Perspective

HIV Preexposure Prophylaxis: New Data and Potential Use

HIV preexposure prophylaxis (PrEP) has demonstrated efficacy in 4 studies: 1) the CAPRISA 004 trial of pericoital administration of 1% tenofovir gel showed moderate (39%) efficacy in reducing risk of HIV acquisition in young women; 2) the iPrEx trial of daily oral emtricitabine/tenofovir had moderate (44%) efficacy in reducing risk of HIV acquisition among high-risk men who have sex with men (MSM); 3) the Partners PrEP Study in African HIV-serodiscordant couples, in which the HIV-seronegative partner received daily oral tenofovir or emtricitabine/tenofovir, showed high efficacy (62% and 73%, respectively); and 4) the TDF2 trial in young heterosexual men and women in Botswana demonstrated 62% efficacy of daily oral emtricitabine/tenofovir. Greater adherence to PrEP is associated with greater efficacy. Resistance to tenofovir and emtricitabine have been rare and were primarily observed during PrEP initiation in those with acute HIV infection. PrEP has been found to be safe and well tolerated. The FEM-PrEP trial of oral emtricitabine/tenofovir and the VOICE trials of daily 1% tenofovir gel and oral tenofovir (both studies conducted in African women) did not show protective benefit, for reasons that currently remain unknown. The Bangkok Tenofovir Study of oral tenofovir in injection drug users, and the emtricitabine/tenofovir study arm of the VOICE trial, are ongoing. Establishing PrEP programs will be a great challenge and a great opportunity. This article summarizes a presentation by Connie L. Celum, MD, MPH, at the IAS–USA live continuing education course held in Chicago in June 2011, and includes updates on PrEP trial results reported since July 2011.

Background on PrEP

Efficacy of topical and oral tenofovir-based preexposure prophylaxis (PrEP) has recently been shown in 4 studies: 1) CAPRISA (Center for the AIDS Programme of Research in South Africa) 004; 2) iPrEx (Chemoprophylaxis for HIV Prevention in Men); 3) Partners PrEP; and 4) TDF2. In contrast, 2 studies among young African women found no efficacy in oral emtricitabine/tenofovir (FEM-PrEP) or in daily tenofovir gel and oral tenofovir (VOICE [Vaginal and Oral Interventions to Control the Epidemic]). The differences in efficacy outcomes in different populations are being explored.

Other types of preventive treatment exist in the form of postexposure prophylaxis (PEP) and the reduced infectiousness resulting from effective postinfection antiretroviral therapy. There are problems with PEP, however, including accurate assessment of the risk associated with the exposure and the need for the exposed individual to present and start treatment within 48 hours of the exposure. It is thus unlikely that PEP will have a large impact from a global perspective. Problems with postinfection antiretroviral therapy, from a global perspective, include the need to scale up programs for identifying and treating HIV-infected individuals, the need for additional resources to do so, the usual problems with long-term adherence (which may present greater challenges for prevention interventions), long-term toxicities, and antiretroviral resistance, although resistance in breakthrough infections has been rare. There may thus be a considerable role for PrEP in the effort to reduce HIV acquisition and transmission.

Much of the data on PrEP has involved use of tenofovir-based approaches, including tenofovir alone as a gel or tablet, or in combination with emtricitabine as a tablet. Both tenofovir and emtricitabine/tenofovir have a number of desirable characteristics for use as PrEP drugs, including broad antiretroviral activity (including all HIV-1 subtypes, HIV-2, and R5-tropic or X4 HIV), ability to block initial infection, and rapid onset of activity (for emtricitabine; tenofovir takes longer to be metabolized). Both agents have favorable safety and tolerability profiles, and use is made easier by once-daily dosing, absence of food restrictions, and few drug interactions.

Concern remains over the potential use of these agents in PrEP, however. If efficacy is low and substantial resistance occurs in breakthrough infections in the form of nucleoside analogue reverse transcriptase inhibitor (nRTI) K65R and M184V resistance mutations and cross-resistance with other nRTIs, there is concern that this could jeopardize future treatment with non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) in those with breakthrough infections who develop resistance on PrEP.

The possibility of PrEP studies was first raised in 2001, with a trial in Cambodian sex workers planned in 2003. However, there was little scale-up of antiretroviral agents for those with HIV infection in Cambodia at this time and considerable protest took place over testing an unproven strategy. A phase II trial of tenofovir in sex workers in West Africa was also disrupted because of community concerns. After the reporting of the safety of daily oral tenofovir as PrEP among female sex workers in West Africa at the 16th International AIDS Conference in Toronto in 2006,[1] a number of phase IIb and phase III trials were initiated from 2007 to 2009. In 2010, the positive findings for tenofovir gel in CAPRISA 004 and oral emtricitabine/tenofovir in iPrEx were reported. In 2011, the positive findings from Partners PrEP and TDF2, and the lack of efficacy observed in FEM-PrEP and VOICE, were reported.

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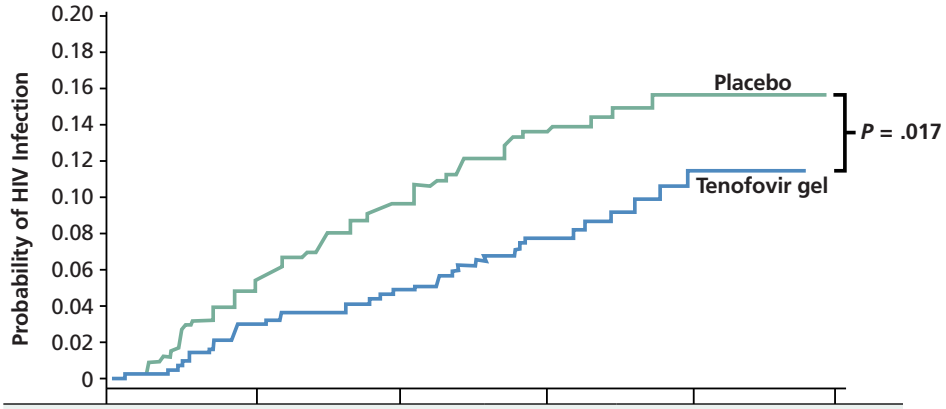
Landmark PrEP Trials: CAPRISA 004, iPrEx, Partners PrEP, and TDF2

The announcement of the CAPRISA 004 trial results was a landmark event, as it provided proof-of-concept that antiretrovirals could be effectively delivered topically. In the phase IIb CAPRISA 004 trial, 889 young unmarried women in Durban, South Africa (aged ≥ 18 years; mean age, 23 years; rural settings, 69%; urban settings, 31%), received pericoital 1% tenofovir gel applied vaginally within 12 hours before and 12 hours after sex (maximum of 2 applications over 24 hours) or placebo. Tenofovir treatment was associated with a 39% reduction in risk of acquiring HIV infection compared with placebo over 30 months of follow-up (Figure 1).[2] The study also showed a 51% reduction in risk for acquiring herpes simplex virus 2 (HSV-2) infection and no development of K65R-mediated resistance to tenofovir.

Treatment was associated with an increase in mild, self-limiting diarrhea. A sobering finding was that the incidence of HIV infection in the placebo group was 9.1%, and the incidence in the treatment group, despite the protection afforded by tenofovir treatment, was 5.6%. In the CAPRISA 004 trial, adherence was crucial for protective efficacy. Adherence of greater than 80% (38% of the treatment group) was associated with 54% protective efficacy, whereas adherence rates of 50% to 80% (20% of the treatment group) were associated with 38% protective efficacy. Adherence less than 50% (42% of treatment group) was associated with protective efficacy of 28%.

Tenofovir gel provides a very high level of active drug in cervicovaginal secretions and tissue, some 100- to 1000-fold higher than levels achieved with oral dosing of the drug.[3] Cervicovaginal tenofovir levels have been found to correlate with HIV and HSV-2 seroconversion.[4] A study comparing daily oral, vaginal, and dual dosing found that oral dosing did not increase drug concentrations in vaginal tissue beyond that achieved with vaginal application.[3] However, it also remains unknown how much active drug is needed mucosally versus systemically for a protective effect.



Months of follow-up	6	12	18	24	30
Cumulative HIV infections	37	65	88	97	98
Cumulative women-years	432	833	1143	1305	1341
HIV incidence rate (tenofovir)	6.0	5.2	5.3	5.6	5.6
HIV incidence rate (placebo)	11.2	10.5	10.2	10.2	9.1
Effectiveness (*P*-value)	47% (.064)	50% (.007)	47% (.004)	40% (.013)	39% (.017)

Figure **1**. Probability of HIV infection in young women receiving tenofovir gel or placebo in the CAPRISA (Center for the AIDS Programme of Research in South Africa) 004 trial. Adapted from Abdool Karim et al.[2]

Results of the iPrEx trial, announced in 2010, were a landmark event for oral PrEP (Figure 2). In the iPrEx trial, 2499 young, high-risk men who have sex with men (MSM) (50% aged < 25 years) from 11 sites in Brazil, Ecuador, Peru, South Africa, Thailand, and the United States (two-thirds from Ecuador and Peru) were randomly assigned to daily oral emtricitabine/tenofovir or placebo. Participants had a median of 18 sex partners in the 12 weeks before enrollment.[5] An updated efficacy estimate indicates that emtricitabine/tenofovir treatment was associated with a 42% reduction in HIV acquisition over 3 years (83 infections in placebo group, 48 in treatment group). No reduction in HSV-2 acquisition was observed, with blood drug levels being well below the 50% effective concentration (EC_{50}) for HSV-2. Effectiveness was dependent on adherence: protective efficacy was 68% in those with high adherence (90% adherence or above, which was estimated for 49% of study visits); 34% with intermediate adherence (50%-90% adherence, 33% of visits); and 16% with low adherence (less than 50% adherence, 18% of visits).

Emtricitabine/tenofovir had a very good safety profile, with the treatment group having an increase in nausea during the first month of treatment and a small decrease in bone mineral density. Among participants who were assessed for intracellular drug levels, levels were measurable in only 2 (9%) of 34 MSM with breakthrough infection in the treatment group. No antiretroviral resistance was found in the participants who acquired infection after study enrollment. Ten participants were retrospectively identified as having been in the process of HIV seroconversion at study entry: among 8 in the placebo arm, 1 had transmitted multiresistant HIV; among 2 in the treatment arm, both had virus with M184 resistance mutations. These findings underscore the need to avoid

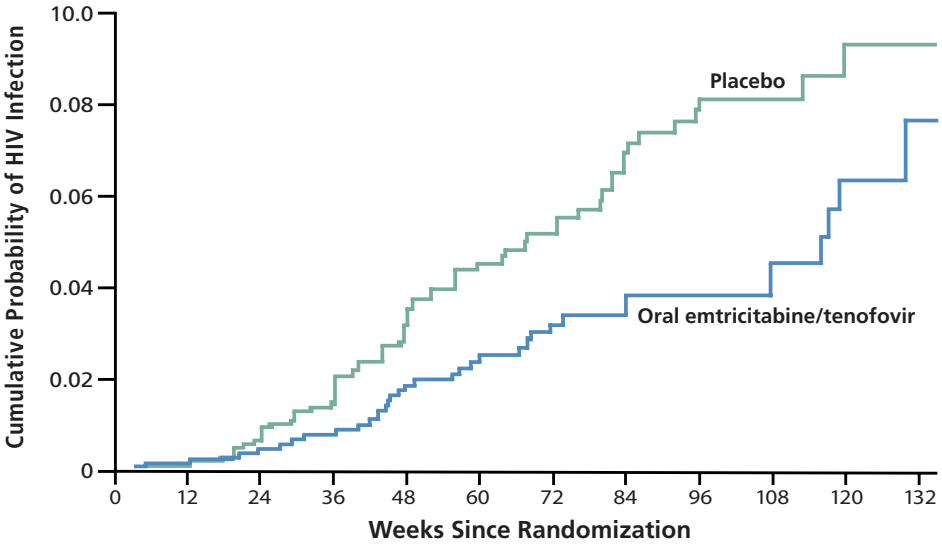


Figure **2**. Probability of HIV infection in men who have sex with men (MSM) receiving emtricitabine/tenofovir or placebo in the iPrEx (Chemoprophylaxis for HIV Prevention in Men) trial. Adapted from Grant et al.[5]

PrEP initiation in persons with acute HIV infection, because it appears likely to select for resistant mutants.

The news from the FEM-PrEP trial was not so positive.[6] This phase III study compared emtricitabine/tenofovir with placebo in a target population of 3900 female sex workers in Africa. It was announced in April 2011, after enrollment of 1951 participants, that the study was being ended prematurely because of lack of efficacy—56 new infections had occurred, evenly divided between the treatment and placebo arms. It is unclear whether lack of PrEP efficacy in this trial involved poor adherence, poor drug penetration into vaginal tissue, or lower efficacy in women for other reasons. All the women in the study were on hormonal contraceptives, and a higher rate of pregnancy was found among those using oral contraceptives; further analyses of this finding are awaited. A final study analysis in early 2012 should shed light on these issues.

The PrEP trials described above were challenging to launch and implement, but they have provided important proof-of-concept for topical and oral antiretroviral-based prevention. CAPRISA 004 and iPrEx showed that adherence is crucial to protective efficacy of PrEP. Efficacy is associated with drug levels, and the only accurate way to assess adherence is through measurement of drug levels. Adherence assessment based on patient report or pill count is unreliable. For example, data from iPrEx showed that among men with adherence greater than 90% based on pill count, only 62% had drug detected in blood samples.[7]

In July 2011, 2 studies reported high efficacy of daily oral tenofovir and emtricitabine/tenofovir—the Partners PrEP Study and TDF2. The Partners PrEP Study is an ongoing, 3-arm, placebo-controlled trial of daily oral tenofovir and tenofovir/emtricitabine in 4758 HIV-serodiscordant couples from Kenya and Uganda, among whom the HIV-infected partner is not eligible for antiretroviral therapy according to national guidelines. HIV-uninfected partners were randomly assigned to receive PrEP or placebo.[8]

On July 10, 2011, the study's Data and Safety Monitoring Board recommended the discontinuation of the placebo arm of the Partners PrEP study, because predetermined stopping guidelines for efficacy had been met. Overall, 62% efficacy of tenofovir (95% confidence interval [CI], 34%-78%) and 73% efficacy of tenofovir/emtricitabine (95% CI, 49%-85%) compared with placebo, were observed. The difference between tenofovir and tenofovir/emtricitabine was not statistically significant (P = .18). Both tenofovir and tenofovir/emtricitabine statistically significantly reduced HIV risk for both men and women in Partners PrEP. The TDF2 study enrolled 1200 heterosexual men and women aged 18 to 40 years in Botswana into a placebo-controlled trial of daily oral tenofovir/emtricitabine. The study reported 62.6% efficacy (95% CI, 21.5%-83.4%) for HIV protection due to PrEP.[9]

The VOICE 003 trial, sponsored by the Microbicide Trials Network (MTN) and National Institutes of Health (NIH) is examining daily oral tenofovir, daily oral emtricitabine/tenofovir, and daily vaginal tenofovir gel in 5000 women in South Africa, Uganda, and Zimbabwe. The Data Safety Monitoring Committee for the VOICE trial recommended discontinuation of the oral tenofovir arm in September 2011 and the tenofovir gel arm in November 2011 because of inability to demonstrate efficacy. Analyses of the VOICE trial will be crucial to understanding the lack of efficacy of daily tenofovir gel compared with the moderate efficacy of pericoital tenofovir gel in CAPRISA 004 and the lack of efficacy of oral tenofovir in women at risk.

Ongoing PrEP studies include the Bangkok Tenofovir study, also sponsored by the Centers for Disease Control and Prevention (CDC). This study is evaluating tenofovir in 2400 male injection drug users receiving directly observed therapy; the trial is fully enrolled, with results expected in 2012. The VOICE trial is anticipated to report results of the ongoing emtricitabine/tenofovir arm in 2013.

Are We Ready to Give PrEP to Men in the United States?

The CDC issued interim guidance for PrEP in MSM in January 2011. More extensive guidelines are expected from the CDC and the World Health Organization in 2012. Current key implementation issues for emtricitabine/tenofovir PrEP include determining who should receive the drug and how it should be made available. If high-risk MSM are targeted, what constitutes "high risk" needs to be de-

termined. Should PrEP be delivered at sexually transmitted infection (STI) clinics, HIV clinics, public health facilities, primary care clinics, or pharmacies? It is clear that to ensure that PrEP has a public health impact—rather than becoming a "boutique" intervention for those who can afford it—widespread access to medication and coverage of persons at highest risk of HIV acquisition is required.

Preliminary guidance from the CDC addresses risk assessment and safety monitoring for PrEP. Risk assessment is crucial before initiating PrEP, and clinicians should remind themselves of the maxim: "If I don't ask, they (often) won't tell." For PrEP eligibility, it must be determined that the individual is HIV-uninfected (ie, is antibody-negative) immediately before starting PrEP. Individuals with symptoms consistent with acute infection should delay treatment for a month until HIV-seronegative status is confirmed, or should be tested for acute HIV infection. Substantial, ongoing, high risk for HIV infection must be confirmed. Adequate renal function must also be confirmed, with the CDC recommending creatinine clearance (using the Cockcroft-Gault formula) of at least 60 mL/min. It is also recommended that patients be screened for hepatitis B virus (HBV) infection. Those who are uninfected should receive HBV vaccine; those who are infected should be treated. Patients should also be screened and treated for other STIs.

PrEP is given as fixed-dose combination tenofovir 300 mg and emtricitabine 200 mg in 1 tablet, taken once daily. Patients should receive no more than a 90-day supply at a time, with the prescription renewable only if HIV testing confirms that the patient remains uninfected and that poor adherence has not been documented. It is not clear yet how adherence should be assessed and documented in the setting of PrEP implementation, but demonstration projects are underway regarding this question. Counseling should focus on risk reduction and PrEP adherence, including the need to achieve and sustain drug levels for protective effect and discussion of adverse effects. Many patients experience mild nausea during the first few weeks of treatment, which typically resolves. There are no data yet on intermittent emtricitabine/tenofovir treatment (studies are being initiated in 2012), so patients should be discouraged from event-driven use and sharing fixed-dose emtricitabine/tenofovir with others.

Follow-up includes HIV testing every 2 to 3 months, with documentation of negative results. Adherence should be evaluated and supported, with re-emphasis that adherence is crucial to protection. Patients should receive continued risk reduction counseling and should be assessed for STI symptoms, with asymptomatic patients being screened every 6 months. Serum creatinine should be measured at 3 months after starting PrEP and annually thereafter.

For patients who become HIV-seropositive while receiving PrEP, PrEP should be stopped, resistance testing performed, and linkage to HIV care established. HIV-seronegative patients who discontinue PrEP should receive risk reduction support services. Those who discontinue PrEP who have chronic HBV infection should undergo liver function tests, as there have been case reports of hepatitis flares after discontinuing fixed-dose emtricitabine/tenofovir.

PrEP is not an inexpensive intervention. The CDC is currently working with insurance companies and payers to facilitate coverage for treatment, with an encouraging response thus far. Final decisions are awaited. Health departments are also awaiting the expanded CDC guidelines on PrEP. Based on models using data from South African women and HIV-serodiscordant couples, PrEP could be very cost-effective if efficacy is high (as has been demonstrated in some populations), if drug and delivery costs are lower than those for antiretroviral therapy (which depends on availability of generic tenofovir or emtricitabine/tenofovir and delivery models), and if it is targeted to those with highest risk (eg, young women in South Africa, MSM in the Americas, HIV-serodiscordant couples in East Africa).

In addition, it needs to be considered whether MSM will be interested in PrEP—particularly after years of telling men not to contract HIV infection because the medications are toxic. Messaging about the safety and tolerability of fixed-dose emtricitabine/tenofovir will be important to efforts to ensure that PrEP is adopted and used correctly. Helping MSM decide whether they are likely to benefit from PrEP is essential for optimal use of this intervention.

There are many unanswered questions regarding PrEP. When current trials are finished, we will have more information on PrEP in women, injection drug users, pregnant and breastfeeding women, adolescents, patients with chronic HBV infection, and on longer-term use and use of tenofovir gel in anal sex. Issues remain with regard to long-term adherence, efficacy with intermittent use, risk of antiretroviral resistance with longer times between HIV tests, potential spread of resistant virus, and potential effects on behavior. With regard to behavior, for example, will behavior become more high-risk with individuals using a partially protective treatment? And how much will an increase in risk behavior reduce the efficacy of PrEP? These key questions are being addressed in demonstration projects.

A major issue is how to roll out PrEP programs when there is a global postinfection treatment gap. Currently, we need to expand antiretroviral therapy access to the approximately 60% of HIV-infected individuals who are eligible for treatment but are not receiving it. The challenge of offering PrEP in this context should be reframed away from "prevention versus treatment" to "treatment and prevention, in parallel." To achieve this, we need to reduce antiretroviral therapy delivery costs, address the treatment gap, improve retention in care, and optimize clinical and public health benefits of antiretroviral therapy. We also need to initiate pilot programs of cost-effective PrEP delivery models and shift prevention resources to fund strategies that actually work.

Antiretroviral Therapy to Reduce Infectiousness and Transmission: Observational Data and the HPTN 052 Study

In a study by Dr Celum and colleagues of HSV disease suppression in 3400 HIV-serodiscordant couples in Africa, only 1 of 103 HIV infections in the initially HIV-seronegative partner occurred when the HIV-infected partner was receiving antiretroviral therapy.[10] In that 1 case of post–antiretroviral therapy HIV transmission, the initially HIV-infected partner had just begun antiretroviral therapy and likely had only partial viral suppression at the time of infection of the seronegative partner. Approximately 10% of HIV-infected partners initiated antiretroviral therapy during follow-up, and the protective effect was a 92% reduction in HIV transmission risk. Plasma HIV RNA level greater than 50,000 copies/mL was highly predictive of risk of transmission. When participants who had not received antiretroviral therapy were stratified by CD4+ cell count, HIV RNA level above 50,000 copies/mL was associated with a greater than 4-fold increased risk of transmission in both the 200/μL to 349/μL CD4+ cell count stratum and the 350/μL and above stratum.

Results of the HIV Prevention Trials Network (HPTN) 052 trial have provided a strong statement in favor of early treatment to further the public health goal of reducing spread of HIV infection. This trial, conducted in 9 countries (Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, United States, and Zimbabwe), assessed the impact of earlier antiretroviral therapy on HIV transmission and disease progression in 1763 HIV-serodiscordant couples. The HIV-infected partners had CD4+ cell counts of 350/μL to 550/μL and were randomly assigned to start highly active antiretroviral therapy immediately (n = 886) or when CD4+ cell count dropped to 250/μL (n = 887). All participants received HIV prevention services.

Participants were to be observed for 5 years, with the coprimary endpoints being HIV infection in the HIV-seronegative partner and HIV disease progression in the HIV-infected partner. After 2 years of follow-up, 1 case of transmission occurred in couples in the immediate-treatment group, versus 27 cases in the delayed treatment group, representing a 96% reduction in transmission risk with earlier treatment. In addition, 3 cases of extrapulmonary tuberculosis were found in the HIV-infected partners in the immediate-treatment group versus 17 in those receiving delayed treatment.[11]

Summary

The initial proof-of-concept for topical and oral tenofovir-based PrEP has been provided by the CAPRISA 004, iPrEx, Partners PrEP, and TDF2 studies. Analyses of the VOICE and FEM-PrEP studies will be crucial to understanding differences in efficacy among different populations. Ongoing PrEP trials and additional analyses of recently completed trials will provide information on safety and efficacy, adherence, and antiretroviral resistance in other populations, such as heterosexuals, injection drug users, adolescents, and pregnant or breastfeeding women. Drug costs, targeting strategies, and delivery strategies are crucial to cost-effectiveness and successful implementation of PrEP programs. Roll-out of these programs will be complicated and demonstration projects are needed to help inform the ultimate design of the programs. However, the challenge is an exciting one in the field of prevention, an area in which practitioners often contend with a sense of futility or frustration, given the many types of preventive programs that have had relatively little success in the past. We now have evidence-based tools with which to work. The strong demonstration that treatment is prevention, provided by observational data and the HPTN 052 trial, gives us another tool.

Lecture presented by Dr Celum in June 2011. First draft prepared from transcripts by Matthew Stenger. Reviewed, edited, and updated by Dr Celum in January 2012.

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