Published in final edited form as:
J Acquir Immune Defic Syndr. 2013 July ; 63(0 2): S122–S129. doi:10.1097/QAI.0b013e3182986f69.

Pre-exposure prophylaxis for HIV prevention: where have we been and where are we going?

Jared M. Baeten, MD, PhD[1,2,3], **Jessica E. Haberer, MD, MS**[4,5], **Albert Y. Liu, MD, MPH**[6,7], and **Nirupama Sista, PhD**[8]

[1]Department of Global Health, University of Washington, Seattle, WA, USA

[2]Department of Medicine, University of Washington, Seattle, WA, USA

[3]Department of Epidemiology, University of Washington, Seattle, WA, USA

[4]Center for Global Health, Massachusetts General Hospital, Boston, MA, USA

[5]Department of Medicine, Harvard Medical School, Boston, MA, USA

[6]Bridge HIV, San Francisco Department of Health, University of California San Francisco, San Francisco, CA, USA

[7]Department of Medicine, University of California San Francisco, San Francisco, CA, USA

[8]FHI360, Durham, NC, USA

Abstract

Pre-exposure prophylaxis (PrEP), in which HIV-uninfected persons with ongoing HIV risk use antiretroviral medications to reduce their risk of acquiring HIV infection, is an efficacious and promising new HIV prevention strategy. The past two years have seen significant new advances in knowledge regarding PrEP, including definitive demonstration that PrEP reduces the risk of HIV acquisition, regulatory approval of combination oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) as the first PrEP agent with a label indication for sexual HIV prevention, and the development of normative guidance for clinical prescribing of PrEP. In PrEP clinical trials, HIV protection was strongly correlated with PrEP adherence; therefore understanding and supporting adherence to PrEP are key to maximizing its public health impact. As would be expected for any new HIV prevention approach, questions remain, including how to motivate uptake of and sustain adherence to PrEP for HIV prevention in high-risk populations, how much use is sufficient to achieve HIV protection, and the potential of “next-generation” PrEP agents to improve this effective prevention strategy. At this important transition point – from demonstration of efficacy

Correspondence and reprints: Jared Baeten, Departments of Global Health, Medicine, and Epidemiology, University of Washington, Box 359927, 325 Ninth Avenue, Seattle, WA 98104, Phone: 206-520-3808, Fax: 206-520-3831, jbaeten@uw.edu.

Conflicts: Sista: owns personal stock as investment in Gilead Sciences; Pfizer, other pharma
Haberer: Received funding for research from IAVI on pre-exposure prophylaxis against HIV infection. This work informed some of my contributions to the submitted manuscript, but did not support the manuscript directly. Recieved salary support from Mass General for clinical care, which is unrelated to the submitted manuscript. Receives funding from Gates Foundation for research on pre-exposure prophylaxis against HIV infection. This work informed some of my contributions to the submitted manuscript, but did not support the manuscript directly. Received a small honorarium for speaking at an IAPAC conference, which was unrelated to the submitted manuscript. Received a small honorarium and travel expenses for speaking at a UW course, which was unrelated to the submitted manuscript. Received Natera stock options as a consultant. This work was unrelated to the submitted manuscript. Received a small honorarium from Harvard CFAR for participating in a CFAR grant review, which was unrelated to the submitted manuscript. Received a small honorarium and travel expenses for participating in an NICHD grant review, which was unrelated to the submitted manuscript. Received a small honorarium and travel expenses for participating in an AHRQ technical expert panel, which was unrelated to the submitted manuscript. Received a small honorarium and travel expenses from FHI 360 for providing consultation on a pre-exposure prophylaxis study. This work informed some of my contributions to the submitted manuscript, but did not support the manuscript directly.

in clinical trials to thinking about implementation and effectiveness – this review addresses where we have been and where we are going with PrEP for HIV prevention.

Keywords

HIV prevention; pre-exposure prophylaxis; sexual HIV transmission

Introduction

In July 2012, the US Food and Drug Administration approved the first label indication for an antiretroviral agent – the oral combination emtricitabine/tenofovir disoproxil fumarate (FTC/TDF), sold as branded Truvada® – to be used as pre-exposure prophylaxis (PrEP) to reduce the risk of sexual acquisition of HIV infection by persons at high risk [1]. More than 2.5 million persons are newly-infected with HIV each year worldwide, resulting in a growing treatment and care burden [2], and thus novel strategies to prevent HIV acquisition, such as PrEP, remain urgently needed. This review will address where we have been and where we are going with PrEP for HIV prevention.

Where have we been?

Rationale and demonstration of PrEP efficacy for HIV prevention

The idea of prophylaxis to reduce the risk of an infectious disease is well-established – one example is malaria chemoprophylaxis in travelers. Evidence to suggest that PrEP could reduce HIV risk grew out of successful HIV prevention of mother-to-child HIV transmission with antiretroviral prophylaxis [3–6] and from non-human primate studies showing that PrEP prior to mucosal simian HIV (SHIV) challenge provided partial or full protection against infection [7–11]. TDF and FTC had biologic properties that made these reverse transcriptase inhibitors attractive as first-generation PrEP agents: potent antiretroviral activity against all HIV subtypes, activity early in HIV's lifecycle, long-intracellular half-life, able to achieve high concentrations in the genital tract, convenient daily dosing with few drug interactions, and established safety profiles from their use as part of combination antiretroviral therapy (ART) regimens. When used for HIV treatment, TDF is a once-daily 300 mg dose, and FTC/TDF includes 200 mg of FTC; these standard doses were chosen for clinical trials of PrEP. In non-human primate studies, there was some evidence of greater HIV protection using FTC/TDF compared to TDF alone, suggesting that combination PrEP could provide greater benefit than from a single agent [8].

Five efficacy trials of TDF and/or FTC/TDF as PrEP for HIV prevention have been completed and two are ongoing (Table 1). Trial protocols included monthly study visits with HIV serologic testing, clinical safety evaluation, and individualized adherence counseling, as well as a package of HIV prevention services provided to all participants (including HIV and risk-reduction counseling, screening and treatment for sexually transmitted infections, and free provision of condoms).

Three of these trials [12–14] – involving men who have sex with men (iPrEx) and heterosexual men and women (Partners PrEP and TDF2) from a diversity of geographic settings – demonstrated that PrEP reduced the risk of HIV acquisition, with intention-to-treat comparisons against placebo showing HIV protection efficacies between 44 and 75%. Importantly, although pharmacokinetic studies suggested lesser accumulation of tenofovir in vaginal compared to rectal tissue after TDF dosing [15,16], subgroup analyses in the two trials that included both sexes (Partners PrEP and TDF2) found comparable HIV protection for

both women and men. Thus, these randomized, placebo-controlled trial results provide definitive evidence that PrEP "works" for HIV prevention.

PrEP adherence and HIV protection

A strong dose-response relationship between adherence to PrEP pill-taking and HIV protection was demonstrated across PrEP efficacy trials (Table 1). Higher HIV protection was seen in trials with higher adherence and no HIV protection was found in two trials (FEM-PrEP and VOICE [17,18]) in which adherence to PrEP, as measured by detection of PrEP medications in blood samples from a random subset of subjects, appears to have been very low. In iPrEx and Partners PrEP, analyses of detection of PrEP medications in blood samples suggests that those using PrEP may have achieved an ~90% reduction in HIV risk, which likely hints at the true biologic efficacy of PrEP for HIV protection. Thus, just as consistent use of ART is needed to achieve HIV treatment benefits [19], adherence is critical to the efficacy of PrEP.

One important factor for achieving high adherence in PrEP trials appears to have been external support. In qualitative work, support from the HIV-infected member of a serodiscordant couple appears to be related to better PrEP pill-taking in the Partners PrEP Study, and participants in iPrEx noted the importance of support from research staff, family and friends [20,21]. Conversely, low perception of HIV risk may explain low PrEP adherence – in FEM-PrEP, 70% of women reported they felt themselves at little risk for acquiring HIV, despite a nearly 5% annualized HIV incidence in that trial [17]. In iPrEx, PrEP efficacy was higher in men reporting (versus not reporting) unprotected receptive anal sex at baseline, suggesting self-perception of risk might increase PrEP use [12]. *A*dditional factors associated with lower adherence in Partners PrEP included younger age, male gender, higher socio-economic status, and heavy alcohol use [22]; in iPrEx, younger age and region (non-US sites compared to US sites) were also associated with lower adherence [23]. In VOICE, adherence was lower in younger, unmarried women, who also had the highest HIV incidence in this trial [18].

Additional outcomes from PrEP trials: safety, resistance, sexual behavior

Trials have found that TDF and FTC/TDF PrEP appear to be well-tolerated, with the rate of both serious and mild adverse events generally balanced between those receiving PrEP and those receiving placebo. The most prominent side effects were gastrointestinal (e.g., nausea) and these symptoms were present only in a minority of subjects (~10% or less), were mild in severity, and were generally limited to the first month after initiation of the medication. PrEP has been associated with an average ~1% reduction in bone mineral density but not with increased fracture risk over the study period [14,24,25]. Although TDF has been associated with renal complications in HIV-infected persons, PrEP clinical trials did not find increased risk of renal complications in healthy HIV-uninfected persons. Finally, data from Partners PrEP [26] and from the Antiretroviral Pregnancy Registry [27] suggest that use of TDF and FTC/TDF in early pregnancy is not associated with increased rates of birth defects, although more data are needed to fully assess the safety of these medications through pregnancy.

Antiretroviral resistance was rare and limited to those with seronegative acute infection at the time of PrEP initiation. The absence of PrEP-selected drug resistance among persons acquiring HIV during the trials is potentially a manifestation of the strong correlation between PrEP use and protection: low use of PrEP provides little HIV protection but little risk of resistance if infection is acquired, whereas high adherence blocks most transmissions. Taking a public health perspective, the number of cases of antiretroviral resistance in PrEP trials is presented against the number of HIV infections prevented by PrEP in Table 2.

Finally, the question of increased sexual risk-taking accompanying PrEP use was explored in iPrEx and Partners PrEP, where self-reported condom use increased and sexually transmitted infection diagnoses decreased during follow-up. Although the self-reported data are potentially limited by recall and social desirability biases, these data potentially suggest that PrEP could work synergistically with other components of the HIV prevention package provided to trial participants [28].

Where are we going?

Unanswered questions from PrEP trials and progress with PrEP demonstration projects

First-generation PrEP trials have demonstrated proof-of-concept that antiretroviral PrEP provides protection against HIV acquisition, but, as expected for this new prevention strategy, a number of important scientific and implementation questions remain (Table 3); many of these same questions are also relevant for implementation of ART to reduce the infectiousness of persons with HIV infection as a prevention intervention [29]. For PrEP, the overarching unknown is whether HIV protection efficacy, as proven in clinical trials, will translate into substantive effectiveness in real-world practice. A number of considerations influence the priority questions for PrEP implementation. First, levels and patterns of adherence to PrEP in the setting of known efficacy are unknown. While medication adherence is often lower when moving from clinical trials to practice settings [30], individuals with ongoing HIV risk who seek out prescription PrEP that is known to "work" may be highly motivated to adhere. Second, sexual risk-taking in the context of known PrEP efficacy is unexplored, including whether risk compensation might result in reduced PrEP benefits and the level and types of behavioral intervention(s) needed to maximize prevention synergy [31]. Third, further study is required to identify optimal HIV testing approaches to reliably detect HIV infections among individuals initiating and continuing PrEP, to minimize selection of resistance. Fourth, the longer term health effects of oral FTC/TDF in HIV-negative PrEP users, including renal safety and bone mineral density, require further evaluation, particularly for those with underlying co-morbidities (e.g. hypertension, diabetes) as well as for women who may use PrEP during pregnancy and breastfeeding. No PrEP clinical trials included pregnant women; however, PrEP has the potential to reduce the risk of seroconversion during conception and pregnancy, particularly for HIV serodiscordant couples desiring pregnancy. Pregnancy is a high-risk period for HIV acquisition and acute infection during pregnancy is associated with higher risk of transmission to the fetus [32], and thus studies of PrEP safety and use in pregnancy should be a priority. Finally, additional research is needed to determine how best to prioritize populations who will benefit most from PrEP, the best time period for use of PrEP as an intervention (e.g. in women when they cannot negotiate safer sex or in women wanting to get pregnant), level of interest in taking PrEP in these communities, and optimal delivery settings for PrEP to maximize public health impact.

To address unanswered questions for PrEP implementation, PrEP demonstration projects are being planned or underway (Table 4). Target populations include MSM and transgender women, heterosexual serodiscordant couples, young sexually active heterosexual men and women, and female sex workers, across five continents and in a diversity of delivery settings. Common objectives across demonstration projects include assessing 1) feasibility, acceptability, and uptake of PrEP, 2) levels and patterns of PrEP adherence, 3) changes in sexual risk behavior, 4) safety and tolerability, and 5) HIV incidence and resistance among seroconverters. Three projects are open-label extensions of PrEP clinical trials and will provide opportunities to determine the impact of providing information about efficacy and safety of PrEP in well-characterized cohorts.

While the current portfolio of PrEP demonstration projects is scientifically, programatically, and geographically diverse, PrEP is not being evaluated in all populations, with important gaps including young African women; projects still in planning or proposal stages may address some of these gaps. In addition, coordination across projects will be important, so that core data are collected and can be compared across time, minimizing duplication and maximizing synergy across projects [33]. The World Health Organization (WHO) is currently compiling a framework for country-level protocol development of PrEP demonstration projects. Key messages include involvement of high-risk populations and measurement of adherence as a primary outcome. A key consideration for PrEP demonstration work is that projects should not simply track retention on PrEP alone, but particularly when PrEP is needed (i.e., during period of high risk) and as PrEP use relates to other HIV prevention services (e.g., condoms, male circumcision).

What adherence means for PrEP outside of clinical trials

Understanding adherence to PrEP in implementation settings must consider whether PrEP is needed and desired. In contrast to ART, which is life-long, PrEP is likely best used for periods (months to a few years) of highest behavioral risk – for example, when attempting to conceive [34], around the time of sexual debut or coming out, and when previously-safe sexual behavior patterns are modified. Perfect adherence during times of no risk (e.g., no sex) is not likely cost-effective or appropriate, but good adherence during periods of higher risk is essential. In iPrEx and in Partners PrEP, participants reporting no sex (and therefore no risk for HIV acquisition) were more likely to have low adherence [22], suggesting self-assessment of risk may be possible to some degree – analogous to other prevention strategies that are not life-long (e.g., oral contraceptives). PrEP implementation should assess when individuals want to take PrEP (i.e., the “season of PrEP”) and how long they take it (i.e., persistence of adherence). Guidance for when and how to start and stop PrEP and still achieve effective protection is needed. In one study (the Partners Demonstration Project), PrEP will be provided to HIV serodiscordant couples as a “bridge” to stable ART initiation by the HIV-infected partner [35].

PrEP studies have used several adherence measures, each with important strengths and weaknesses (Table 5). Objective measurements likely provide the most reliable data, and electronic monitoring is the only way to capture patterns of adherence, which are particularly important for assessing adherence behavior as related to periods of risk. A number of demonstration projects are incorporating drug-level testing to monitor PrEP adherence. If resources in demonstration projects and implementation settings are limited, use of objective adherence measures may still be considered for a subset of the study population.

The level of adherence needed to achieve HIV protection is not clear; however, PrEP use may potentially permit behavioral imperfection. In the iPrEx study, statistical modeling combining pharmacokinetics and drug data estimated that 2 PrEP doses per week might achieve a 76% reduction in HIV, rising to >95% for ≥4 doses per week [36]. However, PrEP concentrations necessary for HIV protection are potentially related to the intensity and route of viral exposure (e.g., penile, vaginal, parenteral, rectal) and the drug (TDF, FTC/TDF, or other agents). There are currently no data to guide less-than-daily dosing of oral FTC/TDF as PrEP. In addition, it is not clear if less-than-daily dosing would necessarily achieve higher adherence: in one small study among MSM in Kenya and serodiscordant couples in Uganda adherence to intermittent (twice weekly and post-coital) PrEP was lower compared to daily PrEP [13, 14]. Adherence may change over time depending on variable risk, preferences, and other factors in an individual’s life (e.g., alcohol use, income). While tailoring PrEP to those most likely to adhere may be an attractive strategy for increasing cost-effectiveness, those individuals may be difficult to identify and may be a moving target.

An important question will be how best to motivate and support ongoing PrEP use, highlighting the need to develop and rigorously evaluate effective, scalable PrEP adherence interventions for diverse populations. PrEP demonstration projects will research a range of interventions to support adherence, risk reduction, and other psychosocial needs. Client-centered brief counseling sessions, directed approaches based on cognitive behavioral therapy and problem-solving therapy for those with low adherence, and use of electronic reminders or text messages are being evaluated in demonstration projects. Good adherence support will be critical to ensure the behavioral success of this biological agent for HIV prevention. That said, counseling should not be so onerous as to present logistical or financial barriers to access the medication. Demonstration projects should explore standardized approaches for providing appropriate counseling within the real world context.

PrEP use outside of demonstration projects

Normative guidance for prescribers regarding PrEP for MSM and high-risk heterosexuals has been released in the US [37,38]. The guidance stresses the importance of delivering PrEP as part of a package of prevention services, including HIV testing, risk reduction counseling, and prevention and treatment of sexually transmitted infections, as well as adherence messaging. HIV testing and PrEP refills are recommended no less frequently than every three months, and attention to acute HIV infection, particularly at PrEP initiation (or re-initiation) is important. To maximize the potential benefits of PrEP, it will need to be accessible to at-risk populations, who are most often not engaged in care. PrEP is a primary prevention intervention, and prescribing by primary and community care providers, who are more likely to encounter the populations most at risk, is needed. For individuals not regularly engaged in care, collaboration with community-based organizations will be needed to identify at-risk HIV-negative individuals, provide education about PrEP, and link them into primary care [39]. Providers in a variety of settings – public clinics, antenatal care, sexually transmitted infection clinics – might be PrEP prescribers or initiate linkages to primary care. Counseling support might be delivered through community-based, non-clinical settings with strong linkages to PrEP clinical providers [40].

Next-generation PrEP studies

Demonstration of efficacy and regulatory approval of daily oral FTC/TDF PrEP was a milestone for HIV prevention [41], but potentially only the first step in developing a suite of PrEP options. Both TDF and FTC have long half-lives (~150 hours and ~48 hours respectively), which provides substantial drug concentrations to be present for several days after each dose [42], and non-human primate models indicate that dosing even as infrequently as once a week may be sufficient for protection if post-exposure dosing is also used [8,43]. The HIV Prevention Trials Network (HPTN) is evaluating different intermittent dosing strategies, and theory-based determinants of sexual and pill-taking behavior in heterosexual women in Africa and in MSM in the US and Thailand (HPTN 067). Nonetheless, careful attention to adherence will be critical in studies of less-frequent PrEP dosing. Alternative PrEP agents to FTC/TDF, including oral and topical vaginal maraviroc, dapivirine and other agents formulated into long-acting vaginal rings, and injectable agents (e.g., rilpivirine), are being evaluated; importantly, formulations to address adherence challenges (e.g., sustained-release injections, long-acting vaginal rings) are under study.

Conclusions

During the past two years, PrEP has moved from hypothesis to proof-of principle: for persons at ongoing risk of HIV infection, PrEP provides a time-limited, highly efficacious HIV prevention strategy. As with all prevention strategies, PrEP is only effective if used, and maximum PrEP benefits, at both individual and population levels, will likely be

achieved by combining PrEP with other effective HIV prevention interventions. Implementation of PrEP, in researched demonstration projects and implementation settings, is the next step. As we move from where we have been to where we are going with PrEP, there is a tremendous opportunity to maximize the benefits of this promising HIV prevention strategy.

Acknowledgments

Funding: US National Institutes of Health (grants R01 MH095507, R01 MH098744, R01 MH095628, UM1 AI068619)

References

1. U.S. Food and Drug Administration. FDA approves first drug for reducing the risk of sexually acquired HIV infection. 2012. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm
2. UNAIDS. World AIDS Day Report 2012. Geneva: UNAIDS; 2012.
3. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. N Engl J Med. 2008; 4:4.
4. Mofenson LM. Protecting the next generation--eliminating perinatal HIV-1 infection. N Engl J Med. 2010; 362:2316–2318. [PubMed: 20554987]
5. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med. 1994; 331:1173–1180. [PubMed: 7935654]
6. Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. Lancet. 1999; 354:795–802. [PubMed: 10485720]
7. Tsai CC, Follis KE, Sabo A, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl)adenine. Science. 1995; 270:1197–1199. [PubMed: 7502044]
8. Garcia-Lerma JG, Otten RA, Qari SH, et al. Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. PLoS Medicine. 2008; 5:e28. [PubMed: 18254653]
9. Garcia-Lerma JG, Cong ME, Mitchell J, et al. Intermittent prophylaxis with oral truvada protects macaques from rectal SHIV infection. Sci Trans Med. 2010; 2:14ra14.
10. Parikh UM, Dobard C, Sharma S, et al. Complete protection from repeated vaginal simian-human immunodeficiency virus exposures in macaques by a topical gel containing tenofovir alone or with emtricitabine. J Virol. 2009; 83:10358–10365. [PubMed: 19656878]
11. Subbarao S, Otten RA, Ramos A, et al. Chemoprophylaxis with tenofovir disoproxil fumarate provided partial protection against infection with simian human immunodeficiency virus in macaques given multiple virus challenges. J Infect Dis. 2006; 194:904–911. [PubMed: 16960777]
12. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010; 363:2587–2599. [PubMed: 21091279]
13. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012; 367:399–410. [PubMed: 22784037]
14. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012; 367:423–434. [PubMed: 22784038]
15. Kashuba AD, Patterson KB, Dumond JB, Cohen MS. Pre-exposure prophylaxis for HIV prevention: how to predict success. Lancet. 2011; 6:6.
16. Patterson KB, Prince HA, Kraft E, et al. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. Sci Transl Med. 2011; 3:112re114.
17. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012; 367:411–422. [PubMed: 22784040]

18. Marrazzo, J.; Ramjee, G.; Nair, G., et al. Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine, or vaginal tenofovir gel in the VOICE (MTN 003). 20th Conference on Retroviruses and Opportunistic Infections; 3–6 March 2013; Atlanta, USA. p. Abstract 26LB
19. Williams A, Friedland G. Adherence, compliance, and HAART. AIDS Clin Care. 1997; 9:51–54. 58. [PubMed: 11364415]
20. Ware NC, Wyatt MA, Haberer JE, et al. What's love got to do with it? Explaining adherence to oral antiretroviral pre-exposure prophylaxis for HIV-serodiscordant couples. J Acquir Immune Defic Syndr. 2012; 59:463–468. [PubMed: 22267018]
21. Tangmunkongvorakul A, Chariyalertsak S, Amico KR, et al. Facilitators and barriers to medication adherence in an HIV prevention study among men who have sex with men in the iPrEx study in Chiang Mai, Thailand. AIDS Care. 2012; 19:19.
22. Bangsberg, D.; Haberer, J.; Psaros, C., et al. High adherence and high effectiveness observed in HIV discordant couples: Partners PrEP Study, adherence monitoring and counseling substudy. 19th Conference on Retroviruses and Opportunistic Infections (CROI); Mar 5–8, 2012; Seattle, WA. p. Abstract 1067
23. Anderson, P.; Lama, J.; Buchbinder, S., et al. Interpreting detection rates of intracellular FTC-TP and TFV-DP: the iPrEx trial. 18th Conference on Retroviruses and Opportunistic Infections; 27 February – 2 March, 2011; Boston, USA. p. Abstract 96LB
24. Mulligan, K.; Glidden, D.; Gonzales, P., et al. Effects of FTC/TDF on bone mineral density in seronegative men from 4 continents: DEXA results of the global iPrEx study. 18th Conference on Retroviruses and Opportunistic Infections; 27 February – 2 March 2011; Boston, USA. p. Abstract 94LB
25. Liu AY, Vittinghoff E, Sellmeyer DE, et al. Bone mineral density in HIV-negative men participating in a tenofovir pre-exposure prophylaxis randomized clinical trial in San Francisco. PLoS ONE. 2011; 6:e23688. [PubMed: 21897852]
26. Mugo, N.; Celum, C.; Donnell, D., et al. Pregnancy incidence and birth outcomes in a clinical trial of PrEP: Uganda and Kenya. 19th Conference on Retroviruses and Opportunistic Infections; 5–8 March 2012; Seattle, USA. p. Abstract 1060
27. Antiretroviral Pregnancy Registry Interim Report 1 January 1989 through 31 July 2011. 2011. http://www.apregistry.com/forms/interim_report.pdf
28. Celum C, Baeten JM. Serodiscordancy and HIV prevention in sub-Saharan Africa. Lancet. 2013; 4:60147–60146.
29. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011; 365:493–505. [PubMed: 21767103]
30. Davidson MH. Differences between clinical trial efficacy and real-world effectiveness. Am J Manag Care. 2006; 12:S405–411. [PubMed: 17112328]
31. Phillips AN, Cambiano V, Nakagawa F, et al. Increased HIV incidence in men who have sex with men despite high levels of ART-induced viral suppression: analysis of an extensively documented epidemic. PLoS ONE. 2013; 8:e55312. [PubMed: 23457467]
32. Mugo NR, Heffron R, Donnell D, et al. Increased risk of HIV-1 transmission in pregnancy: a prospective study among African HIV-1 serodiscordant couples. AIDS. 2011; 21:21.
33. Warren MJ, Bass ES. From efficacy to impact: an advocate's agenda for HIV pre-exposure prophylaxis implementation. Am J Prev Med. 2013; 44:S167–170. [PubMed: 23253762]
34. Matthews LT, Baeten JM, Celum C, Bangsberg DR. Periconception pre-exposure prophylaxis to prevent HIV transmission: benefits, risks, and challenges to implementation. AIDS. 2010; 24:1975–1982. [PubMed: 20679759]
35. Hallett TB, Baeten JM, Heffron R, et al. Optimal Uses of Antiretrovirals for Prevention in HIV-1 Serodiscordant Heterosexual Couples in South Africa: A Modelling Study. PLoS Medicine. 2011; 8:e1001123. [PubMed: 22110407]
36. Anderson PL, Glidden DV, Liu A, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci Transl Med. 2012; 4:151ra125.
37. Interim guidance for clinicians considering the use of preexposure prophylaxis for the prevention of HIV infection in heterosexually active adults. Morb Mortal Wkly Rep. 2012; 61:586–589.

38. Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. Morb Mortal Wkly Rep. 2011; 60:65–68.

39. Norton WE, Larson RS, Dearing JW. Primary care and public health partnerships for implementing pre-exposure prophylaxis. Am J Prev Med. 2013; 44:S77–79. [PubMed: 23253766]

40. Hosek SG. HIV pre-exposure prophylaxis diffusion and implementation issues in nonclinical settings. Am J Prev Med. 2013; 44:S129–132. [PubMed: 23253753]

41. Karim SS, Karim QA. Antiretroviral prophylaxis: a defining moment in HIV control. Lancet. 2011; 17:17.

42. Rodriguez, NS.; Labarga, P.; Soriano, V., et al. Predictors of kidney tubulopathy in HIV patients treated with tenofovir: A Pharmacogenetic Study. 16th Conference on Retroviruses and Opportunistic Infections; 2009; Montreal, Canada. p. Abstract 37

43. Garcia-Lerma, G.; Cong, M-EMJ., et al. Prevention of rectal simian HIV transmission in macaques by intermittent pre-exposure prophylaxis with oral Truvada. 16th Conference on Retroviruses and Opportunistic Infections; 2009; Montreal, Canada. p. Abstract 47

44. Martin M, Vanichseni S, Suntharasamai P, et al. Enrollment characteristics and risk behaviors of injection drug users participating in the Bangkok Tenofovir Study, Thailand. PLoS ONE. 2011; 6:e25127. [PubMed: 21969870]

45. The IPERGAY Study. 2012. http://www.ipergay.fr/

Table 1

Placebo-controlled efficacy trials of PrEP for HIV prevention

Study (location)	Population	Design	Relative reduction in HIV incidence in intention-to-treat analysis	PrEP detection in blood samples from non-seroconverters	HIV protection estimate as related to high adherence	Ref
Completed trials (ordered by decreasing HIV risk reduction in primary intention-to-treat analysis)						
Partners PrEP Study (Kenya, Uganda)	4747 heterosexual men and women with known HIV infected partners (serodiscordant couples)	1:1:1 randomization to daily oral TDF, FTC/TDF, or placebo	TDF: 67% (95% CI 44–81%, p<0.0001) FTC/TDF: 75% (95% CI 55–87%, p<0.0001)	81%	86% (TDF) 90% (FTC/TDF) in subjects with detectable tenofovir levels	12
TDF2 Study (Botswana)	1219 heterosexual men and women	1:1 randomization to daily oral FTC/TDF or placebo	FTC/TDF: 63% (95% CI 22–83%, p=0.01)	79%	78% excluding follow-up periods when subjects had no PrEP refills for >30 days	17
iPrEx (Brazil, Ecuador, Peru, South Africa, Thailand, US)	2499 MSM and transgender women	1:1 randomization to daily oral FTC/TDF or placebo	FTC/TDF: 44% (95% CI 15–63%, p=0.005)	51%	92% in subjects with detectable tenofovir levels	12
FEM-PrEP (Kenya, South Africa, Tanzania)	2120 women	1:1 randomization to daily oral FTC/TDF or placebo	FTC/TDF: 6% (p=0.8) No statistically significant reduction in HIV incidence	35–38% at a single visit, 26% at two consecutive visits	Trial investigators assessed use of PrEP as too low to evaluate efficacy.	14
VOICE (South Africa, Uganda, Zimbabwe)	3019 women (plus 2010 women receiving tenofovir or placebo gel)	1:1:1 randomization to daily oral TDF, FTC/TDF, or placebo	TDF: −49% (p=0.07) FTC/TDF: −4% (p>0.2) No statistically significant reduction in HIV incidence	<30% of samples; ~50% of women never had tenofovir detected in any sample	Trial investigators assessed use of PrEP as too low to evaluate efficacy	18
Trials in progress						
Bangkok Tenofovir Study (Thailand)	2413 injection drug users	1:1 randomization to daily oral TDF or placebo	TDF: Results expected 2013.	Not available	Not available	44
IPERGAY (France, Canada)	1900 men who have sex with men	1:1 randomization to FTC/TDF or placebo, used “on demand”	FTC/TDF (intercourse-associated use): Results expected 2016.	Not available	Not available	45

Table 2

Antiretroviral resistance in PrEP trials demonstrating efficacy of PrEP for HIV prevention

	# of HIV seroconverters assigned FTC/TDF or TDF PrEP with HIV resistance		Comparison: # of HIV infections averted in the PrEP trial (# of infections in placebo arm minus # of infections in FTC/TDF PrEP arm)
	Individuals with seronegative acute HIV infection at enrollment	Individuals who acquired HIV after enrollment	
iPrEx	2/2	0/36	28
Partners PrEP	2/8	0/30	74
TDF2	1/1	0/10	16

Footnote: In iPrEx, the 2 subjects with seronegative acute HIV infection at the time of PrEP initiation both developed M184I/V mutations, conferring resistance to FTC. In Partners PrEP, of 8 subjects with seronegative acute HIV infection at the time of PrEP initiation, 2 developed antiretroviral resistance: one K65R substitution (conferring resistance to TDF) and one M184V substitution. In TDF2, 1 subject, also with seronegative acute HIV infection at the time of randomization to the FTC/TDF PrEP arm, developed both the K65R and M184V substitutions.

Table 3

PrEP for HIV prevention: priority questions for implementation

Topic	Questions
Priority populations	In different geographic and economic settings, who should be prioritized for PrEP? How does PrEP interface, and ideally synergize, with other HIV prevention strategies? What are the key messages about PrEP for priority populations, including ways to minimize the potential for stigma related to PrEP?
Delivery	Where is PrEP best delivered – primary care settings, voluntary counseling and testing centers, specialized HIV prevention or care settings, or other settings? Who are appropriate prescribers for PrEP? Who can appropriately monitor PrEP use and safety? What is the appropriate delivery model for adherence and risk behavior counseling coupled to PrEP?
Uptake	Do those who might benefit most from PrEP want to take it? What level of uptake in a population is sufficient to justify the resources needed for PrEP delivery? Can PrEP use be matched to individuals during periods of highest HIV risk – in order to maximize PrEP utility?
Adherence	Who takes PrEP? Do they take it often enough to achieve protection against HIV? Is PrEP adherence high when risk of HIV infection is high? How can PrEP be safely discontinued when HIV risk is low (since PrEP use will be time-limited and not life-long as with ART)?
Sexual behavior	How does PrEP use vary with sexual behavior? If sexual risk-taking increases for persons receiving PrEP, to what degree and with what potential impact will it have on PrEP effectiveness and other related harms (e.g., sexually transmitted infections)? What are the best counseling approaches and behavioral interventions to minimize risk compensation?
Clinical risks	What is the longer-term safety of PrEP use by healthy HIV-uninfected persons, particularly renal and bone safety? Do clinical risks, if present, resolve with PrEP discontinuation? What is the safety of PrEP use for peri-conception risk reduction and through pregnancy and breastfeeding? How frequently should HIV testing be conducted for persons receiving PrEP? What is the risk of antiretroviral resistance for persons who have break-through HIV infection while receiving PrEP, particularly if HIV testing is less frequent than in clinical trials?
Impact	How can the cost-effectiveness of PrEP be maximized when delivered in real-world settings? How should PrEP be prioritized along with other effective HIV prevention strategies?

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2014 July 01.

Table 4

PrEP demonstration projects

Study	Population (N)	Design, product, and follow-up duration	Locations	Timeline
Extensions of PrEP clinical trials, ordered by timing of initiation				
iPrEx Open Label Extension	MSM and transgender women (n=2499)	Open-label daily oral FTC/TDF Follow-up: 72 weeks	Brazil, Ecuador, Peru, South Africa, Thailand, US	Enrollment began: June 2011 Results expected: 2014
Partners PrEP Study (post-placebo phase)	Heterosexual men and women with known HIV infected partners (HIV serodiscordant couples) (N=4747 couples)	Randomized daily oral TDF vs. FTC/TDF (blinded) Follow-up: 12 months	Kenya, Uganda	Enrollment began: July 2011 Results expected: 2013
CDC 494/TDF2 Open Label Extension	Heterosexual men and women (N=1219)	Open-label daily oral FTC/TDF Follow-up: 12 months	Botswana	Enrollment began: February 2013 Results expected: 2014
New populations, ordered by timing of initiation				
US PrEP Demonstration Project (Demo Project)	MSM and transgender women in STD clinic setting (n=500)	Open-label daily oral FTC/TDF Follow-up: 48 weeks	US (San Francisco, Miami)	Enrollment began: September 2012 Results expected: 2014
Partners Demonstration Project	Heterosexual men and women with known HIV infected partners (HIV serodiscordant couples) (N=1000 couples)	Open-label daily oral FTC/TDF, provided as a “bridge” to ART initiation by HIV-infected partners Follow-up: 24 months	Kenya, Uganda	Enrollment began: November 2012 Results expected: 2014/2015
ATN 110 and 113	Young MSM, ages 15–22 (N=300)	Open-label daily oral FTC/TDF Follow-up: 48 weeks	14 US sites	Enrollment began: December 2012 Results expected: Q4 2014
PROUD	Gay men in genito-urinary medicine clinics (N=500)	Open-label immediate vs. deferred daily oral FTC/TDF Follow-up: 2 years	United Kingdom	Enrollment began: November 2012 Results expected: November 2015
CCTG 595	MSM and transgender women (N=400)	Open-label daily oral FTC/TDF, participants randomized to a text messaging adherence intervention or standard of care Follow-up: 48 weeks	US (Long Beach, Los Angeles, San Diego, Torrance)	Enrollment planned: Q1–2 2013 Results expected: 2016
PATH - PrEP	375 MSM and transgender women (N=375)	Open-label daily oral FTC/TDF for high risk individuals; PEP for low/moderate risk individuals Follow-up: 48 weeks	US (Los Angeles)	Enrollment planned: April 2013 Results expected: 2017
HPTN 073	Black MSM (N=225)	Open-label daily oral FTC/TDF Follow-up: 12 months	US (Los Angeles, Washington DC, Chapel Hill)	Enrollment planned: June 2013 Results expected: December 2015
SCOPE	Female sex workers (N=500)	Open-label daily oral FTC/TDF	Kenya	Enrollment planned: June 2013

Study	Population (N)	Design, product, and follow-up duration	Locations	Timeline
		Follow-up: Until April 2014		Results expected: 2014

Table 5

Strengths and weaknesses of adherence measures

Measure	Strengths	Weaknesses
Subjective		
Self-report	• Easy to collect • Inexpensive • Highly specific	• Often overestimates adherence due to social desirability bias and failure to remember missed doses; highly discrepant with objective measures in multiple clinical trials • Unclear which self-reported measures are optimal for measuring PrEP adherence
Objective		
Clinic-based pill counts	• Easy to collect • Relatively inexpensive	• Susceptible to manipulation prior to the clinic visit (i.e. pill dumping)
Unannounced home-based pill counts	• Highly objective measure	• Labor intensive and expensive • May be challenging to conduct due to stigma, logistics • Still susceptible to manipulation, although less than with clinic-based pill counts
Pharmacy refill	• Relatively easy to collect	• Requires close control over pharmacy use and record keeping • Only provides maximal predicted adherence (i.e. not all pills picked up will be used)
Electronic adherence monitoring	• Typically the most accurate adherence measure • Allows for assessment of patterns of use	• Requires adherence to the adherence monitoring device, which may be limited due to factors such as stigma, inconvenience (e.g., while traveling) • Subject to misclassification (e.g., removal of multiple pills at a single bottle opening) • Expensive • Potential for technical challenges
Drug levels	• Highly sensitive to detecting drug use • Reflects actual ingestion of drug • PrEP detection correlates with HIV protection	• Impractical in many settings (no commercial assay, not viable currently in low-resourced settings) • Plasma levels susceptible to manipulation in that participants may take medications just before a scheduled blood drawn • Subject to both behavioral (i.e. time of dosing) and biological variation (i.e. pharmacokinetics) • Expensive