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?

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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].

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