Published in final edited form as:

Curr HIV/AIDS Rep. 2011 December ; 8(4): 241–248. doi:10.1007/s11904-011-0094-4.

Promising Prevention Approaches: Tenofovir Gel and Prophylactic use of Antiretroviral Medications

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Abstract

Thirty years into the global HIV epidemic, the need for effective prevention strategies remains critical. In July 2010, the CAPRISA-004 study demonstrated that topical administration of a gel containing the antiretroviral agent tenofovir decreased the risk of HIV acquisition among at-risk heterosexual women. Subsequently, the iPrEx study reported that prophylactic use of a daily oral tablet containing tenofovir and emtricitabine reduced the risk of HIV acquisition among high-risk men who have sex with men. These studies illustrate the promise of antiretroviral pre-exposure chemoprophylaxis (PrEP) as an innovative prevention approach. This review discusses the rationale for chemoprophylaxis, compares the advantages of topical and oral delivery, outlines recommended safety monitoring, offers principles to guide selection of antiretroviral agents, and highlights potential unintended consequences of PrEP use. If future studies confirm the safety and efficacy of tenofovir gel and oral PrEP, successful implementation of these strategies could significantly impact the HIV epidemic.

Keywords

HIV; Primary Prevention; Chemoprevention; Anti-HIV Agents; Reverse Transcriptase Inhibitors; Gels; HIV infections/prevention & control; Clinical Trial; Unsafe Sex

Introduction

As the global incidence of HIV infection remains high with 2.6 million new infections annually,[1] effective HIV prevention strategies are needed urgently.[2] In July 2010, the CAPRISA-004 (Centre for the AIDS Programme of Research in South Africa) trial established that antiretroviral pre-exposure chemoprophylaxis (PrEP) with intravaginal tenofovir (TDF) gel could reduce the risk of HIV acquisition among at-risk African women, the first study to demonstrate the efficacy of topical PrEP in humans.[3] Four months later, the iPrEx (Pre-Exposure Prophylaxis Initiative) study established that oral PrEP with a once-daily, fixed-dose combination of tenofovir and emtricitabine (FTC-TDF) could decrease the risk of HIV acquisition among high-risk men who have sex with men (MSM).[4] These groundbreaking studies highlight the promise of PrEP in curbing the spread of HIV, and

they have energized the field of HIV prevention. As with other biomedical prevention strategies, early successes in clinical trials have generated important questions about how to implement PrEP in clinical settings to maximize public health benefits while minimizing potential unintended consequences. For PrEP, clinicians will need to identify persons who are most likely to benefit from PrEP, prescribe an appropriate antiretroviral agent, monitor for potential toxicities and HIV acquisition, and deliver counseling to support adherence and discourage increased HIV risk behaviors. This article discusses the rationale for PrEP, reviews recent and ongoing studies of topical and oral PrEP, and outlines critical implementation issues to provide practicing clinicians with an overview of this emerging field of HIV prevention.

Rationale for the Prophylactic Use of Antiretrovirals

The rationale for PrEP derives from clinical experience with antiretrovirals as post-exposure prophylaxis (PEP) as well as animal models of PrEP. In a retrospective case-control study, administration of the antiretroviral medication zidovudine (AZT) for at least 4 weeks was associated with an 81% decreased risk of HIV acquisition among healthcare workers with occupational exposure to HIV, compared to those who did not take PEP.[5] An observational study in Brazil found that PEP use was associated with a decreased risk of HIV acquisition among MSM,[6] suggesting that PEP could also offer protection after non-occupational exposure to HIV. In a non-human primate model of retroviral challenge, administration of antiretrovirals before rectal exposure offered greater protection than PEP alone, illustrating the importance of blocking viral replication in the mucosa before integration into the host genome.[7] The first randomized controlled trial to test the safety of oral PrEP in humans compared daily oral tenofovir to placebo in 936 at-risk West African women and found PrEP to be safe and well-tolerated compared to placebo.[8] Studies of tenofovir gel have also demonstrated that it is safe and well-tolerated when applied vaginally, [9–11] paving the way for efficacy trials with topical and oral PrEP.

Topical versus Oral Delivery of Antiretroviral Chemoprophylaxis

Topical and oral delivery of prophylactic antiretrovirals both offer potential strengths and limitations (Table 1). Local application of topical PrEP to genital mucosa may provide high antiretroviral concentrations while limiting systemic drug exposure. In healthy women, intravaginal tenofovir gel provides genital tissue concentrations of active drug that are 100 times greater than those found with oral tenofovir, while serum concentration are considerably lower with the gel.[10] Topical PrEP would presumably be associated with a higher degree of adherence compared to daily oral PrEP, as the gel could be applied on an intermittent basis. However, a substantial proportion of women in CAPRISA-004 exhibited suboptimal adherence to pericoital tenofovir gel use based on objective measures (i.e., return of used and unused gel applicators at study visits), suggesting that intermittent dosing of topical PrEP may also be associated with adherence barriers.

In contrast to topical PrEP, daily oral PrEP could provide a continuous barrier to HIV acquisition, which may be beneficial for those who are exposed to HIV on a frequent basis, such as sex workers. Oral delivery would also be more suitable for HIV exposure in the context of injection drug use, as high drug levels in plasma would be advantageous with this route of exposure. A study of PrEP with daily oral tenofovir among injection drug users in Thailand is underway.[12]

For clinicians, the decision to recommend topical versus oral PrEP will need to be individualized in light of the safety, efficacy, and acceptability of each method of delivery in particular populations. Patient preference among delivery routes may vary by culture; in a study where African and American women used intravaginal tenofovir gel and oral tenofovir

in succession, African women preferred the gel, citing enhanced sexual pleasure, whereas American women preferred oral medication.[10] The ongoing VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial will provide a direct comparison of the relative safety, efficacy, and acceptability of oral and topical PrEP among at-risk African women. In this study, participants receive once-daily oral PrEP (with either tenofovir or FTC-TDF), once-daily tenofovir gel, or placebo (either oral or topical gel).[12]

Currently, the only PrEP agents available for prescribing in clinical practice are oral tenofovir and FTC-TDF, though neither has been approved by the U.S. Food and Drug Administration (FDA) for a prevention indication at this time. Tenofovir gel is not yet commercially manufactured or available in clinical practice, and its path to licensure by the FDA is likely to depend on the results of additional studies to confirm its efficacy.[13] Tenofovir gel designed for vaginal use is not well-tolerated with rectal use.[14] New formulations designed for rectal use are undergoing safety studies in the U.S., which could expand the repertoire of agents for use among MSM and others who engage in anal intercourse.

Efficacy and Safety of Tenofovir Gel and Oral PrEP

The CAPRISA-004 study represents the only available efficacy data for tenofovir gel in humans. In this study of young South African women, those who were randomized to pericoital use of intravaginal 1% tenofovir gel had a 39% decreased incidence of HIV acquisition compared to those randomized to placebo, after 30 months of follow-up.[3] The multinational iPrEx trial was the first study to report efficacy data for oral PrEP. In iPrEx, daily oral PrEP with FTC-TDF was associated with a 44% reduction in the risk of HIV acquisition among high-risk MSM and transgender women.[4] More recently, in July 2011, two additional studies reported preliminary results that support the efficacy of oral PrEP in heterosexual populations. The Partners PrEP study compared the use of daily oral tenofovir, FTC-TDF, or placebo by the HIV-uninfected partner in serodiscordant, heterosexual African couples in which the HIV-infected partner was not medically eligible for antiretroviral therapy. This study demonstrated that tenofovir and FTC-TDF decreased the risk of HIV acquisition compared to placebo by 62% and 73%, respectively, in uninfected partners.[15] In the TDF2 study, administration of daily oral FTC-TDF to young, sexually active heterosexual men and women in Botswana reduced the risk of HIV acquisition by 63% compared to placebo.[16]

These well-designed, randomized controlled trials provide strong evidence that both topical and oral PrEP can protect against HIV acquisition in specific at-risk populations. However, caution is warranted when extrapolating results from these studies into new populations. In April, 2011, a study comparing daily oral FTC-TDF to placebo in 2000 at-risk heterosexual women in Africa (FEM-PrEP) reported equal numbers of new HIV infections in women randomized to FTC-TDF and placebo.[17] FEM-PrEP investigators have proposed that the absence of demonstrable efficacy may have been due to suboptimal adherence, a lack of biologic efficacy of daily oral FTC-TDF in women, or other unknown causes. Self-reported adherence was over 90% among trial participants, but objective measures of adherence, including pill counts and the presence of drug in blood samples, have yet to be reported and may shed light on study findings.[17] Importantly, the Partners PrEP study found that oral tenofovir and FTC-TDF were effective in both men and women, and TDF2 reported a trend towards the efficacy of FTC-TDF in women,[15, 16] offering evidence that oral PrEP can be biologically efficacious in at least some populations of women. The VOICE study is testing the efficacy of daily oral FTC-TDF in young African women, and it will likely offer pivotal additional information about the potential for this regimen to protect at-risk heterosexual women. Results from VOICE are expected in 2012.[12]

In terms of safety, in CAPRISA-004, use of tenofovir gel was well-tolerated, though women randomized to tenofovir gel experienced slightly more diarrhea and gastrointestinal symptoms than those randomized to placebo.[3] In iPrEx, serious adverse events were rare and not different among participants randomized to FTC-TDF or placebo. However, compared to MSM assigned to placebo, those randomized to FTC-TDF experienced increased rates of nausea (9% versus 5%) and unintentional weight loss during the first month of the study, though these symptoms tended to resolve. As tenofovir has been associated with renal injury in HIV-infected patients,[18–21] it is important to note that iPrEx participants randomized to FTC-TDF had a trend towards increased creatinine (2% versus 1%; $p=0.08$) compared to those assigned to placebo. Importantly, renal function generally normalized after discontinuation of study drug, and all except one participant was able to safely resume FTC-TDF.[4] These results suggest that renal dysfunction due to FTC-TDF administration is rare and transient, though careful monitoring of renal function is recommended.

Tenofovir has also been associated with loss of bone mineral density in patients with HIV-infection.[22] Rates of bone fracture were no different among participants assigned to receive tenofovir-containing PrEP regimens or placebo in CAPRISA-004 and iPrEx.[3, 4] However, a substudy within iPrEx and a separate trial of daily oral tenofovir both reported that MSM randomized to use PrEP experienced small but statistically significant decreases in bone mineral density (BMD) of 1% or less compared to placebo.[4, 23] Future studies will be needed to assess the clinical consequences of these changes. Given these potential adverse effects with antiretroviral chemoprophylaxis, clinicians who prescribe PrEP will need to monitor patients for toxicities.

Laboratory and Clinical Monitoring

Based on results of iPrEx, the U.S. Centers for Disease Control (CDC) has issued interim guidance for the use of daily oral PrEP with FTC-TDF in high-risk MSM.[24] Before initiating PrEP, MSM should have a negative HIV antibody test to confirm absence of HIV infection. If clinical suspicion for acute retroviral syndrome exists, HIV RNA testing to identify patients in the “window period” of seroconversion should also be performed to prevent inappropriate initiation of antiretrovirals for presumed prophylaxis. Avoiding inadvertent PrEP administration during acute HIV infection deserves particular emphasis, as periods of high-level viremia that often accompany recent infection could pose a heightened risk of developing viral resistance to FTC-TDF. In iPrEx, 2 participants randomized to FTC-TDF tested negative for HIV antibodies at study entry but were later confirmed to have been HIV-infected at that time, and both developed resistance to FTC.[4] though detection of resistant variants waned over time.[25]

To minimize the risk of potential toxicities from FTC-TDF, and to provide comprehensive sexual healthcare for MSM, confirmation of normal renal function (i.e., estimated creatinine clearance ≥ 60 ml/minute), screening and vaccination (if found to be susceptible) against HBV, and screening and treatment of sexually transmitted infections are advised before initiating PrEP. Both tenofovir and emtricitabine are active against hepatitis B virus (HBV), and hepatic inflammation can occur among persons who are chronically infected with HBV and discontinue therapy with these agents. In iPrEx and in a study of daily oral tenofovir among women living in West Africa, where HBV is endemic, increases in hepatic enzymes were not different among participants randomized to tenofovir and placebo.[4, 8] Though these results offer reassuring evidence that tenofovir and emtricitabine may be used safely as chemoprophylaxis in persons with HBV infection, vigilance for hepatic inflammation that could represent uncontrolled HBV replication is warranted when stopping these agents in those infected with HBV.

Clinicians should consider close follow up with MSM for several weeks after starting FTC-TDF to provide reassurance that any nausea they may experience is generally self-limited. CDC recommends additional renal function testing 3 months after starting PrEP and then annually, and HIV antibody testing every 2–3 months.[24] If HIV acquisition occurs, PrEP agents should be discontinued immediately to minimize the risk of developing viral drug resistance. Genotype analysis can help monitor for the presence of viral mutations that confer drug resistance, and baseline genotype testing should be performed for all persons who acquire HIV during PrEP use, though resource-constraints may limit the availability of resistance tests in some settings. In CAPRISA-004, no drug resistance was detected among 35 women who were assigned to use tenofovir gel but acquired HIV.[3] Similarly, no drug resistance was detected with highly sensitive (i.e., deep sequencing) assays in any participant who acquired HIV in the FTC-TDF arm of iPrEx, though antiretroviral drug levels sufficient to promote viral resistance may have been absent in many of those who became infected, presumably due to poor adherence.[4, 25]

Optimal Antiretroviral Agents for Chemoprophylaxis

Tenofovir, a nucleotide reverse transcriptase inhibitor (NRTI), possesses several characteristics that are desirable for chemoprophylaxis. When taken orally, tenofovir is rapidly absorbed and provides sustained concentrations in serum and genital tissues and secretions. [26] The long intracellular half-life of tenofovir would be advantageous for intermittent PrEP regimens, which could minimize cost and overall drug exposure, and studies to test this approach are underway in Africa and in development in Thailand.[12, 27] The genetic barrier to resistance is relatively high for tenofovir compared to other antiretrovirals. As discussed previously, none of the participants who used tenofovir topically in CAPRISA-004 or as oral FTC-TDF in iPrEx developed detectable drug resistance after HIV acquisition, though low drug levels secondary to suboptimal adherence may have limited the potential for drug resistance to evolve.[3, 4, 25]

Tenofovir has been reported to cause acute or chronic renal dysfunction and altered bone metabolism in some HIV-infected persons. [18–22] Daily oral PrEP with FTC-TDF was associated with a trend towards elevated creatinine and a small but measurable decrease in BMD in iPrEx.[4] Tenofovir is a component of most PrEP regimens that are currently being evaluated in human trials, so more data on potential adverse effects associated with its use are likely to be forthcoming.[12]

The NRTIs emtricitabine and lamivudine are well-tolerated and also achieve high concentrations in the genital compartment.[26, 28] Although these NRTIs exhibit a low genetic barrier to resistance, development of resistance to these agents confers decreased viral fitness [29] and increased susceptibility to tenofovir and zidovudine. Maraviroc, a chemokine receptor type 5 (CCR5) inhibitor, concentrates rapidly in genital tissues after a single oral dose, [30] and studies are in development to evaluate its safety and tolerability as a PrEP agent.[27] Dapivirine and UC781, non-nucleoside reverse transcriptase inhibitors (NNRTI), deliver high, sustained local concentrations with limited systemic absorption when administered via intravaginal rings or gels, illustrating that novel medications without an established role in antiretroviral therapy may show promise as prophylactic agents.[31, 32] Protease inhibitors are less attractive for PrEP, as they do not concentrate well in genital tissues.[33] Nevirapine and abacavir can cause severe hypersensitivity reactions in persons who are HIV-uninfected[34] or have particular human leukocyte antigen (HLA) polymorphisms,[35] and should therefore be avoided for chemoprophylaxis.

By selecting antiretrovirals that offer high levels of protection from HIV acquisition and acceptable adverse effect profiles, clinicians can maximize the efficacy and safety of PrEP.

Yet the overall effectiveness of PrEP in clinical practice will also depend on the ability of providers to counsel patients to optimize adherence and avoid increases in high risk behaviors with its use.

Behavioral Aspects of PrEP Use: Adherence and Risk Compensation

The efficacy PrEP is tightly linked to adherence. In CAPRISA-004, use of tenofovir gel before and after $\geq 80\%$ of sex acts conferred a 54% decreased risk of HIV acquisition compared to placebo, whereas use of gel around $\leq 50\%$ of coital events was only 28% effective. Notably, overall adherence was suboptimal, with only 38% of women adhering to gel use for $\geq 80\%$ of sex acts by objective measures (i.e. comparing numbers of used and unused gel applicators) despite high levels of self-reported adherence.[3]

Similar to CAPRISA-004, objective measures of adherence in iPrEx, including pharmacy refill records and pill counts, suggest that actual adherence levels were considerably lower than those reported by study participants.[36] In a nested case-control study within iPrEx, tenofovir and emtricitabine were rarely detectable in plasma and peripheral blood mononuclear cells among MSM who acquired HIV during the study. In contrast, half of the cases who remained uninfected had measureable drug levels,[4] offering strong evidence that the prophylactic effect of oral FTC-TDF was dependent upon adherence. Adherence was suboptimal despite intensive monthly counseling in both studies and, in CAPRISA-004, motivational interviewing and customized adherence support based on individual patterns of missed doses.[3] Therefore, successful implementation of PrEP in clinical settings will require creative approaches to support providers in the delivery of adherence counseling within real-world time and resource constraints.

Numerous potential behavioral interventions to enhance PrEP adherence have been proposed, such as cognitive-behavioral techniques (counseling, motivational interviewing), behavioral strategies (use of pill boxes), and social support (e.g., from relationship partners in serodiscordant couples).[37] Innovative strategies involving wireless technology and the internet to monitor and support adherence may also show promise in resource-rich settings. Further studies will be needed to identify the adherence support strategies that are most feasible and effective for specific populations.

Counseling against risk compensation, whereby PrEP consumers increase risky behaviors under the false assumption that antiretrovirals provide complete protection against HIV acquisition, will be critical to realize the protective benefits of chemoprophylaxis. No completed PrEP studies have observed evidence of risk compensation; participants in CAPRISA-004, iPrEx and a study of daily oral tenofovir as PrEP in West African women reported stable or decreased sexual risk behaviors over the course of study follow up.[3, 4, 38] However, the enhanced intensity of counseling around safe sex practices that was delivered in these studies may be challenging to replicate in many clinical settings,[38] and further studies of risk-taking by PrEP consumers who receive standard counseling will be important. Studies suggest that a potentially significant minority of MSM may increase risky sexual behaviors with PrEP use. Before the release of PrEP efficacy data, 35% of MSM in New York City anticipated that they might decrease condom use with PrEP.[39] After iPrEx, fewer than 20% of MSM sampled from a popular online sexual network reported that they would possibly increase their frequency of unprotected anal intercourse with PrEP use. [40] Until more is known about changes in risk behaviors with chemoprophylaxis, providers should counsel intensively on the importance of condoms and other established prevention methods as essential adjuncts to PrEP use.

Acknowledging the time and resource constraints that could impede rigorous counseling by providers raises other fundamental questions around possible barriers to PrEP

implementation in clinical settings: which types of providers will prescribe chemoprophylaxis, and what funding mechanisms exist to support this strategy?

Who will Provide PrEP in Clinical Settings...and Who Will Pay for it?

Translating clinical trial efficacy into public health benefits will require the engagement of primary care providers who have contact with at-risk individuals. Clinicians who specialize in the care of patients living with HIV infection would presumably be comfortable with the technical aspects of prescribing antiretroviral medications to HIV-uninfected persons. However, HIV clinics in the U.S. are grappling with workforce shortages and inadequate reimbursement,[41] and they are unlikely to be able to accommodate large numbers of potential PrEP consumers. Therefore, it will be essential to train generalist primary care providers to provide PrEP. As intense time constraints compel primary care physicians to prioritize among prevention tasks,[42] innovative ways to deliver PrEP efficiently in clinical settings, such as through task sharing between physicians and clinical officers, could facilitate implementation.

The cost of providing oral PrEP to one individual in the U.S. is estimated to be approximately \$10,000 annually,[43] which is likely to be prohibitive to many individuals who may benefit from PrEP. Modeling simulations suggest that PrEP could be cost-effective among high-risk MSM in the U.S.[43, 44] and among heterosexual women in South Africa, [45] if shown to be efficacious in the latter population. According to CDC officials, at least one third party insurer, a health maintenance organization in California, may cover the expenses associated with PrEP for its members,[12] but it is not yet known if other insurance companies, public insurers (i.e., Medicare and Medicaid), or other federal programs will provide resources to support PrEP provision. The cost of tenofovir gel for clinical use has not yet been determined. However, the expense of manufacturing each dose for CAPRISA-004 was \$0.32, with \$0.30 of the cost attributed to the gel applicators and packaging,[46] suggesting that low-cost production of the gel may ultimately be possible.

If funds can be generated for PrEP provision, clinicians will need to identify those individuals who are most likely to benefit from PrEP use.

Identification of Individuals who are Most Likely to Benefit from PrEP Use

The net benefit of PrEP use for individuals is likely to depend on their risk of HIV acquisition and any medical or psychosocial comorbidities that could complicate safe and effective use of antiretroviral medications. To assess HIV risk, primary care providers and potential PrEP consumers will need to discuss high risk behaviors, though such discussions are infrequent[47] due to suboptimal patient-provider communication.[48] Even if discussions around HIV risk occur, methods to gauge risk are likely to be imperfect.[49] Providers and patients may not always agree on a final estimate of risk, and they may perceive different thresholds of risk that warrant chemoprophylaxis. Therefore, a determination of whether PrEP is appropriate for individuals will ultimately require a shared decision between those individuals and their providers. Given the central role of patient-provider communication in identifying potential PrEP consumers and formulating decisions around its use, designing and testing interventions to enhance communication in the context of PrEP should be prioritized.

Conclusion

Evidence from CAPRISA-004, iPrEx, and several other recently reported studies demonstrate that tenofovir gel and prophylactic uses of oral antiretroviral medications can reduce the risk of HIV acquisition in at-risk individuals.[3, 4] As chemoprophylaxis may not

offer complete protection against HIV acquisition for all at-risk persons, it is likely to be employed as part of a “combination” approach to HIV prevention that capitalizes on the synergies of multiple behavioral and biomedical prevention strategies to reduce the spread of HIV.[50] In addition to condom use and PrEP, these may include male circumcision,[51] prevention of mother to child transmission,[52] and universal treatment of HIV-infected persons with antiretroviral therapy to reduce infectiousness, [53, 54] which was recently found to reduce the risk of transmission between serodiscordant heterosexual couples by 96%.[55] If current and future studies confirm the safety and efficacy of topical and oral chemoprophylaxis, in conjunction with other evidence-based prevention interventions, they offer promising new approaches to arrest the HIV epidemic.

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Table 1

Results from efficacy studies of tenofovir gel and oral antiretroviral pre-exposure prophylaxis, and potential advantages and drawbacks of each method of delivery.

	Tenofovir Gel	Oral Pre-Exposure Prophylaxis
Efficacy studies	<ul style="list-style-type: none"> CAPRISA-004 (South Africa): 39% relative risk reduction among at-risk heterosexual women* 	<ul style="list-style-type: none"> iPrEx (multinational): 44% (FTC-TDF) relative risk reduction among at-risk MSM and transgender women* Partners PrEP (Africa): 62% (tenofovir) and 73% (FTC-TDF) relative risk reduction among HIV-uninfected partners in serodiscordant heterosexual couples* TDF2 (Botswana): 63% (FTC-TDF) relative risk reduction among sexually active, heterosexual males and females* FEM-PrEP (Africa): unable to demonstrate efficacy of FTC-TDF among at-risk heterosexual women*
Advantages	<ul style="list-style-type: none"> High local concentrations in genital tissues and secretions Limited systemic absorption Can be dosed intermittently Lubricants are already used during sex Potential to enhance sexual pleasure Individuals may prefer topical agents to pills 	<ul style="list-style-type: none"> Daily use could provide continuous barrier to HIV acquisition May be used without partner knowledge (e.g., for those who are unable to negotiate the use of protection) Individuals may prefer pills to topical agents Currently available for prescribing in clinical practice
Drawbacks	<ul style="list-style-type: none"> Efficacy data support use in heterosexual women only (as of June 2011) Does not provide continuous protection when used intermittently (i.e., pericoital dosing) Not currently available for prescribing in clinical practice In CAPRISA-004, associated with*: <ul style="list-style-type: none"> Increased diarrhea and gastrointestinal infections 	<ul style="list-style-type: none"> Requires daily use Conflicting data regarding efficacy in heterosexual women (as of August 2011) In iPrEx, associated with*: <ul style="list-style-type: none"> Small but significant decrease in bone mineral density observed in iPrEx Trend towards transient elevation in creatinine Increased rate of nausea and unintentional weight loss during first few weeks of use; generally self-limited

* Compared to placebo.

MSM = men who have sex with men.