Perspective

Maximizing the Benefits of HIV Preexposure Prophylaxis

Preexposure prophylaxis (PrEP) with tenofovir/emtricitabine (slash indicates coformulation) is highly effective in preventing new HIV infections. PrEP efficacy is strongly associated with adherence. In clinical trials, PrEP has been more effective in men who have sex with men and HIV-serodiscordant heterosexual couples than in women, likely reflecting pharmacokinetic differences between levels of tenofovir disoproxil fumarate in vaginal and rectal tissues, and poorer adherence in studies in women. Current guidelines recommend daily PrEP for men and women; however, PrEP taken at least 4 days per week for men may be as effective as daily PrEP, and women must take PrEP 6 to 7 days per week to maximize efficacy. Data are accumulating on the effectiveness of pericoital PrEP for men who have sex with men, but it is not yet recommended in the United States. PrEP is underprescribed for younger individuals, black individuals, and Hispanic and Latino individuals. This article summarizes a presentation by Susan P. Buchbinder, MD, at the IAS–USA continuing education program, Improving the Management of HIV Disease*, held in Chicago, Illinois, in May 2017.*

Keywords: HIV, prevention, preexposure prophylaxis, PrEP, tenofovir, TDF, emtricitabine, adherence, preventive efficacy, men who have sex with men, MSM, women

Preexposure prophylaxis (PrEP) is highly effective in preventing HIV infection. Tenofovir disoproxil fumarate (TDF)/emtricitabine (slash indicates coformulation) is the only form of PrEP currently approved by the US Food and Drug Administration.

Which persons may benefit most from PrEP can be gleaned from data on new HIV infections in the United States. From 2010 to 2014, 81% of new HIV diagnoses were among men. In 2015, man-to-man sexual contact and heterosexual sexual contact were responsible for 82% and 9%, respectively, of new HIV diagnoses among men, and heterosexual contact was responsible for 86% of new HIV diagnoses among women (Figure 1).[1] Between 2008 and 2014, estimated annual new HIV infections decreased by 18%, and HIV incidence decreased among persons who inject drugs (PWID), heterosexual persons, and some groups of men who have sex with men (MSM).[2] Annual HIV incidence has decreased among MSM aged 13 to 24 years but has increased among MSM aged 25 to 34 years.[2] Annual HIV incidence has decreased among white MSM, remained stable among black MSM, and increased among Latino and Hispanic MSM.[2] In 2015, 22% of HIV infections were among persons aged 13 to 24 years, 33% among those aged 25 to 34 years, 19% among those aged 35 to 44 years, and 25% among those aged 45 years or older.[1] These data highlight the urgent need to provide PrEP and other highly effective prevention to MSM, particularly men of color. Although HIV infection is increasing among those aged 25 to 34 years, high infection rates are still observed in younger and older age groups, serving as a reminder that practitioners should obtain sexual histories on all of their patients and should counsel about the potential benefits of PrEP for all persons who may be at risk of HIV acquisition.

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Effectiveness of PrEP

The highest levels of PrEP efficacy were achieved with daily TDF/emtricitabine in the PROUD (Preexposure Option for Reducing HIV in the UK) study of MSM (effectiveness, 86%) in the United Kingdom,[3] event-driven TDF/emtricitabine in the IPERGAY (Action to Prevent Risk Exposure By and For Gay Men) study of MSM in France and Canada (effectiveness, 86%),[4] and daily TDF/emtricitabine in the Partners PrEP study of HIV-serodiscordant heterosexual couples in Uganda and Kenya (effectiveness, 75%).[5]

The effectiveness of PrEP correlates with adherence to PrEP (Figure 2). Adherence to and effectiveness of PrEP have been higher in studies of MSM, heterosexual couples, and combined populations of heterosexual men and women than in several studies of women only. Although social and environmental factors may have contributed to lower adherence among women in some studies, pharmacodynamics also likely contributed to reduced PrEP effectiveness in these populations.

Several studies in clinical rather than research settings have documented high PrEP effectiveness among MSM. In a cohort study from Kaiser Permanente Northern California, there were no new HIV infections among 952 men and 20 women despite a 42% annual cumulative incidence of sexually transmitted infections (STIs).[6] Two new HIV infections occurred in the study population after participants discontinued PrEP. Similarly, in the US PrEP Demonstration Project among 557 MSM and transgender women in San Francisco, California, Miami, Florida, and Washington, DC, no new HIV infections were observed despite an overall STI rate of 51%, although 2 new HIV infections occurred after the individuals had discontinued PrEP.[7]

Rare cases of breakthrough HIV infection in MSM despite high adherence to PrEP have been reported, including 2 MSM who were infected while being treated for hepatitis B virus (HBV) infection with daily TDF,[8] 2 MSM infected with multidrug resistant virus while taking TDF/emtricitabine,[9,10] and 1 man who has sex with men who was infected with wild-type virus while highly adherent to daily TDF/emtricitabine.[11] The latter report of a breakthrough infection with wild-type virus occurred in a man who reported 40 to 75 anal sex

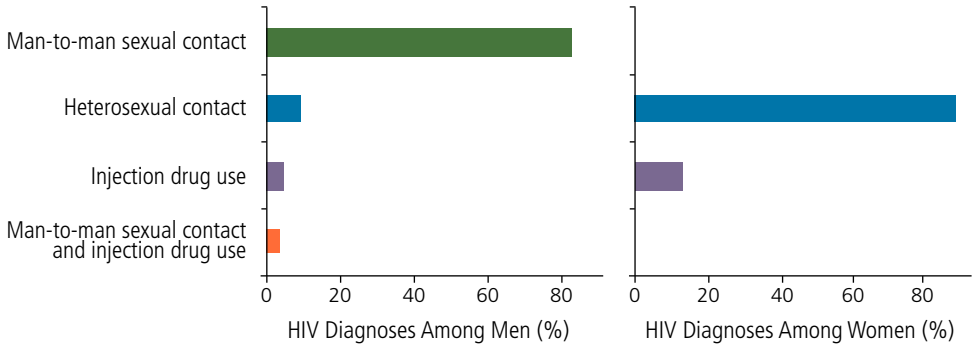

Figure 1. Diagnoses of HIV infection among adult and adolescent men (N=32,422) and women (N=7498) in the United States and 6 dependent areas, by sex and transmission category, 2015. Adapted from Centers for Disease Control and Prevention.[1]

partners per month. Assessment of dried blood spots from this individual showed a high TDF level near the time of infection, indicating daily adherence to the PrEP regimen. This case suggests that even high levels of adherence to PrEP may be overwhelmed by very high levels of exposure to HIV, along with other potentially contributory factors.

Modeling of the frequency of PrEP dosing versus its effectiveness using data from the placebo-controlled iPrEx (Chemophrophylaxis for HIV Prevention in Men) and STRAND studies indicated an estimated preventive efficacy of 96% (95% confidence interval [CI],90%-99%) with 4 doses per week, 99% (95% CI, 96%-99%) with 7 doses per week, and 76% (95% CI, 56%-96%) with 2 doses per week.[12] These data suggest that even missed doses 2 to 3 times per week for MSM prescribed daily PrEP may not negatively impact its effectiveness because of its long intracellular half-life and high concentrations in rectal tissue.

The placebo-controlled IPERGAY study examined the use of sex event–driven PrEP among MSM. Participants took 2 doses of TDF/emtricitabine 2 to 24 hours before sex and 1 dose each 24 and 48 hours after the first dose. If more sexual episodes occurred, participants took PrEP daily until 48 hours after the last sexual encounter. This strategy of event-driven or "on-demand" PrEP had a preventive efficacy of 86% in the double-blind portion of the trial. In the open-label portion of the trial, when participants knew they were receiving active drug, the preventive effectiveness compared with placebo in the double-blind phase increased to 97%.[13] Participants took a median of 18 doses of PrEP per month, equal to more than 4 doses per week. Given that dosing 4 times per week is likely as effective as daily dosing for MSM, it remains unclear whether this trial fully evaluated a more intermittent on-demand PrEP strategy. The Centers for Disease Control and Prevention (CDC) continues to recommend daily dosing of PrEP, although the on-demand approach may be useful in some situations.[14]

To evaluate the extent to which sex is planned among high-risk MSM, an online survey was conducted in 1013 sexually active MSM. Approximately half of the men reported that their last anal sex act was planned. However, when asked how far ahead sex was planned, 17% indicated it was planned only minutes before sex and 45% reported planning several hours before sex, suggesting that a majority of MSM may have difficulty adhering to event-driven regimens that require taking PrEP a minimum of 2 hours before sex occurs.[15] In a separate online survey of 3217 MSM, 46% reported engaging in unplanned condomless anal sex within the prior 3 months, reiterating that other strategies may need to be implemented to ensure adequate PrEP uptake for those who are not planning their sexual encounters.[16] A study of 92 MSM asked to predict daily for 1 month whether or not they would have sex the next day found that participants were much better at predicting if they would *not* have sex than when they would.[17] However, intermittent PrEP may be particularly useful during intermittent periods of heightened sexual activity, such as planned vacations. In another online survey of 7305 MSM, 26% reported engaging in condomless anal sex with new partners while on vacation.[18]

To explore biologic explanations for poorer PrEP efficacy in several PrEP trials in women, investigators from the CAPRISA (Center for the AIDS Programme of Research in South Africa) 004 study of PrEP with tenofovir gel assessed the impact of perturbations of the vaginal microbiome at baseline on PrEP effectiveness. In this analysis, topical PrEP was only effective in women with a *Lactobacillus*-dominant vaginal microbiome.[19] There was no statistically significant topical PrEP efficacy among those with microbial dysbiosis, characterized by dominance of other bacteria, higher pH, and more inflammatory changes. Another study directly examined the impact of baseline vaginal microbiota on topical PrEP efficacy.

Among 41 HIV-uninfected women who received daily tenofovir gel or film for 7 days, those with a *Lactobacillus*-predominant vaginal microbiome showed higher levels of tenofovir in vaginal fluid, cervical tissue, and plasma, and those with vaginal dysbiosis had lower tenofovir levels in these compartments.[20] These findings suggest limitations in the effectiveness of tenofovir gel; other analyses have found no substantial effect of baseline vaginal dysbiosis or bacterial vaginosis on the efficacy of systemic PrEP, taken orally.

An analysis of the Partners PrEP study showed no statistically significant difference ($P = .9$, for interaction) in the preventive efficacy of PrEP versus placebo according to bacterial vaginosis indicated by Nugent Score; efficacy was 73% ($P = .001$) among women who had a score of 0 to 3, 63% among women who had a score of 4 to 6 ($P = .2$), and 77% among women who had a score of 7 to 10, indicating vaginal dysbiosis ($P = .04$).[21] The lower effectiveness of systemic PrEP in women than in MSM may be attributable, in part, to differences in tenofovir levels in vaginal versus rectal tissue. Available data suggest that women need 6 to 7 doses of PrEP per week to achieve and maintain protective drug levels, whereas MSM need 4 to 7 doses per week.[22]

In one study assessing how long daily PrEP should be taken in advance of HIV exposure to provide sufficient concentrations of tenofovir, 89% achieved a 90% effective concentration (EC_{90}) in blood after 7 doses and 98% achieved an EC_{90} after 13 doses.[23] These data have been used to support the current CDC recommendation that MSM initiate PrEP 7 days before sexual activity and continue it for 28 days after.[23] For women, the number of daily doses of PrEP needed to achieve protective drug concentrations remains unknown, because at similar doses, tenofovir concentrations in vaginal tissue are 10- to 100-fold lower than in anal tissue. The CDC currently recommends that women take PrEP for 21 days before sexual activity.[14] Given the possibility of missed doses, a strategy of daily dosing of PrEP for men and women is most prudent at this time.

PWID appear to require high levels of adherence to achieve the same protective effects of PrEP seen in MSM. (Of note, many female PWID also have sexual risk factors for HIV infection.) It is possible that the reduced efficacy seen in PWID in the only efficacy trial of this approach was because TDF alone was used rather than TDF/emtricitabine. In that study, 97.5% adherence under directly observed therapy was needed to achieve greater than 80% effectiveness.[24] It is also possible that PrEP is less effective against parenteral than sexual exposure. Five of 11 breakthrough infections occurred despite apparent complete adherence.[25]

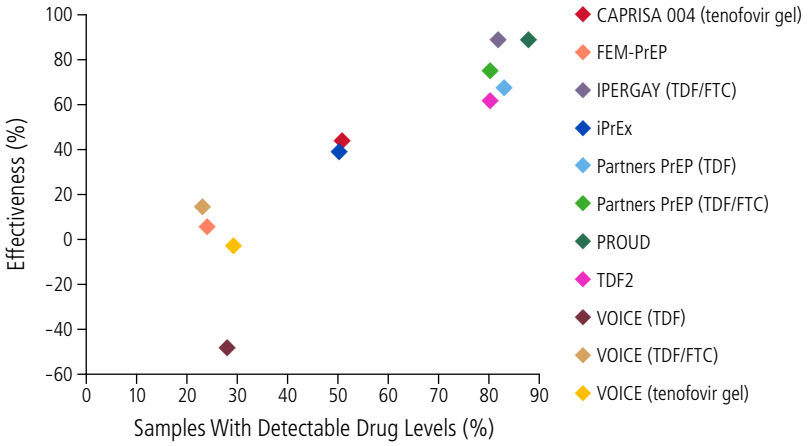

Figure 2. Relationship between adherence (as measured by drug levels) and preventive effectiveness in trials of oral and topical tenofovir disoproxil fumarate (TDF)-based preexposure prophylaxis (PrEP). CAPRISA indicates Center for the AIDS Programme of Research in South Africa; FEM-PrEP, Preexposure Prophylaxis Trial for HIV Prevention Among African Women; FTC, emtricitabine; IPERGAY, Action to Prevent Risk Exposure By and For Gay Men; iPrEx, Chemophrophylaxis for HIV Prevention in Men; PROUD, Preexposure Option for Reducing HIV in the UK; VOICE, Vaginal and Oral Interventions to Control the Epidemic. Adapted from AIDS Vaccine Advocacy Coalition.[42]

PrEP for HIV-Serodiscordant Couples

The HIV Prevention Trials Network (HPTN) 052 study showed that the likelihood of HIV transmission among HIV-serodiscordant couples is exceedingly low once the infected partner has maintained full viral suppression.[26] Data from the Partners PrEP study suggested that HIV transmission risk was very low only after 6 months on antiretroviral treatment.[27] In counseling patients about the risk of HIV acquisition from a sexual partner with full viral suppression, the durability of viral suppression and the consistency of medical care of the partner must be understood. In a cohort of more than 14,000 individuals at 6 US HIV clinics followed for a median of more than 3 years, more than half had HIV RNA levels above 1500 copies/mL at some point, with viral loads above this level accounting for 23% of observation time in the study (average of 83 days per person).[28]

PrEP is effective as a bridge to antiretroviral therapy among HIV-serodiscordant couples. In the Partners PrEP study, HIV-seropositive partners were offered antiretroviral treatment and HIV-seronegative partners were offered PrEP for the first 6 months that their partners were on therapy. If an HIV-seropositive partner declined treatment initially, the HIV-seronegative partner continued PrEP until the HIV-seropositive partner initiated treatment and remained on it for 6 months. Overall, there was a 95% reduction in new HIV infections compared with the expected rate.[29]

One-quarter to one-third of new HIV infections observed among HIV-serodiscordant couples are attributable to sexual contact with someone outside of the relationship, which is another factor to consider when counseling HIV-seronegative persons in HIV-serodiscordant relationships about risk. Some practitioners withhold PrEP because of concerns that patients will increase their risk behaviors, and mistakenly believe that condoms are more effective than PrEP. However, in meta-analyses of condom effectiveness, including more than 10,000 heterosexual HIV-serodiscordant couples, the overall preventive effectiveness of condoms was 71% to 77%.[30] Among 2 large cohorts of MSM, the protective effectiveness of condoms was 70%,[31] and PrEP effectiveness was 86% in the PROUD study.[32]

Initiation and Monitoring of PrEP

Individuals who are candidates for PrEP based on risk assessment should undergo testing for HIV infection, including viral load testing, if any signs or symptoms of an acute viral illness are present. Initiating PrEP before HIV serostatus is known could result in emergence of resistance to TDF or emtricitabine if the person is already HIV infected. Creatinine levels should be measured, and individuals with a creatinine clearance below 60 mL/min should not begin PrEP. After PrEP is initiated, creatinine clearance should be monitored at 3 months and every 6 months thereafter. HBV serostatus should be confirmed, as individuals-chronically infected with HBV may experience viral rebound when TDF is stopped. Individuals should be screened for STIs and pregnancy before initiating PrEP and at 3 month intervals thereafter. HIV testing should be repeated every 3 months during PrEP, with individuals counseled not to stop and restart PrEP on their own. Individuals

Table. Estimated Percentage and Number of Adults With Indications for PrEP, By Risk Group

Transmission Risk Group	With Indications for PrEP, %	Estimated No. (95% CI)
Total		1,232,000 (661,000-1,803,000)
Men who have sex with men, aged 18-59 yrs	24.7	542,000 (212,000-772,000)
Persons who inject drugs, aged ≥18 yrs	18.5	115,000 (45,000-185,000)
Heterosexually active adults, aged 18-59 yrs	0.4	624,000 (404,000-846,000)
Men	0.2	157,000 (62,000–252,000)
Women	0.6	468,000 (274,000-662,000)

Abbreviations: CI, confidence interval; PrEP, preexposure prophylaxis.
Adapted from Smith et al.[39]

should also be counseled about the possibility of start-up syndrome when initiating PrEP (gastrointestinal effects are most common) and informed that symptoms generally resolve within several weeks. They should also be informed that if they lose health insurance or change health providers there are resources available to help connect them with care without a lapse in PrEP services (eg, pleaseprepme.org).

In studies of MSM and heterosexual persons on PrEP with TDF/emtricitabine, persons with lower estimated glomerular filtration rate (eGFR) (below 90mL/min), persons older than 50 years, and those weighing less than 55 kg were at increased risk for experiencing an apparent diminution of eGFR while on PrEP. Analysis of the Partners PrEP and Partners Demonstration Project studies indicated that more than 75% of increases in creatinine level were unconfirmed on repeat testing and that there was no difference in detecting true renal effects whether testing is done every 3 versus every 6 months.[33] In the Thai study of PWID referenced above, recent injection drug use had no effect on creatinine levels, and renal effects were more likely with older age.[34] Available data indicate that creatinine levels return to near normal after PrEP is discontinued.

Decreases in bone mineral density have been observed during PrEP use, with reductions appearing to level off at approximately 1% to 2% loss and density measurements returning to baseline after PrEP is discontinued.[35] Because there is no evidence of adverse clinical outcomes associated with PrEP use, such as fracture, there is no recommendation to monitor bone mineral density before or during PrEP use.

Although use of PrEP may have contributed to the increase in STIs observed over the past several years among high-risk populations, there is no evidence from randomized or open-label studies that STIs lower the efficacy of PrEP. The incidence of syphilis in the iPrEx trial was 7.3 cases per 100 person-years, with no statistically significant interaction with PrEP efficacy observed.[36] Similarly, no difference in PrEP efficacy was observed among participants with versus without STIs in the Partners PrEP study.[37] In the PROUD study, 73% of participants had STIs at baseline and PrEP effectiveness was 86%.[3] In the PrEP Demonstration Project, the incidence of STIs was 90 per 100 person-years and the rate of new HIV infections was 0.43 per 100 person-years.[7] Modeling data indicate that STI screening every 3 months for persons taking PrEP may actually reduce transmission of STIs, as many STIs are asymptomatic.[38]

Is PrEP Scale-Up Reaching the Right People?

The CDC estimates that, as of 2015, approximately 1.2 million persons have indications for PrEP, including approximately 540,000 MSM and 470,000 heterosexual women (Table).[39] Only a fraction of this population is currently receiving PrEP.[40] Available data indicate that younger, black, and Hispanic and Latino populations are undertreated in this regard.[40] Data from 2013 through the first quarter of 2016 indicate that among 3485 women initiating PrEP, only 12.7% were younger than 25 years, and among 24,594 men initiating PrEP, only 5.9% were younger than 25 years.[40] White women were 3.8 and 4.4 times more likely and white men were 8.3 and 6.7 times more likely to initiate PrEP than their black and Hispanic or Latino counterparts, respectively.[40]

In annual surveys of 1500 primary care practitioners from 2009 through 2015, awareness of PrEP increased from 25% to 67%; however, in 2015, only 7% had prescribed PrEP.[41] When PrEP efficacy was described as being greater than 75%, more than 90% of practitioners indicated a willingness to prescribe it. Practitioners indicated that they were most likely to prescribe PrEP for patients in stable HIV-serodiscordant partnerships and least likely to prescribe it for patients with STIs; however, HIV-serodiscordant partnerships in which the HIV-seropositive partner has achieved stable viral suppression are unlikely to benefit from PrEP, while persons with STIs may benefit substantially from PrEP. Practitioners may fear that PrEP will lead to behavioral disinhibition, particularly among persons who do not use condoms regularly. Such findings make it clear that greater effort is needed to provide PrEP for high-risk persons with multiple sex partners.

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