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A New Era of HIV Risk: It's Not What You Know, It's Who You Know (and How Infectious)

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Keywords

HIV prevention, sexual behavior, sexually transmitted infections, sexual networks, health disparities

Abstract

HIV is transmitted in social and sexual relationships, and HIV transmission risks, as well as protective actions, are evolving as HIV epidemics unfold. The current focus of HIV prevention is centered on antiretroviral medications used to reduce HIV infectiousness in persons already infected with HIV [treatment as prevention (TasP)]. The same medications used to treat infected persons can also be used by uninfected persons as pre-exposure prophylaxis (PrEP) to reduce the infectivity of HIV. Both PrEP and TasP are effective when adherence is high and individuals do not have co-occurring sexually transmitted infections. HIV prevention is most effective and efficient when delivered within sexual networks with high HIV prevalence. Specific network characteristics are recognized as important facilitators of HIV transmission; these characteristics include the degree of similarity among network members (homophily), gender role norms, and belief systems. Since 2011, HIV risk has been redefined based on infectiousness and infectivity, ushering in a new era of HIV prevention with the potential to end HIV epidemics.

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INTRODUCTION

The global spread of HIV infection has reached 76 million people and led to 35 million deaths from HIV–AIDS-related conditions. The United Nations AIDS program (UNAIDS) reports that, in 2016, there were 1.8 million new HIV infections worldwide, with 36 million people living with HIV and 57% receiving antiretroviral therapies (ART) (UNAIDS 2017). A common misconception is that HIV is a unified global pandemic or even a single epidemic anywhere. In fact, each region of the world has its own HIV epidemics, characterized by genetically different viral families of HIV with different biological properties and affinities that map onto behaviors with different risks for transmission. For example, subtype C represents the most prevalent genetic strain of HIV in sub-Saharan Africa, where the vast majority of infections are attributable to vaginal intercourse. In contrast, the most prevalent strain of HIV in Western Europe and the Americas is subtype B, with the majority of HIV transmissions resulting from anal intercourse. In Eastern Europe, the predominant subtypes are A, B, and recombinant AB, and these epidemics are driven by shared syringe equipment associated with injection drug use. In the United States, HIV epidemics continue to disproportionately affect gay, bisexual, and other men who have sex with men (i.e., sexual minority men). For instance, in 2015, 63% of all new HIV infections in the United States occurred as a result of anal sex without condoms among sexual minority men. Within this majority of cases, rates of HIV incidence were highest among racial and ethnic minority men, as compared to White men. Black men accounted for 39% of these new infections, a plurality of all new HIV infections among sexual minority men (Cent. Dis. Control Prev. 2016).

HIV epidemics that are driven principally by injection drug use have markedly different trajectories from those associated with sexual transmission. Widespread implementation of harm reduction strategies, which provide an array of services to people who are addicted to injectable drugs, have sharply bent HIV epidemic curves toward zero new infections. Vancouver, British Columbia, a region with a strong commitment of resources to these harm reduction measures, has seen dramatic decreases in HIV infections associated with injection drug use. While 30% of new HIV infections in British Columbia were associated with injecting drugs in 2008, this rate declined to less than 10% of new infections in 2014 (B.C. Cent. Dis. Control 2017). In New York City, a historical epicenter for HIV infection, injection-related HIV infections that once posed a significant public health threat are now relatively rare. In fact, HIV prevalence among injection drug users in New York City has declined from a stable annual rate of 50% in the 1990s to less than 10% today (Des Jarlais et al. 2016a,b).

Disparities exist among people who inject drugs in places where HIV prevention has been largely neglected. Injection drug use that is either ignored or met with oppressive policies leads to HIV outbreaks, despite documented prevention success with readily available interventions (Friedman et al. 2006). For example, Russia continues to experience escalating HIV infections primarily driven by ignorance and policy failures that prohibit harm reduction programs. An estimated 1.2–1.4 million Russians are living with HIV, and incidence rates indicate that there were 100,000 new HIV infections in 2015 (UNAIDS 2016). The rampant spread of HIV in Russia was forecasted decades earlier on the basis of how opportunities were missed in HIV epidemics elsewhere (Kalichman et al. 2000). Furthermore, while some HIV epidemics are on the decline, particularly in the United States, we continue to see a rise in HIV outbreaks in low-income settings not historically considered to be incubators for HIV infection. For example, a rural community in the Midwestern US state of Indiana had a major outbreak of HIV in 2016 that reached 190 confirmed cases, with the estimated HIV prevalence going from 0% to 5% in just 2 years (Kalichman 2017). Similar outbreaks among injection drug users have occurred in Athens, Greece; Dublin, Ireland; and Tel Aviv, Israel, indicating the urgency of a unified approach to injection-related HIV prevention (Des Jarlais et al. 2016b).

Almost 40 years since the first cases of AIDS were clinically determined, and since the discovery that HIV is the cause of AIDS, HIV infection is no longer considered a universally fatal disease, but rather a chronic illness that is medically manageable with ART. Today, HIV is considered more akin to type 2 diabetes than to a lethal viral infection. That is, HIV infection and type 2 diabetes are both recognized as medically manageable with consistent engagement in health care and adherence to medications. However, and of concern, there are substantial health disparities in HIV treatment and related health outcomes.

The HIV treatment cascade offers a simplified conceptual representation of the medical management of HIV infection. The HIV treatment cascade places HIV care along a continuum, where individuals progress through stages of HIV testing and initial diagnosis, linkage to care, initiation of ART, adherence to ART, and finally to HIV suppression (Gardner et al. 2011). **Figure 1** depicts the HIV treatment cascade. Of particular importance, the cascade specifies discrete points of intervention for improving the progression toward management of HIV at the population level. It also offers a framework for defining underserved groups and health disparities in HIV care and clinical management. For example, transgender women are significantly less likely to receive ART, experience more challenges sustaining ART adherence, and demonstrate poorer HIV viral suppression than cisgender persons (Reisner et al. 2014). In one study, multivariable models demonstrated that health disparities among transgender women were predicted by poorer tangible social support over and above other common correlates of health outcomes, such as substance use (Kalichman et al. 2017a).

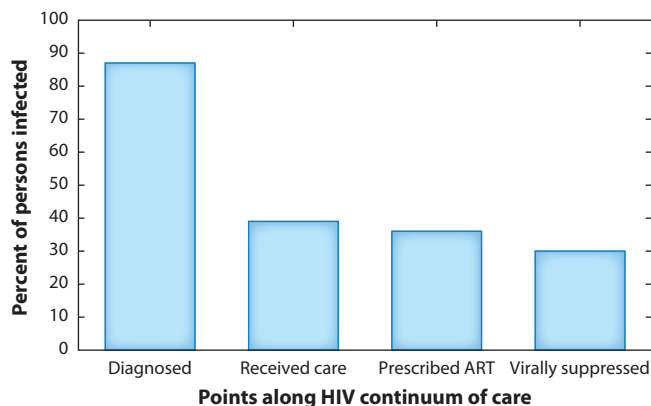


Figure 1

The HIV treatment cascade, also known as the HIV continuum of care. Abbreviation: ART, antiretroviral therapies.

Similarly, HIV-related health disparities are reliably observed among Black individuals, who account for 40% of all persons living with HIV in the United States. More than 45% of new HIV infections occur among Black individuals, who also represent nearly half (48%) of all people diagnosed with AIDS, as well as 58% of AIDS-related deaths (Cent. Dis. Control Prev. 2010). Black sexual minority men continue to be the group most affected by HIV in the United States. Cohort studies of Black men who have sex with men have estimated that, by age 40, 60% of these men will be HIV positive (Cent. Dis. Control Prev. 2010, Matthews et al. 2016, Stall et al. 2009). Furthermore, studies demonstrate that HIV point prevalence among Black sexual minority men is 32%, which is four times higher than what is observed among their White counterparts (Rosenberg et al. 2014).

Within the United States, Black individuals consistently face poorer health outcomes relative to their White and Latino counterparts (Aidala et al. 2016, Cornelius et al. 2017), and these disparities are not distributed evenly across geographic regions. For instance, racial disparities in health are greatest in the southeastern United States. Multiple factors contribute to poorer health outcomes for racial minorities, including limited access to testing for early detection of HIV infection, lack of access to clinical care, and impoverished living conditions, as well as health disparities in comorbid conditions that complicate the course of HIV disease, such as obesity and cardiometabolic syndrome (Monroe et al. 2011).

Today, ending AIDS is a legitimate conversation and a realistic goal given the existing tools for managing HIV disease and preventing new infections. In this article, we sample current and pressing topics in the scale-up of third-generation biobehavioral HIV prevention interventions. We first review the behavioral underpinnings of HIV epidemics and the key targets of effective HIV prevention strategies therein. Next, we focus on patterns of sexual partner selection and sexual networking and their implications for prevention. We then turn our attention to the current state of ART-based approaches to the prevention of sexually transmitted HIV. Finally, we offer directions for how these new advances may translate into a new generation of behavioral interventions that are needed to enhance antiretroviral-based prevention strategies in sexual networks.

PRIMACY OF BEHAVIOR IN HIV TRANSMISSION

As a communicable disease, HIV is completely behaviorally determined. Outside of blood product transfusions and needle stick injuries that occurred in the earliest years of HIV epidemics, no one

has ever contracted HIV outside of an interpersonal relationship. Behavioral routes of HIV transmission differ in their risks and rates of infection. For sexual transmission of HIV, epidemiologists have identified the specific parameters of transmission risk. Anderson & May (1988) showed that a combination of interacting biological and behavioral factors fully account for HIV transmission, and this model has served as the road map to HIV prevention. Anderson & May showed that the probability of HIV infection is a function of a few behavioral parameters, represented as

$$R_0 = \beta cD,$$

where R_0 is the reproductive rate of HIV transmission, β is a measure of infectivity or transmissibility, c is a measure of interaction between the susceptible and infected partners, and D is a measure of duration of infectiousness. The power of this model for prevention is its focus on modifiable elements on the right side of the equation (Fishbein 1997). Early efforts in HIV prevention concentrated on altering c in the model by changing the interaction rate of partners, namely reducing numbers of sexual partners and reducing the overlap of partners in time (sexual partner concurrency). Similarly, early in the HIV epidemic, partner interactions-based HIV prevention focused on the promotion of condom use to decrease or eliminate exposure to HIV during sexual intercourse. Reducing infectiousness, parameter D in Anderson & May's model, is the premise behind current HIV prevention strategies that use HIV treatments as prevention. Furthermore, ART used for pre-exposure prophylaxis (PrEP) aims to reduce HIV infectivity, β in the model. This early model of HIV transmission also explains the continued challenges that we face with even the most potent prevention technologies. Just as obstacles to complete and consistent condom use undermined prevention efforts for 30 years, the same challenges of low uptake, inconsistent adherence, and incomplete coverage plague the implementation of ART-based prevention strategies.

SOCIAL FOUNDATIONS OF HIV TRANSMISSION

Just as injection drug use-driven HIV epidemics are best understood through the social networks of those who share syringe equipment, sexually transmitted HIV epidemics are best understood through sexual networks. With the notable exception of sexual and substance use abstinence, all HIV prevention strategies rely on biomedical technologies. However, it is a mistake to think of biomedical technologies as distinct from the behavioral factors involved in their uptake and use. While current biobehavioral interventions are emerging as a third revolution in HIV prevention, the first revolution in HIV prevention came when the source of infection was discovered, namely exposure to blood via contaminated needles, as well as exposure to genital secretions via anal and vaginal sexual intercourse. Behavioral strategies to promote the use of sterile injection equipment or needles and latex condoms, both biomedical devices, were the key to the prevention of HIV infections and saved countless lives. Needless to say, unused condoms and inaccessible sterile needles do not prevent infections. Thus, the entire first revolution in HIV prevention focused on increased condom use, reduced numbers of partners, and accessibility to sterile or clean injection equipment.

The second revolution in HIV prevention came with the identification of HIV antibody testing as a delivery point for HIV prevention measures. Although an HIV-positive test result may have significant impact on behavior, an HIV-negative result is likely to have no positive impact on risk reduction. In that sense, HIV testing is no different than other medical screening and diagnostic tests, such as mammography and metabolic screenings, which are not expected to reduce risk-related behaviors. For instance, to expect a person who tests HIV negative to stop engaging in

condomless sex would be analogous to a smoker quitting after a negative chest X-ray. Indeed, the impact can be the reinforcement of current behavior. That said, HIV testing did become synonymous with HIV prevention after it was paired with risk reduction counseling, seeding the second revolution in HIV prevention. Early studies demonstrated that risk reduction counseling in the context of HIV testing is effective in reducing HIV transmission risks (Kamb et al. 1998); these results became the basis for numerous evidence-based behavioral interventions delivered to individuals, groups, families, and communities.

ART serves as the basis for the third, currently unfolding, revolution in HIV prevention. The first breakthrough in the use of ART for HIV prevention came in 1994, when the AIDS Clinical Trials Group (ACTG) released findings from their landmark trial Protocol 076. In a randomized clinical design, HIV-positive pregnant women and their newborns received either a course of the single antiretroviral drug zidovudine (AZT) or placebo. Interim analyses showed that, of 364 infants, 53 had HIV infection—13 of whom had received AZT, compared to 40 who had received placebo (Wiznia et al. 1996). In other words, AZT reduced the risk of mother-to-child HIV transmission from 25% in the placebo group to what would amount to 8% in the AZT group. Before the results of ACTG Protocol 076, one in three babies born to HIV-infected mothers would contract HIV, but the success of prevention of mother-to-child HIV transmission strategies has made it possible to entirely eliminate these infections, with countries such as Cuba, Brazil, and Botswana approaching or achieving zero perinatal HIV infections (Esber et al. 2017).

The success of ART in the prevention of mother-to-child HIV transmission, coupled with the recognition that HIV-positive individuals on ART are less infectious, has led to the third revolution in HIV prevention. However, the success of advances in using ART for HIV prevention depends on the basic behavioral realities of HIV transmission. Whether it involves needles, condoms, or ART, the ultimate success of any biomedical prevention technology hinges on social and behavioral interventions as they occur in sexual networks.

SEXUAL NETWORKS: THE CONDUIT OF HIV PREVENTION

As HIV is sexually transmitted, it is within sexual networks that HIV transmission occurs. The role of networks in the propagation of HIV infection is known and has served as the target of intervention since the earliest efforts to prevent injection drug use–related HIV transmission. In drug-using networks, syringe and needle sharing can occur between anonymous partners, as well as within close, intimate, and private relationships. Further complicating these dynamics, drug use involves secrecy due to social and often legal realities. The social networks of injection drug use often overlap with sex partner networks, and the same network principles hold for sexual networks as for networks of injection drug use. Nevertheless, it was more than a decade into the recognized HIV epidemics before sexual networks gained the attention of prevention scientists.

Several key concepts have emerged as central to our understanding of how behavioral interventions may be optimized within sexual networks; most critical of these are concepts related to sexual partner selection and partner sorting. Of particular importance is the notion that nodes in a network share common characteristics, where more similar individuals are more likely to be connected than are dissimilar persons. This principle, based on similarity, can account for preferential attachment in network models, a concept based on social ties joined by similarities—homophily (Brechwald & Prinstein 2011, McPherson et al. 2001). Network scientists are finding that racial sorting (racial homophily) may explain race-based health disparities in HIV epidemics and may offer a gateway to optimizing the scale-up of HIV prevention technologies where they will have the greatest impact.

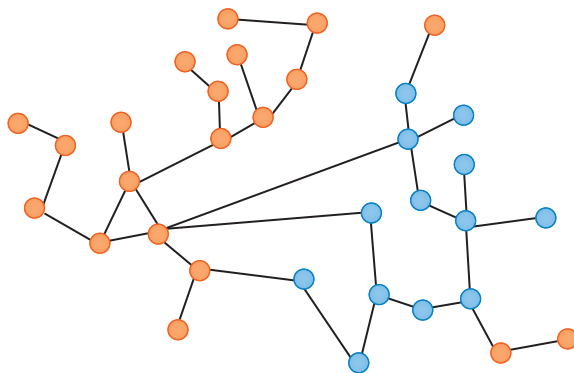


Figure 2

Illustrative example of homophily in two linked sexual networks. The different colored circles represent different racial groups.

RACIAL HOMOPHILY IN SEXUAL NETWORKS

Racial homophily, a property of sexual networks, represents one potential driver of racial disparities in HIV incidence among sexual minority men. Racial homophily (sometimes referred to as racial assortativity) describes differential preference for others of the same racial or ethnic group in the selection of sexual partners. As shown in **Figure 2**, racial homophily can relate to how closed a sexual network is and therefore the risk for rapid spread of HIV. Racial homophily occurs across different races and ethnicities of sexual minority men (Birkett et al. 2015, Grov et al. 2016, Mustanski et al. 2015), with some research suggesting that the highest rates of homophily occur among Black men (Newcomb & Mustanski 2013, Raymond & McFarland 2009). Indeed, studies generally show the highest rates of racial homophily among Black/African American sexual minority men, followed by White men, and the lowest rates among Latino men (Sudhinaraset et al. 2013). Same-race sexual partner selections can propagate HIV transmission through increased HIV prevalence within closed or relatively closed sexual networks. As such, the use of homophily to operationalize partner selection sorting and preferences has the potential to explain racial disparities in HIV incidence and provide network-level diagnostic information for the development of intervention strategies.

SEXUAL PARTNER SELECTION AND RACIAL HOMOPHILY

Studies have examined homophily in subpopulations to compare racial subgroups. The bulk of the evidence indicates that Black sexual minority men demonstrate the highest rates of homophily. Sudhinaraset et al. (2013) conducted one particularly compelling study that implicated the role of racial homophily in the maintenance of HIV prevalence, particularly among Black men. Among sexual minority men living in San Francisco, California, surveys were constructed to measure same-race partnering in a community sample. The study examined these patterns among groups of racial and ethnic minorities and compared them to group-level HIV prevalence rates at three time points: 2004, 2008, and 2011. Results showed that, when considering the sample overall, homophily decreased between 2004 and 2011, suggesting that same-race partnering tendencies among all sexual minority men shifted from being assortative to being neither assortative nor disassortative. Of particular interest, there was a declining trend in HIV prevalence that corresponded with these

changes in partner sorting. Specifically, the decline in HIV prevalence observed in San Francisco was attributed to the decline in same-race partnering among Black sexual minority men, where the decrease in same-race partnering occurred by a factor of four in a seven-year period. Therefore, reductions in HIV prevalence appear to have mapped onto increasing racial mixing with respect to sexual partnerships among Black sexual minority men specifically. While, in 2004, there were significant differences in HIV prevalence among racial and ethnic groups, these differences had diminished by 2011, suggesting the role of homophily (particularly among Black men) in sustaining prevalence rates.

Homophily is a construct most precisely defined, determined, and understood within the context of the network. Network assessments meticulously interview individuals and delineate the linkages among their social and, in these cases, sexual contacts. For instance, one such study constructed an elaborate sexual network from two index cases of HIV-positive Black men who lived in North Carolina (Hurt et al. 2012). In all, close to 400 individuals were examined, with retrieval from a name-based HIV reporting system utilized by the state health department. The final network, composed of three-quarters Black individuals, was composed of 94% same-race partnerships. In another networking study that found high rates of homophily among racially and ethnically diverse men living in Baltimore, Maryland, Black men demonstrated the highest percentage of sexual partnerships with men of the same race (Maulsby et al. 2015).

Although homophily describes sexual partnering at the network level, several studies have estimated homophily with data derived from individual partner reports. Daily diary studies, for example, have estimated general trends in selection and sorting among partners of different races and ethnicities. For instance, diary methods have estimated racial homophily by aggregating the percentage of same-race or same-ethnicity partners reported across diary entries. In one prospective weekly diary study with a racially and ethnically diverse national online sample of young sexual minority men who were either HIV negative or of unknown HIV status, racial homophily was calculated by taking the aggregate of races among up to three sex partners reported over the previous week for 12 weeks (Newcomb & Mustanski 2013). Although Black sexual minority men were 11 times more likely to report same-race sexual partners, it was White men who were most racially homophilous, reporting the greatest percentage of same-race partnerships, followed by Black men and, lastly, Latino men.

In another diary study, Grov et al. (2016) observed the same unexpected pattern among men in New York City, where White men, followed by Black men and, finally, Latino men, demonstrated successively decreasing rates of racial homophily. An important methodological caveat to this study is that sexual partners were only considered when they were reported as casual, rather than as main partnerships. Furthermore, Grov et al. (2016) included men who were HIV positive, a critical characteristic in partner selection and sorting. It is well known that men who have sex with men purposefully select sex partners that they believe are of their same HIV status as an HIV protection and prevention strategy, a practice known as serosorting (Eaton et al. 2010). The degree to which HIV-positive men's serosorting practices impact the race of their selected partners is unknown. While diary methodologies do have the advantage of relying on a shorter time span for recall periods, these methods may also carry other methodological artifacts by measuring homophily on the event level rather than the partner level. Furthermore, any index of homophily outside of network assessments can also be impacted by the racial composition of a given sample. Samples composed solely of one racial group may be biased toward greater homophily, especially when recruitment relies on participant referrals or snowball sampling. In contrast, studies with racially diverse samples may over-represent racially mixed partnerships, leading to an underestimation of homophily in a given sample.

PSYCHOSOCIAL ANTECEDENTS TO AND THEIR INFLUENCE WITHIN RACIALLY HOMOPHILOUS SEXUAL NETWORKS

Partner selection is not random or baseless. While currently a small, emerging body of literature, some research has considered the psychosocial underpinnings and mechanisms that may account for homophilous patterns of partnering and their role in the increased risk of exposure to HIV infection. Of particular importance has been research on how racial homophily manifests among Black sexual minority men as a result of race-based sexual stereotypes endorsed by sex partners of other races and ethnicities. Various race-based sexual stereotypes exist about Black sexual minority men, including those related to sexual prowess, penis size, sexual adventurism, positioning, and sexual aggression and dominance (Husbands et al. 2013, Wilson et al. 2009).

Newcomb et al. (2015) hypothesized that the valence of these stereotypes (e.g., whether perceived large penis size is considered to be a positive or negative attribute to a potential sexual partner) is not the critical factor. In fact, a variety of studies suggest that there is often no consensus among racial and ethnic minority men regarding the valence of particular stereotypes that others may hold of their racial or ethnic group (Paul et al. 2010, Wilson et al. 2009). Rather, mere existence of these stereotypes, particularly in that they are manifestations of sexual objectification, may foster homophily. Such sexual objectification may contribute indirectly to disparate rates of HIV exposure among Black sexual minority men, as these men appear to seek out same-race sexual partners exclusively or primarily (Newcomb & Mustanski 2013, Raymond & McFarland 2009).

However, additional research suggests that the role of sexual stereotypes and associated sexual objectification may be more complicated, and perhaps also directly related to HIV infection among Black sexual minority men, through their influence within the context of a same-race sexual partnership. That is to say, while sexual stereotypes endorsed by out-group members may facilitate racial homophily among Black sexual minority men, within these men's sexual networks, in-group sexual stereotyping may actually contribute to sexual risk behavior. While Black sexual minority men do not demonstrate increased rates of condomless anal sex with other Black men, as compared to rates with other races and ethnicities (e.g., Clerkin et al. 2011), the increased HIV prevalence among these men amplifies the risks for HIV infection (e.g., Millett et al. 2006).

It has been shown that Black sexual minority men hold the same sexual stereotypes about other Black men as out-group members, such as White and Latino men (Newcomb et al. 2015, Wilson et al. 2009). Previous research suggests that exposure to sexual stereotypes endorsed by men of other races and ethnicities, while facilitating same-race partnering patterns, may undermine racial and ethnic minorities' perceived sense of control in sexual situations with same-race partners (Paul et al. 2010, Wilson et al. 2009). While such dynamics have been offered to explain sexual risk behavior with respect to mixed-race partnering among Black sexual minority men, it is likely that such dynamics also exist when these men partner with other Black men. In the studies by Paul et al. (2010) and Wilson et al. (2009), qualitative interviews with racial and ethnic minority men suggested that, in certain sexual situations, feelings of objectification (especially with respect to sexual positioning or the quality of sex) may lead to a decreased sense of sexual autonomy among Black sexual minority men, such that they feel less control over the types of sexual behaviors performed or less ability to dictate the use of safe sex practices. As such, race-based sexual stereotypes and associated sexual objectification may influence the risk for HIV infection in two ways—by driving racially homophilous partnering among Black sexual minority men and by contributing to sexual risk behavior with other Black men within these homophilous networks (Newcomb et al. 2015).

Newcomb et al. (2015) investigated the relationships between specific race-based sexual stereotypes and sexual risk behavior among a racially and ethnically diverse sample of young sexual minority men, presuming (although not measuring this directly) that associations between the

endorsement of these stereotypes and sexual risk behavior represented the erosion of sexual autonomy. Among Black participants, perceptions that sex with other Black men is sexually passionate and hot or that Black men are sexually dominant were not associated with sexual risk behavior with other Black men. However, perceptions that Black men are likely to be the insertive anal sex partner (the top) did demonstrate this association. Black men (but not Latino or White men) endorsing this particular stereotype were less likely to have engaged in condomless insertive anal sex but more likely to have engaged in condomless receptive anal sex, the sexual behavior with the highest risk of HIV infection, with other Black sexual minority men. Thus, while future research is needed to parse out the psychological mechanisms of these associations, sexual stereotypes about Black men, in addition to initially contributing to homophilous patterns of partnering, may contribute to increased risk for HIV infection through the erosion of sexual autonomy that they engender, such as through sexual position objectification.

It should be noted, however, that the influence of race-based sexual stereotypes on racial homophily may not be consistent across race and ethnicity. Latino men, who are the targets of their own set of race-based sexual stereotypes (Newcomb et al. 2015, Wilson et al. 2009), typically demonstrate low, if not the lowest, homophily (Newcomb & Mustanski 2013, Sudhinaraset et al. 2013). In general, individuals tend to hold fewer sexual stereotypes about Latino than about Black sexual minority men (Wilson et al. 2009). While it has been suggested that stereotype valence does not matter with respect to sexual objectification among Black sexual minority men (Paul et al. 2010, Wilson et al. 2009), sex with Hispanic and Latino individuals is often perceived to be hot and passionate by sexual minority men of other races and ethnicities (Newcomb et al. 2015, Wilson et al. 2009). Researchers surmise that such benevolent sexual objectification by men of other races and ethnicities may contribute to greater racial and ethnic diversity in partner selection among Hispanic and Latino sexual minority men, while facilitating less diverse networks among Black men (Newcomb et al. 2015). Thus, the intrarace dynamics of sexual stereotypes, and their impacts on partner selection across various racial and ethnic groups, are not fully understood.

While out-group sexual stereotyping may drive homophilous patterns of partnering and in-group stereotyping may contribute to sexual risk behavior among Black sexual minority men, other partner characteristics appear to influence risk for HIV infection within the context of a racially homophilous network, as well. Having older partners, for instance, appears to increase the risk for HIV among Black men, a moderation that increases in magnitude as the participants' age decreases (Newcomb & Mustanski 2013). This particular finding may have a broad impact on HIV epidemics, given that several studies suggest that Black sexual minority men often engage in age-disparate sexual partnerships (Maulsby et al. 2015, Tieu et al. 2015). Additionally, the degree of familiarity with sexual partners appears to influence risk, as well, as a higher number of previous encounters with a partner is associated with increased likelihood of condomless anal intercourse, as is the case for main partnerships (Mustanski et al. 2015). In fact, relationship status is among the most robust influences on sexual risk behavior within racially homophilous sexual networks (Kelly et al. 2014).

MASCULINITY IDEOLOGY AMONG SEXUAL MINORITIES

Ideals of traditional masculinity ideology, i.e., beliefs regarding the importance of men adhering to cultural behaviors that define being a man, have been well documented as pervasive within many sexual minority communities (Pachankis et al. 2013) and may also play important roles in sexual partner selection, as well as protective sexual health behaviors. An important aspect of masculinity ideology is the heterosexual–homosexual dichotomy, which assumes that only heterosexuality equates to being a real man. Thus, sexual minority men who conform to the social pressures of

masculinity ideology perform gender presentations of masculinity in line with being perceived as heterosexual. Burgeoning interest is focusing on how heterosexual presentation, as well as other aspects of masculinity, influences sexual behaviors, HIV risk, and HIV prevention strategies among sexual minority men. Theories of masculinity ideology, such as Courtenay's (2000) theory of gender and health, provide useful frameworks for understanding how masculinity negatively affects sexual minority men and how masculinity may contribute to health risks in men, particularly sexual health risks for racial and sexual minority men. For Black sexual minority men, research has shown that masculinity ideology is salient in several aspects of their gender performance (Dangerfield et al. 2018a, Fields et al. 2012, Garcia et al. 2016, Hall & Applewhite 2013). For these men, pressures to adhere to the social expectations of masculinity can place them at high risk for HIV and may explain differences in HIV incidence in men who are at the intersection of racial and sexual minority statuses.

Qualitative interviews and community ethnographies have been the most commonly employed methods of examining the influence of masculinity ideology, revealing significant diversity in the expression of gender among Black sexual minority men (Garcia et al. 2016). These methods have indicated that these men rely on a variety of heuristics, cultural stereotypes, and gender role norms to guide their sexual and HIV risk-related behaviors. These behaviors are related to partner selection, sexual role positioning, HIV risk assessment (for the individual and of potential partners), and engagement in HIV prevention strategies. Furthermore, research has provided a nuanced understanding of these men as a category, which could be used to inform future avenues of HIV prevention among the diverse men that make up the category.

GENDER, PARTNER SELECTION, AND SEXUAL ROLE POSITIONING

Studies examining Black sexual minority men have shown that certain heuristics and cultural stereotypes are commonly used in partner selection and sexual role positioning during sexual intercourse (Fields et al. 2012, Garcia et al. 2016). Cultural stereotypes of masculinity within Black gay culture range across a spectrum of gender performance from hypermasculine (e.g., trades) to differing forms of masculine (e.g., butch queens and boys) and feminine (e.g., femme queens and cunts) (Garcia et al. 2016) presentation. Stereotypes that endorse masculinity ideology, typically associated with insertive sexual positioning during anal intercourse, have been reported to provide the perception of keeping one's heterosexual identity intact for men who endorse these stereotypes (Garcia et al. 2016, Hall & Applewhite 2013). Among men, these stereotypes allow for the use of masculinity heuristics in partner selection and sexual role positioning. For example, both the heuristics that masculine partners are insertive partners and that insertive partners have a low risk of HIV influence partner selection, as well as which sexual role may be assumed with a potential partner (Fields et al. 2012). Furthermore, preference for partners perceived as masculine is another prevalent theme found in qualitative research with Black sexual minority men, which may influence HIV risk (Fields et al. 2012). Black sexual minority men who perceive their potential partners as demonstrating culturally defined masculine stereotypes (e.g., being muscular, hood, or thuggish) report assuming the receptive role (Dangerfield et al. 2018a), placing these individuals at risk for HIV when engaging in anal intercourse without protection (e.g., condoms or ART-based prevention use). However, masculinity as a salient factor influencing sexual positioning among Black sexual minority men has not been consistently demonstrated (Dangerfield et al. 2018b). Research suggests that the influence of masculinity is weaker for men who engage in both insertive and receptive sexual role positioning (i.e., being versatile), which may produce equal power dynamics between partners (Dangerfield et al. 2018a). This potential effect may be due to the perception on the part of men who engage in both roles that they are balanced in masculinity

and femininity. Thus, although it is inconclusive, research regarding sexual role positioning among Black sexual minority men suggests that partner selection is influenced by salient contextual factors related to traditional masculinity ideology.

GENDER, HIV RISK ASSESSMENT, AND ENGAGEMENT IN PREVENTATIVE BEHAVIORS

The belief that heterosexuality equates to masculinity strongly influences HIV risk behaviors for some sexual minority men. Not identifying as gay is associated with the belief that one has control over one's risk of HIV infection (Garcia et al. 2016, Hall & Applewhite 2013). Masculinity has also been found to influence power dynamics between romantic or sexual partners in negotiations of condom use and beliefs about HIV prevention strategies (Garcia et al. 2016). For instance, heterosexual self-presentation has been reported in some studies to deter engagement in HIV testing as well as preventative behaviors, such as condom use or PrEP use. Interestingly, men who engage in versatile sexual role positioning (which may subvert the traditional masculine ideology that underlies heterosexual self-presentation) report routine HIV testing (Garcia et al. 2016). Regarding heuristics, the idea that masculine men are tops has also been linked to power dynamics between partners and condom use negotiation. Across studies, Black men report that the more masculine partner within a relationship holds more power in the negotiation of condom use. Hypermasculinity and power dynamics potentially place both the hypermasculine partner and their less masculine (effeminate) counterpart at increased risk of HIV infection. For the hypermasculine partner, endorsement of aspects of masculinity ideology, such as the importance of engaging in sexual activity, is associated with greater HIV risk due to the high numbers of sexual partners of sexual minority men who are also members of minority racial groups (LaPollo et al. 2014, Murray et al. 2018). For the less masculine (and often receptive) partner, control of the risk of HIV is lost, as he typically relinquishes condom use decision making to the masculine partner.

Perceptions of a potential partner's masculinity (e.g., the heuristic that masculinity equates to safety in partners) have also been reported as a means of assessing HIV risk for some men. Receptive partners (i.e., bottoms), often also less masculine partners, are viewed as more promiscuous, engendering the perception that they are more likely to be infected with HIV (Fields et al. 2012). In contrast, potential partners who demonstrate stereotypically masculine behaviors (e.g., straight acting, assuming the insertive role in anal intercourse, or engaging in sexual intercourse with women) are perceived to be at lower risk of HIV (Fields et al. 2012). This assumption occurs because of the notion that a masculine partner is less likely to be open regarding their sexual orientation. Furthermore, partners perceived as masculine are assumed to have less engagement with gay communities and thus less opportunity for contact with HIV.

Indeed, for many Black sexual minority men, perceived conflation of masculinity and sexual orientation may impede HIV prevention efforts. For instance, Hall & Applewhite (2013) found that, for Black sexual minority men who identified as heterosexual, simply discussing HIV made them visibly uncomfortable, as discussions surrounding HIV are typically associated with being homosexual. Moreover, research has shown that, for some Black men, HIV testing is perceived as a threat to their masculinity and is viewed as a behavior to be avoided and a measure to be used only for emergency reasons (Garcia et al. 2016). Interestingly, masculinity norms can have either a negative or a positive influence on HIV testing, depending on how strongly men identify as being gay. Specifically, among Black sexual minority men, masculine norms of not seeking help and the importance of sex reduce engagement in HIV testing in heterosexual-identified men, while norms of responsibility and control influence gay-identified men to engage in HIV testing more often (Hall & Applewhite 2013).

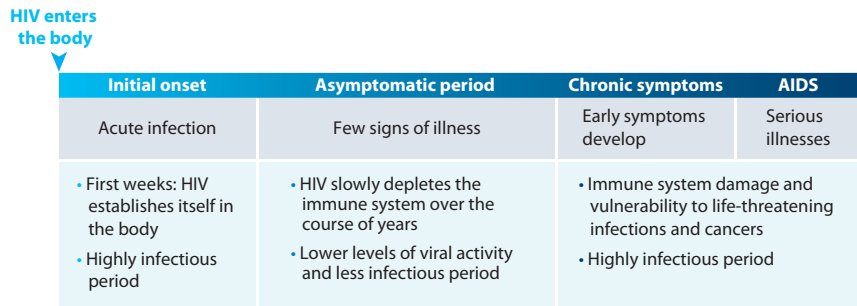


Figure 3

Natural history (or pathogenesis) of HIV infection and its association with HIV infectiousness.

With respect to HIV-preventative behavior, in an assessment of how masculinity influences the acceptance and use of PrEP, one study (Garcia et al. 2016) found that older Black sexual minority men who endorsed masculine cultural stereotypes expressed sentiments that PrEP use was related to identifying as gay. However, among men who identified with feminine identities (e.g., femme queens) PrEP was perceived as a useful prevention strategy. As PrEP use is improving among Black sexual minority men, focused attention regarding the influence of masculinity on PrEP use will be beneficial in the tailoring of prevention methods to Black men.

THE THIRD REVOLUTION IN HIV PREVENTION: ANTIRETROVIRAL PREVENTION STRATEGIES

Today, HIV prevention centers on the use of ART to reduce HIV infectiousness and to limit HIV infectivity. With respect to infectiousness, concentrations of HIV in blood, semen, and vaginal secretions of HIV-positive individuals change over the course of infection. The disease course of HIV infection (HIV pathogenesis) was initially determined through observational cohort studies long before treatments for HIV existed. **Figure 3** illustrates the natural history of HIV infection for a given individual. The period immediately after the onset of infection, the acute infection phase, is a time of heightened infectiousness, as HIV concentrations in blood and genital secretions peak. Over time, HIV establishes itself in the immune system through the rapid replication and depletion of select immune cells. At the late stages of HIV infection and AIDS, HIV concentrations are again elevated, representing another period of increased infectiousness. These two critical stages were determined in observational studies of pre-ART HIV-positive individuals in Rakai, Uganda, which demonstrated that the highest rates of HIV transmission occur during both the acute period of HIV infection and the late stages of the disease, after immune cells are depleted and the virus is again abundant in blood plasma (Mehta et al. 2009, Wawer et al. 2005). Of particular importance, the Rakai studies showed that, when HIV quantities in the blood plasma of HIV-positive participants were low (under 3,500 copies/ml), no HIV infections among their sexual partners were observed. Conversely, more than half of observed HIV infections occurred among individuals whose partners' viral load exceeded 35,000 copies/ml. Taken together, these results indicated that a dose-response relationship exists between HIV concentrations in blood plasma and HIV transmission.

Within the United States, as many as half of HIV infections are thought to occur during the early stages of acute infection. Coupled with the fact that HIV rapidly replicates during the acute infection stage (Remien et al. 2009, Steward et al. 2009), the heightened risk during this

period stems, presumably, from the fact that a newly infected person likely continues to engage in transmission risk behaviors at rates high enough to facilitate infection in the first place (Remien et al. 2009, Steward et al. 2009). Additionally, HIV transmission is amplified further during the acute infection phase when individuals have multiple sex partners overlapping in time (i.e., sexual partner concurrency) (Pines et al. 2017, Senn et al. 2009).

In addition to stage of disease, sexual infectiousness depends on the type or subtype of the virus and its concentration in semen and vaginal fluids. While HIV is harbored in immune cells and concentrations of cell-associated HIV may play important roles in HIV transmission, it is the amount of free virus in blood plasma and plasma-derived fluids, particularly semen and vaginal fluids, that is the key factor leading to most HIV infections. Evidence for this assertion comes from genetic analyses of HIV collected from recently infected men, which show that HIV isolated in blood plasma has the characteristics of free virus, rather than cell-associated HIV, indicating a primacy of free virus over cell-associated virus in HIV transmission events (Butler et al. 2007, 2010). Additional research demonstrates that the amount of virus in semen and vaginal fluids predicts HIV transmission even when HIV concentrations in blood plasma are statistically controlled. Consequently, individuals who believe that they are less infectious, based on information that the amount of HIV in their blood plasma is below levels of detection, may, in fact, be considerably more sexually infectious than they can possibly know.

HIV TREATMENT IS PREVENTION

ART suppresses HIV replication, thereby limiting damage to the immune system. The clinical benefits of ART, apparent by the extension of the lives of people living with HIV, are also extended to public health via reductions in sexual infectiousness. In one compelling observational study (Donnell et al. 2010) investigating the impact of treatment in sexual transmission of HIV among 349 HIV-serodiscordant couples in which the infected partner had initiated treatment, only one incident infection was observed. In contrast, among the 3,032 couples with an untreated HIV-positive partner, 102 new infections emerged. In addition to epidemiological evidence, this study, and a growing number of similar studies suggesting the biological plausibility of the idea that ART reduces HIV infectiousness, provided the basis for the landmark randomized clinical trial HIV Prevention Trials Network Protocol 052 (HPTN 052), which showed definitively that early treatment with ART prevents HIV transmission when delivered in the context of adherence support and comprehensive sexual health care (Cohen et al. 2011, 2012).

Significantly, HPTN 052 was the first randomized clinical trial to test whether HIV treatment prevents sexual transmission of HIV (Cohen et al. 2011, 2012). The study was conducted in nine southern African countries, and participants included 763 mixed-HIV-status couples who were randomly assigned to one of two experimental conditions: (a) early treatment of the HIV-infected partner when CD4 cell counts were between 350 and 500 cells/cc; or (b) delayed treatment for the infected partner until CD4 counts fell below 350 cells/cc, the condition under which treatment is typically started. The core aim of HPTN 052 was to test the hypothesis that, among serodiscordant partners, early initiation of ART prevents sexual transmission to the HIV-uninfected partner (Cohen & Gay 2010). An interim analysis revealed that, indeed, the early initiation of therapy substantially protected the HIV-uninfected partners, with as much as a 96% reduction in risk.

At the time of the interim analysis, of the 39 new HIV infections that had occurred, genetic viral testing determined that 28 were linked to the HIV-infected partner in the study. Of those 28 genetically linked infections, only one had occurred due to sexual contact with a partner receiving early treatment, with the other 27 (96%) occurring among couples in the delayed treatment group.

Furthermore, early treatment showed additional clinical benefits relative to delayed treatment, including slowed HIV disease progression and improved health.

Importantly, the remaining 11 of the 39 HIV infections observed in HPTN 052 that were not genetically linked stemmed from sex partners outside of the index patient relationship. This finding is consistent with observational studies of mixed-HIV-status couples using similar procedures to link the genetics of partners' viruses. These studies find between 9% and 13% of HIV infections involve partners outside of a main partnership. As such, results from HPTN 052 suggest that, if an infected partner on ART is HIV suppressed and receiving high-quality sexual health care, then their sex partners have nearly full protection against HIV infection. However, co-occurring sexually transmitted infections (STIs), as well as ART nonadherence, will degrade the protective benefits. As such, in addition to the risks posed by extra-relationship sexual partners, poor medication adherence could cause the use of treatments as prevention (TasP) to fail as much as 25% of the time (Kalichman 2013). However, under optimal conditions, mathematical models suggest that the scale-up of TasP could reverse the direction of HIV epidemics (Granich et al. 2009, Wilson et al. 2008).

SEXUAL BEHAVIOR AND HIV INFECTIOUSNESS

Sexual behaviors are associated with increased HIV infectiousness above and beyond their impact on the infectiousness of other STIs. Namely, sexual exposure to pathogens that do not cause infection can still stimulate activation of the immune system and thereby cause an inflammatory response that increases HIV infectiousness (Nagot et al. 2008). In one study, men on ART who presented with greater HIV in their semen than in their blood plasma demonstrated higher rates of condomless intercourse compared to men who had either similar or less HIV in their semen relative to their blood (Kalichman et al. 2002). Importantly, in this study, elevated HIV in semen was not attributable to a co-occurring STI, and sexual behavior data confirmed that the most sexually active men could not possibly have known that they were the most infectious.

Taken alongside the known association of nonadherence to ART and HIV replication, as well as common factors that predict both ART nonadherence and condomless sex, a dual-process behavioral model of HIV infectiousness can explain the increased risks for persons who are either (a) ART adherent but with a co-occurring source of genital inflammation or (b) ART untreated or nonadherent (Kalichman 2008a). As can be seen in **Figure 4**, nonadherence to ART is influenced by substance use and mental health (i.e., depression and social isolation), and nonadherence leads to incomplete viral suppression and therefore increased infectiousness. Substance use, depression, and social isolation are key to understanding the behavioral aspects of HIV infectiousness because they represent three different spheres of influence—behavior (substance use), affective regulation (depression), and social relations (social isolation). These three factors are not only among the most robust predictors of both ART nonadherence and sexual risk practices (Amico et al. 2007, Kalichman et al. 2012, Parruti et al. 2006), but are also related to inconsistent engagement in health care (Marks et al. 2010, Mugavero et al. 2013). Because nonadherence and sexual risks share substance use, depression, and social isolation as predictive influences, these three factors can be integrated into the above unified model of sexual infectiousness (Kalichman 2008a, Kalichman & Rompa 2003).

TREATMENT BELIEFS AND PREVENTION

Conclusive evidence that HIV treatment reduces infectiousness and potentially eliminates the risk of HIV transmission led the US Centers for Disease Control and Prevention (CDC) to issue a

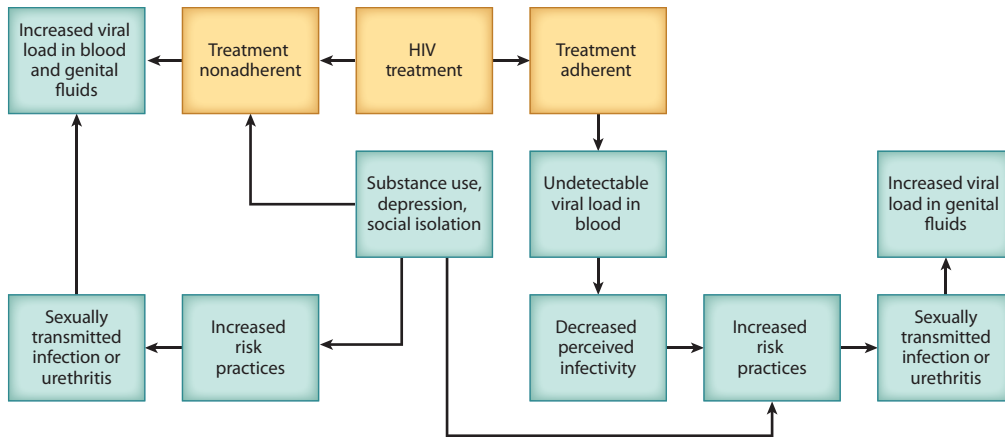


Figure 4

Model of factors accounting for HIV sexual infectiousness with co-occurring genital tract infectiousness in relation to high treatment adherence and in relation to poor adherence. Mental health problems, substance use, and social factors increase risks for high infectiousness in both scenarios.

public statement that individuals with suppressed HIV are at low risk of transmission. The CDC specifically stated,

Scientific advances have shown that antiretroviral therapy (ART) preserves the health of people living with HIV. We also have strong evidence of the prevention effectiveness of ART. When ART results in viral suppression, defined as less than 200 copies/ml or undetectable levels, it prevents sexual HIV transmission. Across three different studies, including thousands of couples and many thousand acts of sex without a condom or pre-exposure prophylaxis (PrEP), no HIV transmissions to an HIV-negative partner were observed when the HIV-positive person was virally suppressed. This means that people who take ART daily as prescribed and achieve and maintain an undetectable viral load have effectively no risk of sexually transmitting the virus to an HIV-negative partner. (McCray & Mermin 2017)

The CDC statement energized community advocates and activists to launch campaigns encouraging people to get tested and treated for HIV with the aim of becoming noninfectious (e.g., undetectable = untransmittable). However, beliefs about HIV infectiousness and the impact of treatment on transmission had been growing, particularly in the lesbian, gay, bisexual, and transgender community, long before the CDC's statement. In the United States, community surveys were launched to assess HIV treatment optimism following the advent of combination ART. In the early years of combination ART, treatment optimism centered on the potential impact of no longer considering HIV an untreatable life-threatening disease. In the following decade, studies showed that HIV was most transmittable during periods of high viral replication, namely the early and later stages of HIV infection, with less transmission occurring during the years of chronic illness (Wawer et al. 2005). Because clinical studies showed that HIV infectiousness was reduced dramatically with HIV treatment, public health officials in Switzerland issued a policy known as the Swiss Statement, indicating that, with sustained HIV suppression and in the absence of any co-occurring source of genital tract inflammation, people living with HIV are not at high risk for transmission to sex partners. Specifically, the Swiss Federal Commission for HIV/AIDS declared that HIV-infected persons should be considered noninfectious when peripheral blood plasma viral load is undetectable for at least 6 months and when there are no co-occurring sexually transmitted

infections (Vernazza et al. 2008). These and other such policy positions and news releases had significant impacts on community-held beliefs, attitudes, and behaviors.

In the United States, HIV transmission risk perceptions have declined and coincide with increased beliefs regarding the minimal risks for people receiving HIV treatment to transmit the virus sexually. A series of repeated cross-sectional surveys conducted in 1997, 2005, 2006, and 2015 at the annual Gay Pride Festival in Atlanta, Georgia show that, at each survey point, beliefs that HIV is less transmittable in the context of HIV treatment have increased, perceptions of risk that a person with HIV will sexually transmit the virus have declined, and there have been significant reductions in condom use during anal sex (Kalichman et al. 2017b). Changes in beliefs, perceptions, and behaviors were apparent at each survey time and occurred irrespective of HIV status. The association between condom use during anal sex and HIV treatment beliefs shifted dramatically by 2015, with men of both HIV-positive and HIV-negative or unknown status demonstrating substantial increases in beliefs that HIV treatments protect against HIV infection and with men who engaged in condomless anal sex endorsing these beliefs significantly more than those who did not. Furthermore, among HIV-positive men, from 1997 to 2015, the proportion of anal sex acts protected by condom use declined from 82% to 47%; the percentage of HIV-positive men reporting condomless anal sex increased from 25% to 67%, and the percentage of HIV-positive men reporting two or more sex partners in the previous 6 months increased from 9% to 33%. Thus, beliefs in HIV treatment as prevention have increased, and perceived risks of HIV transmission have decreased, along with declines in condom use. The implications of these trends are that, while the effects of HIV treatments on HIV transmission risks have the potential to reduce HIV transmission, changes in condom use may lead to parallel increases in STIs, which have the potential to offset the gains of TasP.

Similar patterns of changing beliefs, attitudes, and behaviors are observed among sexual minority men in other countries. Australian researchers, for example, have examined changes in treatment-related beliefs and sexual behaviors among sexual minority men in annual surveillance surveys. These studies show that increases in beliefs that HIV treatment can prevent HIV infections have occurred since ART became available (e.g., Holt et al. 2014). In one study, awareness that HIV treatments prevent HIV transmission increased substantially between 2013 and 2015 among Australian sexual minority men (Holt et al. 2016), and the changes were most apparent among HIV-positive men. In 2013, 9% of HIV-positive men endorsed the belief that HIV treatments prevent HIV transmission, whereas this proportion increased to 46% in 2015 and 48% in 2017. These changes were also observed among HIV-negative men, increasing between 2013, 2015, and 2017 from 2%, to 10%, to 17%, respectively (Holt et al. 2016, Lea et al. 2017).

Studies in the United Kingdom and Brazil also have shown increases in HIV prevention-related HIV treatment beliefs (Hanif et al. 2014, Sewell et al. 2016), suggesting that, as HIV treatments are scaled up, there have been shifts in beliefs and behaviors in these countries. It should be noted, however, that not all countries where HIV treatments are being scaled up demonstrate these same patterns of awareness regarding their prevention benefits. Most notably, a qualitative study conducted in South Africa found that, while HIV-positive men were well aware of the benefits of HIV treatment, there was no evidence that these men were aware of the prevention benefits of ART (Mooney et al. 2017).

Nevertheless, in Vancouver, studies show that, from 2012 to 2015, HIV treatment optimism has increased significantly with increased uptake of treatment, with the most substantial changes in treatment beliefs (including beliefs that a person with an undetectable HIV viral load cannot transmit HIV) occurring among HIV-positive men. However, unlike the observations of studies in the United States and Australia, studies in Vancouver do not show trends toward recent increases in condomless anal sex (Moore et al. 2017). The change in condomless anal sex observed in this

cohort occurred early in the assessment period, with the percentage of HIV-positive men reporting condomless anal sex increasing from less than 30% in late 2012 to nearly 45% in early 2013. At the same time, the percentage of men agreeing that a person with an undetectable viral load cannot transmit the virus increased from 45% to 50%. Over the subsequent 2.5 years, the rate of condomless anal sex remained mostly stable near 45%, with the percentage of people with HIV who endorsed the belief that undetectable = untransmittable increasing only slightly to 55%.

Coinciding with changes in treatment beliefs, sexual minority men in Vancouver have significantly increased their use of a partner selection prevention strategy known as serosorting. This common practice was first identified through observations that people seek sex partners of their same HIV status (Eaton et al. 2007). Changing perceptions of risk in relation to HIV viral load have reshaped serosorting. In Vancouver, both HIV-positive and HIV-negative sexual minority men have increased their use of knowledge of viral load as a basis for sexual partner selection, with HIV-positive men being more inclined to select HIV-negative partners when their viral load is suppressed, and HIV-negative men being more inclined to seek HIV-positive partners with suppressed viral load. Furthermore, this practice is related to increases in HIV treatment optimism (Roth et al. 2018). However, a significant concern with serosorting is that it can be based on faulty assumptions. For example, the choice of HIV-negative sex partners is based on what one person tells another about the results of their most recent HIV test, which might have taken place months or even years beforehand (Eaton et al. 2009). Similarly, an undetectable viral load is not an imputable status. A person may believe that they have an undetectable blood plasma viral load, based on their most recent medical testing, and may assume that an undetectable plasma viral load means uninfectedness, without considering whether there is a co-occurring STI. The impact of treatment beliefs on sexual behavior will continue to become increasingly complex and nuanced as HIV treatments are used for prevention, including by HIV-negative individuals as PrEP.

ANTIRETROVIRAL THERAPIES TO REDUCE HIV INFECTIVITY: PRE-EXPOSURE PROPHYLAXIS

The two-drug ART formulation tenofovir disoproxil fumarate and emtricitabine (TDF/FTC, marketed as Truvada®) has demonstrated high efficacy for HIV prevention in clinical trials, with overall protection of 44% and prevention of over 95% when taken with high daily adherence (Grant et al. 2010). Due to the low cost of TDF/FTC, its low toxicity profile, and its high level of efficacy, the potential for PrEP to be a highly effective tool in halting HIV epidemics is indisputable. Nevertheless, as is the case with the other tools in the HIV prevention repertoire, such as condoms, testing, clean needles, and TasP, the effectiveness of PrEP depends entirely on individuals' behavior. The major hurdles to PrEP are also the same, with HIV stigma, misperceptions of risk, and substance use impeding PrEP uptake and effectiveness (Eaton et al. 2015).

Analogous to the HIV treatment and care cascade, Kelley et al. (2015) proposed the PrEP care cascade to enumerate the steps in PrEP engagement for people who could potentially benefit from its use. **Figure 5** illustrates these steps along the PrEP care cascade. In this context, the cascade shows the steps toward HIV prevention among a given population of potential PrEP candidates: Some of these individuals are aware of and willing to take PrEP; of these individuals, some have access to healthcare; of these individuals, some receive a prescription; and, ultimately, of these individuals, some achieve PrEP adherence and thereby sexual protection against HIV infection. Kelley et al. (2015) demonstrated that, even with optimistic estimates of PrEP uptake relying on current strategies, only approximately 12% of Black sexual minority men will obtain protection from HIV with PrEP use. In short, basic foundational pieces of PrEP uptake have fallen short and contribute to the projected low rate of protection among Black sexual minority men, including via suboptimal awareness of PrEP and difficulties with access to healthcare.

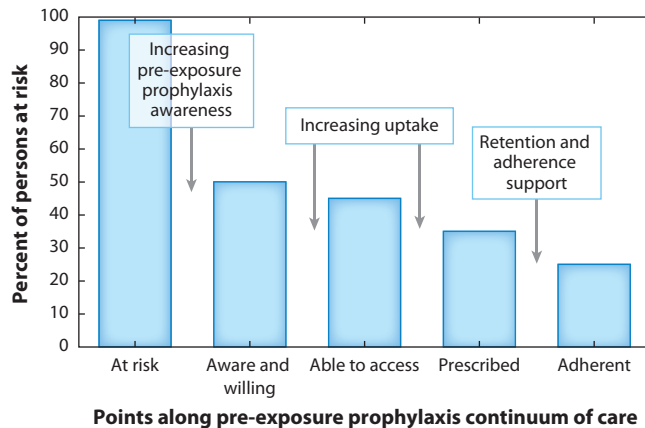


Figure 5

HIV pre-exposure prophylaxis care cascade.

More broadly, fewer than half of persons who could benefit from PrEP are aware of or willing to take it. Furthermore, fewer than half of those who are prescribed PrEP are expected to be adherent. Stigma beliefs about PrEP likely serve as critical barriers to progress along the PrEP care cascade (Arnsten et al. 2002, Calabrese & Underhill 2015). In particular, these challenges impede uptake among Black sexual minority men who report anticipated PrEP stigma more frequently, believing that they will be mistreated for using PrEP by both sex partners and health care providers. While it may be that anticipated stigma within the healthcare system is specific to Black sexual minority men, anticipated stigma from potential sex partners has been highlighted as a barrier to PrEP uptake among sexual minority men of other races and ethnicities more broadly (Biello et al. 2016, Lelutiu-Weinberger & Golub 2016).

Stigma manifests to impede PrEP uptake among Black men in other ways, as well. For instance, structural factors, such as mistrust toward medical institutions or pharmaceutical industries, which may drive and sustain stigma, serve as a barrier to PrEP use (Philbin et al. 2016). Additionally, research demonstrates that many Black sexual minority men endorse beliefs that PrEP is for people who do not choose their sex partners carefully or who are promiscuous and that PrEP will cause people to have riskier sex (Eaton et al. 2017). Men who report that PrEP is for people who are promiscuous are significantly less likely to express interest in the use of PrEP, yet these same men also report greater sexual risk taking (Eaton et al. 2017). These findings suggest that stigma associated with PrEP use is a major barrier to PrEP interest among individuals who would likely benefit most from it.

ALCOHOL AND DRUG USE AND PRE-EXPOSURE PROPHYLAXIS

Because alcohol and other drug use is closely associated with HIV risks, these behaviors are disproportionately prevalent among individuals who are candidates for PrEP. In a latent class analysis to determine characteristics predictive of PrEP candidacy based on HIV seroconversion, researchers found that alcohol and drug use was critically important in the determination of individuals who would benefit most from PrEP (Chan et al. 2015). Considering the literature regarding substance use and ART nonadherence (Arnsten et al. 2002, Hendershot et al. 2009), it is logical and necessary to assess substance use among individuals interested in taking PrEP. Alcohol and other drug use interferes with ART adherence through the direct effects of intoxication, as

well as longer-term cognitive impediments, including memory disruptions and attention deficits, which serve as sources of unintentional nonadherence. However, individuals may avoid PrEP or forego it intentionally when drinking or using other drugs due to concerns about mixing ART with substances (i.e., interactive toxicity beliefs) (Kalichman et al. 2009). Intentional nonadherence to ART is a strong barrier to the achievement of minimally efficacious medication blood levels (Kalichman et al. 2009, 2013, 2015; Pellowski et al. 2016), and these same beliefs will likely impede uptake of and adherence to PrEP.

Alcohol and other commonly abused drugs, as well as certain classes of ART, are metabolized by the liver and share cytochrome P450 (CYP) metabolic pathways (particularly CYP3A4), which creates a risk of potential adverse drug-to-drug interactions (Bracchi et al. 2015). However, TDF/FTC is not metabolized by the liver and does not pose any risk of serious drug-to-drug interactions with alcohol and common drugs of abuse (Kumar et al. 2015). Nevertheless, beliefs regarding the mixture of ART with alcohol and other drugs do impede uptake and interfere with adherence. Interactive toxicity beliefs are prevalent among people living with HIV and are directly associated with intentional nonadherence to the therapeutic use of ART (Altice et al. 2001; Kalichman et al. 2012, 2013, 2015; Sankar et al. 2007). Results from one study showed that 35% of people on treatment indicated that they missed ART doses intentionally when they used illicit drugs (Altice et al. 2001). In addition, 56% of individuals who were intentionally nonadherent when using illicit drugs indicated that they also stopped taking ART when drinking alcohol.

In the first study to examine PrEP interactive toxicity beliefs among HIV-negative, sexually active, sexual minority men, Kalichman & Eaton (2017) showed that 43% of these men would be considered PrEP candidates (based on their sexual behavior or partner status). Among the men in this sample, two-thirds indicated that alcohol and PrEP should never be mixed, and 42% indicated that a person should stop taking PrEP when drinking. In multivariable logistic regression analyses predicting PrEP interest, controlling for several potential confounding variables, only two significant predictors of PrEP interest emerged: binge drinking and PrEP–alcohol interactive toxicity beliefs. Men who were interested in PrEP were significantly less likely to binge drink and endorsed fewer PrEP interactive toxicity beliefs. Furthermore, among 24 men who were already PrEP users, alcohol use was common, with 88% reporting current alcohol use and 54% reporting binge drinking. PrEP-related alcohol interactive toxicity beliefs were frequently reported among men in this sample, with more than 75% endorsing at least one PrEP-related alcohol interactive toxicity belief, 25% endorsing multiple beliefs, and 33% indicating that alcohol and PrEP should never be mixed.

THE NEW ERA FOR BEHAVIORAL HIV PREVENTION INTERVENTIONS

Behavioral research that, for more than 30 years, aimed to design interventions to increase condom use and to reduce numbers of sex partners now has a renewed purpose. Interventions must now aim to increase HIV testing to inform people of their HIV infection, link them to health care, retain them in health care, and have them adhere to ART. Analogously, these same interventions have the new potential to increase PrEP uptake and adherence. The aims, goals and endpoints may differ, but the populations, as well as the theoretical underpinnings of, facilitators of, and barriers to behavior change, are the same. Furthermore, interventions are better informed now than during the early years of HIV. For example, we now know that social and sexual networks offer the optimal level for interventions to advance ART-based prevention (Amirkhanian et al. 2014, Semba et al. 2007). In addition, behavioral interventions that have been used for more than 20 years to improve HIV treatment adherence have a new purpose in prevention. In terms of a

research agenda, a broad array of behavioral interventions are ready for retooling and testing for effects with new targeted outcomes. In this sense, for HIV prevention scientists, everything old is new again (Kalichman 2008b), and from a public health perspective, there is an arsenal of existing evidence-based behavioral interventions that could be used in the future.

As one example, the application of self-regulation theory encompasses all of the components of behavioral counseling interventions that have been demonstrated as effective across multiple chronic disease outcomes (Jacobs et al. 2012, Janssen et al. 2013, Keib et al. 2010, Sullivan et al. 2011), including HIV treatment adherence (Kalichman et al. 2011a,b). Among the components shared across interventions are patient education, self-monitoring skills, direct patient feedback, support, and individualized–personalized problem solving (Zullig et al. 2013). Self-regulation theory informs the content of adherence interventions that directly address challenges by providing accurate information, building behavioral skills, and providing support. Interventions with these same components have demonstrated efficacy in people living with HIV (Campbell & Haberer 2015).

In an early randomized trial conducted as part of ACTG Protocol 731, Reynolds et al. (2008) demonstrated significant improvements in ART adherence and viral suppression resulting from a self-regulation theory–based intervention delivered by phone. This model was subsequently adapted to address substance use as a barrier to adherence and was delivered in a coaching framework (Kalichman et al. 2011b, Signor et al. 2013). Coaching differs from counseling in its approach to finding solutions to self-identified problems and represents a collaborative process that emphasizes directive feedback, reinforcement of successful steps toward goals, and the fostering of self-reliance. The results of a randomized trial testing a self-regulation theory–based adherence coaching intervention demonstrated that five sessions of phone-delivered intervention effectively improved ART adherence and viral suppression (Kalichman et al. 2016). Other trials have shown similar effects with diverse patient populations (Jacobs et al. 2012).

Short message communication also has emerged as a promising intervention modality to influence adherence (Cornelius et al. 2013, Ingersoll et al. 2015). Text messages in and of themselves have been demonstrated to be effective in improving retention to care (Murray et al. 2015), increasing ART adherence, and sustaining HIV suppression. A meta-analysis of randomized trials showed that two-way interactive text messaging consistently and significantly improves ART adherence (Finitsis et al. 2014). Text messaging can also extend the opportunity for support and problem solving within a care and adherence coaching framework. Lester et al. (2010), for example, conducted a seminal trial in Kenya where, at the start of each week, patients received a text message that asked how they were doing, with instructions to reply to let their provider know either that they were doing well or that they wished to have a brief call to discuss problem solving. Results showed that interactive texting effectively improved ART adherence and viral suppression. Furthermore, a meta-analysis of three controlled trials that tested two-way interactive text messaging interventions for ART adherence showed significant improvements in adherence (Mbugabaw et al. 2013). This model of increased patient–provider interaction to improve ART adherence is used in multiple settings and locations, including in the prevention of mother-to-child transmission of HIV (Awiti et al. 2016), as well as among vulnerable populations in Canada (Jongbloed et al. 2016, Smillie et al. 2014). The success of these interventions likely stems from the fact that text messaging can be initiated by patients to reach their providers when in need of assistance, as barriers and challenges occur unexpectedly and outside of weekly intervention sessions: The ability to text providers affords opportunities for intervention beyond the confines of weekly sessions. Similar to phone-delivered adherence coaching, short message texting interventions originally developed for HIV treatment adherence can also be used to improve ART adherence in TasP and PrEP. Indeed, an entirely new family of behavioral interventions is emerging that draws on

existing models of HIV prevention to behaviorally enhance TasP and PrEP (B-TasP and B-PrEP, respectively) (Kalichman et al. 2018).

New applications in cellular communication technologies are readily available and offer opportunities for the advancement of B-TasP and B-PrEP. An example is Wisepill, a real-time medication monitoring device that has attracted considerable attention. Wisepill is an electronic pillbox that holds 30 large pills (or 60 small pills). Each time the device is opened, a time-stamped signal is sent to a web-based server that can be accessed remotely in real time to monitor adherence and to trigger intervention. Monitoring container openings affords the opportunity to intervene when the device is not opened. Specifically, when an individual does not open the Wisepill at the prescribed dose time, an automated text message can be sent. If the Wisepill remains unopened, an interventionist can call the patient to confirm their missed dose, as well as to manage in-the-moment barriers. Furthermore, Wisepill monitoring data can be used to deliver adherence feedback to patients, and feedback is a central feature of effective adherence interventions (de Bruin et al. 2017, Sabin et al. 2010). This approach represents a just-in-time intervention that is, by definition, adaptive to patient needs (Nahum-Shani et al. 2018). Trials have demonstrated the feasibility of Wisepill use in resource-constrained settings (Haberer et al. 2017) and for real-time dose-linked counseling (Pellowski et al. 2014). For example, Sabin et al. (2015) randomized patients receiving ART either to real-time Wisepill adherence monitoring or to usual care. Participants in the real-time adherence intervention who failed to open the Wisepill container within 30 minutes of scheduled doses were sent a text message reminder to take their medication, and those participants who had less than 95% on-time adherence received counseling at their next clinic appointment. This trial demonstrated significant improvements in adherence for patients who received the real-time intervention, relative to the usual care control. In addition, real-time adherence monitoring with dose-linked texting demonstrated significant improvements in HIV suppression among participants between baseline and 9-month follow-up.

CONCLUSIONS

The use of electronic communication technologies to deliver behavioral interventions to individuals, with the aim of diffusing the impacts at the network level, represents the new frontier for health interventions. HIV is spread through sexual and drug-sharing networks, and intervention at the network level offers one of the most powerful avenues to reduce HIV infectiousness and infectivity, as network approaches to HIV prevention match the level of intervention to the level of HIV transmission. Interventions originally developed to reduce sexual risks with condoms at the network level (Knowlton et al. 2005; Latkin et al. 2003, 2009; Purcell et al. 2004; Tobin et al. 2007) can now be adapted to serve as the conduits for social influence to increase uptake and adherence to B-TasP and B-PrEP. For instance, concepts such as racial homophily that are known to define networks and influence risks may be exploited with the infusion of B-TasP and B-PrEP into network structures as a means to increase these measures' protective effects. Our current understanding of HIV risk in networks and the reinvention of behavioral prevention interventions currently give prevention scientists the power to bend HIV epidemic curves toward zero in ways never before seen. There is reason to hope that a fourth revolution in HIV prevention will end these epidemics. While we are close, we are not yet quite there.

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