Perspective

HIV Prevention: Opportunities and Challenges

Preexposure prophylaxis (PrEP) with tenofovir disoproxil fumarate (TDF)-based regimens has been shown to be effective in preventing acquisition of HIV infection, with protective efficacy being dependent on adherence to treatment. Data from the PROUD (Preexposure Option for Reducing HIV in the UK) and IPERGAY (Action to Pre vent Risk Exposure By and For Gay Men) studies, the latter of which employed event-driven PrEP, showed a high rate of protective efficacy of PrEP with TDF and emtricitabine among men who have sex with men. Data from the ASPIRE (A Study to Prevent Infection With a Ring for Extended Use) study of a dapivirine vaginal ring showed a moderate rate of protective efficacy among women older than 21 years. Ongoing investigations are examining long-acting PrEP modalities and combination PrEP and contraception products. This article summarizes a presentation by Jeanne M. Marrazzo, MD, MPH, at the IAS–USA continuing education program, Improving the Management of HIV Disease*, held in Washington, DC, in April 2016.*

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Efficacy and Safety of Preexposure Prophylaxis

Preexposure prophylaxis (PrEP) is an integral part of HIV prevention.[1,2] In numerous clinical trials of biomedical antiretroviral therapy–based HIV prevention, efficacy has ranged from 0% to greater than 80%. Until recently, nearly all of these studies have involved tenofovir disoproxil fumarate (TDF)-based PrEP regimens, and efficacy estimates appear to correlate very highly with adherence to these regimens.

Overall, HIV protective efficacy was 67% with TDF and 75% with TDF/emtricitabine (slash indicates a coformulation) in the Partners PrEP study, 62% in the TDF2 study, and 44% in the iPrEx (Chemoprophylaxis for HIV Prevention in Men) study, while no efficacy was seen in the FEM-PrEP (Study to Assess the Role of Tenofovir/Emtricitabine in Preventing HIV Acquisition in Women) and VOICE (Vaginal and Oral Interventions to Control the Epidemic) studies; in each of these 5 studies, tenofovir was detected in 81%, 79%, 51%, 26%, and 28% of participants' plasma, respectively.[3-6]

These studies demonstrated that PrEP is highly effective with appropriate adherence, and the protective effect appears to be enduring. As an extension to the Partners PrEP study, PrEP and antiretroviral therapy were offered to high-risk HIV-serodiscordant couples. HIV-uninfected partners took daily oral TDF/emtricitabine as PrEP and continued the regimen for 6 months after their HIV-infected partners initiated antiretroviral therapy.[7] At interim analysis, more than 95% of HIV-uninfected partners were using PrEP and 80% of HIV-infected partners had initiated antiretroviral therapy, of which more than 90% achieved viral suppression. Overall, there was a 96% reduction in expected HIV infections (39.7 expected infections vs 5.2 incidence per 100 person-years). In cases of HIV transmission, plasma tenofovir concentrations were undetectable at the time of seroconversion.[7]

Available information continues to support the safety of TDF-based PrEP. Incidences of death, serious adverse events, and laboratory abnormalities (including renal dysfunction) are low and not statistically significantly different between persons who receive PrEP and those who receive a placebo. PrEP is well tolerated, and gastrointestinal adverse effects (eg, nausea which occurred in <10% overall and primarily during the first month of treatment) were more common among persons who received PrEP than those who received a placebo. PrEP is also safe during pregnancy and is not associated with any reductions in contraceptive efficacy.[8,9]

As expected based on experience with TDF-based HIV treatment, bone mineral density (BMD) decreases over time in persons taking TDF/emtricitabine as PrEP. In the iPrEx trial, a 0.91% decrease in spine BMD ($P = .001$) and a 0.61% decrease in total hip BMD ($P = .001$) were observed at week 24 in individuals who received PrEP compared with those who received a placebo. No difference in fracture rate was observed between groups. Six months after discontinuation of treatment and by the start of the open-label extension of the trial, recovery of BMD in both hip and spine was evident, and BMD recovery continued through approximately 1.4 years after discontinuation of TDF/emtricitabine.[10] Recovery of BMD was better in individuals younger than 25 years.

Acquired resistance to PrEP is rare, occurring in approximately 3% of individuals; approximately 12 HIV infections are averted for each case of resistance to PrEP. Resistance is usually due to the emergence of the K65R mutation after exposure to TDF or the M184V mutation after exposure to emtricitabine. However, there has been at least 1 reported case of an individual who acquired multidrug-resistant HIV infection after 2 years of daily PrEP with TDF/emtricitabine.[11] This individual's pharmacy records, plasma HIV RNA level, and clinical history indicated recent and long-term adherence to PrEP, and multidrug-resistant virus was likely transmitted rather than induced through prolonged exposure to tenofovir.

Real-World Issues: PrEP and PEP

Timely initiation of PrEP represents a balance between providing protection for periods of high risk for HIV infection and

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ensuring that HIV infection has not already been established. For an individual who has initiated postexposure prophylaxis (PEP) after a high-risk exposure to HIV, continuation of PrEP depends on assessment of the person's anticipated risk of HIV acquisition going forward. If an individual is considered to be at high risk for HIV infection, there may be an immediate transition from PEP to PrEP. In 2015, the World Health Organization provided guidance indicating that individuals can transition from taking PEP to PrEP after 28 days even if there is substantial continuing risk.[12]

More Recent PrEP Studies: Real-World Effects

The PROUD (Preexposure Option for Reducing HIV in the UK) and IPERGAY (Action to Prevent Risk Exposure By and For Gay Men) studies yielded the highest estimates thus far on the protective efficacy of PrEP. Neither study was placebo controlled; thus, participants knew the efficacy of PrEP that had been derived from the clinical trials discussed above and may have been more likely to use it based on that knowledge.

In the PROUD study, HIV-uninfected men who have sex with men (MSM) from 13 clinics in London, England, were randomly assigned to receive TDF/emtricitabine as PrEP immediately (n = 267) or to defer PrEP for 12 months (n = 256). At 60 weeks, HIV infection had occurred in 3 persons in the group that received immediate PrEP and in 19 persons in the group that received deferred PrEP. In the immediate PrEP group, there was an 86% reduction in risk ($P = .0002$), and the number needed to treat to prevent 1 HIV infection was 13.[13] The data safety and monitoring board interrupted the trial and recommended that all participants be offered PrEP.

In the IPERGAY trial, HIV-uninfected MSM were randomly assigned to receive event-driven, on-demand PrEP with TDF/emtricitabine (n = 199) or a placebo (n = 201), with the event-driven design intended to replicate "real-world" scenarios. In the event-driven PrEP group, participants took 2 tablets 2 to 24 hours before sex, 1 tablet 24 hours after sex, and 1 tablet 48 hours after the first event-driven dose.[14] Event-driven PrEP was associated with an 86% reduction in risk of HIV acquisition ($P = .002$), and the number needed to treat to prevent 1 HIV infection was 18. A median of 16 pills were taken by each participant each month in both groups, indicating a high degree of coverage of high-risk sexual acts.

These data indicate that PrEP can successfully prevent HIV acquisition in real-world settings. Additional data from Kaiser Permanente San Francisco, a large managed care organization, indicated that no new HIV infections occurred among more than 600 persons who initiated PrEP during the first year it was offered.[15] Among individuals taking PrEP, 56% reported no change in condom use, 41% reported a decrease in condom use, and 3% reported an increase in condom use. After 12 months of PrEP, with a 0% incidence of HIV infection, there was a 50% incidence of any sexually transmitted infection (STI), including a 33% incidence of rectal STIs, a 33% incidence of chlamydia, a 28% incidence of gonorrhea, and a 5.5% incidence of syphilis. Based on the incidence of these STIs, the expected incidence of HIV infection would have been 8.9%—a testament to the high efficacy of TDF/emtricitabine as PrEP when the rectal mucosa is the target site of acquisition, largely owing to the high concentrations of TDF/emtricitabine that are achieved in the rectal compartment. Unfortunately, the situation differs in the cervicovaginal environment, which does not achieve protective concentrations of TDF/emtricitabine without very high adherence.[16]

Beyond Oral PrEP?

Because stabilization of the HIV epidemic is likely attainable with a combination of antiretroviral therapy for treatment and PrEP for prevention, sustained delivery systems for PrEP are advancing in development, including use of drugs other than nucleoside analogue reverse transcriptase inhibitors, such as the nonnucleoside analogue reverse transcriptase inhibitor rilpivirine and the investigational integrase strand transfer inhibitor cabotegravir. Further, low rates of adherence to PrEP in some clinical trials suggest limited marketability and uptake for some nonoral formulations (eg, the tenofovir gel studied in the VOICE and Follow-on African Consortium for Tenofovir Studies [FACTS] 001 trials). However, many argue that other modalities should continue to be explored, as they may serve as a bridge to a crucial threshold of antiretroviral therapy and PrEP coverage that has yet to be achieved globally. Moreover, on-demand protection may be important to round out the PrEP portfolio, as not all individuals may have the opportunity to adequately premedicate for optimal protection—particularly women, given the pharmacokinetics of TDF-based delivery to the cervicovaginal environment. Other PrEP modalities would expand choices for personalized protection, could help individuals achieve goals of low or minimal systemic absorption and low systemic toxicity, and could offer the possibility of multipurpose prevention (eg, concomitant protection against herpes simplex virus or other STIs, and contraception).

Two trials have examined the use of a dapivirine-containing vaginal ring versus a placebo for preventing HIV infection in sexually active HIV-uninfected women in sub-Saharan Africa: the ASPIRE (A Study to Prevent Infection With a Ring for Extended Use) study and the Ring Study. The active product was a silicone elastomer vaginal matrix ring containing dapivirine 25 mg, which was inserted once every 4 weeks.[17] In the ASPIRE analysis, which excluded data from 2 sites with low adherence rates, HIV infection occurred in 54 women in the group that received dapivirine compared with 85 women in the group that received a placebo, yielding HIV incidences of 2.8 per 100 person-years and 4.4 per 100 person-years, respectively, and a 37% rate of protective efficacy ($P = .007$). The Ring Study had similar findings; HIV incidence in the group that received dapivirine was 31% lower than in the group that received a placebo (hazard ratio, 0.69; 95% CI, 0.49-0.99).

The ASPIRE investigators further examined the disparity in efficacy by participant age (Figure). Rates of protective efficacy were less than 27% among women aged 18 to 21

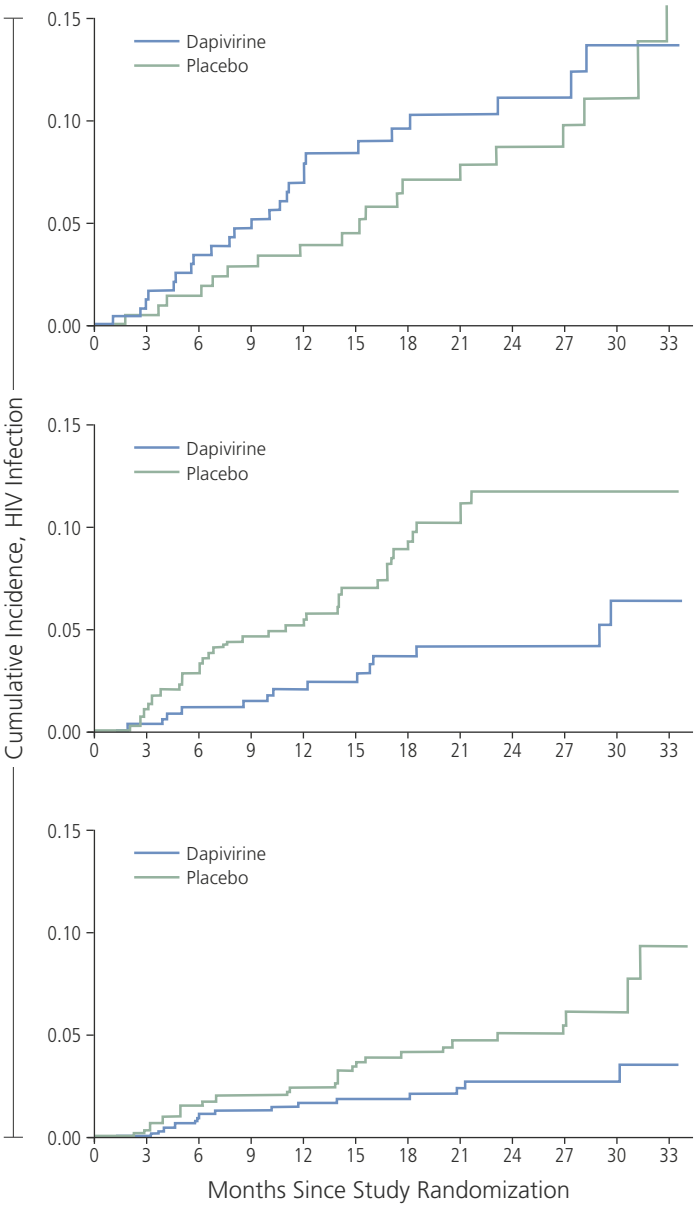

Figure. Protective efficacy of the dapivirine vaginal ring in the ASPIRE (A Study to Prevent Infection With a Ring for Extended Use) trial, by age group: (top) among participants aged 18 to 21 years efficacy of HIV protection was –27% (95% CI, –133 to 31); (middle) among participants aged 22 to 26 years efficacy of HIV protection was 56% (95% CI, 19 to 76); (bottom) among participants aged 27 to 45 years efficacy of HIV protection was 51% (95% CI, 8 to 74). Adapted from Baeten et al.[17]

years (incidence with placebo, 5.4% per year), 56% among those aged 22 to 26 years (incidence with placebo, 6.1% per year), and 51% among those aged 27 to 45 years (incidence with placebo, 3.0% per year). Overall, protective efficacy was 56% ($P = .001$) in women older than 21 years. Although adherence was likely different across these age groups, other factors such as differential rates of STI acquisition are under investigation.

Long-acting formulations of PrEP are an active area of study. The phase IIa ÉCLAIR (Study to Evaluate the Safety, Tolerability, and Acceptability of Long-Acting Injections of the HIV Integrase Inhibitor GSK1265744 in HIV Uninfected Men) study enrolled HIV-uninfected adult men at low risk of HIV infection who were then randomly assigned to receive cabotegravir 30 mg per day orally during a "loading phase" followed by a long-acting formulation of cabotegravir 800 mg intramuscularly every 12 weeks (n = 106) or a placebo (n = 21).[18] The primary end points of the study were safety and tolerability. Study results showed that peak concentrations of long-acting cabotegravir were higher and trough concentrations were lower than predicted owing to more rapid than anticipated drug absorption and clearance after intramuscular injection; approximately 70% of individuals had trough concentrations lower than the target of 4 times the protein-binding adjusted 90% inhibitory concentration. Injection site reactions occurred in 92% of individuals who received cabotegravir and in 56% of individuals who received a placebo, and 4 individuals who withdrew consent noted injection tolerability as a reason. The HIV Prevention Trials Network 083 and 084 clinical trials will study a long-acting formulation of cabotegravir given every 8 weeks. HPTN 083 was recently launched among MSM and transgender women, and HPTN 084 will involve women.

The phase II NEXT-PrEP (Novel Exploration of Therapeutics for Pre-Exposure Prophylaxis) study examined the effect of the entry inhibitor maraviroc on HIV-uninfected men who engaged in condomless anal intercourse with at least 1 HIV-infected man or a man whose HIV serostatus was unknown in the past 90 days.[19] A total of 406 participants were randomly assigned to receive maraviroc 300 mg (n = 101), maraviroc 300 mg plus a standard dose of emtricitabine (n = 106), maraviroc 300 mg plus a standard dose of TDF (n = 99), or emtricitabine plus a standard dose of TDF (n = 100). The incidence of grade 3 or 4 adverse events (n = 67), rates of discontinuation of study drug (total, 9%), and time to discontinuation were similar across groups. Five new HIV infections were reported (annual incidence, 1.4%; 4 new infections in the group that received maraviroc alone and 1 in the group that received maraviroc plus TDF), and the low incidence precluded any efficacy analysis. No transmitted drug resistance was found in cases of HIV infection.

Among other PrEP modalities in development are contraceptive vaginal rings containing sustained-release antiretroviral drugs, including a 30-day vaginal ring containing the investigational nonnucleoside analogue reverse transcriptase inhibitor MIV-150 plus zinc acetate plus levonorgestrel, a 60-day vaginal ring containing dapivirine plus levonorgestrel, and a 90-day vaginal ring containing tenofovir plus levonorgestrel. The Global Advocacy for HIV Prevention (AVAC) website provides detailed information on antiretroviral-based prevention in development.[20]

Conclusion

When taken consistently, PrEP is an effective tool for preventing sexual HIV transmission. However, data on PrEP for women are still limited. Additional options for PrEP, including

long-acting antiretroviral protection and combination options (eg, antiretroviral agents combined with hormonal contraceptives) are expected to be available in the near future.

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