The Evolution of HIV Prevention Interventions and Chronic Disease Management

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Introduction

The Joint United Nations Programme on HIV/AIDS estimates that 2.6 million new infections and 1.8 million AIDS deaths occurred in 2009, and almost 33.3 million adults and children worldwide are currently living with HIV or AIDS, with the great majority of them in low- and middle-income countries (UNAIDS, 2010). Fortunately, the advent of antiretroviral therapy in 1996 has led to drastic positive changes to both the state of HIV prevention and the lives of people living with HIV. Since then, the mortality rate from AIDS has decreased, and the infection has transformed from a fatal illness to a chronic, more manageable one. Meanwhile, 30 years into the HIV epidemic, HIV prevention interventions throughout the world have varied tremendously in both the theories that guide them and the contexts in which they are delivered. Our main aims in this chapter are to (1) selectively review approaches to preventing HIV infection and (2) discuss issues surrounding chronic disease management of HIV.

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In the development of HIV prevention interventions, an important consideration is the distinction between primary prevention (for uninfected individuals) and secondary prevention (for HIV-infected individuals). Primary prevention aims to help persons avoid contracting HIV. Primary prevention interventions can be undertaken at the individual, couple, community, and social-policy or structural level; it can also involve the promotion of HIV testing and counseling for HIV-negative persons who engage in high-risk behaviors. Secondary prevention aims to reduce adverse consequences for persons living with HIV as well as to reduce transmission to uninfected persons. Within secondary prevention, the most significant advancement has been made with antiretroviral therapy (ART) for HIV infection and associated medication adherence. ART works to suppress replication of the virus resulting in improved immune functioning, health, and reduced viral load for people living with HIV. However, the potential maximum benefits of ART will not be realized if people fail to adhere to their medications.

Patient- vs. Disease-Centered Approach

Altogether, with proper adherence to ART, the lives of people living with HIV can potentially be long and productive. Thus, secondary prevention efforts would benefit most when interventions are

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not only disease-centered but also patient-centered. That is, prevention for positives must recognize the many and intertwined aspects affecting disease management, including medication adherence, comorbid conditions, quality of life, and HIV stigma. Further, given the fact that these factors operate at multiple levels and multiple domains of an HIV-positive person's risk environment, prevention interventions are most likely to succeed when they shift the focus outside the individual. Interventions that target not only one's individual psychology but also the structural factors in one's environment are those most likely to achieve long-lasting behavior change.

Historically, HIV prevention interventions have been driven by a number of theories of behavior change. Recently, new biomedical models approaches have emerged that can be paired with behavior change models, including "treatment as prevention" (also known as "seek and treat"), pre-exposure prophylaxis, and male circumcision. Additionally, the HIV risk environment has been targeted as a means to achieve optimal HIV risk reduction among populations at risk for HIV.

HIV Prevention Approaches

Interventions based on theory result in greater behavior change (DiClemente & Peterson, 1994). However, standardization of theory-based interventions may not be optimal in achieving reductions in HIV cases given variations in HIV prevalence and incidence worldwide. Risk populations also vary widely by geographic region. Because of this, HIV prevention interventions must be tailored to account for local conditions and needs. The diverse HIV epidemics around the globe may be due to the infectiousness of the virus itself, the stage of the epidemic (generalized vs. concentrated), or the effectiveness of interventions that have been deployed. Different cultures, risk groups, and social drivers suggest that effective interventions may require different theoretical approaches. One way to organize our thinking about HIV prevention intervention that has gained increasing attention is the risk environment model, which asserts that four types of environmental influences – physical, social, economic, and policy – interact at the micro- and macro-levels to explain HIV transmission in at-risk populations. The micro-risk environment focuses on personal decisions and the influence of community-level norms and practices, while the macro-risk environment encompasses structural factors, such as laws, military actions, economic conditions, and wider cultural beliefs (Rhodes & Simic, 2005). Table 31.1 summarizes the HIV risk environment as it applies to HIV prevention interventions. Table 31.1 also lists behavioral theories that have been incorporated into the intervention examples that have addressed various levels of the risk environment. With the HIV epidemic evolving in magnitude and diversity, the development and implementation of interventions that integrate theoretical frameworks, biomedical models, and the risk environment of targeted populations will offer substantial benefits to efforts to reduce HIV transmission worldwide.

Global HIV prevention efforts have focused on various risk populations, including men who have sex with men (MSM), female sex workers (FSW) and their clients, high-risk heterosexual women, injection drug users (IDU), and transgendered individuals. HIV prevention efforts have scored successes and faced challenges, because each geographic region has a different presentation of the HIV epidemic with different populations that are most at risk.

Theories and Models Used in HIV Prevention Interventions

Behavior Change Theories and Models

A number of theoretical models of HIV-related behavior change have been either adapted or used in entirety to reduce sexual- or drug-related risk behaviors (or both) in various high-risk populations. Some of these models and theories are (1) the Health Belief Model; (2) Transtheoretical Model – Stages of Change; (3) Theory of Reasoned Action; (4) Social Cognitive Theory;

Table 31.1 The HIV risk environment model applied to HIV prevention interventions

Risk environment	Micro-environmental			Macro-environmental		
	Content	Theory	Example	Content	Theory	Example
Physical	• Homelessness • Prisons/Incarceration • Sex work locations • Drug use locations	None	**The Iran Prison Organization's** HIV prevention package for IDU prisoners; MMT programs constitute a main component; other services inc. NSPs and HIV education.	• Drug trafficking and distribution routes • Deportation • Geographical shifts in population	None	**The Living with HIV/AIDS project in Portugal** provides home care, treatment, psychosocial, rehab and legal support for migrants living with HIV and their families.
Social	• Relationship and network dynamics • Peer norms • Physical/sexual violence • Community attitudes • Local policing practices • Sexual orientation	Diffusion of Innovation Theory	**NIMH Project Accept in Africa**, designed to change community norms by (1) making VCT more available in community; (2) engaging community through outreach; and (3) providing post-test support.	• Stigma and discrimination • Exposure to war, conflict, or disasters • Ethnic or racial disparities • Gender inequalities • Social and cultural norms	None	**New York State (US) Human Rights Law** Bans discrimination against individuals with HIV/AIDS or those perceived to be infected with HIV; Office of AIDS Discrimination Issues handles complaints of HIV-related discrimination.
Economic	• Cost of condoms, syringes, medication • Few income generation and employment opportunities • Survival sex work • Cost of health care	None	**Intervention with Microfinance for AIDS and Gender Equity (IMAGE)** Group based microfinance and a gender and HIV education curriculum South African women.	• Scarcity of health service revenue and spending • Employment practices • Economic development	None	**CDC Funding ($359 million annually, FY2012-FY2016) for health department funding**: A new approach that better matches prevention dollars to HIV burden in affected areas focusing on high-impact interventions.
Political	Ensuring widespread coverage of: • HIV/STI testing and counseling • Antiretroviral therapy • Housing assistance for drug users, abused women, etc. • Sterile needles and syringes • Drug treatment • Male and female condoms	None	**HIV testing and linkage to care in US** Goal of 2010 National HIV/AIDS Strategy over the next 5 years is to increase percentage of newly diagnosed people linked to care within 3 months from 65% to 85%.	Laws and policies governing: • Protection of human and health rights • Sex work • Possession of drugs • Syringe access and exchange • Free highly active antiretroviral therapy coverage • Drug treatment	None	**100% Condom Use Campaign in Thailand** Condom use-only policy that requires all sex workers to use condoms with every customer; enlisted the aid of health authorities, governors, police, sex workers, and owners and managers of sex establishments.

Content for the risk environment model adapted from Strathdee, Hallett, et al., (2010) and Rhodes & Simic (2005)
MMT methadone maintenance treatment, *VCT* voluntary counseling and testing

(5) AIDS Risk Reduction Model; (6) Social Networks, Social Influence, and Peer Norms Theory; (7) Diffusion of Innovation Theory; and (8) Theory of Gender and Power. In the below section, we highlight these theories beginning with those focused more on individual factors followed by those focused on social and environmental factors.

Health Belief Model

The Health Belief Model is used to facilitate behavior change through attitudes and beliefs about the behavior (Rosenstock, Strecher, & Becker, 1994). Based on this model, individuals will change their behavior if (1) they regard themselves as susceptible to the condition, (2) they believe the health condition to have potentially serious consequences, (3) they believe that a course of action available to them would be beneficial in reducing either their susceptibility to or the severity of the condition, and (4) they believe that the anticipated barriers to (or costs of) taking the action are outweighed by its benefits (Rosenstock, Strecher, & Becker, 1994). Additional components of the model are (1) cues to action, a component that has not been systematically examined and refers to physical symptoms of a health condition or environmental factors that motivate individuals to change their behavior; (2) diverse demographic, sociopsychological and structural variables that may affect the individual's perceptions and indirectly influence the behavior; and (3) self-efficacy, introduced by Bandura, referring to the belief that one is able to execute the behavior required to produce the desired outcome (Rosenstock, Strecher, & Becker, 1994). Limitations of the Health Belief Model are that often only selected components are used to guide HIV prevention interventions and it does not incorporate the influence of social norms and peer influences on an individual's decision regarding their behaviors. Nonetheless, the model has been used in primary prevention of HIV through increasing condom use and in secondary prevention through early treatment of HIV.

Transtheoretical Model: Stages of Change

The Transtheoretical Model is organized around five distinctive stages through which individuals go through in making behavior changes: (1) *pre-contemplation*, with no intention to change behavior in the foreseeable future; (2) *contemplation*, giving serious consideration to changing behavior by weighing the pros and cons; (3) *preparation*, when individuals are ready to take action and are seriously planning to change their behavior; (4) *action*, when individuals initiate overt changes in their behavior and their efforts to change are visible to others; and (5) *maintenance*, a time of continued behavior change while preventing potential relapses (Prochaska, Redding, et al., 1994). Applied to HIV prevention in the form of condom use behavior: (1) *precontemplation* is not considering using condoms; (2) *contemplation*, recognizing the need to use condoms; (3) *preparation*, thinking about using condoms in the near future; (4) *action*, using condoms consistently for a short period; and (5) *maintenance*, using condoms consistently for a long period.

An important consideration in the application of this model to interventions is the identification of intervention methods linked with each stage. According to the theory, if a given intervention is mismatched to an individual's stage of readiness for change, it is likely to be ineffective (Prochaska, Redding, et al., 1994). Effective HIV prevention interventions are those that have been mapped onto an individual or population's readiness or stage of change. Individuals may pass through all stages but do not necessarily move in a linear manner. For example, in an HIV behavioral intervention for US women at risk for or infected with HIV, stage-tailored intervention print materials based on role model stories were used to model and encourage women's movement from their current stages to the next stage in terms of safe sex practices (Cabral, Cotton, et al., 2004). These stories incorporated a brief narrative about a woman's successful movement from an earlier to a later stage, the processes of change she used

that contributed to her successful movement between stages, the stage of change achieved through this process, and her current stage of change related to HIV risk behaviors (Cabral, Cotton, et al., 2004). Most women reached by this intervention were at early stages of change for condom use, and behavior change overall was a gradual process (Cabral, Cotton, et al., 2004). In another HIV/STD prevention program for adolescents, individual counseling sessions were tailored to each participant based on their stage of readiness and influencing factors (i.e., cognitive, emotional, and behavioral activities and processes that people engage in when attempting to change behavior). With regard to disease prevention (i.e., condom use only or postponing sexual activity), those starting in pre-contemplation/contemplation were more likely to move forward to later stages than those in action/maintenance (Hacker, Brown, et al., 2005). Thus, the intervention was more successful at moving teens forward from lower stages of change than helping teens stay in action and maintenance (Hacker, Brown, et al., 2005).

Theory of Reasoned Action

The Theory of Reasoned Action has been applied to HIV prevention interventions targeting a number of at-risk populations including women, FSWs, MSM, and IDUs, frequently focusing on the promotion of condom use. The central premise of the Theory of Reasoned Action is that individuals make behavioral decisions on the basis of a reasoned consideration of the available information. Behavioral intentions reflect the extent to which an individual is motivated to perform the behavior or the individual's willingness to perform it (Fishbein & Ajzen, 2010). An individual's behavioral intentions are influenced by two conceptually distinguishable factors: (1) *attitude*, which reflects how favorably or unfavorably a person feels toward performing the behavior and which is shaped by an individual's beliefs regarding the behavior's outcomes and the evaluation of consequences of potential outcomes, and (2) *subjective norm*, which refers to the extent of perceived social pressure to perform the behavior and which is shaped by an individual's beliefs regarding other people's views of a behavior and the individual's willingness to conform to those views (Terry, Gallois, & McCamish, 1993). A limitation of the Theory of Reasoned Action is its inability, due to its individualistic approach, to consider the role of structural and environmental issues.

Social Cognitive Theory

Social Cognitive Theory asserts that providing information alone will not change behavior; rather, sustained behavior change requires that the person possess the skills needed to engage in the behavior and the ability to use these skills consistently and under difficult circumstances. In a reciprocal causation model, the following elements in Social Cognitive Theory operate as interacting determinants: (1) personal determinants in the form of cognitive, affective, and biological factors, (2) behavior, and (3) environmental influences (Bandura, 1986, 1994). This theory identifies four components for successful implementation: (1) information or knowledge, (2) mastery of self-protective skills and self-efficacy for implementing the skills, (3) social competency skills acquired through rehearsal and practice, and (4) social support for precautionary changes. Social Cognitive Theory is the most frequently used model for HIV behavioral interventions.

AIDS Risk Reduction Model

The AIDS Risk Reduction Model (Catania, Kegeles, & Coates, 1990) incorporates several variables from other behavior change theories, including the Health Belief Model and Social Cognitive Theory to provide a framework for explaining and predicting behavior change efforts of individuals specifically in relationship to the sexual transmission of HIV/AIDS. The AIDS Risk Reduction Model consists of three stages of behavior change: (1) labeling of high-risk behav-

iors as problematic, (2) making a commitment to changing high-risk behaviors, and (3) seeking and enacting solutions directed at reducing high-risk activities. Movement from stage to stage is expected to be dependent on achieving the goals of prior stages. In addition, several other internal and external motivators may play important roles in maintaining adequate motivation over time. These include (1) knowledge of the risks associated with various sexual practices, (2) perceptions of susceptibility to contracting HIV, (3) perceived costs and benefits associated with reducing high-risk sexual behaviors, (4) self-efficacy beliefs, (5) emotional states, and (6) social factors, including verbal communication skills, reference group norms, help-seeking processes, and social support (Catania, Kegeles, & Coates, 1990). HIV prevention interventions that have been guided by the AIDS Risk Reduction Model often address the reduction of sexual risk behaviors. With minor modifications, the AIDS Risk Reduction Model can be applied to interventions that target reductions in other HIV risk behaviors (e.g., substance abuse, needle sharing) (Catania, Kegeles, & Coates, 1990).

Diffusion of Innovation Theory

Diffusion of Innovation Theory has been used as the rationale for many community-level interventions in the context of HIV prevention. Diffusion of Innovation Theory refers to a process by which an innovation is communicated among members of a social system (Rogers, 2000). An innovation is an idea, practice, or object perceived as new by an individual or other unit of adoption (e.g., an organization). The characteristics of an innovation, as perceived by members of a system, determine the rate at which the innovation is adopted. Five attributes of innovations are (1) *relative advantage*, the degree to which a new idea is perceived as superior to the idea that it replaces; (2) *compatibility*, the degree to which a new idea is perceived as consistent with the existing values, experiences, and needs of potential adopters; (3) *complexity*, defined as the degree to which an innovation is perceived as difficult to understand; (4) *trialability*, the degree to which an innovation may be experimented with on a limited basis; and (5) *observability*, the degree to which the results of an innovation are visible to others (Rogers, 2000).

This model focuses on social networks and utilizes opinion leaders as agents of change. Opinion leaders are trusted, credible, and well-liked people in the community who are recruited and trained to conduct HIV prevention outreach. The Diffusion of Innovation Theory has been applied to HIV interventions in populations at increased risk for HIV through high-risk sexual behaviors. The goal is to diffuse innovative approaches to reducing sexual risk behaviors and increasing use of safer sex strategies. This is accomplished through enlisting a sufficient number of opinion leaders in at-risk communities to support and endorse changes in risk behavior. Although the Diffusion of Innovation Theory provides a framework for conceptualizing how changes in a population's behavior and norms can be achieved by opinion leaders, it does not directly address what opinion leaders should say to influence others to make changes in sexual risk behaviors that are not directly observable (NIMH Collaborative HIV/STD Prevention Trial Group, 2007).

Theory of Gender and Power

The Theory of Gender and Power has been used primarily in prevention interventions that target at-risk women. This theory's conceptual framework incorporates the social influences that compromise disadvantaged women's health and autonomy. The theory distinguishes three primary structures: division of labor, division of power, and the structure of cathexis (Connell, 1987). The sexual division of labor refers to the unequal allocation to women and men of certain occupations, such as "unpaid nurturing work," e.g., child care, housework, and caring for the sick and elderly; this often results in an economic imbalance in which women have to rely on men financially. Applied to HIV prevention, women who are unemployed have a high-demand and

low-control work environment, and limited or no health insurance are at increased risk for HIV acquisition (Wingood & DiClemente, 2000). "Division of power" recognizes the power imbalances in heterosexual relationships that contribute to men's authority, control, and coercion over women. Within this structure, women at increased risk for HIV are those with histories of sexual or physical abuse, low self-assertiveness and self-efficacy, and limited perceived control in their relationships (Wingood & DiClemente, 2000). "Cathexis" refers to society's approved gender roles and its expectations for appropriate sexual behavior. It has been noted that the Theory of Gender and Power, in isolation, implies an intervention with unstructured discussion among the participants about gender and power issues and about how women cope with these issues in their daily lives (St Lawrence, Wilson, et al., 2001).

Biomedical Interventions

Emerging biomedical approaches include medical interventions to block infection, decrease infectiousness, or reduce the risk for HIV infection. Current interventions under investigation or proven to be efficacious are antiretroviral drugs used to reduce infectiousness in HIV-positive individuals or as pre-exposure prophylaxis, male circumcision, microbicides, and HIV vaccines.

Oral Antiretroviral Prevention

Antiretroviral HIV prophylaxis has been very effective in preventing mother-to-child transmission, with widespread use beginning in the 1990s. The use of short-course zidovudine and, subsequently, single-dose nevirapine for pregnant, HIV-infected women has been proven to reduce mother-to-child transmission in non-breastfeeding populations by two-thirds. Since then, several other regimens have been assessed in non-breastfeeding and breastfeeding populations (Padian, Buve, et al., 2008). Currently, there is great hope that this strategy will prove effective against other routes of transmission (Garcia-Lerma, Paxton, et al., 2010). Antiretroviral therapy has been explored as an HIV prevention measure in three domains: (1) reducing infectiousness among HIV-positive persons, (2) preventing infection in high-risk HIV-seronegative populations through pre-exposure prophylaxis (PrEP), and (3) preventing infection among HIV-negative persons through post-exposure prophylaxis (PEP) after occupational or nonoccupational exposure to HIV-infected blood or fluids (Kelesidis & Landovitz, 2011). PrEP uses ART in anticipation of HIV exposure from known or unknown sources with the aim of preventing HIV acquisition or, at least, altering the natural course of infection to attenuate disease progression, reduce morbidity, and/or decrease infectiousness (Kelesidis & Landovitz, 2011). PrEP is a promising prevention strategy consisting of oral administration of continuous (daily) ARV medication by HIV-negative individuals before potential exposure and throughout periods of risk (Garcia-Lerma, Paxton, et al., 2010).

An advantage of PrEP is that it can be used independently of sexual practices and other risk behaviors (Padian, Buve, et al., 2008). Medical prophylaxis is standard for the prevention of many other infections such as malaria, but it is experimental for HIV. Multiple lines of evidence including animal data, human clinical trials, and mathematical models suggest that PrEP might be effective in preventing HIV among high-risk populations (Abbas, 2011; Garcia-Lerma, Paxton, et al., 2010; Kelesidis & Landovitz, 2011). Candidates for use as an oral PrEP agent have largely been selected from drugs that are currently approved for treatment of HIV infection. The characteristics that make for an effective PrEP drug overlap with those for treatment drugs-good tolerability and safety, low pill burden, once-daily dosing, long half-life, high potency, and a good resistance profile (i.e., the HIV virus does not rapidly develop resistance to the drug or broad cross-resistance with other drugs) (Garcia-Lerma, Paxton, et al., 2010). PrEP has been proven effective among MSM, and the US Centers for Disease Control and Prevention (CDC) have issued interim guidance on its use in this population (Centers for Disease

Control and Prevention, 2011c; Grant, Lama, et al., 2010). Other recent studies have shown PrEP to be effective among heterosexual men and women, although important questions remain about which heterosexuals would benefit most (Centers for Disease Control and Prevention, 2011b). And in 2012, the US Food and Drug Administration approved Truvada for PrEP, a drug originally marketed as treatment for people who were already infected with the virus (US Food and Drug Administration, 2012). Truvada is the first drug approved to reduce the risk of HIV infection in uninfected individuals who are at high risk of HIV infection and who may engage in sexual activity with HIV-infected partners. Truvada, taken daily, is to be used for PrEP in combination with safer sex practices to reduce the risk of sexually-acquired HIV infection in adults at high risk.

Male Circumcision

Male circumcision has been shown to be efficacious in preventing female-to-male transmission of HIV infection (Auvert, Taljaard, et al., 2005; Bailey, Moses, et al., 2007; Templeton, 2010). The mechanisms by which male circumcision reduces HIV infection risk have been explored by researchers. The inner surface of the foreskin has a high concentration of HIV target cells. It is lightly keratinized and susceptible to microscopic tears, is exposed to vaginal secretions during sexual intercourse, and provides a moist environment that might sustain the viability of pathogens. Thus, an intact foreskin may facilitate survival and entry of the HIV virus, so that removing the foreskin reduces the risk of HIV infection (Padian, Buve, et al., 2008). Male circumcision also reduces the risk of genital ulcer disease, which has been shown to increase the risk of HIV infection (Padian, Buve, et al., 2008).

The protection benefit of circumcision for male-to-female transmission (the male partner being already HIV positive) has been debated (de Bruyn, Shiboski, et al., 2011; Padian, McCoy, Karim, et al., 2011). Observational studies have suggested lower male-to-female transmission of HIV from circumcised men who were HIV infected (de Bruyn, Shiboski, et al., 2011); whereas randomized controlled trials have shown either that circumcision had no effect on HIV transmission from HIV-infected men with higher CD4 counts or that circumcision reduced male-to-female transmission by up to 46% (de Bruyn, Shiboski, et al., 2011; Padian, McCoy, Karim, et al., 2011). Nonetheless, after three clinical trials demonstrated a strong effect of male circumcision in reducing HIV acquisition, the World Health Organization (WHO) and UNAIDS held a consultation in March 2007, which recommended that circumcision be recognized as an effective intervention for prevention of heterosexual HIV acquisition in men (Padian, Buve, et al., 2008). It also recommended that countries with generalized heterosexual epidemics and low rates of male circumcision be the focus for scaling up of this intervention, within the context of ensuring universal access to comprehensive HIV prevention, treatment, care, and support (de Bruyn, Shiboski, et al., 2011; Padian, Buve, et al., 2008). Implementation of male circumcision as a biomedical intervention in countries has been variable and confounded by human resource constraints, funding shortfalls, ineffective communication strategies, and lack of support from political and traditional leaders (de Bruyn, Shiboski, et al., 2011; Padian, McCoy, Karim, et al., 2011).

Microbicides

Microbicides are chemical agents in the form of creams, gels, and suppositories, applied topically within the vagina or rectum before sexual intercourse in order to prevent HIV and sexually transmitted infections (STIs) (Weber, Desai, et al., 2005). Microbicides were initially conceived as a female-controlled method (vaginal application) to prevent transmission via heterosexual intercourse; however, safe and effective antimicrobial compounds could also serve as important prevention methods for MSM (rectal application) (Padian, Buve, et al., 2008). The majority of microbicide candidates currently under testing are formulated with ARV drugs. The first vaginal microbicide to be studied was nonoxynol-9, an anionic surfactant

initially developed in the 1960s as a contraceptive spermicide with lubricant properties, and latterly used extensively to coat latex condoms (Weber, Desai, et al., 2005). In the 1980s, observational data for nonoxynol-9 gel against HIV/STIs were encouraging. However, in randomized trials in the 1990s, this gel was ineffective in preventing HIV and other STIs (Padian, Buve, et al., 2008). These trials were followed by studies to assess other non-HIV-specific agents, such as vaginal defense enhancers, entry inhibitors, and fusion inhibitors; several of these products have been assessed, with disappointing results (Padian, Buve, et al., 2008). There is hope, however, that better results will be achieved with agents that specifically inhibit HIV and are based on the same ARV drug platforms that have been used successfully for HIV treatment regimens. These ARV drug platforms have shown quite remarkable efficacy in explant tissue and animal infection models.

Unlike their predecessors, these newer-generation products do not have to be applied at the time of sex (Microbicide Trials Network, 2011). Researchers are exploring their daily use as a gel and other formulations, such as a ring, that in theory could be inserted once a month, for example (Microbicide Trials Network, 2011). Tenofovir, a nucleotide analogue reverse transcriptase inhibitor used in HIV/AIDS therapy, represents the most advanced candidate within this category (Hladik & Doncel, 2010). A 1% vaginal gel formulation of tenofovir, delivered into the vaginal vault up to 12 h before and within 12 h after intercourse, reduced HIV acquisition by nearly 40% overall in the recently completed CAPRISA 004 Phase IIb HIV prevention trial, which involved 889 South African women (Hladik & Doncel, 2010; Abdool Karim, et al., 2010).

Tenofovir now represents the first vaginal microbicide proven to be safe and efficacious in the primary prevention of HIV in women. Several other clinical trials are underway investigating anti-HIV microbicides based on non-nucleoside reverse transcriptase inhibitors such as dapivirine. Specifically, the ASPIRE study was recently launched to test the effectiveness and extended safety of a drug-infused vaginal ring for preventing HIV infection in uninfected women in five African countries (Department of Health and Human Services, 2012). Also known as MTN 020, the study aims to determine whether the HIV antiretroviral drug dapivirine can safely and effectively prevent HIV infection when continuously released in the vagina from a silicone ring replaced once every 4 weeks. Significantly, the ASPIRE study is the first effectiveness trial of a vaginal ring for HIV prevention and of a product that contains an antiretroviral other than tenofovir or tenofovir combined with the antiretroviral emtricitabine (Truvada) (Microbicide Trials Network, 2012). Other classes of microbicide candidate involve specific entry inhibitors, including gp120 blockers, gp41 blockers, and CCR5 antagonists, integrase inhibitors, protease inhibitors, and a combination of active ingredients (Hladik & Doncel, 2010; Microbicide Trials Network, 2011). Although the commercial availability of microbicides is likely to be several years away, strategies for regulatory approval and successful product launch should be initiated to address the cultural and educational issues that will be essential to ensure that they be used correctly and in accordance with other prevention strategies (Nuttall, 2010). To date, most microbicide research has focused on vaginal microbicides used for the prevention of HIV in women. Yet receptive anal intercourse is common among MSM, and there is increasing evidence that heterosexual women in both the developed and low- and middle-income countries also practice receptive anal intercourse. Because of the prevalence of this practice, current studies are evaluating the safety of vaginal microbicides when used in the rectum, as well as exploring candidate microbicides formulated specifically for rectal use (Microbicide Trials Network, 2011).

Vaccines

Strategies for vaccine development include innate, cell-mediated, or antibody-mediated resistance to infection, or all three (Padian, McCoy, Karim, et al., 2011). The pursuit of a safe and effective HIV vaccine has met with disappointment over the past three decades, with the termination of studies showing neither protection

from HIV nor alteration in viral replication in vaccine recipients (Munier, Andersen, & Kelleher, 2011; Padian, McCoy, Karim, et al., 2011). More recently, there has been renewed optimism about potential HIV vaccines, resulting from the trial of the Thai RV144 (ALVAC and AIDSVAX) vaccine administered to men and women aged 18–30 in Thailand, which revealed a 26.4% efficacy in the intention-to-treat analysis and 31.2% in the modified intention-to-treat analysis. Vaccination with ALVAC and AIDSVAX modestly reduced the risk of HIV infection but did not affect the viral load or CD4 T-cell counts in participants who were subsequently infected with HIV (Munier, Andersen, & Kelleher, 2011; Rerks-Ngarm, Pitisuttithum, et al., 2009). Research is ongoing to elucidate the underlying mechanisms of these modestly successful compounds (Munier, Andersen, & Kelleher, 2011).

A successful HIV vaccine would ideally be safe, affordable, tolerated by recipients, and elicit an effective and long-lasting immune response comprising both neutralizing antibodies (Nabs) and cytotoxic T-lymphocytes (CTL) that recognize diverse strains of the virus and protect at sites of possible infection (Munier, Andersen, & Kelleher, 2011). It is believed that Nabs would function to prevent infection at mucosal surfaces, whereas CTL would control the spread and amplification of any virus that avoids initial neutralization (Munier, Andersen, & Kelleher, 2011). A successful HIV vaccine might thus have two separate effects, one prophylactic and the other therapeutic, slowing or preventing disease progression and reducing viral load and CD4 cell-count decline in those whose infection is not prevented (Munier, Andersen, & Kelleher, 2011). Both effects would reduce transmission and lead to improved control of the HIV epidemic.

Integrating Behavioral and Biomedical Approaches: Treatment as Prevention

Thirty years after the start of the HIV epidemic, scientists are examining the benefits of integrating behavioral and biomedical approaches in HIV prevention. Given that antiretroviral therapy (ART) works in reducing infectiousness of HIV-positive persons, HIV treatment has received attention as a potentially high-impacting prevention strategy. The utility of treatment as prevention in reducing HIV transmission rates has been supported with mathematical modeling and recently with findings from the HIV Treatment for Prevention Trial (HPTN) 052 (Cohen, Chen, et al., 2011). This trial showed a 96% reduction in HIV transmission within discordant couples. In theory, treatment as prevention can be successful in curbing the epidemic when high-risk individuals engage in frequent testing and if found to be HIV-positive, are linked to care and receive early treatment. Further, the "seek and treat" approach argues that a reduction in a community's viral load may be achieved when masses, ideally every individual, are tested. The effectiveness and feasibility of this approach is currently being tested in the United States in the Test, Link to Care Plus Treat or TLC-plus HPTN 065 study among MSM in Washington, D.C., and New York City (El-Sadr & Branson, 2010).

Individuals infected with HIV must be found, tested, and linked to care in order for seek and treat to achieve maximum outcomes in curbing the epidemic. Therefore, access to hard-to-reach and hidden populations is crucial. There are a number of approaches to finding difficult populations including the use of respondent-driven sampling (RDS) and outreach programs. RDS is a relatively new and arguably most promising sampling approach that involves a mix of snowball sampling and mathematical modeling that weighs the sample to compensate for non-randomness. The expanded HIV testing component of HPTN 065 involves social mobilization with targeted testing messages, as well as implementation of a universal offer of HIV testing in emergency departments and hospital inpatient admissions. However, even when individuals are adequately found and tested, treatment as prevention will fail when some key factors are not recognized. These include intervention adherence, treatment of sexually transmitted coinfections, and risk compensation.

Intervention Adherence

Issues surrounding adherence are receiving more attention with advances in biomedical technologies for HIV prevention. Findings from studies of HIV-serodiscordant couples suggest near zero HIV transmission when infected partners have undetectable blood plasma viral loads (Quinn, Wawer, et al., 2000). Further, in the absence of co-occurring STI, ART can result in undetectable virus in the genital tract. Thus, with proper adherence, HIV treatment can be an effective prevention tool. Strict adherence is also demanded for the success of other biomedical prevention technologies, including pre-exposure prophylaxis (PrEP) and vaginal gel microbicides.

Different prevention strategies require varying degrees of adherence. For example, male circumcision requires one decision (to obtain the intervention or not), whereas other methods like oral antiretroviral drugs for HIV-negative individuals require daily decisions. Just as with reduced infectiousness among HIV-positive individuals on ART, reduced infectability is only achieved and sustained among HIV-negative individuals on PrEP given optimal adherence. The same is true for microbicidal methods. Whereas HIV transmission was reduced by 39% overall in the CAPRISA 004 trial, a 54% reduction was observed among high adherers (>80%). In sum, adherence is demanded for the success of biomedical prevention methods. Consequently, it has become more important for behavioral and biological scientists who engage in HIV prevention research to use their respective tools and skills to work together toward common goals (Padian, Buve, et al., 2008).

Sexually Transmitted Coinfections

Reduced infectiousness among HIV-positive individuals can only be achieved with proper adherence to antiretroviral medications, as well as the treatment of co-occurring STI. Sexually transmitted coinfection makes HIV-positive people much more infectious than their blood viral load indicates. The inflammatory process involved in STI increases the concentration of CD4 (immune) cells in the genital tract, including concentration of those cells already infected with HIV. STIs like trichomoniasis and bacterial vaginosis can also cause genital bleeding, heightening the risk of sexual transmission and mother-to-child intrapartum transmission. An important question however is whether STI treatment to prevent HIV transmission should target the HIV-negative or HIV-positive individual, as both are potentially rendered more vulnerable to becoming infected and infecting someone else, respectively, when they are dually infected.

Whereas there is strong biological plausibility and different studies and meta-analysis have confirmed the association between STI and HIV infection (Johnson & Lewis, 2008), results from intervention research have not been entirely clear on whether there is a causal association. For example, research among dually infected individuals has shown that suppression therapy of herpes simplex virus (HSV) reduces plasma, seminal, and genital HIV viral load (Baeten, Strick, et al., 2008; Zuckerman, Lucchetti, et al., 2009). However, such findings have not been matched by the results of several randomized control trials. One trial that included women who were HIV negative and HSV positive at baseline who received suppressive treatment with acyclovir did not show evidence of decreased HIV incidence (Watson-Jones, Weiss, et al., 2008). Another trial involving over 3000 HIV-serodiscordant couples where the HIV-infected partner was coinfected with HSV also revealed a similar null finding (Lingappa, Kahle, et al., 2009). Interpreting these trials has been challenging however, as each involves complex issues surrounding adherence, statistical power, population, and/or intervention content and implementation. Treatment of sexually transmitted coinfection is still regarded as an important area for HIV prevention.

Risk Compensation

Risk compensation has been a growing concern with the advent of ART (Baggaley, Powers, & Boily, 2011) and other preventive innovations

(Hagel & Meeuwisse, 2004). Risk compensation related to HIV essentially involves an individual's perception that receiving HIV treatment or another preventive intervention (e.g., male circumcision, PrEP) renders HIV transmission less likely, and therefore the individual "compensates" by engaging in higher-risk behavior. The notion of reduced risk is so powerful that studies have shown that the mere promise of expanded access to treatment or to PrEP is associated with significant increases in risk behavior among MSM (Stolte, Dukers, et al., 2004), IDUs (Tun, Celentano, et al., 2003), and heterosexuals (Grémy & Beltzer, 2004). HIV-positive individuals on ART do not appear to be more likely to engage in unprotected sex than individuals not on ART. There is however consistent meta-analytic evidence that individuals have more unsafe sex than persons if they believe that having an undetectable viral load protects against HIV transmission (Crepaz, Hart, & Marks, 2004). Consequently, perceptions of risk must be addressed in antiretroviral counseling.

Adherence

As important as adherence is across all of prevention and disease management, it takes on particular importance with HIV. Only with strict medication adherence does HIV become a chronic not fatal disease. A window of 85–95% adherence is typically demanded in order to achieve viral suppression and thereby reduced infectiousness, with at least 95% adherence to reduce early mortality (Lima et al., 2009). Strict initial adherence is argued to be especially important, as poor initial adherence can lead to failure of first-line medication regimens and drug resistance. However, attention to the Necessity-Concerns Framework is critical in promoting initial adherence, since patients' views and perceptions of the necessity for ART, even before they begin treatment, may determine whether they maintain adherence over the long term (Horne, Cooper, et al., 2007). In a study that applied the utility of the Necessity-Concerns Framework to patients' perceptions of ART in relation to treatment uptake and adherence, perceived necessity of ART was initially high among those accepting ART (Horne, Cooper, et al., 2007). Variation in perceived necessity of ART at this early stage predicted high adherence 12 months later; however, strong concerns predicted low adherence (Horne, Cooper, et al., 2007). Nonadherence can potentially lead to spread of a drug-resistant virus, resulting in a public health disaster. Some have used this argument to justify withholding treatment to populations at risk for nonadherence, including individuals in sub-Saharan Africa. However, research to date has demonstrated that this concern is largely unfounded. The evidence suggests that sub-Saharan Africans are no more likely to be nonadherent than North Americans and that the reverse may actually be true (Mills, Nachega, et al., 2006). Although different populations and settings may experience different barriers to adherence, many of the important barriers to adherence are consistent across developed and developing nations.

Generally, barriers to adherence can be patient related (e.g., self-efficacy), medication related, (e.g., regimen complexity), schedule related (e.g., a chaotic daily schedule), and social related (e.g., poor social support). A systematic review of the literature showed that consistent barriers across multiple settings include fear of disclosure, concomitant substance use, forgetfulness, suspicions surrounding treatment, a lack of understanding of treatment benefits, complicated regiments, poor quality of life, work, and family responsibilities, and access to medication (Mills, Nachega, et al., 2006). The last is of greatest concern in developing settings.

Chronic Disease Management

As people who are living with HIV are now living longer with proper ART adherence, researchers have focused more attention on chronic disease management among people living with HIV. Research on this issue has shown that approaches to HIV care have shifted from tertiary/specialist care to primary care, which was

the approach largely employed at the beginning of the epidemic (Chu & Selwyn, 2011; Northfelt, Hayward, & Shapiro, 1988). Whereas opportunistic infections were of the most significant concern for HIV-positive patients, causes of death have now shifted to end-stage liver and kidney disease, as well as other non-HIV-related malignancies (Hooshyar, Hanson, et al., 2007; Lewden, May, et al., 2008; Palella, Baker, et al., 2006). Thus, HIV care in ambulatory settings has focused on the prevention of common diseases. The HIV-patient population has also evolved since the advent of ART. Aging-related issues have received growing attention in the HIV literature, as most of the people living with HIV are of middle and older age. In fact, 75% of the population living with HIV in the United States are at least 40 years old (CDC, 2007). There is increasing importance to address the needs of aging HIV-positive patients, including financial strain and social isolation (Pitts, Grierson, & Misson, 2005). Living with chronic HIV requires the ability and responsibility of long-term, day-to-day care.

With chronic illness, as opposed to acute illness, the patient is the primary caregiver (Holman & Lorig, 1997). The World Health Organization includes self-management as a best practice to improve clinical care and outcomes for chronic diseases (World Health Organization, 2001). A review of the literature on chronic disease self-management to highlight HIV-specific challenges showed that there are common elements or tasks in chronic disease self-management that fit within the categories of physical health, psychological functioning, and social relationships (Swendeman, Ingram, & Rotheram-Borus, 2009). Self-management programs should include treatment adherence, but this must be nested within a variety of other skillsets, including cognitive techniques for side effect and symptom management, working with healthcare providers, understanding laboratory tests, managing fatigue, and healthy eating and exercise (Gifford & Groessl, 2002). In the section below, we review some of the major factors affecting chronic disease management, including (1) comorbid conditions, (2) quality of life, and (3) stigma.

Quality of Life

As the course of the HIV epidemic has changed with ART, so have the challenges that affect the health-related quality of life of people living with HIV. Health-related quality of life refers to how well one functions and one's perceptions of one's own well-being in physical, mental, and social domains of life (CDC, 2011a). Understanding health-related quality of life among people living with HIV is important as it helps to determine the burden of chronic disease, changes in health over time, and treatment effectiveness.

Research suggests that compared to the general population, people living with HIV have worse health-related quality of life. However, this depends on disease stage and quality of life domain (Imam, Flora, et al., 2012). Individuals who have HIV and are asymptomatic report physical functioning similar to the general population, whereas not surprisingly those who are symptomatic or have AIDS report worse physical functioning (Hays, Cunningham, et al., 2000). In comparison, individuals living with HIV/AIDS regardless of symptoms seem to experience worse emotional functioning or mental health compared to the general population. Further, emotional well-being appears to be worse for people at all stages of HIV than for individuals who have other chronic diseases (e.g., diabetes, multiple sclerosis, end-stage renal disease) but better than individuals with clinical depression (Hays, Cunningham, et al., 2000).

A number of demographic, psychological, and social factors are associated with better health-related quality of life. This includes being employed, higher income, better social support, spirituality/religiousness, engaging in active and positive coping, and physical activity/exercise (Hays, Cunningham, et al., 2000; Remor, Fuster, et al., 2012). From a stress-coping perspective, individuals who utilize adaptive and active coping strategies appear to experience better quality of life than individuals who use maladaptive or passive coping strategies. This body of knowledge has helped lead to the development of interventions aimed to improve quality of life among individuals living with HIV (Brown & Vanable, 2011).

One type of intervention to improve quality of life has focused on exercise. Exercise training improves and maintains health and has been considered an important adjuvant therapy for HIV-positive patients (American College of Sports Medicine, 2006; Stringer, 1999). There has been a focus on improving both physical strength and endurance concurrently. A review of randomized controlled trials testing the efficacy of this concurrent training on health-related quality of life showed that it is safe and may be beneficial for medically stable adults living with HIV (Gomes Neto, Ogalha, et al., 2013). Thus, concurrent training may be an important intervention in the care of people living with HIV.

Other approaches focus on targeting psychological factors and mental or spiritual health (e.g., Brown, Hanson, et al., 2013). One particular intervention that appears to be more comprehensive and efficacious in improving quality of life, as well as HIV outcomes like viral load, uses Cognitive Behavioral Stress Management (CBSM). CBSM interventions directly focus on reducing stress and teaching cognitive coping skills and also indirectly impact perceived environmental control and self-efficacy, thereby also influencing positive social support. CBSM interventions provide relaxation skills training, social skills training, instruction in self-monitoring of environmental stressors, and teaches cognitive restructuring techniques. There is evidence among different populations affected by HIV (e.g., HIV-positive gay men) that CBSM can positively influence a number of outcomes, including reducing sexual risk behavior (Coates, McKusick, et al., 1989), depressed mood (Kelly, Murphy, et al., 1993), and CD4 count (Antoni, Baggett, et al., 1991).

Acknowledging the value of health-related quality of life among people living with HIV means recognizing the significance of mental health. HIV/AIDS is one of the most biologically "strong" diseases with which we deal, yet the roles of emotions and mental health are also substantial. Mental disorders (e.g., depression, bipolar disorder, schizophrenia) make individuals more vulnerable to behaviors that transmit HIV and interfere with HIV treatment adherence (Vlassova, Angelino, & Treisman, 2009). While ART works to improve immune functioning and overall physical health, improving mental well-being should also be a primary goal in prevention for HIV-positive individuals. As others have previously stated, there is "no health without mental health" (Prince, Patel, et al., 2007). Also, improved mental health is associated with other healthy outcomes, including a lower likelihood of substance use, reduced sexual risk behavior, and improved adherence to care and treatment (Sikkema, Watt, et al., 2010). Ultimately then, better mental health among HIV-positive individuals may lead to a reduction in HIV transmission. Secondary prevention efforts must include mental health treatment.

Comorbid Conditions

The most common comorbid conditions with HIV are substance use disorders and depression (Bing, Burnam, et al., 2001). People who receive treatment for substance use are more likely to be HIV-infected than the general population (Woods, Lindan, et al., 2000). Further, data from a large, nationally representative US sample revealed that both substance use and HIV increase the likelihood of having major depression (Hasin, Goodwin, et al., 2005). Depression among people living with HIV is relatively common and may result from multiple stressors including reduced social support, social isolation, and increased exposure to violence (Kokkevi & Stefanis, 1995).

The co-occurrence of HIV and comorbid conditions is associated with reduced self-care, including poor HIV medication adherence and high-risk behavior. For example, in a study of individuals living with HIV who also had an alcohol use disorder, lower self-efficacy was associated with poor medication adherence, which in turn affected viral load (Parsons, Rosof, & Mustanski, 2008). In another study of gay and bisexual men at an outpatient substance abuse treatment, the co-occurrence of HIV and psychiatric diagnoses, including major depressive disorder and social phobia, were associated with an

increased likelihood of STIs (Shoptaw, Peck, et al., 2003). A meta-analysis has also shown that depression is related to accelerated immune system decline and mortality in people living with HIV (Herbert & Cohen, 1993), and a study done with HIV-positive persons from a community health center showed that this relationship exists even beyond the effects of ART nonadherence (Safren, Otto, et al., 2001). A body of research has also shown that poor health conditions co-occur and interact synergistically to contribute to higher-risk behavior and ultimately HIV transmission.

Substance abuse, violence, and AIDS have been understood to co-occur in what has been labeled a syndemic or the co-occurrence of two or more epidemics that interact and synergistically contribute to excess burden of disease in a population (Singer, 1996; Singer & Clair, 2003). Since initially proposed and modeled, researchers have used syndemic theory to examine HIV risk in high-risk and vulnerable populations, including urban ethnic minorities, MSM, and women in resource poor settings (González-Guarda, Florom-Smith, & Thomas, 2011; Parsons, Grov, & Golub, 2012; Pitpitan, Kalichman, et al., 2013; Stall, Mills, et al., 2003). This research has shown that individuals who experience multiple comorbid conditions, including but not limited to depression, history of childhood abuse, history of intimate partner violence, and substance use, are more likely to engage in high sexual risk behavior. A consistent finding is that the relationship is linear, such that individuals who report more psychosocial conditions report higher-risk behavior, and in some samples a higher likelihood of being or becoming HIV infected. Indeed, people are less likely to effectively engage in self-care and self-protection when they are dealing with a number of difficult conditions in their lives. This suggests that HIV interventions must be multifaceted to treat the whole person, not solely the disease.

To address this gap in current interventions, a sexual risk and stress reduction intervention was recently developed and tested for HIV-positive African-American MSM with childhood sexual abuse histories (Williams, Glover, et al., 2013). Compared to a general health promotion intervention, the stress-focused intervention was more efficacious in decreasing unprotected anal insertive sex and reducing depression symptoms (Williams, Glover, et al., 2013). This was observed for MSM with histories of both high and low childhood sexual abuse severity. In another culturally specific HIV risk reduction intervention for Hispanic women (SEPA [Salud/Health, Educación/Education, Promoción/Promotion, Autocuidado/Self-care]), there were five sessions covering STI and HIV prevention, communication, condom negotiation and condom use, and violence prevention (Peragallo, Gonzalez-Guarda, et al., 2012). SEPA was efficacious in decreasing STI incidence, improving condom use, decreasing substance abuse and intimate partner violence, and improving communication with partner (Peragallo, Gonzalez-Guarda, et al., 2012). These select interventions demonstrate that addressing comorbidities or syndemic problems can successfully improve multiple health outcomes.

Stigma

Perhaps nothing is more embedded into the multiple facets of the lives of people living with HIV than stigma. The social stigma attached to HIV is the process of being labeled, stereotyped, devalued, and discriminated against as a function of being HIV positive (Goffman, 1963; Link & Phelan, 2001). The underlying processes surrounding stigma are complex as stigma is socially constructed and is tied to concerns for power and dominance (Parker & Aggleton, 2003). Generally speaking, fear of contagion and negative, morally driven, and value-based assumptions about people who have HIV and its transmission helps to account for the severe stigma attached to the disease (Jones & French, 1984). People living with HIV encounter a great deal of prejudice and discrimination at multiple levels and domains of life.

At an institutional level, people living with HIV are affected by their government's laws and policies about or related to HIV. For example, HIV-positive individuals were denied access to care and treatment under the presidency of Thabo

Mbeki, and the United States currently denies federal funding for syringe exchange programs, which have shown to be instrumental in reducing HIV risk among injecting drug users. At an interpersonal level, people living with HIV often experience discrimination from employers and co-workers, are refused access to medication and health facilities, and are isolated by friends and family. Finally, at an individual level, many people living with HIV personally endorse or internalize the negative beliefs and feelings about being HIV positive, which can result in self-isolation from social supports and healthcare. Consequently, HIV stigma is associated with poor mental health, social and physical isolation, reduced access to care and treatment, higher transmission risk behavior, poor medication adherence, and overall poor quality of life. Worsening the situation is the fact that social stigmas are also attached to virtually all of the frequent comborbid conditions with HIV, including drug abuse, violence victimization, and mental health.

Despite its pervasiveness and the negative outcomes associated with HIV stigma, researchers have done relatively little to acknowledge it in HIV treatment and prevention efforts. This neglect has much to do with inconsistent definitions and relatedly an absence of good measurement tools. In an effort to provide direction to HIV researchers, Earnshaw & Chaudoir (2009) put forth an HIV stigma mechanism model that outlined how HIV stigma can operate from the perspective of the target and the perpetrator. That is, from the perspective of the person who is doing the devaluing and discrimination and of the person who is being devalued and discriminated against. Using this approach, HIV-positive individuals can experience stigma in three ways. One is anticipated stigma, or the extent to which an individual expects to be evaluated and treated negatively as a function of their HIV status. The second is enacted stigma, or the extent to which the individual believes they have experienced prejudice and discrimination from others. Third, as previously mentioned, is internalized stigma, or the extent to which the individual herself or himself endorses the negative beliefs, attitudes, and feelings toward people with HIV.

HIV stigma would be ideally tackled with community and political involvement to institute protections for and reduce prejudice and discrimination toward HIV-positive persons. This can include but is not limited to collective action efforts and public education about HIV and its transmission with the aim of reducing or eliminating the social stigma attached to HIV. HIV prevention interventions may also intervene at one or more of these stigma mechanisms. For example, prevention programs might incorporate strategies to reduce anticipated or internalized stigma among people living with HIV. A review of HIV stigma reduction interventions showed that a number of strategies exist for targeting stigma at its multiple levels (Heijnders & Van Der Meij, 2006). At the individual level, different counseling approaches may help to decrease perceived stigma. These include counseling to reduce emotional distress following an HIV test (Simpson, Johnstone, et al., 1998), selective disclosure of HIV status (Kaleeba, Kalibala, et al., 1997), and cognitive therapy to help reduce internalized stigma (Chan, Kong, et al., 2005; Corrigan & Calabrese, 2005). Self-help, advocacy, and support groups also appear to help reduce stigma at the individual level (Lyon & Woodward, 2003). At the interpersonal level, intervention strategies include educating family, community members, and healthcare providers to help eradicate negative attitudes and beliefs among persons potentially providing care to individuals with HIV (Kidd & Clay, 2003). Both the Memory Book Project in Uganda and the Yale Program for HIV-affected children and families are examples of projects aimed at helping individuals come to terms with stigma, secrecy, disclosure, and loss (Gewirtz & Gossart-Walker, 2000). Finally, at the institutional level, programs to reduce stigma target organizations like the workplace. For example, some projects have targeted instances of discrimination, like mandatory testing of applicants (Busza & Schunter, 2001; POLICY Project, 2003). Other strategies include advocacy and protest (Corrigan & Penn, 1999).

Global Review of Risk Environment Integration into HIV Prevention Interventions

The preceding pages have reviewed theoretical, practical, and disease-specific issues in preventing and managing HIV/AIDS. This has included recognition of the frequent connection between these, as in secondary prevention of AIDS among HIV+ individuals, and the importance of treatment of AIDS to prevent HIV transmission. Thus, HIV/AIDS illustrates a continuum from primary prevention through chronic disease management, as opposed to a view of these as distinct categories. This final section reviews global efforts in these areas, illustrating as noted above how theories and general knowledge about the disease, its prevention, and management need to be tailored to the circumstances in different regions and among different populations. In the interest of economy, we have emphasized prevention, but, as will be seen, many of the prevention efforts reviewed carry over and include elements of treatment and management. This review is selective, not comprehensive. Our examples will highlight strategies used in each setting, with an emphasis on how theories may have been appropriately or inappropriately applied. We conclude with guidance for future intervention efforts that utilize combination HIV prevention methods.

The United States

The Centers for Disease Control and Prevention estimate that more than one million people in the United States are living with HIV (Centers for Disease Control and Prevention, 2008). HIV disproportionately affects certain population groups: MSM, African-Americans, and Latinos. MSM account for more than half of all new HIV infections in the United States, and they are the only risk group in which new HIV infections have been increasing steadily since the early 1990s (Centers for Disease Control and Prevention, 2010; Prejean, Song, et al., 2011). During the period 2006–2009, African-Americans and Latinos consistently had rates of new HIV infection that were 7–8 and three times the rate for whites, respectively (Prejean, Song, et al., 2011). Moreover, in 2009, the rate of new infections among African-American and Latina women were 15 and four times that of white women, respectively (Prejean, Song, et al., 2011). The course of the HIV epidemic in the United States has also been fueled by drug use. The National Institute on Drug Abuse estimates that 25% of all infections are drug related (National Institute on Drug Abuse, 2011).

Numerous evidence-based HIV prevention interventions have been rigorously evaluated in these at-risk populations and have shown significant effects in reducing sex- or drug-related risk behaviors, reducing the rate of new HIV/STI infections, or increasing HIV-protective behaviors. For this region, we present select examples of theory-driven risk reduction interventions, most of which are recommended by the CDC as best-evidence interventions and proven to be efficacious in the populations that are most at risk.

Men Who Have Sex with Men

Tailored for black MSM, *Many Men Many Voices (3MV)* is a group-level intervention guided by Social Cognitive Theory (defined in the section on behavioral theories), Behavioral Skills Acquisition Model, and Transtheoretical Model of Behavior Change and the Decisional Balance Model. The Behavioral Skills Acquisition Model emphasizes effective characteristics for risk reduction counseling (e.g., assessing a person's knowledge of risk behaviors and risk reduction strategies; ensuring an individual's accurate perception of personal degree of risk, building confidence; ensuring commitment and intention to change; developing strategies to reinforce change; incorporating positive attitudes and effective listening skills with participants) (Kelly, 1995). The Transtheoretical Model of Behavior Change focuses on emotional, cognitive, and behavioral factors that influence an individual's decision to change behavior. Stages of Change, as described in the Stages of Change Theory section, is a concept central to the Transtheoretical Model of Behavior Change (Prochaska, Redding, et al.,

1994). The Decisional Balance Model suggests that cognitive and motivational factors influence a person's perceptions about making decisions. Decisional balance assumes that behavior change occurs when an individual perceives change as a gain rather than a loss (Janis & Mann, 1977).

The *3MV* intervention addresses behavioral determinants and the micro-social environment (e.g., cultural, social, and religious norms, identity of black MSM, degree of connectedness to the black and gay communities, racism, homophobia). A unique component of *3MV* is the development of menus of behavior change options for HIV/STI prevention rather than a singular emphasis on condom use that is common in other HIV prevention interventions for MSM (Wilton, 2009). Some of these behavior change options include helping participants recognize how racism and homophobia are related to sexual and substance use risk behaviors, identifying the power and control dynamics that exist in their relationships, and enhancing participants' intentions to change their own risky behaviors (Wilton, 2009). This intervention was shown to be efficacious among a sample of 338 black MSM of HIV negative or unknown HIV serostatus in New York City. Specifically, participants randomly assigned to the *3MV* intervention reported significantly greater reductions in unprotected anal intercourse with casual male partners and number of male sex partners, consistent condom use during receptive anal intercourse with casual male partners, and increases in HIV testing (Wilton, 2009).

For HIV-positive MSM, the *Seropositive Urban Men's Intervention Trial* (*SUMIT*) used enhanced peer-led intervention to reduce sexual risk behaviors. The *SUMIT* intervention is guided by the Theory of Planned Behavior, Social Cognitive Theory, and Information-Motivation-Behavioral Skills Model without consideration of the risk environment (Wolitski, Parsons, et al., 2005). It is led by HIV-positive gay or bisexual peer facilitators. Structured group activities focus on sexual and romantic relationships, HIV/STI transmission, drug and alcohol use, assumptions about the HIV status of sex partners, disclosure of HIV status, and mental health (Wolitski, Parsons, et al., 2005). Compared with the standard intervention, fewer men assigned to the enhanced intervention reported unprotected receptive anal intercourse with a HIV-negative or serostatus-unknown partner at 3 months; however, there were no other significant differences in transmission risk or serostatus disclosure at 3 or 6 months (Wolitski, Gomez, & Parsons 2005).

Finally, a theory-based, psychosocial intervention for HIV-positive MSM, known as the *EDGE* study, was developed to reduce sexual risk behaviors in the context of ongoing drug use, a unique feature in HIV prevention research. The *EDGE* intervention study used a clinical approach, combining motivational interviewing with elements from Social Cognitive Theory and the Theory of Reasoned Action (Mausbach, Semple, et al., 2007). Motivational interviewing is a client-centered, process-oriented counseling approach that incorporates feedback on current behavior, emphasizes readiness for change and personal responsibility for change, delineates alternative strategies for changing behaviors, and promotes counselor empathy and support. To a certain degree, the macro-social environment (e.g., peer and social norms) was addressed in the course of the intervention sessions. Participants in the EDGE intervention demonstrated a significantly greater percentage of protected sex acts at 12 months post-baseline, as well as a greater increase in self-efficacy for condom use over time (Mausbach, Semple, et al., 2007).

Ethnic Minorities

To address the significant impact of HIV among Latinas, the *Women's Health Promotion (WHP) program* has been used for Spanish-speaking, heterosexual, HIV-negative women (Raj, Amaro, et al., 2001). WHP utilizes tenets of the Social Cognitive Theory, the Theory of Reasoned Action, and the Health Belief Model to reduce risky sexual behavior among a community-based sample of Latinas in Boston. In addition to HIV/STD education, condom practice, and negotiation skills, *WHP* included participant-suggested sessions that addressed aspects of the women's micro-social environment such as intimate

partner violence, oppression, social justice, and non-HIV-related partner communication, as well as comprehensive health issues (e.g., mental health, depression, cervical cancer, diabetes, nutrition). Facilitators used psychoeducational strategies through lectures, group discussion, skill-building games, and role playing exercises (Raj, Amaro, et al., 2001). Women in the *WHP* intervention group demonstrated a substantial increase in condom use at the 3-month follow-up evaluation in comparison to women in the control group, who received only HIV prevention material and referrals (Amaro, Raj, et al., 2002). To date, the *WHP* remains the only program on the CDC Best Evidence list that is solely for adult Latinas and is culturally and linguistically tailored to their needs. Although it integrates some components from the micro-social environment, there was lack of evidence of improvements in those components in the 15-month post-intervention follow-up.

The *Eban* HIV/STD risk reduction intervention demonstrates the willingness of couples, specifically African-American HIV-serodiscordant couples, to participate in HIV prevention interventions. *Eban* integrates components of Social Cognitive Theory, such as historical and cultural beliefs about family and community preservation, and an Afrocentric paradigm into a relationship-oriented ecological framework (El-Bassel, Jemmott, et al., 2010). This intervention, facilitated by male and female African-Americans, included four sessions with individual couples and four sessions with groups of couples. Individual couple sessions were designed to address interpersonal factors associated with sexual risk reduction, including communication, problem solving, monogamy, and negotiation skills, while group sessions addressed community-level factors, including (1) increasing positive peer norms for condom use by emphasizing the threat of HIV to African-American communities, (2) reducing the stigma associated with being African-American couples affected by HIV, and (3) increasing social support for HIV risk reduction (El-Bassel, Jemmott, et al., 2010). *Eban* was conducted in four major US cities: Atlanta, Los Angeles, New York, and Philadelphia, and it reported significant reductions in HIV/STD risk behaviors among African-American HIV-serodiscordant couples (El-Bassel, Jemmott, et al., 2010).

Finally, the *SHIELD* program is a peer network-oriented HIV prevention intervention based on Social Identity Theory and peer outreach that was implemented for predominantly African-American HIV-positive and HIV-negative drug users (Latkin, Sherman, & Knowlton, 2003). Participants were asked to make public commitments to increase their own health behaviors and to promote HIV prevention within their social networks and community contacts. The intervention included multiple sessions for training and skill building that involved goal setting, role plays, demonstrations, and group discussions. To present HIV risk within a broader community context, the intervention emphasized the interrelatedness of HIV risk among individuals, their risk partners, and their community. The *SHIELD* intervention showed that by emphasizing pro-social roles and social identity and incorporating peer outreach strategies, interventionists could reduce HIV risk in low-income, drug-using communities (Latkin, Sherman, & Knowlton, 2003).

Western and Central Europe

In Western Europe, MSM were the most commonly diagnosed risk group through 1998. After that year, persons with heterosexual contact have been diagnosed more commonly (Sullivan, Hamouda, et al., 2009). Importantly, however, in Western Europe, MSM remain the group most at risk of acquiring HIV (Sullivan, Hamouda, et al., 2009). In France, for example, MSM accounted in 2009 for more than half the men newly diagnosed with HIV, yet they represented only 1.6% of the country's population (UNAIDS, 2010). In 2007, 3160 new HIV diagnoses were reported among MSM in the United Kingdom, the most ever among that group up to that point (UNAIDS, 2010). Few behavioral HIV prevention interventions have been rigorously evaluated for MSM in Europe; the paucity of studies demonstrates the need for prevention efforts in this area (Berg, 2009).

One of the few interventions designed for MSM with a prior STI diagnosis was conducted in a sexual health clinic in London, England, and drew upon the Transtheoretical Model of Behavioral Change, the Model of Relapse Prevention that focuses on the maintenance phase of the habit change process, and elements from Social Learning Theory (Imrie, Stephenson, et al., 2001). This cognitive behavioral intervention consisted of a one-day cognitive behavioral workshop in addition to a standard, 20-min, one-on-one counseling session through motivational interviewing techniques about sexual risk behaviors. Although this intervention was acceptable to participants and feasible to deliver, it did not succeed in reducing the risk of acquiring a new STI in MSM (Imrie, Stephenson, et al., 2001).

Similar findings were observed for community-based, peer-led interventions modeled after successful opinion leader interventions in the United States (Elford, Sherr, et al., 2002; Flowers, Hart, et al., 2002). For example, *The Gay Men's Task Force* (*GMTF*) intervention was an interagency collaboration in Scotland consisting of three elements, all independently shown elsewhere to be effective in promoting gay men's sexual health but combined here for the first time (Flowers, Hart, et al., 2002). These elements included (1) peer-led sexual health promotion conducted on the commercial gay scene, (2) gay-specific genitourinary medicine services in both hospital and gay community settings, and (3) a free phone "hotline" providing sexual health information and details of local sexual health services (Flowers, Hart, et al., 2002). The *GMTF* intervention did not produce community-wide changes in sexual risk behaviors, but there was higher uptake of hepatitis B vaccination and HIV testing (Flowers, Hart, et al., 2002). The ineffectiveness of the program's intervention for sexual risk behaviors contrasted starkly with the results of North American studies that had shown that peer education was effective for HIV prevention among MSM (Elford, Sherr, et al., 2002; Flowers, Hart, et al., 2002). This suggests that a model of peer education shown to be effective in one country may not be directly transferable to another and may need to be modified according to the risk environment in the target country.

Eastern Europe and Central Asia

In Eastern Europe and Central Asia, the number of people living with HIV has almost tripled since 2000 and reached an estimated 1.4 million in 2009 compared with 760,000 in 2001. The Russian Federation and Ukraine account for almost 90% of newly reported HIV diagnoses (UNAIDS, 2010). Since the early 2000s, there has been a rapid rise in HIV infections among people who inject drugs, causing HIV infection rates in this region to surge. The epidemic is concentrated among IDUs, sex workers and their clients, and, to a much lesser extent, MSM (UNAIDS, 2010). The availability and content of HIV prevention interventions for IDUs have been affected by the region's macro-political environment.

The response in many countries in the region has been heavily influenced by the legacy of the former Soviet Union, with its emphasis on the medical discipline of "narcology" (a subspecialty of psychiatry) to tackle drug dependence and harms. The Russian Federation, the largest country in the region, prohibits the provision of opioid substitution therapy (OST). Similarly, IDUs in Ukraine have traditionally been stigmatized, had no access to treatment, and had little access to prevention. However, in the last few years (and due in part to two large Global Fund grants administered by nongovernmental organizations), Ukraine has made significant improvements in the provision of harm reduction and HIV treatment for IDUs. By mid-2007, 645 needle and syringe programs (NSP) sites had reached more than 120,000 people, and by 2009, Ukraine was one of only seven countries in the world with more than 1000 of these sites (Mathers, Degenhardt, et al., 2010). Additionally, the government recently amended national policies to permit methadone maintenance treatment (MMT).

Although NSPs have been implemented in nearly all countries in the region, overall levels of coverage for the region are low, largely because of low levels of needle-syringe provision in

Russia; although there and in other countries, IDUs can purchase needles in pharmacies. And even though most countries have implemented OST programs, the scale of programs is very limited, with one person receiving OST for every 100 IDUs (Mathers, Degenhardt, et al., 2010). The most significant challenge in the region for IDUs is national policies, particularly in the Russian Federation, that oppose proven, effective, and cost-effective interventions to reduce HIV transmission and acquisition.

South and Southeast Asia

In Asia, an estimated 4.9 million people were living with HIV in 2009, and 360,000 were newly infected (UNAIDS, 2010). However, most national HIV epidemics appear to have stabilized, and no country in the region has a generalized epidemic. Asia's HIV epidemic remains concentrated largely among IDUs and FSWs and their clients (UNAIDS, 2010). HIV prevention interventions for IDUs and FSWs in the region have focused largely on the macro-political risk environment without the guidance of behavioral theories.

In 2008, according to the Reference Group to the United Nations on HIV and Injecting Drug Use, of the estimated 15.9 million (11.0–21.2 million) IDUs globally, 3.9 million (3.5–5.6 million) or 25% live in South, East, and Southeast Asia (Mathers, Degenhardt, et al., 2008). In China, where IDUs account for the largest number of HIV infections, MMT, NSPs, and drug addiction, treatment facilities have been at the forefront of HIV prevention (Chu & Levy, 2005; Li, He, et al., 2009; Qian, Schumacher, et al., 2006). In 2004, a National Task Force comprising the Ministry of Health, Ministry of Public Security, and State Food and Drug Administration was set up in accord with new national guidelines for methadone treatment and NSPs (Chu & Levy, 2005). Methadone treatment for IDUs was initiated as a first-stage pilot program in select provinces. After a 12-month follow-up of IDUs in eight MMT clinics, drug injection rate, drug injection frequency, and needle sharing rate had dramatically declined. By the end of 2007, over 500 officially recorded MMT clinics were available for 40% of heroin abusers, and by 2010, coverage was expected to increase to 70% (Li, He, et al., 2009). NSPs have also produced decreases in needle sharing and HIV infection rates. By the end of 2007, NSPs served at least 30% of officially registered IDUs, and by 2010, coverage was expected to increase to 50% of IDUs (Li, He, et al., 2009). The Chinese government has also actively sought to collaborate with neighboring countries to prevent drug smuggling across borders, discourage new users through anti-drug education campaigns, treat current users through various drug detoxification programs, and encourage community outreach programs to facilitate detoxification, rehabilitation, and harm reduction (Chu & Levy, 2005; Li, He, et al., 2009; Qian, Schumacher, et al., 2006).

For FSWs in the region, the most ambitious and innovative HIV prevention intervention has been the 100% Condom Use Program launched in 1989 in Thailand. The goal of the 100% Condom Use Program was to promote universal use of condoms in commercial sex venues to prevent HIV transmission (Rojanapithayakorn, 2006). Public health officials, brothel owners, local police, and FSWs collaborated at provincial and local levels to implement the program. FSWs were screened for STIs weekly or semi-weekly at government STD clinics, treated, and provided with a box of 100 free condoms. Compliance was checked by tracing male STI patients back to the brothels where they presumably were infected. Health workers could then follow up with visits to the brothels, providing additional information and condoms. The cooperation of law enforcement was also sought; potential sanctions for failing to comply with the program included the threat of closure of the sex establishment (Ainsworth, Beyrer, & Soucat, 2003). The program has increased the use of condoms in sex work from 14% early 1989 to over 90% since 1992, and the number of men presenting to government clinics for STI treatment dropped by 90% from 1989 to 1995 (Ainsworth, Beyrer, & Soucat, 2003; Kilmarx, Palanuvej, et al., 1999). Moreover, the number of FSWs has declined

by 25% since 1989 (Kilmarx, Palanuvej, et al., 1999). Thailand is the only country in this region in which HIV prevalence is close to 1%, and its epidemic appears to be stable overall (UNAIDS, 2010). Since its introduction in 1989, this program has also been successfully implemented in Cambodia, the Philippines, Vietnam, China, Myanmar, Mongolia, and Laos, with variations in program components between countries (e.g., formation of FSWs' self-help groups, peer education, issuance of membership cards by local authorities) (Rojanapithayakorn, 2006).

Middle East and North Africa

An estimated 460,000 people were living with HIV in the Middle East and North Africa at the end of 2009, up from 180,000 in 2001 (UNAIDS, 2010). The number of people newly infected has also increased over the last decade; there were 75,000 people newly infected in 2009, more than twice the number in 2001 (UNAIDS, 2010). The general pattern in different countries in the Middle East and North Africa points toward an HIV epidemic heavily concentrated among IDUs and among prisoners who are also IDUs, with heterogeneity between countries dependent on the relative role of each of these high-risk groups (Abu-Raddad, Hilmi, et al., 2010; McFarland, Abu-Raddad, et al., 2010).

Interventions for IDUs and IDU prisoners in the region have centered around the macropolitical risk environment but without the use of theories and biomedical models. Although drug use via injection has been identified in every country in the region, only 35% of countries have implemented NSPs and even fewer (13%) have implemented OSTs (Mathers, Degenhardt, et al., 2010). In many African countries, laws prohibiting opioids for treatment of pain have created a barrier to prescribing OST, although some promising changes have recently occurred, for example, in Morocco, where the use of MMT has recently been approved (Mathers, Degenhardt, et al., 2010). Regarding NSPs, evidence has been gathered in Tehran, Iran, that access to an NSP may reduce needle- and syringe-sharing practices among community-based IDUs (Zamani, Farnia, et al., 2010).

For IDU prisoners, the political response toward harm reduction programs has been gradual and limited to Iran, where the largest number of people who inject drugs reside (UNAIDS, 2010). Iran, like many countries, began with a supply reduction policy that criminalized any type of drug use, in any quantity (Razzaghi, Nassirimanesh, et al., 2006). Efforts in the early 1990s resulted in policy changes, and although supply reduction approaches continued, the revised policy allowed the Iran Prison Organization (IPO) to adopt harm reduction policies and implement comprehensive HIV prevention interventions for IDU prisoners in many provinces throughout the country (Farnia, Ebrahimi, et al., 2010). The IPO's main activities include drug treatment and prevention programs that encompass MMT, pilot NSPs, education, and epidemiological surveillance (Eshrati, Asl, et al., 2008; Razzaghi, Nassirimanesh, et al., 2006). Iran is the only country in the Middle East or North Africa that has introduced MMT for opioid-dependent prisoners (Farnia, Ebrahimi, et al., 2010). There are currently 142 clinics across the country's 30 provinces that provide MMT to male and female opioid-using prisoners, and most of the large correctional facilities in the 30 provinces have established MMT programs (Farnia, Ebrahimi, et al., 2010). The Iran Prison Organization's HIV prevention package, with MMT programs constituting a main component, is an exceptional model for other countries in the region (Farnia, Ebrahimi, et al., 2010). It is perceived as effective in reducing illicit drug injection in a prison setting as well as for preventing the transmission of blood-borne infections, including HIV, among prisoners (Farnia, Ebrahimi, et al., 2010).

Sub-Saharan Africa

Sub-Saharan Africa still bears an inordinate share of the global HIV burden. Although the rate of new HIV infections has decreased, the total number of people living with HIV continues to rise,

with a 2009 estimate of 22.5 million, 68% of the global total (UNAIDS, 2010). Women represent the majority of those infected and the majority of those dying. Heterosexual sex is the main mode of transmission in the region (Kilmarx, 2009). The key risk factors for heterosexual transmission are transactional or paid sex, concurrent sex partners, high number of lifetime sex partners, coinfection with viral and bacterial STIs, notably herpes simplex virus type 2 (HSV-2), and lack of male circumcision (Chen, Jha, et al., 2007).

Successful HIV prevention interventions have targeted the micro-social, economic, and political environments. Because gender inequalities (i.e., intimate partner violence, relationship power differentials) and lack of economic opportunities for both sexes often contribute to increased rates of HIV infection in women in sub-Saharan Africa, there has been recognition of the need for structural HIV prevention interventions such as microfinance programs. Microfinance programs seek to alleviate poverty by providing access to credit, savings, or business skills (Dworkin & Blankenship, 2009). In addition to providing economic benefits, microfinance may be an effective vehicle for women's empowerment, and newly acquired business skills may be accompanied by improvements in self-esteem and self-confidence, ability to resolve conflicts, household decision-making power, and expanded social networks (Kim, Watts, et al., 2007; Kim, Askew, et al., 2009).

The *Intervention with Microfinance for AIDS and Gender Equity (IMAGE)* study, implemented in South Africa, combined two elements: a poverty-focused microfinance initiative that targeted the poorest women and a two-phase learning and action curriculum of gender and HIV education. The *IMAGE* study's goal was to improve household economic well-being, social capital, and empowerment and thus reduce vulnerability to intimate partner violence and HIV infection. Over a 2-year period, rates of intimate partner violence were reduced by 55% in women enrolled in the intervention group compared to those in the control group; there was also improvement in numerous indicators of empowerment (e.g., challenging gender norms, autonomy in decision-making, communication within the household) (Pronyk, Hargreaves, et al., 2006). Regarding HIV outcomes, young women who took part in the intervention showed significantly higher levels of HIV-related communication, were more likely to have accessed voluntary counseling and testing, and were less likely to have had unprotected sex at last intercourse with a non-spousal partner (Pronyk, Kim, et al., 2008). However, the rate of unprotected sex among youth living in the households of intervention participants did not show a significant reduction (Pronyk, Hargreaves, et al., 2006). This result suggests that the intervention may be more effective for participants directly involved in the program than for those who received the intervention through diffusion (Dworkin & Blankenship, 2009).

Observational evidence has accumulated concerning the effectiveness of male circumcision for reducing HIV infection among men in sub-Saharan Africa. The causal association has been confirmed by three large randomized controlled trials conducted in South Africa, Kenya, and Uganda (Auvert, Taljaard, et al., 2005; Bailey, Moses, et al., 2007; Gray, Kigozi, et al., 2007). Among 3274 uncircumcised men aged 18–24 in South Africa, those randomized to immediate circumcision showed a protection from HIV infection of 61% after accounting for sexual risk behaviors (which increased in the intervention group) (Auvert, Taljaard, et al., 2005). Among 2784 men of similar ages in Kisumu, Kenya, the protection effect of circumcision was also 60% (Bailey, Moses, et al., 2007). Finally, in a trial in Rakai, Uganda, 4996 adult, HIV-negative men aged 18–49 were randomly assigned to either immediate circumcision or circumcision delayed for 24 months. HIV incidence among the circumcised men was significantly reduced compared with the uncircumcised (control) participants. The efficacy of circumcision for preventing incident HIV was 51% in the intention-to-treat analysis; adjustment for enrollment characteristics, behaviors, and symptoms of STIs did not affect this estimate (Gray, Kigozi, et al., 2007). All three trials were halted early by their respective data and safety monitoring boards (Padian, Buve,

et al., 2008). The trials also assessed whether male circumcision could lead to sexual disinhibition because men might believe that they were protected against HIV infection after circumcision. In Kenya and Uganda, there was no evidence for an increase in sexual risk behaviors (Bailey, Moses, et al., 2007; Gray, Kigozi, et al., 2007). However, in South Africa, 21 months after the intervention, the circumcised men reported significantly greater numbers of sex partners per month than those in the delayed circumcision group (Auvert, Taljaard, et al., 2005). The success of this biomedical HIV intervention laid the foundation for rapid and intensive scale-up in some countries; however, in other countries, policy makers have been slow to support male circumcision (Padian, McCoy, Karim, et al., 2011).

Latin America and the Caribbean

In Latin America and the Caribbean, an estimated 1.7 million people were HIV positive in 2007, of whom 140,000 were newly infected (UNAIDS, 2010). More than half of Latin Americans living with HIV reside in the region's four largest countries: Brazil, Columbia, Mexico, and Argentina (Avert, 2011). Although MSM account for a significant proportion of HIV infections in Latin America, sex work and injection drug use have also emerged as significant routes of HIV transmission.

Among FSWs in Mexico, recent interventions have been primarily theory based, with an overlapping emphasis on FSWs' injection drug use behavior and on their clients' behaviors. As a result of these interventions, future directions have been identified that incorporate the risk environment. In Tijuana and Ciudad Juarez, FSWs were enrolled in a behavioral intervention to increase condom use under the premises of Social Cognitive Theory (Strathdee, Mausbach, et al., 2009). This intervention integrated motivational interviewing (e.g., key questions, reflective listening, summarization, affirmation, and appropriate use of cultural cues) and principles of behavior change. Improvements in self-efficacy were predictive of significant increases in condom use with clients among FSWs who received the intervention. And among FSW-IDUs, those who improved in HIV knowledge were more likely to increase condom use with clients (Strathdee, Mausbach, et al., 2009). Recognizing the need to integrate a harm reduction component promoting safer injection as well as safer sex negotiation, Strathdee and colleagues expanded the intervention for FSW-IDUs to include an injection risk reduction component (NIHReporter, 2011a). Additionally, clients of FSWs may serve as a bridge population for transmission of HIV from high- to low-prevalence populations (Goldenberg, Strathdee, et al., 2011).

Few behavioral interventions designed to reduce FSWs' risk of contracting HIV have considered the FSWs' clients. To address this lack, one intervention that is based on Social Cognitive Theory targets US and Mexican clients of FSWs in Tijuana. It uses motivational interviewing, active participation, and problem solving to increase clients' use of condoms with FSWs (NIHReporter, 2011b). In the US-Mexico border region, extensive research has identified numerous factors in FSWs' risk environment that can be taken into account for the development of future interventions for FSWs and FSW-IDUs. The factors range from aspects of the microphysical environment (sex work locations, monetary incentives for condom use by FSWs), the social environment (injecting drugs with clients, social norms such as *familismo*, abuse histories, and violence perpetrated by intimate partners and clients), the economic environment (job training opportunities), and the political environment (unjustified policing practices, NEPs, institutional incentives for promoting condom use) (Larios, Lozada, et al., 2009; Ulibarri, Strathdee, et al., 2011; Strathdee, Lozada, et al., 2011).

Successful HIV prevention programs have been implemented for IDUs in select countries such as Brazil, Argentina, and Mexico. A law implemented in the state of Sao Paulo in 1998 paved the way for Brazil to implement an extensive network of harm reduction programs across the country. The Brazilian Ministry of Health has firmly supported an infection control policy

related to the use of psychoactive substances. Brazil has been recognized throughout the region for its National AIDS Program, a leading example of an integrated program for HIV/AIDS prevention, care, and treatment in a developing country.

Despite many differences between the epidemics within different countries, all countries in this region have to contend with rigid and restrictive social-cultural norms regarding gender roles and sexuality and contraception. These factors pose barriers to the development of effective HIV prevention interventions (Huedo-Medina, Boynton, et al., 2010). Three cultural beliefs relating to HIV risk that are predominant in this region are (a) *machismo* or "male pride," which is the belief that men should be dominant, have multiple sex partners, and engage in unprotected sex; (b) *simpatía*, which endorses a traditional female role emphasizing sexual submission and women's sexual inexperience; and (c) *familismo*, associated with traditional family values which conflict with less socially acceptable forms of sexual expression, such as condom use and homosexuality (Huedo-Medina, Boynton, et al., 2010). Addressing these social factors will facilitate reductions in HIV infections through promotion of safer sex behaviors in all risk populations.

Implications

Global approaches to HIV prevention have varied by geographic region and risk population. Additionally, appropriate theoretical frameworks and risk environment factors at the micro- and macro-levels have been integrated and targeted in HIV prevention interventions. As the HIV epidemic has evolved, most geographic regions have shifted from interventions that focus solely on the individual level to those that also integrate social networks, peers, communities, and biomedical-based (e.g., male circumcision, microbicides) approaches. There has also been a shift from a narrow focus on prevention to a focus to include treatment of HIV-positive individuals (i.e., treatment as prevention). These different approaches may be preferentially suited to certain populations or for certain periods of an individual's life.

Conclusions

Understanding the complexities of behavioral medicine in HIV/AIDS (i.e., the disease itself and infectious processes that surround it) is critical to the comprehensive development and implementation of comprehensive HIV/AIDS treatment and prevention strategies. Because the life expectancy for people with HIV has increased dramatically, there are challenges that must be faced regarding aging with HIV/AIDS. Comorbid conditions such as substance abuse, trauma, mental illness (e.g., depression, dementia), and incidental factors such as stigma may influence adherence to ART and must be taken into account in HIV treatment regimens. Overall, reduced infectiousness among HIV-positive individuals can be achieved only through proper adherence to ART medications and treatment of co-occurring STI. Treatment as prevention in reducing HIV transmission is a focus of ongoing trials to curb new infections.

When designing and applying HIV prevention interventions, researchers and health officials differ in the ways that they use behavioral theories, biomedical models, and the risk environment approach depending upon the geographic region and with the risk levels of the targeted populations. Risks in high-risk populations also frequently overlap. For example, an epidemic among IDUs may ignite an epidemic among FSWs due to the interaction between injection drug use and sex work, as when men and women who inject drugs also purchase or sell sex. Overall, some interventions, even theory-based ones, could conceivably have been more efficacious if they had taken components of the HIV risk environment into account.

HIV prevention experts agree that no single prevention strategy will be 100% effective nor acceptable and applicable to all populations (Kurth, Celum, et al., 2011). Behavioral interventions will be a necessary, but not solely sufficient, component of a successful prevention program worldwide. A number of biomedical interventions such as male circumcision, microbicides, and PrEP have been shown to have a significant impact on curbing new HIV infections in various at-risk populations. Combination HIV preven-

tions that not only incorporate evidence-based behavioral and biomedical approaches but also take account of the risk environment must be developed to be appropriate, acceptable, and deliverable with high levels of coverage and adherence (Kurth, Celum, et al., 2011; Strathdee, Hallett, et al., 2010). Comprehensive combination HIV interventions will be those that address risk factors at the individual, dyadic, social, economic, and political levels, while accounting for the stage of the HIV epidemic in a particular region.

Geographic regions will vary in their approaches to combination HIV interventions. Some are well positioned to proceed with designing such interventions whereas others need to strengthen their political response to the HIV epidemic in populations most at risk. Combination interventions, particularly when implemented at scale, pose significant evaluation challenges, including how best to determine impact and how and whether to measure the effectiveness of component strategies (Padian, McCoy, Karim, et al., 2011; Padian, McCoy, Manian, et al., 2011). Nonetheless, as an initial step, in 2010, as part of the National HIV/AIDS Strategy in the United States, the CDC implemented a high-impact prevention approach. By using combinations of scientifically proven, cost-effective, and scalable interventions targeted to the right populations in the right geographic areas, this approach promises to greatly increase the impact of HIV prevention efforts (Centers for Disease Control and Prevention, 2011b). Additionally, to mark the third anniversary of the National HIV/AIDS Strategy, a new Federal initiative focused on "the HIV care continuum" (also referred to as the HIV treatment cascade) was launched to increase the proportion of individuals who are aware of their HIV status, are successfully linked to care and remain in care, receive ART, and adhere to their treatment to achieve viral load suppression. If the CDC "high-impact prevention approach" (which has clear and measurable targets to be achieved by 2015) proves successful in the United States, a critical challenge will be how to effectively and efficiently disseminate this approach globally, particularly in countries with limited political will to curtail the HIV pandemic. Ultimately, delivery of effective combination prevention packages could represent a new era for HIV prevention and a turning point for both HIV-positive and at-risk populations (Kurth, Celum, et al., 2011; Warren & Bass, 2013).

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