well warranted. Text-based outreach requires additional research
	With the prevalence of technology in the United States, it is likely that these approaches specifically for PrEP use will be the focus of targeted research in the near future
Monitoring with feedback	
Examples	Drug-level feedback
	EDM review and feedback
Pros	Provides PrEP users with external information about product use that can lead to "teachable moments" or opportunities to explore behaviors leading to a given result
	If individuals have memory problems or lifestyles that make recall of doses taken and missed difficult to construct, assessment-based findings can help the individual to realize potential problems or successes in daily dosing
	Provides interveners with data that can be used to direct or target PrEP use support conversations
Cons	Still need to determine which levels of drug are needed to provide high rates of HIV protection, thus presently these results might be misleading
	Showing PrEP users their "non-adherence" can become confrontational or demoralizing. Care and skill in using these data to promote exploration and productive conversations is needed
	Unlike treatment for managing chronic conditions where the threat of deterioration of the disease is constant, use of PrEP may be self-adjusted to reflect times of sexual inactivity. Coverage in this case would be good while "adherence" would be poor
	Sex-dependent PrEP use requires the addition of self-reported sex events and thus cannot be entirely objective

Table 5.5 (continued)

Recommendations	There is something inherently appealing about getting a glimpse of what may be happening in the "real world" if a participant in a demonstration project or PrEP user, and drug levels and monitoring of bottle openings has the appeal of feeling "objective" and accurate. Numerous approaches include an assessment of risk or "adherence" to guide counseling discussions but there is consistent concern over whether or not people alter their report or product returns to avoid appearing nonadherent. Monitoring of drug levels may offer an opportunity to use something other than self-report but ultimately can lead to a situation where the two are in conflict and skill will be needed to move that discrepancy into a productive opportunity for behavior change or shared decision making If drug-level monitoring feedback is used, it should be provided as close as possible to the actual blood draw to be most relevant, provided with information about the limitations of the results in terms of not presently being able to quantify level of protection, and great care and skill in providing discrepant results should be exercised. EDM feedback should similarly use an approach where limitations in this measure are clearly discussed, and additionally for EDM patterns of use and nonuse over time can be explored for events, determinants, and situations that may have contributed to each pattern.

Models of PrEP Adherence

Modeling open-label PrEP use with behavioral theory is a relatively new area, as open-label PrEP use became a reality, first in the United States, only in mid-2012 [78]. The most commonly adapted and adopted model for supporting blinded study product use in PrEP trials conducted to date is the IMB model [46], which guided iPrEx RCT, VOICE, and FEM-PrEP [79] and also has been articulated to microbicide gel use [80]. In Partners PrEP, an adapted CBT model was used [81] and results from the adherence support approach using CBT should be released sometime in 2013. In iPrEx OLE [82] as well as HPTN067 [75], an IMB model was developed to identify the kinds of information, motivation, and skills that would promote PrEP use in the context of other prevention strategies (e.g., HIV testing, condom use) and the local environments and resources in which a given person negotiates PrEP use. The brief counseling check-in used in iPrEx RCT (Next Step Counseling [83]) was later adapted to a discussion that targeted both non-PrEP prevention strategies and PrEP adherence for prevention in a single person-focused conversation promoting sexual health (integrated Next Step Counseling: iNSC [82]). While feasibility and acceptability of NSC from a counselor's perspective was strong, efficacy of NSC-based approaches could not be determined owing to late initiation in the RCT and lack of a time-controlled comparison group. The LifeSteps approach [84] used in Partners PrEP was implemented with participants who were non-adherent based on unannounced home-based pill, and appeared to improve adherence in this group [73, 81]. However, with no comparison condition it is unknown if rates would have been higher or lower without the intervention.

The models adopted to date to explain open-label PrEP use, as opposed to blinded study product use, require examination for overall ability to characterize PrEP use over time. With noteworthy challenges in measuring actual PrEP use [85], studies that leverage state of the art measurement tools and behavioral survey tools are needed to provide specific guidance on which factors are most influential of PrEP adherence. The models previously discussed for ART adherence have potential for adaptation to PrEP use, though as mentioned what type of PrEP (gel, ring, oral tablet, injection) and populations using it (women, men, MSM) will determine the specific drivers and barriers. This is an exciting active area of inquiry that will burgeon over the next decade.

Strategies to Promote PrEP Adherence

Although guidelines for use of PrEP include providing adherence support, there are few resources suggesting specific guidance for which kinds of strategies might be considered in providing PrEP adherence support. An overview of approaches adapted from ART adherence and other prevention literatures, examples, pros and cons and recommendations are grouped into general categories (ordered by their anticipated frequency of use) is provided in Table 5.5. Obviously, strategies already identified in Table 5.3 may apply and there is some duplication of recommendations between Tables 5.3 and 5.5. In Table 5.5, strategies emanate from what has been "tried" in blinded clinical trials and what providers and projects might consider when adopting any one of these approaches. They are not evidence-based as the evidence-base is not yet developed for PrEP adherence. Readers are encouraged to consider their model adopted as an explanation of PrEP adherence for their communities and apply the logic of processes such as intervention mapping to weight the practice- and practical-evidence for promise or futility of any single strategy.

The individual strategies offered and in Table 5.5 are grouped for ease of review into information/education based (common in all trials and part of guidelines for ART adherence support), reinforcement and contingency based (common strategy used in clinical trials and growing interest in contingency-based approaches are clearly emerging in linkage to HIV care and outcomes associated with ART adherence), theory-based approaches (including person-centered delivery, innovations in technology and peer or counselor discussions targeting one or more variables in a specific model of PrEP adherence), community campaigns (common in large RCTs and critical in open-label PrEP awareness and uptake), technology-based interventions (emerging novel intervention approaches currently under evaluation in several demonstration projects), and monitoring (either with plasma or dried blood spot drug levels or electronic drug monitoring [EDM] of dose taking) as an intervention strategy (currently in use as drug-level feedback in iPrEx OLE and as an intervention triaging tool in one of California's AIDS Research Program sponsored programs (the PATH project) launching in Los Angeles (http://www.californiaaidsresearch.org/funded_research/abstracts/2012_wohl.html).

Background literature relevant to recommendations in Table 5.5 are provided later with an emphasis on strategies to promote open-label PrEP (versus blinded study product use in RCTs which likely involve a host of additional considerations as the target is compliance to a study protocol versus adherence to an effective HIV prevention strategy).

Information

All clinical trials and demonstration PrEP projects provide information about PrEP and regimen requirements. Information often serves two purposes; to promote knowledge and literacy, which has been associated with adherence in other domains [86] and as a method of persuasion by presenting information intended to promote adherence. Providing education around PrEP may be challenging, as the concepts of efficacy or protective benefit are difficult to convey. Multimedia approaches may be ideal for demonstrating such concepts. Effects of informational messaging on motivation, however, are complex; even the impact of message framing in terms of gains or loss appears to interact with numerous individual factors (e.g., dispositional motivation) [87]. As suggested in Table 5.5, avoiding repetitive information, scare tactics, or "lectures" would be recommended. Also, it is likely that information alone will be necessary but insufficient to produce lasting behaviors, and thus should be combined with targeting other important factors, such as motivation, social support, and skills.

Persuasion, Reinforcement, and Contingency

Reinforcement (tangible or social) and contingency-based strategies to produce changes in behavior have reasonable support [88], but there are a number of caveats and assumptions [89, 90] to this that are frequently in conflict with common use of these strategies in trials and clinical care alike. Simply, social persuasion and reinforcement are strategies that attempt to promote high rates of PrEP use by emphasizing the importance of it, positive results of it, and negative results of not doing it. When implemented by health care team members or study team members, this produces interactions around adherence that praise compliance while noncompliance produces negative responses (disappointment, longer visits, "lectures"). Contingencies include added consequences to adherence or nonadherence which can be outwardly positive (e.g., cash incentives) or negative (e.g., failure to get incentive, specific cost). While cash incentives for ART adherence (viral suppression more specifically) has received considerable attention in recent research agendas, if and how such approaches may apply to PrEP use (which lacks a biological marker such as viral suppression and includes regimens that are coitally dependent making expected drug levels variable) remains uncertain. More subtle reinforcement through

social interactions with providers of PrEP (and study team members in the context of blinded RCTs) remains challenging as well because the relative balance between emphasizing PrEP adherence and remaining neutral enough to promote open discussion of real challenges or nonadherence in social discourse with providers is not well understood. From blinded RCTs (Table 5.4) overreporting of adherence and underreporting of nonadherence was common enough to raise concerns about the potential collateral damage incurred when overemphasizing need for adherence (underemphasis of adherence and need for it was not common in any of the trials included in Table 5.4). Excessive reinforcement is known to "backfire" by attenuating one's sense of ownership or control over the behavior and promoting the "appearance" of being perfectly adherent to secure positive or avoid negative consequences to that report.

Reinforcement, subtle or more over, of adherence will occur as surely as social communication around adherence will occur. Leveraging praise or negative responses specifically in relation to observable behaviors associated with PrEP use (e.g., coming in for clinic visits, openly communicating with providers, drug levels when available) rather than on self-report may help to avoid potential for "backfire." Use of "neutrality" when in response to self-reported adherence should be considered. In person-centered counseling "neutrality" involves intentionally avoiding praise or negative reactions in response to reports of adherence. Instead, individuals are asked to clarify experiences around adherence or nonadherence. This style of social interaction seeks to avoid conveying personal judgment over behaviors, as in the end the person considering the behavior is the one that must assign meaning and muster motivation to adhere to PrEP. Note that this is also consistent with concepts in Motivational Interviewing [91] that emphasize the value of asking about reasons *not* to adopt a health behavior or to continue with "unhealthy" behaviors, and suggest that the alternative (e.g., focusing on why one should adhere and should not be nonadherent) can shut down open discourse. Thus, specific adoption of reinforcement strategies should clearly delineate what is reinforced (presenting as adherent versus actual adherence) and how reinforcement is envisioned to foster internal motivation and open discourse.

Theory Based

Like ART adherence interventions, adoption of strategies that are linked to theories of PrEP adherence or health behavior adoption is highly recommended. As noted above, IMB and CBT have been used in blinded PrEP trials and are also in the field in demonstration and open-label projects. While the evidence base is still emerging, the role of theory in intervention development is critical [54, 92]. Whether developing comprehensive packages or discrete strategies, health behavior theory offers nuanced understanding of how and why a given strategy might be effective in a given community. At minimum, strategies to support PrEP use should have an articulated foundation in evidence-based models that provide a rationale for why a given approach would "work" to promote adherence in a given population.

Community

Several surveys have identified moderate levels of community awareness of PrEP and intentions to adopt PrEP in the United States if effective and side effects are minimal [93–95]. Community work concerning use of PrEP is only now emerging as PrEP starts to penetrate some communities. Currently approved PrEP is not marketed, and thus knowledge of PrEP is entirely based on research and demonstration project awareness campaigns and dissemination of research findings. Additionally, because several kinds of PrEP (gel, ring) are not yet available to communities outside of research settings community knowledge of and reactions to these products also include beliefs about research trials more generally.

For open-label PrEP use, engagement in community discourse on PrEP, efficacy, adherence, and fit of PrEP in larger prevention packages will be critical. Strategies to promote community-level support for PrEP have to date included use of community advisory boards, community forums, and community events. Wide-scale community discourse surrounding PrEP in the United States also occurs in social networks and social media. While community-level interventions for PrEP adherence have not yet been evaluated, some of the community-based interventions used for ART adherence may be of value. Several community-based interventions are provided in CDC's treatment adherence EBIs (http://www.cdc.gov/hiv/topics/research/prs/subset-best-evidence-interventions.htm), with promising approaches (e.g., MPOWER [96]) appearing particularly applicable to PrEP uptake and support. Readers interested in demonstrated intervention packages that could be adapted to PrEP adherence support are encouraged to visit the CDC EBI site.

Methods and strategies for building community support for a given innovation varies, but at a basic level tends to include the use of community venues and media to promote accurate information and foster positive attitudes. Negative community attitudes toward PrEP and PrEP users will pose barriers for those attempting to adopt this strategy within that community. Continued use of community advisory boards in the development and monitoring of early roll-out and demonstration programs, engaging the community and stakeholders directly, and educating health care providers are recommended. Marketing models that leverage attributes that are currently "attractive" or desirable in a given community (e.g., cleanliness of sex, dry or lubricated sex, gender norms in introducing methods of protection) in framing benefits of PrEP products may be particularly useful, and qualitative work with PrEP trial participants will help to identify which dimensions of products are considered valued and which are considered costs.

Technology

Innovative PrEP support strategies in development include the use of interactive text messaging similar to what was effective in promoting ART adherence for treatment in Kenya [97, 98], monitoring strategies to provide feedback on actual levels of drug

detection among PrEP users and discussion-based approaches to "checking in" on PrEP use to provide tailored person-centered support. Reminder messaging appears mixed in terms of impact in other behavioral areas [99–104], and mobilizing social networks through websites is an innovative strategy for communities where internet and mobile technologies are common.

Monitoring

Monitoring PrEP use through drug detection strategies and providing feedback and/or specific intervention activities based on results of that monitoring is under development. Partners in PrEP (Table 5.4) triaged intensity of intervention based on results of unannounced home-based pill counts [81], and the PATH demonstration project previously noted is adopting a similar triaging approach using drug-level detection. The open-label extension of the iPrEx trial also uses drug-level feedback with participants to inform them of whether or not drug was detected, however, intensity of intervention for adherence support is not tied to these results. As methods to monitor PrEP use increase in sophistication (and accuracy), folding in these data to target or intensify intervention efforts may provide valuable benefits for streamlining resources to those who may be in most need of such support. Drug-level monitoring may be limited to PrEP regimens that have predictable and expected patterns of dosing; sex-dependent PrEP use may prove more challenging in this regard. Use of real-time monitoring (electronic drug monitoring that provides date and time of each opening of a drug-containing device) is also under evaluation, although costs of such devices likely prohibit use in clinical practice. However, use of monitoring devices to signal need for intervention may ultimately prove cost-effective. This emerging area of intervention will amass additional evidence over the next several years.

Integrated Prevention Practices

Finally, although not noted in Table 5.5, approaches that target sexual health protection through both non-PrEP and PrEP-related prevention strategies are of particular interest. Concerns about risk compensation [105] may be best addressed through conversations that highlight the use of multiple strategies to promote HIV-risk reduction. The open-label extension of the iPrEx trial and several demonstration projects are adopting these combined risk reduction and adherence counseling approaches (typically referred to as "sexual health promotion counseling"). Use of packaged intervention approaches are also under evaluation in a number of MP3 projects (Methods for prevention packages program (http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-08–019.html) which include test-prevent-link-retain-and treat into

compendium intervention packages. HIV testing has been noted as one of the most valuable avenues for engaging individuals in either PrEP or treatment, and thus integration of resources for PrEP and for rapid linking to and early retention in HIV care would be ideal.

Cautions

The biology of PrEP for prevention is gaining clarity more rapidly than the social behavioral aspects that will ultimately play a significant role in the individual and public health benefits of this strategy. Efficacy of TDF and TDF/FTC for prevention is converging, particularly for MSM and serodiscordant couples. Basic science is advancing to identify what rates of PrEP use are needed to provide what levels of protection and different methods to deliver PrEP are under investigation. Behaviorally, our evidence and knowledge base for which factors will be most influential of adequate and long-term use is limited. Rates of actual use of PrEP in the "real world" even if made widely available are unknown and they could be reasonably far higher or far lower than what has been observed in terms of study-product use. Thus, the proportion of individuals adopting PrEP that will experience PrEP success is hard to estimate. Moreover, we may not have a good estimate of this for several years as early adopters of this innovation may have patterns of use that are different from those adopting PrEP for prevention several years from now. In addition, it is not known if the patterns of adherence we have seen in ART for treatment, where adherence over time tends to decrease [106, 107], will pattern similarly for PrEP use.

For a number of reasons, study-product use is likely a distinct phenomenon from actual PrEP use. Thus even approaches leveraged to promote study-product use will likely require adaptation for providing PrEP use support. Conversely, it is possible that strategies avoided in RCTs might be effective in demonstration projects. Research focused on the identification of core psychosocial factors that influence one's adoption of and use of PrEP and the constellation of support strategies that are most effective in both promoting and maintaining adequate rates of use over time are needed. Furthermore, the role of PrEP in prevention for specific groups (e.g., women, commercial sex workers) needs more targeted attention as self-directed, discrete methods of prevention that could offer greater control than negotiating for a partner to use a condom.

Similar to ART adherence, the role of consistent engagement in "preventative care" will likely emerge as a major facilitator or threat to PrEP success. Nonpersistence with PrEP followed by unmonitored PrEP restarts runs the risk of promoting the development of drug-resistant strains of HIV owing to suboptimal drug pressure in newly infected individuals. Adherence to HIV testing requires consistent engagement with PrEP prescribers. Furthermore, patterns of PrEP use, or rather nonuse, in the context of sexual behavior will be critical in determining whether PrEP coverage

is achieved. While all of these factors are on the "radar" a evidence base will only emerge over the next several years. PrEP may offer unique opportunities to provide protection to HIV-negative individuals at times of high/higher risk of exposure, such as conception or while an HIV-positive partner achieved viral suppression. Whether it would be an approach adopted widely or used for extended periods of time is unknown. A number of open-label and ongoing efficacy trials gathering evidence for PrEP gel in women and rectal gel in MSM and novel delivery technologies (e.g., long acting injections and slow release vaginal rings) are under way; several of these are summarized in Table 5.6.

Summary

Both viral suppression for prevention (aka.,TasP) and PrEP rely heavily on access to ARVs, adherence and engagement in HIV care or preventative care, respectively. Who is offered ART or PrEP is an area of debate entrenched in the reality of limited resources and struggling economies. With global objectives for universal access to ART in 2015 [108], adding PrEP delivery in communities struggling to cover treatment for PLWH can feel unmanageable. At the same time, if an AIDS-free generation is to be realized, the HIV epidemic likely needs to be "book ended" with aggressive biobehavioral prevention tools to both minimize exposure events and prevent infection if exposed. For the first time in over a decade, the tool kit for prevention of HIV transmission has expanded rapidly for both HIV-positive and HIV-negative individuals. In the roll out of TasP and PrEP, the behavioral pathway from initiation to realized success share a number of commonalities (engagement in care, execution, persistence and strategies promoting memory, organization, and social support for dose-taking). Early treatment with ART and PrEP use share potential challenges inherent in using a medication that may cause side effects producing the feeling that the "cure is worse than the disease [one has or one is trying to prevent]." Models to understand and strategies to promote adherence to ART and to PrEP will continue to emerge over the next decade. As a critical part of the scientific and practice agenda, TasP and PrEP should be framed fully within the biopsychosocial factors that contextualize successful HIV treatment and prevention.

Table 5.6 Selected ongoing large (over 200 participants) PrEP trials. (Adapted from http://data.avac.org/SummaryTables.aspx)

Trial name	Phase/Aims	Locations	Population	Intervention arms	Start/Results expected
ANRS IPERGAY	Double blind RCT safety, tolerability and feasibility	Canada, France	1,900 MSM	Intermittent oral TDF/FTC of placebo or TDF/FTC dosed as 2 tablets pre sex and 1 tablet post sex plus 1 tablet 24 h after post sex dose	January 2012/December 2016
ATN 110/113	Open-label PrEP safety and adherence	United States	MSM and transgender women ages 15–18 and 18 and above	Daily TDF/FTC	Just starting
California HIV/AIDS Research Program (CHRP) awardees	Open-label PrEP demonstration projects	CA United States	MSM and transgender women	Daily TDF/FTC with additional randomization to adherence support methods in some awarded sites	Just starting
CAPRISA 008	Open-label uptake and adherence in former RCT (CAPRISA 004) participants Uptake, adherence, and safety	South Africa	700 women	1 % tenofovir gel taken before and after sex distributed by study site or family planning clinic	October 2012/February 2015
CDC 4370 (Bangkok Tenofovir Study)	Double Blind RCT safety and efficacy of TDF/FTC in IDUs	Thailand	2,400 injecting drug users	Daily oral TDF/FTC	June 2005/2013

Table 5.6 (continued)

Trial name	Phase/Aims	Locations	Population	Intervention arms	Start/Results expected
CDC 494 (TDF2 Follow-Up Open-Label Extension)	Open-Label uptake and adherence in former PrEP RCT participants	Botswana	1,200 women, men	Daily oral TDF/FTC	November 2012/November 2013
FACTS 001	Double blind RCT Safety and efficacy of PrEP gel	South Africa	2,900 women, heterosexual	1 % tenofovir gel taken before and after sex	October 2012/December 2014
HPTN 067 (ADAPT)	Adherence to daily and intermittent PrEP regimens	South Africa, Thailand, United States	360 MSM, Heterosexual women	Daily TDF/FTCTwice weekly plus within 2 h of sex dose Pre (up to 48 h before sex) and post (within 2 h after sex)	January 2011/2013–2014
HPTN 069/ACTG 5305 (NEXT-PrEP)	Blinded RCT safety, tolerability and adherence	United States	400 gay men and other men who have sex with men, men	Maraviroc (300 mg) Maraviroc + TDF (300 mg) Maraviroc + FTC (200 mg) TDF + FTC	February 2012/January 2014
IPM 027 (The Ring Study)	Double blind RCT Long-term safety and efficacy of ring	Rwanda, South Africa	1,650 women	Vaginal dapivirine ring (replaced every 4 weeks)	April 2012/August 2015
iPREX OLE	Open-label uptake and adherence in former PrEP RCT participants	Brazil, Ecuador, Peru, South Africa, Thailand, United States	1,500 men	Daily oral TDF/FTC	June 2012/November 2013

Table 5.6 (continued)

Trial name	Phase/Aims	Locations	Population	Intervention arms	Start/Results expected
MTN 020 (ASPIRE)	Double blind RCT Long-term safety and efficacy of ring	Malawi, South Africa, Uganda, Zambia, Zimbabwe	3,476 women	Vaginal dapivirine ring (replaced every 4 weeks)	July 2012/December 2014
PrEP Demonstration Project	Open-label uptake and adherence	United States; San Fran, Miami, Washington DC	500 Transgender, gay men and other men who have sex with men	Daily oral TDF/FTC	October 2012/2013–2014
PROUD	Open-label RCT immediate or deferred access Safety, tolerability, adherence	United Kingdom	500 MSM	Immediate vs. deferred, TDF + FTC	November 2012/November 2015

ACTG AIDS Clinical Trials Group, *ANRS* Agence Nationale de Recherche sur le Sida (National Agency for AIDS Research), *ATN* Adolescent Trials Network, *CAPRISA* Center for AIDS Program Research South Africa, *CDC* Centers for Disease Control, *FACTS* Follow-on African Consortium for Tenofovir Studies, *HPTN* HIV Prevention Trials Network, IPM International Partnership for Microbicides, *MTN* Microbicide Trials Network, *RCT* randomized controlled trial, *Blinded RCT* participants assigned to active drug or placebo without knowledge (by participant or staff) of which they are getting, *TDF/FTC* coformulated tenofovir disoproxil fumarate/emtricitabine (single tablet), *TDF + FTC* tenofovir disoproxil fumarate tablet and emtricitabine tablet taken separately

References

1. Kobin AB, Sheth NU. Levels of adherence required for virologic suppression among newer antiretroviral medications. Ann Pharmacother. 2011;45(3):372–9. Epub 2011/03/10.
2. Foundation KF. The Global HIV/AIDS Epidemic. Fact Sheet. December 2012.
3. Cohen M. Prevention of HIV-1 infection 2013: glimmers of hope. J Int AIDS Soc. 2012;15 Suppl 4:18066. Epub 2012/12/12.
4. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6):493–505. Epub 2011/07/20.
5. Cohen MS, Dye C, Fraser C, Miller WC, Powers KA, Williams BG. HIV treatment as prevention: debate and commentary–will early infection compromise treatment-as-prevention strategies? PLoS Med. 2012;9(7):e1001232. Epub 2012/07/18.
6. Ortego C, Huedo-Medina TB, Llorca J, Sevilla L, Santos P, Rodriguez E, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. AIDS Behav. 2011;15(7):1381–96. Epub 2011/04/07.
7. Munro S, Lewin S, Swart T, Volmink J. A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS? BMC public health. 2007;7:104. Epub 2007/06/15.
8. Amico KR, Harman JJ, Johnson BT. Efficacy of antiretroviral therapy adherence interventions: a research synthesis of trials, 1996–2004. J Acquir Immune Defic Syndr. 2006;41(3):285–97. Epub 2006/03/17.
9. Bruin M de, Viechtbauer W, Schaalma HP, Kok G, Abraham C, Hospers HJ. Standard care impact on effects of highly active antiretroviral therapy adherence interventions: A meta-analysis of randomized controlled trials. Arch Intern Med. 2010;170(3):240–50. Epub 2010/02/10.
10. Simoni JM, Pearson CR, Pantalone DW, Marks G, Crepaz N. Efficacy of interventions in improving highly active antiretroviral therapy adherence and HIV-1 RNA viral load. A meta-analytic review of randomized controlled trials. J Acquir Immune Defic Syndr. 2006;43 Suppl 1:S23–35. Epub 2006/11/30.
11. Thompson MA, Mugavero MJ, Amico KR, Cargill VA, Chang LW, Gross R, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. Ann Intern Med. 2012;156(11):817–33. Epub 2012/03/07.
12. Vernazza P, Hirschel B, Bernasconi E, Flepp M. Les personnes seropositives ne souffrant d'aucune autre MST et suivant un traitement antiretroviral efficace ne transmettent pas le VIH 2 voie sexualle. Bulletin des médecins suisses. 2008;89(5):5.
13. WHO. Programmatic update: Antiretroviral treatment as prevention (TasP) of HIV and TB. WHO/HIV/201212June 2012.
14. Eaton JW, Johnson LF, Salomon JA, Barnighausen T, Bendavid E, Bershteyn A, et al. HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. PLoS Med. 2012;9(7):e1001245. Epub 2012/07/18.
15. Kilmarx PH, Mutasa-Apollo T. Patching a leaky pipe: the cascade of HIV care. Curr opin HIV AIDS. 2013;8(1):59–64. Epub 2012/12/06.
16. El-Sadr WM, Holmes CB, Mugyenyi P, Thirumurthy H, Ellerbrock T, Ferris R, et al. Scale-up of HIV treatment through PEPFAR: a historic public health achievement. J Acquir Immune Defic Syndr. 2012;60 Suppl 3:S96–104. Epub 2012/09/14.
17. Mehta M, Semitala F, Lynen L, Colebunders R. Antiretroviral treatment in low-resource settings: what has changed in the last 10 years and what needs to change in the coming years? Expert Rev Anti Infect Ther. 2012;10(11):1287–96. Epub 2012/12/18.
18. Dombrowski JC, Harrington RD, Golden MR. Evidence for the long-term stability of HIV transmission-associated sexual behavior after HIV diagnosis. Sex Transm Dis. 2013;40(1):41–5. Epub 2012/12/21.

19. Goodreau SM, Carnegie NB, Vittinghoff E, Lama JR, Sanchez J, Grinsztejn B, et al. What drives the US and Peruvian HIV epidemics in men who have sex with men (MSM)? PloS one. 2012;7(11):e50522. Epub 2012/12/05.
20. Ganguli I, Bassett IV, Dong KL, Walensky RP. Home testing for HIV infection in resource-limited settings. Curr HIV/AIDS Rep. 2009;6(4):217–23. Epub 2009/10/24.
21. Carballo-Dieguez A, Frasca T, Dolezal C, Balan I. Will gay and bisexually active men at high risk of infection use over-the-counter rapid HIV tests to screen sexual partners? J Sex Res. 2012;49(4):379–87. Epub 2012/02/02.
22. Alemnji G, Nkengasong JN, Parekh BS. HIV testing in developing countries: what is required? Indian J Med Res. 2011;134(6):779–86. Epub 2012/02/09.
23. Chow EP, Wilson DP, Zhang L. The rate of HIV testing is increasing among men who have sex with men in China. HIV medicine. 2012;13(5):255–63. Epub 2012/01/19.
24. Fonner VA, Denison J, Kennedy CE, O'Reilly K, Sweat M. Voluntary counseling and testing (VCT) for changing HIV-related risk behavior 2 developing countries. Cochrane Database Syst Rev. 2012;9:CD001224. Epub 2012/09/14.
25. Hermans L, Wensing A, Hoepelman A, Dutihl J, Mudrikova T. Delayed HIV testing in internal medicine clinics—a missed opportunity. The Netherlands J Med. 2012;70(2):69–73. Epub 2012/03/16.
26. Kaai S, Bullock S, Burchell AN, Major C. Factors that affect HIV testing and counseling services among heterosexuals in Canada and the United Kingdom: an integrated review. Patient edu couns. 2012;88(1):4–15. Epub 2011/12/27.
27. Owen SM. Testing for acute HIV infection: implications for treatment as prevention. Curr opin HIV and AIDS. 2012;7(2):125–30. Epub 2012/02/09.
28. Thornton AC, Delpech V, Kall MM, Nardone A. HIV testing in community settings in resource-rich countries: a systematic review of the evidence. HIV medicine. 2012;13(7):416–26. Epub 2012/03/15.
29. Tripathy S, Pereira M, Tripathy SP. HIV testing in India. Clini lab med. 2012;32(2):175–91. Epub 2012/06/26.
30. Altice FL, Friedland GH. The era of adherence to HIV therapy. Ann Intern Med. 1998;129(6):503–5. Epub 1998/09/12.
31. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. Ann rev of pharmacol and toxicol. 2012;52:275–301. Epub 2011/09/29.
32. Thompson MA, Mugavero MJ, Amico KR, Cargill VA, Chang LW, Gross R, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. Ann Intern Med. 2012;156(11):817–33, W-284, W-5, W-6, W-7, W-8, W-9, W-90, W-91, W-92, W-93, W-94. Epub 2012/03/07.
33. Ammassari A, Lorenzini P, Mussini C, Cozzi-Lepri A, Baldelli F, Gori A, et al. Impact of antiretroviral dosing frequency and daily pill burden on virological success rates in patients of the ICoNA cohort starting their first ART. J Int AIDS Soc. 2012;15(6):18233. Epub 2012/12/14.
34. Bae JW, Guyer W, Grimm K, Altice FL. Medication persistence in the treatment of HIV infection: a review of the literature and implications for future clinical care and research. AIDS. 2011;25(3):279–90. Epub 2011/01/18.
35. Osterberg LG, Urquhart J, Blaschke TF. Understanding forgiveness: minding and mining the gaps between pharmacokinetics and therapeutics. Clin Pharmacol Ther. 2010;88(4):457–9. Epub 2010/09/22.
36. Bassett IV, Wang B, Chetty S, Mazibuko M, Bearnot B, Giddy J, et al. Loss to care and death before antiretroviral therapy in Durban, South Africa. J Acquir Immune Defic Syndr. 2009;51(2):135–9. Epub 2009/06/09.
37. Fleishman JA, Yehia BR, Moore RD, Korthuis PT, Gebo KA. Establishment, retention, and loss to follow-up in outpatient HIV care. J Acquir Immune Defic Syndr. 2012;60(3):249–59. Epub 2012/04/26.

38. Ma Y, Zhao D, Yu L, Bulterys M, Robinson ML, Zhao Y, et al. Predictors of virologic failure in HIV-1-infected adults receiving first-line antiretroviral therapy in 8 provinces in China. Clin Infect Dis. 2010;50(2):264–71. Epub 2009/12/19.
39. Sayles JN, Rurangirwa J, Kim M, Kinsler J, Oruga R, Janson M. Operationalizing treatment as prevention in Los Angeles County: antiretroviral therapy use and factors associated with unsuppressed viral load in the Ryan White system of care. AIDS Patient Care STDS. 2012;26(8):463–70. Epub 2012/07/11.
40. Yehia BR, Fleishman JA, Metlay JP, Moore RD, Gebo KA. Sustained viral suppression in HIV-infected patients receiving antiretroviral therapy. JAMA. 2012;308(4):339–42. Epub 2012/07/24.
41. Fox MP, Cutsem GV, Giddy J, Maskew M, Keiser O, Prozesky H, et al. Rates and predictors of failure of first-line antiretroviral therapy and switch to second-line ART in South Africa. J Acquir Immune Defic Syndr. 2012;60(4):428–37. Epub 2012/03/22.
42. Simoni JM, Yard SS, Huh D. Prospective prediction of viral suppression and immune response nine months after ART initiation in Seattle, WA. AIDS care. 2013;25(2):181–5. Epub 2012/05/30.
43. Colfax GN. Beliefs about viral load and the risk of HIV transmission and associated sexual risk behavior among San Francisco men who have sex with men. XIV International AIDS Conference; Barcelona, Spain2002.
44. Lafeuillade A. Eliminating the HIV reservoir. Curr HIV/AIDS Rep. 2012;9(2):121–31. Epub 2012/03/15.
45. Fisher JD, Amico KR, Fisher WA, Harman JJ. The information-motivation-behavioral skills model of antiretroviral adherence 2 its applications. Curr HIV/AIDS Rep. 2008;5(4):193–203. Epub 2008/10/08.
46. Fisher JD, Fisher WA, Amico KR, Harman JJ. An information-motivation-behavioral skills model of adherence 2 antiretroviral therapy. Health Psychol. 2006;25(4):462–73. Epub 2006/07/19.
47. Tarakeshwar N, Srikrishnan AK, Johnson S, Vasu C, Solomon S, Merson M, et al. A social cognitive model of health for HIV-positive adults receiving care in India. AIDS Behav. 2007;11(3):491–504. Epub 2006/10/10.
48. Safren SA, Gonzalez J, Soroudi N. Coping with chronic illness: a cognitive-behavioral therapy approach for adherence and depression: therapist guide (treatments that work). Oxford:Oxford University Press; 2008.
49. El-Sadr WM. HPTN065 TLC-Plus: A study to evaluate the feasibility of an enhanced test, link to care, plus treat approach for HIV prevention in the United States (Protocol v2.0). HIV Prevention Trials Network. 2010.
50. Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? J Health Soc Behav. 1995;36(1):1–10. Epub 1995/03/01.
51. Mugavero MJ. Improving engagement in HIV care: what can we do? Top HIV Med. 2008;16(5):156–61. Epub 2008/12/25.
52. Amico K. A situated-Information Motivation Behavioral Skills Model of Care Initiation and Maintenance (sIMB-CIM): an IMB model based approach to understanding and intervening in engagement in care for chronic medical conditions. J Health Psychol. 2011;16(7):1071–81. Epub 2011/04/05.
53. Smith LR, Fisher JD, Cunningham CO, Amico KR. Understanding the behavioral determinants of retention in HIV care: a qualitative evaluation of a situated information, motivation, behavioral skills model of care initiation and maintenance. AIDS Patient Care STDS. 2012;26(6):344–55. Epub 2012/05/23.
54. Bartholomew LK, Parcel GS, Kok G. Intervention mapping: a process for developing theory- and evidence-based health education programs. Health Educ Behav. 1998;25(5):545–63. Epub 1998/10/13.
55. Johnson BT, Carey MP, Chaudoir SR, Reid AE. Sexual risk reduction for persons living with HIV: research synthesis of randomized controlled trials, 1993–2004. J Acquir Immune Defic Syndr. 2006;41(5):642–50. Epub 2006/05/03.

56. Amico KR, Orrell C. Antiretroviral therapy adherence support: recommendations and future directions. J Int Assoc Provid AIDS Care. 2013;12(2):128–37. Epub 2013/01/22.
57. Amico KR, Orrell C. ART Adherence Support: Recommendations and Future Directions. J Int Assoc Provid AIDS Care. 2013;in press.
58. Simoni JM, Amico KR, Pearson CR, Malow R. Strategies for promoting adherence to antiretroviral therapy: a review of the literature. Curr infect dis rep. 2008;10(6):515–21. Epub 2008/10/24.
59. Simoni JM, Amico KR, Smith L, Nelson K. Antiretroviral adherence interventions: translating research findings to the real world clinic. Curr HIV/AIDS Rep. 2010;7(1):44–51. Epub 2010/04/29.
60. Dieffenbach CW. Preventing HIV transmission through antiretroviral treatment-mediated virologic suppression: aspects of an emerging scientific agenda. Curr opin HIV and AIDS. 2012;7(2):106–10. Epub 2012/01/10.
61. Forsyth AD, Valdiserri RO. Reaping the prevention benefits of highly active antiretroviral treatment: policy implications of HIV Prevention Trials Network 052. Curr opin HIV and AIDS. 2012;7(2):111–6. Epub 2012/01/10.
62. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367(5):399–410. Epub 2012/07/13.
63. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363(27):2587–99. Epub 2010/11/26.
64. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012;367(5):423–34. Epub 2012/07/13.
65. Kelesidis T, Landovitz RJ. Preexposure prophylaxis for HIV prevention. Curr HIV/AIDS Rep. 2011;8(2):94–103. Epub 2011/04/06.
66. Myers GM, Mayer KH. Oral preexposure anti-HIV prophylaxis for high-risk U.S. populations: current considerations in light of new findings. AIDS Patient Care STDS. 2011;25(2):63–71. Epub 2011/02/03.
67. Prevention CfDCa. Morbidity and mortality weekly report (MMWR), Interim guidance: Preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. MMWR Morb mortal wkly rep. 2011;60(03):4.
68. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012;367(5):411–22. Epub 2012/07/13.
69. Amico KR, Liu A, McMahan V, et al. Adherence Indicators and Pre-exposure Prophylaxis (PrEP) Drug Levels in the iPrEx Study. 18th Conference on Retroviruses and Opportunistic Infections (CROI); Boston, US 2011.
70. Anderson PL, Lama J, Buchbinder S, et al. Interpreting detection rates of intracellular emtricitabine-triphosphate (FTC-TP) and tenofovir-diphosphate (TFV-DP) in the iPrEx trial. 18th Conference on Retroviruses and Opportunistic Infections (CROI); Boston, US 2011.
71. Amico KR. Adherence to preexposure chemoprophylaxis: the behavioral bridge from efficacy to effectiveness. Curr opin HIV and AIDS. 2012;7(6):542–8. Epub 2012/09/12.
72. Amico KR, Liu A, Marcus JL, McMahan V, et al. Correlates of Study Product Use Among U.S. Participants in the iPrEx Randomized Controlled Trial of Daily Oral Preexposure Prophylaxis. International AIDS Conference July 2012; Washington, DC 2012.
73. Haberer J. Near perfect early adherence to antiretroviral pre-exposure prophylaxis (PrEP) against HIV infection among HIV-serodiscordant couples as determined by multiple measures: preliminary data from the Partners PrEP study. 18th Conference on Retroviruses and Opportunistic Infections; Boston, US 2011.
74. Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci transl med. 2012;4(151):151ra25. Epub 2012/09/14.

75. Robert M Grant FvG. HPTN 067: The ADAPT study: A Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Oral Emtricitabine/Tenofovir Disoproxil Fumarate Pre-Exposure Prophylaxis (PrEP). 2012.
76. Roy Gulick KM, Timothy W. HPTN 069: NEXT-PREP: Novel Exploration of Therapeutics for PREP: A Phase II Randomized, Double-Blind, Study of the Safety and Tolerability of Maraviroc (MVC), Maraviroc + Emtricitabine (MVC + FTC), Maraviroc + Tenofovir disoproxil fumarate (MVC + TDF), or Tenofovir disoproxil fumarate + Emtricitabine (TDF + FTC) for Pre-Exposure Prophylaxis (PrEP) to Prevent HIV Transmission in At-Risk Men Who Have Sex with Men. 2012 Contract No.: Protocol Version 2.0.
77. Spire BMJ, Aboulker JP, Le Gall JM. Pre-exposure prophylaxis in France: IPERGAY. TasP PrEP evidence summit 2012 (International Association of Physicians in AIDS Care and British HIV Association); June 11–12 2012; London, UK 2012.
78. Administration UFaD. FDA approves first drug for reducing the risk of sexually acquired HIV infection. 2012 [cited 2012 July]; http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm.
79. Amico KR, Mansoor LE, Corneli A, Torjesen K, Straten A van der. Adherence support approaches in biomedical HIV prevention trials: experiences, insights and future directions from four multisite prevention trials. AIDS and behavior. 2013. Epub 2013/02/26.
80. Ferrer RA, Morrow KM, Fisher WA, Fisher JD. Toward an information-motivation-behavioral skills model of microbicide adherence in clinical trials. AIDS Care. 2010;22(8):997–1005. Epub 2010/06/17.
81. Psaros C. Evaluation and Process Outcomes from an Adherence Intervention to Support HIV Pre-Exposure Prophylaxis (PrEP) Adherence in HIV-Serodiscordant Couples in Uganda. 7th Annual HIV Treatment and Prevention Adherence Conference of the International Association of Providers in AIDS Care; June 2012; Miami, FL 2012.
82. Amico KRMV, Marcus J, Goicochea P, Vargas L, Grant R, Liu A. Integrated Next Step Counseling (iNSC): A discussion based sexual health promotion conversation to support men who have sex with men using PrEP in the iPrEx open label extension. 7th Annual HIV Treatment and Prevention Adherence Conference of the International Association of Providers in AIDS Care; June, 2012; Miami, FL 2012.
83. RA K, McMahan V, Goicochea P, Vargas L, Marcus JL, Grant RM, et al. Supporting study product use and accuracy in self-report in the iPrEx study: next step counseling and neutral assessment. AIDS Behav. 2012;16(5):1243–59.
84. Safren SA, Otto MW, Worth JL, Salomon E, Johnson W, Mayer K, et al. Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. Behav Res Ther. 2001;39(10):1151–62. Epub 2001/10/03.
85. Straten A van der, Van Damme L, Haberer JE, Bangsberg DR. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. AIDS. 2012;26(7):F13–9. Epub 2012/02/16.
86. Kalichman SC, Pope H, White D, Cherry C, Amaral CM, Swetzes C, et al. Association between health literacy and HIV treatment adherence: further evidence from objectively measured medication adherence. J Int Assoc Physician AIDS Care. 2008;7(6):317–23. Epub 2008/12/06.
87. Mann T, Sherman D, Updegraff J. Dispositional motivations and message framing: a test of the congruency hypothesis in college students. Health Psychol. 2004;23(3):330–4. Epub 2004/04/22.
88. Ferster CB, Culbertson S. Behavior principles (3rd ed). Englewood Cliffs: Prentice-Hall; 1982.
89. Festinger L. A theory of cognitive dissonance. Stanford: Standford University Press; 1957.
90. Rogers RW. A protective motivation theory of fear appeals and attitude change. J Psychol. 1975;91:93–114.
91. Rollnick S, Miller W, Butler CC. Motivational interviewing in health care: helping patients change behavior (applications of Motivational Interviewing). New York: Guilford Press; 2008.

92. Kok G, Mesters I. Getting inside the black box of health promotion programmes using intervention Mapping. Chronic illness. 2011;7(3):176–80. Epub 2011/09/09.
93. Barash EA, Golden M. Awareness and use of HIV pre-exposure prophylaxis among attendees of a seattle gay pride event and sexually transmitted disease clinic. AIDS Patient Care STDS. 2010;24(11):689–91. Epub 2010/09/25.
94. Brooks RA, Kaplan RL, Lieber E, Landovitz RJ, Lee SJ, Leibowitz AA. Motivators, concerns, and barriers to adoption of preexposure prophylaxis for HIV prevention among gay and bisexual men in HIV-serodiscordant male relationships. AIDS care. 2011;23(9):1136–45. Epub 2011/04/09.
95. Golub SA, Kowalczyk W, Weinberger CL, Parsons JT. Preexposure prophylaxis and predicted condom use among high-risk men who have sex with men. J Acquir Immune Defic Syndr. 2010;54(5):548–55. Epub 2010/06/01.
96. Kegeles SM, Hays RB, Coates TJ. The Mpowerment Project: a community-level HIV prevention intervention for young gay men. Am J Public Health. 1996;86(8):1129–36. Epub 1996/08/01.
97. Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet. 2010;376(9755):1838–45. Epub 2010/11/13.
98. Kop ML,K van der, Gelmon L, et al. In-depth analysis of patient-clinician cell phone communication during the WelTel Kenya1 antiretroviral adherence trial. PloS one. 2012;7(9):e46033. Epub 2012/10/11.
99. Bourne C, Knight V, Guy R, Wand H, Lu H, McNulty A. Short message service reminder intervention doubles sexually transmitted infection/HIV re-testing rates among men who have 2 with men. Sex Transm Infect. 2011;87(3):229–31. Epub 2011/02/08.
100. Costa TM da, Barbosa BJ, Gomes eCDA, Sigulem D, Fatima MH de, Filho AC, et al. Results of a randomized controlled trial to assess the effects of a mobile SMS-based intervention on treatment adherence in HIV/AIDS-infected Brazilian women and impressions and satisfaction with respect to incoming messages. Int J Med Inform. 2012;81(4):257–69. Epub 2012/02/03.
101. Dowshen N, Kuhns LM, Johnson A, Holoyda BJ, Garofalo R. Improving adherence to antiretroviral therapy for youth living with HIV/AIDS: a pilot study using personalized, interactive, daily text message reminders. J Med Internet Res. 2012;14(2):e51. Epub 2012/04/07.
102. Haberer JE, Kiwanuka J, Nansera D, Wilson IB, Bangsberg DR. Challenges in using mobile phones for collection of antiretroviral therapy adherence data in a resource-limited setting. AIDS Behav. 2010;14(6):1294–301. Epub 2010/06/10.
103. Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, Walque D de, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. AIDS. 2011;25(6):825–34. Epub 2011/01/22.
104. Sidney K, Antony J, Rodrigues R, Arumugam K, Krishnamurthy S, D'Souza G, et al. Supporting patient adherence to antiretrovirals using mobile phone reminders: patient responses from South India. AIDS care. 2012;24(5):612–7. Epub 2011/12/14.
105. Eaton LA, Kalichman S. Risk compensation in HIV prevention: implications for vaccines, microbicides, and other biomedical HIV prevention technologies. Curr HIV/AIDS Rep. 2007;4(4):165–72. Epub 2008/03/28.
106. Howard AA, Arnsten JH, Lo Y, Vlahov D, Rich JD, Schuman P, et al. A prospective study of adherence and viral load in a large multi-center cohort of HIV-infected women. AIDS. 2002;16(16):2175–82. Epub 2002/11/01.
107. Mannheimer S, Friedland G, Matts J, Child C, Chesney M. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons 2 clinical trials. Clin Infect Dis. 2002;34(8):1115–21. Epub 2002/03/27.
108. Cooper D. Treatment optimization in low- and middle-income countries. J Int AIDS Soc. 2012;15 Suppl 4:18080. Epub 2012/12/12.

109. Emamzadeh-Fard S, Fard SE, Seyedalinaghi SA, Paydary K. Adherence to anti-retroviral therapy and its determinants in HIV/AIDS patients: A review. Infect Disord Drug Targets. 2012;12(5):346–56. Epub 2012/09/29.
110. Kalichman SC, Grebler T. Stress and poverty predictors of treatment adherence among people with low-literacy living with HIV/AIDS. Psychosom Med. 2010;72(8):810–6. Epub 2010/08/19.
111. Waite KR, Paasche-Orlow M, Rintamaki LS, Davis TC, Wolf MS. Literacy, social stigma, and HIV medication adherence. J Gen Intern Med. 2008;23(9):1367–72. Epub 2008/06/20.
112. Waldrop-Valverde D, Osborn CY, Rodriguez A, Rothman RL, Kumar M, Jones DL. Numeracy skills explain racial differences in HIV medication management. AIDS Behav. 2010;14(4):799–806. Epub 2009/08/12.
113. Mugglin C, Estill J, Wandeler G, Bender N, Egger M, Gsponer T, et al. Loss to programme between HIV diagnosis and initiation of antiretroviral therapy in sub-Saharan Africa: systematic review and meta-analysis. Trop Med Int Health. 2012. Epub 2012/09/22.
114. MacPherson P, Corbett EL, Makombe SD, Oosterhout JJ van, Manda E, Choko AT, et al. Determinants and consequences of failure of linkage to antiretroviral therapy at primary care level in Blantyre, Malawi: a prospective cohort study. PloS one. 2012;7(9):e44794. Epub 2012/09/18.
115. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010;329(5996):1168–74. Epub 2010/07/21.
116. Marrazzo J, Ramjee G, Nair G, Palanee T, Mkhize B, Nakabiito C, et al. Pre-exposure Prophylaxis for HIV in Women: Daily Oral Tenofovir, Oral Tenofovir/Emtricitabine, or Vaginal Tenofovir Gel in the VOICE Study (MTN 003). 20th Conference on Retroviruses and Opportunistic Infections; March 3–6, 2013; Altanta, Gorgia USA 2013.

Chapter 6
Risk Compensation in Response to HIV Prevention

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With each passing decade, various fields of science have developed increasingly more efficient forms of treatment and prevention options to curb the spread of HIV. We have established highly effective medical regimens to extend the life of a person infected with HIV. Research focusing on halting the HIV epidemic has also resulted in various strategies regarding behavioral forms of HIV prevention and risk reduction. However, with the exception of antiretrovirals (ARV) for prevention of mother-to-child HIV infection, currently available biomedical and behavioral HIV prevention and treatment options are limited in their ability to fully protect an individual from acquiring or transmitting HIV. Despite continued progress in the development of prevention and treatment options, the most efficient avenues of HIV prevention still remain safer sex techniques like consistent condom usage. However, as biomedical technologies take center stage in HIV prevention strategies, it is universally recognized that behavioral approaches to sexual risk reduction must work hand-in-hand with biomedical technology and that the *combination* of approaches could potentially, significantly impact the spread of HIV.

Here, we focus on the role of behavioral factors in implementing biomedical HIV prevention. We specifically look at the effect of risk compensation on implementing

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male circumcision (MC), ARV-based prevention (microbicides, treatment as prevention (TasP), and pre-exposure prophylaxis (PrEP)), and vaccine interventions. The concept of risk compensation highlights the potential for increases in risk-taking in response to the introduction of risk reducing technologies [1]. Risk compensation can minimize or potentially nullify the benefits of biobehavioral HIV prevention techniques. Therefore, the concerns surrounding risk compensation lay in whether or not individuals will increase their sexual risk-taking if they believe that biomedical forms of prevention lower their likelihood of becoming HIV-infected or passing the virus on to others.

Prior research has found evidence for the existence of risk compensation in HIV prevention [1] and, ultimately, findings warrant further investigation. Specifically, we update and extend work conducted by Eaton and Kalichman [1] by reviewing studies investigating risk compensation or trials that provide behavioral data from tests of efficacy regarding MC, ARV-based prevention, and vaccines for the prevention of HIV. Overall, this chapter provides a brief overview of studies published prior to 2008 (i.e., publications included in Eaton and Kalichman [1]) and a more extensive review of risk compensation-related studies published since that time.

Theoretical Rationale for the Study of Risk Compensation

Understanding how people's behavior changes in light of their perceived level of risk-taking is fundamental to understanding risk compensation. This area of inquiry was originally explored by Wilde (1994) [2] who developed the risk homeostasis theory. This theory highlights the various strategies people use to adjust their risk-taking by behaving in response to the level of risk-taking they are comfortable with [2]. One of the assumptions central to this theory is the idea that there exists a subjectively estimated optimal level of risk-taking that individuals are willing to accept in exchange for the potential benefits they expect from this activity. Any deviations from this optimal level in either direction may cause a change in behavior in order to counteract it.

In the specific case of HIV transmission, according to risk homeostasis theory, individuals accept a certain level of risk-taking for HIV and they will adjust their behaviors to reflect the level of risk they are comfortable taking. The level of risk-taking one is comfortable with is not necessarily static; as individuals learn new information about the level of risk they are taking, they adjust their behavior accordingly. Therefore, the introduction of risk-reducing technologies such as biomedical HIV prevention may induce a lower perceived risk level that can potentially cause behavioral adjustments that put an individual at an overall higher risk. This concept is particularly important in the case of biomedical technologies that are only partially effective. The concern for risk compensation is moot when a prevention technology is entirely effective; however, thus far, biomedical technologies have proven to be partially effective in preventing HIV.

Here, we present two lines of research: (a) a review of the available literature on risk compensation as it relates to HIV prevention and (b) empirical data (from three studies) investigating the relationship between MC and risk compensation. Our chapter covers studies that include the following: (a) reporting on measures of risk

compensation or (b) reporting behavioral outcomes for biomedical HIV prevention trials. For our empirical work, we present data from: (a) two studies in Kenya: the sexual health, attitudes, and behaviors (SHABS) study—an observational prospective study of risk compensation and the circumcision impact study (CIRCIS)—a random-household study of MC impact; and (b) one cross-sectional, survey study from South Africa conducted in six alcohol-serving establishments located in townships. We include empirical data on MC (and not other forms of prevention) as the bulk of risk compensation-related research has focused on this prevention tool and believe it to be an important complement to the reviewed studies. The remainder of the chapter proceeds as follows: a review of MC and reports from two empirical studies of MC and risk compensation, a review of ARV-based HIV prevention (TasP, PrEP, microbicides), HIV vaccines, and concluding remarks.

Male Circumcision

Evidence for MC as an HIV Prevention Strategy

Three recent randomized controlled trials (RCTs) in sub-Saharan populations have demonstrated, beyond any reasonable doubt [3], the efficacy of MC in reducing the risk of female-to-male HIV transmission by as much as 60 % [4–6]. Following these results, the United Nations Joint Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) recommended MC as an important additional strategy for the prevention of heterosexually acquired HIV infection in men [3]. Several modeling studies found that the long-term population-level impact of widespread implementation and scale-up of voluntary medical male circumcision (VMMC) services would result in substantial reductions in HIV incidence for both men and women [7–11]. One such study estimated that universal circumcision coverage in sub-Saharan Africa could avert approximately 2 million new infections in the first 10 years and over 5.5 million over 20 years [11], with estimates of one HIV infection averted for every 5–15 VMMCs performed [10].

Circumcision has been shown to be safe [4–6, 12], cost-effective [13], and acceptable in a variety of non-circumcising communities across Africa [14]. As a result, several high-priority countries in the region are actively engaged in VMMC program scale-up [15, 16]. The effectiveness of these programs will ultimately depend on a variety of factors, including the epidemiological setting, speed of scale-up and uptake, the proportion of men engaging in sex before full wound healing, the HIV risk profile of newly circumcised men, and any significant behavioral risk compensation following the procedure.

Risk Compensation and MC

If men believe that circumcision provides protection from HIV, they may be more likely to engage in riskier sexual behavior when circumcised. [17, 18]. Risk compensation can reduce the protective effect of circumcision and, if of sufficient

magnitude, completely negate protection [19]. In addition to newly circumcised men, behavioral shifts are possible in other segments of the population not directly benefiting from VMMC programs, including women [12], uncircumcised and previously circumcised men [20, 21], and men who have sex with men (MSM) [22–24].

Epidemiological modeling studies suggest that only extreme levels of increased risk behavior will offset the protection offered to circumcised men [8, 9, 13, 19, 25–30], however, the impact of circumcision is more sensitive to changes in behavior in low HIV incidence settings [30]. More realistically, moderate levels of risk compensation in men could result in increased female risk, especially in the short term and in populations with continued low circumcision prevalence [25–27,29]. The consensus is that risk compensation will negatively impact MC-driven HIV prevention efforts only if risk behaviors increase across the entire population in response to generalized perceptions of decreased risk [10, 19, 25].

Empirical Evidence of Risk Compensation in MC Intervention Studies

An optimal study of risk compensation following MC would include three key components: (1) longitudinal design to determine temporality and trends of behavior over time; (2) a baseline behavioral assessment occurring before the MC procedure to enable comparison of behaviors before and after circumcision; and (3) a control group of men remaining uncircumcised for the duration of follow-up to allow comparison between circumcised and uncircumcised men over time, and in part to control for possible changes in behavior on the community level. This optimal design is intensive in time and resources and while congruent studies are underway, the current empirical evidence meeting these criteria is limited to the MC intervention studies, including the three RCTs.

In the analysis of behavioral change before the procedure and throughout follow-up in circumcision and control groups, the Rakai, Uganda trial found no consistent evidence of risk compensation [5] (See Table 6.1 for summaries of risk compensation-related findings). Extended follow-up confirmed the lack of risk compensation over a longer period of observation, as well as in newly circumcised control participants [31]. In Orange Farm, South Africa, circumcised participants reported a higher mean number of sexual partners during 4–12 months (5.9 vs. 5.0, $p < 0.001$) and 13–21 months (7.5 vs. 6.4, $p = 0.002$) of follow-up [6]. Despite this higher-risk behavior, however, the protective effect of circumcision was sustained [6] and was remarkably consistent with results of the two other trials [32, 33]. In Kisumu, Kenya [4], there was also some evidence of higher-risk behavior in circumcised men. Although risk behaviors declined in both the circumcised and uncircumcised groups, several differences in the rate of the decline were observed. Most notably, the proportion of men reporting two or more sex partners declined steadily in the uncircumcised controls, but declined and stabilized after 6 months in circumcised participants. Additionally, uncircumcised men reported more protected sex and greater condom use at 24 months follow-up than circumcised men.

Table 6.1 Review of studies providing risk compensation-related findings post 2008

Reference	Participants	Study design	Risk compensation-related results
MC			
Mattson [34]	1,319 men in RCT of MC in Kenya	Interviews conducted with participants who enrolled in the substudy in addition to data acquired from the RCT	There was a significant reduction in sexual risk behavior among both circumcised and uncircumcised men from baseline to 6 and 12 months post enrollment. Longitudinal analyses indicated no statistically significant differences between their sexual risk propensity scores
Riess [38]	30 sexually active circumcised men recruited from Kisumu, Kenya	Qualitative semistructured interviews that lasted between 40 and 120 min	MC does not necessarily lead to risk compensation. A minority of participants reported increasing risk behavior after circumcision
Andersson [42]	7,464 participants aged 15–29 from Botswana, Namibia, and Swaziland	Representative cluster sample study. Interviews lasting between 20 and 30 min as well as HIV testing	More than 10 % of respondents thought that a circumcised man is fully protected against HIV infection. About 18 % believed that HIV-positive men who are circumcised cannot transmit HIV
Ayiga [107]	1,257 men aged 15 or older	Cross-sectional data analysis	Circumcision was not significantly associated with condom use. Nonuse of condoms was significantly affected by religious beliefs, low level of education, marriage, drunkenness, and misconceptions regarding antiretroviral therapy (ART)
Grund [39]	33 men recruited from Swaziland and circumcised in the past 12 months	Qualitative interviews inquiring about sexual risk behavior post circumcision	Most of the participants described protective changes. A minority, however, experienced increased sexual risk-taking, typically during a brief period of sexual experimentation shortly after circumcision
Eaton [20]	304 HIV-negative men attending a health clinic in South Africa	Cross-sectional surveys	Men aware of MC for HIV prevention perceived endorsed risk compensation related to MC, lowered perceived risk of HIV, and reported more sexual risk-taking
Gust [41]	10,108 men in the US	Cross-sectional surveys	18 % indicated the potential for engaging in risk compensation behaviors relating to MC
Maughan-Brown [20]	453 men and 690 women recruited from the Cape Area Panel Study	Survey data consisting of interviews collected as part of a prior RCT	Men informed of circumcision for HIV prevention perceived slightly higher risk of contracting HIV and were more likely to use condoms at last sex. Informed women perceived lower HIV risk, were less likely to use condoms both at last sex and in general, and more likely to forego condoms with partners of positive or unknown serostatus

Table 6.1 (continued)

Reference	Participants	Study design	Risk compensation-related results
Wang [40]	353 clients of female sex workers in Hong Kong	Interviewer- and computer-assisted interviews	20.9 % of uncircumcised participants anticipated less condom use after circumcision. Inconsistent condom use and STD history were associated with anticipated risk compensation
Westercamp [44]	1,548 women and uncircumcised men in Kenya	Community-based surveys	A minority of participants expressed beliefs suggesting that behavioral risk compensation with increased MC prevalence and awareness is a possibility
Kelly [48]	276 men in Papua New Guinea	Qualitative study with focus groups and in-depth interviews	A minority of men were against the introduction of MC, primarily due to concerns regarding sexual risk compensation
Pelzer [49]	160 men undergoing traditional circumcision in South Africa	HIV risk-reduction counseling intervention trial	Intervention did not reduce sexual risk-taking behavior among men recently circumcised
ARV prevention			
Initiation of HAART and treatment as prevention			
Cohen [79]	1,655 people from Kisumu, Kenya including 749 men and 906 women	General population-based survey	ART-related risk compensation was associated with an increased HIV seroprevalence in men but not women after controlling for age. In particular, ART-related risk compensation was associated with an increased HIV seroprevalence in young (aged 15–24 years) men
Bechange [81]	455 HIV-uninfected non-spousal household members of ART patients	Longitudinal cohort study	Risky sex declined from 29 % at baseline to 15 % at the end of 24 months. Perceiving AIDS as curable and lower AIDS-related anxiety were independently associated with risky sex
Marshall [108]	457 ART-naive HIV-positive adults who had a history of injection drug use	Longitudinal cohort study	Among 457 individuals who were ART-naive at baseline, 260 (56.7 %) participants initiated ART. ART initiation was not associated with sexual activity, unprotected intercourse, or multiple sexual partnerships
Venkatesh [82]	1,544 men and 4,719 women who were HIV-positive recruited from primary care HIV clinics in South Africa	Longitudinal cohort study	Among 6,263 HIV-infected men and women, over 37.2 % initiated HAART during study follow-up. In comparison to pre-HAART follow-up, visits while receiving HAART were associated with a decrease in those reporting being sexually active, having unprotected sex and having >1 sex partners

Table 6.1 (continued)

Reference	Participants	Study design	Risk compensation-related results
Kuyper [91]	380 ART-naive HIV-positive IDUs in Vancouver, Canada	Longitudinal cohort study	Syringe sharing was not associated with ART initiation
Ncube [80]	267 HIV-positive individuals attending Kumasi South Regional Hospital	Cross-sectional surveys	Participants on ART were 80 % less likely to have used condoms during last sexual intercourse than participants not on ART
Fu [88]	362 HIV-infected IDUs initiating ART	Longitudinal cohort study	ART initiation was associated with a 75 % reduction in the likelihood of unprotected sex
PrEP			
Guest [76]	400 women participating in an oral tenofovir prevention trial in Ghana	Randomized double-blind placebo-controlled clinical trial	No increase in sexual risk behavior during the trial. Number of sexual partners and rate of unprotected sex acts decreased across the 12-month period of study enrollment
Golub [83]	180 HIV-negative high-risk MSM recruited from bars and clubs in New York City	Cross-sectional surveys	Of the participants who reported that they were likely to use PrEP if it were at least 80 % effective, over 35 % reported that they would be likely to decrease condom use while on PrEP. In multivariate analyses, risk perception motivations for condom use significantly predicted decreased condom use on PrEP
Grant [70]	2,499 HIV-negative participants including men and transgender women who have sex with men	ART or placebo once daily. Combined with HIV testing, risk-reduction counseling, condoms, and management of sexually transmitted infections	The total numbers of sexual partners with whom the respondent had receptive anal intercourse decreased, and the percentage of those partners who used a condom increased after participants enrolled in the study
Liu [78]	400 HIV-negative MSM recruited from San Francisco, Atlanta, and Boston	Double-blind, placebo-controlled clinical trial. Half randomized to receive study medication at enrollment, other half after a 9-month delay	Mean number of sex partners and unprotected anal sex decreased over the 2-year period. No significant differences in change from baseline for number of partners between immediate vs. delayed arms. Trend toward a greater decline in UAS from baseline to period 1 in the immediate vs. delayed arm
Baeten [77]	4,758 serodiscordant couples from Uganda and Kenya	Randomized trial of drug therapy comparing ART vs. placebo	The proportion of seronegative participants reporting sex without a condom with their seropositive partner decreased over the course of the study

Table 6.1 (continued)

Reference	Participants	Study design	Risk compensation-related results
Thigpen [68]	1,219 HIV-negative participants recruited in Botswana	Randomized double-blind control trial comparing ART vs. placebo combined with prevention services	Over the course of the study, condom usage among the groups was similar at baseline and remained stable over time. The number of sexual partners declined over the course of the study for all groups
Van Damme [69]	2,120 at-risk HIV-negative women recruited from Kenya, Tanzania, and South Africa	Randomized double-blind placebo-controlled trial comparing a combination of tenofovir and emtricitabine to a placebo	There was no evidence of increased HIV risk behavior during the trial, with modest but significant reductions in the numbers of partners, vaginal sex acts, and sex acts without a condom reported by women at the last follow-up visit, as compared with 7 days before enrollment
Karim [100]	884 HIV-negative sexually active women aged 18–40 recruited from Kwazulu-Natal, South Africa	Double-blind, RCT comparing tenofovir gel with a placebo gel	Over the 30 months, reported coital frequency declined steadily from 7.2 sex acts per month in the first 6 months to 3.1 sex acts per month in months 18–24 ($p < 0.001$). The mean number of sex acts in the high, intermediate, and low gel adherers was 3.2, 5.0, and 6.7 per month, respectively, thereby showing a decline in risk behavior, but a relationship between adherence and risk-taking
HIV vaccines			
Newman [104]	1,164 high-risk adults in Los Angeles recruited from STD clinics, needle/syringe exchange programs, Latino community health/HIV prevention programs	Structured interviews and cross-sectional surveys investigating hypothetical HIV vaccine acceptability	9.7 % of participants indicated they would use condoms less frequently for vaginal sex if they received an HIV vaccine; 10.4 % would use condoms less for anal sex; and 10.4 % would increase their number of sexual partners
Newman [105]	255 MSM and transgendered women recruited in Thailand	Structured questionnaire	Over one-third (34.6 %) reported intentions to increase postvaccination risk behaviors in response to a highly efficacious HIV vaccine
Sayles [106]	42 participants recruited in South Africa	Focus groups with semistructured discussions to explore future vaccine acceptability	Majority of men cited the ability to have sex without a condom and having multiple sexual partners as advantages of taking the HIV vaccine. Several men in each group stated that if a vaccine was available they would not need to worry about HIV prevention

HAART highly active antiretroviral therapy, *MC* male circumcision, *ARV* antiretrovirals, *MSM* men who have sex with men

In an in-depth study, specifically addressing risk compensation in a subset of Kisumu trial participants, Mattson et al. were able to confirm the initial reductions observed in sexual risk behavior, but found no significant differences between the two groups in an overall HIV risk propensity score or the incidence of laboratory-diagnosed sexually transmitted infections (STIs) [34]. An independent nonrandomized prospective cohort study, conducted in a rural community near Kisumu and completed before trial results were known, confirmed these conclusions, finding that men electing to become circumcised had similar sexual behaviors 1 year after the procedure when compared with men who remained uncircumcised [35].

Although this evidence on risk compensation is encouraging, the results from these intervention studies should be interpreted with caution, as men were followed, interviewed, counseled, and provided with HIV prevention materials in controlled and structured conditions. Additionally, participants in each of these studies could not be certain about the HIV protective effect of MC and were exposed to little or no circumcision messages, which would later become common through VMMC mobilization and the mass media [36, 37]. Consequently, valid concerns remain that MC could lead to increases in high-risk sexual behavior as VMMC is integrated and promoted as an HIV prevention strategy in the general population.

Qualitative Descriptions of Risk Compensation

Qualitative evaluations of behavioral risk compensation following MC can provide important insights into the motivations and mechanisms behind observed or possible changes in behavior. To date, there have been two qualitative studies investigating MC-related sexual behavior change following the dissemination of trial results in populations targeted for VMMC programs. Research with newly circumcised men in Kenya observed several behavior changes, but the majority of men were consistent with increases in protective behaviors, due to enhanced HIV risk awareness, increased serial HIV testing, fuller appreciation of risk-reduction counseling, and a greater desire to stay HIV-negative [38]. A second study found similar ideas expressed by recently circumcised men in Swaziland [39]. Both studies concluded that newly circumcised men appeared to be largely adopting increased protective behaviors after circumcision with the understanding that behaviors can negate the protection afforded by circumcision. However, both studies did note a minority of participants who increased sexual risk-taking behaviors during a brief period of sexual experimentation shortly after circumcision [38, 39].

Hypothetical and Perceived Risk Compensation

One method of assessing potential MC-related risk compensation quickly and at low cost is through scenarios and misconceptions about partial HIV protection provided by MC to explore the prevalence and patterns of beliefs. For example, following

the provision of information about HIV protection provided by MC, over 20 % of uncircumcised clients of sex workers in Hong Kong anticipated less condom use if they became circumcised [40]. In a US population, 18 % of both circumcised and uncircumcised men agreed with the statement: "men who are circumcised don't have to worry about using condoms or having more sexual partners" [41]. In sub-Saharan populations, 21 % of male respondents in cross-sectional surveys in Botswana, Namibia, and Swaziland [42] agreed that it would be acceptable for a circumcised man to expect sex without a condom. Additionally, 13 % believed that a circumcised man is fully protected against HIV infection and 18 % believed erroneously that circumcised HIV-positive men cannot transmit the virus. Similarly, in South Africa, 19 % of men in Orange Farm maintained that MC fully protects against HIV and circumcised men were more likely to believe that condom use was unnecessary after circumcision [43]. Finally, a random-household survey carried out with VMMC scale-up in Kenya, found that approximately 20 % of uncircumcised men and women in Kisumu thought condom use was less necessary and HIV a less serious threat now that circumcision is available [44].

Although expressing a belief is not comparable to an actual change in behavior, concerns about potential risk compensation have acted as barriers to circumcision acceptance as people feared that the circumcision of men will increase sexual promiscuity, adultery, and decrease gains in condom use [45–48].

Risk Compensation in Men Circumcised Outside of VMMC Programs

As information about the protective effect of MC has become more widely available, it is possible that the risk perception and behaviors of men who have been circumcised for reasons other than for HIV prevention may be impacted. This idea is of special concern as these men are less likely to receive the MC/HIV counseling that is bundled with VMMC service provision [3].

To our knowledge, only two studies have specifically explored changes in behavior in traditionally circumcising populations following the widely publicized RCTs results, both done in Cape Town, South Africa. The first by Eaton et al. found that men who were aware of the protective effect of MC and endorsed beliefs consistent with risk compensation were more likely to report unprotected sex and multiple sexual partners [20]. These findings were not observed by Maughan-Brown et al., who found no such differences between informed and uninformed traditionally circumcised men [21]. Although risk compensation has not been confirmed in such groups, at least two experimental studies have been carried out to evaluate the effect of educational interventions on limiting potential risk compensation or increasing safer sex behaviors in traditionally circumcised men. Neither study was able to produce significant changes in either behavior or the expressed behavioral intentions of traditionally circumcised men by providing MC-related HIV counseling messages [49, 50].

It is possible that circumcisions performed outside of the VMMC settings may not provide the same benefit as medical MC procedures due to the lack of targeted risk-reduction counseling, incomplete foreskin removal [51, 52], and procedural incompetence leading to high complication rates and adverse outcomes [53, 54]. However, it may also be true that men circumcised for reasons other than for HIV prevention may be less prone to risk compensation. Regardless, traditional and religious circumcision is highly prevalent in sub-Saharan Africa [55], and VMMC scale-up will occur in populations of mixed circumcised and non-circumcising peoples. To best protect the entire population, it will be important to closely monitor and further explore the dynamic relationship between MC information and promotion, and the behaviors of traditionally circumcised men.

Risk Compensation among Women

MC initiatives could place women at greater risk of HIV transmission if circumcised men engage in higher-risk behaviors as a response to the intervention and if the newly circumcised men resume sexual activity before complete wound healing. Furthermore, women who become aware of the protective benefits of circumcision may increase their risk by erroneously perceiving all circumcised men as HIV-negative and altering their condom use accordingly. This situation is worsened when women have limited access to high-quality circumcision-related information and MC-specific risk counseling, like that provided through VMMC service provisions.

Similar to the observational evidence of risk compensation in men, findings in women are limited. Several studies identified misconceptions about the protection MC provides. Random-household surveys in Botswana, Namibia, and Swaziland found that women were more likely than men to believe that HIV-positive men cannot transmit infection after MC, and over 15 % of women agreed that it would be acceptable for a circumcised man to expect sex without a condom [42]. In the traditionally circumcised population in Cape Town, South Africa, women, unlike their male counterparts, who appreciated the HIV protective benefits of MC had lower self-perceived HIV risk and were less likely to use condoms with partners of HIV-positive or unknown serostatus [21].

In Kenya, a population-based survey conducted early in the VMMC program scale-up, found that women who believed themselves less likely to use a condom now that MC is available, were more likely to prefer uncircumcised partners. The authors hypothesized that this finding may reflect women's concern about their ability to negotiate condom use with circumcised men [44]. Additionally, in-depth qualitative interviews in this population noted little differential condom use based on a partner's circumcision status, and identified few female respondents believing that circumcision provides full protection against HIV or that circumcision status played a significant role in partner selection [56, 57]. Lastly, a trial looking at HIV transmission in serodiscordant couples following MC in Uganda found no evidence of changes in risky behaviors in the female partners of HIV-positive newly circumcised men over time [58].

Increase in risky behaviors by both circumcised men and their female partners has the potential to substantially increase HIV risk for women. Involving women in the circumcision decision-making process and developing targeted educational messages about partial protection of MC against HIV should be an integral part of VMMC scale-up.

Data from Operations Research on Risk Compensation from Kenya

Nyanza Province, Kenya, is home to the Kenyan RCT of MC for HIV prevention and the epicenter of the most successful VMMC campaign in Africa, to date. The scale-up of the Kenya's VMMC program was accompanied by a comprehensive package of operations research designed to monitor a number of key programmatic issues, including the evaluation of risk compensation.

Two studies in particular were designed to evaluate behavioral change following circumcision and augmented each other through complementary methodologies. The first, the SHABS study was an observational prospective study of risk compensation that recruited 1,588 men seeking circumcision services at Nyanza Province health facilities participating in the VMMC scale-up. Age and residence matched controls ($n = 1{,}598$) were recruited from surrounding communities and offered circumcision, but declined the procedure at enrollment. Both groups were followed and interviewed every 6 months for 2 years. A small sample ($n = 101$) of long-term female partners of recently circumcised men was recruited to gain the female perspective on MC. The main objective of this study was to compare the behaviors of circumcised and uncircumcised men over time.

The second, the CIRCIS was a random-household study of MC impact carried out as a series of three cross-sectional surveys completed every 2 years in Kisumu municipality, the capital of Nyanza Province. To date, the CIRCIS study has completed two survey rounds collecting data from a representative sample of male ($n_{2008/2009} = 675$; $n_{2011} = 1{,}087$) and female ($n_{2008/2009} = 1{,}372$; $n_{2011} = 1{,}540$) residents of Kisumu. The objective of this study was to assess MC prevalence, changes in perceptions and beliefs, and monitor for population-level changes in sexual risk behaviors in residents of Kisumu.

Both studies started in November of 2008, concurrent with the launch of the VMMC program in Kenya. SHABS completed participant follow-up in late 2011, the year the second round of CIRCIS was conducted. Both studies monitored changes in sexual risk behavior over time in comparable populations and were designed to maximize comparability by utilizing the same set of questions addressing beliefs consistent with risk compensation. Each belief was assessed in the context of "Now that circumcision is available" in order to gauge various possible areas of sex behavior change.

Table 6.2 Risk compensation endorsing beliefs among CIRCIS and SHABS study participants in the first 3 years of the VMMC scale-up in Nyanza, Kenya

Now that circumcision is available...	2008/09: Start (SHABS)/round 1 (CIRCIS; %)	2011: End (SHABS)/round 2 (CIRCIS; %)
HIV is a less serious threat than it used to be		
CIRCIS men[a]	20	10
CIRCIS women	22	19
SHABS circumcised men[a]	68	42
SHABS uncircumcised men[a]	49	29
I am less worried about HIV infection		
CIRCIS men	14	10
CIRCIS women[a]	21	15
SHABS circumcised men[a]	33	16
SHABS uncircumcised men[a]	23	11
Condom use during sex is less necessary		
CIRCIS men[a]	18	9
CIRCIS women[a]	25	15
SHABS circumcised men[a]	18	7
SHABS uncircumcised men[a]	18	8
I am more likely to have more than one sexual partner		
CIRCIS men[a]	10	5
CIRCIS women[a]	6	3
SHABS circumcised men[a]	10	4
SHABS uncircumcised men[a]	9	5

SHABS sexual health, attitudes, and behaviors study, *CIRCIS* circumcision impact study [a]Change over time, $p < 0.05$

Both the SHABS and CIRCIS studies found that beliefs consistent with risk compensation declined between 2008 and 2011—representing the initial 3 years of VMMC program activities (Table 6.2). Furthermore, CIRCIS found that while such beliefs decreased in all groups, two beliefs, "HIV is a less serious threat" and "I am more likely to have more than one sexual partner," were more commonly expressed by circumcised men than uncircumcised men. This relationship was not significant when limited to men circumcised during the VMMC scale-up. Notably, two beliefs, "HIV is a less serious threat than it used to be" and "I am less worried about HIV infection," were much more prevalent among the SHABS participants—possibly related to MC sensitization efforts in their communities and their personal interest in circumcision.

Beliefs consistent with risk compensation were more prevalent in female participants across the board, with the exception of justification for multiple sexual partnerships (i.e., "Now that MC is available, I am more likely to have more than one sexual partner"). This was noted in both CIRCIS (Table 6.1) and the female partner sample in SHABS (Fig. 6.1). The SHABS analysis of discordant beliefs within couples indicated that differences in three out of four beliefs were statistically significant. Women were more likely than their partners to agree that they are less worried about HIV infection, that condom use during sex is less necessary, and that they are more likely to have more than one partner, now that circumcision is available.

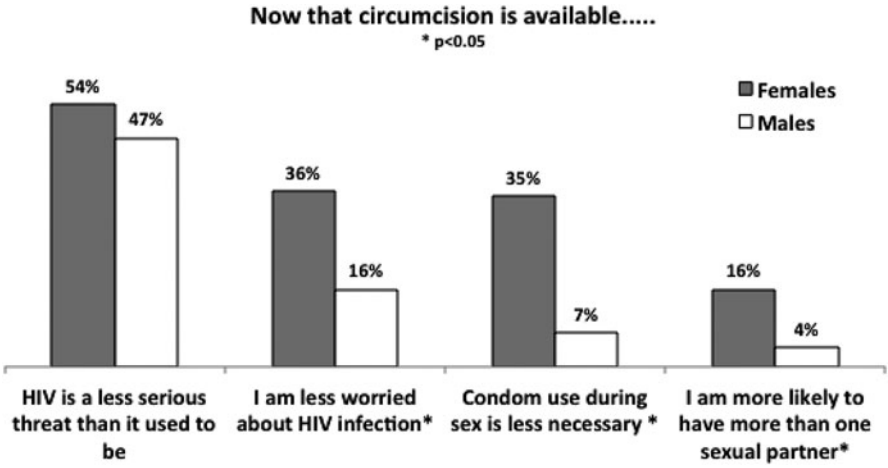

Fig. 6.1 Risk compensation endorsing beliefs among recently circumcised men and their female partners (SHABS). Note: Statistical significance was determined by the McNemar's test for paired analysis, to assess the within couple differences in circumcision beliefs

Table 6.3 Change in sexual behavior in circumcision and control group participants from baseline to 24 months following MC/enrolment (SHABS)

	Baseline (%)	6 months (%)	12 months (%)	18 months (%)	24 months (%)	Time effect *p*-value	Group effect *p*-value
Used a condom last time had sex						< 0.0001	0.01
Circumcised	48	53	58	61	62		
Uncircumcised	48	52	51	54	52		
Used condom with nonregular partner at last sex						< 0.0001	0.40
Circumcised	49	63	63	65	68		
Uncircumcised	59	61	64	69	68		
Had more than two partners in the past 6 months						< 0.0001	0.08
Circumcised	22	24	18	17	13		
Uncircumcised	24	24	22	19	13		
In the past 6 months exchanged money or gifts for sex						< 0.0001	0.08
Circumcised	24	19	18	14	12		
Uncircumcised	27	22	19	17	12		

Mixed effect methods were used to analyze differences between the groups over time. All models were adjusted for participants' age. Time effect evaluated change over time, while group effect detected differences between the behaviors in the circumcision and control group participants

The risk compensation study found that sexual risk behaviors decreased in both circumcised and uncircumcised men over time and no evidence of risk compensation was observed (Table 6.3). The only significant difference between the two groups was in the proportion of men reporting condom use at last sex, which steadily increased

Table 6.4 Change in sexual behaviors in male and female Kisumu population between the first two rounds of CIRCIS (2008/2009 and 2011)

	2008/2009: Round 1 (CIRCIS) (%)	2011: Round 2 (CIRCIS) (%)
> Four (men) or > two (women) lifetime partners		
CIRCIS men	41	43
CIRCIS women	39	38
Ever used a condom		
CIRCIS men[a]	67	76
CIRCIS women[a]	51	61
Used a condom with last non-spousal partner		
CIRCIS men	38	39
CIRCIS women	17	16
Ongoing casual partnership		
CIRCIS men	9	6
CIRCIS women	2	2

[a]Change over time, $p < 0.05$

over 2 years of follow-up in circumcised men, but remained stable in uncircumcised men. In CIRCIS, higher-risk sexual behaviors showed no prevalent increase between 2008 and 2011 in the Kisumu population (Table 6.4). Similar to the risk compensation study, the only significant change was the increased reported condom use by 13 % in men and 20 % in women. The study found no association between high-risk behavior change and circumcision status or being circumcised between 2008 and 2011.

In conclusion, the operations research carried out concurrently with the scale-up of the medical MC services in Nyanza Province, Kenya, found no evidence of risk compensation in men undergoing the procedure or in the general population, including both women and uncircumcised men. The prevalence of risk compensation endorsing beliefs declined over time, as public health education on circumcision reached wider population coverage. However, the concern about the potential risk compensation tendencies among women remains, highlighting the need for MC education targeted at women.

Empirical Risk Compensation-Related Data from Men and Women in Cape Town, South Africa

Orange Farm, South Africa is the site of one of the main trials to test the efficacy of MC for HIV prevention [6]. Although South Africa has been criticized for a slow rollout of VMMC, progress has been made in shaping policies and strategies regarding VMMC and VMMC is becoming more available. However, concerns about the effects of VMMC on traditional practices of circumcision and lack of political support have been problematic for VMMC rollout [59, 60]. Even with these concerns, MC remains a key component in HIV prevention for South Africa.

Table 6.5 Demographic characteristics of women and circumcised men in a South African township

	Women $N = 395$		Circumcised men $N = 301$	
	M	SD	M	SD
Age	29.6	10.2	29.9	7.92
Education	2.45[a]	0.90	2.92[b]	0.88
	n	%	*n*	%
Race				
Black African	154	39.0	221	73.4
Colored	235	59.5	71	23.6
Other	6	1.5	9	3.0
Married	67	17.0	73	24.3
Employed	143	36.2	195	64.8
HIV-positive	18	4.6	17	6.6
Risk compensation-related beliefs				
HIV is less of a threat if the man is circumcised	1.75	1.00	1.65	0.93
Condom use is not necessary if the man is circumcised	1.78	1.02	1.56	0.92
Number of male sex partners	1.21	3.62		
Number of female sex partners			2.06	2.68
Unprotected vaginal sex	3.46	8.92	3.62	9.10
Unprotected anal sex	0.67	2.39	0.88	3.14

[a]Corresponds to grade 8–11
[b]Corresponds to grade 12

In order to assess risk compensation-related beliefs among South African men and women, we surveyed participants attending shebeens (informal alcohol-serving establishments) in a peri-urban township in Cape Town, South Africa. Using an adaptation of the Priorities for Local AIDS Control Efforts (PLACE) community mapping methodology [61], we located and defined shebeens in the township of focus for this assessment. Alcohol-serving venues were systematically identified by approaching a total of 210 members of the community at public places such as bus stands and markets, and asking them to identify places where people go to drink alcohol. Anonymous surveys were collected from patrons from a total of six alcohol-serving venues. Individuals inside the venue were approached by field workers and asked to fill out surveys [62]. Participants were asked to report on demographics, beliefs related to MC, and sexual risk behavior over the past 4 months. Participants were given a small token of appreciation for completing surveys, such as a keychain or coffee mug.

Participants were 696 women ($n = 395$) and circumcised men ($n = 301$) attending shebeens (total survey $N = 1{,}074$, however, here we report only on men who were circumcised and women). On average, women and men were 30 years old. Women reported an average education of 8th–11th grade, and men reported an average education of 12th grade. Most women were Colored (59.5 %) with the remaining women being Black African (39.0 %). Men were most likely to be Black African (73.4 %) with the remaining men being Colored (23.6 %). Around one in five participants reported being married. Around 6 % of the sample reported HIV-positive status (Table 6.5).

Table 6.6 Risk compensation endorsing beliefs and sexual risk behavior among women and circumcised men in a South African township

Among circumcised men	Number of female sex partners Risk ratio (95 % CI)	Number of unprotected vaginal sex acts Risk ratio (95 % CI)	Number of unprotected anal sex acts Risk ratio (95 % CI)
HIV is less of a threat if the man is circumcised	1.24 (1.15–1.34)***	0.95 (0.89–1.01)	1.37 (1.23–1.54)***
Condom use is not necessary if the man is circumcised	1.05 (1.04–1.22)	1.15 (1.08–1.22)***	1.10 (0.97–1.24)
Among women	Number of male sex partners Risk ratio (95 % CI)	Number of unprotected vaginal sex acts Risk ratio (95 % CI)	Number of unprotected anal sex acts Risk ratio (95 % CI)
HIV is less of a threat if the man is circumcised	0.98 (0.90–1.08)	1.12 (1.06–1.18)***	1.25 (1.12–1.39)***
Condom use is not necessary if the man is circumcised	0.95 (0.87–1.04)	0.86 (0.81–0.91)***	1.40 (1.27–1.56)

***p<.001

With regard to risk compensation-related beliefs, both men and women, on average, reported being more likely to disagree than to agree with these items (Table 6.5). Men and women reported similar rates of unprotected sex acts and number of sex partners. In order to assess the relationships between risk compensation beliefs and number of unprotected sex acts and sex partners, we conducted general linear modeling (Table 6.6; we report risk ratios and 95 % confidence intervals). Among circumcised men, we found a significant relationship between endorsing the belief that "HIV is less of a threat if the man is circumcised" and number of female sex partners and number of unprotected anal sex acts. Among women, this belief was significantly associated with number of unprotected vaginal sex acts and number of unprotected anal sex acts. Among women and circumcised men, "Condom use is not necessary if the man is circumcised" was significantly associated with number of unprotected vaginal sex acts.

These results offer evidence for a link between risk compensation-related beliefs and greater sexual risk-taking. It is possible that having more favorable beliefs about the protective effects of circumcision led to a greater likelihood of engaging in greater sexual risk-taking. However, the beliefs were not associated with all sex behavior acts and data were cross-sectional, therefore, causal conclusions cannot be made. These findings highlight the need to ascertain whether or not participants who are already engaging in risk-taking endorse risk compensation-related beliefs, or if risk compensation-related beliefs motivate individuals to take risk who would not normally take risk.

Summarizing Remarks on MC

The limited evidence of risk compensation following MC as an HIV prevention strategy gained from the RCTs and observational studies is encouraging, but should be interpreted with caution. As we are moving from efficacy trials of circumcision toward programmatic implementation, HIV risk perception and behaviors in populations could change considerably. In VMMC promotion, as with any partially protective intervention, the educational messages about the effectiveness of the intervention must be carefully balanced with the emphasis on continuing other risk-reducing practices. In addition to the rigorous counseling as part of the VMMC procedure, a wider audience should be targeted with educational messages about the partial protection of MC against HIV, including traditionally circumcised men, women, and population as a whole. To maximize the impact of MC on HIV epidemic, it is essential to integrate VMMC with behavioral interventions.

ARV-Based Prevention

Treatment as Prevention and PrEP

For years, the benefits of initiating HIV ARV treatment early in the course of disease progression were debated with proponents arguing that early treatment is able to slow the progression of HIV to AIDS, and opponents arguing against early treatment due to medication side effects and lack of data supporting the treatment of HIV when viral replication is low. However, more recent data have documented that the costs of early initiation of HIV treatment are generally outweighed by the benefits [63–66]. Furthermore, it is now established that early initiation of HIV treatment can result in a decreased likelihood of further spreading HIV to uninfected sex partners—a strategy that has been referred to as TasP. In HIV Prevention Trials Network (HPTN) study 052, antiretroviral therapy (ART) for the HIV-positive partner in a serodiscordant couple resulted in a 96 % reduction in the likelihood of HIV transmission among individuals receiving early (350–550 CD4 counts) ARV treatment versus individuals who received delayed ART [67] (See also Thigpen et al. [68]). However, TasP has not demonstrated efficacy in all trials and medication adherence has emerged as the apparent Achilles' heel of this approach [69] (See Table 6.1).

HIV researchers and prevention and treatment advocates, are currently facing a related yet new debate regarding the benefits of starting ARV medications as an HIV prophylaxis among HIV-negative individuals at risk for infection. The results from the multinational, randomized controlled trial PrEP Initiative (iPrEX) study demonstrated a 44 % reduction in the likelihood of HIV infection among HIV-negative MSM who received oral tenofovir-emtricitabine versus those who received placebo [70].

Research conducted prior to the groundbreaking results of iPrEX and HPTN 052 on the effects of ART on risk behavior has documented the possibility of risk compensation-related behaviors. There does appear to be a relationship between being treated for HIV infection, believing one has an undetectable viral load, and increased sexual risk-taking. [71–75] However, it is important to note that the majority of these studies are limited to cross-sectional data and thus, the causal relationship has not been established.

Data from participants involved in clinical trials of both PrEP and TasP have demonstrated results similar to those that we observed in prior biomedical HIV prevention trials. This means that sexual risk-taking tends to decline among both intervention and control group participants over the course of the trial [70, 76–78]. As mentioned, these findings are consistent with the considerable risk-reduction counseling provided in this context. Furthermore, although scholarly papers have reviewed the possibility of risk compensation occurring among clinical trial participants, we must acknowledge that clinical trials are not the right environment for testing risk compensation. To begin, there is no available information on the efficacy of the product that is being tested in the trial. Furthermore, most biomedical HIV prevention trials are blinded, placebo-controlled studies. Therefore, even if participants do harbor beliefs about efficacy, they are unaware of whether they are receiving an efficacious product, an important distinction from MC trials where men are aware of their intervention condition. In sum, the sex behavior findings that emerge from clinical trials are limited to the context of that trial.

Outside of RCTs, population-based and cross-sectional surveys have identified linkages between accessing ART and increasing sexual risk behavior [79, 80]. However, in longitudinal cohort studies, initiation of ART has generally been unassociated with sexual risk-taking with some finding a decline in sexual risk behavior associated with ART. [81, 82] This finding is somewhat in contrast with regard to PrEP; in cross-sectional surveys, a substantial minority of participants reported that they would decrease their use of condoms with the availability of PrEP [83]. A considerable amount of research has focused on the effects of ARV treatments among populations of injection drug users. Specifically, prior research has focused on the influence of ARV on injection sharing behaviors and sexual risk behavior (see Marshall [84] commentary). The data on injection drug use and sexual risk behavior, and ART treatment have produced varying results [85]. Among HIV-positive intravenous drug users (IDUs), Tun et al. [86, 87] found that there is a significant association between perceiving that HIV treatments reduce the likelihood of HIV transmission, initiating ART treatment, and engaging in unprotected sex acts. However, Fu et al. [88] note a substantial reduction in unprotected sex acts post initiation of ART (similar results found in Bouhnik [89]). Furthermore, similar patterns were observed in a prospective study of HIV-positive IDUs initiating ART treatment; those participants receiving ART demonstrated an increase in unprotected sex, and there was a trend toward increasing needle sharing behaviors [90]. In contrast, this relationship, between sharing needles and initiating ART, was not observed among Canadian IDUs [91].

Microbicides

Microbicides are compounds that can be applied internally to the rectum or vagina to offer protection against STI and HIV [92]. Microbicide development has involved testing numerous delivery pathways including gels, creams, films, and suppositories. Although both men and women would benefit considerably from the availability of an effective microbicide, prior research has focused, in particular, on the advantages of these products for heterosexual women and gay/bisexual men. Microbicides offer an important addition to the arsenal of HIV prevention options as they are generally deemed as a product that women can control, which many have highlighted as being a critically important aspect for women living in areas that are resource-poor and where gender inequality is pervasive [93, 94]. Microbicides are advantageous to women who are unable to negotiate their sexual health (e.g., condom usage with their sex partner) as these products can be applied prior to sexual activity and possibly without their partners' knowledge. Furthermore, the rates of HIV infection among gay/bisexual men remain alarmingly high; therefore, there has been considerable push and support for biomedical HIV prevention for these men. Rectal microbicides may prove to be a critical prevention option for gay/bisexual men and women who engage in anal sex. Although research on rectal microbicides is limited to phase I studies, considerable work is being invested in this area of prevention [95].

Concerns for risk compensation in the context of microbicide research have been raised as a possibility in prior studies [1,96–99]. Recent advances in microbicides have led to a greater urgency to understand behavioral responses to the availably of microbicides. In one trial, CAPRISA 004, an ARV-laced formulation microbicide was 39 % effective in reducing the likelihood of HIV infection among women receiving an experimental vaginal microbicide compared with women receiving a placebo lubricant [100]. Unfortunately, subsequent larger trials did not replicate the effects found in CAPRISA 0004. Nevertheless, this reduction in HIV incidence with product adherence is certainly promising and hopefully future generations of microbicide development will reveal products that continue to show effectiveness. However, with 39 % reduction (54 % reduction among women who reported high product adherence) concerns for behavioral adaptation in response to using microbicides are valid. It is important to recognize that although the population incidence may decline with the availability of microbicides, on an individual level, people who use the product will still become infected. Furthermore, microbicides will rely on continual and consistent usage—as opposed to vaccines or MC, which require either one or a limited number of steps to attain.

In the only study to date to follow women who received microbicides, Karim et al. observed a decline in risk behavior over the course of the study [100]. This finding is consistent with many RCTs where individuals are followed over the course of multiple years and provided with regular risk-reduction counseling. It is unclear as to what the exact mechanisms are that drive risk-taking to lower levels, but it is likely related to either the intensive risk-reduction counseling provided during the course of the trial, regression to the mean (a phenomenon where high level of risk-taking will

lower toward the mean during follow-up assessments—this is particularly critical when sexual risk-taking is tied to study eligibility), or due to reactivity, wherein participants engage in fewer acts of sexual risk-taking because they are aware that they will be reporting on these behaviors.

Although risk compensation generally focuses on sexual risk-taking, data from Karim et al.'s [100] work also highlight an interesting extension of this phenomenon. Again, in the first large-scale trial to show effectiveness of a microbicide to prevent HIV infection, Karim et al. note an important relationship between adherence to microbicides and sexual risk-taking. "The mean number of sex acts in the high, intermediate and low gel adherers was 3.2, 5.0 and 6.7 per month respectively." Therefore, there appears to be a relationship between sexual risk-taking and regimen adherence. This finding is interesting in that it highlights the notion that those who engage in sexual risk-taking—or may be even those who engage in greater sexual risk-taking in response to biomedical HIV prevention—are more likely to erroneously use prevention products or use prevention products inconsistently. This relationship is critical as it suggests that those who are in most need of prevention options may be most likely to use them ineffectively. In our efforts to move forward with making biomedical HIV prevention technologies available, we must note the need to effectively intervene with those at greatest risk for HIV infection. Although the exact relationship is unclear at this point, this finding draws attention to the possibility that sexual risk-taking may vary with poor product regimen adherence, and furthermore, may exacerbate the potential effects of risk compensation.

HIV Vaccine

Arguably, a vaccination for HIV has been the most awaited and heavily invested prevention technology in the field of HIV/AIDS research. Although several HIV vaccine candidates have proceeded to phase I clinical trials, only a select few have made it to phase III and none have warranted widespread availability to the general public. Yet, there remain multiple active research trials in search of an effective and safe vaccine. The availability of an effective HIV vaccine remains the most plausible solution to eradicate the HIV virus (See Table 6.1).

There have been several studies that have explored the possibility of risk compensation in the context of HIV vaccination research. Some of the earliest studies in these areas have found that concerns for risk compensation may play an important role in the implementation of vaccines. In one focus group study, conducted with commercial sex workers, participants reported that if they were vaccinated the desire for condom usage among their customers would likely decrease due to a reduction in the concern for HIV acquisition [101]. In a similar cross-sectional survey conducted with gay men, African-American women, and people who use illicit drugs, "nearly one-quarter of the sample indicated a likelihood that their HIV-risk behavior would increase after vaccination. This increase was positively associated ($r = 0.24$) with increased intent to be vaccinated" [102]. Furthermore, in a longitudinal study

of participants in phase I and II vaccine trials, changes in sexual risk behavior were studied and it was concluded that there was a significant increase in unprotected anal intercourse over time [103]. Increases in such types of risky behaviors can potentially reverse the effects of HIV vaccines, especially considering that these vaccines candidates are only partially effective against HIV acquisition.

More recently, several studies focused on risk compensation in relation to HIV vaccinations. A study conducted among high-risk adults in Los Angeles in 2009, contained a cross-sectional survey consisting of structured interviews where participants rated hypothetical vaccine acceptability and postvaccine risk behavior intentions [104]. This study ($n = 1{,}164$) showed that efficacy was the most important factor for acceptability, followed by side effects and out of pocket cost. 10 % of participants reported that they would decrease condom usage after vaccination. This finding was true in the case of both vaginal as well as anal sex. Participants also reported that intentions to increase sexual risk behavior were greater when presented with a highly effective vaccine as opposed to a less effective vaccine. Additionally, as vaccine efficacy increased, greater numbers of participants reported intentions to increase their number of sexual partners. Overall, 10 % of participants reported that they would increase their number of sexual partners.

Similar results were also seen in a study conducted in Thailand in 2010, with transgender women and MSM [105]. This mixed method study that had both interviews and venue-based surveys contained questions about preventive HIV vaccine acceptability and sexual risk behaviors. The results of this study also showed that over one-third of participants reported intentions to increase postvaccination risk behaviors ($n = 255$). Around 15 % of participants planned to decrease condom use for anal sex and 22 % planned on decreasing condom use for vaginal sex. Moreover, 25 % of participants reported intentions to increase their number of sex partners. Further analysis revealed no significant association between risk compensation and vaccine acceptability. These studies stress the need for behavioral interventions and counseling to accompany vaccinations in order to counteract the effects of risk compensatory behavior. It is also essential that these interventions occur both before and during the time when prevention technologies are administered.

In a further vaccine acceptability study conducted among youth in South Africa in 2010 [106], beliefs and knowledge about HIV vaccines were assessed among participants in focus groups. This study also contained important gender-based differences relating to motivations for HIV vaccine uptake. Protection against HIV transmission that is out of an individual's control was the most discussed motivator for vaccine uptake among both genders. In terms of gender differences, female participants described the ability to raise children and have a family with one HIV-positive partner as most important reasons for vaccine uptake, while the majority of male participants "cited the ability to have sex without a condom and having multiple sexual partners as advantages of taking the HIV vaccine" [106].

These studies demonstrate that risk compensation is an important behavioral factor in implementing vaccines. Unless a widely available HIV vaccine is highly effective at preventing HIV acquisition, risk compensation remains a potential barrier that can mitigate the benefits of vaccination. As current vaccine candidates are no more

than 30–40 % efficacious, potential increases in risky sexual behavior following vaccination should be of considerable concern. Therefore, counseling and public health awareness are essential components that need to be supplemented with HIV vaccine approaches.

Conclusions

Based on our review, there is mixed evidence for risk compensation occurring as a result of HIV prevention technologies. However, there is clearly a dearth of data from studies designed specifically to test risk compensation. The overwhelming majority of studies that we report on were designed to test a primary outcome indirectly related to risk compensation. Furthermore, many studies reported on behavioral intentions and attitudes, which do provide important insight into how individuals process perceptions of risk, but do not allow us to make projections about the impact of risk compensation on HIV prevention technology. With the currently available data, we recommend that understanding the impact of risk compensation be prioritized as an intervention outcome. Moreover, in order to accurately assess this information, longitudinal cohort studies of risk compensation with behavioral counseling that mimic real-world available intervention methods need to be completed.

Similarly, we must shift our focus away from RCTs of biomedical HIV prevention trials as a resource for assessing risk compensation as the methods required in these trial designs and the resulting behavioral outcomes do not accurately reflect real-world patterns of counseling and sexual risk-taking. For instance, we note fairly divergent findings relating to risk compensation when comparing results from RCTs versus other study designs. If we relied solely on evidence from RCTs to determine the effects of risk compensation, we would likely cease investigation into this area as across-the-board we only identified evidence of risk reducing behaviors in this context (albeit with rates of reduction in risk-taking varying by arms in some RCTs). However, multiple studies outside of RCTs give us reason to believe that risk compensation is very much a concern among individuals who are from populations that would be targeted for rolling out biomedical technologies. In sum, future research on risk compensation must include study designs that are specifically tailored to answer research questions relating to this area of inquiry.

We also note the need for further research in the area of risk compensation relating to TasP and PrEP. Interestingly, studies investigating risk compensation and *initiation* of ART do offer some evidence of risk compensation, however, this research has not been translated to specifically focusing on the effects ARV for HIV prevention on sex behavior. Moreover, given that TasP and PrEP are highly effective when they are adhered to and that these technologies are currently available, we should be especially cognizant of prioritizing research on risk compensation in these areas.

Moreover, the degree to which individuals may or may not compensate their risk behaviors and the contextual factors that influence risk behaviors are currently unclear. Similarly, the degree to which different prevention technologies affect behavior

is unknown but would most likely vary as a function of the perceived lowered risk associated with that technology. Thus, assessing the likelihood and strength of risk compensation would be the first step in understanding the impact of it. Similarly, researching psychosocial factors that may affect risk compensation will also be important. The studies reviewed in this chapter are based on data collected from a wide variety of cultural, economic, and religious backgrounds. Understanding how risk compensation manifests itself in certain contexts may not be applicable to other scenarios. Education around the effectiveness of a prevention technology and in what ways individuals can expect to benefit from a technology will likely be critical.

References

1. Eaton LA, Kalichman S. Risk compensation in HIV prevention: implications for vaccines, microbicides, and other biomedical HIV prevention technologies. Curr HIV/AIDS Rep. 2007 Dec;4(4):165–72.
2. Wilde GJS. Target risk: dealing with the danger of death, disease and damage in everyday decisions. Toronto: PDE Publications; 1994.
3. World Health Organization, Joint United Nations Programme on HIV/AIDS. New data on male circumcision and HIV prevention: policy and programme implications. 2007. http://libdoc.who.int/publications/2007/9789241595988_eng.pdf. Accessed September 21, 2012.
4. Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet. 2007 Feb 24;369(9562):643–56.
5. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007 Feb 24;369(9562):657–66.
6. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med. 2005 Nov;2(11):e298.
7. Bollinger LA, Stover J, Musuka G, Fidzani B, Moeti T, Busang L. The cost and impact of male circumcision on HIV/AIDS in Botswana. J Int AIDS Soc. 2009;12:7.
8. Gray RH, Li X, Kigozi G, Serwadda D, Nalugoda F, Watya S, et al. The impact of male circumcision on HIV incidence and cost per infection prevented: a stochastic simulation model from Rakai, Uganda. AIDS (London, England). 2007 Apr 23;21(7):845–50.
9. Nagelkerke NJ, Moses S, de Vlas SJ, Bailey RC. Modelling the public health impact of male circumcision for HIV prevention in high prevalence areas in Africa. BMC Infect Dis. 2007;7:16.
10. UNAIDS/WHO/SACEMA Expert Group on Modelling the Impact and Cost of Male Circumcision for HIV Prevention. Male circumcision for HIV prevention in high HIV prevalence settings: what can mathematical modelling contribute to informed decision making? PLoS Med. 2009 Sep;6(9):e1000109.
11. Williams BG, Lloyd-Smith JO, Gouws E, Hankins C, Getz WM, Hargrove J, et al. The potential impact of male circumcision on HIV in Sub-Saharan Africa. PLoS Med. 2006 Jul;3(7):e262.
12. Weiss HA, Dickson KE, Agot K, Hankins CA. Male circumcision for HIV prevention: current research and programmatic issues. AIDS (London, England). 2010 Oct;24 Suppl 4:S61–9.
13. Kahn JG, Marseille E, Auvert B. Cost-effectiveness of male circumcision for HIV prevention in a South African setting. PLoS Med. 2006 Dec;3(12):e517.
14. Westercamp N, Bailey RC. Acceptability of male circumcision for prevention of HIV/AIDS in sub-Saharan Africa: a review. AIDS Behav. 2007 May;11(3):341–55.

15. de Bruyn G, Martinson NA, Gray GE. Male circumcision for HIV prevention: developments from sub-Saharan Africa. Expert Rev Anti Infect Ther. 2010 Jan;8(1):23–31.
16. Hankins C, Forsythe S, Njeuhmeli E. Voluntary medical male circumcision: an introduction to the cost, impact, and challenges of accelerated scaling up. PLoS Med. 2011 Nov;8(11):e1001127.
17. Cassell MM, Halperin DT, Shelton JD, Stanton D. Risk compensation: the Achilles' heel of innovations in HIV prevention? BMJ (Clinical research ed). 2006 Mar 11;332(7541):605–7.
18. Kalichman S, Eaton L, Pinkerton S. Circumcision for HIV prevention: failure to fully account for behavioral risk compensation. PLoS Med. 2007 Mar 27;4(3):e138; author reply e46.
19. White RG, Glynn JR, Orroth KK, Freeman EE, Bakker R, Weiss HA, et al. Male circumcision for HIV prevention in sub-Saharan Africa: who, what and when? AIDS (London, England). 2008 Sep 12;22(14):1841–50.
20. Eaton LA, Cain DN, Agrawal A, Jooste S, Udemans N, Kalichman SC. The influence of male circumcision for HIV prevention on sexual behaviour among traditionally circumcised men in Cape Town, South Africa. Int J STD AIDS. 2011 Nov;22(11):674–9.
21. Maughan-Brown B, Venkataramani AS. Learning that circumcision is protective against HIV: risk compensation among men and women in Cape Town, South Africa. PLoS One. 2012;7(7):e40753.
22. Anderson J, Wilson D, Templeton DJ, Grulich A, Carter R, Kaldor J. Cost-effectiveness of adult circumcision in a resource-rich setting for HIV prevention among men who have 2 with men. J Infect Dis. 2009 Dec 15;200(12):1803–12.
23. Templeton DJ, Millett GA, Grulich AE. Male circumcision to reduce the risk of HIV and sexually transmitted infections among men who have sex with men. Curr Opin Infect Dis. 2010 Feb;23(1):45–52.
24. Wei C, Raymond HF, McFarland W, Buchbinder S, Fuchs JD. What is the potential impact of adult circumcision on the HIV epidemic among men who have sex with men in San Francisco? Sex Transm Dis. 2011 Apr;38(4):353–5.
25. Alsallaq RA, Cash B, Weiss HA, Longini IM Jr, Omer SB, Wawer MJ, et al. Quantitative assessment of the role of male circumcision in HIV epidemiology at the population level. Epidemics. 2009 Sep;1(3):139–52.
26. Andersson KM, Owens DK, Paltiel AD. Scaling up circumcision programs in Southern Africa: the potential impact of gender disparities and changes in condom use behaviors on heterosexual HIV transmission. AIDS Behav. 2011 Jul;15(5):938–48.
27. Dushoff J, Patocs A, Shi CF. Modeling the population-level effects of male circumcision as an HIV-preventive measure: a gendered perspective. PLoS One. 2011;6(12):e28608.
28. Hallett TB, Alsallaq RA, Baeten JM, Weiss H, Celum C, Gray R, et al. Will circumcision provide even more protection from HIV to women and men? New estimates of the population impact of circumcision interventions. Sex Transm Infect. 2011 Mar;87(2):88–93.
29. Hallett TB, Singh K, Smith JA, White RG, Abu-Raddad LJ, Garnett GP. Understanding the impact of male circumcision interventions on the spread of HIV in southern Africa. PLoS One. 2008;3(5):e2212.
30. Njeuhmeli E, Forsythe S, Reed J, Opuni M, Bollinger L, Heard N, et al. Voluntary medical male circumcision: modeling the impact and cost of expanding male circumcision for HIV prevention in eastern and southern Africa. PLoS Med. 2011 Nov;8(11):e1001132.
31. Gray R, Kigozi G, Kong X, Ssempiija V, Makumbi F, Wattya S, et al. The effectiveness of male circumcision for HIV prevention and effects on risk behaviors in a posttrial follow-up study. AIDS (London, England). 2012 Mar 13;26(5):609–15.
32. Siegfried N, Muller M, Deeks JJ, Volmink J. Male circumcision for prevention of heterosexual acquisition of HIV in men. Cochrane Database Syst Rev (Online). 2009(2):CD003362.
33. Eaton L, Kalichman SC. Behavioral aspects of male circumcision for the prevention of HIV infection. Curr HIV/AIDS Rep. (Research Support, N.I.H., Extramural Review). 2009 Nov;6(4):187–93.
34. Mattson CL, Campbell RT, Bailey RC, Agot K, Ndinya-Achola JO, Moses S. Risk compensation is not associated with male circumcision in Kisumu, Kenya: a multi-faceted assessment of men enrolled in a randomized controlled trial. PLoS One. 2008;3(6):e2443.

35. Agot KE, Kiarie JN, Nguyen HQ, Odhiambo JO, Onyango TM, Weiss NS. Male circumcision in Siaya and Bondo Districts, Kenya: prospective cohort study to assess behavioral disinhibition following circumcision. J Acquir Immune Defic Syndr. 2007 Jan 1;44(1):66–70.
36. Wang AL, Duke W, Schmid GP. Print media reporting of male circumcision for preventing HIV infection in sub-Saharan Africa. Bull World Health Organ. 2009 Aug;87(8):595–603.
37. Communication for Change (C-Change) Project. Voluntary medical male circumcision communication guide for Nyanza Province. Nairobi, Kenya 2011.
38. Riess TH, Achieng MM, Otieno S, Ndinya-Achola JO, Bailey RC. "When I was circumcised I was taught certain things": risk compensation and protective sexual behavior among circumcised men in Kisumu, Kenya. PLoS One. 2010;5(8):e12366.
39. Grund JM, Hennink MM. A qualitative study of sexual behavior change and risk compensation following adult male circumcision in urban Swaziland. AIDS Care. 2012;24(2):245–51.
40. Wang Z, Lau JT, Gu J. Acceptability of circumcision among clients of female sex worker in Hong Kong. AIDS Behav. 2012 Nov 13;16(7):1836–45.
41. Gust DA, Kretsinger K, Pals SL, Gaul ZJ, Hefflefinger JD, Begley EB, et al. Male circumcision as an HIV prevention intervention in the U.S.: influence of health care providers and potential for risk compensation. Prev Med. 2011 Mar–Apr;52(3–4):270–3.
42. Andersson N, Cockcroft A. Male circumcision, attitudes to HIV prevention and HIV status: a cross-sectional study in Botswana, Namibia and Swaziland. AIDS Care. 2012;24(3):301–9.
43. Lissouba P, Taljaard D, Rech D, Dermaux-Msimang V, Legeai C, Lewis D, et al. Adult male circumcision as an intervention against HIV: an operational study of uptake in a South African community (ANRS 12126). BMC Infect Dis. 2011;11:253.
44. Westercamp M, Agot KE, Ndinya-Achola J, Bailey RC. Circumcision preference among women and uncircumcised men prior to scale-up of male circumcision for HIV prevention in Kisumu, Kenya. AIDS Care. 2012;24(2):157–66.
45. Bailey RC, Muga R, Poulussen R, Abicht H. The acceptability of male circumcision to reduce HIV infections in Nyanza Province, Kenya. AIDS Care. 2002 Feb;14(1):27–40.
46. Ngalande R, Levy J, Kapondo C, Bailey RC. Acceptability of male circumcision for prevention of HIV infection in Malawi. AIDS Behav. 2006;10(4):377–85.
47. Rain-Taljaard RC, Lagarde E, Taljaard DJ, Campbell C, MacPhail C, Williams B, et al. Potential for an intervention based on male circumcision in a South African town with high levels of HIV infection. AIDS Care. 2003 Jun;15(3):315–27.
48. Kelly A, Kupul M, Fitzgerald L, Aeno H, Neo J, Naketrumb R, et al. "Now we are in a different time; various bad diseases have come." Understanding men's acceptability of male circumcision for HIV prevention in a moderate prevalence setting. BMC Public Health. 2012;12:67.
49. Godlonton S, Munthali A, Thornton R. Behavioral Response to information? Circumcision, information, and HIV prevention. Bureau for Research and Economic Analysis of Development Working Paper no. 313; 2011.
50. Peltzer K, Simbayi L, Banyini M, Kekana Q. HIV risk reduction intervention among traditionally circumcised young men in South Africa: a cluster randomized control trial. J Assoc Nurses AIDS Care. 2011 Sep–Oct;22(5):397–406.
51. Brown JE, Micheni KD, Grant EM, Mwenda JM, Muthiri FM, Grant AR. Varieties of male circumcision: a study from Kenya. Sex Transm Dis. 2001 Oct;28(10):608–12.
52. Maughan-Brown B, Venkataramani AS, Nattrass N, Seekings J, Whiteside AW. A cut above the rest: traditional male circumcision and HIV risk among Xhosa men in Cape Town, South Africa. J Acquir Immune Defic Syndr. 2011 Dec 15;58(5):499–505.
53. Bailey RC, Egesah O, Rosenberg S. Male circumcision for HIV prevention: a prospective study of complications in clinical and traditional settings in Bungoma, Kenya. Bull World Health Organ. 2008 Sep;86(9):669–77.
54. Wilcken A, Keil T, Dick B. Traditional male circumcision in eastern and southern Africa: a systematic review of prevalence and complications. Bull World Health Organ. 2010 Dec 1;88(12):907–14.

55. World Health Organization & United Nations Joint Programme on HIV/AIDS. Male circumcision: global trends and determinants of prevalence, safety and acceptability. Geneva: WHO; 2007.
56. Riess TH, Achieng MM, Otieno S, Bailey RC. Risk compensation associated with the scale up of medical male circumcision among women in Kisumu, Kenya. 2012.
57. Lanham M, L'Engle KL, Loolpapit M, Oguma IO. Women's roles in voluntary medical male circumcision in Nyanza Province, Kenya. PLoS One. 2012;7(9):e44825.
58. Wawer MJ, Makumbi F, Kigozi G, Serwadda D, Watya S, Nalugoda F, et al. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomised controlled trial. Lancet. 2009 Jul 18;374(9685):229–37.
59. IRIN. South Africa: male circumcision: why the delay? Humanitarian News and Analysis. 2009. http://www.irinnewsorg/Report/87315/SOUTH-AFRICA-Male-circumcision-why-the-delay. Accessed March 15, 2013.
60. Ondoa C. Africa: renew commitment to male circumcision. allAfrica. 2012. http://allafrica-com/stories/201208080073html. Accessed March 15, 2013.
61. Weir SS, Pailman C, Mahlalela X, Coetzee N, Meidany F, Boerma JT. From people to places: focusing AIDS prevention efforts where it matters most. AIDS. 2003 Apr 11;17(6):895–903.
62. Miller KW, Wilder LB, Stillman FA, Becker DM. The feasibility of a street-intercept survey method in an African-American community. Am J Public Health. 1997 Apr;87(4):655–8.
63. Schackman BR, Freedberg KA, Weinstein MC, Sax PE, Losina E, Zhang H, et al. Cost-effectiveness implications of the timing of antiretroviral therapy in HIV-infected adults. Arch Intern Med. 2002 Nov 25;162(21):2478–86.
64. Siegfried N, Uthman OA, Rutherford GW. Optimal time for initiation of antiretroviral therapy in asymptomatic, HIV-infected, treatment-naive adults. Cochrane Database Syst Rev. 2010(3):CD008272.
65. When To Start Consortium, Sterne JA, May M, Costagliola D, de Wolf F, Phillips AN, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. Lancet. 2009 Apr 18;373(9672):1352–63.
66. Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. New Eng J Med. 2009 Apr 30;360(18):1815–26.
67. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. New Eng J Med. 2011 Aug 11;365(6):493–505.
68. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. New Eng J Med. 2012 Aug 2;367(5):423–34.
69. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. New Eng J Med. 2012 Aug 2;367(5):411–22.
70. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. New Eng J Med. 2010 Dec 30;363(27):2587–99.
71. Hart GJ, Williamson LM. Increase in HIV sexual risk behaviour in homosexual men in Scotland, 1996–2002: prevention failure? Sexually Transm Infect. 2005 Oct;81(5):367–72.
72. Kalichman SC. Post-exposure prophylaxis for HIV infection in gay and bisexual men. Implications for the future of HIV prevention. Am J Prev Med. 1998 Aug;15(2):120–7.
73. Dukers NH, Goudsmit J, de Wit JB, Prins M, Weverling GJ, Coutinho RA. Sexual risk behaviour relates to the virological and immunological improvements during highly active antiretroviral therapy in HIV-1 infection. AIDS. 2001 Feb 16;15(3):369–78.
74. Stolte IG, de Wit JB, van Eeden A, Coutinho RA, Dukers NH. Perceived viral load, but not actual HIV-1-RNA load, is associated with sexual risk behaviour among HIV-infected homosexual men. AIDS. 2004 Sep 24;18(14):1943–9.

75. Ostrow DE, Fox KJ, Chmiel JS, Silvestre A, Visscher BR, Vanable PA, et al. Attitudes towards highly active antiretroviral therapy are associated with sexual risk taking among HIV-infected and uninfected homosexual men. AIDS. 2002 Mar 29;16(5):775–80.
76. Guest G, Shattuck D, Johnson L, Akumatey B, Clarke EE, Chen PL, et al. Changes in sexual risk behavior among participants in a PrEP HIV prevention trial. Sex Transm Dis. 2008 Dec;35(12):1002–8.
77. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. New Eng J Med. 2012 Aug 2;367(5):399–410.
78. Liu A, Vittinghoff E, Chillag K, Mayer KH, Grohskopf L, Thompson M, et al. No evidence of sexual risk compensation among HIV-uninfected men who have sex with men (MSM) participating in a tenofovir Pre-Exposure Prophylaxis (PrEP) trial. IAS Conference on HIV Pathogenesis and Treatment: Abstract no MOPE381. 2011.
79. Cohen CR, Montandon M, Carrico AW, Shiboski S, Bostrom A, Obure A, et al. Association of attitudes and beliefs towards antiretroviral therapy with HIV-seroprevalence in the general population of Kisumu, Kenya. PLoS One. 2009;4(3):e4573.
80. Ncube NM, Akunna J, Babatunde F, Nyarko A, Yatich NJ, Ellis W, et al. Sexual risk behaviour among HIV-positive persons in Kumasi, Ghana. Ghana Med J. 2012 Mar;46(1):27–33.
81. Bechange S, Bunnell R, Awor A, Moore D, King R, Mermin J, et al. Two-year follow-up of sexual behavior among HIV-uninfected household members of adults taking antiretroviral therapy in Uganda: no evidence of disinhibition. AIDS Behav. 2010 Aug;14(4):816–23.
82. Venkatesh KK, de Bruyn G, Lurie MN, Mohapi L, Pronyk P, Moshabela M, et al. Decreased sexual risk behavior in the era of HAART among HIV-infected urban and rural South Africans attending primary care clinics. AIDS. 2010 Nov 13;24(17):2687–96.
83. Golub SA, Kowalczyk W, Weinberger CL, Parsons JT. Preexposure prophylaxis and predicted condom use among high-risk men who have sex with men. J Acquir Immune Defic Syndr. 2010 Aug;54(5):548–55.
84. Marshall BD, Wood E. Putting risk compensation to rest: reframing the relationship between risk behavior and antiretroviral therapy among injection drug users. AIDS. 2012 Nov 28;26(18):2405–7.
85. Rusch ML, Farzadegan H, Tarwater PM, Safaeian M, Vlahov D, Strathdee SA. Sexual risk behavior among injection drug users before widespread availability of highly active antiretroviral therapy. AIDS Behav. 2005 Sep;9(3):289–99.
86. Tun W, Celentano DD, Vlahov D, Strathdee SA. Attitudes toward HIV treatments influence unsafe sexual and injection practices among injecting drug users. AIDS. 2003 Sep 5;17(13):1953–62.
87. Tun W, Gange SJ, Vlahov D, Strathdee SA, Celentano DD. Increase in sexual risk behavior associated with immunologic response to highly active antiretroviral therapy among HIV-infected injection drug users. Clin Infect Dis. 2004 Apr 15;38(8):1167–74.
88. Fu TC, Westergaard RP, Lau B, Celentano DD, Vlahov D, Mehta SH, et al. Changes in sexual and drug-related risk behavior following antiretroviral therapy initiation among HIV-infected injection drug users. AIDS. 2012 Nov 28;26(18):2383–91.
89. Bouhnik AD, Moatti JP, Vlahov D, Gallais H, Dellamonica P, Obadia Y. Highly active antiretroviral treatment does not increase sexual risk behaviour among French HIV infected injecting drug users. J Epidemiol Community Health. 2002 May;56(5):349–53.
90. Vlahov D, Safaien M, Lai S, Strathdee SA, Johnson L, Sterling T, et al. Sexual and drug risk-related behaviours after initiating highly active antiretroviral therapy among injection drug users. AIDS. 2001 Nov 23;15(17):2311–6.
91. Kuyper L, Milloy MJ, Marshall BD, Zhang R, Kerr T, Montaner JS, et al. Does initiation of HIV antiretroviral therapy influence patterns of syringe lending among injection drug users? Addict Behav. 2011 May;36(5):560–3.
92. WHO. World Health Organization, HIV/AIDS, Microbicides. 2012. http://www.who.int/hiv/topics/microbicides/microbicides/en/. Accessed March 15, 2013.

93. Venables E, Stadler J. 'The study has taught me to be supportive of her': empowering women and involving men in microbicide research. Cult Health Sex. (Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't). 2012;14(2):181–94.
94. Raphael MC. Microbicides are promoted as offering a 'female-controlled' HIV prevention method: so can they revolutionize the HIV crisis of young women in Kenya? J Public Health (Oxf). 2012 Dec 10;34(4):625–30.
95. McGowan I. Rectal microbicide development. Curr Opin HIV AIDS. 2012 Nov;7(6):526–33.
96. Rader M, Marks G, Mansergh G, Crepaz N, Miller LC, Appleby PR, et al. Preferences about the characteristics of future HIV prevention products among men who have sex with men. AIDS Educ Prev. 2001 Apr;13(2):149–59.
97. Carballo-Dieguez A, O'Sullivan LF, Lin P, Dolezal C, Pollack L, Catania J. Awareness and attitudes regarding microbicides and Nonoxynol-9 use in a probability sample of gay men. AIDS Behav. (Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't). 2007 Mar;11(2):271–6.
98. Hogben M, Liddon N. Disinhibition and risk compensation: scope, definitions, and perspective. Sex Transm Dis. (Comment Editorial). 2008 Dec;35(12):1009–10.
99. Crosby RA, Ricks J, Young A. Condom migration resulting from circumcision, microbicides and vaccines: brief review and methodological considerations. Sex Health. (Review). 2012 Mar;9(1):96–102.
100. Karim QA, Karim SSA, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010 Sep 3;329(5996):1168–74.
101. Nyamathi AM, Suhadev M, Swaminathan S, Fahey JL. Perceptions of a community sample about participation in future HIV vaccine trials in south India. AIDS Behav. 2007 Jul;11(4):619–27.
102. Crosby RA, Holtgrave DR. Will sexual risk behaviour increase after being vaccinated for AIDS? Int J STD AIDS. 2006 Mar;17(3):180–4.
103. Chesney MA, Chambers DB, Kahn JO. Risk behavior for HIV infection in participants in preventive HIV vaccine trials: a cautionary note. J Acquir Immune Defic Syndr Hum Retrovirol. 1997 Dec 1;16(4):266–71.
104. Newman PA, Lee SJ, Duan N, Rudy E, Nakazono TK, Boscardin J, et al. Preventive HIV vaccine acceptability and behavioral risk compensation among a random sample of high-risk adults in Los Angeles (LA VOICES). Health Serv Res. 2009 Dec;44(6):2167–79.
105. Newman PA, Roungprakhon S, Tepjan S, Yim S. Preventive HIV vaccine acceptability and behavioral risk compensation among high-risk men who have sex with men and transgenders in Thailand. Vaccine. 2010 Jan 22;28(4):958–64.
106. Sayles JN, Macphail CL, Newman PA, Cunningham WE. Future HIV vaccine acceptability among young adults in South Africa. Health Educ Behav. 2010 Apr;37(2):193–210.
107. Ayiga N, Letamo G. Impact of male circumcision on HIV risk compensation through the impediment of condom use in Botswana. Afr Health Sci. 2011 Dec;11(4):550–9.
108. Marshall BD, Milloy MJ, Kerr T, Zhang R, Montaner JS, Wood E. No evidence of increased sexual risk behaviour after initiating antiretroviral therapy among people who inject drugs. AIDS. 2010 Sep 10;24(14):2271–8.

Chapter 7
Mental Health and Substance Use in the Scale-Up of HIV Prevention

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The past several years have witnessed dramatic advances in the potential for effective biomedical HIV prevention interventions, including but not limited to topical vaginal and rectal microbicides [1], oral preexposure prophylaxis (PrEP) [2], and early initiation of antiretroviral therapy (ART) for HIV-infected individuals to prevent HIV transmission [3, 4]. Recent landmark clinical trials, such as CAPRISA 004 [5] and

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iPrEx [6], have shown that vaginal microbicides and PrEP can reduce the likelihood of HIV infection by 39 and 44 %, respectively. Additionally, the results of HIV Prevention Trials Network (HPTN) 052 showed that early initiation of ART reduced HIV transmission by over 96 % by decreasing viral load to undetectable levels in HIV-serodiscordant couples, thereby firmly establishing ART as a potential biomedical intervention to prevent HIV transmission [3]. These successes demonstrate that opportunities for biomedical prevention of HIV are promising, and future research should determine how best to implement these different prevention strategies with high-risk populations in conjunction with behavioral interventions and community-level structural change [7]. Nonetheless, many previous trials of microbicides and PrEP failed to show a decrease in HIV incidence [8–10]. For example, results of the VOICE trial found that neither the PrEP nor microbicide strategies showed efficacy in protecting against HIV [8]. Across these trials, it has been hypothesized that poor levels of treatment adherence accounted for the ineffectiveness of the interventions [9, 11, 12].

It is well known that numerous mental health and substance use issues impact adherence to ART, but there are relatively little data on adherence to PrEP and microbicides, and the mental health and substance use issues implicated therein. In this chapter, we discuss the impact of mental health and substance use on key HIV health behaviors, specifically HIV transmission risk behavior and ART adherence. Using the lessons learned from this research, we then examine how mental health and substance use issues are implicated in PrEP and microbicide adherence and effectiveness. Finally, we discuss future research directions for addressing mental health and substance use issues in biomedical prevention interventions.

Mental Health and HIV Sexual Transmission Risk

Individuals living with, or at risk for acquiring HIV, have higher prevalence rates of mental health problems compared with the general population, an important consideration when utilizing biomedical prevention agents for this population. Epidemiological studies demonstrate that sexual minorities are at increased risk for depressive and anxiety disorders [13–15], and gay, bisexual, and other men who have sex with men (MSM) are, by far, the highest risk group for HIV acquisition in the USA. Similarly, among HIV-infected individuals, there are elevated rates of depression, posttraumatic stress (PTSD), and other anxiety disorders [16, 17], and the extent to which risk factors or the disorders themselves were present before or after acquiring HIV is not known. Hence, these problems are likely part of a profile that places individuals at risk for acquiring HIV (i.e., those who would be candidates for chemoprophylaxis).

Among those living with HIV, the best data likely come from a nationally representative probability sample from the HIV Cost and Services Utilization Study (HCSUS), which found, among HIV-infected individuals, a prevalence rate for major depressive disorder of 36 %, which contrasts with a 7.6 % prevalence rate in a national sample of uninfected individuals using a similar assessment instrument [17]. This study focused on individuals who were already in care, which may represent

approximately 77 % of the HIV-infected population (CDC, 2011); the rates of mental health problems may be even higher in those who are not aware of their diagnosis and linked to/retained in care [18]. If medications to prevent HIV are only to be used among those at highest risk for acquiring the disease, taken together, these data suggest that such individuals would be also among those at highest risk for mental health/psychosocial problems.

Among MSM, the population from which the iPrEx study was sampled from, HIV risk appears to occur in the context of intertwined psychosocial problems, or *syndemics*. Stall et al. were the first to report this phenomenon: they examined depression, childhood sexual abuse, intimate partner violence, and substance use, and reported that as MSM endorsed a greater number of psychological problems, their risk for engaging in sexual risk behaviors grew, as did their risk for HIV infection [19]. Mustanski et al. found synergistic effects of multiple psychological risk factors on sexual risk taking in young HIV-negative MSM [20]. Our own work suggests that this phenomenon may also extend to HIV-infected MSM. In a sample of 380 HIV-infected MSM, those with one to three syndemic indicators (childhood sexual abuse, PTSD, anxiety disorders, depression, polysubstance use, alcohol abuse) had a greater than twofold increase in the likelihood of sexual transmission risk behavior, whereas those with four or more syndemic indicators experienced a fourfold increase in likelihood of sexual transmission risk behavior [21]. Similar findings from our group have been shown in a study of over 30,000 HIV-infected MSM in Latin America (where many of the iPrEx participants were enrolled), Spain, and Portugal, in which participants with higher numbers of syndemic indicators exhibited heightened risk of serodiscordant unprotected anal intercourse acts [22]. Hence, the data reviewed earlier suggest that if PrEP is to be implemented among MSM, those with the highest risk are likely to have intertwined mental health and substance abuse problems, which may impair the uptake or adherence to biomedical prevention agents.

Elevated levels of mental health problems among individuals living with, or at risk for, HIV are salient for both biomedical and behavioral HIV prevention programs in that the adherence interventions to PrEP or other biomedical agents will need to account for these issues. As posited by Sikkema et al. [23], treatment of mental health problems likely causes reductions in HIV transmission through initial decreases in mental health symptoms, and subsequent reductions in HIV sexual transmission risk behaviors and improvements in ART adherence. In accordance with this model, there is some evidence that mental health problems may also moderate the effect of HIV prevention interventions on HIV transmission and on interventions for adherence. For instance, examining data from the EXPLORE Study, the largest HIV prevention intervention among MSM in the USA to date, participants reporting a history of childhood sexual abuse (which in turn predicted higher rates of depression and substance use) showed no reductions in HIV risk over the course of the intervention [24]. Thus, explicitly addressing mental health problems in the context of HIV prevention interventions may be a particularly effective approach [25]. Accordingly, when considering adherence interventions for PrEP in MSM populations, only utilizing very brief adherence counseling based on traditional psychological models that do not address mental health and substance use problems may result in inadequate uptake or adherence to prophylactic medication.

Substance Use and HIV Transmission Risk Behavior

There is consensus that substance use is a significant contributing factor for a host of negative health outcomes among HIV-positive people and those at risk for HIV infection, and similarly, this has implications for the use of biomedical agents to prevent HIV. Empirical studies have consistently found that substance use is associated with HIV risk behaviors and transmission [26–33] and that it interferes with effective and consistent treatment among HIV-positive people [34–37]. In addition, substance use also interacts with various psychosocial factors such as mental health that place people at risk for becoming infected with HIV.

In the Bing et al. study referenced earlier of 2,864 HIV-positive people in the USA, 50.2 % reported using an illicit drug in the past year. Among those that reported drug use, 12.1 % disclosed using only marijuana in the last 12 months, 25.6 % reported using an illicit drug besides marijuana, and 12.5 % were screened positive for drug dependence to at least one illicit drug [17]. Although these data do not indicate whether those who were currently using substances did so before acquiring HIV, they do suggest that substance use and HIV risk are intertwined, and that this has implications for using ART for prevention. Substance use is a contributing factor to HIV acquisition among groups who are already vulnerable (i.e., Black and Latino heterosexual women, transgendered people, and MSM) to HIV because of other factors such as poverty and other systemic issues. Harlow et al. [38] found that among heterosexual women substance use was associated with having higher HIV risk markers such as unprotected vaginal sex, perceived partner-related **risk**, number of sexual partners, and unprotected anal sex. Substance use becomes an HIV risk factor for newborns as well when pregnant women engage in substance use. Women who use drugs during pregnancy have an increased chance of perinatal transmission of HIV to their infants through a variety of mechanisms such as complications caused by damage to the placenta, induced preterm birth, and increased maternal plasma viral load [33].

Substance use compounds HIV risk for those with minority sexual orientations and gender identities. Alcohol, cocaine, crack, and methamphetamines have been shown to be commonly used substances among transgendered women [39], a group at exceptionally high risk for HIV who would therefore be candidates for biomedical HIV prevention agents. Additionally, Clements et al. [40] found that while transgendered women reported use of marijuana, methamphetamines, and crack, transgendered men only endorsed marijuana use. Parsons [41] has suggested that, among some HIV-positive MSM, drugs—particularly club drugs such as ecstasy, methamphetamine, cocaine, GHB, and ketamine—may be used to facilitate cognitive escape and alleviate feelings of distress or anxiety regarding decisions to engage in unprotected sex.

Researchers have found HIV risk to be compounded among substance users through at least three mechanisms. First, substance use increases sexual risk behaviors such as inconsistent condom use, transactional sex, having multiple sex partners, and high-risk injection substance use behaviors [42]. Second, substance use is associated with physiological risks that put one at risk for HIV infection as

well. For example, Drumright et al. [28] reported on the link between substance use, decreased experience of pain, and vasodilation, and acquisition of HIV. If one's threshold for pain is lowered, tissue damage during sex might not be readily noticed, this leaves one exposed to blood-to-blood/blood-to-semen contact, which is highly associated with HIV infection. Third, substance use complicates HIV treatment because disease progression is accelerated [35] and neuropsychological functioning is impaired [36] for HIV-positive drug users. Inconsistent adherence to ART is a major contributing factor to these findings. It is evident that substance use has detrimental consequences on the health and lives of HIV-positive people and those at risk for HIV acquisition.

Mental Health and ART Adherence

Given that nonadherence has been proposed as a key factor explaining the failure of previous trials of microbicides and PrEP [8, 43], the development of effective adherence interventions for new biomedical prevention technologies will be essential. Additionally, landmark findings from HPTN 052 on the utility of ART as a tool for preventing the transmission of HIV warrant redoubled efforts to ensure optimal ART adherence among HIV-infected individuals [3]. However, in order to be effective, these interventions should address psychosocial problems that can interfere with ART adherence [44].

Depression is a consistent and well-studied predictor of poor adherence among individuals living with HIV. A meta-analysis from our group identified 95 studies focused on the association between depression and nonadherence in HIV, and showed that those with depression were significantly less adherent to their medication regimens than those without ($r = .19$) [45]. Moreover, there was an incremental relationship between depressive symptoms and adherence, with degree of depressive symptoms associated with declines in adherence. This also extends to initiation or retention in medication treatment. For example, Tegger et al. [46] found that individuals with depression who were not already on a stable antidepressant regimen were much less likely to initiate ART treatment and took longer to do so than those who were similarly newly eligible for ART but not depressed. Furthermore, Carrico et al. [35] found that individuals reporting greater numbers of depressive symptoms at baseline were 39 % more likely to discontinue ART by follow-up, even after controlling for associated factors such as baseline adherence score. The impact of depression on ART adherence has been discerned clearly by Kacanek et al. [47], who determined that the onset of depression was temporally linked to the development of consequent suboptimal adherence. In their longitudinal study, individuals who were not depressed at baseline but developed depression by follow-up had significantly lower rates of adherence after depression onset compared with those who did not enter into a depressive episode. Importantly, rates of adherence at baseline were identical between those who became depressed and those who did not. The onset of depression impairing subsequent ART adherence underscores the deleterious effects of depression on self-care and disease management among HIV-infected individuals.

Although the relationship between depression and nonadherence has been clearly established, the mechanisms that drive the relationship remain somewhat unclear. Cognitive behavioral theories of depression, however, have aided in formulating explanatory models. For example, core depressive symptoms such as feelings of worthlessness, hopelessness, loss of interest, concentration problems, and negative thoughts about one's self and the future, can serve as obstacles to self-care behaviors required for optimal health outcomes and disease management [48]. In addition, the presence of somatic depressive symptoms, such as diminished appetite, can also act as direct obstacles to antiretroviral adherence, for example, if patients have been instructed to take medications with meals or experience adverse gastrointestinal side effects [49].

The impact of depression on ART adherence should also be understood in the context of the syndemic model referenced earlier [19]. In a sample of HIV-infected individuals screening for a depression treatment trial, participants reporting higher numbers of syndemic indicators including depression, substance use, childhood sexual abuse, and interpersonal violence reported poorer ART adherence [50]. We also found that higher numbers of syndemic indicators predicted suboptimal ART adherence in our sample of over 30,000 MSM referenced earlier [22]. The array of logistical, psychological, and physiological barriers to taking ART confers significant challenges to adherence among HIV-infected individuals living with comorbid depression. For this population, depressive symptoms can significantly hinder adherence to a drug therapy that is already intensive to manage. From a broader public health perspective, addressing depression to improve ART adherence may result in more HIV-infected individuals achieving viral suppression, thereby reducing rates of HIV transmission. Thus, as ART begins to be utilized as a "treatment as prevention" strategy, it will be important to continue addressing interfering mental health problems that threaten to limit the effectiveness of this new breakthrough in biomedical prevention.

Substance Use and ART Adherence

Substance use has been consistently shown to negatively impact ART adherence [35,37,51–56]. Gonzalez et al. [57] recently found that among 121 HIV-positive men and women use of cocaine and multiple substances as well as using substances as a coping tool was significantly associated with decreased ART adherence. The substance use in this sample was especially persistent given that all participants were enrolled in a drug treatment program at the time of the study but still reported continued opiate and cocaine use. However, Lehavot et al. [58] found that when people received social support uniquely related to them taking ART as prescribed, their adherence was stable even when their alcohol and substance use increased. These findings suggest that ART adherence still needs to be specifically addressed even in the context of substance abuse treatment.

Substance use affects ART adherence among HIV-positive people regardless of their demographics but there are special issues that should be considered when examining this problem among vulnerable groups such as racial minorities [59, 60] and the homeless [61, 62]. For example, in a sample of 1,354 racially/ethnically diverse women, alcohol use was significantly associated with nonadherence to ART [59]. However, ART adherence was not solely a function of alcohol use, but was also significantly associated with being uninsured, which was more prevalent among African–American and Latina women. If women of color are more likely to be uninsured than their white counterparts, then access to treatment for HIV, affordability of ART, and continuity of care may also be issues of concern.

Increasing adherence to ART is of extreme importance in the effort to increase its effectiveness at HIV prevention. Adherence strategies must appropriately address substance use. Recommendations include: connecting opioid substance users with medical drug treatment such as methadone and buprenorphine (as they have been found to increase medication adherence and positive biomarkers of health among HIV-positive people) [63] and directly administering and monitoring the consumption of ART in substance use treatment and clinical settings [64]. These strategies have proved promising in increasing adherence among substance users who are usually hard to reach and retain in treatment.

Mental Health, Substance Use, and Biomedical HIV Prevention

Given that psychosocial problems such as mental illness and substance use are known to be salient, but generally overlooked factors in HIV prevention and treatment trials, it is important to consider the impact that these conditions may have on the implementation of biomedical prevention tools such as microbicides, PrEP, and ART. Numerous studies have shown that co-occurring substance use and mental health problems are predictive of sexual risk behavior and HIV transmission among HIV-uninfected individuals [19, 21], as well as poor ART adherence among HIV-infected individuals [44, 65]. The lessons learned from this literature should shape future research on how mental health and substance use problems impact biomedical prevention interventions, particularly as they concern adherence. Indeed, recent reviews on adherence to PrEP and microbicides have suggested that biomedical strategies may be subject to the same barriers to adherence that can interfere with antiretroviral treatment, including mental illness and substance use [66]. However, few studies have examined risks for nonadherence to biomedical interventions [6, 66, 67] and of those that did, only one examined mental health and substance use variables as potential risks for nonadherence [68]. Findings from existing efficacy trials of PrEP and microbicides demonstrate that optimal adherence increases the efficacy of these biomedical interventions [66]; thus, further research on the impact of mental illness and substance use on the implementation and effectiveness of biomedical interventions, and subsequently, the development of adherence interventions, which address mental health and substance use problems, may be necessary to maximize the effectiveness of PrEP and microbicides.

Mental Health and PrEP

Although to our knowledge no studies have directly examined the links between mental health problems and PrEP adherence or intent to use PrEP, it is possible that findings from related studies on HIV health behaviors may also apply to PrEP implementation and use, and some researchers have specifically recommended that such comparisons be drawn [69]. Many researchers have outlined considerations for successful PrEP implementation, with particular attention focused on optimizing PrEP adherence and attempting to reduce sexual risk among PrEP users, both of which are individual-level behaviors in which mental health issues have been shown to be greatly influential [69–73]. That being said, optimal candidates for PrEP are those who are likely not able to meet sexual risk reduction goals via counseling, because if they were, they would not need PrEP.

It is important to consider the impact that depression could have on PrEP adherence given that populations at risk for HIV, including MSM, have higher rates of depression than the general population [13–15]. As reviewed earlier, it has been well-established that depression is related to ART nonadherence in HIV-infected individuals [45, 49]. It is likely that depressive symptoms could interfere with an individual's self-care, including their adherence to a PrEP regimen. Additionally, negative mood states have been shown to predict increased concerns about the potential negative side effects of ART, which could also serve as a deterrent to taking medications [74]. Initial evidence suggests that concern about the potential side effects of PrEP decreases willingness to use PrEP [75]; thus, providers should be aware of the possibility that negative mood states and depressive symptoms may interfere not only with PrEP adherence but also with willingness to initiate PrEP.

Based on a review of PrEP efficacy trials that included adherence-counseling components, Koenig et al. [43] identified a number of recommendations for future PrEP adherence interventions, many of which may depend on addressing the interfering mental health problems previously discussed. Some of their recommendations included promoting adherence self-efficacy, social support, medication optimism, mental health resources, and accurate understanding of the potential benefits of PrEP [43]. Promoting medication optimism and adherence self-efficacy will require alleviating concern about negative side effects, which has been shown to be predicted by depression [74].

Stigma

Internalized HIV stigma is another factor that is deeply connected to mental health and can interfere with HIV prevention behaviors and treatment adherence among HIV-infected [76–78] and HIV-uninfected [79, 80] individuals. Furthermore, stress and depression can lead to higher levels of HIV stigma [81–83], which can in turn lead to poor HIV self-care behaviors. For example, high levels of HIV stigma and depression led to poor adherence, decreased likelihood of serostatus disclosure, and delays in seeking healthcare among HIV-infected individuals [84–86]. It is possible that HIV stigma may have similar implications for PrEP.

Stigma associated with being perceived to have HIV or being perceived to be at risk for HIV may interfere with HIV prevention behaviors. HIV stigma may serve as a deterrent to HIV testing [87, 88]. With regard to PrEP use, qualitative studies revealed that some individuals have concerns that use of PrEP could be interpreted by others as an admission to engaging in HIV risk behavior, or that PrEP use could lead others to believe that one is HIV-positive [89]. One Thai study that analyzed the iPrEx sample also found that stigma related to fear of being identified as HIV-positive and unintentional disclosure of sexual identity and/or sexual risk behavior to family and friends [90] might also prove as barriers to adherence, and a review by Myers and Mayer [91] also argued that concerns around disclosure of sexual identity and behaviors among MSM would need to be addressed to ensure optimal PrEP utilization among this population. Fears of unintentional disclosure of sexual identity and sexual risk behavior may be of particular concern to MSM, especially considering that stigma related to sexual identity can exacerbate depression, sexual risk behaviors, retention in care, substance use, and medication nonadherence among MSM [83,92–94].

It is plausible that stigma associated with being perceived to be gay or bisexual may also be a deterrent to PrEP use for heterosexual men who do not wish to be perceived as MSM. Interventions for reducing depression and stigma may be helpful to combat the deterrent effect that these psychosocial problems may have on PrEP use. For heterosexuals, particularly serodiscordant couples, HIV stigma can reduce the likelihood of HIV disclosure, communication about HIV and sex, and access to HIV services and health care [95]. It was shown within a subsample of the Partners PrEP study that PrEP adherence may have been higher in serodiscordant couples with higher levels of relationship stability, motivation to maintain their relationship, and mutual support and reminders for PrEP adherence [43, 96]. Thus, HIV stigma, as it impacts relationship stability and communication, may be an important target for PrEP adherence in heterosexual serodiscordant couples as well.

Risk Compensation

Despite the current paucity of research on mental health and PrEP, it is generally well understood by researchers and providers that psychosocial issues can interfere with PrEP use, and as such many have recommended that PrEP be prescribed as part of a combination prevention approach that addresses numerous behavioral and psychosocial issues, including sexual risk reduction [70]. It has been theorized that an individual on a PrEP regimen may engage in "risk compensation"—in other words, owing to the belief that PrEP provides protection against HIV infection, individuals on PrEP may engage in higher rates of unprotected intercourse compared with individuals not taking PrEP, thereby potentially attenuating any benefits of PrEP by increasing their exposure to HIV [71, 97, 98]. Accounting for risk compensation will be particularly important for PrEP users because individuals most suited for PrEP are those who are unable to achieve reductions in transmission risk behavior through risk-reduction counseling alone. Although both empirical evidence and mathematical

projections remain mixed on the potential for risk compensation to occur [71, 99, 100], sexual risk reduction counseling is important among populations at risk for HIV infection given that rates of risk behavior remain high in this population regardless of whether risk compensation occurs. For example, in the iPrEx study, 79 % of participants in the experimental arm and 81 % of participants in the placebo arm had engaged in unprotected anal intercourse with an HIV-positive or unknown status partner within the previous 6 months [6]. Of course, it is important to understand the mental health context in which high rates of sexual risk behavior occur. As reviewed earlier, numerous studies continue to show that depression [101, 102] and PTSD [103, 104] are risk factors for increased sexual risk behavior for MSM and heterosexuals of diverse age groups and sociocultural settings. Thrun [73] has put forth guidelines for provider-initiated brief risk reduction counseling for patients seeking to initiate PrEP; however, it will be important for initial screening of sexual risk to also include screening for mental health problems that may increase sexual risk behavior.

As research on the effectiveness of PrEP continues to grow, the impact of mental health problems on PrEP adherence, willingness to use PrEP, and sexual risk reduction within a PrEP regimen will be important areas of focus. It will also be important to understand the specific mental health contexts of the different groups at risk for HIV, such as MSM, sex workers, and men and women living in different regions of the world, such as sub-Saharan Africa, Asia, and South America. Ultimately, addressing mental health issues as part of PrEP implementation will optimize its effectiveness within these populations.

Substance Use and PrEP

To date, there is little research on the associations between substance use and PrEP. Yet, given the similarities between ART and PrEP, substance use is likely to affect adherence to PrEP in similar ways that it influences adherence to ART. Historically, drug users are less likely to be prescribed ART [105]—which is partly influenced by medical providers' reluctance to prescribe based on assumption that they would be less adherent [106]; and, in fact, data suggest that substance users are less likely to adhere to ART regimens [107, 108]. As such, it is reasonable to suspect substance users will experience the same obstacles related to PrEP access and adherence. Substance use is also likely to exacerbate the adverse side effects of PrEP such as developing resistance to PrEP [109], flair ups of hepatitis B associated with inconsistent use [110], rashes, headaches, kidney damage, gastrointestinal problems, and dizziness [98].

Some substance users might increase their substance use or reduce their condom use while using PrEP under the assumption that PrEP will eliminate all risks of HIV acquisition. This example of risk compensation has negative implications for the effectiveness of PrEP. If substance users increase their substance use, increase needle

sharing, or decrease their condom use, in the context of less than optimal PrEP adherence, they could increase their risk for HIV infection. Golub et al. [111] found that among 180 MSM in New York City, 33 % reported that they would be likely to reduce their condom usage if they were using PrEP. Furthermore, having screened positive for substance dependence significantly predicted a greater hypothetical likelihood of reducing condom use if using PrEP. This decrease in condom usage is hazardous owing to the risk of contracting other STIs, which potentiates HIV acquisition. Studies using mathematical models to simulate the effects of antiretrovirals and PrEP on HIV transmission have found that risk compensation can substantially increase new infection incidences [100, 112]. However, it should be noted that these findings have not been replicated in human studies, and risk compensation does not always increase when individuals use PrEP [113, 114].

Using substances while taking PrEP also has the potential for fatal consequences. Combining antiretroviral medications with methamphetamine and ecstasy have been linked to death [115, 116]. As preparation for large-scale PrEP implementation moves forward, more focus should be placed on the relationship between substance use and PrEP. If PrEP is to be successful at significantly reducing new HIV infections, this issue must be addressed.

Mental Health and Microbicides

Mental health problems likely impact the potential effectiveness of microbicides, particularly with regard to adherence and safer sex negotiation. Adherence in the CAPRISA 004 trial was low; only 38 % of women reported using tenofovir gel for at least 80 % of intercourse acts, which was necessary to achieve an optimal 54 % reduction in HIV acquisition risk (compared with women who used microbicides during 50 % or fewer intercourse acts, for whom tenofovir gel was only 28 % effective) [117]. Adherence in the VOICE trial was even lower; tenofovir gel was only detected in 22 % of available plasma samples throughout the study [8]. Ferrer et al. have proposed an information–motivation–behavioral (IMB) skills model for microbicide adherence, in which they recommend a number of components for future microbicide adherence interventions, including the promotion of microbicide-psychoeducation, decision-making skills, social support for microbicide use, coping skills for potential side effects, and skills for discussing microbicide use with one's partner [118]. Importantly, they also identify factors similar to the *syndemics* framing as the context for HIV risk and infection among MSM, reviewed earlier [19, 22, 50]. These factors include depression, anxiety, substance use, and intimate partner violence as major moderating factors that inhibit microbicide adherence [118]. These psychosocial factors will be important targets for microbicide adherence interventions, especially given that they have been theorized as syndemic conditions predictive of negative health outcomes in women living with and at risk for HIV [59, 119].

To understand potential barriers to microbicide use among women, it is important to examine the mental health context in which sexual risk behavior occurs. Depression and other mental illnesses are known risk factors for unprotected sex among women at risk for HIV, which may be explained by increased fear of communication and negotiation about condom use, as well as increased rates of having sex while under the influence of drugs and/or alcohol [120–122]. Moreover, women experiencing intimate partner violence are at greater risk for PTSD, which in turn predicts increased sexual risk behavior among HIV-uninfected women [123]. Many women at risk for HIV are in violent and/or abusive relationships, and hence may not be able to control when sexual intercourse occurs or whether or not condoms will be used during intercourse. In these situations, microbicides are an ideal intervention option because women are more capable of using them independently, or without their partner's knowledge [118, 123, 124]. However, within a context of intimate partner violence and interfering mental health problems, microbicide effectiveness may appear low; indeed, the relatively low efficacy rates observed in many recent microbicide trials are likely due to poor adherence rather than the drug itself being inefficacious [8, 117, 118]. Thus, addressing depression, PTSD, and other mental illnesses, particularly in women who have a history of intimate partner violence, will be crucial to promoting safer sex negotiation and HIV prevention behaviors, not only to increase microbicide use and adherence among women at risk for HIV but also to obtain more accurate efficacy estimates in future microbicide trials. Additionally, given that previous microbicide trials were conducted in a variety of countries such as Kenya, South Africa, Nigeria, Ghana, Cameroon, and Thailand, any efforts to address psychosocial barriers to microbicide use must be attuned to the specific regional, structural, and sociocultural settings, and contexts in which mental health problems, substance use, and intimate partner violence occur [9, 119, 125].

It remains to be seen how the treatment of mental illness in the context of microbicide use will or could be implemented. The CAPRISA 004 trial provided participants with adherence counseling and motivational interviewing that was implemented during its second year; however, this counseling centered mainly on proper use of the tenofovir gel, safety concerns, and other practical aspects of microbicide use. Indeed, no support for any ongoing mental health problems or intimate partner violence was provided as part of this adherence counseling [5]. Now that initial efficacy has been established by the CAPRISA 004 trial, future adherence counseling should incorporate screenings and referrals for mental illness and intimate partner violence as part of a microbicide treatment regimen, as has been recommended for ART regimens for HIV-infected individuals [126, 127]. Researchers have also encouraged applying established methods learned from years of research on ART adherence to other biomedical interventions including microbicides, such as cognitive behavioral techniques and social support interventions [117, 128]. Future research on microbicides should also examine the acceptability, safety, and efficacy of rectal microbicides for both heterosexual women and MSM, with specific attention to behavioral and mental health risk factors for both groups [129].

Substance Use and Microbicides

Substance use is likely to pose similar threats to the effectiveness of microbicides as it does to the effectiveness of PrEP and ART. Thus, issues of microbicide nonadherence and resistance development are potential problems that will be influenced by substance use. However, research regarding microbicides is still very new and no studies to date address the effect of substance use on microbicide effectiveness, adherence, or resistance. Substance use could also intensify the adverse side effects that have been reported in some microbicide trials. For example, microbicides have been found to cause genital lesions [130] and substance use has been found to decrease one's ability to feel pain and increase vasodilation [28]. Genital lesions might go unnoticed among substance users whose threshold for pain has been impaired and thus create a genital environment more susceptible to acquiring HIV. Increases in compensatory risk may also be a factor among drug users who use microbicides. For example, researchers found that among a sample of MSM in San Francisco, 41 % out of 193 men who had had sex in the previous year had used nonoxynol-9 as a protective agent and had forgone condoms [131].

Future Research

The research overwhelmingly provides evidence that issues of mental illness and substance use have the strong potential to negatively impact the effectiveness of HIV biomedical preventive strategies such as ART, PrEP, and microbicides. Addressing these issues will mitigate many of their associated problems. The study of biomedical HIV prevention strategies is relatively new and the study of the interactions of biomedical HIV prevention with mental health and substance use is in its infancy. There is much more to be learned. In 2012, Thompson et al. provided some evidence-based guidelines for improving entry in and retention in care and antiretroviral adherence for people with HIV [64]. Presented below are recommendations adapted from those guidelines related to possibilities for future research conducted by scientists and stakeholders in various academic disciplines and professional fields that examines the intersections of mental health, substance use, and HIV biomedical prevention strategies.

There needs to be more research that focuses on the influence of mental health disorders beyond depression. What is the relationship between body image disturbance, anxiety disorders, psychotic disorders, or personality disorders and the effectiveness of ART, PrEP, and microbicides? Researchers need to expand their inquiry to address these psychosocial problems as well. Similarly, research on screening for mental health disorders needs to be implemented among people who are HIV-positive and at risk for HIV infection who also might benefit from biomedical HIV prevention strategies. This type of research will help to determine the types of mental health issues that affect this population and set the foundation for the development of strategies to alleviate them. Research that assesses the link between access and adherence

to biomedical HIV prevention strategies and mental health symptoms is needed to illuminate the mechanisms by which these constructs influence each other. Furthermore, there needs to be more of an effort among researchers to examine biomedical HIV prevention strategies among vulnerable populations such as pregnant women, currently and previously incarcerated people, sexual minorities besides MSM, and people of color in all socioeconomic categories (not just those in the lowest socioeconomic categories) who are diagnosed with mental illness. In addition, more research is needed about how to adapt biomedical HIV prevention strategies for these traditionally disenfranchised groups as well as immigrants and people in countries besides the USA who have diagnoses of mental disorders.

Regarding the interactions of substance use and biomedical HIV prevention, more research is warranted that will examine interventions for patients with substance use disorders who are naïve to biomedical HIV prevention. For example, how do stakeholders go about effectively engaging and educating substance users about these prevention methods? We also need empirical studies that pilot and test the development of transitional models that sustain the long-term benefit of effective substance use interventions. There needs to be evaluation of the overall effectiveness, cost-effectiveness, and feasibility of comanaging HIV and opioid replacement treatment. One related research question is: To what extent will providing this type of treatment impact the organizations providing treatment as well as funding infrastructures? The continued assessment of the efficacy of substance use treatment programs such as educational counseling, adherence case management, timer and reminder interventions, and peer-driven and family-support interventions is important. There also need to be studies that assess the feasibility and effectiveness of directly administered biomedical HIV medications such as ART and PrEP, as well as continued monitoring of their consumption among those who use substances. Discovery of effectiveness in this area might help adherence to biomedical HIV prevention strategies and thus their overall effectiveness.

Conclusions

In conclusion, there are many findings from studies of ART as treatment adherence and behavioral HIV prevention studies that can be applied to antiretrovirals (ARVs) as prevention research. One of the most important conclusions from this literature is that individuals at highest risk for poor adherence to PrEP or microbicides are also at highest risk for psychosocial problems that occur in the context of this risk. Among MSM, these problems may include depression, adult effects of childhood sexual abuse, substance abuse problems, and domestic violence. Among heterosexual men and women, these problems may include substance use and problems that are syndemic to poverty. Such problems do not have easy solutions; and to implement effective ARV as prevention models, stepped care adherence interventions should be included as part of the prescription of these drugs. Accordingly, basic adherence counseling should be provided to all who intend to use ARVs as prevention, covering

the typical IMB skills-related topics. However, for the high percentage of those who are likely to have co-occurring syndemics, these problems may interfere with the ability of individuals to benefit from basic adherence counseling or messaging. More intensive but evidence-based interventions to decrease the mental health and substance use burden that is syndemic to HIV risk should be implemented alongside adherence counseling for ARV as prevention. Although potentially more costly and burdensome, cost-effectiveness studies, accounting for both decreased HIV risk and also decreased mental health or substance abuse-related distress, have yet to be conducted. In sum, to increase the effectiveness of biomedical HIV prevention efforts, focus must be paid to the psychosocial context of HIV risk, particularly among those who are most likely to be nonadherent.

References

1. Padian NS, Buvé A, Balkus J, Serwadda D, Cates W Jr. Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward. Lancet. 2008;372(9638):585–99.
2. Celum CL. HIV preexposure prophylaxis: new data and potential use. Top Antivir Med. 2011;19(5):181–5.
3. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6):493–505.
4. MacQueen KM. Framing the social in biomedical HIV prevention trials: a 20-year retrospective. J Int AIDS Soc. 2011;14(Suppl 2):S3.
5. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010;329(5996):1168–74.
6. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363(27):2587–99.
7. Rudy BJ, Kapogiannis BG, Lally MA, et al. Youth-specific considerations in the development of PrEP, microbicide and vaccine research trials. J Acquir Immune Defic Syndr. 2010;54(Suppl 1):S31–S42.
8. Marrazzo J, Ramjee G, Nair G, et al. Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine, or vaginal tenofovir gel in the VOICE study (MTN 003) [Internet]. Presented at the 20th Conference on Retroviruses and Opportunistic Infections; 2013 Mar 3–6; Atlanta, GA. http://www.retroconference.org/2013b/Abstracts/47951.htm.
9. Omar RF, Bergeron MG. The future of microbicides. Int J Infect Dis. 2011;15(10):e656–60.
10. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012;367(5):411–22.
11. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012;367(5):423–34.
12. Van der Straten A, Van Damme L, Haberer JE, Bangsberg DR. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. AIDS. 2012;26(7):F13–9.
13. Cochran SD, Mays VM. Relation between psychiatric syndromes and behaviorally defined sexual orientation in a sample of the US population. Am J Epidemiol. 2000;151(5):516–23.
14. Cochran SD, Mays VM, Sullivan JG. Prevalence of mental disorders, psychological distress, and mental health services use among lesbian, gay, and bisexual adults in the United States. J Consult Clin Psychol. 2003;71(1):53–61.
15. Sandfort TG, De Graaf R, Bijl RV, Schnabel P. Same-sex sexual behavior and psychiatric disorders: findings from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Arch Gen Psychiatry. 2001;58(1):85–91.

16. Applebaum A, Bullis JR, Traeger L, et al. Rates of mood and anxiety disorders and contributors to continued heroin use in methadone maintenance patients: a comparison by HIV status. Neurobehav HIV Med. 2010;2:49–57.
17. Bing EG, Burnam MA, Longshore D, et al. Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. Arch Gen Psychiatry. 2001;58(8):721–8.
18. Pence BW, O'Donnell JK, Gaynes BN. Falling through the cracks. AIDS. 2012;26(5):656–8.
19. Stall R, Mills TC, Williamson J, et al. Association of co-occurring psychosocial health problems and increased vulnerability to HIV/AIDS among urban men who have sex with men. Am J Public Health. 2003;93(6):939–42.
20. Mustanski B, Garofalo R, Herrick A, Donenberg G. Psychosocial health problems increase risk for HIV among urban young men who have sex with men: preliminary evidence of a syndemic in need of attention. Ann Behav Med. 2007;34(1):37–45.
21. O'Cleirigh CM, Mimiaga MJ, Safren SA, Stall R, Mayer KH. Synergistic effects of psychosocial and substance use problems on increased sexual transmission risk among HIV-infected men who have sex with men [Internet]. Presented at the XVIII International AIDS Conference; 2010 Jul 18–23; Vienna, Austria. http://www.aids2010.org/WebContent/File/AIDS2010_Abstracts_Vol_2_Wednesday_21July_web.pdf
22. Mimiaga MJ, Biello KB, O'Cleirigh CM, et al. High prevalence of syndemic conditions associated with suboptimal ART adherence in a large multinational on-line sample of HIV-infected MSM. Presentation submitted to the 141st Annual Meeting and Exposition of the American Public Health Association; 2013 Nov 2–6; Boston, MA.
23. Sikkema KJ, Watt MH, Drabkin AS, Meade CS, Hansen NB, Pence BW. Mental health treatment to reduce HIV transmission risk behavior: a positive prevention model. AIDS Behav. 2010;14(2):252–62.
24. Mimiaga MJ, Noonan E, Donnell D, et al. Childhood sexual abuse is highly associated with HIV risk-taking behavior and infection among MSM in the EXPLORE study. J Acquir Immune Defic Syndr. 2009;51(3):340–8.
25. Safren SA, Blashill AJ, O'Cleirigh CM. Promoting the sexual health of MSM in the context of comorbid mental health problems. AIDS Behav. 2011;15(1):30–4.
26. Browne FA, Wechsberg WM. The intersecting risks of substance use and HIV risk among substance-using South African men and women. Curr Opin Psychiatry. 2010;23(3):205–9.
27. Colfax G, Guzman R. Club drugs and HIV infection: a review. Clin Infect Dis. 2006;42(10):1463–9.
28. Drumright LN, Patterson TL, Strathdee SA. Club drugs as causal risk factors for HIV acquisition among men who have sex with men: a review. Subst Use Misuse. 2006;41(10–12):1551–601.
29. El-Bassel N, Gilbert L, Witte S, Wu E, Chang M. Intimate partner violence and HIV among drug-involved women: contexts linking these two epidemics–challenges and implications for prevention and treatment. Subst Use Misuse. 2011;46(2–3):295–306.
30. Ferrando SJ, Batki SL. Substance abuse and HIV infection. New Dir Ment Health Serv. 2000;87:57–67.
31. Grov C, Parsons JT, Bimbi DS. In the shadows of a prevention campaign: sexual risk behavior in the absence of crystal methamphetamine. AIDS Educ Prev. 2008;20(1):42–55.
32. Parsons JT, Lelutiu-Weinberger C, Botsko M, Golub SA. Predictors of day-level sexual risk for young gay and bisexual men. AIDS Behav. 2012:1–13 (Epub 2012).
33. Purohit V, Rapaka RS, Shurtleff D. Mother-to-child transmission (MTCT) of HIV and drugs of abuse in post-highly active antiretroviral therapy (HAART) era. J Neuroimmune Pharm. 2010;5(4):507–15.
34. Altice FL, Kamarulzaman A, Soriano VV, Schechter M, Friedland GH. Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs. Lancet. 2010;376(9738):367–87.
35. Carrico AW. Substance use and HIV disease progression in the HAART era: implications for the primary prevention of HIV. Life Sci. 2011;88(21–22):940–7.

36. Norman LR, Basso M, Kumar A, Malow R. Neuropsychological consequences of HIV and substance abuse: a literature review and implications for treatment and future research. Curr Drug Abuse Rev. 2009;2(2):143–56.
37. Parsons JT, Rosof E, Mustanski B. Medication adherence mediates the relationship between adherence self-efficacy and biological assessments of HIV health among those with alcohol use disorders. AIDS Behav. 2008;12(1):95–103.
38. Harlow LL, Rose JS, Morokoff PJ, et al. Women HIV sexual risk takers: related behaviors, interpersonal issues, and attitudes. Womens Health. 1998;4(4):407–39.
39. Reback CJ, Lombardi EL. HIV risk behaviors of male-to-female transgenders in a community-based harm reduction program. Int J Transgenderism. 1999;3(1/2):1.
40. Clements K, Kitano K, Wilkinson W, Marx R. HIV Prevention and health service needs of the transgender community in San Francisco. Int J Transgenderism. 1999 Jan;3(1/2):2–17.
41. Parsons JT, Grov C, Kelly BC. Comparing the effectiveness of two forms of time-space sampling to identify club drug-using young adults. J Drug Issues. 2008;38(4):1061–81.
42. Halkitis PN, Pollock JA, Pappas MK, et al. Substance use in the MSM population of New York City during the era of HIV/AIDS. Subst Use Misuse. 2011;46(2–3):264–73.
43. Koenig LJ, Lyles C, Smith DK. Adherence to antiretroviral medications for HIV pre-exposure prophylaxis. Am J Prev Med. 2013;44(1):S91–8.
44. Blashill AJ, Perry N, Safren SA. Mental health: a focus on stress, coping, and mental illness as it relates to treatment retention, adherence, and other health outcomes. Curr HIV/AIDS Rep. 2011;8(4):215–22.
45. Gonzalez JS, Batchelder AW, Psaros C, Safren SA. Depression and HIV/AIDS treatment nonadherence: a review and meta-analysis. J Acquir Immune Defic Syndr. 2011;58(2):181–7.
46. Tegger MK, Crane HM, Tapia KA, Uldall KK, Holte SE, Kitahata MM. The effect of mental illness, substance use, and treatment for depression on the initiation of highly active antiretroviral therapy among HIV-infected individuals. AIDS Patient Care STDS. 2008;22(3):233–43.
47. Kacanek D, Jacobson DL, Spiegelman D, Wanke C, Isaac R, Wilson IB. Incident depression symptoms are associated with poorer HAART adherence: a longitudinal analysis from the Nutrition for Healthy Living study. J Acquir Immune Defic Syndr. 2010;53(2):266–72.
48. Rabkin JG. HIV and depression: 2008 review and update. Curr HIV/AIDS Rep. 2008;5(4):163–71.
49. Gonzalez JS, Psaros C, Batchelder A, Applebaum A, Newville H, Safren SA. Clinician-assessed depression and HAART adherence in HIV-infected individuals in methadone maintenance treatment. Ann Behav Med. 2011;42(1):120–6.
50. Safren SA, Blashill AJ, Lerner J, et al. Higher levels of psychosocial syndemics associated with non-adherence in individuals with HIV screening for a depression treatment trial. Presentation submitted to the 8th International Conference on HIV Treatment and Prevention Adherence; 2013 Jun 2–4; Miami, FL.
51. Arnsten JH, Demas PA, Grant RW, et al. Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. J Gen Intern Med. 2002;17(5):377–81.
52. Berg CJ, Michelson SE, Safren SA. Behavioral aspects of HIV care: adherence, depression, substance use, and HIV-transmission behaviors. Infect Dis Clin North Am. 2007;21(1):181–200.
53. Chander G, Lau B, Moore RD. Hazardous alcohol use: a risk factor for non-adherence and lack of suppression in HIV infection. J Acquir Immune Defic. Syndr. 2006;43(4):411–7.
54. Cohn SE, Jiang H, McCutchan JA, et al. Association of ongoing drug and alcohol use with non-adherence to antiretroviral therapy and higher risk of AIDS and death: results from ACTG 362. AIDS Care. 2011;23(6):775–85.
55. Fogarty L, Roter D, Larson S, Burke J, Gillespie J, Levy R. Patient adherence to HIV medication regimens: a review of published and abstract reports. Patient Educ Couns. 2002;46(2):93–108.
56. French T, Tesoriero J, Agins B. Changes in stress, substance use and medication beliefs are associated with changes in adherence to HIV antiretroviral therapy. AIDS Behav. 2011;15(7):1416–28.

57. Gonzalez A, Mimiaga MJ, Israel J, Andres Bedoya C, Safren SA. Substance use predictors of poor medication adherence: the role of substance use coping among HIV-infected patients in opioid dependence treatment. AIDS Behav. 2013;17(1):168–73.
58. Lehavot K, Huh D, Walters KL, King KM, Andrasik MP, Simoni JM. Buffering effects of general and medication-specific social support on the association between substance use and HIV medication adherence. AIDS Patient Care STDS. 2011;25(3):181–9.
59. Lillie-Blanton M, Stone VE, Snow Jones A, et al. Association of race, substance abuse, and health insurance coverage with use of highly active antiretroviral therapy among HIV-infected women, 2005. Am J Public Health. 2010;100(8):1493–9.
60. Sharpe TT, Lee LM, Nakashima AK, Elam-Evans LD, Fleming PL. Crack cocaine use and adherence to antiretroviral treatment among HIV-infected black women. J Commun Health. 2004;29(2):117–27.
61. Friedman MS, Marshal MP, Stall R, et al. Associations between substance use, sexual risk taking and HIV treatment adherence among homeless people living with HIV. AIDS Care. 2009;21(6):692–700.
62. Royal SW, Kidder DP, Patrabansh S, et al. Factors associated with adherence to highly active antiretroviral therapy in homeless or unstably housed adults living with HIV. AIDS Care. 2009;21(4):448–55.
63. Altice FL, Springer S, Buitrago M, Hunt DP, Friedland GH. Pilot study to enhance HIV care using needle exchange-based health services for out-of-treatment injecting drug users. J Urban Health. 2003;80(3):416–27.
64. Thompson MA, Mugavero MJ, Amico KR, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. Ann Intern Med. 2012;156(11):817–33.
65. Gonzalez A, Barinas J, O'Cleirigh C. Substance use: impact on adherence and HIV medical treatment. Curr HIV/AIDS Rep. 2011;8(4):223–34.
66. Muchomba FM, Gearing RE, Simoni JM, El-Bassel N. State of the science of adherence in pre-exposure prophylaxis and microbicide trials. J Acquir Immune Defic Syndr. 2012;61(4):490–8.
67. Haberer JE, Baeten JM, Celum CL, et al. Near perfect early adherence to antiretroviral pre-exposure prophylaxis (PrEP) against HIV infection among HIV-serodiscordant couples as determined by multiple measures: preliminary data from the Partners PrEP Study. Presented at the 18th Conference on Retroviruses and Opportunistic Infections; 2011 Feb 27–Mar 2; Boston, MA.
68. Haberer JE, Baeten JM, Campbell J, et al. High efficacy and high adherence with pre-exposure prophylaxis (PrEP) for HIV prevention: a prospective study of HIV serodiscordant couples in East Africa (under review).
69. Golub SA, Operario D, Gorbach PM. Pre-exposure prophylaxis state of the science: empirical analogies for research and implementation. Curr HIV/AIDS Rep. 2010;7(4):201–9.
70. Dearing JW, Smith DK, Larson RS, Estabrooks CA. Designing for diffusion of a biomedical intervention. Am J Prev Med. 2013;44(1 Suppl 2):S70–6.
71. Malotte CK. Brief risk-reduction counseling in clinical settings for HIV pre-exposure prophylaxis. Am J Prev Med. 2013;44(1 Suppl 2):S112–8.
72. Smith DK, Dearing JW, Sanchez T, Goldschmidt RH. Introducing wicked issues for HIV pre-exposure prophylaxis implementation in the U.S. Am J Prev Med. 2013;44(1 Suppl 2):S59–62.
73. Thrun MW. Provider-initiated HIV-risk behavior counseling in the context of HIV pre-exposure prophylaxis. Am J Prev Med. 2013;44(1 Suppl 2):S108–11.
74. Gonzalez JS, Penedo FJ, Llabre MM, et al. Physical symptoms, beliefs about medications, negative mood, and long-term HIV medication adherence. Ann Behav Med. 2007;34(1):46–55.
75. Zhou F, Gao L, Li S, et al. Willingness to accept HIV pre-exposure prophylaxis among Chinese men who have sex with men. PLoS One. 2012;7(3):e32329.

76. Lee RS, Kochman A, Sikkema KJ. Internalized stigma among people living with HIV-AIDS. AIDS Behav. 2002;6(4):309–19.
77. Rintamaki LS, Davis TC, Skripkauskas S, Bennett CL, Wolf MS. Social stigma concerns and HIV medication adherence. AIDS Patient Care STDS. 2006;20(5):359–68.
78. Wolitski RJ, Pals SL, Kidder DP, Courtenay-Quirk C, Holtgrave DR. The effects of HIV stigma on health, disclosure of HIV status, and risk behavior of homeless and unstably housed persons living with HIV. AIDS Behav. 2009;13(6):1222–32.
79. Earnshaw VA, Chaudoir SR. From conceptualizing to measuring HIV stigma: a review of HIV stigma mechanism measures. AIDS Behav. 2009;13(6):1160–77.
80. Starks TJ, Rendina HJ, Breslow AS, Parsons JT, Golub SA. The psychological cost of anticipating HIV stigma for HIV-negative gay and bisexual men. AIDS Behav. 2013: 1–10 (Epub 2013).
81. Galvan FH, Davis EM, Banks D, Bing EG. HIV stigma and social support among African Americans. AIDS Patient Care STDS. 2008;22(5):423–36.
82. Prachakul W, Grant JS, Keltner NL. Relationships among functional social support, HIV-related stigma, social problem solving, and depressive symptoms in people living with HIV: a pilot study. J Assoc Nurse AIDS Care. 2007;18(6):67–76.
83. Wohl AR, Galvan FH, Myers HF, et al. Do social support, stress, disclosure and stigma influence retention in HIV care for Latino and African American men who have sex with men and women? AIDS Behav. 2011;15(6):1098–110.
84. Kingori C, Reece M, Obeng S, et al. Impact of internalized stigma on HIV prevention behaviors among HIV-infected individuals seeking HIV care in Kenya. AIDS Patient Care STDS. 2012;26(12):761–8.
85. Steward WT, Bharat S, Ramakrishna J, Heylen E, Ekstrand ML. Stigma is associated with delays in seeking care among HIV-infected people in India. J Int Assoc Provid AIDS Care. 2013;12(2):103–9.
86. Vanable PA, Carey MP, Blair DC, Littlewood RA. Impact of HIV-related stigma on health behaviors and psychological adjustment among HIV-positive men and women. AIDS Behav. 2006;10(5):473–82.
87. Chesney MA, Smith AW. Critical delays in HIV testing and care. Am Behav Sci. 1999;42(7):1162–74.
88. Mahajan AP, Sayles JN, Patel VA, et al. Stigma in the HIV/AIDS epidemic: a review of the literature and recommendations for the way forward. AIDS. 2008;22(Suppl 2):S67–79.
89. Smith DK, Toledo L, Smith DJ, Adams MA, Rothenberg R. Attitudes and program preferences of African-American urban young adults about pre-exposure prophylaxis (PrEP). AIDS Educ Prev. 2012;24(5):408–21.
90. Tangmunkongvorakul A, Chariyalertsak S, Amico KR, et al. Facilitators and barriers to medication adherence in an HIV prevention study among men who have sex with men in the iPrEx study in Chiang Mai, Thailand. AIDS Care (Epub 2012).
91. Myers GM, Mayer KH. Oral preexposure anti-HIV prophylaxis for high-risk U.S. populations: current considerations in light of new findings. AIDS Patient Care STDS. 2011;25(2):63–71.
92. Johnson MO, Carrico AW, Chesney MA, Morin SF. Internalized heterosexism among HIV-positive, gay-identified men: implications for HIV prevention and care. J Consult Clin Psychol. 2008;76(5):829–39.
93. Preston DB, D'Augelli AR, Kassab CD, Cain RE, Schulze FW, Starks MT. The influence of stigma on the sexual risk behavior of rural men who have sex with men. AIDS Educ Prev. 2004;16(4):291–303.
94. Wohl AR, Galvan FH, Carlos J-A, et al. A comparison of MSM stigma, HIV stigma and depression in HIV-positive Latino and African American men who have sex with men (MSM). AIDS Behav (Epub 2012).
95. Przybyla SM, Golin CE, Widman L, Grodensky CA, Earp JA, Suchindran C. Serostatus disclosure to sexual partners among people living with HIV: examining the roles of partner characteristics and stigma. AIDS Care (Epub 2012).

96. Ware NC, Wyatt MA, Haberer JE, et al. What's love got to do with it? Explaining adherence to oral antiretroviral pre-exposure prophylaxis for HIV-serodiscordant couples. J Acquir Immune Defic Syndr. 2012;59(5):463–8.
97. Hogben M, Liddon N. Disinhibition and risk compensation: scope, definitions, and perspective. Sex Transm Dis. 2008;35(12):1009–10.
98. Paxton LA, Hope T, Jaffe HW. Pre-exposure prophylaxis for HIV infection: what if it works? Lancet. 2007;370(9581):89–93.
99. Leibowitz AA, Parker KB, Rotheram-Borus MJ. A US policy perspective on oral preexposure prophylaxis for HIV. Am J Public Health. 2011;101(6):982–5.
100. Supervie V, García-Lerma JG, Heneine W, Blower S. HIV, transmitted drug resistance, and the paradox of preexposure prophylaxis. Proc Natl Acad Sci U S A. 2010;107(27):12381–6.
101. Koblin BA, Husnik MJ, Colfax G, et al. Risk factors for HIV infection among men who have sex with men. AIDS. 2006;20(5):731–9.
102. Mustanski BS, Newcomb ME, Du Bois SN, Garcia SC, Grov C. HIV in young men who have sex with men: a review of epidemiology, risk and protective factors, and interventions. J Sex Res. 2011;48(2–3):218–53.
103. Beidas RS, Birkett M, Newcomb ME, Mustanski B. Do psychiatric disorders moderate the relationship between psychological distress and sexual risk-taking behaviors in young men who have sex with men? A longitudinal perspective. AIDS Patient Care STDS. 2012;26(6):366–74.
104. Sikkema KJ, Hansen NB, Meade CS, Kochman A, Fox AM. Psychosocial predictors of sexual HIV transmission risk behavior among HIV-positive adults with a sexual abuse history in childhood. Arch Sex Behav. 2009;38(1):121–34.
105. Andersen R, Bozzette S, Shapiro M, et al. Access of vulnerable groups to antiretroviral therapy among persons in care for HIV disease in the United States. HCSUS Consortium. HIV Cost and Services Utilization Study. Health Serv Res. 2000;35(2):389–416.
106. Bogart LM, Kelly JA, Catz SL, Sosman JM. Impact of medical and nonmedical factors on physician decision making for HIV/AIDS antiretroviral treatment. J Acquir Immune Defic Syndr. 2000;23(5):396–404.
107. Hinkin CH, Barclay TR, Castellon SA, et al. Drug use and medication adherence among HIV-1 infected individuals. AIDS Behav. 2007;11(2):185–94.
108. Mellins CA, Havens JF, McDonnell C, et al. Adherence to antiretroviral medications and medical care in HIV-infected adults diagnosed with mental and substance abuse disorders. AIDS Care. 2009;21(2):168–77.
109. Kelesidis T, Landovitz RJ. Preexposure prophylaxis for HIV prevention. Curr HIV/AIDS Rep. 2011;8(2):94–103.
110. Liu AY, Grant RM, Buchbinder SP. Preexposure prophylaxis for HIV: unproven promise and potential pitfalls. JAMA. 2006;296(7):863–5.
111. Golub SA, Kowalczyk W, Weinberger CL, Parsons JT. Preexposure prophylaxis and predicted condom use among high-risk men who have sex with men. J Acquir Immune Defic Syndr. 2010;54(5):548–55.
112. Blower SM, Gershengorn HB, Grant RM. A tale of two futures: HIV and antiretroviral therapy in San Francisco. Science. 2000;287(5453):650–4.
113. Baeten J, Celum C. Antiretroviral pre-exposure prophylaxis for HIV-1 prevention among heterosexual African men and women: the Partners PrEP Study. Proceedings of the 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention. 2011 Jul 17–20; Rome, Italy. p. 17–20.
114. Guest G, Shattuck D, Johnson L, et al. Changes in sexual risk behavior among participants in a PrEP HIV prevention trial. Sex Transm Dis. 2008;35(12):1002–8.
115. Hales G, Roth N, Smith D. Possible fatal interaction between protease inhibitors and methamphetamine. Antivir Ther. 2000;5(1):19–22.
116. Henry JA, Hill IR. Fatal interaction between ritonavir and MDMA. Lancet. 1998;352(9142):1751–2.
117. Krakower D, Mayer KH. Promising prevention approaches: tenofovir gel and prophylactic use of antiretroviral medications. Curr HIV/AIDS Rep. 2011;8(4):241–8.

118. Ferrer RA, Morrow KM, Fisher WA, Fisher JD. Toward an information-motivation-behavioral skills model of microbicide adherence in clinical trials. AIDS Care. 2010;22(8):997–1005.
119. González-Guarda RM, Florom-Smith AL, Thomas T. A syndemic model of substance abuse, intimate partner violence, HIV infection, and mental health among Hispanics. Public Health Nurs. 2011;28(4):366–78.
120. Collins PY, Geller PA, Miller S, Toro P, Susser ES. Ourselves, our bodies. our realities: an HIV prevention intervention for women with severe mental illness. J Urban Health. 2001;78(1):162–75.
121. Collins PY, Von Unger H, Putnins S, Crawford N, Dutt R, Hoffer M. Adding the female condom to HIV prevention interventions for women with severe mental illness: a pilot test. Community Ment Health J. 2011;47(2):143–55.
122. Seth P, Patel SN, Sales JM, DiClemente RJ, Wingood GM, Rose ES. The impact of depressive symptomatology on risky sexual behavior and sexual communication among African American female adolescents. Psychol Health Med. 2011;16(3):346–56.
123. Cavanaugh CE, Hansen NB, Sullivan TP. HIV sexual risk behavior among low-income women experiencing intimate partner violence: the role of posttraumatic stress disorder. AIDS Behav. 2010;14(2):318–27.
124. Stockman JK, Ludwig-Barron N, Hoffman MA, Ulibarri MD, Dyer TVP. Prevention interventions for human immunodeficiency virus in drug-using women with a history of partner violence. Subst Abuse Rehabil. 2012;2012(3):45–57.
125. Kippax S, Stephenson N. Beyond the distinction between biomedical and social dimensions of HIV prevention through the lens of a social public health. Am J Public Health. 2012;102(5):789–99.
126. Bhatia R, Hartman C, Kallen MA, Graham J, Giordano TP. Persons newly diagnosed with HIV infection are at high risk for depression and poor linkage to care: results from the Steps Study. AIDS Behav. 2011;15(6):1161–70.
127. Freeman M, Patel V, Collins PY, Bertolote J. Integrating mental health in global initiatives for HIV/AIDS. Br J Psychiatry. 2005;187:1–3.
128. Stirratt MJ, Gordon CM. Adherence to biomedical HIV prevention methods: considerations drawn from HIV treatment adherence research. Curr HIV/AIDS Rep. 2008;5(4):186–92.
129. McGowan I. Rectal microbicides: can we make them and will people use them? AIDS Behav. 2011;15(Suppl 1):S66–71.
130. Obiero J, Mwethera PG, Hussey GD, Wiysonge CS. Vaginal microbicides for reducing the risk of sexual acquisition of HIV infection in women: systematic review and meta-analysis. BMC Infect Dis. 2012;12:289.
131. Mansergh G, Marks G, Rader M, Colfax GN, Buchbinder S. Rectal use of nonoxynol-9 among men who have sex with men. AIDS. 2003;17(6):905–9.

Chapter 8
Substance Use Treatment in the Era of New HIV Prevention Technologies

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In December 1981, just a few months after the morbidity and mortality weekly report MMWR reported on a cluster of *pnuemocystis carinii* (PCP) cases that would later be recognized as the first wave of the AIDS epidemic, a report was published in the New England Journal of Medicine describing an outbreak of "community-acquired" PCP among 15 young men from New York City. One of the men was described as a heterosexual alcohol abuser, six were reported to be heterosexual drug abusers, six as men who had sex with men (MSM), and two as both drug users and MSM [1]. These cases had been identified at hospitals in the city during the previous two years and were among the first AIDS cases to be carefully examined. Importantly, in this first report, substance use (both injection and non-injection) was present in the majority of identified individuals, among both MSM and heterosexuals. Necessarily, the epidemiological and scientific interest of the time became sharply focused on mechanisms of transmission and strategies for preventing widespread transmission—protecting the blood supply, use of condoms, and the use of sterile injection equipment.

Prior to 1981, there was not much awareness of, or scientific interest in drug use other than at the few specialty care centers which had been established to treat the most severe forms of substance use disorders. Aside from a few studies of alcohol abuse, there were no meaningful data on the prevalence of substance use in the community or the impact of this use on public health. Researchers and clinicians working with drug users did not typically ask questions about sexual behaviors or practices that could transmit blood-borne viruses and other sexually transmitted infections. While there was much attention focused on the relationship between crime and heroin use, there was little support for drug treatment programs and little attention was paid to the link between drug use and public health. After all, only a few members of a

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few communities were affected and those who were, hidden from the public's eye. Researchers, treatment professionals, and public health agencies were unprepared to respond to the growing epidemic of HIV infection among injection drug users and their sexual partners [2]. There was little concern regarding the relationship between alcohol and non-injection drug use, sexual behavior, and viral transmission.

From the start of the AIDS epidemic, a variety of strategies have been implemented in an attempt to respond to reduce transmissions among drug users, but these efforts have been narrowly defined, are limited in scope and focused almost exclusively on injection drug use and related risks. The role of non-injection substance use in sustaining sexual transmission and inhibiting effective antiretroviral (ARV) treatment was underestimated since the first cases of HIV infection were identified.

Despite awareness of the prevalence of substance use from the earliest days of the epidemic and its direct and indirect role in transmission, substance use remains one of the greatest global challenges to effective risk reduction, access to and retention in HIV care, adherence to ARV medications, and sustained suppression of viral load. As prevention strategies have become sharply focused on "treatment as prevention", it is likely that alcohol and non-injection drug use will become more prominent components of the efforts to improve coverage and effectiveness of ARV treatment. This chapter reviews accomplishments and discusses the opportunities and challenges facing the scale-up of prevention technologies that have the potential to minimize the role of substance use in the transmission of HIV infection. Building on lessons learned from the first 30 years of the epidemic, the focus here is on maximizing the future impact of treatment interventions for harmful substance use. Three major topics will be addressed: (1) defining the challenge, (2) medication-assisted treatments for substance use disorders as prevention technologies, and (3) opportunities and challenges for scale-up.

Defining the Challenge

Current estimates suggest that there are approximately 34,000,000 people living with HIV [3]. There is some indication that the number of infected individuals has stabilized globally with new infections roughly equal to the number of deaths among HIV-infected individuals [4]. Nearly 50 % of the global burden of HIV infections is found in sub-Saharan Africa. Because most of the people in this region have been infected through heterosexual transmission, the role of substance use has not been well documented or appreciated.

The number of individuals estimated to be living with HIV infection caused by injection drug use ranges from 1 to 6 million. With significant regional variations, it is estimated that 10–25 % of infections outside of sub-Saharan Africa are attributable to injection drug use. Though monitored by AIDS surveillance systems globally, the estimate of injection-related infections is imprecise due to the illegality of the behavior, the stigma of disclosing, and a lack of interest among governments to accurately monitor injection drug use [5]. Also, given the fact that injectors are able

to be infected through unprotected sexual activity it is likely that some infections classified as injection related, are in fact sexual transmissions [6].

While estimates of the numbers of individuals who have become infected as a result of injections are imprecise, we have even less understanding of the number of individuals who are infected from risk behaviors associated with alcohol and non-injection drug use. There are no global estimates of the role of non-injection substance use in the transmission of HIV but it is likely to represent a major portion of all infections. Alcohol and illicit substance use is common globally, and it appears to be much more prevalent among individuals (and their partners) who become infected with HIV. There is increasing recognition of the role of non-injection substance use in fueling the HIV epidemic globally [7].

In studies focused on understanding heterosexual transmissions, alcohol and drug use is consistently found to be a predictor of HIV risk behavior and incident HIV infection [6, 8, 9]. Among heterosexual transmissions, alcohol use and non-injection drug use, particularly stimulant use, are commonly reported as factors associated with unprotected sexual activity [10]. Among MSM, substance use is not only more common when compared to the general population, but also recognized as a significant risk factor in explaining both HIV risk behaviors and infections [11]. In cross-sectional studies of MSM, alcohol and non-injection stimulant use are associated with HIV risk and prevalence while in prospective studies substance abuse has been found to be a powerful predictor of new infections [12, 13]. Among more than 4,000 MSM who participated in Project Explore, the largest prevention intervention trial ever conducted among HIV-negative MSM, drug and alcohol use prior to sex was found to be a stronger predictor of incident infections than unprotected receptive anal intercourse with a partner of unknown HIV status [14, 15].

From the earliest days of the epidemic, data have been available to suggest that substance use played a major role in the sexual transmission of HIV. Yet, most of the intervention literature has been focused on injection drug use and many interventions targeting sexual transmissions among heterosexuals and MSM have paid only minimal attention to substance use. This has resulted in a persistent and substantial under estimation of the role of substance use in sustaining the AIDS epidemic globally. Substance use, does not define a risk group—it is a behavior common among individuals in all risk groups and contributes not only to risk behaviors but also to access to and retention in adherence and sustained viral suppression.

Substance Use Disorders: A Chronic Disease Model

HIV prevention responses to substance use by governments and organizations tend to be rooted in how substance use itself is perceived and defined. Although not mutually exclusive, these "strategic definitions" can be seen as falling into several broad approaches—legal, harm reduction, and medical. When substance use is viewed primarily as a legal problem, prevention responses concentrate on interdiction, arrest, detoxification, and incarceration. Within this framework, people who use substances

are criminals and perceived as "weak," unable to control their behaviors. While it is true that individuals who become dependent on substances experience a loss of control, the legal responses have proven completely ineffective in both restricting access and use. A cornerstone of the criminal justice response to substance use and HIV prevention has been mandated detoxification. Harm-reduction responses view the problems associated with substance use as the health and disease consequences associated with use. From this perspective, interventions focus not on controlling drug use, but on preventing the harmful consequences caused by the use of substances. The primary harm-reduction strategies related to HIV prevention have been to ensure access to sterile injection equipment, condom distribution, and the use of methadone treatment to reduce risky injection behaviors. These strategies have been most successful in reducing the transmission of HIV among injectors when access to these services is available. Finally, medical views of the harms associated with substance use are viewed as behavioral and biological processes that need to be directly modified through evidence-based treatment strategies. Health-oriented interventions tend to focus on assisting individuals in controlling, reducing, and eliminating substance use to prevent a range of harmful health consequences and improve social functioning of the individual and those affected by their use. This approach includes behavioral interventions, counseling, and medication-assisted treatments.

While not all substance use is harmful, it is critically important to be able to identify harmful substance use when it is present. There is growing recognition that quantity and frequency of use alone are poor measures of harm. Certainly, high volume and high frequency alcohol and illicit substance use are associated with higher rates of harmful consequences, both acute and chronic. It is also true that even small or moderate amounts of substance use can be harmful, particularly in risky environments and among those with pre-existing medical conditions. Thus, the perception of substance use harm and its' assessment is a critical step in the process of determining the need for and type of response. In HIV prevention thus far, the harms associated with substance use have focused on the reuse of contaminated injection equipment. While injection drug use remains a very important behavior in the global epidemic, in communities with both medication-assisted treatments and syringe exchange programs, new injection-related transmissions have been successfully controlled. Given the greater prevalence and potential harm associated with alcohol and non-injection drug use, it will become increasingly important to understand the way in which we develop a response to substance use.

The latest revisions to the diagnostic and statistical manual (DSM5) provide a new and useful framework for classification of substance use disorders and the conceptualization of associated harms. These revisions intentionally move away from the "discrete" diagnostic categories of abuse and dependence to a classification of use as existing on a continuum of severity—mild, moderate, and severe. The severity of the substance use disorder is measured by assessing the number of symptoms present. These symptoms include: tolerance, withdrawal, more use than intended, craving for the substance, unsuccessful efforts to cut down, excessive time spent in acquisition, activities given up because of use, continued use despite negative effects, failure to

fulfill major role obligations, recurrent use in hazardous situations, and continued use despite consistent social or interpersonal problems.

In considering how best to respond to substance use disorders and the harms they cause, it's important to begin with the awareness that there are no behavioral or biological "cures" and there is increasing recognition of the genetic susceptibility of some individuals as well as the biological changes to the central nervous system that occur after prolonged use. These factors help to define substance use disorders as chronic health problems with common behavioral and biological diagnostic features and treatment responses. As the severity of substance use disorders increases, the intensity of treatment responses must also increase. While some treatments include the use of medications, all include behavior management strategies delivered via counseling interventions of various types. The most efficacious counseling strategies have been those that help individuals view their behaviors as changeable habits that can be altered by clearly identifying the behaviors that lead to use and developing strategies to achieve short term goals. These "cognitive-behavioral" strategies are non-judgmental and begin with the expectation that progress will not follow a linear trajectory. Given the biologically reinforcing properties of substance use, relapse is common, even among highly motivated individuals committed to behavior change. This is simply a characteristic of substance use disorders, and a defining characteristic of all chronic diseases.

Medication-Assisted Treatments as Biomedical Prevention Interventions

The findings from studies of medication-assisted treatments for opiate-dependent injection drug users identify agonist medication-assisted treatments as among the most powerful prevention interventions reported for any intervention with any at-risk population. The data from these studies link participation in these treatments not only to reduced risk behaviors but also to fewer new infections and they provide a clear "proof of concept" for the effective treatment of substance use as a prevention strategy. While these treatments do not cure substance use disorders, they represent powerful tools in their effective management. Using a model of chronic disease management, these agonist approaches to medication-assisted treatments address both the biological aspect of the substance use disorder and its behavioral components through counseling interventions. The findings from studies of opiate agonist treatments often referred to as opiate substitution treatment (OST), have been replicated over time and in diverse cultural and economic settings. In this chapter, we will not use the term OST for two reasons. First, one of the most common reasons for opposing the use of agonist treatments is that they merely substitute a legal medication for an illegal one and do nothing to treat the condition. Second, agonist-based medication-assisted treatments as described here are strategies for the medical management of

chronic substance use disorders and as such, much more that substitution. The consistency of these findings is impressive and reflects the fact that opiate dependence is a biological condition with important behavioral components.

Agonist medications (methadone and buprenorphine) work by activating the mu opioid receptors in the central nervous system. Unlike the direct administration of heroin, the activation by the molecules of the agonist medication is controlled, in both intensity and duration. For methadone, a pure agonist, individuals are able to achieve a stable level of activation through single daily dosing. For buprenorphine, a partial agonist, the attachment to the opiate receptor is much stronger and consequently, the medication occupies the receptor for a longer period of time, allowing for less frequent dosing. Because activation takes place through the occupation of the receptor, subsequent administration of opiates is "blocked" when dosing is appropriate. This activation effectively prevents withdrawal symptoms and sustains dependence on the medication. Symptoms of opiate withdrawal will occur when the medication is insufficient in dosage or discontinued.

Methadone

Methadone is a full opiate agonist and despite serious limitations on its availability, remains globally, the most widely used medication for the treatment of opiate dependence. Research conducted over the past 25 years provides strong evidence that methadone treatment can be an effective HIV prevention intervention. Observational and retrospective studies conducted in the USA, Australia, Europe, and more recently Asia, have consistently shown strong associations between participation in methadone treatment and reductions in the frequency of opiate use, fewer injections and injection-related HIV risk behaviors, and lower rates of HIV prevalence and incidence. Collectively these data show that patients are less likely to practice injection-related risk behaviors and become infected with HIV while they remain on methadone. Thus, the data on methadone as a protective prevention strategy are strong and widely accepted [16–18].

For ethical reasons, there are no randomized controlled trials comparing treated and untreated opiate-dependent individuals and thus there is the potential for selection bias to influence these observations. It is possible that those who enter methadone treatment have greater concern for their health and engage on less risk taking. However, the consistency of the positive findings with methadone treatment over time and across diverse settings is compelling and collectively they have been used to advocate for the expanded use of methadone maintenance as primarily an HIV prevention intervention. The support of methadone treatment as an HIV prevention intervention is most notable in eastern Europe, and Central and Southeast Asia where the dual epidemics of HIV and opiate injection began in the mid-to-late 1990s [19]. In these regions, new treatment systems were established to respond to the rapid transmission of HIV among opiate injectors. The most notable is China's enormous investment in the creation of a national methadone treatment system. In less than 10 years, over 700

clinics treating more than 160,000 patients have been established and have become the largest single drug treatment system in the world, propelled primarily as an HIV prevention strategy [20].

While the data on the impact of methadone treatment are impressive, methadone treatment alone can be expected to have only a limited impact on the global epidemic because not all individuals are at risk from opiate use and not all opiate users are appropriate for, or have access to, methadone treatment. And as discussed previously, the majority of drug-related infections are likely associated with non-injection drug use and sexual transmission. This is not to diminish the importance of methadone treatment as an HIV prevention intervention, but to acknowledge that additional treatment approaches will be needed to effectively respond to substance-related transmission. Perhaps most importantly, the data on methadone as an HIV prevention strategy provide what might be considered a "proof of concept"—effective drug treatments reduce drug use, risk behavior, and HIV transmission.

Buprenorphine

The US FDA approved buprenorphine and the combination of buprenorphine-naloxone for the treatment of opiate dependence on October 8, 2002. For several reasons, the introduction of this medication represented a significant development in the treatment of opiate dependence, particularly in the USA, because primary care providers could use it outside the highly regulated methadone system [21, 22]. Data on the HIV prevention impact of buprenorphine have begun to appear. They show significant reductions in risk behaviors using both office-based and clinic-based treatment models among adults and adolescents and are quite consistent with those of methadone maintenance treatment [21, 23–27]. While the public health impact of buprenorphine and its combination with naloxone has been impacted by their higher cost per daily dose relative to methadone, cost effectiveness studies have resulted in very favorable comparisons with methadone [28, 29]. In a randomized double-blind trial among heroin injectors in Malaysia, those assigned to buprenorphine not only reduced risk behaviors significantly but also remained in treatment longer that those assigned to naltrexone or placebo [30].

As mentioned earlier, buprenorphine has a longer period of attachment to the opioid receptor. This reduces the required frequency of administration. Thrice weekly dosing of buprenorphine–naloxone has been reported recently in an HIV prevention trial of 1,250 opiate-dependent injectors in Thailand and China [31].

Naltrexone

Naltrexone is the most widely used *antagonist* and has been available for over 25 years as a medication for the treatment for opiate dependence. As an antagonist, naltrexone works by blocking access to the mu-opioid receptor. Antagonists are non-addictive and have been found to reduce heroin use and crime for patients who

accept it (Brahen et al. 1984; Chan 1996). Naltrexone has none of the reinforcing properties of opiate agonists (methadone and buprenorphine) and in its oral form must be taken on a daily basis to maintain its blockade effect—the primary mechanism of action. Naltrexone prevents opiates from accessing and stimulating the opiate receptor and importantly, if opiate molecules are already present, naltrexone will replace them, precipitating withdrawal and this has important clinical implications. First, as an antagonist, the medication does not produce or sustain dependence. Second, the treatments for opiate use cannot begin comfortably in individuals until opiates are no longer present. For those who have recently used opiates, the initiation of antagonists will precipitate abrupt withdrawal. Consequently, the use of antagonists must begin with detoxification or, a sufficient period of abstinence.

While there is much data on the safety and efficacy of both oral and long-acting naltrexone, much less research has focused on the impact of naltrexone treatment as HIV prevention. Naltrexone is an opiate antagonist that has been available as a treatment for opiate dependence for over 25 years. Also, patients who are about to start naltrexone must be opiate free in order to avoid precipitated withdrawal on their first dose. Unless highly motivated to remain abstinent, this blockade strategy has not been effective over the long term for many opiate-dependent individuals seeking treatment [32–34].

As a result of its prohibition against the use of agonist medications, the Russia Federation has accumulated considerable experience in the use of naltrexone [35]. Addiction treatment typically begins with 7–10 days of inpatient detoxification using clonidine and other non-opioid medications followed by 2–4 weeks of rehabilitation with referral to local health centers for follow-up, but few patients keep these follow-up appointments and relapse rate are high. Family members often bring patients to treatment since the heroin problem began in the 1990s after the Soviet Union dissolved, thus many of the patients are young and live with their parents who can supervise adherence. These cultural differences likely contributed to the findings in two earlier, placebo-controlled studies where over 75 % of patients who met admission criteria enrolled, and 42–44 % of those randomized to oral naltrexone remained in treatment and did not relapse over 6 months as compared to 10–12 % of those randomized to naltrexone placebo [36–38]. Although these results were better than those seen in the US studies, adherence continued to be a problem, which led to the study of sustained-release (SR) naltrexone that is reported here. SR naltrexone is currently available in two formulations—depot injections and implants. Vivitrol® (http://www.vivitrol.com), a long-acting injectable formulation developed in the USA, was FDA approved for alcohol dependence in 2006 and for opioid dependence in 2010 based on the results of a clinical trial led by Krupitsky [39].

Non-Injection Substance Use and Sexual Risk

Risky sexual behaviors have frequently been found to co-occur with both injection and non-injection drug use, particularly with stimulant use [40–42]. Early reports

focused on substances used by MSM and cocaine use among opiate-dependent individuals in methadone treatment. There is now widespread recognition of cocaine and other stimulant use and HIV risk and incident infections. Studies from Brazil, Canada, and the USA have linked HIV risk and incidence to cocaine use (Pechanski et al. 2000). More recently, data have emerged on the elevated prevalence and incidence of HIV infection among stimulant (primarily methamphetamine) using populations in the USA, Russia, and Thailand (Shaptow et al. 2005; Koblin et al. 2005; Srirak et al. 2005; Colfax and Guzman 2006; Kozlov et al. 2006; Colfax et al. 2006). Increasing use of methamphetamine has also been reported in South Africa (Morris and Parry 2006).

HIV prevention efforts targeting stimulant users have faced significant challenges given the widespread desirability and availability of these drugs, the frequency with which they are often administered and the strong association between use and sexual activity. Although some success has been reported using psychosocial treatments for harmful stimulant use, for most, behavioral interventions alone have proven insufficient to show sustained impact on drug use and related risk behavior [43]. It is not uncommon for drug treatment programs that use a variety of behavioral intervention strategies, to report dropout rates of greater than 50 % during the first few weeks of treatment. Even patients who remain in treatment rarely achieve periods of sustained abstinence.

While medications have demonstrated efficacy for the treatment of alcohol and opiate use, there are no medications for assisting with treating stimulant use disorders. Over the past 20 years, there has been a concerted effort by the National Institute on Drug Abuse (NIDA) to support the development of new treatment agents and to test existing medications for use in the treatment of stimulant use disorders. This search is complicated by the fact that no clear pathway for central nervous system activation by stimulants has been identified. Progress has also been slowed by the general lack of interest among the pharmaceutical industry in developing medications useful in the treatment of substance use disorders. Thus far, no medications have reliably demonstrated success in reducing craving for, or use of, cocaine or other stimulants.

In the absence of efficacious medication-assisted treatments for stimulant use, psycho-social and behavioral interventions of various designs have been evaluated. Generally, multi-session psycho-social interventions directed at reducing sexual risk among substance users recruited in community settings have not shown greater efficacy than more basic educational approaches that are typically used in as control or comparison conditions [42]. Several studies, however, have reported positive findings with sexual risk reduction interventions that were delivered within drug treatment programs. A variety of intervention delivery strategies have been tested including individual and group, gender specific, and gender mixed [44–46]. However, the diversity of programs and populations makes it difficult to make broad conclusions regarding efficacy.

The delivery of sexual risk reduction interventions within drug treatment programs can be considered an example of a combination prevention strategy [47]. Using the drug treatment program as a platform for the delivery of the intervention not only makes sense but also shows signs of efficacy [43, 48]. It seems clear that sexual risk reduction is more difficult to achieve than reduction in injection risk behaviors.

Thus, in contrast to the powerful prevention impact of agonist treatments for opiate injection, few substance abuse treatment interventions have shown consistent efficacy in reducing sexual risk associated with non-injection drug use.

HIV Treatment as Prevention

With the introduction of effective HIV disease management, global HIV initiatives became focused on the scale-up of ARV treatment. Along with this scale-up came recognition of the potential for HIV treatment to have important impact on the course of the epidemic. Not only was the health of infected individuals dramatically improved but also the sustained reduction of viral load was accompanied by the potential to reduce transmission risks. There was growing consensus regarding the potential prevention impact associated with participation in ARV treatment and the achievement of sustained virologic response [49–51]. This recognition led to the development of prevention models built around engaging sufficient numbers of infected individuals in ARV treatment. This led to efforts to identify HIV positive individuals and engage them in ARV treatment. This "seek, test, and treat" model was rooted in the evidence that risk behaviors were lower among patients in HIV care and that sustained reductions in viral load were able to be achieved by the majority of adherent patients, regardless of the mode of initial infection [52].

With the growing consensus that ARV treatment was an effective prevention strategy, the findings of HPTN 052 had a powerful impact and altered the HIV prevention landscape. In this study, the protective effects of ARV medication were identified by measuring the rate of transmissions from treated individuals to their uninfected partners. Patients were randomized to start on ARV medications either when their CD4 cell counts were between 500 and 350, or when CD4 cell counts were 350 or less (the WHO recommendation for treatment initiation). The HIV incidence rate in the partners of the earlier treatment group was compared to that of partners of those who started treatment later. Only 1 of the 28 infections observed among all partners occurred in the group that initiated treatment early [53]. These dramatic findings confirmed earlier observations and placed a sharp focus on the "treatment cascade" as a framework for prevention—identifying people who are HIV infected, engaging and retaining them in HIV treatment, maintaining adherence to ARV medication, and achieving sustained suppression of viral load. Importantly, at each step of this treatment cascade, substance use inhibits success.

Despite the personal and public health benefits of ARV treatment, continued substance use has frequently been associated with poorer access to ARV treatment, slower initiation of highly active antiretroviral treatment (HAART), poorer adherence to treatment, and less success in achieving viral suppression [54–56]. There is a growing body of evidence linking substance use treatment to improved access to HIV treatment, adherence while in treatment, and sustained viral suppression. Most of this work has been reported among injection drug users in methadone or buprenorphine treatment. For example, in a prospective observational study of 231 HIV-infected

opiate using injection drug users, participation in methadone treatment was found to be a significant, independent predictor of more rapid entry into ARV treatment. Data from this study also demonstrate higher rates of adherence to HIV treatment among those in methadone treatment [57, 58].

Similarly, in a retrospective analyses of 276 HIV-positive drug injectors in France, the relationship between drug use, treatment participation, and adherence was more clearly defined [59]. The findings of this study are particularly important because those patients who continued to inject drugs, regardless of their substance use treatment participation, showed poorer rates of adherence. For patients who were in methadone or buprenorphine maintenance and not injecting drugs, adherence did not differ from patients with no history of drug use. However, for those who continued to inject adherence, it was two to three times worse, despite the fact that they were receiving agonist medications. The findings of this study were the first to identify continued injection and not merely participation in drug treatment. This same cohort produced data showing that retention in medication-assisted treatment was linked to long-term virologic suppression [60]. These data are consistent with earlier reports of poorer adherence among patients that continue substance use and improved adherence among those in drug treatment [61].

The Search for New Biomedical Tools and Strategies

As discussed earlier, harmful substance use is best viewed as a chronic medical condition requiring attention to both behavioral and biological forces that promote and reinforce continued use. While the treatment of harmful opiate use can be seen as a model for the medical management of substance use disorders and associated problems, most harmful substance use involves substances other than opiates: alcohol, stimulants, and other drugs. The biomedical treatment of these conditions is much more limited. Despite an intensive and sustained search for effective medications for cocaine and other stimulant use over the past 15 years, there is little reason for optimism that we will quickly determine the mechanism of action or develop effective treatment agents that can inhibit craving or reduce effects.

Scaling Up Prevention Strategies for Substance Users

From the earliest days of the AIDS epidemic, substance use has been known to be both a direct mode of transmission via injection and a common co-factor in sexual transmission. The primary focus of prevention science has been to stop new infections among injection drug users. While this was, and continues to be, an important mechanism of transmission and focus of prevention efforts, it has predominated the thinking about the role of substance use in the HIV epidemic and has contributed to a limited understanding of the role of substance use in sustaining the AIDS epidemic.

Even if all injection drug use ceased, substance use will remain a major factor in HIV transmission and treatment. In fact, the objectives of identifying HIV-infected individuals who are unaware of their status and engaging and retaining them in treatment will bring force to the recognition of the important role of non-injection substance use.

This chapter has focused on the consistent evidence that effective treatments for drug abuse and dependence reduce the frequency of use, risk behaviors, and infections. While these findings were observed during the first 15 years of the epidemic primarily from countries with existing drug treatment systems, more recent data provide evidence of these same impacts, particularly in countries with more recently established treatment programs and systems. The consistency of this relationship over time and across cultural settings is impressive and serves as a reminder that harmful substance use, like other chronic medical conditions, has predicable responses when treated using effective strategies.

Importantly, there is increasing evidence of the positive effects of medication-assisted treatments other than methadone. Results of interventions using buprenorphine, buprenorphine–naloxone, and naltrexone are producing findings consistent with those of methadone treatment for those who reduce their drug use. This is particularly important considering the need for multiple treatment options in communities affected by HIV and other blood-borne and sexually transmitted infections.

The current focus on treatment as prevention provides an opportunity to more fully integrate substance use screenings and interventions into the HIV treatment delivery system. This strategy significantly expands the role of effective substance abuse treatments as HIV prevention. First, the data suggest that for the most serious cases of substance use disorders (addiction) effective substance use treatments improve access to ARV treatment, adherence to those treatments, and the chances of sustained reductions in viral load.

Also, just as substance use inhibits adherence to ARV medications, it is likely to play a similar role with other prevention strategies that require regular attention. Adherence issues have become a primary concern in other biomedical prevention strategies for HIV—vaginal microbicides, pre-exposure prophylaxis (PrEP). In fact, questions of efficacy and more importantly, effectiveness, of these strategies remain unanswered mainly due to poor adherence during clinical trials testing these strategies.

Recent research has also provided strong evidence that current use of substances, not past diagnosis, mode of infection, or individual characteristics, is associated with poor adherence. Findings that medication-assisted treatments for opiate injectors reduce risk of infection with HIV have been widely promulgated. While such “low demand” interventions will undoubtedly help many dependent individuals avoid withdrawal, risk behaviors, and other negative consequences associated with dependence, it is not clear that this strategy is a very effective treatment for addiction.

Given the fact that only a small portion of drug users ever enter formal treatment, research is also needed to develop and evaluate strategies for embedding effective drug treatments in non-traditional settings where risk behaviors are common and

HIV infection is prevalent. Enormous opportunities exist for the delivery of health promoting drug treatment messages outside of drug treatment programs. New, long-acting formulations of existing medications (naltrexone and buprenorphine) offer more efficient strategies for treatment coverage and opportunities for significant advances in HIV prevention efforts.

As stated throughout this chapter, given the important role of heroin injection in propelling the spread of HIV via injection-related risk, most of the published research has involved opiate users and their treatment with methadone and buprenorphine-naloxone. The literature is quite clear that these medication-assisted treatments are effective HIV prevention strategies.

Unfortunately, comparably effective medication-assisted treatments for cocaine and other stimulant use are not currently available. While treatment strategies that do not use medications, most notably, interventions using contingency management strategies, have shown some evidence of efficacy among high-risk stimulant users, the development of a safe and effective treatment medication for stimulant abuse and dependence must remain a high priority.

Clearly, drug treatment programs play a critical role in controlling the spread of HIV and improving its treatment in many communities around the world. Still, the great majority of drug users do not have access to effective substance abuse treatments—even in countries considered to be more highly developed [67]. While the scale-up of substance abuse treatment programs remains an important priority, it is not likely that these specialty treatment programs alone will be sufficient to stop the spread of HIV infection or ensure effective ARV treatment of people who use substances. Consequently, there is both need and opportunity to scale up the screening and intervention for substance use within HIV clinics. The integration of substance use monitoring and response is necessary to maximize the success of the treatment as prevention strategy.

The role of substance use in the AIDS epidemic has never been fully recognized and goes far beyond that which is represented by injection drug use. Alcohol and non-injection substance use does not define a risk group—it is common in all risk groups not only as a factor in the direct transmission of HIV but also in inhibiting access to and retention in HIV care, adherence to ARV medication, and in the sustained suppression of viral load. As the AIDS epidemic progresses through its fourth decade, the role of non-injection substance use must move to the forefront of prevention science. While continuing efforts to control injection-related transmissions, harmful substance use must be monitored and treated in the community and in the HIV clinic. This will be necessary not only to achieve the goals of the national and global AIDS strategies but also to have any chance of eventual eradication of the virus.

References

1. Masur H, Michelis MA, Greene JB, Onorato I, Stouwe RA, Holzman RS, et al. An outbreak of community-acquired *Pneumocystis carinii* pneumonia: initial manifestation of cellular immune dysfunction. N Engl J Med. 1981;305(24):1431–8.

2. Ginzburg HM. Intravenous drug users and the acquired immune deficiency syndrome. Public Health Rep. 1984;99(2):206–12.
3. De Cock KM, Jaffe HW, Curran JW. The evolving epidemiology of HIV/AIDS. AIDS. 2012;26(10):1205–13.
4. Mahy M, Warner-Smith M, Stanecki KA, Ghys PD. Measuring the impact of the global response to the AIDS epidemic: challenges and future directions. J Acquir Immune Defic Syndr. 2009;52(Suppl 2):S152–9.
5. Mathers BM, Degenhardt L, Adam P, Toskin I, Nashkhoev M, Lyerla R et al. Estimating the level of HIV prevention coverage, knowledge and protective behavior among injecting drug users: what does the 2008 UNGASS reporting round tell us? JAIDS-J Acquir Immune Defic Syndr. 2009;52:S132–42.
6. Bogart LM, Kral AH, Scott A, Anderson R, Flynn N, Gilbert ML, et al. Sexual risk among injection drug users recruited from syringe exchange programs in California. Sex Transm Dis. 2005;32(1):27–34.
7. Kalichman SC, Rompa D, Cage M. Group intervention to reduce HIV transmission risk behavior among persons living with HIV/AIDS. Behav Modif. 2005;29(2):256–85.
8. Bogart LM, Kral AH, Scott A, Anderson R, Flynn N, Gilbert ML, et al. Condom attitudes and behaviors among injection drug users participating in California syringe exchange programs. AIDS Behav. 2005;9(4):423–32.
9. Bluthenthal RN, Do DP, Finch B, Martinez A, Edlin BR, Kral AH. Community characteristics associated with HIV risk among injection drug users in the San Francisco Bay Area: a multilevel analysis. J Urban Health. 2007;84(5):653–66.
10. Townsend L, Mathews C, Zembe Y. A systematic review of behavioral interventions to prevent HIV infection and 2 among heterosexual, adult men in low-and middle-income countries. Prev Sci. 2013;14(1):88–105.
11. Woody GE, VanEtten-Lee ML, McKirnan D, Donnell D, Metzger D, Seage G, et al. Substance use among men who have sex with men: comparison with a national household survey. J Acquir Immune Defic Syndr. 2001;27(1):86–90.
12. Chesney MA, Koblin BA, Barresi PJ, Husnik MJ, Celum CL, Colfax G, et al. An individually tailored intervention for HIV prevention: baseline data from the EXPLORE study. Am J Public Health. 2003;93(6):933–8.
13. Menza TW, Hughes JP, Celum CL, Golden MR. Prediction of HIV acquisition among men who have sex with men. Sex Transm Dis. 2009;36(9):547–55.
14. Koblin B, Chesney M, Coates T, Mayer K, Agredano F, Aguilu E, et al. Effects of a behavioural intervention to reduce acquisition of HIV infection among men who have sex with men: the EXPLORE randomised controlled study. Lancet. 2004;364(9428):41–50.
15. Koblin BA, Husnik MJ, Colfax G, Huang Y, Madison M, Mayer K, et al. Risk factors for HIV infection among men who have sex with men. AIDS. 2006;20(5):731–9.
16. MacArthur GJ, Minozzi S, Martin N, Vickerman P, Deren S, Bruneau J et al. Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. Br Med J. 2012;345.
17. Sorensen JL, Copeland AL. Drug abuse treatment as an HIV prevention strategy: a review. Drug Alcohol Depend. 2000;59(1):17–31.
18. Metzger DS, Woody GE, O'Brien CP. Drug treatment as HIV prevention: a research update. JAIDS-J Acquir Immune Defic Syndr. 2010;55:S32–6.
19. Bao YP, Liu ZM. Systematic review of HIV and HCV infection among drug users in China. Int J STD AIDS. 2009;20(6):399–405.
20. Li J, Ha T, Zhang C, Liu H. The Chinese government's response to drug use and HIV/AIDS: a review of policies and programs. Harm Reduct J. 2010;7(1):4.
21. Fiellin DA, Pantalon MV, Chawarski MC, Moore BA, Sullivan LE, O'Connor PG, et al. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. N Eng J Med. 2006;355(4):365–74.
22. Bridge TP, Fudala PJ, Herbert S, Leiderman DB. Safety and health policy considerations related to the use of buprenorphine/naloxone as an office-based treatment for opiate dependence. Drug Alcohol Depend. 2003;70(2 Suppl):S79–85.

23. Sullivan LE, Fiellin DA. Buprenorphine: its role in preventing HIV transmission and improving the care of HIV-infected patients with opioid dependence. Clin Infect Dis. 2005;41(6):891–6.
24. Sullivan LE, Metzger DS, Fudala PJ, Fiellin DA. Decreasing international HIV transmission: the role of expanding access to opioid agonist therapies for injection drug users. Addiction. 2005;100(2):150–8.
25. Sullivan LE, Moore BA, Chawarski MC, Pantalon MV, Barry D, O'Connor PG, et al. Buprenorphine/naloxone treatment in primary care is associated with decreased human immunodeficiency virus risk behaviors. J Subst Abuse Treat. 2008;35(1):87–92.
26. Meade CS, Weiss RD, Fitzmaurice GM, Poole SA, Subramaniam GA, Patkar AA, et al. HIV risk behavior in treatment-seeking opioid-dependent youth: results from a NIDA clinical trials network multisite study. J Acquir Immune Defic Syndr. 2010;55(1):65–72. doi:10.1097/QAI.0b013e3181d916db.
27. Woody GE, Poole SA, Subramaniam G, Dugosh K, Bogenschutz M, Abbott P et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth a randomized trial. JAMA-J Am Med Assoc. 2008;300(17):2003–11.
28. Schackman BR, Merrill JO, McCarty D, Levi J, Lubinski C. Overcoming policy and financing barriers to integrated buprenorphine and HIV primary care. Clin Infect Dis. 2006;43:S247–53.
29. Doran CM, Shanahan M, Mattick RP, Ali R, White J, Bell J. Buprenorphine versus methadone maintenance: a cost-effectiveness analysis. Drug Alcohol Depend. 2003;71(3):295–302.
30. Schottenfeld RS, Chawarski MC, Mazlan M. Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomised, double-blind, placebo-controlled trial. Lancet. 2008;371(9631):2192–200.
31. Lucas GM, Beauchamp G, Aramrattana A, Shao YM, Liu W, Fu LP, et al. Short-term safety of buprenorphine/naloxone in HIV-seronegative opioid-dependent Chinese and Thai drug injectors enrolled in HIV prevention trials network 058. Int J Drug Policy. 2012;23(2):162–5.
32. Fram DH, Marmo J, Holden R. Naltrexone treatment—the problem of patient acceptance. J Subst Abuse Treat. 1989;6(2):119–22.
33. Tucker TK, Ritter AJ. Naltrexone in the treatment of heroin dependence: a literature review. Drug Alcohol Rev. 2000;19(1):73–82.
34. Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev. 2006;(1).
35. Krupitsky E, Woody GE, Zvartau E, O'Brien CP. Addiction treatment in Russia. Lancet. 2010;376(9747):1145.
36. Krupitsky EM, Zvartau EE, Masalov DV, Tsoi MV, Burakov AM, Egorova VY, et al. Naltrexone for heroin dependence treatment in St. Petersburg, Russia. J Subst Abuse Treat. 2004;26(4):285–94.
37. Krupitsky E, Zvartau E, Masalov D, Tsoi M, Egorova V, Burakov A et al. A double-blind, placebo controlled trial of naltrexone and fluoxetine for heroin addiction treatment. Eur Neuropsychopharmacol. 2005;15:S284.
38. Krupitsky EM, Zvartau EE, Masalov DV, Tsoy MV, Burakov AM, Egorova VY, et al. Naltrexone with or without fluoxetine for preventing relapse to heroin addiction in St. Petersburg, Russia. J Subst Abuse Treat. 2006;31(4):319–28.
39. Krupitsky E, Nunes EV, Ling W, Illeperuma A, Gastfriend DR, Silverman BL. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet. 2011;377(9776):1506–13.
40. Tross S, Hanner J, Hu M-C, Pavlicova M, Campbell A, Nunes EV. Substance use and high risk sexual behaviors among women in psychosocial outpatient and methadone maintenance treatment programs. Am J Drug Alcohol Abuse. 2009;35(5):368–74.
41. Rudy ET, Shoptaw S, Lazzar M, Bolan RK, Tilekar SD, Kerndt PR. Methamphetamine use and other club drug use differ in relation to HIV status and risk behavior among gay and bisexual men. Sex Transm Dis. 2009;36(11):693–5.
42. Meader N, Li R, Des Jarlais DC, Pilling S. Psychosocial interventions for reducing injection and sexual risk behaviour for preventing HIV in drug users. Cochrane Database Syst Rev. 2010(1):CD007192.

43. Shoptaw S, Reback CJ, Peck JA, Yang XW, Rotheram-Fuller E, Larkins S, et al. Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. Drug Alcohol Depend. 2005;78(2):125–34.
44. Tross S, Campbell ANC, Cohen LR, Calsyn D, Pavlicova M, Miele GM et al. Effectiveness of HIV/STD sexual risk reduction groups for women in substance abuse treatment programs: results of NIDA clinical trials network trial. JAIDS-J Acquir Immune Defic Syndr. 2008;48(5):581–9.
45. Calsyn DA, Hatch-Maillette M, Tross S, Doyle SR, Crits-Christoph P, Song YS, et al. Motivational and skills training HIV/sexually transmitted infection sexual risk reduction groups for men. J Subst Abuse Treat. 2009;37(2):138–50.
46. Calsyn DA, Crits-Christoph P, Hatch-Maillette MA, Doyle SR, Song YS, Coyer S, et al. Reducing sex under the influence of drugs or alcohol for patients in substance abuse treatment. Addiction. 2010;105(1):100–8.
47. Chang LW, Serwadda D, Quinn TC, Wawer MJ, Gray RH, Reynolds SJ. Combination implementation for HIV prevention: moving from clinical trial evidence to population-level effects. Lancet Infect Dis. 2013;13(1):65–76.
48. Shoptaw S, Reback CJ, Larkins S, Wang PC, Rotheram-Fuller E, Dang J, et al. Outcomes using two tailored behavioral treatments for substance abuse in urban gay and bisexual men. J Subst Abuse Treat. 2008;35(3):285–93.
49. Volkow ND, Montaner J. Enhanced HIV testing, treatment, and support for HIV-infected substance users. JAMA-J Am Med Assoc. 2010;303(14):1423–4.
50. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009;373(9657):48–57.
51. De Cock KM, Crowley SP, Lo Y-R, Granich RM, Williams BG. Preventing HIV transmission with antiretrovirals. Bull World Health Organ. 2009;87(7):488–A.
52. Lima VD, Johnston K, Hogg RS, Levy AR, Harrigan PR, Anema A, et al. Expanded access to highly active antiretroviral therapy: a potentially powerful strategy to curb the growth of the HIV epidemic. J Infect Dis. 2008;198(1):59–67.
53. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Eng J Med. 2011;365(6):493–505.
54. Chander G, Himelhoch S, Fleishman JA, Hellinger J, Gaist P, Moore RD et al. HAART receipt and viral suppression among HIV-infected patients with co-occurring mental illness and illicit drug use. AIDS Care-Psychol Socio-Med Asp AIDS/HIV. 2009;21(5):655–63.
55. Krusi A, Wood E, Montaner J, Kerr T. Social and structural determinants of HAART access and adherence among injection drug users. Int J Drug Policy. 2010;21(1):4–9.
56. Wu ES, Metzger DS, Lynch KG, Douglas SD. Association between alcohol use and HIV viral load. JAIDS-J Acquir Immune Defic Syndr. 2011;56(5):E129–30.
57. Lucas GM, Mullen BA, Weidle PJ, Hader S, McCaul ME, Moore RD. Directly administered antiretroviral therapy in methadone clinics is associated with improved HIV treatment outcomes, compared with outcomes among concurrent comparison groups. Clin Infect Dis. 2006;42(11):1628–35.
58. Lucas GM, Griswold M, Gebo KA, Keruly J, Chaisson RE, Moore RD. Illicit drug use and HIV-1 disease progression: a longitudinal study in the era of highly active antiretroviral therapy. Am J Epidemiol. 2006;163(5):412–20.
59. Roux P, Carrieri MP, Villes V, Dellamonica P, Poizot-Martin I, Ravaux I, et al. The impact of methadone or buprenorphine treatment and ongoing injection on highly active antiretroviral therapy (HAART) adherence: evidence from the MANIF2000 cohort study. Addiction. 2008;103(11):1828–36.
60. Roux P, Carrieri MP, Cohen J, Ravaux I, Poizot-Martin I, Dellamonica P, et al. Retention in opioid substitution treatment: a major predictor of long-term virological success for HIV-infected injection drug users receiving antiretroviral treatment. Clin Infect Dis. 2009;49(9):1433–40.

61. Spire B, Lucas GM, Carrieri MP. Adherence to HIV treatment among IDUs and the role of opioid substitution treatment (OST). Int J Drug Policy. 2007;18(4):262–70.
62. Centers for Disease Control and P. HIV infection among injection-drug users—34 states, 2004–2007. MMWR Morb Mortal Wkly Rep. 2009;58(46):1291–5.
63. Pollack HA, D'Aunno T, Lamar B. Outpatient substance abuse treatment and HIV prevention: an update. J Subst Abuse Treat. 2006;30(1):39–47.
64. Knudsen HK, Oser CB. Availability of HIV-related health services in adolescent substance abuse treatment programs. AIDS Care-Psychol Socio-Med Asp AIDS/HIV. 2009;21(10):1238–46.
65. Sorensen JL, Haug NA, Delucchi KL, Gruber V, Kletter E, Batki SL, et al. Voucher reinforcement improves medication adherence in HIV-positive methadone patients: a randomized trial. Drug Alcohol Depend. 2007;88(1):54–63.
66. Barnett PG, Sorensen JL, Wong W, Haug NA, Hall SM. Effect of incentives for medication adherence on health care use and costs in methadone patients with HIV. Drug Alcohol Depend. 2009;100(1–2):115–21.
67. Mathers BM, Degenhardt L, Ali H, Wiessing L, Hickman M, Mattick RP, et al. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. Lancet. 2010;375(9719):1014–28.

Part III
Global Perspectives

Chapter 9
Revolution or Evolution? What Can Approaches Based on the Use of Antiretroviral Drugs Contribute to HIV Prevention in Gay Communities in High-Income Countries?

John B. F. de Wit and Philippe C. G. Adam

As has been noted by leading researchers and commentators [1, 2], the field of HIV prevention research and practice is very much re-invigorated and transformed by findings from recent randomized controlled trials (RCTs). These trials have showed that antiretroviral drugs (ARVs) can prevent HIV transmission and infection when used for early treatment of people living with HIV (PLHIV) (Cohen et al. 2011) or as pre-exposure prophylaxis (PrEP) for HIV-negative people [3]. Initial statistical modeling of the theoretical impact of treatment-as-prevention (TasP) approaches on efforts to eradicate HIV in hyper-endemic contexts [4] has undoubtedly contributed to optimistic views that the HIV epidemic can now be brought under control and that an "AIDS-free generation" is within reach [5]. With its double effect of improving the health and lives of PLHIV and preventing onward transmission, antiretroviral therapy (ART) has been labeled a "game changer" in HIV prevention [6], and recent research findings have provided important impetus to the setting of bold targets to curb the global HIV epidemic [7].

However, at the same time that sustained successes in driving down overall annual numbers of new HIV infections worldwide are being achieved [8], HIV epidemics among gay men and other men who have sex with men (GMSM) in most resource-rich countries continue to grow [9]. Despite decades of extensive HIV prevention, HIV epidemics among GMSM in North America, Western Europe, and Australia are found to be re-emerging, resurging, increasing in specific demographic groups or stable

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at best [10–13]. Moreover, epidemics among GMSM in low-income and middle-income countries remain largely unaddressed [14], and may be exploding in some settings [15]. ARV-based HIV prevention approaches are thought to hold promise for controlling the HIV epidemics in GMSM worldwide [9]. This chapter examines the potential for TasP as well as PrEP to contribute to a much needed strengthening of HIV prevention among GMSM. Focus will be on the potential of ARV-based HIV prevention to drive down HIV infections among GMSM in resource-rich settings, which has been mostly studied in the USA. We extend considerations of the practice implications of ARV-based approaches to gay communities in other high-income country settings, by drawing on findings from the well-documented HIV epidemics among gay men in Australia and Western Europe, including The Netherlands and the UK.

In what follows, we first outline the rapidly changing HIV prevention landscape and briefly summarize the current evidence for the efficacy of novel biomedical HIV prevention approaches. We specifically consider the available evidence to support emerging biomedical HIV prevention among GMSM. To date, empirical data from robust studies with GMSM are limited, including for TasP and PrEP, and there is evidence to suggest that prevention benefits of ARV-based HIV prevention among GMSM in high-income countries may have been offset by increases in sexual risk. We also examine the extent to which available research findings can be extrapolated to other contexts than those of the studies and that may differ in the prevalence and incidence of HIV among GMSM and the extent to which GMSM living with HIV are aware of their HIV status, linked to care, receive and adhere to ART, and have undetectable viral load. The subsequent analysis of the extent to which the implementation of ARV-based HIV prevention approaches can make a difference to the HIV epidemics among GMSM is especially concerned with the role of two further behaviors that shape their success: adoption of ARV-based HIV prevention approaches by those who are eligible and adherence to regimens by those who adopt them [16]. We conclude with a consideration of the importance of increasing HIV testing and key challenges for behavioral prevention.

However inspiring a professed "HIV prevention revolution" [17] may be, we more cautiously hope that the world is seeing an "HIV prevention evolution." As noted by Buchbinder and Liu [18], "pills will never completely control the AIDS epidemic," and addressing people's behavior and the circumstances in which they live remains critical to the success of HIV prevention. Importantly, the use of ARVs for HIV prevention may reduce HIV incidence, but this does not necessarily change underlying drivers and may not result in sustainable effects [19]. In particular, ARV-based HIV prevention approaches are unlikely to alleviate the structural inequalities that shape differential vulnerability to HIV infection or the social stressors such as stigma, discrimination, and exclusion of that compound living with HIV [20].

Strengthening HIV Prevention and Doing It Differently

Since the advent of life-saving treatments with combinations of ARVs in the mid-1990s [21], making ART available to eligible PLHIV worldwide has been a major focus of the global HIV response [22]. Since the early 2000s, much has been achieved

in promoting universal access to ART, in particular in low- and middle-income countries [23]. Despite major investments much more remains to be done however and, by the end of 2011, only 8 million (54 %) of an estimated 15 million eligible people are receiving ART [23]. Furthermore, despite reductions in HIV incidence and accelerated access to ART, annual new HIV diagnoses continue to outnumber people newly initiating treatment by a factor of almost 2 [22, 23]. According to current guidelines [24], less than half (44 %) of the 34 million people with HIV worldwide are eligible for ART [23]. Substantially more people will become eligible as evidence continues to accumulate regarding the benefits of earlier initiation of ART [25], and some expert guidelines, in particular in the USA, already recommend ART for all PLHIV to reduce the risk of disease progression and for the prevention of onward transmission of HIV [26].

Recognition of the many challenges and considerable human and financial resources required to ensure universal access to ART, coupled with an underinvestment in HIV prevention compared to treatment, care, and support [23, 27], has resulted in calls for a "prevention revolution" [17]. The XVIIth International AIDS Conference (Mexico City, 2008) was a landmark event contributing significantly to a renewed focus on HIV prevention. Consideration and discussion of the much-needed strengthening of HIV prevention was in particular facilitated by a Lancet Series of papers on HIV prevention, launched at the conference [28]. In addition to a call for improvements in behavior change strategies to reduce risk of HIV [29], the series showcased contemporary perspectives on HIV prevention that underscored the importance of a combination of approaches to respond to the complexities of and opportunities for HIV prevention [30]. This combination prevention discourse is aligned with an ecological approach to health promotion [31], acknowledging the multiple layers of concurrent influence on individuals and communities that shape social differences [32]. It also highlights the multiple opportunities for intervention addressing different distal and proximal determinants [33], including through so-called structural interventions to address social, cultural, political, and economic inequities that shape and compound vulnerability to HIV [34].

In recent years, research into biomedical approaches to HIV prevention has in particular attracted considerable interest, including continued efforts to develop a preventive vaccine, treatment of sexually transmitted infections (STIs), medical male circumcision, topical microbicides, and the use of ARVs to reduce the likelihood of HIV transmission and infection [35]. Biomedical HIV prevention approaches are especially championed for their potential to expand the HIV prevention toolkit and providing alternative means of protection when condom use is not an option [2]. Biomedical HIV prevention approaches may also rely less on event-related decision-making, which could promote their use and effect [2]. Illustrating skepticism regarding the potential of behavior change interventions to curb the HIV epidemic, at least on their own, it is also noted that efficacy in reducing new HIV infections has only been proven in RCTs of biomedical interventions [36], with most robust findings for medical male circumcision [33].

ARV-based HIV prevention approaches hold particular potential to contribute to reducing the HIV epidemics among GMSM. Other biomedical approaches are either nascent (e.g., development of a protective vaccine) or generally not supported by the outcomes of RCTs (e.g., treatment of STIs). While medical male circumcision could in theory be relevant for HIV prevention among GMSM, a meta-analysis of observational studies found no significant association between the circumcision status of men and their likelihood of being HIV positive [37]. The results of mathematical modeling further suggest that circumcision as a public health intervention will not produce substantial decreases in HIV prevalence or incidence among GMSM in the context of an epidemic similar to that in Australia [38]. Circumcised GMSM who predominantly take the insertive role in anal intercourse between men may be at a lower risk of HIV infection [39], but in view of substantial role versatility (i.e., taking both insertive and receptive roles in anal sex [40]), the population-level beneficial effect of circumcision among GMSM may remain limited.

ARVs substantially reduce the infectiousness of PLHIV, and are effective in preventing mother-to-child transmission of HIV [23]. ARVs are also successfully used as post-exposure prophylaxis (PEP) by HIV-negative people to reduce the likelihood of HIV transmission following possible occupational or non-occupational exposure [41]. Extending these established preventive uses of ARVs, findings from three RCTs released since 2010 have provided proof of concept that ARVs, in particular the nucleotide reverse transcriptase inhibitor tenofovir disoproxil fumarate (TDF) alone or in combination with the nucleoside reverse transcriptase inhibitor emtricitabine (FTC; the fixed dose combination of TDF/FTC is marketed as Truvada®), can reduce the likelihood of sexual acquisition of HIV when used as PrEP by HIV-negative individuals [42], either orally in a pill [43–45] or topically in a vaginal gel [46]. Furthermore, a recently reported trial found oral PrEP to be efficacious among people who inject drugs in Thailand found that [47]. One further RCT has confirmed previous observational studies and demonstrated that early initiation of ART by PLHIV can reduce the likelihood of onward transmission [48]. While these findings have generated much excitement about the prospects of new HIV prevention approaches that may be effective in reducing new infections, it should also be noted that two PrEP trials have been unsuccessful, suggesting that there are critical moderators of the effect of PrEP that need to be understood and addressed, such as adherence. An RCT of TDF/FTC among women in sub-Saharan Africa was halted for futility [49], and an RCT of TDF-only oral PrEP, oral TDF/FTC PrEP, and a tenofovir-only vaginal gel in young African women found no effect of the daily use of any of these products [50].

Are ARV-Based HIV Prevention Approaches Truly Game Changers?

Worldwide, GMSM are disproportionately affected by HIV, while in many country settings HIV prevention, treatment, and care responses for GMSM remain insufficient or lacking, often because of stigma and discrimination [14, 51, 52]. The public

health and human rights imperative to address the HIV epidemic among GMSM globally is increasingly recognized, and a recent call to action in particular notes that advances in ARV-based prevention of HIV "opens up real possibilities for the eventual achievement of control of HIV subepidemics in MSM" [53]. It has also been suggested that the priorities of HIV prevention research "have expanded from biomedical discovery to include implementation, effectiveness, and the effect of combination prevention at the population level" [1].

Facilitating the implementation of TasP, US Department of Health and Human Services guidelines for the use of ARVs in adolescents and adults recommend ART for all PLHIV, including for the prevention of onward transmission [26]. Of relevance to HIV prevention among GMSM is also that, in the USA, TDF/FTC has been approved for use as PrEP among sexually active adults. Furthermore, the US Centers for Disease Control and Prevention have released interim guidance for clinicians considering the use of PrEP [54, 55], including for GMSM. The World Health Organization has also released guidance regarding the use of PrEP in the context of demonstration projects [56], which is recommended as a possible additional intervention for the HIV-negative partner in serodiscordant couples as well as for GMSM and transgender women. The evidence for these recommendations originates from RCTs and is indicated to be of high quality. However, what is also of importance is that the evidence base for the use of PrEP is limited and mixed. Notably, of the six reported PrEP trials to date, four of which been conducted amongst people at risk for HIV through heterosexual transmission, three found significant effects and two did not (both conducted among at risk heterosexual people), suggesting qualified recommendations are indicated that reflect an understanding of potential moderating variables. Also, PrEP trials to date have predominantly been conducted among participants in low-income and middle income countries and the influence of setting on outcomes needs to be considered when developing recommendations for implementation into practice.

Despite high expectations, which reflect urgent needs, the evidence base for the potential of ARV-based HIV prevention to contribute to curbing the epidemic among GMSM remains limited. To date, one ecological study has been reported that suggests that increased access to ART could reduce population-level HIV transmission among GMSM [57]. Also, one RCT has been reported examining the efficacy of PrEP among GMSM and transgender women [44]. One earlier safety trial was undertaken among GMSM in the USA, but no efficacy data were obtained [18]. Rectal microbicides, including tenofovir-containing gels, are in development and could be of use in HIV prevention for GMSM, in particular when formulations become available that are well tolerated in the rectum [58]. In addition, several studies have been undertaken to statistically model the potential impact and cost-effectiveness of PrEP and TasP in various gay communities, mostly in the USA.

The most robust evidence to date for the efficacy of ARV-based HIV prevention among GMSM comes from the iPrEx study (Iniciativa Profilaxis Pre Exposicion or Pre-exposure Prophylaxis Initiative [44]). This study enrolled almost 2,500 HIV-negative GMSM and transgender women in six countries (USA, Brazil, Ecuador, Peru, South Africa, and Thailand). The study found that a regimen of once-daily use

of TDF/FTC reduced the likelihood of HIV transmission by 44 %; efficacy might be lower in younger GMSM [59]. Several PrEP studies among GMSM are ongoing or planned and these will provide further data regarding the implementation of PrEP programs in non-trial settings, the use of other classes of ARVs for PrEP, the implications of intermittent dosing schedules, and PrEP use in young, high-risk GMSM [60].

In the absence of effectiveness data from implementation research and demonstration projects, statistical modeling can provide estimates of the potential contribution of PrEP to HIV prevention among GMSM, as well as the cost-effectiveness of strategies to implement PrEP. An early study statistically modeled the hypothetical impact and cost-effectiveness of a PrEP program among GMSM in New York City [61]. This study predicted that, in 2008, HIV prevalence among GMSM in New York City was 14.6 %; HIV incidence was predicted to be 1.35 %. To assess the impact and cost-effectiveness of PrEP, a base case scenario was constructed assuming that a PrEP program would achieve 25 % coverage among GMSM at very high risk that are thought to make up about 30 % of all GMSM in New York City [61]. Further assuming a 50 % efficacy of PrEP and 50 % program adherence, the base case scenario suggests that 8.7 % of new HIV infections could be prevented over a period of 5 years. The number of new infections averted was sensitive to assumption regarding efficacy, mechanism of protection, coverage, and adherence, and ranged from 0.3 to 23.1 %. Assuming a coverage of 25 % of high-risk men, a PrEP program would be cost-effective under most variations in mechanism of protection, efficacy, program adherence, and cost of HIV care [61].

Another early study modeled the impact of PrEP in a US population of GMSM at high risk of infection (i.e., 1.6 % mean annual incidence) [62]. Assuming a 50 % efficacy, this study predicted that the introduction of PrEP in a cohort of GMSM with a mean age of 34 years could reduce lifetime risk of HIV infection from 44 to 25 %; impact on lifetime risk was much larger at higher levels of potential efficacy. Nevertheless, while the study found that PrEP could substantially reduce HIV incidence among GMSM at high risk, authors conclude that the benefits of PrEP are unlikely to justify current cost [62]. A review of mathematical modeling of PrEP programs for GMSM concluded that, given currently high cost, PrEP (defined as once daily Truvada®) among GMSM in the USA will be most cost-effective when targeting those at highest risk, in particular population groups of men with HIV incidence > 2 % [63]; this targeting may however limit the population-level impact of PrEP among GMSM. The trade-off between impact and cost is illustrated in a recent modeling study that found that initiating PrEP in 20 % of GMSM in the USA could reduce new HIV infections by 13 %, with more infections prevented by initiating PrEP in a larger proportion of GMSM [64]. However, this extended initiation of PrEP negatively affected cost-effectiveness and cost-effectiveness was in particular improved when PrEP was limited to high-risk GMSM [64]. PrEP programs may be most attractive when identification and linkage to care of people with HIV is poor, and high rates of HIV testing in target groups may reduce the attractiveness of PrEP [62]. This resonates with findings of a combined modeling of effects of PrEP and TasP [65]. This study found that, in a hyper-endemic setting similar to that in KwaZulu-Natal, South Africa, a financially capped PrEP intervention is unlikely to

result in large reductions in HIV incidence. The study also found that maximum population-level cost-effectiveness is achieved by scaling up early initiation of ART.

A Closer Look at the Potential for TasP for GMSM

While generally considered the most promising ARV-based HIV prevention approach, to date there is no evidence from an RCT establishing the efficacy of increasing coverage of ART in reducing the likelihood of HIV transmission in GMSM. There is however some ecological evidence consistent with this hypothesis, including among GMSM. Evaluations of the population-level impact of increasing coverage of ART on HIV transmission are based on the assumption that increased rates of HIV testing facilitate initiation of ART, and that increased coverage of ART will result in a reduced community viral load (CVL), as viral load of effectively treated PLHIV will go down [66]. A study in San Francisco found that CVL, measured as the mean and the total of the most recent viral load of all reported PLHIV in the local population, decreased from 2004 to 2008, when the proportion of undiagnosed GMSM decreased and the proportion of PLHIV receiving ART increased [57]. Importantly, and in support of the potential public health impact of ART, decreasing CVL was significantly associated with decreasing numbers of reported new HIV diagnoses, and was consistent (but not significantly associated) with reductions in HIV incidence. A study in Denmark found that while sexual risk-taking had increased dramatically between 1995 and 2010, the incidence of GMSM diagnosed with HIV had not [67]. The prevalence of HIV-positive GMSM with detectable viral load decreased by 75 % in this same period, leading authors to conclude that ART has decreased the risk of HIV transmission [67]. The uptake of ART is similarly thought to have contributed to limiting HIV incidence among GMSM in the UK [68, 69].

Support for the potential of TasP approaches to significantly reduce HIV infections among GMSM is also provided by several mathematical modeling studies. An influential early model of the impact of increased usage of ART among GMSM in San Francisco found that this could substantially reduce HIV incidence between 2000 and 2010, but also suggested that the net effect of widespread usage of ART could be close to zero if it resulted in significant increases in risk behavior [70]. Assuming a stable distribution of risk among GMSM in San Francisco (80 % low risk, 20 % high risk), a more recent model suggests that expanding coverage of ART can further reduce new infections among GMSM in San Francisco between 2009 and 2029 [71]. This study in particular compared different expansion strategies with baseline practice of ART initiation when CD4 cell counts fall below < 350 cells/mm^3: treatment of all individuals receiving HIV care with CD4 cell counts < 500 cells/mm^3, treatment of all individuals receiving HIV care, and intensified annual HIV testing combined with initiation of treatment of all HIV-infected individuals (i.e., test-and-treat). Each of these strategies reduced new HIV infections at least by 33 % over 20 years and the test-and-treat approach resulted in the highest maximum impact of 81 % fewer infections [71]. Mathematical modeling of a test-and-treat approach based on the HIV

epidemic among GMSM in New York City found that the cumulative number of new HIV infections could be reduced by up to 69.1 %, contingent on improvements in annual HIV testing rates, notification of test results, linkage to care, and viral load suppression [72].

Mathematical modeling of the impact of a test-and-treat strategy on the HIV epidemic in Washington, DC, in contrast, found that this will increase life expectancy of PLHIV, but will have modest impact on HIV transmission over 5 years and is unlikely to halt the HIV epidemic [73]. Extending mathematical modeling of the impact of HIV prevention interventions beyond local epidemics or epidemics in specific communities, Long et al. [74] assessed the impact of expanding HIV testing, uptake of ART, and their combination on the HIV epidemic in the US population. Falling far short of eliminating the HIV epidemic in the USA over a period of two decades, this mathematical modeling finds that universal annual HIV screening and immediate initiation of ART for all who test HIV positive may prevent 24 % of new infections. The study further finds that to substantially reduce HIV incidence, expanding testing and treatment programs will need to be accompanied by behavioral risk reduction interventions. What seems not to have received much attention is that the initial mathematical modeling, which has generally been taken to show that annual universal voluntary HIV testing with immediate initiation of ART (universal test-and-treat approach) could eliminate HIV transmission in a hyper-endemic setting, in fact also assumed that "other interventions together would reduce HIV transmission by 40 % and would be rolled out at the same rate as ART programmes" [4]. This underlines that it is unlikely that TasP approaches per se will be able to eliminate HIV infections.

The outcomes of mathematical modeling of the potential impact and cost-effectiveness of TasP critically depend on the parameter values chosen to mirror an epidemic in a specific community or location and to estimate the potential improvements that can be achieved. Leaving aside the question to what extent the "extremely ambitious assumptions" [19] realistically reflect HIV epidemics in GMSM across settings, the variability in parameter values and resulting outcomes powerfully illustrates that any impact of TasP is highly contingent on the epidemiological context in which the intervention is implemented [75]. Notably, modeling of the impact of alternate test-and-treat interventions in a hyper-endemic context shows that, depending on assumptions regarding variations in sexual mixing and risk distribution, similar reductions in HIV incidence may be achieved with less ambitious interventions or that more ambitious interventions may achieve less [75].

Context Matters: The Attenuating Role of Behavioral Trends and Local Achievements

The divergent outcomes of mathematical modeling of the impact of ART on HIV incidence among GMSM reinforce concerns whether findings regarding the impact of ARV-based HIV prevention can be translated to population groups and settings that

differ from those of the intervention [76]. It has been suggested that, ideally, proof-of-concept of the use of TasP in reducing new HIV infections should be established independently in communities that differ geographically, demographically, socially as well as in epidemiological characteristics [77]. Cohen et al. [76] note, not without concern, that while the potential of ART for HIV prevention was being investigated and remained to be established, "a virtual parallel universe of researchers have been making the case that the benefits of ART are both inevitable, and already visible." A review of the biological and epidemiological evidence concluded that while the benefits of treatment as prevention for GMSM are highly plausible, they are not certain and may be attenuated by a number of factors, in particular increases in sexual risk-taking and sexually transmissible infections [78].

The population-level dynamics of the HIV epidemic reflect the complex interplay between a range of factors that increase or decrease the likelihood of HIV transmission. The potential for increases in sexual risk behavior to offset any benefits of the use of ART for HIV prevention has been a particular concern since early considerations of the approach [70, 79], as have been concerns that the availability and efficacy of ART could result in changed views about the importance of safe sex [80]. Eaton and Kalichman [81] have suggested that perceptions of decreased risk of HIV that may result from HIV prevention technologies, including the use of ARVs for treatment, prevention, and prophylaxis, could contribute to a countervailing increase in risk behavior. For instance, to the extent that GMSM perceive a reduction in the risk of HIV transmission from having unprotected sex with a partner with undetectable viral load, they may be more likely to engage in unprotected sex, which could attenuate the potential reduction in risk of HIV transmission from ART. This so-called risk compensation complements and compounds any behavioral effects of HIV treatment optimism, referring to the potential for beliefs that ART has rendered HIV a much less serious condition to result in increased sexual risk [82].

Several sources of evidence can provide answers to the pivotal question whether changes in sexual risk behaviors that can offset any benefits from ARV-based HIV prevention might occur or are already occurring among GMSM [83], including data from recent PrEP trials. In the iPrEx trial among GMSM and transgender women, rates of sexual risk behaviors and STIs were similar for participants in the PrEP arm and in the placebo arm [44]. Similarly, no evidence of risk compensation was observed in an extended safety trial of TDF among GMSM in the US [84]. Risk compensation was also not observed in a pilot study among young GMSM of a randomized, placebo-controlled PrEP trial following a behavioral intervention [85]. However, these and other PrEP trials provided an extensive package of free HIV prevention services [42], making them unlikely contexts in which to expect and examine risk compensation. Demonstration projects providing standard care offer more appropriate contexts to assess increases in sexual risk behavior that can result from the availability of PrEP in non-trial settings.

The possible inadvertent effects of ARV-based HIV prevention have been examined in ecology studies seeking to explain the ongoing or resurging HIV epidemics in gay communities in San Francisco and Australia, concluding that any prevention benefits of ART among GMSM have been counterbalanced by increases in sexual

risk-taking [86, 87]. Studies modeling the HIV epidemics among GMSM in Amsterdam, Switzerland, and the UK also concluded that the epidemiological benefits of ART have been offset by increases in risk behavior [68, 69, 88, 89]. Furthermore, despite high proportions of HIV-positive men on ART, estimates of the per-contact rate of HIV transmission among GMSM in Sydney suggest that these may be similar to those in developing countries in the pre-ART era [90]. There is also evidence linking the introduction of ART to increases in sexual risk among HIV-negative as well as positive GMSM in Amsterdam [91, 92], and this effect has been found to be mediated by optimistic beliefs about treatment and the need for condoms [93, 94]. Optimistic beliefs among GMSM in The Netherlands have also been associated with incidence of STIs and HIV seroconversion [95]. Furthermore, a cohort study of PLHIV in Switzerland found that unprotected sex with HIV-negative or HIV-status unknown stable partners was more likely after the publication of the "Swiss Statement" [96].

The impact that can be expected of TasP (and any other intervention) on the HIV epidemic in a particular local community also depends on the current and evolving HIV testing, treatment, and prevention needs in that community and reflects past achievements as well as the extent to which these can be sustained. In a general sense, the potential for any intervention to make a difference will depend on the likelihood that new HIV infections occur, as reflected in HIV incidence. All else being equal, a comparable intervention will have a higher absolute impact among, for instance, GMSM in San Francisco where HIV is hyper-endemic [97], than on the concentrated HIV epidemics among GMSM in cities such as Sydney and Amsterdam. The impact of specific HIV prevention interventions will further depend on the drivers of new infections in a local context at a specific point in time. Notably, the potential benefits of promoting regular HIV testing and timely initiation of ART on new HIV infections will be less if high proportions of GMSM already test annually and uptake of ART among diagnosed PLHIV is high. In other words, the better the baseline situation, the less difference an intervention will make as there is "less room for improvement." As Wilson [98] notes, in many high-income country settings, in particular Australia and countries in Western Europe, rates of HIV testing and uptake of ART have been attained that "many countries would aspire to as targets for a TasP strategy." In those settings, the impact of TasP on HIV incidence may hence be less than expected [99].

The prevention benefit that a local epidemic in a particular point in time has accrued from the uptake of ART and, conversely, the additional gains that can be expected from a TasP approach, is ultimately reflected in the proportion of PLHIV with undetectable viral load. This is the result of achievements in engaging PLHIV across the spectrum of HIV care that consists of a number of conditional steps or milestones [100]. This HIV care cascade illustrates that for individuals to benefit from ART and for the uptake of ART to benefit public health, individuals need to be aware that they are HIV infected, be linked to and remain in care, initiate ART when appropriate, and sufficiently adhere to prescribed treatment regimens. As each subsequent step is conditional on all previous steps, this so-called HIV care cascade illustrates that even when achievements at every single step are very high (e.g., 90 %), the proportion of PLHIV who achieve undetectable viral load can still be limited (e.g., $90\,\% \times 90\,\% \times 90\,\% \times 90\,\% = 66\,\%$ for a four-step process; 100).

Carefully mapping local achievements against the HIV care cascade enables a robust comparison of HIV responses in different contexts and can also assist in identifying targets for improvement. For instance, it is thought that currently only 19–28 % of all PLHIV in the USA have undetectable viral load [100, 101], while this may be between 34–41 % in Sydney and the state of New South Wales, Australia [102]. Furthermore, the HIV care cascade illustrates that there are multiple areas for improvement, each of which will only make a limited contribution to HIV prevention [100].

Making ARV-Based HIV Prevention Work: The Critical Role of Uptake and Adherence

A *conditio sine qua non* for any HIV prevention intervention to have an effect, in addition to its availability, is the adoption and appropriate use by those who are eligible. In the past decade, attention was mostly focused on ensuring universal access to ART for eligible PLHIV in low- and middle-income countries. What has long received less attention is that, as underscored by emerging surveillance and research data as well as population estimates, many PLHIV in high-income countries are not currently taking ART. In their influential analysis, Gardner et al. [100] estimate that only 75 % of all people with diagnosed HIV infection in the USA may be linked to care, and only 30 % of people with diagnosed HIV infection may be on ART. Estimates from the UK suggest that the proportion of people with diagnosed HIV infection who are on ART could be as high as 80 % [69], which reflects that in the UK linkage to HIV care is thought to be high (95 % within 3 months), as is retention in HIV care (95 % after 1 year). These potential country differences illustrate the important role that health care systems and health service delivery models may play in ensuring timely and sustained access to high quality care and treatment for individuals and communities most affected by HIV, including GMSM, that is affordable [103], as well as comprehensive, integrated, and culturally sensitive [104]. Furthermore, access to ARV-based HIV prevention requires that prescribers are knowledgeable about new options as they become available and approved, and are willing to recommend them to their patients [105]. A recent survey amongst ART prescribers in Australia shows that over half (54.6 %) very strongly feel that their primary concern regarding commencement of ART is with the clinical benefits to individual patients rather than any population benefit and only one third (31.5 %) of the participating ART prescribers in Australia currently endorse recommendations to initiate ART early (i.e., at CD4-cell count > 350 cells/mm^3) or upon diagnosis [106].

Differences in estimates of PLHIV receiving HIV-related care and treatment also underscore the importance of robust empirical data obtained through comprehensive monitoring and surveillance, as illustrated by triangulation of Australian data from different sources that finds that the proportion of people who know they are infected with HIV that receive ART may vary between 54 % and 70 % [11, 102, 107]. In addition to the increasingly recognized limitations in estimates of people in high-income countries with diagnosed HIV infection who are linked and retained in care and taking ART, little is known of the relative importance of various reasons why

some people with diagnosed HIV are not on ART. It remains unclear what proportion of people with diagnosed HIV who are not currently on treatment have been taking ART before and might commence a different regimen, are ART naïve and not yet eligible under applicable guidelines, or are eligible but choose to defer ART. A prospective follow-up study of PLHIV in the UK, predominantly GMSM, who received a recommendation from their physician to commence ART found that as many as 28 % of patients initially rejected treatment [108]. This study also found that ART uptake was associated with individuals' perceptions of personal necessity of treatment and concerns regarding potential adverse effects, independent of clinical variables and depression.

The clinical and prevention benefits of ART result from sustained reductions in viral load and immunological improvements that require high levels of adherence to ARV regimens, which has sparked interest in long-acting delivery strategies that are less dependent on adherence. Adherence to ART remains challenging and a recent meta-analysis of 84 observational studies conducted in 20 countries estimated that the average proportion of PLHIV on ART who achieved 90 % or more adherence was only 62 % [109]. Importantly, while adherence was found to be higher among GMSM, adherence levels did not increase over time as ARV regimens may have improved. Adherence levels also were not associated with the types of adherence measures employed, which included self-reports, refill-based assessments, pill counts, electronic devices, and plasma drug concentration. Adherence is a highly complex behavior that is shaped by a range of personal and environmental factors [108, 110–113], including the treatment (e.g., regimen complexity, side effects, and satisfaction with effects), patient characteristics (e.g., information, knowledge, beliefs, motivation, skills and psychosocial issues including drug use and depression), and aspects of the patient-provider relationship (e.g., joint decision making and support). Effective adherence support for people taking ART remains a critical priority and requires multi-faceted interventions [110, 113], including careful regimen selection and adjustment, provision of adherence tools such as pill boxes, health systems, and service delivery interventions facilitating comprehensive case management and addressing patients' basic needs, as well as adherence education, counseling, and peer support [114, 115].

Uptake and Adherence to ARVs for Prevention and Prophylaxis

The acceptability of ART for treatment is generally high, as evidenced in rates of uptake, but this is not necessarily the case for the use of ART for prevention or prophylaxis. For instance, an online study of GMSM in Australia conducted in 2011 showed that HIV-negative men, as well as HIV-positive men to a somewhat lesser extent, are generally not convinced that an HIV-positive person who is on ART is unlikely to transmit HIV [116]. Since the mid-2000s, a rapidly growing body of research addresses the acceptability of PrEP among GMSM. To date, studies have been conducted among GMSM in San Francisco [117, 118], New York City [119–121], Boston [122], Seattle [123], other major US cities [124, 125], and the USA nationally [126], as well as in Australia [127, 128], Toronto [129], and London [130].

Studies have recruited men online [121, 126, 127], from gay community venues and social events [117, 123–125, 128, 130], bathhouses [119], and sexual health clinics [128, 129], as well as through modified respondent-driven sampling [122] and population-based sampling [117].

Despite the wide diversity in sampling and data collection, studies typically find that awareness of PrEP among HIV-uninfected GMSM is low (12 %–38 %; a higher estimate was found in a study of serodiscordant and concordant HIV-positive gay couples [118], which however partly reflected confusion with PEP). Use of PrEP has also remained low and is mostly reported by less than 2.5 % of the study sample (one early study found that 5 % of participants reported having used PrEP [124], and in this and other studies some reported use of PrEP may reflect confusion with PEP). Interest in future use of PrEP, if proven safe and effective, varies widely, from a lower estimate of 28 % among GMSM participating in an online study based in Australia [127], to a higher estimate of 79 % in an online sample of MSM in the US [126]. This variation likely reflects differences in the specific questions asked and in information provided about PrEP [122, 126]. Findings regarding covariates of reported and/or intended use of PrEP are consistent across studies and include drug use, sexual risk behavior, previous PEP use, recruitment from sexual health clinics, perceived risk of infection, younger age, lower education, and lower income, suggesting that acceptability of an interest in PrEP may be highest amongst GMSM at highest risk of infection who are likely to benefit most.

To date health care providers report little or no demand for PrEP [131], but this may change in the future, at least in the USA where Truvada® has been approved for PrEP and interim guidance regarding the use of PrEP has been issued for clinicians [54, 55], in particular when PrEP is available for free [122]. However, we caution that interest in PrEP does not guarantee demand, and uptake of other HIV prevention approaches has also remained slow despite proven efficacy (cf. medical male circumcision [132]). Potential limited uptake of novel HIV prevention interventions may reflect more than barriers related to operational challenges regarding implementation and scale up, including the need to engage, educate, and support health care providers [133]. Rather, we contend that a need to "create demand" for novel biomedical interventions [1], raises the same fundamental questions regarding their cultural, social, and personal appropriateness and acceptability that have also been noted for established HIV prevention interventions, including condom use.

PrEP may have potential as a time-bound HIV prevention modality for people at high risk for HIV in specific situations and at a particular point in their lives. However, such a boutique HIV prevention intervention is unlikely to have a major influence on the HIV epidemics among GMSM. Any preventive effect of PrEP will also depend on levels of adherence users achieve [134, 135], and it is expected that adherence levels will be lower when ARVs are used for prevention than for treatment [136]. While it has been suggested that adherence to open-label use of PrEP may be higher than in RCTs as people opt-in to receive a demonstrated product [134], this motivational effect may be offset when less adherence support is available for open-label use than in RCTs and open-label adherence may still fall short of optimal levels. Furthermore, research among GMSM and female sex workers in Kenya suggests that

adherence to fixed intermittent dosing (55 %) and coitus-dependent dosing (26 %) of PrEP may be substantially lower than for daily dosing (83 %) [137].

So Now What? Some Concluding Thoughts on HIV Testing and Behavioral Interventions

After a long period in which much of the world's HIV response was aimed at scaling up access to ART, a renewed focus on HIV prevention is timely in view of declining but nevertheless still very high numbers of new HIV diagnoses worldwide [8], and resurging epidemics among GMSM [9]. Results of RCTs showing that ARV-based approaches can prevent new infections have been welcomed as the first robust evidence that prevention can curb the HIV epidemic. However, it is increasingly acknowledged that the use of ARVs for prevention provides "no magic bullet" [6], and their use alone will not suffice to curb the HIV epidemic [138]. Leading investigators caution that "the hypothesis that widespread ART can eliminate HIV infection may have raised expectations beyond what we can achieve" [99]. This is not only because of the many financial and other operational challenges that affect implementation, but because the success of ARV-based HIV prevention critically depends on the behaviors of the people who might benefit from their use [16]. Classic and emerging HIV prevention approaches differ in the exact biomedical modality they promote to reduce risk (e.g., condoms, ARVs), but the success of each is affected by a myriad of behavioral, social, and structural factors. Extending Amico's observation for PrEP, we posit that any HIV prevention approach is inherently biopsychosocial [134]. Behavioral and structural interventions are required to promote the adoption as well as appropriate and consistent use of all approaches [139], be it condom use, HIV testing, HIV-status-based risk reduction, use of PrEP, or uptake of ART. Moreover, many of the challenges are similar for different prevention responses and, for instance, there is no guarantee that consistent use of ARVs for HIV prevention will be more likely than consistent condom use. Furthermore, in high-income settings a diversity of approaches contributing to HIV prevention is typically available to GMSM (mostly with the exception of PrEP), suggesting that in these settings combination HIV prevention, which some consider the next generation of HIV prevention [140], has *de facto* been the modal approach for quite some time. The main issue with respect to strengthening HIV prevention efforts for GMSM is hence not so much which approaches to combine, but which ones to scale up and how to best do that.

There is substantial evidence to suggest that increasing rates of HIV testing among GMSM should be an HIV prevention priority. Regular testing for HIV has long been a cornerstone of the HIV response that is instrumental to the timely initiation of effective treatment and provides important opportunities for HIV prevention. In high-income countries, between one-quarter and one-third of GMSM with HIV infection may be undiagnosed [141, 142], and could account for 50–90 % of all new HIV infections among GMSM [68, 89, 141, 143, 144]. Various strategies have been proposed and are being tested to promote regular testing and reduce the number of

GMSM who are unaware of being infected with HIV. Currently favored approaches aim to make regular testing more normative and convenient, including through routinely offering HIV testing in health care settings [145], opt-out HIV testing protocols at sexual health clinics [146], SMS reminder systems [147], rapid testing and testing facilities at community organizations [148], home HIV self-testing [149–151], and social marketing [152]. However, while HIV testing rates may have increased in communities where these previously were low [153], there is little recent and robust research that provides evidence for the efficacy of approaches to promote HIV testing [154]. Also, HIV testing is affected by a diversity of personal, social, and structural factors [155], and it is unclear to what extent continuing barriers related to HIV-testing, such as stigma and fears [1, 153], are effectively addressed by interventions to make HIV testing easier and that bear resemblance to nudging approaches developed in behavioral economics [156]. Further, as for any HIV prevention approach used in isolation, mathematical modeling suggests that increasing the coverage and frequency of HIV testing among GMSM may only modestly reduce new infections [149, 157]. In contrast, inclusion of approaches that promote reductions in sexual risk behavior are found to have a substantial impact on the HIV epidemics among GMSM in high income countries [74, 143]. This is consistent with the extensive body of research suggesting that the prevention benefits of ART may have been offset by increases in sexual risk [68, 69, 86–96].

It is clear, and widely acknowledged, that behavioral approaches remain critical to effective HIV responses, for GMSM and more generally. If anything, the scope of behavioral interventions has only increased as prevention responses for GMSM have diversified from condom use and client initiated HIV testing in health care settings, to include provider-initiated testing, rapid testing and testing in non-traditional settings, HIV-status and viral load-based sexual risk reduction, and uptake and adherence to ARVs for prevention by HIV-positive as well as HIV-negative men. To curb the HIV epidemic among GMSM, behavioral approaches need to be urgently strengthened [20, 29], which entails addressing at least four critical challenges. The first challenge is to ensure that HIV prevention for GMSM achieves not only sufficient coverage but also appropriate intensity and comprehensiveness, and it is currently largely unknown to what extent this is being achieved. The second challenge, related to the diversification of HIV prevention options, is how to move from traditional, generic recommendations (i.e., to consistently use condoms) to enabling tailored risk-reduction responses that fit the needs and possibilities of specific individuals, without undermining condom use as the most practiced preventive behavior [158]. The third, long-standing challenge is to bridge the gap between HIV behavioral prevention research and practice [159]. As we have noted elsewhere [20], a large body of research, summarized in numerous meta-analyses, convincingly shows that HIV-related behaviors can be effectively changed using a variety of approaches [160]. What is not clear, however, is to what extent proven behavioral interventions are used in practice and to what extent interventions used in practice are effective. The fourth challenge is to innovate HIV behavioral intervention research, which continues to rely on social-cognitive theories and cognitive-behavioral strategies of change.

Contemporary behavioral theorizing recognizes a wide range of, often implicit, influences on behavior and highlights the potential of brief, personalized interventions that make use of self-regulation principles [161, 162]. More generally, it is critical to make much better use of the extensive science of behavior change, which underlines the importance of systematic intervention development that is based on a comprehensive, theory-informed understanding of factors that shape behavior that are addressed using proven strategies of change [31, 163, 164]. More than 30 years into the HIV epidemic, effective behavioral prevention continues to require substantially more investment, as well as "at least the same vigor as the promising host of technological innovations" [79].

References

1. Padian NS, McCoy SI, Karim SS, Hasen N, Kim J, Bartos M, et al. HIV prevention transformed: the new prevention research agenda. Lancet. 2011;378:269–78.
2. Padian NS, Isbell MT, Russell ES, Essex M. The future of HIV prevention. J Acquir Immune Defic Syndr. 2012;60 Suppl 2:S22–6.
3. Baeten J, Celum C. Systemic and topical drugs for the prevention of HIV infection: antiretroviral pre-exposure prophylaxis. Annu Rev Med. 2013;64:219–32.
4. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009;373:48–57.
5. Clinton HR. Remarks on creating an AIDS free generation. Speech presented at the National Institutes of Health, Bethesda, MD; 8 Nov 2011.
6. Sidibé M. Antiretrovirals for prevention: realizing the potential. Curr HIV Res. 2011;9:470–2.
7. United Nations General Assembly. Political declaration on HIV and AIDS: intensifying our efforts to eliminate HIV and AIDS. Resolution adopted by the UN General Assembly, 10 June 2011, A/RES/65/277. New York: UN General Assembly; 2011. http://www.un.org/ga/search/view_doc.asp?symbol = A/RES/65/277. Accessed 5 Apr 2013.
8. Joint United Nations Programme on HIV/AIDS (UNAIDS). Global report: UNAIDS report on the global AIDS epidemic 2012. Geneva: UNAIDS; 2012. http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_UNAIDS_Global_Report_2012_en.pdf. Accessed 5 Apr 2013.
9. Beyrer C, Baral SD, van Griensven F, Goodreau SM, Chariyalertsak S, Wirtz AL, et al. Global epidemiology of HIV infection in men who have sex with men. Lancet. 2012;380:367–77.
10. Jansen IA, Geskus RB, Davidovich U, Jurriaans S, Coutinho RA, Prins M, et al. Ongoing HIV-1 transmission among men who have sex with men in Amsterdam: a 25-year prospective cohort study. AIDS. 2011;25:493–501.
11. Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2012. Sydney: Kirby Institute, University of New South Wales; 2012.
12. Prejean J, Song R, Hernandez A, Ziebell R, Green T, Walker F, et al. Estimated HIV incidence in the United States, 2006–2009. PLoS One. 2011;6:e17502.
13. Sullivan PS, Hamouda O, Delpech V, Geduld JE, Prejean J, Semaille C, et al. Reemergence of the HIV epidemic among men who have sex with men in North America, Western Europe, and Australia, 1996–2005. Ann Epidemiol. 2009;19:423–31.
14. Adam PCG, de Wit JBF, Toskin I, Mathers BM, Nashkhoev M, Zablotska I, et al. Estimating levels of HIV testing, HIV prevention coverage, HIV knowledge, and condom use among men who have sex with men (MSM) in low-income and middle-income countries. J Acquir Immune Defic Syndr. 2009;52 Suppl 2:S143–15.

15. Van Griensven F, Thienkrua W, McNicholl J, Wimonsate W, Chaikummao S, Chonwattana W, et al. Evidence of an explosive epidemic of HIV infection in a cohort of men who have sex with men in Bangkok, Thailand. AIDS. 2013;27:825–32.
16. Golub SA, Operario D, Gorbach PM. Pre-exposure prophylaxis state of the science: empirical analogies for research and implementation. Curr HIV/AIDS Rep. 2010;7:201–9.
17. Sidibé M, Buse K. Fomenting a prevention revolution for HIV. Lancet. 2010;375:533–5.
18. Buchbinder SP, Liu A. Pre-exposure prophylaxis and the promise of combination prevention approaches. AIDS Behav. 2011;15 Suppl 1:S72–9.
19. HIV Modelling Consortium Treatment as Prevention Editorial Writing Group. HIV treatment as prevention: models, data, and questions–towards evidence-based decision-making. PLoS Med. 2012;9:e1001259.
20. De Wit JBF, Aggleton P, Myers T, Crewe M. The rapidly changing paradigm of HIV prevention: time to strengthen social and behavioural approaches. Health Educ Res. 2011;26:381–92.
21. Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet. 2008;372:293–9.
22. World Health Organization (WHO), Joint United Nations Programme on HIV/AIDS (UNAIDS), United Nations Children's Fund (UNICEF). Gobal HIV/AIDS response: epidemic update and health sector progress towards universal access—progress report 2011. Geneva: WHO; 2010. http://whqlibdoc.who.int/publications/2011/9789241502986_eng.pdf. Accessed 5 Apr 2013.
23. Joint United Nations Programme on HIV/AIDS (UNAIDS). Countdown to zero: Global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive 2011–2015. Geneva: UNAIDS; 2011. http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/20110609_JC2137_Global-Plan-Elimination-HIV-Children_en.pdf. Accessed 5 Apr 2013.
24. World Health Organization (WHO). Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach: 2010 revision. Geneva: WHO; 2010. http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf. Accessed 5 Apr 2013.
25. Le T, Wright EJ, Smith DM, He W, Catano G, Okulicz JF, et al. Enhanced CD4 + T-cell recovery with earlier HIV-1 antiretroviral therapy. New Eng J Med. 2013;368:218–30.
26. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Washington, DC: Department of Health and Human Services; 2013 [updated 2013 Feb 12]. http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed 5 Apr 2013.
27. Schwartländer B, Stover J, Hallett T, Atun R, Avila C, Gouws E, et al. Towards an improved investment approach for an effective response to HIV/AIDS. Lancet. 2011;377:2031–41.
28. Horton R, Das P. Putting prevention at the forefront of HIV/AIDS. Lancet. 2008;372:421–2.
29. Coates TJ, Richter L, Caceres C. Behavioural strategies to reduce HIV transmission: how to make them work better. Lancet. 2008;372:669–84.
30. Piot P, Bartos M, Larson H, Zewdie D, Mane P. Coming to terms with complexity: a call to action for HIV prevention. Lancet. 2008;372:845–59.
31. Green L, Kreuter M. Health program planning: an educational and ecological approach. 4th ed. New York: McGraw-Hill; 2005.
32. Dahlgren G, Whitehead M. Policies and strategies to promote social equity in health. Stockholm: Institute for Future Studies; 1991.
33. Hayes R, Kapiga S, Padian N, McCormack S, Wasserheit J. HIV prevention research: taking stock and the way forward. AIDS. 2010;24 Suppl 4:S81–92.
34. Rao Gupta G, Parkhurst JO, Ogden JA, Aggleton P, Mahal A. Structural approaches to HIV prevention. Lancet. 2008;372:764–75.
35. Padian NS, Buvé A, Balkus J, Serwadda D, Cates W. Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward. Lancet. 2008;372:585–99.

36. Padian NS, McCoy SI, Balkus JE, Wasserheit JN. Weighing the gold in the gold standard: challenges in HIV prevention research. AIDS. 2010;24:621–35.
37. Millett GA, Flores SA, Marks G, Reed JB, Herbst JH. Circumcision status and risk of HIV and sexually transmitted infections among men who have sex with men: a meta-analysis. JAMA. 2008;300:1674–84.
38. Londish GJ, Templeton DJ, Regan DG, Kaldor JM, Murray JM. Minimal impact of circumcision on HIV acquisition in men who have sex with men. Sex Health. 2010;7:463–70.
39. Templeton DJ, Millett GA, Grulich AE. Male circumcision to reduce the risk of HIV and sexually transmitted infections among men who have sex with men. Curr Opin in Infect Dis. 2010;23:45–52.
40. McDaid LM, Hart GJ. Serosorting and strategic positioning during unprotected anal intercourse: are risk reduction strategies being employed by gay and bisexual men in Scotland? Sex Transm Dis. 2012;39:735–8.
41. Tolle MA, Schwarzwald HL. Postexposure prophylaxis against human immunodeficiency virus. Am Fam Physician. 2010;82:161–6.
42. Baeten J, Celum C. Oral antiretroviral chemoprophylaxis: current status. Curr Opin HIV AIDS. 2012;7:514–9.
43. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. New Eng J Med. 2012;367:399–410.
44. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. New Eng J Med. 2010;363:2587–99.
45. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. New Eng J Med. 2012;367:423–34.
46. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010;329:1168–74.
47. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2013;381:2083–90.
48. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. New Eng J Med. 2011;365:493–505.
49. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. New Eng J Med. 2012;367:411–22.
50. Marrazzo J, Ramjee G, Nair G, Palanee T, Mkhize B, Nakabiito C, et al. Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine, or vaginal tenofovir gel in the VOICE Study (MTN 003). Paper presented at the 20th Conference on Retroviruses and Opportunistic Infections, 3–6 Mar 2013, Atlanta, GA (Abstract #26LB).
51. Baral S, Sifakis F, Cleghorn F, Beyrer C. Elevated risk for HIV infection among men who have sex with men in low- and middle-income countries 2000–2006: a systematic review. PLoS Med. 2007;4:e339.
52. Cáceres CF, Aggleton P, Galea JT. Sexual diversity, social inclusion and HIV/AIDS. AIDS. 2008;22 Suppl 2:S45–55.
53. Beyrer C, Sullivan PS, Sanchez J, Dowdy D, Altman D, Trapence G, et al. A call to action for comprehensive HIV services for men who have sex with men. Lancet. 2012;380:424–38.
54. Centers for Disease Control and Prevention. Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. MMWR Morb Mortal Wkly Rep. 2011;60:65–8.
55. Centers for Disease Control and Prevention. Interim guidance for clinicians considering the use of preexposure prophylaxis for the prevention of HIV infection in heterosexually active adults. MMWR Morb Mortal Wkly Rep. 2012;61:586–9.

56. World Health Organization (WHO). Guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV. Recommendations for use in the context of demonstration projects. Geneva: WHO; 2012. http://apps.who.int/iris/bitstream/10665/75188/1/9789241503884_eng.pdf. Accessed 5 Apr 2013.
57. Das M, Chu PL, Santos GM, Scheer S, Vittinghoff E, McFarland W, et al. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. PLoS One. 2010;5:e11068.
58. McGowan I. Rectal microbicide development. Curr Opin HIV AIDS. 2012;7:526–33.
59. Bekker LG, Glidden D, Hosek S, Brown B, Liu A, Amico R, et al. Pre-exposure prophylaxis in young men who have sex with men: Needs and challenges. Paper presented at the 20th Conference on Retroviruses and Opportunistic Infections, 3–6 Mar 2013, Atlanta, GA (Abstract #997).
60. Poynten IM, Zablotska I, Grulich AE. Considerations regarding antiretroviral chemoprophylaxis in MSM. Curr Opin HIV AIDS. 2012;7:549–56.
61. Desai K, Sansom SL, Ackers ML, Stewart SR, Hall HI, Hu DJ, et al. Modeling the impact of HIV chemoprophylaxis strategies among men who have sex with men in the United States: HIV infections prevented and cost-effectiveness. AIDS. 2008;22:1829–39.
62. Paltiel AD, Freedberg KA, Scott CA, Schackman BR, Losina E, Wang B, et al. HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. Clin Infect Dis. 2009;48:806–15.
63. Schackman BR, Eggman AA. Cost-effectiveness of pre-exposure prophylaxis for HIV: a review. Curr Opin HIV AIDS. 2012;7:587–92.
64. Juusola JL, Brandeau ML, Owens DK, Bendavid E. The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men. Ann Intern Med. 2012;156:541–50.
65. Cremin I, Alsallaq R, Dybul M, Piot P, Garnett G, Hallett TB. The new role of antiretrovirals in combination HIV prevention: a mathematical modelling analysis. AIDS. 2013;27:447–58.
66. Montaner JS, Hogg R, Wood E, Kerr T, Tyndall M, Levy AR, et al. The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. Lancet. 2006;368:531–6.
67. Cowan SA, Gerstoft J, Haff J, Christiansen AH, Nielsen J, Obel N. Stable incidence of HIV diagnoses among Danish MSM despite increased engagement in unsafe sex. J Acquir Immune Defic Syndr. 2012;61:106–11.
68. Phillips AN, Cambiano V, Nakagawa F, Brown AE, Lampe F, Rodger A, et al. Increased HIV incidence in men who have sex with men despite high levels of ART-induced viral suppression: analysis of an extensively documented epidemic. PLoS One. 2013;8:e55312.
69. Birrell PJ, Gill ON, Delpech VC, Brown AE, Desai S, Chadborn TR, et al. HIV incidence in men who have sex with men in England and Wales 2001–10: a nationwide population study. Lancet Infect Dis. 2013;13:312–8.
70. Blower SM, Gershengorn HB, Grant RM. A tale of two futures: HIV and antiretroviral therapy in San Francisco. Science. 2000;287:650–4.
71. Charlebois ED, Das M, Porco TC, Havlir DV. The effect of expanded antiretroviral treatment strategies on the HIV epidemic among men who have sex with men in San Francisco. Clin Infect Dis. 2011;52:1046–9.
72. Sorensen SW, Sansom SL, Brooks JT, Marks G, Begier EM, Buchacz K, et al. A mathematical model of comprehensive test-and-treat services and HIV incidence among men who have sex with men in the United States. PLoS One. 2012;7:e29098.
73. Walensky RP, Paltiel AD, Losina E, Morris BL, Scott CA, Rhode ER, et al. Test and treat DC: forecasting the impact of a comprehensive HIV strategy in Washington DC. Clin Infect Dis. 2010;51:392–400.
74. Long EF, Brandeau ML, Owens DK. The cost-effectiveness and population outcomes of expanded HIV screening and antiretroviral treatment in the United States. Ann Intern Med. 2010;153:778–89.

75. Dodd PJ, Garnett GP, Hallett TB. Examining the promise of HIV elimination by 'test and treat' in hyperendemic settings. AIDS. 2010;24:729–35.
76. Cohen MS, Muessig KE, Smith MK, Powers KA, Kashuba AD. Antiviral agents and HIV prevention: controversies, conflicts, and consensus. AIDS. 2012;26:1585–98.
77. Williams B, Wood R, Dukay V, Delva W, Ginsburg D, Hargrove J, et al. Treatment as prevention: preparing the way. J Int AIDS Soc. 2011;14 Suppl 1:S6.
78. Muessig KE, Smith MK, Powers KA, Lo YR, Burns DN, Grulich AE, et al. Does ART prevent HIV transmission among MSM? AIDS. 2012;26:2267–73.
79. Cassell MM, Halperin DT, Shelton JD, Stanton D. Risk compensation: the Achilles' heel of innovations in HIV prevention? BMJ. 2006;332:605–7.
80. Dilley JW, Woods WJ, McFarland W. Are advances in treatment changing views about high-risk sex? New Eng J Med. 1997;337:501–2.
81. Eaton LA, Kalichman S. Risk compensation in HIV prevention: implications for vaccines, microbicides, and other biomedical HIV prevention technologies. Curr HIV/AIDS Rep. 2007;4:165–72.
82. Crepaz N, Hart TA, Marks G. Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review. JAMA. 2004;292:224–36.
83. Williams BG, Lima V, Gouws E. Modelling the impact of antiretroviral therapy on the epidemic of HIV. Curr HIV Res. 2011;9:367–82.
84. Liu AY, Vittinghoff E, Chillag K, Mayer K, Thompson M, Grohskopf L, et al. Sexual risk behavior among HIV-uninfected men who have sex with men (MSM) participating in a tenofovir pre-exposure prophylaxis (PrEP) randomized trial in the United States. J Acquir Immune Defic Syndr. Epub 2013 Mar 11 (in press).
85. Hosek S, Siberry G, Bell M, Lally M, Kapogiannis B, Green K, et al. The acceptability and feasibility of an HIV pre-exposure prophylaxis (PrEP) trial with young men who have sex with men (YMSM). J Acquir Immune Defic Syndr. 2013;62:447–56.
86. Katz MH, Schwarcz SK, Kellogg TA, Klausner JD, Dilley JW, Gibson S, et al. Impact of highly active antiretroviral treatment on HIV seroincidence among men who have sex with men: San Francisco. Am J Public Health. 2002;92:388–94.
87. Law MG, Woolley I, Templeton DJ, Roth N, Chuah J, Mulhall B, et al. Trends in detectable viral load by calendar year in the Australian HIV observational database. J Int AIDS Soc. 2011;14:10.
88. Bezemer D, de Wolf F, Boerlijst MC, van Sighem A, Hollingsworth TD, Prins M, et al. A resurgent HIV-1 epidemic among men who have sex with men in the era of potent antiretroviral therapy. AIDS. 2008;22:1071–7.
89. Van Sighem A, Vidondo B, Glass TR, Bucher HC, Vernazza P, Gebhardt M, et al. Resurgence of HIV infection among men who have sex with men in Switzerland: mathematical modelling study. PLoS One. 2012;7:e44819.
90. Jin F, Jansson J, Law M, Prestage GP, Zablotska I, Imrie JC, et al. Per-contact probability of HIV transmission in homosexual men in Sydney in the era of HAART. AIDS. 2010;24:907–13.
91. Dukers NH, Goudsmit J, de Wit JBF, Prins M, Weverling GJ, Coutinho RA. Sexual risk behaviour relates to the virological and immunological improvements during highly active antiretroviral therapy in HIV-1 infection. AIDS. 2001;15:369–78.
92. Van Sighem A, Jansen I, Bezemer D, de Wolf F, Prins M, Stolte I, et al. Increasing sexual risk behaviour among Dutch men who have sex with men: mathematical models versus prospective cohort data. AIDS. 2012;26:1840–3.
93. Stolte IG, de Wit JBF, van Eeden A, Coutinho RA, Dukers NH. Perceived viral load, but not actual HIV-1-RNA load, is associated with sexual risk behaviour among HIV-infected homosexual men. AIDS. 2004;18:1943–9.
94. Stolte IG, Dukers NH, Geskus RB, Coutinho RA, de Wit JBF. Homosexual men change to risky sex when perceiving less threat of HIV/AIDS since availability of highly active antiretroviral therapy: a longitudinal study. AIDS. 2004;18:303–9.
95. Van der Snoek EM, de Wit JBF, Mulder PG, van der Meijden WI. Incidence of sexually transmitted diseases and HIV infection related to perceived HIV/AIDS threat since highly

active antiretroviral therapy availability in men who have sex with men. Sex Transm Dis. 2005;32:170–5.
96. Hasse B, Ledergerber B, Hirschel B, Vernazza P, Glass TR, Jeannin AE, et al. Frequency and determinants of unprotected sex among HIV-infected persons: the Swiss HIV cohort study. Clin Infect Dis. 2010;51:1314–22.
97. Scheer S, Kellogg T, Klausner JD, Schwarcz S, Colfax G, Bernstein K, et al. HIV is hyperendemic among men who have sex with men in San Francisco: 10-year trends in HIV incidence, HIV prevalence, sexually transmitted infections and sexual risk behaviour. Sex Transm Infect. 2008;84:493–8.
98. Wilson DP. HIV treatment as prevention: natural experiments highlight limits of antiretroviral treatment as HIV prevention. PLoS Med. 2012;9:e1001231.
99. Smith MK, Powers KA, Muessig KE, Miller WC, Cohen MS. HIV treatment as prevention: the utility and limitations of ecological observation. PLoS Med. 2012;9:e1001260.
100. Gardner EM, McLees MP, Steiner JF, del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis. 2011;52:793–800.
101. Hull MW, Wu Z, Montaner JS. Optimizing the engagement of care cascade: a critical step to maximize the impact of HIV treatment as prevention. Curr Opin HIV AIDS. 2012;7:579–86.
102. New South Wales Health. NSW HIV Strategy 2012–2015—A new era. Sydney: New South Wales Ministry of Health; 2012.
103. McAllister J, Beardsworth G, Lavie E, MacRae K, Carr A. Financial stress is associated with reduced treatment adherence in HIV-infected adults in a resource-rich setting. HIV Med. 2013;14:120–4.
104. Mayer KH, Bekker LG, Stall R, Grulich AE, Colfax G, Lama JR. Comprehensive clinical care for men who have sex with men: an integrated approach. Lancet. 2012;380:378–87.
105. White JM, Mimiaga MJ, Krakower DS, Mayer KH. Evolution of Massachusetts physician attitudes, knowledge, and experience regarding the use of antiretrovirals for HIV prevention. AIDS Patient Care STDs. 2012;26:395–405.
106. Mao L, de Wit J, Adam P, Post JJ, Crooks L, Kidd MR, et al. Australian prescribers' perspectives on ART initiation in the era of "treatment as prevention". AIDS Care. Epub 2013 Feb 13 (in press).
107. De Wit J, Holt M, Treloar C, editors. HIV/AIDS, hepatitis and sexually transmissible infections in Australia: Annual report of trends in behaviour 2012. Sydney: National Centre in HIV Social Research, University of New South Wales; 2012.
108. Horne R, Cooper V, Gellaitry G, Leake Date H, Fisher M. Patients' perceptions of highly active antiretroviral therapy in relation to treatment uptake and adherence: the utility of the necessity-concerns framework. J Acquir Immune Defic Syndr. 2007;45:334–41.
109. Ortego C, Huedo-Medina TB, Llorca J, Sevilla L, Santos P, Rodríguez E, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. AIDS Behav. 2011;15:1381–96.
110. Chesney M. Adherence to HAART regimens. AIDS Patient Care STDs. 2003;17:169–77.
111. Fisher JD, Amico KR, Fisher WA, Harman JJ. The information-motivation-behavioral skills model of antiretroviral adherence and its applications. Curr HIV/AIDS Rep. 2008;5:193–203.
112. Rothman AJ. Toward a theory-based analysis of behavioral maintenance. Health Psychol. 2000;19 Suppl 1:S64–9.
113. Thompson MA, Aberg JA, Hoy JF, Telenti A, Benson C, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. JAMA. 2012;308:387–402.
114. Kalichman SC, Cherry C, Kalichman MO, Amaral CM, White D, Pope H, et al. Integrated behavioral intervention to improve HIV/AIDS treatment adherence and reduce HIV transmission. Am J Public Health. 2011;101:531–38.
115. Simoni JM, Amico KR, Smith L, Nelson K. Antiretroviral adherence interventions: translating research findings to the real world clinic. Curr HIV/AIDS Rep. 2010;7:44–51.

116. Holt M, Murphy D, Callander D, Ellard J, Rosengarten M, Kippax S, et al. HIV-negative and HIV-positive gay men's attitudes to medicines, HIV treatments and antiretroviral-based prevention. AIDS Behav. 2013;17:156–61.
117. Liu AY, Kittredge PV, Vittinghoff E, Raymond HF, Ahrens K, Matheson T, et al. Limited knowledge and use of HIV post- and pre-exposure prophylaxis among gay and bisexual men. J Acquir Immune Defic Syndr. 2008;47:241–7.
118. Saberi P, Gamarel KE, Neilands TB, Comfort M, Sheon N, Darbes LA, et al. Ambiguity, ambivalence, and apprehensions of taking HIV-1 pre-exposure prophylaxis among male couples in San Francisco: a mixed methods study. PLoS One. 2012;7:e50061.
119. Mehta SA, Silvera R, Bernstein K, Holzman RS, Aberg JA, Daskalakis DC. Awareness of post-exposure HIV prophylaxis in high-risk men who have sex with men in New York City. Sex Transm Infect. 2011;87:344–8.
120. Nodin N, Carballo-Diéguez A, Ventuneac AM, Balan IC, Remien R. Knowledge and acceptability of alternative HIV prevention bio-medical products among MSM who bareback. AIDS Care. 2008;20:106–15.
121. Rucinski KB, Mensah NP, Sepkowitz KA, Cutler BH, Sweeney MM, Myers JE. Knowledge and use of pre-exposure prophylaxis among an online sample of young men who have sex with men in New York City. AIDS Behav. 2013;17:2180–4.
122. Mimiaga MJ, Case P, Johnson CV, Safren SA, Mayer KH. Preexposure antiretroviral prophylaxis attitudes in high-risk Boston area men who report having sex with men: limited knowledge and experience but potential for increased utilization after education. J Acquir Immune Defic Syndr. 2009;50:77–83.
123. Barash EA, Golden M. Awareness and use of HIV pre-exposure prophylaxis among attendees of a seattle gay pride event and sexually transmitted disease clinic. AIDS Patient Care STDs. 2010;24:689–91.
124. Kellerman SE, Hutchinson AB, Begley EB, Boyett BC, Clark HA, Sullivan P. Knowledge and use of HIV pre-exposure prophylaxis among attendees of minority 2 pride events, 2004. J Acquir Immune Defic Syndr. 2006;43:376–7.
125. Voetsch AC, Heffelfinger JD, Begley EB, Jafa-Bhushan K, Sullivan PS. Knowledge and use of preexposure and postexposure prophylaxis among attendees of Minority Gay Pride events, 2005 through 2006. J Acquir Immune Defic Syndr. 2007;46:378–80.
126. Krakower DS, Mimiaga MJ, Rosenberger JG, Novak DS, Mitty JA, White JM, et al. Limited awareness and low immediate uptake of pre-exposure prophylaxis among men who have sex with men using an internet social networking site. PLoS One. 2012;7:e33119.
127. Holt M, Murphy DA, Callander D, Ellard J, Rosengarten M, Kippax SC, et al. Willingness to use HIV pre-exposure prophylaxis and the likelihood of decreased condom use are both associated with unprotected anal intercourse and the perceived likelihood of becoming HIV positive among Australian gay and bisexual men. Sex Transm Infect. 2012;88:258–63.
128. Zablotska IB, Prestage G, de Wit J, Grulich AE, Mao L, Holt M. The informal use of antiretroviral medications for pre-exposure prophylaxis (PrEP) of HIV among gay men in Australia. J Acquir Immune Defic Syndr. 2013;62:334–8.
129. Leonardi M, Lee E, Tan DH. Awareness of, usage of and willingness to use HIV pre-exposure prophylaxis among men in downtown Toronto, Canada. Int J STD AIDS. 2011;22:738–41.
130. Aghaizu A, Mercey D, Copas A, Johnson AM, Hart G, Nardone A. Who would use PrEP? Factors associated with intention to use among MSM in London: a community survey. Sex Transm Infect. 2013;89:207–11.
131. Arnold EA, Hazelton P, Lane T, Christopoulos KA, Galindo GR, Steward WT, et al. A qualitative study of provider thoughts on implementing pre-exposure prophylaxis (PrEP) in clinical settings to prevent HIV infection. PLoS One. 2012;7:e40603.
132. Reed JB, Njeuhmeli E, Thomas AG, Bacon MC, Bailey R, Cherutich P, et al. Voluntary medical male circumcision: an HIV prevention priority for PEPFAR. J Acquir Immune Defic Syndr. 2012;60 Suppl 3:S88–95.
133. Krakower D, Mayer KH. Engaging healthcare providers to implement HIV pre-exposure prophylaxis. Curr Opin HIV AIDS. 2012;7:593–9.

134. Amico KR. Adherence to preexposure chemoprophylaxis: the behavioral bridge from efficacy to effectiveness. Curr Opin HIV AIDS. 2012;7:542–8.
135. Van der Straten A, Van Damme L, Haberer JE, Bangsberg DR. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. AIDS. 2012;26:F13–9.
136. Weiss HA, Wasserheit JN, Barnabas RV, Hayes RJ, Abu-Raddad LJ. Persisting with prevention: the importance of adherence for HIV prevention. Emerg Themes Epidemiol. 2008;5:8.
137. Mutua G, Sanders E, Mugo P, Anzala O, Haberer JE, Bangsberg D, et al. Safety and adherence to intermittent pre-exposure prophylaxis (PrEP) for HIV-1 in African men who have sex with men and female sex workers. PLoS One. 2012;7:e33103.
138. Harris M, Montaner JS. Exploring the role of "treatment as prevention". Curr HIV Res. 2011;9:352–4.
139. Sullivan PS, Carballo-Diéguez A, Coates T, Goodreau SM, McGowan I, Sanders EJ, et al. Successes and challenges of HIV prevention in men who have sex with men. Lancet. 2012;380:388–99.
140. Kurth AE, Celum C, Baeten JM, Vermund SH, Wasserheit JN. Combination HIV prevention: significance, challenges, and opportunities. Curr HIV/AIDS Rep. 2011;8:62–72.
141. Marks G, Crepaz N, Janssen RS. Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. AIDS. 2006;20(10):1447–50.
142. Pedrana AE, Hellard ME, Wilson K, Guy R, Stoové M. High rates of undiagnosed HIV infections in a community sample of gay men in Melbourne, Australia. J Acquir Immune Defic Syndr. 2012;59(1):94–9.
143. Bezemer D, de Wolf F, Boerlijst MC, van Sighem A, Hollingsworth TD, Fraser C. 27 years of the HIV epidemic amongst men having sex with men in the Netherlands: an in depth mathematical model-based analysis. Epidemics. 2010;2(2):66–79.
144. Wilson DP, Hoare A, Regan DG, Law MG. Importance of promoting HIV testing for preventing secondary transmissions: modelling the Australian HIV epidemic among men who have sex with men. Sex Health. 2009;6:19–33.
145. Branson BM, Handsfield HH, Lampe MA, Janssen RS, Taylor AW, Lyss SB, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep. 2006;55(RR-14):1–17.
146. Heijman RL, Stolte IG, Thiesbrummel HF, van Leent E, Coutinho RA, Fennema JS, et al. Opting out increases HIV testing in a large sexually transmitted infections outpatient clinic. Sex Transm Infect. 2009;85:249–55.
147. Bourne C, Knight V, Guy R, Wand H, Lu H, McNulty A. Short message service reminder intervention doubles sexually transmitted infection/HIV re-testing rates among men who have sex with men. Sex Transm Infect. 2011;87:229–31.
148. Gray RT, Prestage GP, Down I, Ghaus MH, Hoare A, Bradley J, et al. Increased HIV testing will modestly reduce HIV incidence among gay men in NSW and would be acceptable if HIV testing becomes convenient. PLoS One. 2013;8:e55449.
149. Ventuneac A, Carballo-Diéguez A, Leu CS, Levin B, Bauermeister J, Woodman-Maynard E, et al. Use of a rapid HIV home test to screen sexual partners: an evaluation of its possible use and relative risk. AIDS Behav. 2009;13:731–7.
150. Greacen T, Friboulet D, Fugon L, Hefez S, Lorente N, Spire B. Access to and use of unauthorised online HIV self-tests by internet-using French-speaking men who have sex with men. Sex Transm Infect. 2012;88:368–74.
151. Bavinton BR, Brown G, Hurley M, Bradley J, Keen P, Conway DP, et al. Which gay men would increase their frequency of HIV testing with home self-testing? AIDS Behav. 2013;17:2084–92.
152. Pedrana A, Hellard M, Guy R, El-Hayek C, Gouillou M, Asselin J, et al. Stop the drama Downunder: a social marketing campaign increases HIV/sexually transmitted infection knowledge and testing in Australian gay men. Sex Transm Dis. 2012;39:651–8.
153. Flowers P, Knussen C, Li J, McDaid L. Has testing been normalized? An analysis of changes in barriers to HIV testing among men who have sex with men between 2000 and 2010 in Scotland, UK. HIV Med. 2013;14:92–8.

154. Lorenc T, Marrero-Guillamón I, Aggleton P, Cooper C, Llewellyn A, Lehmann A, et al. Promoting the uptake of HIV testing among men who have sex with men: systematic review of effectiveness and cost-effectiveness. Sex Transm Infect. 2011;87:272–8.
155. De Wit JBF, Adam PCG. To test or not to test: psychosocial barriers to HIV testing in high-income countries. HIV Med. 2008;9 Suppl 2:20–2.
156. Thaler RH, Sunstein CR. Nudge: improving decisions about health, wealth, and happiness. New Haven, CT: Yale University Press; 2008.
157. Juusola JL, Brandeau ML, Long EF, Owens DK, Bendavid E. The cost-effectiveness of symptom-based testing and routine screening for acute HIV infection in men who have sex with men in the USA. AIDS. 2011;25:1779–87.
158. Mao L, Kippax SC, Holt M, Prestage GP, Zablotska IB, de Wit JB. Rates of condom and non-condom-based anal intercourse practices among homosexually active men in Australia: deliberate HIV risk reduction? Sex Transm Infect. 2011;87:489–93.
159. Fisher JD, Fisher WA. Changing AIDS-risk behavior. Psychol Bull. 1992;111:455–74.
160. Noar SM. Behavioral interventions to reduce HIV-related sexual risk behavior: review and synthesis of meta-analytic evidence. AIDS Behav. 2008;12:335–53.
161. De Wit JBF, Adam PCG. HIV/AIDS: the role of behavior and the social environment in a global pandemic. In: Ramachandran V, editor. Encyclopedia of Human Behavior. 2nd ed. Amsterdam: Elsevier; 2012.
162. Hofmann W, Friese M, Wiers RW. Impulsive versus reflective influences on health behavior: a theoretical framework and empirical review. Health Psychol Rev. 2008;2:111–37.
163. Bartholomew LK, Parcel GS, Kok G, Gottlieb NH, Fernandez ME. Planning health promotion programs: an intervention mapping approach. 3rd ed. San Francisco: Jossey-Bass; 2011.
164. Michie S, Johnston M, Francis J, Hardeman W, Eccles M. From theory to intervention: mapping theoretically derived behavioural determinants to behaviour change techniques. Appl Psychol Int Rev. 2008;57:660–80.

Chapter 10
Implementing Biomedical HIV Prevention Advances in Uganda

Joseph KB Matovu and Nuala McGrath

The first cases of "slim disease" (as HIV/AIDS was known then) were reported in 1982 from two fish landing sites, Lukunyu and Kasensero, in Rakai district [1]. In 1983, 17 more cases were reported. By 1986, 910 cases had been reported, rising to 7,249 cases by 1988. Initially, the epidemic was concentrated among the young, single, and largely unmarried individuals with pockets of concentrated epidemics in different population subgroups. A study conducted between 1986 and 1987 found that 86 % of sex workers, 33 % of truck drivers, 14 % of blood donors, and 15 % of antenatal clinic attendees in major urban centers were HIV positive [2]. By the early 1990s, HIV had spread throughout the country, resulting in a severe, mature, and generalized epidemic spread predominantly through heterosexual intercourse. HIV prevalence continued to rise through the early 1990s, reaching an average of 18 % by 1992 (Fig. 10.1).

In response to the growing HIV/AIDS epidemic, the government of Uganda, through the commitment and personal leadership of President Yoweri Kaguta Museveni, established the National AIDS Control Program and the National Committee for the Prevention of AIDS in 1987. The government implemented a multisectoral HIV prevention strategy that was reinforced by a strong information, education, and communication (IEC) campaign. The IEC campaign (implemented by the Health Education Division of the Ministry of Health (MoH)) emphasized messages such as "zero grazing" (which meant "stick to one partner") and "love faithfully," and included messages disseminated through a multiplicity of channels including radios, billboards, and question-and-answer scripts inserted in daily newspapers. Through

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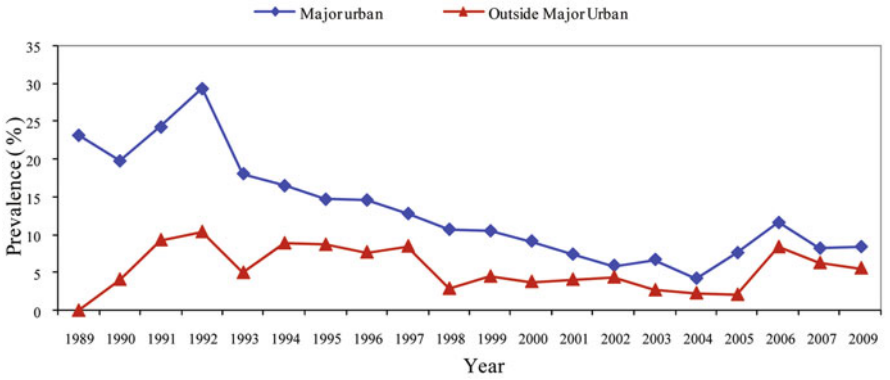


Fig. 10.1 Median HIV prevalence of antenatal care attendees in major urban and outside major urban sentinel surveillance sites in Uganda: 1989–2009. (Source: Ministry of Health HIV Surveillance Report 2010)

the technical oversight and direction of the MoH, the first national blood transfusion service, the first voluntary, confidential HIV counseling and testing service in Africa, the first HIV/AIDS care and support organization, and the first national sexually transmitted disease (STD) control program were initiated in Uganda between 1987 and 1990. As a result of these efforts, changes in sexual risk behaviors were noted, and these are believed to have contributed to a decline in HIV prevalence observed between 1990 and 2000 [3].

Uganda has been heralded as one of the few countries in the world to decrease the prevalence of HIV from a peak of 18 % in 1992 to a low of 6.1 % in 2002 through HIV prevention interventions emphasizing abstinence from sex, being faithful to one's partner, and using condoms during risky sexual encounters (ABC approach) coupled with visionary political leadership [4, 5]. However, this success appears to have waned by the beginning of the twenty-first century coinciding with a period of stabilization and subsequent increase in HIV prevalence in the wake of a changing HIV/AIDS landscape. Among women, HIV prevalence increased from 7.5 % in 2004–2005 to 8.3 % in 2011, whereas among men, HIV prevalence increased from 5 to 6.1 % over the same period [6].

We acknowledge that in the absence of country-level HIV incidence data, the increase in HIV prevalence may not necessarily project a worsening HIV/AIDS situation in Uganda given that with the increased rollout of antiretroviral therapy (ART), mortality has declined substantially [7] and survival rates among people living with HIV have improved greatly [8]. The end result is that there are more people living with HIV/AIDS now than 10 years ago. This observation does not rule out an increasing contribution of new HIV infections to Uganda's rising HIV prevalence. Indeed, estimates from mathematical modeling suggest that there were 130,000 new HIV infections in 2010 alone, and this number is believed to have risen to 145,000 in 2011, representing an increase in new HIV infections by 11.5 % in 1 year. Although it is not easy to translate these absolute numbers into actual

HIV incidence rates, the rising HIV prevalence coupled with the increasing numbers of new HIV infections may explain the national and international focus on Uganda following the release of the Uganda AIDS Indicator Survey findings in 2012. Indeed, when Hillary Clinton, the US Secretary of State, visited Uganda in August 2012, she did not hide her concerns about the rising new HIV infections in a country that was once heralded as an HIV prevention success story. Clinton's concerns came after the US Government through the Presidential Emergency Plan for AIDS Relief (PEPFAR) had provided funds up to $ 1.7 billion to support HIV prevention, care, and treatment programs in Uganda over the last 8 years (2004–2012).

HIV Prevention Response

The face of the HIV epidemic in Uganda has evolved over the years. During the 1980s and 1990s, HIV prevalence disproportionately affected young individuals with peak HIV prevalence among young men (25–30 years) and slightly younger women (20–24 years) [4, 5]. In addition, the majority of new HIV infections during the 1980s and 1990s predominantly occurred among young unmarried individuals, driven mainly by unprotected casual sex. However, this scenario has since evolved, with HIV transmission predominantly occurring among slightly older individuals in stable sexual partnerships [9, 10]. The Modes of HIV Transmission study used mathematical modeling to determine the sources of new HIV infections in Uganda. The study reported that the majority of new HIV infections in Uganda in 2008 occurred among couples in stable long-term partnerships (43 %) and persons engaged in multiple sexual partnerships (46 %). HIV transmission involving sex workers, their partners, and bridging infections to the general population accounted for close to 10 % of new HIV infections. The study further revealed that HIV prevention interventions were not aligned to the sources of new HIV infections [10].

On the basis of these observations, the Uganda AIDS Commission, the national HIV/AIDS coordinating body in Uganda, commissioned a review of the HIV epidemiology and HIV prevention response in 2010 that informed the design of the National HIV Prevention Strategy in 2011.The findings of the review indicated that despite Uganda's commitment to promote HIV prevention, many people did not have access to key HIV prevention services. For example, over 50 % of pregnant women were not accessing prevention of mother-to-child transmission (PMTCT) of HIV services; there were few outreach programs for key populations at high risk of HIV infection such as female sex workers, truckers, and men who have sex with men. To complicate this situation, only about one half of risky sex acts, defined as sexual acts with HIV-positive partners or partners whose HIV status is unknown, were protected using condoms [9]. Although sexually transmitted infection (STI) services were fully integrated into primary health care and were available in 60 % of primary health-care facilities by 2007, the review found that the quality of services was low with less than half of clients being appropriately diagnosed and managed, and there were chronic shortages of STI drugs. These findings provided a basis for

the formulation of new strategic objectives and targets included in the National HIV Prevention Strategy (2011–2015).

The implementation of the National HIV Prevention Strategy is anticipated to result in a 30 % reduction in new cases of HIV during 2011–2015. The National HIV Prevention Strategy embraces the current thinking in the HIV prevention response known as combination HIV prevention. The combination HIV prevention approach recommended in the strategy involves implementing multiple HIV prevention interventions with known efficacy in a specific area at a scale, quality, and intensity to impact the epidemic. The aim is to impede different points in the HIV transmission cycle by combining strategies to reduce HIV susceptibility among uninfected individuals and strategies to reduce infectiousness of persons living with HIV. The National HIV Prevention Strategy's priority objectives are as follows:

a. To expand coverage, quality, and uptake of HIV prevention services to critical coverage levels, defined as coverage levels of 80–90 % of the population with key HIV prevention interventions (including biomedical, behavioral, and structural interventions).
b. To increase adoption of safer sexual behaviors (such as partner reduction, consistent condom use, reduction in casual sex, and early sexual debut) and reduce risk-taking behaviors.
c. To create a sustainable enabling environment that mitigates the underlying sociocultural and other structural drivers of the epidemic.
d. To achieve a more coordinated HIV prevention response by the Uganda AIDS Commission.
e. To strengthen information systems for HIV prevention at all levels of the health system.

This chapter focuses on the planned implementation of biomedical HIV prevention interventions in Uganda (objective (a) above).

Biomedical HIV Prevention Interventions: Progress to Date

The National HIV Prevention Strategy identifies four priority biomedical HIV prevention interventions for Uganda, including provision of HIV counseling and testing (HCT) services, PMTCT of HIV, voluntary medical male circumcision (VMMC), and use of ART for prevention. At the moment, the coverage of these interventions is still suboptimal, and will have to be scaled up to between 80 and 90 % of the adult population in order for Uganda to reduce HIV infections by 30 % by 2015 as specified in the revised National HIV and AIDS Strategic Plan (2011–2015). The national HIV and AIDS Strategic Plan is the overriding document that guides HIV prevention, care and treatment, and social support interventions in Uganda. The National HIV Prevention Strategy defines how the HIV prevention component of the National HIV and AIDS Strategic Plan will be implemented. The following subsections illustrate the progress made in scaling up these interventions.

HIV Counseling and Testing

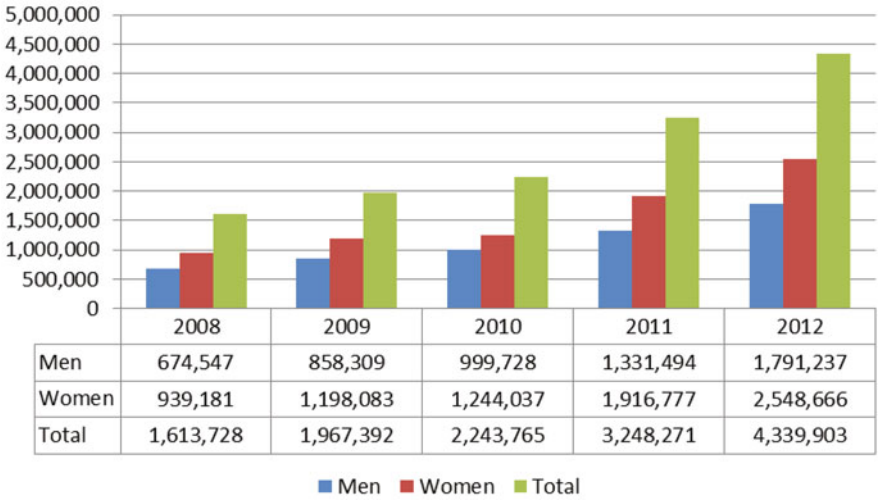
HCT denotes the provision of pretest counseling, HIV test results, and postresult counseling to individuals or couples that have voluntarily sought to receive these services. In this chapter, HCT is used in the broad sense to encompass various models including voluntary HIV counseling and testing (VCT), provider-initiated testing and counseling (PITC), and home-based HIV counseling and testing (home-based HCT).

In 2002, the Ugandan MoH developed the first national VCT policy in order to place high-quality HCT services within the reach of every Ugandan. This worked well but only a small percentage of the population accessed HCT services. With the advent of ART, there arose a need to broaden HCT approaches in order to improve timely HIV diagnosis and immediate linkage to HIV care. Consequently, the HCT policy was revised in 2005 to cater for new HCT approaches including PITC in the health-care setting and home-based HCT. Using the 2005 HCT policy guidelines, strides were made in the implementation of HCT services, with the proportion of health facilities offering HCT increasing from 37% (1,840 of 4,980) in 2009/10 to 38% (1,904 of 5,033) in 2011/12. The 2005 policy emphasized new models of HCT (e.g., PITC and home-based HCT), expanded entry points into HIV care; put emphasis on the provision of HCT services to children; and provided for use of lay counselors in providing HCT. In 2010, the 2005 policy was revised to respond to emerging evidence and updates in HCT at national and international levels. These changes included the 2007 World Health Organization (WHO) recommendations on including voluntary medical male circumcision (VMMC) as an additional HIV prevention strategy; the guidance on provision of PITC in health-care settings; and the need to target couples for HCT on the basis of findings of the Modes of HIV Transmission study conducted in Uganda in 2008. The coverage of HCT services has improved since 2010, with HCT services currently being provided at all hospitals and Health Center IVs, 80 % of Health Center IIIs, and 20 % of Health Center IIs.[1]

HCT Uptake to Date

Figure 10.2 shows the number of males and females who were counseled and tested and who received their HIV test results between 2008 and 2012, on the basis of reports available from the Monitoring and Evaluation of the Emergency Plan Progress (MEEPP, http://www.meepp.or.ug). As shown, the number of males and females

[1] Government health facilities are graded into Health Centers and Hospitals, depending on the population and geographical areas served. The lowest level facility is Health Center I (HC I) which serves the village level, approximately 1,000 people. From HC I, the assignment of levels increases in grade as the population and geographical areas served increase—from HC II (which serves a parish, approximately 5,000 people) through HC III (which serves a subcounty, approximately 20,000 people) and HC IV (which serves a county, approximately 100,000 people) to a District Hospital (district level, approximately 500,000 people), Regional Referral Hospital (which serves approximately 3 million people or 3-5 districts), and National Referral Hospital, which serves approximately 10 million people.



	2008	2009	2010	2011	2012
Men	674,547	858,309	999,728	1,331,494	1,791,237
Women	939,181	1,198,083	1,244,037	1,916,777	2,548,666
Total	1,613,728	1,967,392	2,243,765	3,248,271	4,339,903

Fig. 10.2 HIV counseling and testing uptake among men and women in Uganda: 2008–2012. (Source: MEEPP website http://www.meepp.or.ug)

who received their HIV test results increased from 674,547 and 939,181 in 2008 to 1,791,237 and 2,548,666 in 2012, respectively. There were more women than men who received their HIV test results during this period, possibly because many more women were tested at antenatal care (ANC) sites during pregnancy. Overall, the number of individuals who received their HIV test results increased from 1,613,728 in 2008 to 4,339,903 in 2012; a 169 % increase in HCT uptake over a 5-year period. However, these figures should be interpreted with caution as they do not indicate what proportion of those who received their HIV test results were repeat testers.

Recent findings from the Uganda AIDS Indicator Survey (UAIS) [6] show that two-thirds (66 %) of 11,160 women (15–49 years) reported that they had ever been tested for HIV and received their results in 2011, a marked increase from 13 % in 2004–2005. HIV testing among men (15–49 years) has increased fourfold, from 11 % in 2004–2005 to 45 % ($n = 8{,}735$) in 2011. These findings suggest that the increase in HCT uptake documented in Fig. 10.2 may be a true reflection of the HIV testing experiences of most Ugandans. Nevertheless, HCT uptake remains below the 80 % target set in the revised National HIV/AIDS Strategic Plan, calling for a need to expand and implement alternative demand-creation approaches to improve HCT uptake in Uganda. Some of these approaches are discussed below.

HIV Counseling and Testing Approaches

Voluntary HIV Counseling and Testing

VCT is offered on clients' request as a stand-alone service in clinical, community, and workplace settings. VCT was the first approach used in Uganda to provide HCT services to those who were interested in knowing their HIV status. The first institution

to offer VCT in Uganda was the AIDS Information Center (AIC). AIC was established in February 1990 to provide anonymous, voluntary, and confidential HIV testing and counseling services in response to the growing demand for HIV testing that was placing a burden on the national blood bank at Nakasero in Kampala, the capital city of Uganda [11]. AIC started as a small testing center in Kampala. Between 1990 and 1996, AIC provided HCT services through a two-visit protocol where clients would have their blood drawn at the first visit and then asked to return for HIV test results 2 weeks later. At that time, approximately 25 % of the clients did not receive their HIV test results either by not returning for the second visit or by returning but being discouraged when results were not ready. Beginning in 1997, a rapid HIV testing and same-day protocol was initiated and has been implemented since then. AIC currently supports over 200 MoH hospitals, Health Center IVs, Health Center IIIs, and private health facilities (indirect sites) to scale up HCT services to communities in 53 out of 112 districts. According to the AIC annual report for 2012, a total of 269,720 individuals were reached with HCT services at AIC regional offices, community outreaches, and supported sites between July 2011 and June 2012. Of these, 18,102 were couples, representing 6.7 % of the total number of clients served during this period.

AIC uses several approaches in providing HCT. These include use of "couple days" to encourage couples to test for HIV together free of charge; stand-alone HCT at the main branches; indirect sites (government and private health facilities that provide HCT in conjunction with AIC), and special HCT promotion programs (such as "community camping" and "moonlight HCT") for hard-to-reach and key populations at a higher risk of HIV infection. These populations are usually missed through conventional HCT approaches. Moonlight HCT aims at providing opportunities for individuals who are busy during the day to access services at night and its primary targets are sex workers, long distance truck drivers, the business community, *boda-boda* riders, market and evening tea venders, bar maids, and people working in restaurants and lodges. Implementation of the moonlight HCT approach began in 2007. As part of moonlight HCT, a clinical officer is always on-site to ensure that HIV-positive individuals are provided with co-trimoxazole before immediate referral to private and public institutions for follow-on care and support services.

Home-Based HIV Counseling and Testing

Home-based HCT was adopted into the HCT policy in 2005 following evidence that HCT could be effectively offered in people's homes [12, 13]. This approach was upheld in the revised version of the policy in 2010, after subsequent studies confirmed the role of home-based HCT in improving uptake of HCT and in identifying previously undiagnosed HIV infections and couple HIV discordance [14–16]. Recent evidence shows that home-based HCT can also contribute to a reduction in stigma associated with receipt of HCT [17].

Home-based HCT can be provided through two models: the *door-to-door* model and the *index-patient* model. The door-to-door model involves provision of HCT services to residents of every homestead or household who would like to have an HIV

test. On the other hand, the index-patient model (sometimes referred to as "targeted testing") involves HCT providers visiting the homes of people diagnosed with HIV (and who are already accessing HIV care) and offering home-based HCT to their sexual partners and other family members. The homes are visited with knowledge and permission of the index patient. Both models have been utilized in Uganda [18, 19].

The *door-to-door* model has been implemented by a number of programs in Uganda, including the Rakai Health Sciences Program in Rakai district and the Integrated Community-based Initiatives (ICOBI) in Bushenyi district. In Rakai district, the Rakai Health Sciences Program has implemented home-based HCT since 1994 through use of community resident counselors who provide HIV test results in people's homes. Between 1994 and 2000, uptake of HCT almost doubled from 35 to 65 % [18], and by 2002, uptake of HCT had reached 80 % of the study population aged 15–49 years.[2] In Bushenyi, ICOBI implemented home-based HCT from September 2004 to March 2007 [15]. The program reached 92,984 (63 %) of all the homes in the district during this period. Within these homes, 323,621 people aged 18–49 years were eligible for HCT and 282,857 (87 %) were present at home and were offered pretest counseling. A total of 264,966 (94 %) accepted testing and received their results, of whom 11,359 (4.3 %) were HIV positive. Ninety percent of those tested had never tested before, suggesting that home-based HCT can be a useful strategy for identifying previously undiagnosed HIV infection. It should be noted that these programs offered home-based HCT in rural areas, and may not necessarily represent uptake of HCT in urban settings. However, a recent study by Sekandi et al. [16] has indicated that door-to-door HCT can also be successfully implemented in urban settings. Sekandi et al. [16] found that of the 588 targeted with home-based HCT, 69 % accepted HCT; of these, 7.4 % previously undiagnosed HIV-positive individuals were identified and linked to HIV care.

Between 2004 and 2007, Nuwaha et al. [17] conducted serial cross-sectional surveys before and after implementation of the home-based HCT program in Bushenyi district and interviewed 1,402 randomly selected adults (aged 18–49 years) at the baseline survey in 2004 and 1,562 adults at the follow-up survey in 2007. Study findings show that the proportion of people who had ever tested for HIV increased from 18 to 62 % following the implementation of the home-based HCT program. Among people who had ever tested, the proportion of people who shared HIV test results with a sexual partner increased from 41 to 57 %. The proportion of persons who did not want to reveal the infection status of a family member decreased from 68 to 57 %. These findings suggest that use of home-based HCT can increase HIV status disclosure among sexual partners as well as promote stigma reduction in the communities. Measures of stigma and discrimination used in this study were adapted from those recommended by UNAIDS [20] and these included respondents' views on the hypothetical questions of whether respondents would buy vegetables from an

[2] HCT was provided as a service to study participants. Therefore, HCT services were available to community residents who had participated in research and who had provided a blood sample. Approximately 15,000 adults (15–49 years) were followed up through annual HIV surveillance surveys conducted in 50 communities in Rakai district.

HIV-positive vendor, whether they would wish to disclose HIV status in the home, and whether they thought that disclosure of HIV increased respect of the person disclosing. All indicators assessed for stigma and discrimination were favorable after the implementation of districtwide home-based HCT. For instance, the proportion of people who said that disclosure of HIV results increases respect increased from 40 to 75 %, people who said they would buy vegetables from an HIV-positive vendor increased from 70 to 82 %, and persons who did not want to reveal the infection status of a family member decreased from 68 to 57 % [17].

The *index-patient* model, on the other hand, has been implemented by the US Centers for Disease Control and Prevention (CDC) and The AIDS Support Organization (TASO), among other institutions. Between May 2003 and December 2004, CDC implemented a home-based AIDS care project in Tororo district, eastern Uganda. In this project, 2,373 household members of 730 index clients who were enrolled in an HIV care program were visited in the home and offered HCT. Of these, 2,348 (99 %) accepted HCT [21]. HIV prevalence among household members was 7.5 % and varied by age with 9.5 % among children aged 0–5 years, 2.9 % among persons aged 6–24 years, and 37.1 % among adults aged 25–44 years. Of the household members with HIV, 74 % had never been previously tested, and 39 % of these were clinically eligible for ART. Of the 120 spouses of ART patients who were tested for HIV, 52 (43 %) were HIV negative, and of these, 99 % had not been previously tested. These findings suggest that an index-patient model can identify previously undiagnosed HIV infection and couple HIV discordance among family members of people enrolled in HIV care. At TASO in Jinja (one of TASO branches), HIV-infected persons attending an AIDS clinic were randomized to a home-based or clinic-based ART program including HCT for household members. Of the 7,184 household members, 4,798 (66.8 %) were visited in the home. Study findings show that household members visited in the home were more likely to receive HCT than those randomized to the clinic-based arm (55.8 vs. 10.9 %). Thus, providing at-home counseling and testing led to an increase in the identification of HIV-positive spouses, children, and other family members [19].

Provider-Initiated Testing and Counseling

The provision of HCT in health facilities was informed by studies that showed that there are many missed opportunities when people access health facilities but do not utilize HCT services [22]. Consequently, pilot studies were implemented in Mulago National and Mbarara Regional Referral Hospitals to assess levels of acceptability of HCT when offered by health-care providers. These studies found high levels of acceptability of provider-initiated HCT. For instance, a study conducted at Mulago and Mbarara hospitals between 2004 and 2006 found high acceptance of HCT (98 %) among 51,642 patients who were offered PITC [23]. In this study, HIV prevalence was 25 % (12,107 of 48,454) among tested patients; 10 % among those who had ever tested for HIV, and 28 % among those who had never tested for HIV. The majority of the HIV-positive patients had never tested for HIV previously, suggesting that

PITC was able to identify a high proportion of previously undiagnosed HIV-positive individuals. In this study, provider-initiated HIV testing and counseling was also able to identify a high proportion of HIV-positive family members (20 %) and a high proportion (18.5 %) of HIV-discordant couples (224 of 1,213 couples). In 2007, Nakanjako et al. [24] found high acceptance of HCT (95 %) associated with PITC among 208 adult patients at Mulago hospital, with half (50 %) of those tested being HIV positive. Of those who were HIV positive, 77 % were diagnosed for the first time. Evidence from recent studies continues to show that PITC is highly acceptable in clinical settings [25] and can help to identify a high proportion of previously undiagnosed HIV-positive individuals who can then be linked to appropriate HIV care and treatment services as early as possible.

Couples' HIV Counseling and Testing

Findings from the Uganda HIV/AIDS Sero-Behavioral Survey of 2004–2005 indicate that approximately 13 % of currently married women and men have ever tested for HIV and received the results, and only 3 % of married women and 4 % of married men have done so in the last 12 months. Incredibly, in 2008, 90 % of married women and 89 % of married men did not know the HIV status of any of their partners or spouses [9], despite evidence suggesting that a significant proportion of new HIV infections in Uganda (43 %) occur among married couples [10]. In order to improve uptake of couples' HCT and improve linkage of HIV-tested couples to appropriate HIV prevention, care, and treatment services, the government of Uganda initiated a campaign in 2009 to promote couples' HCT and increase the proportion of couples who are aware of each other's HIV status. This campaign (dubbed "*Go Together. Test Together. Know Together*") was premised on available evidence that shows that couples' HCT can reduce sexual risk behaviors and rates of HIV seroconversion among couples who have received couples' HCT [26, 27]. To facilitate this campaign, the Ugandan MoH in conjunction with other partners developed a National Couples' HCT Communication Strategy that was intended to increase the proportion of couples who know their own and their partners' HIV status [28]. This strategy defines key message points, support points for the messages, and desired action responses for different types of audiences including couples (concordant HIV-negative, concordant HIV-positive, and HIV-discordant couples) and religious leaders. During the implementation of the campaign between 2009 and 2012, the MoH's AIDS Control Program (ACP) served as the major coordinating body for this campaign while AIC was the lead implementing agency. The Health Communication Partnership (HCP) provided technical assistance to the design, implementation, monitoring, and evaluation of the communication campaign through funding from USAID/Uganda.

The campaign used interactive radio programs, community drama, and videotaped testimonies to promote couples' HCT among those who had never received this intervention. These channels were reinforced with radio and television (TV) spots, billboards, posters, and print and electronic media coverage. To recognize and reward couples that had tested for HIV, the Ugandan MoH together with the

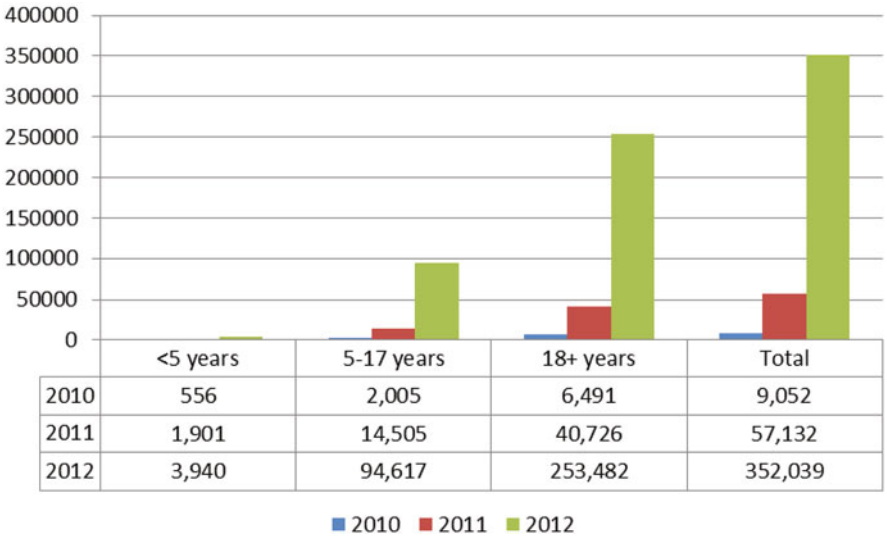
AIDS Information Center and Health Communication Partnership issued certificates to couples that had received couples' HCT as a sign of appreciation and recognition. As a result of these initiatives, the number of couples counseled and tested for HIV at the eight AIC branches and indirect sites increased from 31,093 couples in 2008 to 100,034 in 2012; 30–40 % of the couples who came for couples' HCT during this period were referred by couples who had tested at AIC.

Voluntary Medical Male Circumcision

Evidence from the three randomized trials of adult male circumcision conducted in Uganda, Kenya, and South Africa has shown that medical male circumcision can reduce the risk of female-to-male HIV transmission in initially HIV-negative men by 50–60 % [29–31]. On the basis of these results and other accumulated evidence, Uganda developed a male circumcision policy to guide nationwide implementation of voluntary medical male circumcision (VMMC) services. This policy was launched in 2010. In addition, a safe male circumcision communication strategy has been developed to guide the implementation of the policy. The overall prevalence of *male circumcision* in Uganda has increased from 24.9 % in 2004–2005 to 26.4 % in 2011 [6]. However, this increase in coverage of male circumcision should be interpreted with caution since it includes men who were circumcised for religious and culture reasons, those circumcised in infancy, as well as those circumcised before the efficacy of medical male circumcision had been proved through clinical trials. Thus, as noted below, the actual number of men who were circumcised since the launch of the safe male circumcision policy in Uganda in 2010 is not known. What is known, though, is that Uganda aims to circumcise 4,245,000 initially uncircumcised adult men (15–49 years) between 2011and 2015, and this is expected to result in a 20 % decline in HIV incidence among men and their female partners.

Progress to Date

As noted, the number of men who have received medical male circumcision since the launch of the male circumcision policy is not known because of weaknesses in reporting systems coupled with weak coordination mechanisms between VMMC-implementing partners and the MoH. However, reports from PEPFAR indicate that the number of circumcised male children and adults has increased from 9,052 in 2010, 57,132 in 2011, to 352,039 in 2012 (PEPFAR Annual Reports for Uganda 2010–2012; available at: http://www.meepp.or.ug). Cumulatively, these statistics suggest that a total of 418,223 males (children and adults) were circumcised between 2010 and 2012. This represents 9.8% of the estimated 4,250,000 men that need to be circumcised by 2015, according to the Uganda National HIV Prevention Strategy. Of these, 6,397 were aged < 5 years of age, 111,127 were aged 5–17 years, whereas 300,699 were aged 18 years and above (Fig. 10.3).



	<5 years	5-17 years	18+ years	Total
2010	556	2,005	6,491	9,052
2011	1,901	14,505	40,726	57,132
2012	3,940	94,617	253,482	352,039

Fig. 10.3 Number of males (children and adults) who received medical male circumcision in Uganda: 2010–2012. (Source: MEEPP website: http://www.meepp.or.ug)

Other reports show that approximately 149,400 adult males (15–49 years) received VMMC services between 2010–2012, although recent estimates from the MoH put the number of adult males who have been circumcised since 2010 at 708,000, representing 16.7% of the national target (Ario A, personal communication) [32]. These reports suggest that the uptake of VMMC services is still well below the set target for 2015. Nevertheless, reports from key implementing partners suggest that uptake of VMMC services could be improving in Uganda. For instance, reports from Rakai Health Sciences Program (one of the sites where the male circumcision clinical trial was conducted) show that 17,737 adult men were circumcised in Rakai and other neighboring districts between 2007 and 2010 (Rakai Health Sciences Program Status Report 2007–2010). Between 2010 and 2012, an additional 13,278 circumcisions were performed in Rakai; over 80 % with adult men aged 18 or older (PEPFAR Reports for Uganda: 2010 and 2011). Similarly, in Kayunga district, east-central Uganda, the Makerere University Walter Reed Project circumcised 15,500 men between 2009 and 2011, of whom 10,300 were circumcised in 2011 alone. The Walter Reed Project has also trained more than 250 clinicians to perform safe male circumcision.

VMMC Promotional Efforts

Most promotional approaches have included provision of VMMC through surgical camps, training of Health Center staff in how to offer VMMC with minimum adverse events, as well as conducting VMMC mobile outreach to populations that

are not yet well served by conventional VMMC promotional efforts. For instance, the Northern Uganda Malaria, AIDS and TB Program developed a communication strategy to engage VMMC stakeholders and educate the population about VMMC as an HIV prevention intervention. The program trained 11 specialist surgeons as regional trainers who then trained 66 health staff from 21 Health Center IIIs, thereby scaling up services through extensive task shifting. The program procured VMMC kits and distributed them to functional facilities. VMMC was offered through static sites, mobile outreach, and surgical camps. Within 7 months (June 2011 to January 2012), 12,429 men out of the targeted 26,000 men (47.8 %) in the 15 districts where this program operates were circumcised following these efforts [33]. Another agency, Strengthening Tuberculosis and AIDS Response in East Central Uganda (STAR-EC), used these and several other approaches to increase uptake of VMMC from 4,600 men to 21,581 men between April 2009 and December 2011. To improve uptake of VMMC, STAR-EC trained more surgical teams, introduced task-shifting initiatives (for instance, HCT was delegated to lay counselors), procured prepackaged circumcision kits, and conducted VMMC outreaches at targeted weekdays. In addition, it increased the number of static service outlets from 5 to 15 and week-long circumcision camps were initiated in hard-to-reach areas, including islands [34].

Recent advances in VMMC have included exploration of the possibility of offering VMMC using nonphysicians, especially in settings where there is an acute shortage of doctors, as well as assessing the acceptability of newer circumcision devices including the Shang Ring method. In a study conducted to assess the safety and efficiency of the dorsal slit and sleeve methods of male circumcision provided by physicians and clinical officers in Rakai, Uganda, Buwembo et al. [35] found that the dorsal slit method is faster than sleeve resection, and can be safely performed by nonphysicians. In another study conducted to assess the acceptability and safety of the Shang Ring for adult male circumcision in Rakai, Uganda, Kigozi et al. [36] found high acceptability of the Shang Ring (81.8 %; 508/621) with minimal adverse events (for instance, there were only four failures of Ring placement (0.8 %), which required surgical hemostasis and wound closure). These findings suggest that the Shang Ring method is acceptable and safe in improving VMMC uptake in Uganda.

Long-Term Effects of VMMC

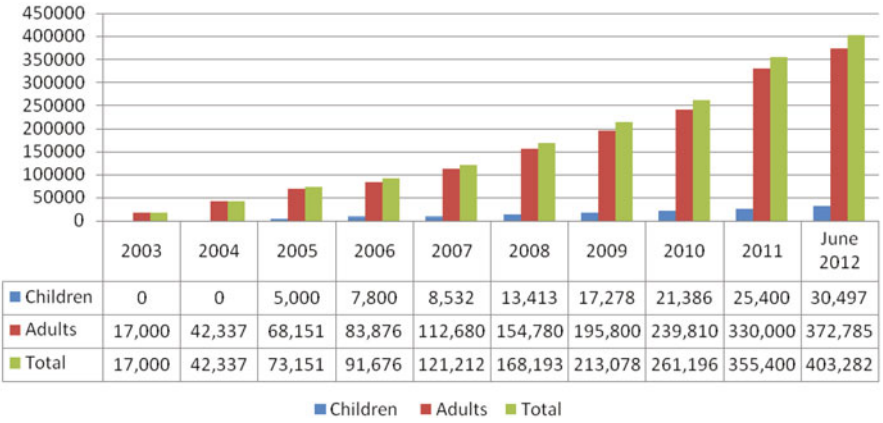
Findings from extended follow-up of men who participated in circumcision studies in Rakai between 2002 and 2005 show that the protective effect of VMMC is sustained over time. To assess the effect of VMMC over time, Gray et al. [37] followed up men enrolled in the male circumcision clinical trial in Rakai, Uganda, for up to 4.8 years following the end of the trial. Gray et al. [37] found that 78.4 % of uncircumcised trial participants had accepted male circumcision. In the intervention arm, posttrial HIV incidence was 0.50/100 person-years in circumcised men and 1.93/100 person-years in uncircumcised men, translating into a protective effect of 73 % (95% confidence interval (CI), 55 to 84%). In control arm participants, posttrial HIV incidence was

0.54/100 person-years in circumcised and 1.71/100 person-years in uncircumcised men, translating into a protective effect of 67 %(95% CI, 38 to 83%). These findings suggest that the protective effect of VMMC was sustained over a 5-year period. In this study, there was no evidence that circumcised men engaged in more risky sexual behavior because they perceived their risk to have decreased.

It should be noted, however, that the efficacy of VMMC in preventing male-to-female HIV transmission requires further scrutiny. In a study conducted in Rakai district in which 922 uncircumcised, HIV-infected, asymptomatic men aged 15–49 years with CD4-cell counts of 350 cells/mm^3 or more were enrolled and followed up for up to 24 months, Wawer et al. [38] found that circumcision of HIV-infected men did not reduce HIV transmission to female partners over the duration of the follow-up. In this study, HIV-positive men were randomly assigned to receive immediate circumcision (intervention; $n = 474$) or circumcision delayed for 24 months (control; $n = 448$). HIV-negative female partners of the randomized men were concurrently enrolled (intervention, $n = 93$; control, $n = 70$) and followed up at 6, 12, and 24 months to assess HIV acquisition by male treatment assignment (primary outcome). The trial was stopped early because of futility. Ninety-two couples in the intervention group and 67 couples in the control group were included in the modified intention-to-treat analysis. Seventeen (18 %) women in the intervention group and eight (12 %) women in the control group acquired HIV during follow-up. Cumulative probabilities of female HIV infection at 24 months were 21.7 % in the intervention group and 13.4 % in the control group, suggesting that female partners of HIV-infected circumcised men were 1.5 times more likely to acquire HIV than those whose partners were not circumcised. Nevertheless, a prospective study enrolling 1,096 HIV serodiscordant couples in which the male partner was HIV positive, found a promising, although not statistically significant, 40 % reduction in seroconversions of women whose male partners were circumcised [39]. While there is no evidence of a direct benefit to women, there is evidence of an indirect benefit that accrues over time. Modeling estimates suggest that properly implemented VMMC programs that lower HIV prevalence among the male population would thereby also reduce women's risk of exposure to men infected with HIV [40]. Circumcision may also help to protect women from contracting human papillomavirus (HPV) and thus help to prevent cervical cancer. A study conducted in Rakai district found that male circumcision reduced HPV incidence among long-term female partners of circumcised men by 77 % over a period of 24 months [41].

Antiretroviral Treatment as Prevention

In 2003, the Ugandan MoH developed guidelines for use of ART in adults and children [42]. According to these guidelines, HIV-positive individuals were eligible to initiate ART in the absence of a CD4 test result if they were in the WHO stage IV disease or had advanced WHO stage III disease including persistent or recurrent oral thrush and invasive bacterial infections. When a CD4 test result was available, ART eligibility was defined as WHO stage I, II, or III with CD4 cell counts $\leq 200/\text{mm}^3$.



	2003	2004	2005	2006	2007	2008	2009	2010	2011	June 2012
Children	0	0	5,000	7,800	8,532	13,413	17,278	21,386	25,400	30,497
Adults	17,000	42,337	68,151	83,876	112,680	154,780	195,800	239,810	330,000	372,785
Total	17,000	42,337	73,151	91,676	121,212	168,193	213,078	261,196	355,400	403,282

Fig. 10.4 Number of active ART clients in Uganda: 2003–2012. (Source: Namagala E (2013): HIV care and treatment policies in Uganda)

These guidelines were revised (MoH 2011) to reflect changes in recommendations made by WHO in 2010. Specifically, the WHO guidelines recommended that all adolescents and adults with CD4 counts of ≤ 350 cells/mm^3 should start ART regardless of the presence or absence of clinical symptoms. Those with severe or advanced clinical disease (WHO clinical stage III or IV) should start ART irrespective of their CD4 cell count.

ART Coverage in Uganda

ART became widely available in Uganda in 2003 with funding from PEPFAR. The initial distribution plan included provision of ART at selected health facilities, especially at the district hospitals, regional referral hospitals, and the national referral hospital based at Mulago, Kampala, Uganda. Gradually, the number of health facilities providing ART increased to 432 in 2011 and 1,073 (out of 1,250 health facilities that have been accredited to provide ART) by June 2013. With this level of scale-up, all 112 districts in Uganda have got at least one ART center. ART services are currently provided at all national, regional, and district hospitals; 97 % of all Health Center IVs; 6 % of Health Center IIIs; and 2 % of Health Center IIs. As a result of these efforts, the number of people receiving ART has increased from 17,000 in 2003 to 372,785 adults by June 2012. The number of children (under 15 years of age) receiving ART has also increased from 5,000 in 2005 to 30,497 (representing 8 % of those eligible to receive ART) by June 2012 (Namagala E, personal communication) (Fig. 10.4). According to reports from the MoH, the number of HIV-positive individuals who are on ART stood at 540,000 by June 2013. This represents 73% of an estimated 733,127 HIV-positive adults and children who were eligible for ART on the basis of a CD4 cell count of ≤ 350 cells/mm^3) by June 2013.

Successes in Scaling Up ART Services in Uganda

Uganda has registered several successes in its scale-up of ART, including continued expansion and adoption of new guidelines as well as improved quality of life and treatment outcomes for people enrolled on ART. These successes are summarized below.

Continued Expansion and Adoption of New Ugandan Guidelines

Uganda continues to be responsive to new international HIV treatment policies and guidelines. For instance, the 2011 Uganda integrated national guidelines on ART, PMTCT, and infant and young child feeding—the first document to comprehensively cover the three broad areas—takes into account the 2010 revision of the WHO global ART recommendations; the revised PMTCT guidelines aimed at elimination of new pediatric HIV infection resulting from mother-to-child transmission (MTCT) of HIV; and incorporates nutrition as an integral component of comprehensive HIV care. The number of health facilities providing treatment and the number of individuals accessing care have continued to increase except among some subpopulations (e.g., children, pregnant women, uniformed forces, and fishing communities/islands). Generally, the access, availability, and uptake of ART have improved nationally. The coverage of ART sites has improved with all the 112 districts having at least one treatment site.

Improved Quality and Treatment Outcomes

Treatment outcomes including patient retention, CD4 increase, and survival have continued to improve since 2003. A recent study among 22,315 patients aged 14 years or older who were initiated on combination ART at TASO and followed up between 2000 and 2009 found that Ugandans on ART can be expected to have a near-normal life expectancy [8]. For example, life expectancy at age 20 years for the overall cohort was 26.7 (95 % confidence interval (CI), 25.0 to 28.4) additional years and at age 35 years was 27.9 (95 % CI, 26.7 to 29.1) additional years [8]. The WHO Global Health Observatory estimates life expectancy in Uganda at age 20 years as an additional 41 years. Thus, the additional life years come close to what would be expected in the general Uganda population. In addition, there has been improved clinical efficacy of first-line regimens: between 2010 and 2011, 97.3 % of patients were maintained on first-line treatment.

Prevention of Mother-to-Child Transmission of HIV

Uganda's program for PMTCT of HIV continues to evolve in line with evolving evidence and international guidelines. The PMTCT program was established in the year 2000, after the successful HIVNET 012 study that had been conducted in Uganda

[43], with a goal of reducing MTCT by 25 % by 2005 through provision of a comprehensive PMTCT package to pregnant women and their spouses. The program aimed at establishing PMTCT services in at least one health facility per district by the end of the year 2004 and then scale up to Health Center IVs in the year 2005. The 2004 target was achieved and by December 2005, 86 % (133/154) of Health Center IVs were providing PMTCT services. By June 2007, close to 30 % (258/905) of Health Center IIIs were providing PMTCT services in addition to 92 % of Health Center IVs and 97 % of hospitals. By the end of 2009, 77 % ($n = 1{,}229$) of all health facilities up to Health Center IIIs were providing PMTCT services, and this increased to 93.5 % by June 2010. When Health Center IIs are included in the overall number of health facilities in Uganda, the current coverage of PMTCT services stands at 2,000 health facilities (40 %) out of an estimated 5,000 health facilities in the country.

Uganda launched the first PMTCT policy in 2002, 2 years after the initiation of the PMTCT program. At that time, the main drug used for PMTCT was a single-dose nevirapine for mothers (at onset of labor) and nevirapine syrup for babies (offered within the first 72 hours after birth), based on the HIVNET 012 study. These guidelines were revised in 2006 and provided for use of dual therapy (two drugs for PMTCT). In 2012, the Ugandan MoH adopted the WHO guidance on the use of ART in pregnancy and took a major decision to adopt Option B+ for Uganda's setting. Through Option B+, all HIV-positive pregnant women will be given triple ART regardless of their CD4 cell count for life, and their babies will be given nevirapine from birth up to 6 weeks. It is anticipated that this approach will save at least 23,000 babies from contracting HIV from their parents each year. This shift in policy follows evidence that early treatment for HIV-infected pregnant women reduces the risk of MTCT by more than 50 % [44].

Uganda's PMTCT program is based on a four-pronged approach to provide earlier initiation of ART during pregnancy for reducing MTCT of HIV; ART provision throughout breastfeeding to reduce MTCT; ART provision for life to improve maternal health; and ART provision to HIV-discordant couples. The government plan is to roll out Option B+ in a phased manner starting off with high HIV prevalence regions of Uganda and subsequently move on to the lower HIV prevalence regions. Uganda began rolling out Option B+ for elimination of MTCT of HIV in October 2012. The plan is to provide Option B+ in 2,000 health facilities providing PMTCT services by December 2013.The overall aim of the PMTCT program is virtual elimination of MTCT (reduction of vertical transmission rate to < 5 % at population level and reduction of new pediatric HIV infection by 90 %) by 2015. At the moment, the PMTCT package is currently provided in 84% of hospitals (n=143), 95% of HC IVs (n=190), 93% of HC IIIs (n=1,177) and 12% of HC IIs (n=3,470) with support from various implementing partners. Overall, the percentage of health facilities providing PMTCT services has increased from 23% (1,150 of 4,980) in 2009/10 to 36% (1,816 of 4,980), although this level of coverage remains sub-optimal. The national target is to reach at least 90 % of all HIV-positive pregnant women who attend ANC with PMTCT services by 2015.

PMTCT Promotional Approaches

Several approaches are used in promoting PMTCT in Uganda, particularly through enhancing the PMTCT-ART linkages, use of peer mothers and mentor fathers, as well as facility-based promotion as presented in the following subsections.

Enhancing PMTCT-ART Linkages

Since 2009, special consideration has been given to PMTCT-ART linkages with enhanced screening of pregnant women for ART eligibility. These interventions have been made available at 32 ART sites throughout the country. Several programs have contributed to the integration of PMTCT-ART linkages, including Northern Uganda Malaria, AIDS and TB Program, AIDS Relief, Traditional and Modern Health Practitioners Together Against AIDS and Other Diseases (THETA), and ICOBI. For instance, the Northern Uganda Malaria, AIDS and TB program conducts CD4 testing for ART eligibility as well as provides on-site support and mentoring for providers at Health Center IIs and IIIs in Apac district. Overall, 14 sites within Apac district have been supported, resulting in 1,721 (35 %) pregnant mothers being assessed for ART eligibility (out of 4,888 HIV-infected women) and 901 being initiated on ART. On the other hand, AIDS Relief has computerized their PMTCT registers and integrated PMTCT tools into the HIV/ART data management system. The system has enhanced tracking of mothers and their infants and document referrals to ART clinics. THETA is implementing a program at the community level aimed at increasing uptake of PMTCT services by strengthening/building community-based support models that can be replicated nationwide. Increasing awareness for and enhancing linkages for early infant diagnosis (EID) are among some of the activities implemented by THETA. In addition to THETA and AIDS Relief, ICOBI is also implementing a similar program in western Uganda, working with community structures including village health teams (VHTs) to promote community-based PMTCT program uptake.

Peer Mothers and Father Mentors

Several programs have started using peer mothers to improve uptake of services and retention of HIV-positive mothers and their exposed infants in HIV care. Groups of peer mothers are called *Maama Clubs* or "mentor mothers". *Maama Clubs* are groups of HIV-positive mothers of childbearing age, organized around income-generating activities such as hair braiding, beadwork, and food preparation. *Maama Club* members are trained in and given information on HIV prevention including condoms for dual protection and PMTCT. These clubs have been established by several institutions in Uganda, including the Makerere University–Johns Hopkins University (MUJHU) research collaboration, PREFA, and TASO.

In Soroti district, north-eastern Uganda, peer mothers who have understood the importance of PMTCT and benefited from it have been invited to work with health facilities as volunteers. These women mobilize pregnant mothers in their communities to attend antenatal clinics in order to benefit from the PMTCT program. The key

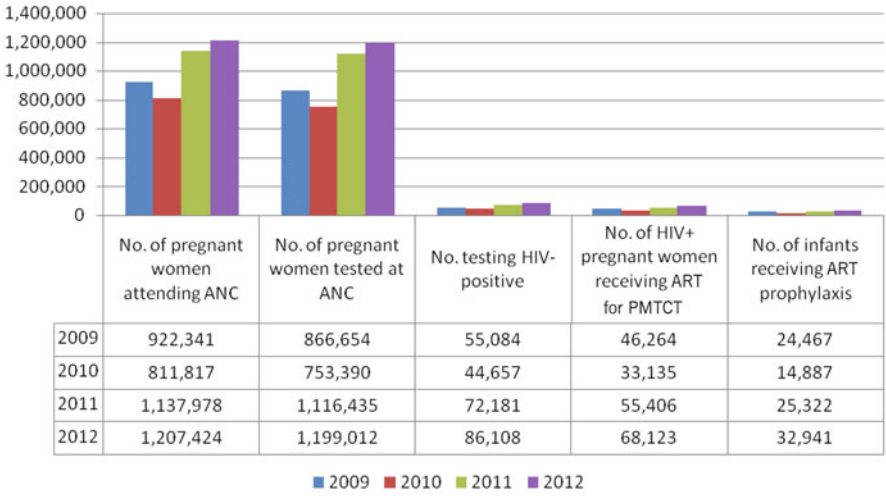
challenge is how to keep the peer mothers motivated to do this work because they are volunteers and do not receive any allowances. The idea of having father mentors has not yet taken root, yet this would be an opportunity to reach men and increase male involvement in PMTCT.

Facility-Based Promotion

One of the key institutions involved in promoting PMTCT in Uganda is PREFA. PREFA is a national nongovernmental organization that was formed in 2004 with a mission to assist Uganda to enhance access to quality HIV/AIDS prevention, care, treatment, and support to families with emphasis on PMTCT. It is funded by CDC and other donors. PREFA operates in 40 districts reaching 13,232,900 people, approximately 40 % of Uganda's population. PREFA works in the context of the Global Plan Towards the Elimination of New HIV Infections Among Children by 2015 and Keeping Their Mothers Alive, and promotes integration of PMTCT, pediatric HIV, and maternal, neonatal, and child health services through delivery of an integrated package for pregnant women and young children. PREFA uses a district-led approach that engages district leadership in planning and implementation with oversight from MoH so as to strengthen district health systems. PREFA activities are implemented by the district health workers at public and private not-for-profit health facilities, as well as through village health teams at community level. The village health team members and health workers keep track of HIV-positive mothers and their babies from ANC through delivery and postnatal care and support appropriate linkages for HIV care to reduce loss to follow-up and improve the quality of services. Between 2006 and 2010, PREFA tested 992,738 pregnant women for HIV. Of these, 59,522 (6 %) were HIV positive and 45,631 (77 %) of them received ART for PMTCT. In addition, PREFA identified 26,457 HIV-exposed babies born to HIV-positive women and provided ART prophylaxis to 23,860 (90 %) babies during this period (PREFA Annual Report, July 2010–June 2011).

Antenatal Clinic Attendance, HIV Testing, and Access to ART for PMTCT

On the basis of program reports from the MoH, the number of pregnant women attending ANC at facilities providing PMTCT services increased from 922,341 in 2009 to 1,207,424 in 2012 (Fig. 10.5). The proportion of pregnant women attending ANC services who were tested for HIV increased from 94 % (866,654 of 922,341) in 2009 to 99.3 % (1,199,012 of 1,207,424) in 2012. This increase is a reflection of the successful promotion of provider-initiated HIV testing and counseling programs at all health facilities throughout the country. On the basis of data presented in Fig. 10.5, the proportion of HIV-positive pregnant women who received ART prophylaxis to reduce the risk of MTCT of HIV was 84 % (46,264 of 55,084 HIV-positive women) in 2009, 74.2 % (33,135 of 44,657) in 2010, 76.8 % (55,406 of 72,181) in 2011, and



	No. of pregnant women attending ANC	No. of pregnant women tested at ANC	No. testing HIV-positive	No. of HIV+ pregnant women receiving ART for PMTCT	No. of infants receiving ART prophylaxis
2009	922,341	866,654	55,084	46,264	24,467
2010	811,817	753,390	44,657	33,135	14,887
2011	1,137,978	1,116,435	72,181	55,406	25,322
2012	1,207,424	1,199,012	86,108	68,123	32,941

Fig. 10.5 Number of pregnant women navigating through the PMTCT cascade in Uganda: 2009–2012. (Source: MEEPP website: http://www.meepp.or.ug)

79 % (68,123 of 86,108) in 2012. Based on the 2010/11 PMTCT report from the Ministry of Health, there were an estimated 1,550,000 pregnant women in 2010/11; 71% (1,100,650) of whom attended ANC during their pregnancy. Ninety four per cent of those who attended ANC (1,034,667 of 1,100,650) were counseled and tested and received their HIV test results. Of these, 5.4% (55,795 of 1,034,667) were found to be HIV-positive. Approx. 87.4% of all HIV-positive women identified received prophylactic ART to reduce mother-to-child transmission of HIV, constituting approx. 52% of all expected HIV-positive pregnant women during the reporting period [45].

These statistics should be interpreted with caution because they are based on program reports and may, therefore, not be representative of population-level data. The number of women who were tested for HIV, when expressed as a percentage of all expected pregnant women, would be much lower than that obtained through program data. For instance, in 2007–2008, the proportion of pregnant women tested for HIV as a proportion of *all expected* pregnant women was 43 %. This proportion increased to 69 % in 2008–2009 but dropped to 59.3 % in 2009–2010. Similarly, the proportion of *all expected* HIV-positive pregnant women who received ART for PMTCT increased from 35.3 % in 2007–2008, 48.5 % in 2009–2010, to 52 % in 2010–2011[45].

Early Infant Diagnosis

The Ugandan MoH started providing services for early infant HIV diagnosis and care among infants in December 2006 in collaboration with the Joint Clinical Research Center. One month later, in January 2007, testing of HIV among infants and young

children below 18 months started. Since polymerase chain reaction (PCR) technology was not available in health facilities at the time, the MoH reached an understanding with the Joint Clinical Research Centre to conduct the testing of infants. Seven Joint Clinical Research Centre reference laboratories located in different regions of the country with DNA PCR capacity were involved in this testing. In order to make the service accessible nationally, a referral network for samples and results was developed to connect the seven laboratories to health facilities. To support the referral network, services of a courier company were contracted by the MoH to transport samples and results between the testing labs and the health facilities.

Despite these efforts, in 2009, a review of EID services in regional referral hospitals revealed that overall only 40 % of exposed infants testing HIV positive through the EID program were ever enrolled for HIV care and treatment at an ART clinic [45]. Factors responsible for the low linkage to pediatric HIV care included (i) weaknesses in identifying and testing or referral for testing of HIV-exposed infants at various venues, (ii) failure to return results to parents and care givers owing to delays in processing and returning results to facilities coupled with weaknesses in the tracking of tested children, and (iii) poor linkage to care for infants diagnosed with HIV infection owing to weaknesses in the referral mechanisms and limited integration between EID and HIV chronic care sites. In response to these findings, the MoH established a consolidated laboratory at the Central Public Health Laboratories in Kampala in 2010 with appropriate transport hubs at district level. By 2010, the EID program was being offered in 616 health facilities (51 % of the recommended health facilities) including all 112 hospitals, 96 % of 163 Health Center IVs, 27 % of 955 Health Center IIIs, and also in 60 Health Center IIs and 30 special clinics/research laboratories in the country. Since then, there has been an increase in the number of infants tested as a percentage of all the estimated HIV-exposed children from 12.3 % in 2007–2008 to 40.2 % in 2010–2011. Over the same period, the proportion of tested infants who were found to be HIV positive declined from 19.4 % in 2008 to 7.4 % in 2011, indicating that the PMTCT service is having a positive impact on newly born children [45].

Challenges and Opportunities for Scaling-Up Biomedical HIV Prevention Interventions in Uganda

The coverage of biomedical interventions is still suboptimal, with coverage of key interventions still below the 80–90 % coverage necessary to have a significant impact on the HIV epidemic. For instance, the coverage of male circumcision is 26 %, ART coverage is 69.9 %, prevention of MTCT coverage stands at 51 %, whereas 34 % of women and 55 % of men are not aware of their HIV status. Several challenges still exist that explain why performance is much lower than targets but opportunities for scaling up these interventions exist as discussed below.

HCT-Related Challenges and Opportunities

The provision of HCT in Uganda is still constrained by inadequate human resources and the distance to the nearest HCT facilities. There are few providers/counselors at the health facilities, and the majority of them have not received training in HCT. There is a lack of formal accreditation of HIV counselor training coupled with a lack of a national training curriculum for HIV counselors. In most cases, HIV counselors learn on the job and do not receive continued medical education to update them on recent trends in HIV counseling and testing. The low staffing levels particularly at Health Center IIIs and IIs continue to affect service delivery in terms of quality and numbers served. In addition, there is inadequate access to and uptake of HCT by some subgroups including HIV-exposed children, couples, men, and some high-risk groups such as female sex workers, fisher folk, and men who have sex with men. As a result, there is still a significant proportion of Ugandans (34 % of women and 55 % of men) who have never tested for HIV [46].

Weak monitoring and evaluation systems continue to hamper effective interventions targeting populations that have inadequate access to HCT services. Figures at the national level are not complete and do not always capture the testing that happens in the private sector. The other challenge is that most supervision is conducted by individual HCT implementing programs that are parallel mechanisms to the MoH and public sector supervision structures. These programs tend to report directly to their donors and rarely share their reports with the MoH. In addition, it is difficult to distinguish between repeat vs. first time testers because most tests are conducted anonymously. Anecdotal evidence suggests that up to 40 % of individuals testing for HIV are repeat testers. Currently, no strategic plan is in place to distinguish between repeat and first testers, and this problem is likely to remain.

Despite these challenges, the existing policy framework supports rapid expansion of HCT countrywide to increase coverage to 80 % of the population, and this presents a window of opportunity for the scaling up of HCT services in Uganda. The National HIV Prevention Strategy (2011–2015) recognizes HCT as an important entry point for appropriate HIV prevention, care, and treatment services, and includes a target of 80 % coverage of HCT among the general adult population. This target is in line with the need for increased coverage of HCT services in Uganda, as spelled out in the 2010 National HIV Counseling and Testing Policy. The policy recognizes the need for implementation of alternative HCT approaches, including those discussed in this chapter. In addition, a National Couples' HIV Counseling and Testing Communication Strategy was launched in 2009 together with support documents for the promotion of couples' HCT including a national HCT training manual and other promotional materials. These documents provide the impetus for increased promotion and scale-up of HCT services in Uganda. The other opportunity is that HCT services are now available in lower-level health centers (up to Health Center II) and there are a number of implementing partners that offer HCT services in the country. Many of these implementing partners are currently offering HCT through mobile outreaches, home-based HCT, provider-initiated HCT, and other approaches including moonlight HCT where HCT services are provided at night to people who are not easy to reach during the day.

Voluntary Medical Male Circumcision Challenges and Opportunities

Although evidence that VMMC was an effective HIV prevention strategy became available in 2007, there was no policy framework in Uganda to guide scale-up of safe male circumcision services until 2010. There has also been some level of political and religious opposition to male circumcision scale-up within Uganda, suggesting a need to obtain the necessary buy-in prior to male circumcision scale-up. In addition, although the male circumcision policy calls for improved access to quality VMMC services at all levels in both public and private health facilities, carried out by appropriately skilled personnel, the necessary groundwork for effective provision of safe male circumcision services is yet to be put in place. Specifically, at the moment, there is no minimum training package for personnel to perform safe male circumcision; there is no recommended method of circumcision in Uganda (the commonly used surgical methods include dorsal slit or sleeve method); the minimum package of equipment necessary to perform safe male circumcision is not yet defined; there are no standard operating procedures to guide clinical practice in line with WHO-recommended techniques; and the capacity of health facilities to provide safe male circumcision is still lacking. In addition, there is no systematic tracking system to document the number of VMMC surgeries conducted by different organizations in Uganda, and the attainment of the set target of circumcising 80 % of initially uncircumcised men by 2015 seems to be unattainable considering the current trend in VMMC uptake.

Despite these challenges, the launch of the male circumcision policy and the male circumcision communication strategy in 2010 offers an opportunity for the rapid scale-up of VMMC services. In addition, the MoH intends to train nonmedical officers to perform VMMC in a bid to address the shortage of skilled clinical/medical personnel to perform VMMC. Evidence from Rakai Health Sciences Program suggests that safe male circumcision can be offered by clinicians (in Uganda, these are medical professionals trained at Diploma level, and are thus different from Doctors who have a Degree in Medicine), making it possible for safe male circumcision to be offered in lower-level health units, up to Health Center II, without doctors in place [35]. This, coupled with a high acceptability of male circumcision among uncircumcised men in traditionally noncircumcising communities [46], will result in improved uptake of VMMC in Uganda. VMMC is already incorporated into Uganda's national HIV prevention strategy and this creates the opportunity for nationwide scale-up. VMMC is also part of the interventions that are going to be pilot-tested in eight districts (by the MoH with support from development partners) to assess the impact of combination HIV prevention approaches on HIV acquisition. The MoH aims to circumcise ~900,000 men per year for the next 5 years in order to reach VMMC prevalence of 80 % and avert HIV infection by 20 % [47].

Antiretroviral Therapy Scale-Up Challenges and Opportunities

The main challenge for the scale-up of ART services in Uganda is a lack of adequate resources to put everybody who is eligible for ART on treatment. At the moment, only about 69.9 % of ART-eligible patients (patients with CD4 < 350 cells/μl, or stage III/IV disease) in Uganda are receiving therapy, in part owing to low coverage of HCT, lack of funds to put every eligible HIV-positive person on treatment, and inadequate systems to ensure that eligible patients are initiated and retained on ART. This suggests that initiation of all HIV-infected individuals whose CD4 cell count is > 350 cells/μl is still beyond reach as a strategy in Uganda. In addition, although results from the HPTN 052 study suggest that early initiation of ART can reduce the risk of HIV transmission among HIV-discordant couples by 96 %, the cost-effectiveness of ART for patients with CD4 counts > 350 cells/μl as a prevention strategy is still unknown. There are concerns about ART drug resistance especially if adherence is poor.

Another challenge is that the majority of Ugandans present late for HIV diagnosis and HIV care. In a study assessing late presentation to an HIV clinic conducted among 2,311 patients presenting at Mbarara University Teaching Hospital between 2007 and 2008, Kigozi et al. [48] found that 40 % of patients were late presenters, defined as patients with WHO disease stage III or IV. Another study of late HIV diagnosis (defined as having a CD4 cell count of ≤ 250 cells/μl at the time of HIV diagnosis) among 1,966 patients at Mulago National Referral Hospital in Kampala, Uganda, between May 2008 and March 2010 found that 616 (31.3 %) of the patients were HIV infected; of these, 48 % were late presenters [49]. These findings suggest a need to explore approaches that can identify HIV-positive individuals at an early stage, including use of community-based HIV testing approaches, with timely linkage and appropriate referrals to HIV care among those identified as HIV positive.

Nevertheless, recent evidence suggests that many would-be users of ART are willing to take it up if availed to them. A recent study aimed at assessing patients' attitudes toward ART initiation at higher CD4 cell counts found high willingness to initiate ART at higher CD4 cell counts among enrolled individuals with CD4 cell count > 350 cells/μl. Ninety per cent of those who expressed this willingness cited their desire to stay healthy as the main reason, 52% also cited desire to continue working, and another 52% cited the desire to continue caring for their families. Other reasons cited included desire not to transmit HIV to their partners and concerns about the future of their children [50]. The findings from this study suggest that there is demand for ART initiation at CD4 cell counts > 350 cells/μl.

PMTCT Challenges and Opportunities

There are still numerous challenges to the effective scale-up of PMTCT programs throughout the country. These challenges include low male involvement in PMTCT programs; low proportions of pregnant mothers delivering at health facilities (57 %)—mainly owing to cultural reasons and at times because of attitudes of

staff who conduct the deliveries, and low postnatal care (33 %). As a result, not all HIV-positive pregnant mothers have access to PMTCT services, although PMTCT services are being provided in all hospitals, Health Center IVs, many Health Center IIIs, and some Health Center IIs. Some mothers still prefer to deliver outside health facilities, for example, at home, traditional birth attendants' facilities, or health units that do not provide PMTCT services. In addition, pregnant women are not accessing ANC services early because of insufficient community mobilization for early attendance at antenatal clinics coupled with prohibitive transport costs, particularly for women in rural areas. Furthermore, HIV-positive pregnant women who attend ANC services do not return for follow-up antenatal clinic visits for continued monitoring, counseling, and refill of medications yet health facilities are unable to track mothers through the antenatal period (Esiru G, personal communication).

Another problem is the interrupted and irregular supply of essential commodities in health facilities and districts leading to frequent stock out. Inadequate supply of commodities such as ART for PMTCT; family planning commodities such as condoms and contraceptives; and laboratory test kits for HIV, hemoglobin (Hb), STIs, CD4, and other biomeasures continue to hamper effective service delivery. There are also weak linkages, referrals, and integration of PMTCT and maternal, child, and neonatal health services in health facilities, resulting in significant loss-to-follow-up of mothers and their infants. There are weak community components to facilitate follow-up of mother–baby pairs with more than 50 % of HIV-exposed babies not receiving ART for PMTCT prophylaxis. This is worsened by persistent health workforce challenges such as staff attrition, frequent transfers of health workers, and limited numbers of health workforce that often affect service delivery, especially ART service delivery.

The frequency with which PMTCT policy guidelines have changed over a short time has called for more contact time between the MoH officials and the health workers at the implementing facilities. Related to this are the changes in indicators and data collection tools that have also affected the quality and type of data collected. For instance, in 2009/2010, PMTCT data collection tools were reviewed and a phased approach was used to roll out the tools through training and mentoring of health workers. The phased approach meant that while some facilities were using the old tools, others were reporting with the revised tools. As a result, some of the new indicators introduced in the new tools were not reported by several facilities.

Unmet need for contraception among Ugandan women remains high at 34 % [11], despite a slight decline from 41 % in 2006 [11]. A study exploring the uptake of family planning methods and unplanned pregnancies among 1,100 HIV-infected Ugandans found that 53 % of HIV-positive pregnant women ($n = 216$) did not plan to have their current pregnancy [51]. Mathematical modeling suggests that prevention of unwanted pregnancies among HIV-positive women in its own right could substantially reduce the number of new infant HIV infections. This reinforces the need for better integration of family planning and PMTCT services, including expanding services to ART clinics. Models suggest that elimination of MTCT will require addressing family planning and breast-feeding needs of HIV-positive women.

Despite these challenges, the move toward Maternal and Child Health strengthening/integration through the Global Health Initiative (GHI) will likely improve follow-up/tracking of PMTCT initiatives. In addition, the recent adjustment of the mode of delivery of HIV services by PEPFAR partners to ensure a more comprehensive approach coupled with efforts to increase the existence of partners supporting PMTCT services within districts can be leveraged to improve pediatric care and treatment. Uganda has recently developed several plans and guidelines, including the 2011 integrated guidelines for provision of ART, PMTCT, and infant and young child feeding. These guidelines provide an opportunity to scale up integrated services for HIV-positive Ugandans, including support for the scale-up of PMTCT programs.

Way Forward

Available evidence suggests that biomedical HIV prevention interventions can contribute to significant reductions in the risk of HIV acquisition and transmission [32, 37, 52]. However, to have an effective response, there is a need to combine biomedical HIV prevention interventions together with other interventions including behavioral and structural interventions. Evidence shows that most biomedical interventions depend on the behavioral antecedents of individuals. For instance, studies assessing the efficacy of early ART on HIV infection have found that adherence to ART—a behavioral antecedent of individuals—is key to improved outcomes. In the same vein, behavioral interventions alone nor structural interventions alone cannot stem the tide of the epidemic. It is for this reason that Uganda has adopted a combination HIV prevention approach that involves implementation of biomedical, behavioral, and structural interventions in order to reduce HIV incidence by 30 % by 2015.

Recent findings from the Uganda AIDS Indicator Survey [6] show a worsening trend for sexual risk behaviors among Ugandans. Among men aged 15–49 years, the proportion reporting multiple (2 or more) sexual partners in the past 12 months increased from 24 % in 2001 to 29 % in 2005, and was reported to be 25.4 % in 2011; in this same group, nonspousal sex increased from 28 % in 2001 to 37 % in 2005, and was reported to be 34 % in 2011. Among women aged 15–49 years, the proportion reporting nonspousal sex increased from 15 % in 2005 to 16.6 % in 2011. Among those reporting nonspousal sex, condom use at last higher-risk sex (defined as sexual intercourse with a nonmarital, noncohabitating partner) declined from 53 to 38 % among men and 47 to 29 % among women between 2005 and 2011, suggesting that a significant majority of those who engage in sexual risk behaviors do not use condoms for protection from the risk of HIV infection. Surprisingly, despite these risky behaviors, findings from the 2011 Uganda AIDS Indicator Survey [6] show that two-thirds of men (15–49 years) believe that they have a low risk of getting infected with HIV as opposed to 53.5 % of women of the same age group. The National HIV Prevention Strategy aims to reduce multiple sexual partnerships in the past 12 months by 50% and increase the proportion of Ugandans reporting consistent condom use during risky sexual encounters to 80%. Achieving these targets requires implementation of behavior-change communication programs aimed at reducing sexual risk

behaviors among Ugandans while scaling up biomedical HIV prevention interventions and structural interventions to create an enabling environment within which behavior change can occur.

Structural factors such as HIV stigma and discrimination remain a critical problem in 2011 Uganda. Results from the Uganda AIDS Indicator Survey [6] suggest that up to 60 % of Ugandans want to keep their HIV infection status a secret (and not shared with anyone) because of widespread stigma whereby living with HIV/AIDS continues to be viewed as shameful and the disease perceived to be a result of personal irresponsibility. For instance, about one in five people believe that people with HIV should be ashamed of themselves and blamed for bringing the disease into the community[6]. These findings suggest that stigma still hinders HIV prevention efforts in Uganda. The National HIV Prevention Strategy aims to eliminate stigma and discrimination in order to enhance HIV prevention efforts in the country. Attaining this target would require changing the attitudes of the 16.6 % of women and 21.8 % of men who believe that people with HIV should be ashamed of themselves and the 18 % of women and 22 % of men who believe that people with HIV should be blamed for bringing the disease into the community [6].

There is an acute shortage of health workers in Uganda. At the end of 2009, only 52 % of positions in the health sector were filled [53]. The biggest proportion of unfilled positions was at Health Center II where 64 % positions were vacant, followed by Health Center III with 54 % positions vacant and Health Center IV with 45 % positions vacant. These findings present a precarious situation for the provision of health services in general and HIV prevention services in particular. This means that although HIV prevention services have been rolled down to the lower-level health facilities, e.g., HCT services are now available at 80 % of Health Center IIIs, the provision of these services remains hampered by insufficient numbers of staff. These health worker challenges stem from several factors including inadequate motivation as evidenced by a series of complaints over low salaries and health worker allowances; inability of health systems to recruit and retain sufficient numbers of health professionals (especially skilled workers); slow and lengthy recruitment processes; delays encountered in accessing the payroll; poor working conditions; and high levels of absenteeism possibly owing to low morale [53] . The difficulty in attracting and retaining human resources for health is particularly critical in the remote, rural, and difficult-to-reach and difficult-to-stay districts. Reports from the Ugandan MoH show that medical doctors, dentists, pharmacists, as well as diagnostic personnel are extremely unequally distributed throughout the country, serving only a fraction of the population and providing better coverage in urban areas.

Last but not least, the scale-up of critical HIV prevention interventions will only be possible with increased financial commitments from the Government of Uganda in addition to support from the donor community. On the basis of current estimates from the Uganda AIDS Commission, Uganda requires about US$ 1,023.37 million (about 2.4 trillion Uganda shillings) to significantly reduce new HIV infections in the next 4 years. A recent National AIDS Spending Assessment suggests that the Government of Uganda contributes only 11 % of funding spent on HIV/AIDS, with the majority of funding (68 %) coming from the donor community. The remainder comes from

individual contributions (20 %) and the private sector (1 %). Calls for increased government ownership of HIV/AIDS prevention, care, and treatment programs by the donor community mean that stemming the rising tide of HIV infections will require additional government commitment and support for the next 4 years and beyond.

References

1. Serwadda D, Mugerwa RD, Sewankambo NK, Lwegaba A, et al. Slim disease: a new disease in Uganda and its association with HTLV-III Infection. Lancet. 1985;326(8460):849–52.
2. Slutkin G, Okware S, Naamara W, Sutherland D, Flanagan D, et al. How Uganda reversed its HIV epidemic. AIDS Behav. 2006;10(4):351–60.
3. Green EC, Halperin DT, Nantulya V, Hogle JA. Uganda's HIV prevention success: the role of sexual behavior change and the national response. AIDS Behav. 2006;10(4):335–46.
4. Asiimwe-Okiror G, Opio AA, Musinguzi J, Madraa E, Tembo G, Carael M. Change in sexual behaviour and decline in HIV infection among young pregnant women in urban Uganda. AIDS. 1997;11(14):1757–63.
5. Kirungi WL, Musinguzi J, Madraa E, Mulumba N, Callejja T, Ghys P, Bessinger R. Trends in antenatal HIV prevalence in urban Uganda associated with uptake of preventive sexual behaviour. Sex Transm Infect. 2006 Apr;82:Suppl 1:i36–41.
6. Uganda Bureau of Statistics (UBOS) and ICF International Inc. Uganda AIDS Indicator Survey 2011. Kampala, Uganda/Calverton, Maryland: UBOS/ICF International Inc; 2012.
7. Kasamba I, Baisley K, Mayanja BN, Maher D, Grosskurth G. The impact of antiretroviral treatment on mortality trends of HIV-positive adults in rural Uganda: a longitudinal population-based study, 1999–2009. Trop Med Int Health. 2012;17(8):e66–73.
8. Mills EJ, Bakanda C, Birungi J, Chan K, Ford N, et al. Life expectancy of persons receiving combination antiretroviral therapy in low-income countries: a cohort analysis from Uganda. Ann Intern Med. 2011;155:209–16.
9. Ministry of Health and ORC Macro. Uganda HIV/AIDS Sero-behavioural Survey. Calverton, Maryland, USA: Ministry of Health/ORC Macro; 2006.
10. Wabwire-Mangen F, Odiit M, Kirungi W, Kaweesa Kisitu D. Modes of transmission study, analysis of HIV prevention response and modes of HIV transmission: the Uganda country synthesis report. Kampala, Uganda: GoU/UNAIDS/UAC; 2009.
11. UNAIDS. Knowledge is power: voluntary HIV counselling and testing in Uganda. Geneva: UNAIDS; June 1999.
12. Matovu JK, Gray RH, Makumbi F, Wawer MJ, et al. Voluntary HIV counseling and testing acceptance, sexual risk behavior and HIV incidence in Rakai, Uganda. AIDS. 2005;19:503–11.
13. Were W, Mermin J, Bunnell R, Ekwaru JP, Kaharuza F. Home-based model for HIV voluntary counselling and testing. Lancet. 2003;361(9368):1569.
14. Wolff B, Nyanzi B, Katongole G, Ssesanga D, Ruberantwari A, Whitworth J. Evaluation of a home-based voluntary counselling and testing intervention in rural Uganda. Health Policy Plann. 2005;20(2):109–16.
15. Tumwesigye E, Wana G, Kasasa S, Muganzi E, Nuwaha F. High uptake of home-based, district-wide, HIV counseling and testing in Uganda. AIDS Patient Care STDS. 2010;24(11):735–41.
16. Sekandi JN, Sempeera H, List J, Mugerwa MA, Asiimwe S, Yin X, Whalen CC. High acceptance of home-based HIV counseling and testing in an urban community setting in Uganda. BMC Public Health. 2011;11:730.
17. Nuwaha F, Kasasa S, Wana G, Muganzi E, Tumwesigye E. Effect of home-based HIV counselling and testing on stigma and risky sexual behaviours: serial cross-sectional studies in Uganda. J Int AIDS Soc. 2012;15(2):17423.

18. Matovu JK, Kigozi G, Nalugoda F, Wabwire-Mangen F, Gray RH. The Rakai project counseling program experience. Trop Med Int Health. 2002;7(12):1064–67.
19. Lugada E, Levin J, Abang B, Mermin J, Mugalanzi E, Namara G, Gupta S, Grosskurth H, Jaffar S, Coutinho A, et al. Comparison of home and clinic-based HIV testing among household members of persons taking antiretroviral therapy in Uganda: results from a randomized trial. J Acquir Immune Defic Syndr. 2010;55(2):245–52.
20. UNAIDS. National AIDS programmes: a guide to monitoring and evaluation. Geneva: UNAIDS (UNAIDS/00.17E); 2000.
21. Were WA, Mermin JH, Wamai N, Awor AC, Bechange S, Moss S, Solberg P, Downing RG, Coutinho A, Bunnell RE. Undiagnosed HIV infection and couple HIV discordance among household members of HIV-infected people receiving antiretroviral therapy in Uganda. J Acquir Immune Defic Syndr. 2006;43(1):91–5.
22. Wanyenze R, Kamya M, Liechty CA, Ronald A, Guzman DJ, Wabwire-Mangen F, Mayanja-Kizza H, Bangsberg DR. HIV counseling and testing practices at an urban hospital in Kampala, Uganda. AIDS Behav. 2006;10(4):361–7.
23. Wanyenze RK, Nawavvu C, Namale AS, Mayanja B, Bunnell R, Abang B, et al. Acceptability of routine HIV counselling and testing, and HIV seroprevalence in Ugandan hospitals. Bull World Health Organ. 2008;86:302–9.
24. Nakanjako D, Kamya M, Daniel K, Mayanja-Kizza H, Freers J, Whalen C, et al. Acceptance of routine testing for HIV among adult patients at the medical emergency unit at a national referral hospital in Kampala, Uganda. AIDS Behav. 2007;11:753–58.
25. Baggeley R, Hensen B, Ajose O, Grabbe KL, et al. From caution to urgency: the evolution of HIV testing and counseling in Africa. Bull World Health Organ. 2012;90:652–8B.
26. Allen S, Tice J, Van de Perre P, Serufilira A, Hudes E, Nsengumuremyi F, et al. Effect of serotesting with counselling on condom use and seroconversion among HIV discordant couples in Africa. BMJ. 1992;304(6842):1605–09.
27. Dunkle KL, Stephenson R, Karita E, Kayitenkore K, et al. New heterosexually transmitted HIV infections in married or cohabiting couples in urban Zambia and Rwanda: an analysis of survey and clinical data. Lancet. 2008;371:2183–91.
28. Ministry of Health (MoH). National couplesÊ¼ HIV counseling and 2 communication strategy. Kampala: MoH; 2009.
29. Auvert B, Taljaard D, Lagarde E, et al. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial. PLoS Med. 2005;2(11):e298.
30. Gray RH, Kigozi G, Serwadda D, Makumbi F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007;369(9562):657–66.
31. Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomized controlled trial. Lancet. 2007;369:643–56.
32. Reed JB, Njeuhmeli E, Thomas AG, Bacon MC, et al Voluntary medical male circumcision: an HIV prevention priority for PEPFAR. J Acquir Immune Defic Syndr. 2012;60(Suppl. 3): S88–S95.
33. Ocero AA, Kisembo G, Ciccio L, Fullem A, Beal K. Scaling-up medical male circumcision for HIV prevention in a non-circumcising community. XIX International AIDS Conference, Washington, D.C. July 22–27, 2012. Abstract#: WEPE242.
34. Ndifuna M, Kironde S, Tibenderana E, Serumaga Mulema V, Mutesasira K. Moving from tens to thousands: how using multiple approaches in East Central Uganda is rapidly scaling-up voluntary medical male circumcision in traditionally non-circumcising areas. XIX International AIDS Conference, Washington, D.C. July 22–27, 2012. Abstract#: WEPE241.
35. Buwembo DR, Musoke R, Kigozi G, Ssempijja V, Serwadda D, Makumbi F, et al. Evaluation of the safety and efficiency of the dorsal slit and sleeve methods of male circumcision provided by physicians and clinical officers in Rakai, Uganda. BJU Int. 2012;109(1):104–8.
36. Kigozi G, Musoke R, Watya S, Kighoma N, et al. The acceptability and safety of the Shang Ring for adult male circumcision in Rakai, Uganda. J Acquir Immune Defic Syndr. 2013 Apr 22 [Epub ahead of print].

37. Gray R, Kigozi G, Kong X, Ssempijja V, Makumbi F, Watya S, et al. The effectiveness of male circumcision for HIV prevention and effects on risk behaviors in a post-trial follow-up study. AIDS. 2012;26(5):609–15.
38. Wawer MJ, Kigozi G, Serwadda D, et al. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomized controlled trial. Lancet. 2009;374:229–37.
39. Baeten JM, Donnell D, Kapiga SH, et al. Male circumcision and risk of male-to-female HIV-1 transmission: a multinational prospective study in African HIV-1 serodiscordant couples. AIDS. 2010;24(5):737–44.
40. Weiss HA, Hankins CA, Dickson K. Male circumcision and risk of HIV infection in women: a systematic review and meta-analysis. Lancet Infect Dis. 2009;9(11):669–77.
41. Wawer MJ, Tobian AA, Kigozi G, Kong X, Gravitt PE, Serwadda D, Nalugoda F, Makumbi F, et al. Effect of circumcision of HIV-negative men on transmission of human papillomavirus to HIV-negative women: a randomised trial in Rakai, Uganda. Lancet. 2011;377(9761):209–18.
42. Katabira E, Kamya M (edtors). National antiretroviral treatment and care guidelines for adults and children. Kampala, Uganda: Ministry of Health; 2003.
43. Guay LA, Musoke P, Fleming T, Bagenda D, Allen M, Nakabiito C, Sherman J, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet. 1999;354(9181):795–802.
44. WHO. Use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. Geneva: WHO; 2012.
45. Commission UAIDS. Mid-term evaluation of the National HIV and AIDS Strategic Plan (2007/08–2011/12). Kampala: Uganda AIDS Commission; 2011.
46. Albert LM, Akol A, L'Engle K, Tolley EE, et al. Acceptability of male circumcision for prevention of HIV infection among men and women in Uganda. AIDS Care. 2011;23(12):1578–85.
47. Ministry of Health. Integrated national guidelines on antiretroviral therapy, prevention of mother to child transmission of HIV and infant & child feeding. Kampala, Uganda: Ministry of Health; 2011.
48. Kigozi IM, Dobkin LM, Martin JN, Geng EH, Muyindike W, et al. Late-disease stage at presentation to an HIV clinic in the era of free antiretroviral therapy in sub-Saharan Africa. J Acquir Immune Defic Syndr. 2009;52(2):280–89.
49. Wanyenze RK, Kamya MR, Fatch R, Mayanja-Kizza H, Baveewo S, Sawires S, et al. Missed opportunities for HIV testing and late-stage diagnosis among HIV-infected patients in Uganda. PLoS One. 2011;6:e21794.
50. Jain V, Byonanebye D, Muhaawe J, Kabami J, Black D, et al. Patient attitudes toward initiating early antiretroviral therapy at high CD4+ cell counts above national guideline thresholds. XIX International AIDS Conference, Washington, D.C. July 22–27, 2012. Abstract#: TUPE081.
51. Wanyenze RK, Tumwesigye NM, Kindyomunda R, Beyeza-Kashesya J, Atuyambe L, et al. Uptake of family planning methods and unplanned pregnancies among HIV-infected individuals: a cross-sectional study among clients at HIV clinics in Uganda. J Int AIDS Soc. 2011;14:35.
52. Cohen MS, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, et al. HPTN 052 study team. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365:493–505.
53. Matsiko D. The Uganda country case study: enhancing health worker and health system performance. The Global Health Workforce Alliance; 2010.

Chapter 11
Implementing Biomedical HIV Prevention Advances in Thailand

Suwat Chariyalertsak, Kriengkrai Srithanaviboonchai and Nittaya Phanuphak

In the early to mid-1980s, while other parts of the world were beginning to deal with serious HIV epidemics, Asia remained relatively unaffected. By the early 1990s however, AIDS epidemics had emerged in several Asian countries, and by the end of the decade, HIV was spreading rapidly in many countries of this continent including Thailand [1].

Thailand is frequently cited in the HIV prevention literature as a key example of success relative to other developing countries in the world, in regards to its public policy on preventing the epidemic of HIV on a national scale. In the mid-1990s, a massive program began to control HIV through reducing visits to commercial sex workers by half, raising condom usage by promoting "the 100 per cent condom use" program, decreasing the prevalence of sexual transmitted infections (STIs) dramatically, and achieving substantial reductions in new HIV infections especially among heterosexual populations for the past three decades. Thailand's prevention efforts in the previous three decades have averted more than 6 million HIV infections, and the current number of annual new HIV infections has decreased from more than 130,000 cases in the early 1990s to approximately 10,450 estimated new infections in 2011. Even with this decrease in infections, however, more than 1.1 million Thais have been infected with HIV since the mid-1980s. Of those, approximately half of them have passed away, leaving an estimated 500,000 Thai adults and children living with HIV throughout the country in 2011 [2]. Figure 11.1 shows the total number of

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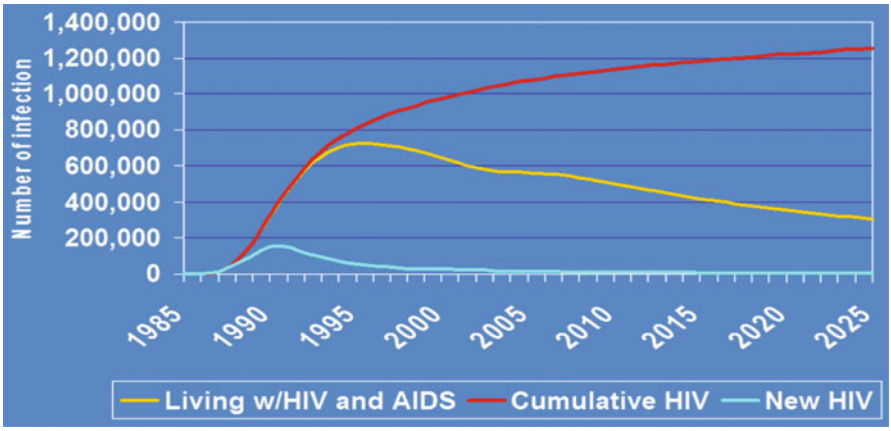

Fig. 11.1 Projection of HIV infections and AIDS in Thailand, 1985–2025. (Developed by Wiwat Peerapatanapokin MD; [3])

adults currently living with HIV, new HIV infections, and cumulative HIV infections over time in Thailand between 1985 and 2025.

In 2001, the Thai government made a commitment to providing antiretroviral (ARVs) drugs free of charge to people living with HIV under the National Access to Antiretroviral Program for People Living with HIV/AIDS (NAPHA) [4]. Initially, branded drugs were mostly available. However, there was a subsequent increase in the production of less expensive generic drugs plus the issuing of compulsory license for some high-cost ARV drugs (efavirenz, lopinavir/ritonavir). The use of generic drugs led to more than an eightfold expansion in treatment provision between 2001 and 2003, with only 40 % increase in government budget [4]. According to the 2012 Global AIDS Response country progress report for Thailand, 225,272 (64.61 %)of eligible adults and children living with HIV and AIDS are on antiretroviral therapy [2].

However, successes in the field of HIV treatment can be unsteady and the country needs to reinvent and enhance its efforts in both HIV treatment and comprehensive prevention programs. These programs need to include new biomedical prevention technologies such as male circumcision, oral Preexposure Prophylaxis (PrEP), and vaginal microbicides. Unless past efforts on effective HIV prevention strategies are sustained and new sources of infection are addressed appropriately, the striking achievements made in controlling the HIV epidemic could now be put at risk. Factors such as an increase in risky sexual behavior among young people, men who have sex with men (MSM) including transgender women (TG), and a rising number of STI cases among these subpopulation have led to concern that Thailand could face a resurgence of the HIV/AIDS epidemic in coming years [5].

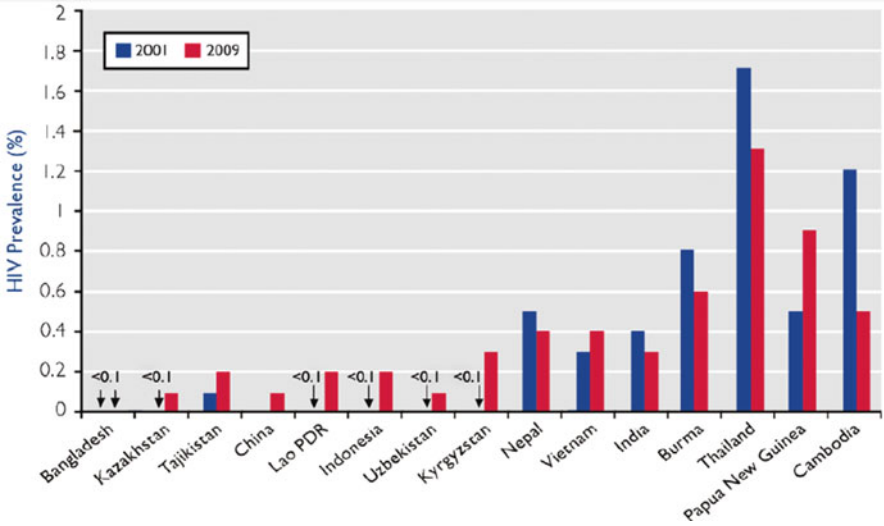

Fig. 11.2 HIV prevalence among selected countries in Asia between 2001 and 2009. (Source: UNAID Report on the Global AIDS Epidemic 2010. No data are available for Turkmenistan or for 2001 in China)

Status of the HIV/AIDS Epidemic in Thailand: Past, Present, and Future

Since 1981, when the first cases of AIDS were reported, HIV infections have grown massively across the globe and the epidemic has emerged as the most formidable challenge to public health and development. In Asia, the first few cases were reported among homosexual men in Thailand in 1984, after which the disease continued to spread throughout the regions. Since the epidemic's peak in 1996, new HIV infections in South and Southeast Asia have declined by 40 %. HIV prevalence among the general adult population in South and Southeast Asia is 0.3 % compared with East Asia, where the HIV prevalence is 0.1 % [6]. HIV incidence continued further declining between 2001 and 2010, although the number of people living with HIV/AIDS (PLWHA) increased. There were 360,000 people newly infected with HIV in 2010 compared with 450,000 in 2001. However, about 4.8 million people were living with HIV in the region in 2010, 11 % more than the 4.2 million people in 2001.

Thailand still has the highest adult HIV prevalence in Asia (HIV prevalence in adults was at 1.3 % in 2009). At present, this region has the second highest burden of HIV/AIDS in the world after sub-Saharan Africa [7] (Fig. 11.2). Even though Thailand has had a National Strategic Plan on HIV/AIDS since 1992 which helped the country succeed in rapidly slowing the spread of HIV during the decade that followed, HIV has continued to spread (heavily in the Upper-North region especially

in Chiang Mai, Chiang Rai, and Phayao provinces) during the first decade among the general population. In particular, this spread has affected female sex workers (FSW), MSM, and people who inject drugs (PWID).

Although HIV prevalence among pregnant women declined from its peak of 3.4 % in 1992, to less than 1 % in 2009, data regarding the risk behaviors among youth demonstrated an increasing trend of having sex without using condoms—potentially contributing to the increased risk for STIs and unwanted pregnancy. The number of teenage births per 1,000 girls aged 15–19 years had increased from 33.7 in 1989 to 50.1 in 2010 [2]. Data from the HIV Sentinel Surveillance Survey among venue-based FSW found that HIV prevalence among these women had declined steadily over time: 2.8 % to 2.2 % and to 1.8 % in 2008, 2010, and 2011, respectively. Condom use with the last customer was reported by 95.7 % of FSW; yet only 45.4 % of FSW reported using condoms with a lover or husband. The recent evidence from HIV prevalence surveys among nonvenue-based FSW in three big tourist cities, Chiang Mai, Phuket, and Chonburi, revealed higher HIV prevalence than venue-based FSW. The level of HIV infection in nonvenue-based FSW was 2.6 % among the younger than 25 years' age group. This is of great concern since proportionally more of the nonvenue-based FSW are outside of the formal HIV prevention program than the venue-based FSW. In addition, they may not fully adhere to "the 100 % condom use program" and have the same level of care and information about prevention of HIV and STIs services as FSW in venue-based settings. An effective approach for HIV prevention among this hard-to-reach group needs to be urgently developed and implemented.

Besides FSW, the increasing burden of HIV infection documented among MSM and TG in many countries in the Asia-Pacific region constitutes an urgent health crisis. Since 2003 in Thailand, the rapid spread of HIV among MSM and TG has been determined from *Integrated Biological and Behavioral Sentinel Surveillance* (IBBS) which collected data in large tourist cities (Thailand IBBS report: 2003, 2005, 2007, and 2010). In Bangkok, the HIV prevalence among MSM grew from 17.3 % in 2003 to 28 % in 2005, to 30.8 % in 2007, and to 31.3 % in 2010. In Chiang Mai, the HIV prevalence was 15 % in 2005, 17 % in 2007, and 13 % in 2010. In Phuket, the HIV prevalence was 5.5 % in 2005 and 6.9 % in 2010, with no indication of declines in the near future. There were also significant differences in HIV prevalence by age. The HIV prevalence survey among MSM in 2010 revealed that HIV prevalence among MSM aged 25–29 years was 32.4 % while the rate among those in the age group of 15–24 years was 12.1 %. The trend of HIV prevalence among TG was lower than MSM. The IBBS survey among TG from 12 provinces in 2010 revealed an HIV prevalence of 10.4 % (varied from 5.5 % –16 %) [8]. But the trend did not decline over the past years. Among male sex workers (MSW), the trend of HIV prevalence from the sentinel surveillance sites also did not decline and was still high at 16 % in 2010.

The prevalence of HIV among PWID attending detoxification centers is still high at around 30–40 % in the past years. The IBBS conducted in 2010, using the respondent driven sampling (RDS) method to represent PWID in communities, revealed HIV prevalence at 21.9 % [2].

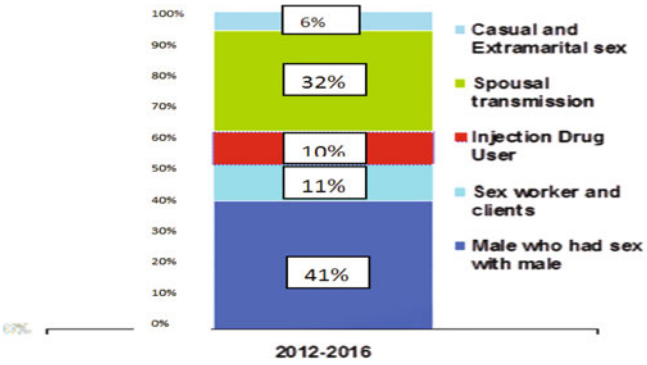

Fig. 11.3 Categories of new HIV infections in Thailand, 2012–2016. (Source: The Asian Epidemic Model estimates that 43,000 new infections will occur from 2012–2016)

Finally, HIV prevalence among migrant workers who have come to Thailand in large numbers from Myanmar, Laos, and Cambodia is around 2.5 %, a rate that is much higher than that of the general Thai population. This rate reflects a need for improved access to HIV prevention programs and health services in the country for these migrant populations.

The Asian Epidemic Model (AEM) and policy analysis were used to estimate new HIV infections as well as number of people living with HIV (PLHIV) for the purpose of planning for the antiretroviral treatment (ART) program. It is estimated that 43,040 new infections will occur during 2012–2016. Among the estimated number of new infections, 41 % will be through transmission among MSM and 32 % will be through intimate partners. The proportion of new HIV infections among risk groups in the past decade showed the different direction between MSM and spousal transmission [9] (Fig. 11.3).

In summary, the epidemiological and behavioral data indicate that the number of new HIV infections in Thailand has decreased in general. However, a trend of increasing spread of HIV is noted among key affected populations including MSM, TG, MSW, FSW, and PWID as well as certain subgroups of general population [2].

Thailand recently began an acceleration plan for reducing HIV incidence among its most vulnerable populations. Equipped with support from the Global Fund (Round 8) and technical assistance from various United Nations (UN) agencies, Thailand remains determined to meet its targets outlined in its new National AIDS Strategy for 2012–2016. There remain several challenges to Thailand's vision of the three zeros: zero new infections, zero AIDS-related deaths, and zero stigma and discrimination. Among these challenges are the fragmented responses to HIV among government agencies, demographic and epidemiologic changes, and a rapidly moving political decentralization process. The nation has set a $ 1.4 billion (43,000 million baht) budget for implementation of the National AIDS strategic plans from 2012–2016 with a target goal of having fewer than 4,900 new HIV-infected persons by 2016. It is often thought that due to the huge cost of treating AIDS patients, HIV should

also be considered an economic issue for the country. Many believe that in order to lessen the economic burden, effective HIV prevention strategies include new biomedical HIV prevention technologies for fighting against HIV epidemic in the next decade [10].

Achievement and Barriers in Using Available Effective HIV Prevention Strategies in Thailand

Thailand has been frequently praised as an example of a rare success story fighting against HIV/AIDS within developing countries [11]. While the country has showed progress and achievements in both HIV prevention and HIV care and support, we will focus only on HIV prevention for this part in which the HIV prevention measures that were considered achievements will be discussed. These include HIV Voluntary Counseling and Testing (VCT) services, the 100 % Condom Campaign, prevention of mother to child HIV transmission (PMTCT), and antiretroviral therapy as HIV prevention.

HIV Voluntary Counseling and Testing

Although HIV VCT is not considered to be an HIV prevention strategy by itself, it is the entry point for prevention and care interventions. Health academics and policy makers in Thailand recognized the importance of HIV testing and psychological support for people who have been HIV infected since the early stages of the HIV epidemic when there were no effective medications and the levels of stigma and discrimination were high.

The first anonymous HIV testing clinic named "Eungpung Clinic" was established in Chiang Mai, northern Thailand in 1991 under the support from Norwegian Church Aid [12]. Not too long after that, the Thai Red Cross opened its anonymous clinic in Bangkok. The two clinics served as role models for the HIV counseling and testing activities that were about to follow.

In 1993, the Department of Mental Health, Ministry of Public Health (MOPH) took the lead in a nation-wide program aimed to establish HIV VCT service in public hospitals. Since there was generally no professional counselor positioned in the hospitals, nurses were usually trained to be HIV counselors. The standard HIV counseling training course was 5 days long and focused on basic HIV pre- and posttest counseling. Subsequently, HIV VCT service was initiated in every public hospital in the country within 3 years [13]. Networks of HIV counselors at provincial and regional level were also organized in order to support the trained HIV counselors. Ultimately, these counselors/nurses played a central role in implementing HIV-related tasks in the hospitals including PMTCT and ART programs. Although a variety of

HIV counseling techniques and programs were later introduced (same day HIV testing, premarital counseling, couple counseling, family counseling, drug adherence counseling, provider-initiated HIV counseling and testing (PICT), etc.), none were adapted to full capacity like the basic pre- and posttest counseling.

The knowledge that ART reduces the possibility of sexual HIV transmission among serodiscordant couples raised the significance of HIV VCT since it is the main entry point for ART treatment. Recent reports have revealed that the coverage of HIV VCT among key affected populations namely MSM, sex workers, intravenous drug users, and prisoners are still low [2]. New strategies to increase the coverage of HIV VCT services among these populations must be put in place in order to achieve HIV prevention through this "Treatment as Prevention" (TasP) strategy. These strategies include rapid HIV testing, mobile VCT, routine HIV testing, and public communication toward normalization of HIV testing including a campaign promoting National HIV testing days. It is the crucial challenging implementation for Thailand to move into these next steps of HIV testing effectively.

100 % Condoms Campaign

Thailand's 100 % Condoms Campaign was frequently cited as an achievement in terms of HIV prevention programs [14]. The program was based on a decisive national policy and was implemented through a strong public health system that was already in-place. The campaign focused on direct sex establishments, which included brothels, massage parlors, bars, and restaurants. This health intervention was unique in the way that it reflected the flexibility of Thai society in which certain rules could be dropped if the foreseen collective benefit was large enough. The premise of the program was cooperation among three local parties namely the health authorities, the sex establishments, and the policemen. They all worked together to ensure that condoms were used among FSW and their customers. Health care personnel provided HIV education, STI screening and treatment, and guaranteed continued supplies of free condoms. While prostitution was illegal, under this initiative the authorities promised to the employers that the policemen would allow their businesses to continue as long as they complied with the health interventions.

The program was piloted in Ratchaburi province in central Thailand in 1989 and was eventually adopted throughout the country in 1992 [15]. A study found that HIV incidence among military conscripts in the North, typical customers of the target sex establishments, was 78 % lower at the peak of the intervention compared to the beginning of the program [16]. In a review article [15], Rojanaphithyakorn, who was the director of the program, cited the following as key factors to the success of the campaign: public perception that the program focused on health and not on prostitution, strong public health infrastructures, good liaison between the health authorities and the owners of the brothels, and the nonconfrontational approach of the Thai culture.

In recent years, the sex businesses in the country have dramatically changed in that they provide services from "direct" to "indirect." The indirect sex services were nonvenue based and the service providers tended to hide their status, so it was difficult to identify the target groups since the authorities did not know where they were. The restructuring of the health authorities in regards to STI screening and treatment responsibilities that were transferred from the provincial health offices to the hospitals, whose personnel had less field work experiences, also weakened the effectiveness of the campaign. Thailand now faces the challenging situation of how to reduce the risk of HIV transmission in the context of the current sex services.

Prevention of Mother to Child HIV Transmission

If strict scientific definition is followed, PMTCT is probably the only biomedical HIV prevention strategy that has been successfully implemented in Thailand. All parties viewed high prevalence of HIV infection in pregnant women during the first half of 1990's as a public health crisis. Shortly after AIDS Clinical Trial Group Study 076 (ACTG 076) demonstrated the efficacy of zidovudine (AZT) in reducing the risk of mother to child HIV transmission, the Thai Red Cross AIDS Research Center took the lead regarding this intervention by initiating the PMTCT program in 1996. The project was under the patronage of Royal Highness Princess Soamsawali and used the ART regimen that was modified from ACTG 076. The project sought donations from the general public and requested cooperation from the hospitals throughout the country [17]. The campaign also caught the attention from academics, MOPH, and the general public.

Since the intervention used in ACTG 076 was considered expensive and too complicated to implement in developing countries, a randomized, double-blind, placebo-controlled trial to evaluate the efficacy of short course zidovudine in PMTCT was conducted in Bangkok during 1996–1997. It was found that the transmission rate could be reduced by half with this simpler regimen [18]. Although there were extensive debates whether it is ethical to do a placebo-controlled trial given that an effective intervention was already in place, the ART regimen used in this study became a basis for later PMTCT programs in developing countries.

After successfully piloting a PMTCT program in Bangkok and the North-eastern region, the Department of Health, MOPH, scaled up the program to all government hospitals in 2000 [19]. In order to achieve high coverage of HIV testing, the opt-out strategy, where every pregnant woman was offered HIV testing and had to actively deny the offering, was used. Since 2010, the National PMTCT program has recommended the use of three-drug PMTCT regimens in HIV-infected pregnant women regardless of their CD4 count [20]. With more effective ART regimens, the transmission rate has been steadily reduced. The most recent figure showed that the transmission rate from infected mother to child in 2011 was at 3.2 % [2].

One key success factor of the PMTCT program in Thailand was high coverage of antenatal care and delivery. Other elements that helped to preserve the quality and sustainability of the program included un-interrupted supplies of medications, precision laboratory tests, and continued training and supervision. However, there are still some remaining challenges faced by the PMTCT program.

Antiretroviral Treatment as Prevention

It may be strange to view ART as a biomedical HIV prevention since it was originally aimed for, as the name implies, treatment for HIV infected individuals. However, the effectiveness of ART for prevention of HIV transmission has been demonstrated by the results of HPTN 052 in 2011 [21]. Thailand was criticized for spending too much money on treatment, especially the ART program, and too little on HIV prevention. Ironically, in retrospect, ART was perhaps the most important and cost effective HIV prevention that the country has invested in during the past decade. Although we do not know the impact of this unintentional intervention, it is worth investigating the history of this important HIV prevention strategy.

The first public health program to provide Highly Active Antiretroviral Treatment (HAART) to patients was called Access to Care (ATC) and was started in 2000. The national ATC project was announced in Chiang Mai on the Saint Valentine day of the year 2001. The program was piloted in Northern Thailand under the coordination of the Office of Disease Prevention and Control 10 (DPC 10). Promptly after the project was acknowledged, the DPC 10 staff organized a steering committee meeting involving all stakeholders in HIV/AIDS issues in the region to discuss how to administer the project. Representatives from community based organizations (CBO), PLWHA, nongovernment organizations (NGOs), academics from universities, and DPC 10 staff were then appointed by the steering committee to form a technical working group [22].

Access to HAART would soon be increased by three main factors: (1) the production of a generic, fixed dose combination pill by the Government Pharmaceutical Organization (GPO) in 2002, (2) assistance from the Global Fund to finance the medications and needed infrastructures, and (3) more government spending on the treatment program. The HAART program was later transferred to respective health insurance systems in 2007. Currently, more than 200,000 patients receive medications at around 1,000 health care facilities throughout the country free of charge.

As TasP is considered to be one of the most important strategies for HIV prevention in the near future, Thailand needs to address existing limitations and challenges for the ART program in order to cover more HIV-infected individuals at the earlier stage of infection. For example, 51.9 % of patients who started ART in 2009 had AIDS symptoms and/or CD4 levels less than 100 cells/mm [23]. Some key affected populations such as people who inject drug (PWID) and migrant workers still did not have full access to the treatments. Also, HIV testing must be promoted and normalized in order to increase demand among the general public as well as key affected populations.

Current Situation and Perspectives on New Biomedical HIV Prevention Technologies Among Different Governmental and Nongovernmental Stakeholders in Thailand

Thailand is also participating in randomized, controlled trials of PrEP to follow-up on Iniciativa Profilaxis Pre-Exposición (iPrEx), the study that tested the use of daily oral emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) as PrEP among MSM and TG and demonstrated an efficacy of 44 % in preventing HIV infection [24]. The subsequent iPrEx open-label extension (OLE) is ongoing to determine how adherence and risk behavior may change now that people know PrEP can reduce HIV infection. The Bangkok Tenofovir Study (ClinicalTrials.gov number NCT00119106) has been completed with Thai PWID. This double-blind phase III trial enrolled 2,413 participants and found that 17 participants who received tenofovir became HIV infected during the follow-up period compared with 33 % in the placebo group, a 49 % difference [25].

Two study sites in Thailand are currently conducting the Microbicide Trials Network Protocol 017 (MTN-017) study (ClinicalTrials.gov number NCT01687218) which is a phase II safety and acceptability study of daily oral FTC/TDF, daily rectally applied 1 % reduced-glycerin tenofovir gel, and coitally dependent use of 1 % reduced-glycerin tenofovir gel among MSM. One study site in Bangkok is also participating in the HPTN 067 (ADAPT) study (ClinicalTrials.gov number NCT01327651), a phase II study to examine the feasibility of oral FTC/TDF taken daily, twice weekly, and on a coitally dependent basis among MSM and TG. These studies are trying to determine the optimal methods of delivering oral and rectally applied PrEP which aim at enhancing PrEP adherence while reducing its adverse effects.

The HTPN 052 study which aimed to study HIV prevention effect of early ART for seropositive partners of the serodiscordant couples also had Thailand as one of the study sites. This study successfully proved the efficacy of the TasP concept and demonstrated 96 % reduction in HIV infection among seronegative partners of the index patients in the early treatment arm compared to the delayed treatment arm [21].

Thailand is also the study site for the ongoing PROMISE study (ClinicalTrials.gov number NCT00955968) which compares the preservation of maternal health among postpartum women who received ART for PMTCT and then discontinue ART after delivery or continue ART after delivery (this equals PMTCT option B+).

Current scientific evidences on PrEP and TasP have led nongovernmental and governmental stakeholders in Thailand to the mutually agreed question of “how and when” the country should implement the strategic use of ARV for HIV prevention. These strategies are not 100 % effective and require broad uptake and high adherence for effectiveness. In December 2010, after the launch of iPrEx study result, the first national stakeholder consultation on future action for PrEP was held in Bangkok with support from World Health Organization (WHO) and AIDS Vaccine Advocacy Coalition (AVAC) [26]. An overall 44 % HIV prevention efficacy of PrEP was seen as too low to consider rolling out the program at that time. It was clear, however, that PrEP would need to be part of a comprehensive HIV prevention package.

Following the 6th IAS Conference on HIV Pathogenesis, Treatment, and Prevention in Rome in July 2011 where results from the TDF2 study (62 % efficacy of oral FTC/TDF) [27] and the Partners PrEP study (67 % efficacy for oral TDF and 75 % for oral FTC/TDF) [28] were released, the Asian Regional Consultation on HIV PrEP was held in October 2011 in Bangkok as part of the collaborative effort by WHO, UNAIDS, Imperial College of London, the London School of Hygiene & Tropical Medicine, and Georgetown University, with support from the Bill & Melinda Gates Foundation. Research and civil society stakeholders from Thailand and other ten Asian countries including China, Cambodia, India, Indonesia, Malaysia, Myanmar, Nepal, the Philippines, Sri Lanka, and Vietnam, composed of people from various sectors, e.g., Ministry of Health, National AIDS Control Program, country Food and Drug Administration, researchers, local HIV/AIDS and MSM NGOs, joined this consultation meeting and proposed short-term and long-term steps needed for PrEP implementation in the region, along with identifying research gaps. Results from a survey conducted by the Imperial College London among MSM in Bangkok and Chiang Mai were presented which showed 70 % of MSM who said they would use PrEP as soon as it becomes available. There was another survey conducted in Chiang Mai in February 2012 about acceptability of HIV PrEP with oral FTC/TDF among MSM and TG, which revealed that 41 % of MSM and 37 % of TG were "very likely" to use PrEP; including respondents who were "somewhat likely" to use PrEP, the rates increased to 75 % for MSM and 77 % for TG [29]. Not surprisingly, besides Thailand, most of the presentations from the representatives of each country revealed that using PrEP as a new biomedical HIV prevention strategy was a relatively new phenomenon. The need for frequent HIV testing and the time needed to spend on PrEP services were the two major concerns among potential PrEP users.

With publicly available PrEP information and the promising results from the HPTN 052 study, Thailand held its National Consultation on the Strategic Use of ARVs in August 2012 [30]. Action items were identified within six major work streams which included a service delivery model, monitoring and evaluation system, policy recommendations on testing and treatment, modeling on ARV use as prevention, operational research, and public communications. This consultation has led to the formation of three National Working Groups on HIV Counseling and Testing, HIV Treatment and Care, and Modeling for Strategic Use of ARVs for HIV Prevention. The three working groups consist of representation from academics, research field, and civil society and are now working collaboratively to best position Thailand in roll-outing prevention technologies.

HIV counseling and testing is the most critical step for the planning of any strategies which use ARVs for HIV prevention. Early and regular HIV counseling and testing is necessary as an entry point for high-risk HIV-negative persons into a PrEP program and for HIV-positive persons in early stage of HIV disease into a TasP program. Repeated HIV counseling and testing is also a key to the PrEP program in order to prevent HIV drug resistance among PrEP users who seroconvert during the use.

Thailand is now aiming for the use of 1-hour HIV test result [31]. Clearly, the sense of urgency of HIV testing is lacking in the country. It will need extensive and collaborative works from various stakeholders in order to change the whole mindset of counselors, medical professionals, laboratory technicians, and most importantly the target population for HIV counseling and testing in the country. Public communications and trainings for health care professionals are now working toward this national goal. Based on the same goal, the Medical Technology Council of Thailand is considering recommending this new turnaround time for HIV testing in its guidelines. This turnaround time will be achieved by revising the machine-based HIV testing algorithm and the management system in the facility-based settings and implementing the rapid HIV testing algorithm in community-based settings. Representatives from the NGOs, laboratory professionals, and medical professionals are planning to work with the National Health Security Office Program to establish a lower reference price for rapid HIV tests to be used in Thailand (the current price is approximately US$ 4 per test).

Community-based testing and counseling has been demonstrated to be successful, especially among MSM and youths, in several pilot studies in the urban and rural settings throughout Thailand. The NIMH Project Accept/HPTN 043, a multicountry study which was also conducted in Thailand, demonstrated that community-based counseling and testing can identify more HIV-positive people than a facility-based setting [32]. It can also detect HIV-positive people at an earlier stage in the course of their HIV infection [33]. Compared to a facility-based testing and counseling service in Bangkok where 60 % of MSM clients who tested HIV-positive (29 % HIV prevalence) had CD4 count < 350 cells/mm^3 which means they were already eligible for ART [34], only 40 % of MSM who tested HIV positive in the mobile clinics in sauna and spa venues in Bangkok (18 % prevalence) had CD4 count < 350 cells/mm^3 (Phanuphak N, personal communication). Task shifting of HIV counseling and testing to civil society and private facilities and various options to shorten the pretest counseling session, including telephone or group pretest education, are in the planning steps. There is also a focus on how to get Thai people and health systems ready for HIV selftesting as the test is already available over the internet and its use is expected to increase. Structural barriers for HIV counseling and testing among youths under 18 years of age in Thailand have long been discussed and now are in the final stages of review by the MOPH and the Medical Council of Thailand.

The 2010 Thai National Guidelines on ART for HIV-1 Infected Adults and Adolescents recommended ART for everyone with a CD4 count < 350 cells/mm^3 and have the following criteria: for ART initiation regardless of CD4 count active tuberculosis, hepatitis B, hepatitis C, HIV nephropathy, and those who are > 50 years of age [35]. Long-term adherence among HIV-positive people who start ART early while they are healthy is the main concern and measures to increase ART adherence are in need. With the goal to achieve ART for all regardless of CD4 count, the current priority groups of population for the implementation of TasP in Thailand include pregnant women (PMTCT option B+), seropositive partners of the serodiscordant couples, and MSM. It was agreed that, in order to possibly avoid unnecessary stigma and discrimination issues when implementing TasP programs, PWID and sex workers

would be included in the program when the country is ready for ART for all regardless of CD4 count [36]. Task shifting of HIV treatment and care by the training of nurses and other nonmedical personnel has been used for more than a decade in Thailand and the country now plans to work with the Nurse Council of Thailand to officially certify trained nurses for ART refill without the need for doctors' supervision. Decentralizing HIV treatment and care to subdistrict health care centers and civil society are also part of the next steps.

Thailand recognizes that demonstration projects on strategic use of ARVs for HIV prevention are needed and are the most powerful advocacy tools given if they are implemented with rigorous measurement and evaluation. Currently, Thailand is implementing a demonstration project on the Test and Treat strategy among Thai MSM and TG in three provinces with in-country financial and logistical supports. This project will test the feasibility of repeated HIV testing among HIV-negative participants and the acceptability of and adherence to immediate ART among participants who are tested positive in the project. Additional national consultation on PMTCT option B+ and follow-up consultations on PrEP are planned. The plan for PrEP demonstration projects among high-risk populations such as MSM and seronegative partners in serodiscordant relationship is now being discussed.

Challenges and Controversies on Rolling-Out and Implementing New Biomedical HIV Prevention Strategies in Thailand

Lessons Learned

All successful HIV prevention interventions in Thailand in the past few decades shared similar characteristics. These include scientific leadership from health academics as the starter. The consensus for the necessity of the program was usually based on relevant novel scientific findings and concrete epidemiological data. Most of the time, the interventions were piloted in a small number of clients in small geographical areas before scaling up. A governmental public health agency who acts as the program coordinator in order to help sustain the implementation of the program is of critical importance. All strategies that are considered a success have effectively dealt with the needs of target groups who are easy to reach, for example, HIV-infected pregnant women in the case of PMTCT. This may explain why Thailand has not achieved high coverage of HIV prevention services among hard-to-reach population such as indirect sex workers, MSM, TG, and PWID.

As mentioned previously, Thailand is one of the several sites worldwide, where a variety of PrEP clinical trials are underway such as Global iPrEx that studied among MSM and TG populations in Chiang Mai and the PrEP study among PWID in Bangkok. There will be another microbicide trial conducted under the Microbicide Trials Network (MTN) namely MTN 017 study, which will be a phase II study for testing the rectal microbicide gel in MSM participants that will be conducted in four

countries using six sites, including two sites in Thailand (Chiang Mai and Bangkok) in early 2013.

Since the initial results of Global iPrEx were announced in November 2010, other important trial results have followed from studies conducted in 2011 and 2012. Despite the initially successful iPrEx outcomes at that time, the challenges in translating research into effective implementation could be considerable, particularly in terms of delivering PrEP as part of a comprehensive HIV prevention package and ensuring adequate and sustained financing for new programs. Additional studies on certain issues related to PrEP implementation, monitoring, and evaluation will almost certainly be needed.

There have been two consultative meetings (one National and one Asian regional) on PrEP conducted in Bangkok in the past few years as mentioned previously [25]. The consensus among stakeholders was that PrEP is not to be regarded as a standalone solution and should not replace condoms, but should only be used as part of a comprehensive HIV prevention package; sustained financing for new programs is to be ensured, and there is consensus that people need ongoing reminders about the effectiveness of condoms and encouragement to keep using them.

A number of unresolved research questions were raised by participants from these consultative meetings. These questions included different dosing strategies for PrEP, routes of PrEP administration (injection, oral, vaginal, and rectal gels), using PrEP and ART as prevention in serodiscordant couples, impact of PrEP use on risk compensation, research needs that involve TG, understanding acceptability of PrEP in the country, how to increase drug adherence among PrEP users, how to monitor safety and drug resistance, how to provide regular VCT services for people who are on PrEP, drug interaction between PrEP and hormone use especially in TG, and the operational research about optimization/different service deliveries for PrEP strategies as a pilot study in the country before implementation on a wide scale.

In conclusion, there is no "magic bullet" for HIV prevention. None of the new prevention methods currently being tested is likely to be 100 % effective, and all will need to be used as part of combination packages. The following are a number of key recommendations that need to be addressed for national policy on any new biomedical HIV prevention technologies including PrEP to be implemented:

- PrEP implementation must occur as an integral part of comprehensive HIV prevention programs.
- PrEP implementers must take an integrated approach, bringing together related prevention, treatment, and care systems and processes, getting buy-in from policymakers, working with media, continued use and enhancement of existing tools and programs, and collaborating actively with community members.
- The rights of affected people, including key groups with high risk-associated behaviors and PLWHA must be considered during any implementation process. More opinions and information need to be collected from MSM, TG, FSW and MSWs, and other groups of most-at-risk before an implementation strategy is designed and adopted.
- Clear and efficient public communication and education strategies to introduce PrEP and other new biomedical HIV prevention technologies to the general public

are needed in advance to prevent misunderstandings and misinformation within affected communities and society as a whole.

- A practical way forward before implementing PrEP or other new biomedical technologies is to begin with demonstration projects examining the feasibility, health service system to deliver PrEP, communication with community, and social strengthening. The outcome of these demonstration projects will help the country gain more experiences and learn how to scale-up PrEP as a new biomedical HIV prevention strategy for specific target populations which are most-at-risk for HIV infection in Thailand.

References

1. AVERTing HIV and AIDS. HIV and AIDS in Asia [Internet]. United Kingdom: AVERTing HIV and AIDS. 2013. http://www.avert.org/aids-asia.html. Accessed 26 Sept 2012.
2. National AIDS Committee Thailand. Thailand global AIDS response progress report [Internet]. 2012. http://www.aidsdatahub.org/dmdocuments/UNGASS_2012_Thailand_Narrative_Report.pdf. Accessed 26 Sept 2012.
3. National Consultation on the Strategic Use of ARVs. Report on National Consultation on the Strategic Use of ARVs, 9–10 August 2012, Bangkok, Thailand. Nontaburi: Ministry of Public Health; 2012. Figure 4: Baseline scenario for HIV in Thailand; p. 15.
4. Chasombat S, Lertpiriyasuwat C, Thanprasertsuk S, et al. The National Access to Antiretroviral Program for PHA (NAPHA) in Thailand. Southeast Asian J Trop Med Public Health. 2006 Jul;37(4):704–15.
5. AVERTing HIV and AIDS. HIV & AIDS in Thailand [Internet]. United Kingdom: AVERTing HIV and AIDS. 2013. http://www.avert.org/thailand-aids-hiv.html. Accessed 26 Sept 2012.
6. UNAIDS. World AIDS day Report 2011. Geneva: UNAIDS; 2011.
7. WHO. Regional health sector strategy on HIV, 2011–2015. New Delhi: WHO, Regional Office for South-East Asia; 2012.
8. Nontaburi: Ministry of Public Health. 2007. http://www.gfaidsboe.com/Downloads/book/2554/IBBS_MSM_2553_Mar%202011.pdf Thai. Accessed 26 Sept 2012.
9. Committee NAIDS. 2012 Thailand AIDS response progress report: Status at a glance. Nontaburi: National AIDS Management Center; 2012.
10. The fight against AIDS in Thailand [Internet]. China: China Central Television. 2012. http://english.cntv.cn/program/asiatoday/20120724/100108.shtml. Accessed 26 Sept 2012.
11. UNAIDS. HIV prevention needs and successes: a tale of three countries—an update on HIV prevention success in Senegal, Thailand and Uganda. Geneva: UNAIDS; 2001.
12. Chaikhuangaew S, Radchadamat P, Saimee A, Wanna A. AIDS counselling service clients at Eungpung Clinic, Chiang Mai. J Health Sci. 1996;5(2):173–9.
13. Tantipiwatanaskul P. Country watch: Thailand. Sex Health Exch. 1999(3):9–10.
14. Dwyer JM, Mahathir M, Nath LM. Challenge and response: HIV in Asia and the Pacific. Med J Aust. 1996 Nov 4;165(9):489–93.
15. Rojanapithayakorn W, Hanenberg R. The 100 % condom program in Thailand. AIDS. 1996 Jan;10(1):1–7.
16. Celentano DD, Nelson KE, Lyles CM, et al. Decreasing incidence of HIV and sexually transmitted diseases in young Thai men: evidence for success of the HIV/AIDS control and prevention program. AIDS. 1998 Mar 26;12(5):F29–36.
17. Thisyakorn U, Khongphatthanayothin M, Sirivichayakul S, et al. Thai Red Cross zidovudine donation program to prevent vertical transmission of HIV: the effect of the modified ACTG 076 regimen. AIDS. 2000 Dec 22;14(18):2921–7.
18. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok Collaborative Perinatal HIV Transmission Study Group. Lancet. 1999 Mar 6;353(9155):773–80.

19. Kanshana S, Simonds RJ. National program for preventing mother-child HIV transmission in Thailand: successful implementation and lessons learned. AIDS. 2002 May 3;16(7):953–9.
20. Phanuphak N, Lolekha R, Chokephaibulkit K et al. Thai national guidelines for the prevention of motherto-child transmission of HIV: March 2010. Asian Biomed. 2010;4(4):529–40.
21. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011 Aug 11;365(6):493–505.
22. Srithanaviboonchai K, Leusaree T, Lo YR, et al. Preparation for the Implementation of Thailand's First Program on Access to Free HAART: An Experience from Northern Thailand [Internet]. Oral Abstract: The XIV International AIDS Conference: Abstract no. TuOrG1246. Geneva: International AIDS Society. 2013. http://www.iasociety.org/Abstracts/A2881.aspx Accessed 7 Nov 2012.
23. Prevention NAIDS, Committee A. UNGASS country progress report Thailand—reporting period January 2008–December 2009. Nontaburi: National AIDS Prevention and Alleviation Committee; 2010.
24. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010 Dec 30;363(27):2587–99.
25. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock P, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2013;381(9883):2083–90. http://dx.doi.org/10.1016/ S0140–6736(13)61127–7. Accessed 13 June 2013
26. Likhitwonnawut U, Sirinrund P, Miller L, Suwannapattana N, Nacapew S, editors. Pre-exposure Prophylaxis (PrEP) in Thailand: report of the stakeholder meeting. Nonthaburi: Ministry of Public Health; 2010.
27. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012 Aug 2;367(5):423–34.
28. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012 Aug 2;367(5):399–410.
29. Yang D, Chariyalertsak C, Wongthanee A, et al. Acceptability of HIV pre-exposure prophylaxis (PrEP) with Truvada among men who have sex with men (MSM) and male-to-female transgender persons (TG) in northern Thailand [Internet]. Oral abstract at 19th International AIDS Conference: Abstract no. TUAC0303 Geneva: International AIDS Society. 2013. http://iset.aids2010.org/Abstracts/A200744180.aspx. Accessed 26 Sept 2012.
30. National Consultation on the Strategic Use of ARVs. Report on the National Consultation on the Strategic Use of ARVs—Thailand. 9 and 10 August 2012 [Internet]. Nontaburi: Ministry of Public Health. 2012. www.aidsstithai.org/contents/download/221. Accessed 26 Sept 2012.
31. Thailand National Working Group on HIV Counseling and Testing. Minutes from the National Working Group on HIV Counseling and Testing Meeting, 5 October 2012, Bangkok, Thailand. Bangkok: Thailand National Working Group on HIV Counseling and Testing; 2012.
32. Sweat M, Morin S, Celentano D, et al. Community-based intervention to increase HIV testing and case detection in people aged 16–32 years in Tanzania, Zimbabwe, and Thailand (NIMH Project Accept, HPTN 043): a randomised study. Lancet Infect Dis. 2011 Jul;11(7):525–32.
33. Lugada E, Millar D, Haskew J, et al. Rapid implementation of an integrated large-scale HIV counseling and testing, malaria, and diarrhea prevention campaign in rural Kenya. PLoS One. 2010;5(8):e12435.
34. Phanuphak N, Pattanachaiwit S, Pankam T, et al. Active voluntary counseling and testing with integrated CD4 count service can enhance early HIV testing and early CD4 count measurement: experiences from the Thai Red Cross Anonymous Clinic in Bangkok, Thailand. J Acquir Immune Defic Syndr. 2011 Mar 1;56(3):244–52.
35. Sungkanuparph S, Techasathit W, Utaipiboon C et al. Thai national guidelines for antiretroviral therapy in HIV-1 infected adults and adolescents 2010. Asian Biomed. 2010;4(4):515–28.
36. Thailand National Working Group on HIV Treatment and Care. Minutes from the National Working Group on HIV Treatment and Care Meeting, 2 October 2012, Bangkok, Thailand. Bangkok: Thailand National Working Group on HIV Treatment and Care; 2012.

Chapter 12
Implementing Biomedical HIV Prevention Advances in Ecuador and Peru

Pedro Goicochea and Orlando Montoya

Throughout the Andean region, there are overlapping themes of the HIV epidemic : sexual intercourse as the main route of transmission (> 90 %) [1], low HIV prevalence in the general population (0.1– < 0.5 %) [2], and elevated prevalence in men who have sex with men and male-to-female transgender women (MSM/TG; 13.9–21.9 %) [1], limited information systems, and substantial underreporting [3]. However, several independent studies indicate that the HIV/AIDS epidemic in the region is driven mainly by MSM/TG [4–6], who are at elevated risk for HIV infection [7]. We have selected Ecuador and Peru for case studies for this chapter because despite having epidemics with similar characteristics, the political responses in these countries have yielded different developments. Furthermore, both countries hosted studies of pre-exposure prophylaxis (PrEP) for HIV prevention [8] the successful results of which contributed toward the approval of tenofovir/emtricitabine for PrEP by the US Food and Drug Administration in 2012 (FDA) [9].

Ecuador

Ecuador is a country 99,706 square miles in area, with a population of 14,483,499 inhabitants [10] and an estimated sex ratio of 0.99 male(s)/females [11] Guayas is the most populated province with 25 % of the country's population residing there.

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The first AIDS case in the country was reported at the *Sociedad de Lucha contra el Cancer* hospital in 1984 [12], in a man who had lived in the USA. In 1986, after a few more cases, the Ecuadorian Minister of Health (MPH) created the National AIDS Control Program [13] that had very limited funding.

Between 1984 and 2010, there have been 18,524 cumulative cases of HIV infection, 8,338 cases of AIDS, and 7,031 deaths owing to AIDS reported to the MPH. A large proportion of these cases occurred in MSM/TG people. The prevalence of HIV in these populations is 19.4 % compared to 3.2 % in female sex workers (FSWs), the group with the next-highest HIV prevalence in the country [14]. According to the United Nations General Assembly Special Session (UNGASS) Country Report of 2010, a large proportion of the HIV/AIDS cases are concentrated in the coastal provinces of the country, specifically in the province of Guayas [15].

In 2000, the Ecuadorian Congress passed the "Law for the Prevention and Comprehensive Care of HIV/AIDS," which declares the fight against AIDS to be of national interest, and states that the country will enforce the prevention of the disease, assure epidemiological surveillance, facilitate treatment to people affected by HIV, assure the diagnosis of HIV in blood banks and laboratories, and protect the rights, dignity, and confidentiality of people affected by HIV/AIDS [16].

In 2001, the National AIDS/HIV/sexually transmitted infection (STI) Control Program from Ecuador produced a Multisectorial Strategic Plan for the period 2001–2003 (PEM 2001–2003), thereby setting the first political and programmatic framework to organize the national response to the AIDS epidemic. However, according to the UNGASS Country Report 2012, this plan did not have a meaningful effect [15]. A second Multisectorial Strategic Plan of the National Response to HIV/AIDS (PEM 2007–2015) was produced in early 2007 with the participation of nearly 150 organizations from the public and private sectors. This plan was aimed at (a) reducing HIV and STI in the most vulnerable populations, (b) reducing mortality due to AIDS, (c) enhancing HIV and STI services offered by the MPH, (d) strengthening the HIV/AIDS and STI information systems, epidemiological surveillance, and monitoring and evaluation of the HIV/AIDS and STI health services, and (e) strengthening the multisectorial national response to the epidemic [17]. An updated version of this plan was released in 2011 incorporating Multisectorial Operational Plans for the period 2011–2013 [14].

Peru

Peru has an area of 496,225 square miles with an estimated population of 30,475,144 [18] and an estimated sex ratio of 0.97 male(s)/female [11]. In Lima, the capital city and the neighboring province Callao, the country's most important port, is where 35 % of the population of the country resides.

The first case of AIDS was diagnosed in 1983 at Hospital Nacional Cayetano Heredia. Similar to the case in Ecuador, this first case was a man who was living in New York where he was diagnosed with AIDS and returned to the country to die [19].

In 1987, the Ministry of Health (MoH) created the AIDS Control Special Program (PECOS), "special" meant that the program had no budget provided by the MoH and that most of its activities had to be funded by external sources mainly international donors [20, 21].

From 1983 to 2012, the cumulative number of HIV infections and AIDS cases reported to the MoH was 47,907 and 29,588, respectively [22]. Of these cases, 71 % were reported in Lima and the majority was concentrated in MSM/TG. The prevalence of HIV in these populations was 12.4 % according to the 2011 MSM sentinel surveillance [23]. Prevalence of HIV in FSW was 1 % in a cross-sectional study conducted in 2002 [24].

In 1996, the Peruvian Congress passed the Law 26626 CONTRASIDA that delegated the coordination of HIV/AIDS and STI prevention, control, and care to the MoH, and required the MoH to keep the statistics of HIV/AIDS and STI cases [25]. This law was updated in May 2004 to declare the public need for the fight against HIV, AIDS, and STI and that every person living with HIV/AIDS has the right to receive comprehensive care including HIV treatment provided by the State [26].

The national response to the HIV/AIDS epidemic can be described in three phases [20]:

- The period between 1983 and 1994, which was characterized by weak planning centralized in the health sector with little outreach to the affected populations, supported mainly by international cooperation funds coming from the Pan American Health Organization (PAHO), the United States Agency for International development (USAID), and the European Union (EU).
- The period between 1995 and 2000, with a very strong planning process and the generation of a regulatory and legal framework to guide the STI/AIDS Control Program (PROCETSS) activities that included the Manual of Rules and Procedures to Control STI and AIDS in Peru [27], the first HIV/AIDS Law [25], and an interest to work multisectorially together with the public sector and the civil society; the production of national guidelines to frame HIV/AIDS/STI care including the prevention of HIV vertical transmission and congenital syphilis, syndromic management of STIs, control of blood banks, HIV counseling and testing, and interventions in vulnerable populations that included peer educator programs for MSM/TG and FSW. Health services were adapted to implement biomedical interventions targeted mainly at vulnerable populations (MSM/TG and FSW). PROCETSS also designed and implemented the first information system to collect epidemiological data and funded research initiatives with funds from the international cooperation: cross-sectional studies in MSM/TG, FSW, and pregnant women; the establishment of the first MSM/TG cohort named the "Alaska cohort[1]"; evaluation of the quality of care provision at STI, sexual and reproductive health services in the MoH health system; and the implementation of the MSM/TG sentinel surveillance system. This period was also characterized by

[1] "Alaska" is the name of a Spanish-Mexican singer who in 1986, together with her group, Dinarama popularized the song "*A quien le importa*" (Who cares) that became a gay hymn. This MSM/TG cohort chose the name "Alaska" to honor the singer.

a substantial increment of public funds in the national response to the HIV/AIDS epidemic that raised tenfold in a 5-year period from US$ 600,000 a year in 1996 to US$ 6,000,000 by the year 2000 [28].

- The period between 2001 and present, saw a national response characterized by disruption of the HIV/AIDS/STI prevention and control policies that had been previously developed [29], and a weak STI/AIDS Control Program. PROCETSS was downgraded from being a national program to a cross-sectional strategy, and the head of the program became a "coordinator" from having been an "Executive Director." Funds devoted to fight the epidemic were decentralized from the National AIDS Program to the Health Regions and the program became more "normative and regulatory" rather than executive, limiting its capacities to implement control activities since health priorities were defined at the decentralized health bodies which did not necessarily consider HIV/AIDS a priority. During this period, the AIDS program was in charge of coordinating and organizing the first country application to the Global Fund to Fight AIDS, Tuberculosis and Malaria, which was rejected on the first submission but was eventually granted in 2003. This period has a more active participation of different stakeholders that includes affected and vulnerable populations impacted by the epidemic and the AIDS strategy officers have to negotiate more with the civil society.

In 2004, in preparation to implement the Global Fund intervention activities, the MoH convened the National Multisectorial Commission on Health (CONAMUSA) that, among other functions, was in charge of organizing the AIDS national strategic plan. In November 2006, the Multisectorial Strategic Plan for the Prevention and Control of HIV/AIDS/STI in Peru (PEM 2007–2011) was approved by Supreme Decree and it was aimed at achieving the following goals by 2011: (a) to reduce the number of new cases of HIV and STI in MSM/TG, FSW, and prison inmates by 50 %, (b) to reduce the number of new cases of STI in the general population by 50 %, (c) to promote HIV/STI prevention education, healthy lifestyles, and healthy sexual behaviors in adolescents, (d) to reduce vertical transmission of HIV to less than 2 %, (e) to warrant 100 % safe blood supply in blood banks, (f) to provide comprehensive and quality care to 90 % of people living with HIV/AIDS (PLWHA), (f) to provide a favorable environment to address HIV/AIDS issues in a comprehensive way including human rights and sexual diversity and ensure the participation of the communities with the highest HIV/STI prevalence as well as PLWHA, and (g) to ensure a multisectorial response for the prevention and control of STI/HIV/AIDS [30]. The PEM 2007–2011 evaluation was very critical in emphasizing that the plan did not achieve its original epidemiologic goals, and that it was too focused on the clinical and biological components of the epidemic, ignoring its social determinants [31]. A draft of a strategic plan for the period 2013–2017 was produced by the MoH and, in December 2012, presented to different stakeholders [32] The PEM document was criticized so hardly by the affected communities that in February 2013, the Minister of Health extended the period for the production of the final version for 120 days, meaning that the PEM 2013–2017 was expected to be available by May 2013 [33].

The Global Fund to Fight AIDS, Tuberculosis and Malaria

The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) has been one of the most important funding mechanisms supporting health improvement initiatives in Ecuador and Peru. Between 2003 and 2012, the Fund has invested 22.7 million and 71.9 million dollars to fight HIV/AIDS in Ecuador and Peru, respectively [34].

Support from the Global Fund in Ecuador was initiated in mid-2005 and has funded the improvement of access to integral health care services, including expansion of antiretroviral (ARV) therapy and treatment of opportunistic infections, and distribution of condoms among vulnerable populations. These activities have also included training of health professionals in syndromic management of STI, counseling, and other activities related to the promotion and defense of human rights with vulnerable populations and PLWHA [35].

In Peru, the Global Fund support started in late 2003, aimed to broaden the national response to the AIDS epidemic by scaling up ARV therapy provision to PLWHA, train and update personnel from the national health system, support information, education, and communication campaigns in HIV/AIDS and HIV prevention for the general population, and contribute toward organizing the civil society response [36].

The Global Fund continues to support activities related to HIV/AIDS in these two countries, and in a way, defines the agenda and priorities of the national responses to the epidemic as suggested by some officers and activists who were interviewed for this chapter. The Fund also facilitates the achievement of Multisectorial Strategic Plan aims and generates forums for the interaction between the State and civil society.

ARV Treatment for PLWHA and Treatment as Prevention

The provision of highly active antiretroviral treatment (HAART) for the general population, known as TARMA in Ecuador and TARGA in Peru, started in 2004 in both countries with initial support from the Global Fund to Fight AIDS, Tuberculosis and Malaria. However, HAART in Peru was available previously through private practice or in the military health system. For the implementation of HAART access programs, Ecuador and Peru prepared national guidelines for the comprehensive care of PLWHA according to World Health Organization (WHO) recommendations. One guideline is the initiation of HAART at CD4 count < 200 (units, e.g., /ml). This criterion continued to be valid until 2011 in Ecuador and 2012 in Peru, when guidelines were updated following a second round of WHO recommendations to initiate treatment at CD4 count < 350. Only recently Ecuador started to provide HAART at (CD4 count < 500) following the most recent WHO guidelines released in July 2013.

Accordingly, the UNGASS Country Report of 2010 for Ecuador states that 30 % of people with CD4 count < 350 were receiving treatment [37]. Similarly, Peru's UNGASS Country Report 2012 reported that 92.2 % of people with CD4 countg < 200 were receiving HAART.

In 2011, results from a randomized control trial showed that early initiation of ARV therapy (CD4 count < 550) substantially reduces the rates of sexual transmission of HIV-1 by 96 %, revealing significant public health benefits from this intervention [38]. Nevertheless, this strategy, which could be the most feasible in the context of these two countries, would require certain considerations, according to the expert opinion of coordinators of the HIV/AIDS/STI National Strategies of the MPH in Ecuador and MoH in Peru. First, ARV treatment guidelines would require to be updated based on a review of evidence, a step that became challenging in Peru since updated ARV guidelines had recently been released in 2012. Second, there are programmatic and political implications since increasing the CD4 count criterion from 350 to 550 to be eligible for HAART will affect performance indicators by increasing the gap of ARV coverage to PLWHA that need it. Third, it has budgetary implications by increasing coverage to treat more people. Fourth, there are concerns from the community of PLWHA regarding this criterion, since it could affect health at earlier stages by exposing subjects to medications that are toxic when not absolutely necessary. Finally, there are also urban rumors in both countries that these recommendations are being promoted by the pharmaceutical industry to increase sales, reason why there are sectors of the affected communities that are reluctant to initiate treatment at an earlier stage.

In Ecuador, new guidelines are about to be released where the > 500 criteria will be included, whereas in Peru it has not yet been decided upon officially.

Medical Male Circumcision

Medical male circumcision (MMC) is a new HIV-prevention technology that has proven to be effective in preventing HIV infection among sexually active men [39–41]. WHO and UNAIDS have released recommendations and guidelines for the implementation of MMC programs for HIV prevention, especially in high HIV-prevalence settings [42–50].

MMC is not a common practice in either Ecuador or Peru and little data are available on the prevalence of male circumcision (MC) in these countries, with the exception of specific evaluations in MSM/TG at sentinel surveillance and screening procedures in clinical trials. As a reference, the prevalence of MC among the MSM/TG sentinel surveillance participants in 2006 that included three provinces in Peru (Arequipa, Lima, Ica) and Guayaquil in Ecuador, was 3.7 % in 2006 [51].

In a 2008 qualitative feasibility study in Brazil, Ecuador, and Peru, designed to assess willingness to participate in a MSM/TG MMC trial for the prevention of HIV acquisition[2], it was identified that despite most participants considering MMC to be a feasible new technology for the prevention of HIV acquisition, cultural factors were among the major barriers to acceptance. Specific concerns reported by participants

[2] Feasibility, acceptability and willingness to participate in a Male Circumcision Trial for the Prevention of HIV Acquisition in Men who Have Sex with Men (NIH grant P30 AI027757).

in this research were related to the effect of MMC on virility, sexual sensitivity, and appearance of the penis [unpublished data] [52].

In another qualitative research study aimed at assessing the feasibility of implementing a neonatal male circumcision (NMC) program in the Peruvian Amazon basin[3], partners of pregnant women recruited as informants for this research mentioned that they would rather educate their sons in HIV prevention than have them circumcised. Pregnant women, on the other hand, were more likely to let their newborn sons be circumcised, to prevent potential "urinary infections," "painful intercourse," and HIV acquisition [unpublished data].

Sanchez et al. [53] analyzed the association between male circumcision, insertive anal sex practices, and HIV acquisition in the MSM/TG cohort of herpes simplex-2 (HSV-2) suppression for HIV prevention trial (HPTN 039), where participants from the Americas were from Peru and the USA. They found that circumcision did not have a significant protective effect against HIV acquisition among MSM/TG from Peru and the USA, although there may be reduced risk for men who are primarily insertive with their male partners [53].

From a political perspective, the implementation of routine MMC for HIV prevention has not been considered as a preventive option in either Ecuador or Peru. On the one hand, Ecuadorian authorities at the STI/HIV/AIDS National Strategy mentioned that they are prioritizing other prevention alternatives, such as scaling up HIV treatment for PLWHA and promoting condom use; they added that circumcision is not a tradition in the Ecuadorian culture. On the other hand, Peruvian authorities added that to have MMC as another tool for HIV prevention in Peru would require the generation of local evidence that the intervention will be beneficial, a process that could take a long time [54].

HIV Prevention Clinical Research in Peru

The creation of *Asociacion Civil Impacta Salud y Educacion* (Impacta) in the year 2000 set the landmark of HIV prevention clinical research in Peru. The organization was funded by former Executive Director of the STI/AIDS Control Program (PROCETSS) of the Peruvian MoH after concluding his 1995–2000 appointment; and during its beginning hosted the implementation of clinical research sponsored by the US National Institutes of Health/Division of AIDS (NIH/DAIDS). Impacta conducted domestic HIV prevention research focused on evaluating innovative clinical interventions and HIV preventive vaccines. These clinical trials were funded by DAIDS through the HIV Prevention Trials Network (HPTN) and HIV Vaccines

[3] This information was collected during interviews with urologists during the conduct of a USAID sponsored research; "Introducing male neonatal circumcision in selected peruvian populations: a feasibility study considering medical, legal, economic, social and political implications" (RFP N° 201002).

Trials Network (HVTN).[4] Impacta set the course for state-of-the-art HIV/AIDS research in the country and the opportunity for evaluating innovative HIV prevention interventions in the national setting.

Impacta devoted a great deal of resources to educating the local community in Lima, to raise awareness about the HIV/AIDS epidemic and the need for conducting research to find alternative HIV prevention interventions. In 2001, following DAIDS requirement for the conduct of clinical research, Impacta organized the first Community Advisory Board (CAB) in the country aimed at involving the community in the clinical research design and activities. The CAB worked with Impacta investigators, providing advice on different aspects of institutional research conduct, and acted as a liaison with their constituencies to inform them about HIV/AIDS prevention and treatment research.

In mid-2002, after 18 months of community preparedness, Impacta investigators initiated the implementation of HIV-prevention trials. Two studies set the milestones in HIV-prevention research in the country. The first was a randomized, double blind, placebo-controlled phase II trial to evaluate the immunogenicity and safety of Alvac-HIV vcp1452, an anti-HIV vaccine, alone and combined with mn rgp120 (HVTN 026). This study enrolled 40 participants at low risk for acquiring HIV [55]. The second was a phase III, randomized, double blind, placebo-controlled trial to assess the efficacy of acyclovir for the reduction of HIV acquisition among high-risk HSV-2 seropositive and HIV seronegative individuals (HPTN 039) that had 1,384 MSM/TG enrolled in Peru [56].

Since then, Impacta has been evaluating innovative HIV-prevention interventions with strong community support and promoting the creation of decentralized clinical research institutions in Iquitos, Pucallpa, Arequipa, and Sullana in Peru, and in Guayaquil in Ecuador, generating a diverse state-of-the-art clinical research infrastructure in the Andes. Based on these capacities, Impacta was granted the US NIH sponsored Clinical Trials Unit in 2005 and has conducted more than 15 clinical trials in the areas of HIV vaccines, clinical interventions, and treatment (www.impactaperu.org).

PrEP for HIV Prevention

This section includes a focus on the implementation of a PrEP clinical trial, conducted in Ecuador and Peru as part of a larger scale clinical study: “Chemoprophylaxis for HIV Prevention in Men” also known as the iPrEx Study [8]. The initial idea of conducting a PrEP trial in South America was conceived at the 11th Conference of Retrovirus and Opportunistic Infections (CROI) in 2004. At this meeting, an investigator from the Gladstone Institute of Virology and Immunology, who at the time was one of the lead investigators conducting a tenovir PrEP clinical trial in Cambodia, met Peruvian investigators from Impacta Salud y Educación, and discussed

[4] Impacta also conducted studies for the DAIDS sponsored AIDS Clinical Trials Group (ACTG) and the pharmaceutical industry.

the feasibility of doing an efficacy PrEP study in a population yet not considered in PrEP trial design at the time, MSM/TG, but at high risk for acquiring HIV.[5]

The idea of conducting a safety and efficacy PrEP trial in MSM/TG in Peru was logistically feasible. Impacta had shown that there was clinical research infrastructure with a capacity to recruit and retain large MSM/TG cohorts; the observed HIV incidence in this population at the time was high (between 3.5 and 6.5 per 100 persons/year [Alaska cohort and HPTN 036,[6] respectively, unpublished data]); and the local regulatory approval of a clinical research protocol was reasonable (approximately 6 months).

Between 2004 and 2006, the investigators underwent extensive consultation with study sponsors (US NIH), potential participants from the MSM/TG community in Peru and Ecuador, and stakeholders from both countries to assess the feasibility of implementing a PrEP trial. The response was positive. In 2007, after a new round of consultations with potential study participants, members of the MSM/TG community in Peru and Ecuador decided to name the study "iPrEx" that stands for Pre-Exposure Prophylaxis Initiative (*Iniciativa Profilaxis Pre Exposición* in Spanish), and in June of that year the study was launched in four Andean sites: two in Lima, one in Iquitos, Peru, and one in Guayaquil, Ecuador.

The iPrEx study expanded to seven other sites in 2008, but participants from the Andean sites constituted 67 % of the total iPrEx cohort of 2,499 MSM/TG. The iPrEx study was the first trial to show the efficacy of PrEP in men [8]. In 2011, the iPrEx study continued a follow-up phase as an open label extension, iPrEx OLE becoming one of the first and largest multinational MSM/TG PrEP demonstration project that enrolled 1,770 MSM/TG. From these, 63 % participants were from the Andean study sites (Peru and Ecuador).

Expectations about PrEP for HIV prevention were very high in Lima. In a small qualitative research conducted among MSM/TG and FSW, it was determined that an acceptable PrEP intervention should be one where the cost of the PrEP medication was US$ 10 per month, with 95 % efficacy and no side-effects, and that could be used immediately before sex [57].

PrEP Consultations in Ecuador and Peru

In 2011, the WHO sponsored PrEP consultations in Peru and Ecuador. The meetings convened a diverse audience, including representatives from UNAIDS, the PAHO

[5] In August of 2005, the Centers for Disease Control and Prevention sponsored the conduct of "CDC 4323," a safety trial of the daily use, once a day of the antiretroviral drug tenofovir for the prevention of HIV infection in MSM. The study was conducted in collaboration with the San Francisco Department of Public Health, the AIDS Consortium of Atlanta and Fenway Health in Boston http://www.avac.org/ht/display/ContentDetails/i/1837/pid/1891.

[6] "HPTN 036: HIV prevalence, incidence and HSV-2 prevalence among high-risk MSM in Lima, Peru" was a preparedness study to assess the capacity to enroll and retain a large cohort of participants at high risk of acquiring HIV and enrolled 254 MSM/TG in Lima, Peru.

and WHO, officers from the Peruvian and Ecuadorian Ministers of Health, health practitioners, community leaders, iPrEx study participants, and researchers. Consultations in both countries raised similar concerns that could be summarized as follows:

- *Prioritization of prevention methods based on cost-benefit analyses*: The discussion about prevention raised three issues: (a) individual responsibility, as people at risk should protect themselves using condoms; (b) the well-being of uninfected people, as people not infected with HIV should not be exposed to the toxicity of the ARV medications; and (c) the cost of the intervention, since the use of condoms is still less expensive than the use of ARV. In both consultations, the recommendation was the conduct of cost-benefit analyses of the use of PrEP.
- *The challenge of adherence to the PrEP medication*: One of the outcomes of the iPrEx study was that adherence to the study medication presented challenges in some groups of participants, so a recommendation was proposed to look for better approaches to improve medication adherence for PrEP.
- *Potential of viral resistance*: Despite adherence difficulties, the iPrEx results showed no resistance to tenofovir and only two cases of resistance to emtricitabine in the active arm. Consultants suggested continuing to investigate this potential side effect.
- *Potential for "behavioral desinhibition"*: Consultation brought up concerns related to the potential of "behavioral desinhibition" and the lack of the use of condoms in the context of PrEP, generating the conditions for the increase in STI rates. Most of the recommendations were targeted at considering approaches to support PrEP programs with strategies for encouraging behavioral change, such as using condoms.
- *Implementation of "Demonstration Projects" prior to policy design*: Discussion about efficacy data concluded that PrEP outcomes were the result of randomized controlled trials, so consultants mentioned that there was the need of assessing the feasibility of the intervention in "real life" in the context of existing health systems and that demonstration projects could provide that evidence before designing prevention policies around this innovation.
- *PrEP medication accessibility and licensure in Peru*: During this consultation Truvada® was not yet approved in Peru so a point was raised that it should be first approved and licensed in the country before discussing the implementation of a PrEP program[7].

[7] Gilead Science Inc. submitted an application for licensure of Truvada to the Peruvian Directorate of Medicines, Supplies and Drugs (DIGEMID) in September 2012. At the time of the consultation in Ecuador, Truvada was not licensed in Ecuador either, but Gilead had already submitted an application in 2010. In October of 2012, the Ecuadorian MPH approved Truvada for the treatment of HIV infection.

Peruvian Forum on HIV Prevention Technologies

In early November of 2011, the Universidad Peruana Cayetano Heredia organized a public forum and stakeholder consultation entitled "New Perspectives on HIV Prevention—Opportunities and Challenges for Peru" [58]. The forum was introduced with a description of state-of-the-art HIV-prevention technologies: treatment as prevention, topical microbicides and oral PrEP.

Based on the evidence presented at this forum, conclusions on the implementation of biomedical strategies for HIV prevention in Peru faced some challenges that included (a) the lack of leadership of the HIV/AIDS/STI Prevention and Control Strategy of the MoH, (b) the need for further research to assess if health services are prepared and have all the conditions to implement these innovative strategies, (c) the high dependence of funding from international donors, which still provide 47 % of the funding for HIV/AIDS, (d) the need to improve education of the population on STI as well as public distribution of condoms, and (e) the need to develop a sense of ownership of new HIV-prevention strategies as part of the HIV combination/prevention package.

Discussion

Effective clinical interventions for the control and prevention of HIV infection [59–61] have been available for some time, however, the process of adopting these innovations in Ecuador and Peru has varied. For instance, available epidemiological data characterize Ecuador and Peru's HIV/AIDS epidemics as concentrated in MSM/TG populations and prevention interventions that have proven to be effective in these populations have already been recommended by the WHO and UNAIDS. While MSM/TG comprehensive targeted interventions were being implemented in Peru in the second half of the 1990s, Ecuador started their more systematic work with these populations in the late 2000s.

Nonetheless, Ecuador and Peru have developed legal frameworks that play an extremely important role in the modernization of the national response to their HIV/AIDS epidemics. These legal initiatives have created the conditions to work multisectorially, including in affected communities, the civil society, and other government sectors. There are planning mechanisms that set short-, mid-, and long-term goals, and there is the political will to address the epidemic in a more comprehensive way. These conditions provide room to consider the adoption of innovations to more efficiently address specific challenges in HIV prevention since plans are continuously reviewed and evaluated.

On the one hand, new HIV prevention clinical interventions are in their initial stages, outcomes have proven to be partially effective except for a few, and have been obtained in very controlled settings (randomized controlled trials); other clinical trial outcomes have contradictory results to what already been seen. In the case of PrEP and microbicides, there are some demonstration projects that are either taking place

or in planning phases, policy makers especially in low and middle income countries are cautious to adopt innovations that have not yet been proven to work in real life and in most cases these implementations require the generation of local evidence by conducting local pilot projects which require resources that are not always available.

The diffusion of information about these new HIV prevention technologies has been slow and little is known about them by the general population thus limiting demand, and also by prescribers, thus limiting supply. Moreover, currently available information tends to be confusing; efficacy data from clinical trials tend to have different interpretations that are not familiar to the end user (i.e., modified intent to treat analysis; as treated analysis, efficacy when drug concentration was found, etc.) making it more challenging to properly inform providers and making it difficult to understand for the potential user.

Access to the innovation is also a challenge; ARV-based microbicides are not yet available and the tenofovir/emtricitabine compound is still pricy, even for the US standards; increasing CD4 count to > 500 to start treatment requires resources, and MMC (that do not necessarily apply in the context of concentrated epidemics) has cultural barriers associated with manhood, so that there is no interest in looking into that.

There is also the issue of attitudes toward the innovation and whom the innovation should be targeted for. As an anecdote, at the PrEP consultation meeting in Peru that took place in February 2011 (no results of PrEP trials in heterosexuals were yet known) an MoH officer stated "*. . . let's wait for the results of PrEP trials in women before discussing the feasibility of PrEP in the country. . .* ", this statement has no sense in a country with a concentrated epidemic in MSM/TG.

Finally, there is the aspect of financial resources. HIV/AIDS programs in Ecuador and Peru still have a great proportion of their funding depending on external sources. The implementation of the Multisectorial Strategic Plans has had a tremendous support from the Global Fund in both countries; however, the Global Fund is reducing its activities in countries that are improving their economical situation, as is the case of these two countries. To supplement the gap that these funds provide will require leadership in the coordination of the HIV/AIDS/STI Control Strategies and political will to prioritize the epidemic.

These circumstances generate barriers to an easy and fast adoption of HIV prevention innovations by both, the political/public health official and by the end user. From our perspective, the gaps in the adoption of innovations are affected by interrelated factors that have to do with (a) prioritization of health challenges in-country, (b) leadership from the HIV/AIDS programs, (c) communications and diffusion of information that will enable the policy, decision makers, and stakeholders to have evidence-based decisions, (e) political desire to work with the affected populations, and (d) availability of resources.

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References

1. Kusunoki L, Nagles J. Análisis de Situación de VIH en la Subregión Andina 2003–2005. Organización Panamericana de la Salud, Organismo Andino de Salud, ONUSIDA, 2007 Aug 29. Report No.
2. UNAIDS. Global Report: UNAIDS report on the global AIDS epidemic 2012. 2012 Jul.
3. Garcia-Abreu A, Noguer I, Cowgill K, Garcia-Abreu A, Noguer I, Cowgill K. HIV/AIDS in Latin America: the challenges ahead. Washington DC: The International Bank for Reconstruction and Development/The World Bank; 2004.
4. Bautista CT, Sanchez JL, Montano SM, Laguna-Torres VA, Lama JR, Sanchez J, et al. Seroprevalence of and risk factors for HIV-1 infection among South American men who have sex with men. Sex Transm Infect. 2004;80:498–504 (PubMed PMID: 6549).
5. Hierholzer J, Montano S, Hoelscher M, Negrete M, Hierholzer M, Avila MM, et al. Molecular epidemiology of HIV Type 1 in Ecuador, Peru, Bolivia, Uruguay, and Argentina. AIDS Res Hum Retroviruses. 2002 Dec 10;18(18):1339–50 (PubMed PMID: 12487805. Epub 2002/12/19. eng).
6. Montano SM, Sanchez JL, Laguna-Torres A, Cuchi P, Avila MM, Weissenbacher M, et al. Prevalences, genotypes, and risk factors for HIV transmission in South America. J Acquir Immune Defic Syndr. 2005 Jul 28;40(1):57–64 (PubMed PMID: 16123683. eng).
7. Baral S, Sifakis F, Cleghorn F, Beyrer C. Elevated risk for HIV infection among men who have sex with men in low- and middle-income countries 2000–2006: a systematic review. PLoS Med. Dec 2007;4(12):e3390001–11.
8. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010 Dec 30;363(27):2587–99 (PubMed PMID: 21091279; PubMed Central PMCID: 3079639).
9. FDA. FDA approves first drug for reducing the risk of sexually acquired HIV infection Washington, DC: Food and Drug Administration. 2012. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.html. Accessed 3 Feb 2013.

10. INEC. Población del Ecuador: Instituto Nacional de Estadística y Censos. 2010. http://www.inec.gob.ec/cpv/. Accessed 3 Feb 2013.
11. CIA. Country Fact Sheet: Ecuador 2013. 2013. https://http://www.cia.gov/library/publications/the-world-factbook/geos/ec.html. Accessed 3 Feb 2013.
12. A 30 aos del primer caso de VIH, crece el número de afectados. El Universo. 2011 June 5th, 2011; Sect. Comunidad.
13. Kusunoki L, Navarro MdC, Guanira-Carranza JV, Velasquez C. Priorizacion para el Acceso Universal a la Prevención, Atención Integral, Cuidado y Apoyo en VIH/SIDA. Ecuador 2008–2013. 2008 April 2008. Report No.
14. MSP. Actualizacion del Plan Estrategico Multisectorial de la Respuesta Nacional al VIH/SIDA 2007–2015. Planes Operativos multisectoriales 2011–2013. Quito, Ecuador: Ministerio de Salud Pública. Porgrama Nacional de Prevención y Control del VIH/SIDA e ITS, 2011.
15. MSP. Informe Nacional sobre los Progresos Realizados en la Aplicación del UNGASS Ecuador. Periodo Enero 2008–Diciembre 2009. Quito, Ecuador: Ministerio de Salud Pública del Ecuador, 2010 April 19th, 2009. Report No.
16. Ley para la Prevención y Asistencia Integral del VIH SIDA, Ley 11 (2010).
17. MSP. Plan EstrateÌgico Multisectorial de la Respuesta Nacional al VIH/SIDA 2007–2015. Quito, Ecuador: Ministerio de Salud Publica del Ecuador, 2007 Jun 23. Report No.
18. INEI. Perú: Población total estimada y proyectada, según aos calendarios: 1990–2050: Instituto Nacional de Estadistica e Informatica. 2013. http://www.inei.gob.pe. Accessed 3 Feb 2013.
19. Patrucco R. El Sindrome de Inmunodeficienica Adquirida en el Peru: Estudios Inmunologicos. Revista Diagnostico. 1985;16(5) (PubMed PMID: 4241).
20. HPI USAID. Política Nacional VIH-SIDA. 2007.
21. Cueto M. Culpa y coraje. Historia de las politicas sobre el VIH/SIDA en el Peru. Lima, Peru: Consorcio de Investigacion Economica y Social; 2001.
22. DGE. Boletin Epidemiológico Epidemiológico Mensual. Lima, Peru: Ministerio de Salud, 2012 Noviembre 2012. Report No.
23. MINSA. UNGASS: Informe Nacional sobre los Progresos Realizados en el País. Peru: Enero 2010–Diciembre 2011. 2012 May 27:1–246.
24. Bautista CT, Sanchez JL, Montano SM, Laguna-Torres A, Suarez L, Sanchez J, et al. Seroprevalence of and risk factors for HIV-1 infection among female commercial sex workers in South America. Sex Transm Infect. 2006 Aug 1;82(4):311–6 (PubMed PMID: 16877581. eng).
25. Ley CONTRASIDA, 26626 (1996).
26. Ley CONTRASIDA ampliada y modificada, 28243 (2004).
27. Doctrina, Normas y Procedimientos para el Control de las ETS y el SIDA en el Perú, (1996).
28. Frasca T. AIDS in Latin America. New York: Palgrave Macmillan; 2005. p. 261.
29. SituacioÌ'n de las ITS y el VIH/Sida en el PeruÌ', 2006. Lima, Peru: Iniciativa de Políticas en Salud, 2006 Sep 09. Report No.
30. CONAMUSA. Plan Estratégico Multisectorial para la Prevención y control de las ITS y el VIH/SIDA en el Peru (2007–2011). Lima, Peru: Comisión Nacional Multisectorial de Salud, 2006 Nov 26. Report No.
31. MINSA. Evaluacion del Plan Estratégico Multisectorial VIH/SIDA 2007–2011. Lima, Peru: Ministerio de Salud del Peru, 2012.
32. MINSA. Plan EstrateÌgico Multisectorial de PrevencioÌn y Control de ITS y VIH. AnaÌlisis de situacioÌn de la epidemia y de la respuesta. 2012.
33. Modifican la RM N° 775–2012/MINSA a fin de ampliar periodo de duración del Plan Estratégico Multisectorial para la Prevención y Control de las ITS/VIH y Sida en el Perú, así como el plazo para su elaboración, N° 775–2012/MINSA (2013).
34. Fund TG. The Global Fund to Fight AIDS, Tuberculosis and Malaria 2013. Available from: http://www.theglobalfund.org.
35. Fund TG. Grant Portfolio—Ecuador: The Global Fund to Fight AIDS, Tuberculosis and Malaria. 2013. http://portfolio.theglobalfund.org/en/Country/Index/ECU. Accessed 3 Feb 2013

36. Fund TG. Grant Portfolio—Peru: The Global Fund to Fight AIDS, Tuberculosis and Malaria. 2013. http://portfolio.theglobalfund.org/en/Grant/Index/PER-202-G01-H-00. Accessed 3 Feb 2013
37. Ecuador MdSPd. Informe Nacional sobre los Progresos Realizados en la Aplicacion del UNGASS. Ecuador. Ministerio de Salud Publica del Ecuador, 2010 April 19th, 2010. Report No.
38. Cohen M, Chen Y, McCauley M. Prevention of HIV-1 infection with early antiretroviral therapy. New Eng J. 2011 Jan 1 (PubMed PMID: 13290838847807409145).
39. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med. 2005 Nov;2(11):e298 (PubMed PMID: 16231970. eng).
40. Weiss HA, Halperin D, Bailey RC, Hayes RJ, Schmid G, Hankins CA. Male circumcision for HIV prevention: from evidence to action? AIDS. 2008 Mar 12;22(5):567–74 (PubMed PMID: 18316997. Epub 2008/03/05. eng).
41. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007 Feb 24;369(9562):657–66 (PubMed PMID: 17321311. eng).
42. WHO/UNAIDS. Male circumcision for HIV prevention in high HIV prevalence settings: what can mathematical modelling contribute to informed decision making? PLoS Med. 2009 Sep;6(9):e1000109 (PubMed PMID: 19901974; PubMed Central PMCID: 2731851. Epub 2009/11/11. eng).
43. WHO/UNAIDS. Male circumcision for HIV prevention: the research evidence and some critical responses. Reprod Health Matters. 2007 May;15(29):9–10 (PubMed PMID: 17512368; Epub 2007/05/22. eng).
44. WHO/UNAIDS. International AIDS Society conference update. Male circumcision as a prevention method? Study was controversial from day one. AIDS Alert. 2005 Sep;20(9):101–2 (PubMed PMID: 16206400; Epub 2005/10/07 eng).
45. WHO/UNAIDS. Male circumcision: global trends and determinants of prevalence, safety and acceptability. 2007.
46. WHO/UNAIDS. Safe, voluntary, informed male circumcision and comprehensive HIV prevention. 2008 Jan 1:34 (PubMed PMID: 7Je6PwAACAAJ).
47. WHO/UNAIDS. New data on male circumcision and HIV prevention: policy and programme implications. Montreux, Geneve: 2007.
48. WHO/UNAIDS. Male circumcision: global trends and determinants of prevalence, safety and acceptability. 2008 Aug 11. Report No.
49. WHO/UNAIDS. WHO/UNAIDS announce recommendations about male circumcision as HIV prevention. Strategy should be employed with care. AIDS Alert. 2007 Jun;22(6):66–7 (PubMed PMID: 17633775; Epub 2007/07/20. eng).
50. WHO/UNAIDS. Male circumcision for HIV prevention: research implications for policy and programming. WHO/UNAIDS technical consultation, 6–8 March 2007. Conclusions and recommendations (excerpts). Reprod Health Matters. 2007 May;15(29):11–4 (PubMed PMID: 17512369; Epub 2007/05/22. eng).
51. Guanira JV, Lama JR, Goicochea P, Segura P, Montoya O, Sanchez J, editors. How willing are gay men to "cut off" the epidemic? Circumcision among MSM in the Andean Region. 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 2007; Sydney, Australia.
52. Goicochea P, Sanchez J, Casapia M, Montoya O, Morales M, Grinsztejn B, et al., editors. Feasibility, acceptability and willingness to participate in a male circumcision trial for the prevention of HIV acquisition in men who have sex with men in the Andes. 5th International AIDS Society Conference; 2009 18–22 July 2009; Cape Town, South Africa.
53. Sánchez J, Sal yRVG, Hughes JP, Baeten JM, Fuchs J, Buchbinder SP, et al. Male circumcision and risk of HIV acquisition among men who have sex with men. AIDS. 2010 Nov;1:1.
54. Normas paralaElaboración de Documentos Normativos del Ministerio de Salud, (2011).
55. Adis International L. HIV gp120 vaccine—VaxGen: AIDSVAX, AIDSVAX B/B, AIDSVAX B/E, HIV gp120 vaccine—Genentech, HIV gp120 vaccine AIDSVAX—VaxGen, HIV vaccine

AIDSVAX—VaxGen. Drugs in R & D. 2003;4(4):249–53 (PubMed PMID: 12848591. Epub 2003/07/10. eng).
56. Celum C, Wald A, Hughes J, Sanchez J, Reid S, Delany-Moretlwe S, et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Jun 21;371(9630):2109–19 (PubMed PMID: 18572080. eng).
57. Galea JT, Kinsler JJ, Salazar X, Lee S-J, Giron M, Sayles JN, et al. Acceptability of pre-exposure prophylaxis as an HIV prevention strategy: barriers and facilitators to pre-exposure prophylaxis uptake among at-risk Peruvian populations. Int J STD AIDS. 2011 May 1;22(5):256–62 (PubMed PMID: 21571973. eng).
58. iessdh. Consultation on New HIV Prevention Strategies in Peru—Executive Summary 13 12 11 final. 2011 Dec 13. Report No.
59. Grosskurth H, Mosha F, Todd J, Senkoro K, Newell J, Arnold K, et al. A community trial of the impact of improved sexually transmitted disease treatmen on the HIV epidemic in rural Tanzania: 2. Baseline survey results. AIDS. 1995;32676:919–26.
60. Sperling R, Shapire D, Coomvs R. Maternal viral load, zidovudine treatment and the risk of transmission of human immunodeficiency virus type 1 from mother to infant. N Engl J Med. 1996;335:7.
61. WHO/ILO. Joint WHO/ILO guidelines on post-exposure prophylaxis (PEP) to prevent HIV infection. Geneva: WHO; 2005.

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