# Advances in the prevention of heterosexual transmission of HIV/AIDS among women in the United States

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## Abstract

Despite recent advances in testing and treatment, the incidence of HIV/AIDS in the United States has remained stagnant with an estimated 56,300 new infections every year. Women account for an increasing proportion of the epidemic. The vulnerability of women to HIV stems from both increased biologic susceptibility to heterosexual transmission and also the social, economic, and structural disadvantages they often confront. This review describes the main reasons for the increased vulnerability of U.S. women to HIV transmission with particular emphasis on specific high-risk groups including: non-Hispanic blacks, women who use drugs, women with a history of incarceration, and victims of intimate partner violence. Although behavioral approaches to HIV prevention may be effective, pragmatic implementation is often difficult, especially for women who lack sociocultural capital to negotiate condoms with their male partners. Recent advances in HIV prevention show promise in terms of female-initiated interventions. These notably include female condoms, non-specific vaginal microbicides, and antiretroviral oral and vaginal pre-exposure prophylaxis. In this review, we will present evidence in support of these new female-initiated interventions while also emphasizing the importance of advocacy and the political support for these scientific advances to be successful.

## Introduction

HIV is the leading cause of death and disease among women aged 15-49 years worldwide.[1] In sub-Saharan Africa, which bears a disproportionate burden of the world's HIV epidemic, 60% of people living with HIV are women.[1,2] In the United States, although the epidemic has predominantly affected men, women are increasingly impacted. In 1992, women accounted for 14% of those with living with AIDS in the United States,[3] but by 2008 this proportion rose to 25%.[4]

Despite advances in HIV knowledge, prevention, and treatment, the annual incidence of HIV infection in the U.S. has remained stable at an estimated 56,300 new infections per year since 1999.[5] Sexual contact is the predominant mode of HIV transmission in the world.[2] Among HIV-infected women in the United States, 72% were exposed through heterosexual contact.[6] Here we will review factors associated with women's increased vulnerability to HIV with a specific focus on heterosexual transmission of HIV in the United States. We highlight four main groups of women who are particularly vulnerable to HIV in the U.S.: black women, women with substance use disorders, incarcerated women, and victims of interpersonal violence. We subsequently discuss evolving strategies to prevent transmission of HIV/AIDS to women, including universal HIV screening, test and treat strategies, and medication-assisted treatment for substance use disorders. Lastly, we present and demonstrate the need for female-initiated strategies for HIV prevention, including pre-exposure prophylaxis (PrEP) and vaginal microbicides.

## Vulnerability to HIV

The vulnerability of women to HIV stems from both increased biologic susceptibility to heterosexual transmission and the social, economic, and structural disadvantages they often confront. The greatest risk of sexual transmission is through receptive anal and vaginal intercourse, at rates of approximately 0.1-30% per episode for unprotected receptive anal intercourse, and 0.1-10% per episode in unprotected vaginal intercourse.[7-10] The wide range in per-act estimates is due to the heterogeneity of factors influencing HIV transmissibility, including concurrent genital ulcer disease, stage of HIV infection, low-income setting, and commercial sex exposure (CSE)[9,10] Some debate exists whether or not the risk is greater for male-to-female transmission than for female-to-male transmission but the meta-analysis by Boily et al.found that after controlling for CSE and high-income setting, the female-to-male transmission estimates were approximately half that of the male-to female transmission rates.[9]

Any disruption of the natural protection of the vaginal or rectal mucosa increases vulnerability to HIV transmission. Several different factors influence the susceptibility of the vaginal/rectal mucosa to HIV infection. Menstruation or bleeding during intercourse can increase a women's HIV infection risk.[11] Having any sexually transmitted infection, both ulcerative and non-ulcerative, has been shown to increase risk for HIV transmission.[9-11] Vaginal douching, which is more prevalent among non-Hispanic black women than non-Hispanic white or Hispanic women, can also disrupt the normal vaginal flora resulting in increased risk for sexually transmitted infections including HIV.[12] Vaginal douching also predisposes women to bacterial vaginosis that in itself increases susceptibility to HIV.[12,13] Finally any sexual trauma, whether overt or inadvertent microtrauma, damages the vaginal/rectal mucosa, thereby increasing susceptibility to HIV. This is particularly important in areas of sub-Saharan Africa, in which *dry sex*, the practice of having vaginal intercourse without vaginal lubrication, is a culturally condoned practice.[14]

In addition to factors influencing the biologic susceptibility to HIV acquisition, economic disempowerment and other socioeconomic forces can result in power differentials that influence a woman's sexual risk behaviors and thereby her HIV risk. Gender roles and power inequalities are a consequence of a variety of factors including societal norms of patriarchy, female economic dependence on male partners, and low educational attainment.[15] The dependency of women on men impacts a woman's ability to negotiate condom use and safer sex practices.[15,16] Other factors that can

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affect HIV/STD risk are concurrent sexual relationships (relationships that overlap in time). Concurrency leads to a more rapid spread of sexually transmitted infections (STIs) within a sexual network compared to a network of sequential monogamous partnerships.[17] Concurrent partnerships not only drive the speed of the epidemic's spread, but also the total number of individuals who are infected.[17,18] Since concurrency is also associated with low marriage rates and history of incarceration, it is often more common in areas of poverty where access to STI testing and treatment centers is often limited. All of these factors contribute to a disproportionate increase in HIV and STI prevalence in poor, urban communities. In the following section we will highlight some of the populations at greatest risk for HIV transmission.

## High-risk groups: black women

Although African American/non-Hispanic blacks represent 14% of the U.S. population, they account for 66% of incident HIV cases among women from 2005-2008.[19] The HIV prevalence rate for non-Hispanic blacks is 1122.4 infected per 100,000 women, almost 18 times the rate for non-Hispanic white women (62.7/100,000).[6] Over 85% of non-Hispanic black women contract HIV through heterosexual contact and 14% through injection drug use.[19]

Differences in sexual network patterns can help explain the disproportionate effect of HIV/AIDS on non-Hispanic black women. In the United States, there exists a sex ratio imbalance in the black community in which there are approximately 9 men to every 10 women.[20] The low sex ratio is due to a variety of factors including higher mortality rates from disease and violence among black men compared to their female counterparts at all stages of life, from infancy to adulthood.[17] The low sex ratio has led to a power imbalance between genders. This *shortage* of eligible black men has resulted in a disadvantage for black women in terms of negotiating and maintaining mutually monogamous relationships. In one qualitative study of non-Hispanic black women in North Carolina, focus-group participants voiced awareness of the sex ratio imbalance and reported being more accepting of a man who is abusive or has other sexual partners because *a piece of a man is better than no man at all.*[20]

Incarceration also plays a large role in disrupting social and sexual networks. Black men are overwhelmingly overrepresented in prison systems, with approximately 20% of black men having served time in prisons by their early thirties.[21,22] The low sex ratio, is thus compounded by the disruption in sexual networks that results from incarceration affecting the structure of sexual networks, marriage patterns, and family stability.[17] Thus, the low sex ratio and social instability caused by high rates of incarceration all increase the likelihood of concurrent partnerships within a sexual network.[17,18] As a result, the rate of STIs is much higher among non-Hispanic blacks than for any other race/ethnic group.[23]

Poverty is a destabilizing force that has also adversely affected sexual network formation within non-Hispanic black communities. This group has the highest rate of poverty compared to any other racial or ethnic group in the United States.[24] In the past, practices of mortgage lenders and realtors led to racial segregation and a concentration of poverty in distinct neighborhoods.[17] People tend to choose sexual partners from the neighborhoods in which they live so that even if an individual does not engage in high-risk behaviors herself, segregation increases the likelihood that her partner engages in high-risk behaviors.[17,25] This has led to the phenomenon of assortative mixing by race, but disassortative mixing by risk in the black community. A black woman with low sexual risk behavior may show racial preference in choosing a black partner (assortative mixing); however because of her limited sexual network her only partner option may be one who engages in high-risk behaviors (disassortative mixing) such as concurrent relationships, injection drug use, etc.[25] Poverty is also associated with marital instability. Lower rates of marriage in impoverished communities lead to higher rates of concurrent partnerships and increased spread of STIs.[25] Lastly, poverty is associated with reduced access to high-quality health care. Public STI clinics that serve poor urban neighborhoods often suffer from a lack of funding and shortage of healthcare providers which then impacts hours of operation and access to care.[26] In the poor urban black community in Onondaga County, NY, even though rates of *gonorrhea* and *chlamydia* are 16-41 times higher among non-Hispanic blacks than whites, there is only one STI clinic that provides services only 11 hours per week, resulting in patients waiting an average of 7-10 days from onset of symptoms before receiving services.[27] The delay in treatment means that there is more time and opportunity for undiagnosed and untreated disease to spread within the community.

The multiple facets of the HIV epidemic among non-Hispanic blacks in the United States require a multi-pronged approach to HIV prevention. These include structural interventions to lessen the impact of poverty and incarceration on the black community as well as innovative approaches to target high-risk sexual networks. A detailed discussion of macro-level interventions is beyond the scope of this paper. However we will discuss different female-initiated HIV prevention techniques that can empower the women to prevent disease transmission despite their involvement in high-risk sexual networks. In general, any successful HIV prevention strategy must incorporate biomedical approaches into the behavioral and structural context in which the intervention is being used.

## High risk group: women who use drugs

Approximately 26% of U.S. women living with HIV during 2005-2008 acquired the infection through injection drug use (IDU).[4] The risk of transmission through sharing of needles among injection drug users is approximately 0.7% per exposure.[28] Needle-sharing is a particularly important risk factor among women who inject drugs. Female IDUs are more likely than their male counterparts to use drugs with a partner and to either be injected by someone else or to be *second on the needle*.[29-32] Rates of HIV infection directly attributable to IDU have dropped dramatically over the past twenty years owing largely to the effectiveness of needle/syringe exchange programs and opiate substitution therapy.[33] Many drug-involved women face double-risk for HIV infection because of overlapping sex and drug networks. Thirty-two percent of AIDS cases among women are acquired through sex with an IDU and thus indirectly attributable to injection drug use.[34] Therefore drug use increases susceptibility to HIV, not only through direct transmission risk from needle sharing, but also through increased participation in high-risk sexual networks.

High-risk sexual behaviors are often common among those who use non-opioid drugs as a result of behavioral disinhibition during intoxication. Women who use crack cocaine have been found to engage in riskier sexual behaviors than non-users, including exchange of sex for drugs or money, having multiple partners, and inconsistent condom use.[35] In addition, higher rates of concurrent partnerships and STIs have also been found among women who use crack cocaine.[35,36] Methamphetamine use is a growing problem and has been associated with increased sexual risk behavior and increased risk of STIs which increase susceptibility to HIV infection.[37] Although needle-exchange programs and opioid substitution treatment programs have been largely successful in preventing HIV transmission through IDU over the past years,[33] the impact of drug use on heterosexual transmission of HIV is still substantial.

## High risk groups: incarcerated women

Female inmates have rates of HIV that are three to five times that of the general population.[38] The prevalence of HIV among incarcerated women is even higher than that of incar-

cerated men.[38] It is difficult to define the HIV risk specifically associated with incarceration because of the cyclical relationship between drug use and incarceration.[39] Several studies have shown that women with a history of incarceration are more likely than non-incarcerated women to exchange sex for money or drugs, to have multiple and concurrent sexual relationships, and to have experienced intimate partner violence.[39,40] In addition, involvement in the criminal justice system itself may increase HIV risk by disrupting social support and sexual networks and exacerbating economic instability thereby increasing HIV risk-taking behaviors.[39] The convergence of poverty, social instability, and drug use on the incarcerated population are important structural factors that contribute to HIV risk.

## High risk groups: victims of intimate partner violence

Women who experience intimate partner violence (IPV) are at especially high risk for HIV and in need of effective targeted prevention measures. Worldwide, HIV is compounded by an epidemic of violence against women. In an 11-country study conducted by the World Health Organization, 15-71% of women surveyed reported ever experiencing physical or sexual abuse by an intimate partner.[41] Rates were highest in areas of the developing world that also bear the world's most explosive HIV epidemics. In the United States and worldwide, association between IPV and HIV is multifaceted and embedded in cultural and individual-level psychological interpretations of violence against women. Women in violent relationships are less likely to successfully negotiate condom use by their male partners, refuse sex with an HIV-infected partner, seek HIV testing or treatment, or disclose their own HIV status to a partner because of fear of violent repercussions.[42-46] Women in abusive partnerships are also more likely to engage in other high-risk behaviors including needle-sharing, transactional sex, sex in the setting of concurrent drug or alcohol use, or sex with multiple partners.[31,47-51] The immediate as well as prolonged emotional and physical trauma from IPV has long-lasting effects on increasing the vulnerability of women to HIV. Addressing IPV is thus important for the primary and secondary prevention of HIV in U.S. women.

## Methods of HIV prevention

Although behavioral methods for HIV prevention are well established, the sustained rate of 56,300 incident HIV infections per year[5] and the rising incidence of HIV among women in the United States[4] are evidence of the challenge of successfully putting these behavioral interventions into practice. Although abstinence, low-risk monogamous sexual partnerships, and condom use are ideal and effective behaviors for preventing HIV transmission, these are not practical options for many women. Here we will review some of the more recent advances in HIV prevention strategies most pertinent to the prevention of heterosexual transmission of HIV to women.

### Screening and treatment for sexually transmitted infections

Sexually transmitted infections (STIs) have been associated with increased HIV risk. Given the biologic synergy between and common behavioral risks associated with HIV and STIs, one might expect that treatment of STIs might lower HIV acquisition; clinical trials at individual and population levels, however, have had conflicting results. A randomized controlled trial in Tanzania demonstrated a 42% reduction in HIV incidence among individuals who were treated for symptomatic STIs compared to those who were not treated.[52] In Uganda, however, researchers did not find any difference in HIV transmission between communities who were randomized to STI treatment versus no treatment.[53] The contrasting findings may be due to differences in the study approaches. The Ugandan study randomized communities to mass treatment every 10 months with either STI treatment or placebo, while the Tanzanian study randomized communities to establishment of an STI clinic where symptomatic individuals could go for STI testing and treatment.[52,53] Although there is evidence that STI treatment of HIV-infected individuals reduces viral shedding in genital fluids,[54,55] population-based randomized controlled trials have found conflicting evidence on the effectiveness of STI treatment in reducing HIV transmission.[52,53,56] Recently there had been debate over whether the increasing herpes prevalence was affecting the HIV epidemic and if treatment of genital herpes infection would impact HIV transmission rates. There is no doubt that genital herpes is associated with increased HIV acquisition.[57] However, chronic suppression of herpes with acyclovir maintenance therapy has not been shown to decrease transmission of HIV despite the successful reduction of recurrent genital ulcers.[58] Therefore, although STIs are associated with increased HIV risk, clinical trials have not conclusively shown that treating STIs alone decreases HIV risk. Since the same high-risk behaviors that lead to STI acquisition can also lead to HIV infection, STI clinics are, at the very least, important access points for simultaneously counseling and testing women for HIV.

### Routine HIV testing and the *test and treat* strategy

Since 2001, the CDC has recommended HIV screening as a part of routine prenatal care in the United States. In 2006, the CDC expanded this recommendation to include opt-out screening for everyone aged 13-64 years in any healthcare setting.[59] The reason for the expansion in screening was because an estimated one quarter of persons living with HIV are unaware of their infection, and transmission of HIV infection is 3-5 times higher among persons who are unaware of their infection compared to those who are aware of their serostatus.[59,60] Studies have shown that those who are aware of their status are less likely to engage in unprotected vaginal or anal intercourse than those who are unaware.[61] Routine testing will ideally lead to earlier detection of HIV and timely enrollment into HIV treatment and care. As higher viral loads increase risk of HIV transmission, reduction in viral load may reduce transmission even for HIV-infected patients who do not change their risk behavior.[62,63] Although routine HIV testing is not necessarily a female-oriented HIV prevention method, it has important implications for the control of the HIV epidemic in women. As more people become aware of their HIV status, this will ideally lead to reduced risk behaviors and/or earlier initiation of HIV treatment, both behaviors that can lead to decreased HIV transmission in the general population, including women. In addition, universal screening removes the stigma associated with targeted testing based on race, sexual orientation, or social economic status.[59]

In 2009, a mathematical modeling study showed that universal annual HIV testing for adults >15 years old and immediate treatment of those testing HIV-positive could decrease HIV mortality by 55% compared to the strategy of starting ART when $CD4^+$ cell counts fall below 350 cells per microliter.[64] From this study, a new strategy for HIV prevention emerged, aptly named *test and treat*.[64] In 2010, the Donnell *et al*. study reported a 92% reduction in HIV transmission among serodiscordant couples if the HIV-infected partner was treated with antiretroviral therapy.[65] In addition, a San Francisco, California study found that decreases of mean and total community viral load were associated with decreases in HIV incidence.[66] Since then, there has been an upsurge of interest in using antiretroviral therapy for secondary prevention of HIV at the community level. Through the *test and treat* strategy, earlier identification and earlier treatment of HIV-infected individuals would lead to decreased infectiousness and decreased transmission of HIV, thereby affecting the epidemic among women. Recently, there has been greater recognition of the importance of incorporating the *test and treat* strategy with linkage to and retention in regular HIV care. A simulation model suggests that a comprehensive, test, link, retain, treat, and maintain on ART strategy could lead to a 47% increase in the number of people living with

HIV in the United States who have an undetectable viral load.[67] This ideal scenario would have profound implications for women living in communities and at risk of acquiring HIV.

### Medication-assisted treatment for substance use disorders

Medication-assisted treatments (MAT) for substance use disorders are effective not only as treatment for opioid dependence, but also as HIV prevention. Drug use increases vulnerability to HIV transmission through risky injection practices as well as engagement in high-risk sexual behaviors while intoxicated. MAT for opioid dependence treats both the biological and behavioral aspects associated with drug use. Several studies have shown that effective medical treatment for substance use is associated with decreased drug use and therefore decreased HIV-associated risk behaviors with potentially resultant decreased HIV incidence.[68-73] Although most of the studies have involved methadone treatment for opioid dependence, recent data show evidence that buprenorphine treatment is associated with not only decreased injection drug use, but also decreased sexual risk behavior.[70,74] Although several studies are currently ongoing (listed at www.clinicaltrials.gov) to examine the association of MAT with HIV risk reduction, only three are evaluating the effect of opioid substitution therapy on HIV seroconversion rates. Naltrexone, an opiate antagonist, has also been found to be an effective treatment for opioid use disorders that also results in HIV risk reduction, and recent formulation of naltrexone as a monthly depot injection will likely improve adherence to the medication and thereby potentially decrease HIV risk.[70,73] Currently there are over 20 studies listed at www.clinicaltrials.gov in which naltrexone is being studied for alcohol, cocaine, and methamphetamine use disorders. Because behavioral disinhibition and increased sexual risk behavior are common under the influence of these substances, MAT may be a promising form of HIV prevention for women and their sexual partners.[34,35,37]

### Male condom

The male condom has been one of the main cornerstones of HIV/STI prevention. Latex male condoms are effective contraceptive barriers that also offer protection against HIV and STIs. Consistent male condom use has been shown to decrease a woman's risk of HIV by at least 85%, and some studies have reported 100% effectiveness among consistent condom users.[75] However, condoms must be used correctly and consistently in order to prevent HIV transmission and several studies have shown low rates of condom usage overall in the United States.[76,77] Women must also navigate the process of negotiating male condom use with their partners, which is often difficult especially in the setting of gender power imbalances or intimate partner violence. In addition, the cultural acceptability of condom use varies. Non-condom use may be seen as a gesture of intimacy, and both men and women may complain of the decreased sensation of pleasure with condom use.[75] Other issues arise when substance use or alcohol is involved in sexual encounters because condom usage decreases with intoxication-induced behavioral disinhibition.[35,37] Thus, although the male condom may be clinically effective in preventing HIV transmission, in reality, there are many social and cultural barriers to its implementation. Although some behavioral impediments to consistent male condom usage will also affect compliance with female condom use, the female condom puts the power of HIV/STI and pregnancy prevention in the hands of the woman.

## Female-initiated HIV prevention methods

Behavioral risk reduction strategies have proven inadequate for preventing HIV infection in women. Women who are forced to rely on sexual bartering or expected to be deferent to men may not have the social capital to negotiate condom use by their male partners. For women involved in violent intimate partner relationships, condom negotiation itself may instigate or perpetuate violence.[42] Women may thus avoid discussing condom use with their partners as a way to avoid escalation of abuse. Given these limitations in risk reduction strategies, the most effective HIV prevention measures for women are likely to be those that are initiated by women. As Stein wrote in the seminal paper on the topic, (p. 460) *The empowerment of women is crucial for the prevention of HIV transmission to women. It follows that prophylaxis must include procedures that rely on the woman and are under her control*.[78]

The scientific and public health communities have looked towards novel female-initiated biomedical approaches for HIV primary prevention. To date, there have been 37 Phase II/III HIV prevention randomized controlled trials on 39 different biomedical interventions: 17 exclusively enrolled women, 16 included both men and women, and 3 involved adolescents. Unfortunately, many of these studies showed negative or non-significant effects on HIV acquisition, suggesting the need for combination approaches that target high-risk subpopulations of women.[79,80] These will be explored further here. First, however, we describe other female-initiated methods of HIV prevention that have been previously investigated.

### Female-initiated methods: female condom

Until recent advances, the only available female-initiated method for HIV prevention was the female condom. Mathematical models estimate that female condoms are up to 82% effective at preventing HIV infection, assuming perfect use in areas with high HIV prevalence.[81] These results have not yet been confirmed in randomized controlled trials. Female condoms are recommended by the World Health Organization as an effective HIV prevention measure and may be an important component of evolving dual protection technologies that protect against both unintended pregnancy and sexually transmitted infections.[82] Widespread use of the female condom, however, has been limited by the need for perfect use and by cultural proscriptions against touching female genitals. While the technology is female-initiated, male partners may still be physically aware of the female condom during sex because an external ring remains outside of the vulva while in use.[82] Another impediment to use is that female condoms are much more expensive than male condoms, limiting use in resource-poor areas.[83,84]

### Female-initiated methods: non-specific vaginal microbicides

Vaginal microbicides have long held promise as a female-initiated HIV prevention method. Mathematical models have shown them to be cost effective in settings in which the male prevalence of HIV exceeds 2.4%. In these areas, a microbicide that is 55% effective at preventing HIV and used in 30% of heterosexual encounters would prevent an estimated 1,908 new infections at a cost savings of US$6,712 per infection averted.[85] Analysis of each of the completed and ongoing clinical trials of vaginal microbicides is beyond the scope of this article and has been described elsewhere.[86,87]

The first topical vaginal microbicides under investigation were non-specific with activity against HIV as well as herpes simplex virus (HSV) and other sexually transmitted infections. Briefly, these non-specific vaginal microbicides are categorized by their molecular properties: i) Surfactants, including Nonoxynol-9 (N9) and C31G (Savvy), cause non-specific disruptions of mucosal membranes. Clinical trials of surfactants have been disappointing, showing this class to be either ineffective at preventing HIV infection or actually associated with increased HIV incidence related to vaginal mucosal irritation with genital ulcers and vulvitis.[88-91] Undesirable properties of the N9 compound are reflective in local vaginal up-regulation of pro-inflammatory COX-2.[92] A newer product, sodium laurel sulfate (the *invisible condom*), has been found to be safe and well tolerated though its efficacy at preventing HIV transmission remains

unclear;[93] ii)Acidifying agents, including Carbopol 974P (BufferGel), Acidform (Amphora), and natural lemon/lime/vinegar douches are also non-specific agents with activity against HIV, HSV-2 and *chlamydia* by maintaining the naturally acidified milieu of the vagina. While anti-HIV activity has been confirmed *in vitro*, these agents are cytotoxic to human vaginal cell lines with associated vaginal discharge and ulcerations that may actually serve to facilitate HIV entry.[94] Furthermore, acidic douches have reduced potency in the presence of semen.[95] Theoretically, probiotic bioengineered lactobacilli should also maintain the naturally acidic vaginal environment and thereby prevent HIV transmission. Though probiotics have been shown to prevent recurrent bacterial vaginosis, there have been no clinical trials to date for HIV prevention and none are currently registered at www.clinicaltrials.gov;[96] iii)Anionic polymers/entry inhibitors include naphthalene sulfonate (PRO2000), Carrageenan (Carraguard/PC-515), cellulose sulfate (Ushercell), Cellulose acetate phthalate (CAP), and dendrimers (SPL7013 (Vivagel)). Concluded trials have associated these products with lack of or inconclusive efficacy at preventing HIV transmission.[97-99] Other late stage clinical trials of entry inhibitors are ongoing.

These evaluations must continue to grapple with outcomes that rely on self-reported measures of adherence and sexual behavior, especially within cultural contexts of highly-stigmatized sexual activity. One recent analysis, for example, suggests that the evaluated efficacy of vaginal microbicides at preventing HIV may be limited by under-reported heterosexual receptive anal intercourse, an activity associated with higher risk of HIV transmission.[100] In general, however, non-specific vaginal microbicides have fallen out of favor because of their limited demonstrated efficacy at preventing HIV transmission and their relatively poor safety profile. Scientific research and drug development have thus turned towards the use of antiretrovirals to prevent HIV transmission, as both vaginal and oral pre-exposure prophylaxis.

### Female-Initiated methods: antiretroviral pre-exposure prophylaxis

Antiretroviral pre-exposure prophylaxis (PrEP) was borne out of successful use of this strategy in prevention of maternal to child HIV transmission during pregnancy. PrEP involves daily- or intermittently-dosed oral or vaginally-applied antiretroviral therapy given to an HIV-uninfected individual in order to prevent HIV acquisition during a high risk sexual encounter. PrEP is thought to be more practical than post-exposure prophylaxis (PEP), especially for high risk cohorts with repeated exposures to the virus including injection drug users, commercial sex workers, or women in serodiscordant heterosexual relationships.[86] While PEP has been proven effective at preventing HIV acquisition in post-natal and occupational exposures, there have never been randomized controlled trials of this strategy's efficacy in non-occupational exposures because of ethical constraints.[101] Despite limited evidentiary support, current U.S. Department of Health and Human Services guidelines do recommend PEP for women who have been victims of sexual assault or have had high-risk vaginal sex with a known HIV-infected partner if ART can be initiated within 72 hours of the event and continued for 28 days.[102] Although there is limited data available on the efficacy of PEP in other high risk groups, it is likely that the lines between pre- and post-exposure prophylaxis become blurred when using a coitally related dosing strategy in groups with repeated high risk sexual activity.

On a cellular level, PrEP as a vaginal microbicide is practical: by targeting the initial step of mucosal invasion at the point of entry, PrEP blocks the establishment of a founder population of HIV-infected T-cells.[103] Other oral agents for PrEP operate at different stages of HIV replication and these will be described in further detail. Regardless of formulation, with successful PrEP, acute or latent HIV infection is prevented in spite of exposure to the virus. PrEP has also been shown to be cost effective in resource-limited settings with high HIV prevalence. It is estimated that, prior to antiretroviral therapy scale-up, if PrEP was given to all 15-35 year old women in South Africa, 10-25% of new infections would be averted with a savings of US$12,500-$20,000 per infection avoided.[104] The promise of PrEP for HIV prevention is balanced by concerns over medication non-adherence with resultant lower efficacy for HIV prevention, development of drug resistant HBV virus among individuals chronically infected with hepatitis B, side effects, and associated behavioral disinhibition, known as *risk compensation*. In resource-limited settings, there is also appropriate concern about ethical allocation of PrEP medications.[105,106] If shown to be successful at preventing HIV transmission, it remains unclear whether PrEP provision should be universal or targeted only to high-risk groups.

A promising candidate drug for PrEP is tenofovir disoproxil fumarate (TDF or in co-formulation with emtricitabine [FTC] as TDF/FTC), an adenosine nucleos(t)ide reverse transcriptase inhibitor with excellent safety, tolerability, and efficacy. Its pharmacokinetic profile is also favorable, allowing for once daily oral dosing and easy vaginal dosing with stable cellular penetration into the vaginal mucosa.[107] Preclinical trials of oral and vaginal dosing have established the effectiveness of TDF/FTC in preventing vaginal HIV-1 transmission in humanized mouse models.[108] Both daily and intermittently dosed TDF/FTC completely blocked infection with rectally transmitted simian-human immunodeficiency virus (SIV) in macaques.[109] The effect of intermittent prophylaxis was lost, however, if the post-inoculation dose was given more than 24 hours following viral exposure.[110]

Although we have generally focused our discussion thus far on HIV primary prevention in U.S. women, most trials of PrEP are from Africa where higher rates of incident HIV make studies more feasible. If these clinical trials demonstrate efficacy at HIV prevention, however, regimens could be applied to U.S. cohorts of women. The most ground-breaking work in HIV primary prevention in women to date derives from the CAPRISA 004 trial, a double-blinded randomized controlled trial of TDF vaginal gel vs. placebo in 889 HIV uninfected non-pregnant women in KwaZulu-Natal, South Africa.[111,112] Dosing was intermittent and coitally related. After 12 months of follow-up, preliminary HIV incidence rate in the treated group was 50% lower than in the placebo group irrespective of condom use, urban or rural community site, sexual behavior, or concurrent HSV-2 infection. Importantly, there was no evidence of increased sexual risk-taking in either group (*risk compensation*), drug resistance, or flares of HIV after completion of each pre-exposure course (known as HIV *unmasking*). Adherence was a major issue in the study but, for women with >80% adherence, there was an associated 54% reduction in incident HIV compared to placebo.[111,112]

Regarding oral PrEP, there is limited data in women. Recently reported results of the iPrEx study of TDF/FTC (*vs* placebo) for PrEP in men who have sex with men (MSM), however, were impressive; in the intention-to-treat analysis, TDF/FTC was associated with a 44% reduction in HIV acquisition.[113,114] As in the CAPRISA 004 trial of vaginal TDF among women, HIV risk in iPrEx was associated with medication adherence: in a post-hoc analysis, participants whose adherence to TDF/FTC was >90% experienced a 73% reduction in HIV acquisition compared to placebo.[114] The iPrEx study also revealed some potential downsides to universal expansion of PrEP with TDF/FTC. A total of 10 subjects discontinued study drug because of creatinine elevations (7 in the TDF/FTC group), although the clinical significance of this abnormality remains unclear. Associated renal effects may be the major limitation to universal use of oral TDF as PrEP. Another area for concern prior to universal rollout is development of drug resistant mutations in subjects with unidentified HIV infection who were using PrEP inconsistently. In the iPrEx study, 10 subjects were enrolled because they were classified as being HIV seronegative when, in

fact, they had preexisting HIV infection with ongoing viremia (2 in the TDF/FTC group). Both subjects with preexisting HIV in the TDF/FTC group developed M184V or I mutations and TDF/FTC was stopped.[114,115]

These results still need to be replicated in future clinical trials enrolling women. At the present time, only one clinical trial of oral PrEP in women has been completed with reported results. A Phase II, RCT of daily oral TDF vs. placebo included 936 HIV-uninfected, high risk women in Ghana, Cameroon, and Nigeria. No increased adverse clinical or laboratory events were noted with TDF compared to placebo nor was there any significant difference between the two groups in terms of incident HIV infections. Two of the study sites closed mid-trial, which may have contributed to the small number of incident HIV infections overall (N=8).[116] Recently, investigators decided to terminate early the phase III FEM-PrEP trial, as interim analysis suggested that the study would be unlikely to show the effectiveness of oral TDF/FTC in preventing HIV infection in this study population.[117] The FEM-PrEP study was a randomized control trial of TDF/FTC versus placebo among heterosexual women in four African countries. The preliminary results are surprising and disappointing given the success of this approach among MSM in the iPrEx study. Final analyses of the FEM-PrEP study are pending, and as there may be several reasons for the lack of effectiveness seen in the preliminary analysis, researchers caution against concluding that oral TDF/FTC as PrEP is ineffective against preventing HIV infection in all women.[117] Results from the highly anticipated VOICE trial may, therefore, help guide future use of oral and vaginal PrEP in women. This is an ongoing Phase IIb RCT comparing 1) daily TDF vaginal gel vs. placebo gel and 2) daily oral TDF and oral TDF/FTC vs. oral placebo in terms of long-term safety and efficacy at preventing HIV acquisition in sexually active young women. (Details are available at www.clinicaltrials.gov, identifier NCT0070 5679).

Perhaps because of uncertainties around universal expansion of TDF/FTC as PrEP, it is not yet FDA approved although off-label use will certainly increase since publication of the iPrEx results. In the meantime, multiple other PrEP regimens are currently under pre-clinical and clinical evaluation. TDF and TDF/FTC are being studied as oral and vaginal gel preparations and in intermittent and daily dosing strategies. There are currently three Phase I/II and four Phase IIb/III ongoing clinical trials involving women; they are in various stages of enrollment or data collection and are described in more detail elsewhere.[118] Other classes of antiretroviral agents are also being targeted for use as PrEP in women. These include a non-nucleoside reverse transcriptase inhibitor, dapivirine (TM120), formulated as an intravaginal ring and being evaluated in Phase I/II trials (NCT01071174).[119] Unfortunately, safety trials of another non-nucleoside reverse transcriptase inhibitor, rilpivirine (TMC 278) were prematurely terminated due to additional safety concerns. Other drug classes under evaluation include the integrase inhibitor, raltegravir, and CCR5 antagonist, maraviroc, which have demonstrated effective prevention of vaginal HIV-1 infection in humanized mouse models.[120]

The results of these clinical trials may help determine the future of HIV prevention for women. PrEP is complicated by its entanglement in ethics, human rights, and cultural perceptions of sex and sexually transmitted diseases. Regardless of whether they are packaged in oral or vaginal formulations, the most effective strategies for HIV prevention in women overall will be female-initiated, cost effective, ethically allocated in resource-limited settings, and culturally acceptable to both women and their partners.

## Discussion

Despite recent advances in testing and treatment, women account for an increasing proportion of the HIV epidemic in the United States.[3-6] Several factors influence women's risk for heterosexual transmission of HIV including: properties inherent to the vaginal mucosa, cultural proscriptions of gender roles, poverty and economic dependence on men, low male-female sex ratios, incarceration, drug use, and social instability. These factors reinforce the lack of control many women have in choosing behavioral methods of HIV prevention (i.e. male condom use, monogamous relationships, low-risk sexual partners, and abstinence). However recent advances in HIV prevention show promise because they are female-initiated strategies. Pre-exposure prophylaxis with antiretrovirals, vaginal microbicides, and female condoms are all within the control of women to ensure self-protection against HIV.

Even with the success of these female-initiated interventions in clinical trials, adoption of these interventions into practice is not ensured, as evidenced by barriers faced in implementing the female condom. The female condom is by no means a new method for HIV prevention but, despite trials showing its social and cultural acceptability, it has not been globally adopted.[84] Several studies have found that when properly introduced, female condoms have high acceptability rates.[84,121] Unfortunately, lack of knowledge by health care providers along with media propagation of the myth that women dislike the condom have been barriers to its adoption. Another common reason cited for lack of adoption of the female condom has been affordability.[83,84] However, male circumcision, which has not been shown to reduce HIV transmission to female partners, has received much more global support and media attention even though it is undoubtedly more expensive.[84,122,123] Male circumcision has been shown to reduce HIV acquisition by 60% among men.[124-126] Studies have not shown, however, any benefit in terms of reduced HIV transmission to the female partners of circumcised males.[122,123] Although there may still be some benefit of male circumcision to HIV prevention among women through the theoretical benefit of decreasing the community viral load, this has not yet been studied. The benefit of male circumcision for HIV prevention among men has resulted in the implementation of male circumcision programs in several African countries.[127] The contrast between the global support for male circumcision programs as compared to lack of support for provision of female condoms for HIV prevention highlights the importance of advocacy and media coverage for the adoption of scientific technology.

In the past, especially in the United States, the focus on HIV prevention has been on the male-to-male sexual transmission as it is still the leading cause of HIV transmission in the United States.[4,6] However as the global HIV epidemic now predominantly affects women and with the growing proportion of HIV diagnoses among women in the United States, female-initiated forms of HIV prevention are essential to curbing the growth of this epidemic. The same barriers that prevented the widespread adoption of female condoms need to be counteracted by advocacy and the political will to promote these female-initiated strategies to HIV prevention.

Our review of the literature emphasizes the importance of structural as well as behavioral interventions to prevent the heterosexual transmission of HIV among women in the United States. We have highlighted the importance of recent prevention strategies including the *test and treat* strategy, STI screening and treatment, medication-assisted treatment for substance use disorders, female condoms, PrEP, and vaginal antiretroviral gels. These scientific advances must be coupled with advocacy and political support in order to ensure long-term success.

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