Published in final edited form as:

Expert Opin Pharmacother. 2013 September ; 14(13): 1777–1785. doi:10.1517/14656566.2013.812072.

Pre-exposure Prophylaxis (PrEP) for HIV Infection: How Antiretroviral Pharmacology helps to Monitor and Improve Adherence

Jill Blumenthal and

HIV Research Fellow, University of California, San Diego, Antiviral Research Center, 220 Dickinson Street, Suite A, San Diego, CA 92103, Phone (619) 471-3913, Fax (619) 543-5094

Richard Haubrich

Professor of Medicine, University of California, San Diego, Antiviral Research Center, 220 Dickinson Street, Suite A, San Diego, CA 92103

Jill Blumenthal: jblumenthal@ucsd.edu; Richard Haubrich: rhaubrich@ucsd.edu

Abstract

Pre-exposure prophylaxis (PrEP) with antiretroviral drugs is a novel biomedical intervention that can prevent HIV transmission among high-risk populations. As findings from multiple PrEP studies have suggested that adherence is vital to achieve the full prevention benefits of PrEP, it is important to understand the clinical pharmacology and pharmacokinetic (PK) properties of PrEP antiretrovirals, the association of PK and PrEP efficacy and the potential for drug concentration measurement to be used as a tool to monitor PrEP adherence. In this review, we examine studies related to PrEP adherence with attention to the clinical pharmacology and pharmacokinetics of current and novel PrEP agents. Studies of animal models, pharmacokinetics and clinical trials related to PrEP and adherence were reviewed. In summary, when combined as part of a comprehensive prevention strategy that includes use of condoms and risk reduction counseling, PrEP has tremendous promise as a adjunctive biomedical HIV prevention intervention, providing that adherence is maintained.

Keywords

Pre-exposure prophylaxis; adherence; pharmacology; pharmacokinetics

I. Introduction

Given the failure of the most promising HIV vaccine candidates, most experts agree that combination prevention strategies will be needed to control the HIV epidemic. In addition to encouraging early and effective therapy for those already diagnosed with HIV infection--to interrupt transmission to others as well as for the benefit of reducing HIV disease progression--newer strategies have focused on the use of antiretroviral agents in high-risk, HIV-uninfected populations. Because of the improved tolerability, ease of administration and efficacy of newer agents, several recent clinical trials have evaluated single and dual antiretroviral agents for pre-exposure prophylaxis (PrEP). These studies confirmed the findings in animal models that PrEP, when used correctly, can prevent HIV-infection in high-risk populations.

On July 16, 2012, the Food and Drug Administration (FDA) approved a once daily fixed dose combination of emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) to reduce the risk of HIV infection in uninfected individuals who are at high risk of HIV infection and

who may engage in sexual activity with HIV-infected partners.¹ Several randomized controlled trials (RCTs) of FTC/TDF for PrEP have shown a statistically significant reduction in HIV acquisition among at-risk individuals.^{2–5} However, not all studies support the use of PrEP; in two studies, there was no reduction in the risk of HIV transmission in high-risk heterosexual women.^{6,7} In both of these studies, inadequate adherence to PrEP medication reduced potential benefit of PrEP and undermined the trials' ability to determine the efficacy. In fact, data from all the PrEP studies suggest that maintaining adherence to the drug is critical to realize the full prevention benefits of PrEP. In this paper, we will review studies related to PrEP adherence with a focus on defining how the clinical pharmacology of oral PrEP can be used to understand efficacy and as a potential adherence measurement.

II. Pharmacology of TDF and FTC

Both TDF and FTC are nucleos(t)ide analogue reverse transcriptase inhibitors (NRTIs) which must be taken up into cells and sequentially phosphorylated in the cell to the pharmacologically active diphosphate (DP) and triphosphate (TP) anabolites. Thus, the clinical pharmacology of TDF and FTC is dependent on their intracellular half-life.^{8,9} The longer intracellular NRTI anabolite half-life enables less frequent dosing; the strategy of NRTI dosing based on the intracellular half-life has been confirmed by many clinical studies.^{10–12} The half-lives of intracellular tenofovir-DP (~150h) and emtricitabine-TP (~39h) are the longest for the NRTI class, a potentially favorable pharmacological characteristic for PrEP from an adherence perspective.^{9,13} However, these long half-lives could be harmful in terms of clinical toxicities and drug and food interactions.

Animal models of simian immunodeficiency (SIV), HIV or SHIV (SIV/HIV chimera) transmission have shown valuable proof-of-concept information regarding the prophylactic efficacy of oral and topical PrEP with ARV drugs through varying routes of mucosal exposure. In one study, a model of rectal infection to assess the efficacy of TDF, FTC or FTC/TDF at equivalent human exposure found that FTC/TDF was more protective compared to either TDF or FTC alone.¹⁴ Other animal models have been used to explore the efficacy of intermittent oral dosing with TDF or FTC/TDF. Studies in macaques showed protection from oral or rectal SIV/SHIV exposures by a two-dose subcutaneous regimen of TFV or TFV/FTC.^{14,15}

Understanding the distribution and persistence of virus, introduced during an HIV exposure, can help to ensure that ARV agents used for PrEP are available at the site of infection for adequate time to prevent infection. Two studies used simulations of rectal and vaginal sex acts and a virus surrogate to model the distribution of cell-free and cell-associated HIV that would be present in the colon and vagina following sex. The investigators found that rectally dosed HIV surrogates concentrated in the recto-sigmoid colon and vaginally dosed HIV surrogates concentrated in the peri-cervical area, and both were usually cleared within 24 hours.^{16,17} These studies suggest that optimal PrEP medications deliver HIV-inhibiting ARV concentrations to the peri-cervical region or into the recto-sigmoid prior to and for at least 24 hours after sex.

Mucosal tissue distribution after PrEP delivery has been examined to determine drug concentrations in relevant anatomic compartments. In Microbicide Trials Network (MTN)-001, a randomized cross-over trial in which African and US high-risk women received daily oral TDF, TFV vaginal gel, or both; several important findings emerged. There was 60-fold greater serum TFV concentrations after oral dosing compared with vaginal dosing and greater than 130-fold higher vaginal tissue TFV-DP (the intracellular active form of the drug) concentrations with vaginal compared to oral dosing.¹⁸

In the CAPRISA 004 trial, which tested tenofovir gel in heterosexual women, the HIV incidence rate in women with tenofovir cervicovaginal concentrations greater than 1000 ng/mL was significantly lower than the HIV incidence in the placebo group.² Active treated subjects with cervicovaginal concentrations less than 1000 ng/mL had HIV incidence rates close to that in the placebo group. These tissue (i.e., cervicovaginal) tenofovir concentrations may reflect drug exposure at the actual time of HIV exposure; however, other non-measured confounders between these three groups of women might have accounted for some of the variations in HIV risk. Nevertheless, these data suggest that cervicovaginal fluid concentrations of tenofovir greater than 1000 ng/mL were required to prevent HIV infection. The cervicovaginal concentration of 1000 ng/mL is more than ten times the concentration seen with oral tenofovir disoproxil fumarate and emtricitabine.¹⁹

Similar to vaginal dosing, in the Rectal Microbicide Program-02/MTN-006 which compared a single oral TDF dose to a rectal TFV gel dose, plasma TFV concentrations were 23-fold greater after oral compared to rectal dosing, and tissue TFV-DP concentrations were 10-fold greater after rectal compared to oral dosing.²⁰ In a single dose oral TDF-FTC study of 6 men and 6 women with 2 weeks of post-dose sampling, rectal biopsy homogenates in men showed TFV-DP concentrations more than 100 times greater than TFV-DP in vaginal homogenates in women twenty-four hours after dosing. Interestingly, FTC-TP was 10-fold greater in vaginal tissue compared with rectal tissue but was not detectable in either after 2 days. Although the significance of this difference is unknown, these findings suggest that different PrEP agents may be more effective for different HIV routes of exposure.²¹ Taken together, these studies highlight the differences in plasma, lumen and tissue concentrations of antiretroviral agents and that these concentrations are dependent upon patient sex, drug used and method of delivery. All of these factors need to be considered when selecting PrEP agents for clinical use and assessed when interpreting the results of randomized clinical trials. However, these studies should be interpreted cautiously as definitive association of tissue concentrations with efficacy of PrEP has not been demonstrated.

III. Pharmacokinetic Considerations

In addition to the value of drug concentrations and pharmacokinetics (PK) to the selection of ARV for PrEP and in the design of PrEP efficacy studies, drug concentration measures and PK can be useful for interpreting the results of studies and as surrogate measures of patient adherence to therapy. Characterization of the PK of FTC, TDF and their triphosphate anabolites in plasma, red blood cells (RBCs) and peripheral blood mononuclear cells (PBMCs) is essential to developing informative pharmacologic adherence metrics. In general, long half-life drugs are viewed favorably as they may offer “pharmacokinetic forgiveness” during times of suboptimal adherence and may be less impacted by drug-drug or drug-food interactions. This idea of “pharmacokinetic forgiveness” is most important once concentrations are at steady state, which is reached in approximately 4 half-lives of continuous dosing.²²

The key element in being able to accept a pharmacologic metric as a surrogate for patient adherence to medication is to establish a relationship between measured drug concentration and response to therapy. In the case of PrEP studies, a concentration-prevention association must be established. PK data from several oral PrEP RCTs offer evidence of concentration-response. In the Pre-exposure Prophylaxis Initiative (iPrEx) study, the detection of any of TVF and FTC in blood plasma and PBMCs was associated with 92% relative risk reduction in HIV transmission compared to 44% reduction in transmission for all participants randomized to the drug.³ Thus, in the sub-group of subjects with presumed better PrEP adherence based on detection of drug in their specimens, the benefit of PrEP was increased from 44% to 92%. Relatively sparse PK sampling showed clear demonstration of

concentration-response in the Partners PrEP trial with a small increase in relative risk reduction in both TDF and TDF/FTC arms from 67 to 86% and 75 to 90%, respectively, in the overall cohort compared to subjects who had detectable TFV levels.⁴ In the CDC TDF2 study, TVF and FTC were more commonly detected in nonseroconverters (~80%) compared with seroconverters (50%) for both drugs.⁵

From these oral PrEP RCTs, the TFV plasma concentrations were different not only among subjects but also among studies. TFV concentration data contain significant heterogeneity due in part to variability between individuals which is further increased by variation in the timing of the previous dose of medication relative to the time of concentration measurement. In addition, the confidence intervals of relative risk reduction are also quite large in some studies due to few seroconversions or small sample size. However, the variation seen in concentrations among RTCs goes beyond the variability that would be expected if due solely to either inter-individual variability or prescribed daily dosing time in the day prior to blood testing.

Not all studies that use oral TDF or TDF/FTC have demonstrated protection against HIV compared to placebo controls. While reduction in HIV transmission was seen in the iPrEX, Partners' PrEP and TDF2 trials, no reduction in transmission was found in FEM-PrEP and Vaginal and Oral Interventions to Control the Epidemic (VOICE) studies. Similarly, the use of tenofovir gel for topical protection against HIV transmission was effective in Centre for AIDS Programme of Research in South Africa (CAPRISA) 004 when used peri-coitally but not in VOICE study when it was used daily.¹⁹ A potential unifying mechanism underlying the lack of efficacy in the studies which failed to show benefit is poor adherence to administered treatment. Further, it is the objective measures, i.e., measured drug concentrations, and not self-reported adherence measures that highlighted the lack of benefit. For example, in each treatment arm in VOICE, participants reported ~90% medication adherence, with product-return data suggesting similarly high levels of adherence. Plasma TFV levels, however, were detectable in 30% or fewer women in all three arms that were given active drug.⁷ Together, these findings not only underscore the importance of adherence to achieve adequate drug levels but the difficulty with which it is to accurately measure adherence, an integral monitoring strategy for effective PrEP implementation.

IV. Selection of Antiretroviral (ARV) Agents for PrEP

FTC and TDF quickly emerged as viable and practical PrEP agents based upon safety and tolerability from studies in HIV-infected subjects, potential cost-effectiveness, penetration into target tissues and expected HIV resistance profile if HIV infection were to occur during PrEP use. In addition, these agents have favorable pharmacological characteristics that allow for once daily and potentially less frequent dosing, few drug interactions and theoretical effectiveness during periods of missed doses.²² The combination of FTC/TDF was the first oral agent to demonstrate clinical efficacy in reducing HIV transmission in randomized, controlled trials. A major drawback of the use of TDF and FTC is their central role in current treatment strategies for HIV-infected patients; if HIV infection were to occur during PrEP exposure with these agents, treatment efficacy of TDF/FTC containing regimens might be reduced due to the development of HIV drug resistance at the time of infection. Thus, antiretroviral drugs that are less commonly used for HIV treatment would have an advantage for use in PrEP.

Additional drugs under consideration for use as PrEP include maraviroc, long-acting rilpivirine and the investigational drugs S/GSK1265744, ibalizumab and dapivirine. Maraviroc, a CCR5 antagonist, has a low rate of adverse events, remains active for several

days and concentrates in vaginal secretions²³ and rectal tissue²⁴. Mutations associated with drug resistance are infrequent during treatment of HIV-infected patients--the main mechanism of viral escape has been emergence of low levels of non-CCR5 containing virus among pre-existing quasispecies within treated patients. As most transmitted virus is CCR5 tropic, this mechanism of resistance is posited to be less problematic for prevention strategies.²⁵ As there is limited clinical data in HIV-uninfected persons, a phase 2 study of maraviroc is currently underway to assess safety and tolerability.

A parenteral, long-acting form of rilpivirine (RPV-LA), a nonnucleoside reverse transcriptase inhibitor (NNRTI), was developed in an effort to improve treatment adherence for HIV-infected patients and for potential use as a PrEP agent. The greatest advantage to this drug for PrEP use is its very long half-life. Preclinical studies in rats and dogs demonstrated effective concentrations of the drug being measured for more than 3 weeks and 3 months, respectively.²⁶ A long half-life and concentration of rilpivirine in tissues was seen in men and women in a phase Ia study of a single 600 mg intramuscular dose of long-acting RPV nanosuspension. RPV persisted for more than 80 days and had a terminal half-life in women of 33 days and 35 days in men. Vaginal fluid and rectal tissue concentrations were higher than matched plasma concentrations in women and men, respectively.²⁷

An early investigational HIV integrase inhibitor, S/GSK1265744, appears to be a promising agent for PrEP. Although safety and efficacy data in HIV-uninfected individuals is currently being analyzed²⁸, S/GSK1265744 has a 30-hour half-life²⁹ and has been formulated as a long-acting parenteral form. This nanosuspension formulation of S/GSK1265744 has a half-life of 21 to 50 days after a single injection in HIV-negative human subjects, suggesting that once monthly or even less frequent dosing may be possible.³⁰ The long acting preparation of GSK1265744, when given to rhesus macaques exposed to Simian-human Immunodeficiency Virus (SHIV), was found to completely prevent infection in test animals from repeated rectal SHIV challenge.³¹

Finally, ibalizumab is an investigational CD4 attachment inhibitor that can be given as weekly or biweekly injections.³² Its novel mechanism of action, initial favorable safety profile and pharmacokinetics favoring infrequent dosing make it a promising PrEP agent. However, lack of data on tissue distribution and the observation of drug resistance when used as monotherapy in HIV-infected individuals warrant further exploration.

Vaginal rings containing ART are a new mode of drug delivery for HIV prevention. Phase III trials are underway of a vaginal ring which slowly releases dapivirine, a potent NNRTI. This ring, which is used monthly, has the potential to give women a convenient, discreet, long-acting method of self-protection against HIV.³³ In a monkey study, an intravaginal ring impregnated with tenofovir (TDF) replaced every 4 weeks completely protected female monkeys from SHIV.³⁴ This study showed for the first time that a ring can deliver enough of the widely used TDF to offer complete protection for monkeys against SHIV.

V. Non-pharmacological Measurements of Adherence

Adherence to prescribed treatment can be difficult to assess. Monitoring adherence to ART continues to be challenging as there is no gold standard and most measures rely on patient self-report. The most objective and accurate measure of adherence is directly observed therapy (DOT). Directly administered antiretroviral therapy (DAART) is a strategy that has been used to improve adherence among HIV-infected individuals; DAART has been shown to be effective in drug users, in methadone clinic attendees and in subject that are incarcerated.³⁵⁻³⁷ However, directly observed therapy is invasive, expensive and time-consuming and may be difficult to implement in a real world setting.

Various self-report adherence questionnaires have been used to assess recent ART adherence including the AIDS Clinical Trials Group four-day recall Instrument³⁸, the Visual Analog Scale (VAS)³⁹, the Likert scale^{40,41} and the Morisky Self-reported Medication Taking Scale (MSMTS).⁴² However, self-reported adherence questionnaires are subjective tools that assume rather than prove the patient's actual medication intake. In addition, self-reported medication adherence is frequently over-reported, and lack of standardization limits the ability to interpret findings across studies.⁴³

Electronic drug monitoring (EDM) devices, which record each time a pill bottle has been opened, were initially praised for their potential to provide a less biased estimate than self-report. However, EDM may underestimate adherence because they can be inconvenient and patients may remove more than one dose at a time, i.e., when a patient uses a multiple day pill container. Other disadvantages that reduce the success and accuracy of EDM include cost, loss of the device and malfunction.⁴⁴

A new adherence approach developed by Proteus Digital Health, Inc. consists of an ingestible indicator (which can be attached to a medication or used in an over-encapsulation) and an on-body wearable sensor which, together, electronically confirm unique medication ingestions and record the date/time of the ingestion. The recorded ingestion events can be synced from the monitor worn by the patient with a paired cell phone and uploaded to a patient management web site. The adherence results can be shared with family and care providers. Results from a feasibility study using an early prototype in active TB patients suggested that the system is able to correctly identify ingestible indicators with high accuracy, poses a low risk to users and may have high patient acceptability.⁴⁵ Some cited concerns about this device include cost and patient privacy.

VI. Pharmacological Measurements of Adherence

One objective way to assess adherence is to measure plasma drug concentrations. Both FTC and TDF concentrations in plasma remain detectable throughout the dosing interval. While many factors contribute to variability in plasma concentrations, completely undetectable plasma concentrations of FTC suggest non-adherence, if the subject is correctly taking a once daily TDF/FTC medication regimen. The reported half-lives for FTC-TP (39 hours)⁴⁶ and TFV-DP (150 hours)⁴⁷ suggest that both should be detectable for 7 to 14 days if dosing is consistent. Thus, undetectable concentrations can be assumed to represent missed doses rather than pharmacokinetic variability.⁴⁸

However, there are several limitations to using blood plasma concentrations as adherence metrics. Most importantly, plasma concentrations only reflect adherence to the most recently ingested doses. If a patient knows they will have a clinic visit the next day, they may 'remember' to take a dose of medication the day prior to the visit and render the concentration detectable during the clinic visit (i.e., the "white coat phenomena"). Hence, plasma sampling represents short-term adherence and can be influenced by patient knowledge of concentration monitoring. Despite this limitation, in clinical trials, multiple random samples of plasma drug concentrations, drawn throughout the study follow-up, have been associated with both self-reported adherence and with study outcomes of HIV RNA suppression in HIV-infected subjects⁴⁹ and transmission in HIV-uninfected subjects²⁻⁵.

Venous sampling itself has many drawbacks including the need for trained personnel and specialized equipment for sample processing. In addition, measuring trough levels is often recommended for drug monitoring which can be difficult with a once daily dosing regimen (e.g., when the subject normally takes medication at night, drawing blood prior to the next dose is logistically challenging). If a qualitative measurement is taken to obviate the need for trough level monitoring, the information that can be obtained is the presence of drug or not,

which is less useful for adherence monitoring than a quantitative measure; however, if undetectable levels are documented, then lapses in adherence can be objectively inferred.

Novel measures are being developed to monitor antiretroviral adherence in both HIV-infected and uninfected populations. The use of dried blood spots (DBS) is an easy way to obtain stable, transportable specimens for drug analysis for the purpose of therapeutic drug monitoring or assessment of medication adherence in a routine clinical setting. DBS can be collected by patients with a finger stick after which blood is collected on filter paper cards.⁵⁰ DBS contain tens of millions of RBC and thus could offer an easy and efficient means to measure TFV, FTC and/or TFV-DP for adherence monitoring.^{51–53} TFV-DP has a long half-life (17 days) in RBC; concentrations remain quantifiable in RBC for at least 30 days after drug discontinuation. Thus, the RBC concentration of TFV-DP is unlikely to be undetectable from a single missed dose and may be a good objective marker of longer term adherence to TDF.

As discussed above, poor adherence to PrEP medications may be largely responsible for decrements in effectiveness of TDF-based PrEP regimens in randomized studies. A sub-study from the iPrEx trial examined plasma and intracellular (cryopreserved peripheral blood mononuclear cells (PBMC)) drug concentrations for association with reduction in HIV transmission. Among subjects in the active TDF-containing PrEP arms, the presence of TFV in plasma samples was lower in cases who acquired HIV than in controls who were exposed but did not acquire HIV, suggesting that infected subjects were less adherent to TDF regimens than those who were not infected. Additionally, a statistical model was developed to define the risk of HIV transmission based on the intracellular PBMC concentration of TFV-DP. From this model, the risk of contracting HIV was reduced by 90%, relative to placebo, among subjects taking TDF that had a TFV-DP concentration 15.6 fmol/million PBMC.⁵⁴ Although PBMC TFV-DP concentrations were good markers of adherence and were highly associated with HIV acquisition, the sample collection and preparation for viable PBMC precludes their routine use in clinical or expanded research studies. Studies are currently underway to examine intracellular RBC levels in HIV uninfected individuals taking PrEP as a possible measurement of adherence monitoring.⁵⁵ Various combinations of pharmacologic metrics of adherence (e.g., detectable FTC plasma and quantitative RBC TFV-DP concentrations) will be explored in order to best characterize TDF/FTC adherence behavior and determine the most useful in therapeutic drug monitoring as an adherence measure.

Another recent study, which characterized the pharmacokinetics of TFV-DP and FTC-TP in RBCs and PBMCs, used complex PK-PD modeling to predict theoretical reduction in HIV transmission from 3 dosing strategies. TFV-DP levels were measured in subjects assigned to 2, 4 or 7 TDF/FTC doses per week. The model predicted that 4 or more doses of TDF/FTC per week would lower the risk of HIV acquisition by more than 95%. Additional analyses from the models were used to define DBS RBC concentration thresholds that might be used as surrogates for adherence in future studies.⁵⁶

Other pharmacologic approaches to adherence monitoring have been explored. TFV levels in scalp hair have been evaluated and showed a clear and consistent correlation with dose. Using hair samples to monitor PrEP medication levels is a promising marker of TFV dosing and exposure with feasibility advantages over other expensive and labor intensive methods.⁵⁷ Concentrations of TFV-DP and FTC-TP measured in the upper layer packed cells (ULPC) from whole blood centrifugation to isolated PBMCs had been used as a possible alternative marker of adherence; ULPC based concentrations were found to correlate significantly with PBMC concentrations and may offer a simply-collected, surrogate measure of ARV adherence.⁵⁸ Finally a breath test for adherence to antiretroviral

vaginal gel was created by adding ester taggants to vaginal gels that would generate exhaled alcohol and ketone metabolites. A recent study found this breath test to be both physiologically and scientifically feasible.⁵⁹

VII. Conclusions

Clinical pharmacology studies help inform our understanding of concentration-response in PrEP RCTs and suggest that differences in anatomic site of HIV risk and adherence are important variables that will impact PrEP as an HIV prevention strategy. Maintaining high levels of adherence to ART, among those who are HIV-infected, has consistently demonstrated a strong relation to better treatment outcomes and survival. In the burgeoning arena of PrEP, adherence is again emerging as a critical component to the efficacy and application of PrEP. As the prophylactic benefits of PrEP are substantially strengthened by adherence, effective PrEP implementation programs will need to focus on this behavioral variable. In order to directly address adherence on both a per-patient and global scale, we will not only need to find the most appropriate agent for PrEP but we will also need an objective, standardized measure of adherence that will allow for monitoring of PrEP adherence in order to assure the safety and effectiveness during implementation of PrEP.

IIIX. Expert Opinion

In the past few years, we have made great strides toward adding PrEP as an option into a multimodal biomedical HIV prevention strategy. We have identified several potential PrEP agents, many of which have been or are currently being studied in clinical trials. We have a strong understanding of the clinical pharmacology which guides our interpretations of concentration-response in PrEP RCTs. The approval of FTC/TDF by the FDA has made PrEP more readily available outside of the clinical research arena. In communities at high risk for HIV acquisition, PrEP awareness and interest are increasing, although post-approval data is lacking.

Several studies support the use of PrEP (iPrEx³, Partners PrEP⁴, CAPRISA-004², TDF2⁵) by demonstrating significant reductions in the relative risk of HIV infection in active versus control arms overall. This benefit of lowering the risk of HIV infection is augmented when sub-groups of subjects with detectable plasma drug concentrations are compared to control. However, more sobering news came with the results of FEM-PrEP⁶⁰ and VOICE⁷, in which no reduction in the risk of HIV transmission was seen. Poor adherence appeared to explain the lack of benefit seen in these studies. Furthermore, even though women in VOICE self-reported high rates of medication adherence, less than one third of subjects had detectable plasma drug levels, suggesting not only medical noncompliance but also imperfection in adherence monitoring that relied on self-report.

Given the mixed results from the landmark PrEP studies, the implications of these findings should be used to design and interpret future studies. New animal models of PrEP need to be explored that allow for a greater understanding of tissue-specific concentrations and the relationship between tissue concentration and efficacy. In particular, additional animal models are needed that assess vaginal challenge after oral dosing. In women, where the concentration of tenofovir in vaginal tissue and fluid is lower than plasma concentrations after oral dosing, future tenofovir clinical trials should attempt to maintain high drug concentrations in the vagina. Combinations of oral and topical ARVs and other innovative formulations should be investigated. Studies of new PrEP formulations, such as use of long acting parenteral preparations and intravaginal rings, will need to carefully examine the association between the drug concentrations achieved at the site of viral exposure and the efficacy of preventing HIV infection.

As RCTs have shown the potential efficacy of PrEP, we must press on to perform demonstration projects to understand real-world implementation issues, help develop best practices and define effectiveness of PrEP strategies in the context of the combination HIV prevention agenda. These projects are focused on populations most vulnerable to HIV (gay and bisexual men, transgender women, high-risk heterosexual women and men including those in serodiscordant partnerships and sex workers) and thus who could benefit most from HIV prevention efforts. PrEP, as a biomedical prevention intervention, has great potential as long as medications are well tolerated and easy to adhere to and are accompanied by medical and behavioral interventions to ensure adherence, minimize risk compensation and monitor for adverse events.

Although currently only TDF + FTC is approved for use as PrEP, additional agents are under investigation that are safe, well tolerated, potentially have a high barrier to resistance and penetrate into target tissues. Long-acting injectable antiretroviral formulations, such as RPV-LA and S/GSK1265744, and intravaginal rings containing dapivirine or TDF show promise to mitigate the issues of poor adherence. However, until such agents are available, more objective adherence measurement tool are needed that do not rely on patient self-report. Measurement and monitoring using intracellular TFV-DP in dried RBC may provide such a measure. As RBC concentrations reflect days to weeks of TDF exposure, they may be a more accurate and sensitive measure of longer term adherence than self-report or random plasma TFV or FTC plasma concentrations, which only reflect medication adherence over the past 2–4 days. Further, the sample is easy to obtain, does not require complex processing at the local laboratory and is stable for shipping to central labs. However, measurement of RBC intracellular TFV-DP concentrations are currently specialized, expensive, are not commercially available and few labs are capable of performing the assay. Thus, current use of PrEP will have to rely on traditional, imperfect adherence assessment while the more objective pharmacologic measures will be reserved for research and demonstration projects.

Clearly, successful implementation of PrEP at the population level will need to go beyond simply providing medications. A potential future step will be the integration of PrEP into a broader comprehensive care program as part of both a preventative health and treatment as prevention strategy. Ideally, a PrEP intervention strategy will follow general guiding principals that will also integrate into a local context and suit the unique needs and experiences of vulnerable populations.

References

1. FDA. [Accessed March 12, 2013] <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm>. 2012
2. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. Sep 3; 2010 329(5996):1168–1174. [PubMed: 20643915]
3. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *The New England journal of medicine*. Dec 30; 2010 363(27):2587–2599. [PubMed: 21091279]
4. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *The New England journal of medicine*. Aug 2; 2012 367(5):399–410. [PubMed: 22784037]
5. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *The New England journal of medicine*. Aug 2; 2012 367(5):423–434. [PubMed: 22784038]
6. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *The New England journal of medicine*. Aug 2; 2012 367(5):411–422. [PubMed: 22784040]

7. 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 Study (MTN 003). Paper presented at: 20th Conference on Retroviruses and Opportunistic Infections; 2013; Atlanta, GA. Paper#26LB
8. Robbins BL, Srinivas RV, Kim C, Bischofberger N, Fridland A. Anti-human immunodeficiency virus activity and cellular metabolism of a potential prodrug of the acyclic nucleoside phosphonate 9-R-(2-phosphonomethoxypropyl)adenine (PMPA), Bis(isopropylloxymethylcarbonyl)PMPA. *Antimicrob Agents Chemother.* Mar; 1998 42(3):612–617. [PubMed: 9517941]
9. Wang LH, Begley J, St Claire RL 3rd, Harris J, Wakeford C, Rousseau FS. Pharmacokinetic and pharmacodynamic characteristics of emtricitabine support its once daily dosing for the treatment of HIV infection. *AIDS Res Hum Retroviruses.* Nov; 2004 20(11):1173–1182. [PubMed: 15588339]
10. Taburet AM, Paci-Bonaventure S, Peytavin G, Molina JM. Once-daily administration of antiretrovirals: pharmacokinetics of emerging therapies. *Clin Pharmacokinet.* 2003; 42(14):1179–1191. [PubMed: 14606928]
11. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *JAMA.* Jul 14; 2004 292(2):191–201. [PubMed: 15249568]
12. Saag MS, Cahn P, Raffi F, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naïve patients: a randomized trial. *JAMA.* Jul 14; 2004 292(2):180–189. [PubMed: 15249567]
13. Hawkins T, Veikley W, St Claire RL 3rd, Guyer B, Clark N, Kearney BP. Intracellular pharmacokinetics of tenofovir diphosphate, carbovir triphosphate, and lamivudine triphosphate in patients receiving triple-nucleoside regimens. *Journal of acquired immune deficiency syndromes* (1999). Aug 1; 2005 39(4):406–411. [PubMed: 16010161]
14. 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.* Feb.2008 5(2):e28. [PubMed: 18254653]
15. Van Rompay KK, Berardi CJ, Aguirre NL, et al. Two doses of PMPA protect newborn macaques against oral simian immunodeficiency virus infection. *AIDS (London, England).* Jun 18; 1998 12(9):F79–83.
16. Louissaint NA, Nimmagadda S, Fuchs EJ, et al. Distribution of cell-free and cell-associated HIV surrogates in the colon after simulated receptive anal intercourse in men who have sex with men. *Journal of acquired immune deficiency syndromes* (1999). Jan 1; 2012 59(1):10–17. [PubMed: 21937920]
17. Louissaint NA, Fuchs EJ, Bakshi RP, et al. Distribution of cell-free and cell-associated HIV surrogates in the female genital tract after simulated vaginal intercourse. *J Infect Dis.* Mar 1; 2012 205(5):725–732. [PubMed: 22279121]
18. Hendrix CW, Chen BA, Guddera V, et al. MTN-001: randomized pharmacokinetic cross-over study comparing tenofovir vaginal gel and oral tablets in vaginal tissue and other compartments. *PLoS one.* 2013; 8(1):e55013. [PubMed: 23383037]
19. Karim SS, Kashuba AD, Werner L, Karim QA. Drug concentrations after topical and oral antiretroviral pre-exposure prophylaxis: implications for HIV prevention in women. *Lancet.* Jul 16; 2011 378(9787):279–281. [PubMed: 21763939]
20. Anton, P.; Cranston, R.; Carballo-Diequez, A., et al. RMP-02/MTN-006: a phase 1 placebo-controlled trial of rectally applied 1% vaginal TFV gel with comparison to oral TDF. Paper presented at: 18th Conference on Retroviruses and Opportunistic Infections; 2011; Boston, MA. Paper #34LB
21. 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.* Dec 7.2011 3(112):112re114.
22. Anderson PL, Kiser JJ, Gardner EM, Rower JE, Meditz A, Grant RM. Pharmacological considerations for tenofovir and emtricitabine to prevent HIV infection. *J Antimicrob Chemother.* Feb; 2011 66(2):240–250. [PubMed: 21118913]

23. Dumond JB, Patterson KB, Pecha AL, et al. Maraviroc concentrates in the cervicovaginal fluid and vaginal tissue of HIV-negative women. *Journal of acquired immune deficiency syndromes* (1999). Aug 15; 2009 51(5):546–553. [PubMed: 19546811]
24. Brown KC, Patterson KB, Malone SA, et al. Single and multiple dose pharmacokinetics of maraviroc in saliva, semen, and rectal tissue of healthy HIV-negative men. *J Infect Dis.* May 15; 2011 203(10):1484–1490. [PubMed: 21502084]
25. Roche M, Jakobsen MR, Sterjovski J, et al. HIV-1 escape from the CCR5 antagonist maraviroc associated with an altered and less-efficient mechanism of gp120-CCR5 engagement that attenuates macrophage tropism. *J Virol.* May; 2011 85(9):4330–4342. [PubMed: 21345957]
26. Baert L, van 't Klooster G, Dries W, et al. Development of a long-acting injectable formulation with nanoparticles of rilpivirine (TMC278) for HIV treatment. *Eur J Pharm Biopharm.* Aug; 2009 72(3):502–508. [PubMed: 19328850]
27. Else, L.; Jackson, A.; Tjia, J., et al. Pharmacokinetics of long-acting rilpivirine in plasma, genital tract and rectum of HIV-negative females and males administered a single 600 mg dose. Paper presented at: 13th International Workshop on Clinical Pharmacology of HIV Therapy; 2012; Barcelona, Spain. p. O_12
28. GlaxoSmithKline. [Accessed March 26, 2013] A single Dose Escalation Study to Investigate the Safety, Tolerability and Pharmacokinetics of Intramuscular and Subcutaneous Long Acting GSK1265744 in Healthy Subjects. <http://clinicaltrials.gov/ct2/show/NCT01215006>
29. Min, S.; DeJesus, E.; McCurdy, L., et al. Pharmacokinetics (PK) and safety in healthy and HIV-infected subjects and short-term antiviral efficacy of S/GSK1265744, a next generation once daily HIV integrase inhibitor. 49th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2009; San Francisco, CA. p. H-1228
30. Spreen, E.; Ford, S.; Chen, S., et al. Pharmacokinetics, safety, tolerability of the HIV integrase inhibitor S/GSK1265744 long acting parenteral nanosuspension following single dose administration to healthy adults. XIX International AIDS Conference; 2012; Washington, DC. TUPE040
31. Andrews, C.; Gettie, A.; Russell-Lodrigues, K. Long-acting Parenteral Formulation of GSK1265744 Protects Macaques against Repeated Intrarectal Challenges with SHIV. Paper presented at: 20th Conference on Retroviruses and Opportunistic Infections; 2013; Atlanta, GA. Abstract 24LB
32. Jacobson JM, Kuritzkes DR, Godofsky E, et al. Safety, pharmacokinetics, and antiretroviral activity of multiple doses of ibalizumab (formerly TNX-355), an anti-CD4 monoclonal antibody, in human immunodeficiency virus type 1-infected adults. *Antimicrob Agents Chemother.* Feb; 2009 53(2):450–457. [PubMed: 19015347]
33. International Partnership for Microbicides, Inc. [Accessed April 8, 2013] Phase 3 Safety and Effectiveness Trial of Dapivirine Vaginal Ring for Prevention of HIV-1 in Women (ASPIRE). <http://http://clinicaltrials.gov/show/NCT01617096>
34. Smith, J.; Rastogi, R.; Teller, R., et al. A Tenofovir Disoproxil Fumarate Intravaginal Ring Completely Protects against Repeated SHIV Vaginal Challenge in Nonhuman Primates. Paper presented at: 20th Conference on Retrovirals and Opportunistic Infections; 2013; Atlanta, GA. Abstract 25LB
35. Lucas GM, Mullen BA, Weidle PJ, Hader S, McCaul ME, Moore RD. Directly administered antiretroviral therapy in methadone clinics is associated with improved HIV treatment outcomes, compared with outcomes among concurrent comparison groups. *Clin Infect Dis.* Jun 1; 2006 42(11):1628–1635. [PubMed: 16652321]
36. Altice FL, Maru DS, Bruce RD, Springer SA, Friedland GH. Superiority of directly administered antiretroviral therapy over self-administered therapy among HIV-infected drug users: a prospective, randomized, controlled trial. *Clin Infect Dis.* Sep 15; 2007 45(6):770–778. [PubMed: 17712763]
37. Kirkland LR, Fischl MA, Tashima KT, et al. Response to lamivudine-zidovudine plus abacavir twice daily in antiretroviral-naïve, incarcerated patients with HIV infection taking directly observed treatment. *Clin Infect Dis.* Feb 15; 2002 34(4):511–518. [PubMed: 11797179]
38. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. *Patient*

- Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care*. Jun; 2000 12(3):255–266. [PubMed: 10928201]
39. Amico KR, Fisher WA, Cornman DH, et al. Visual analog scale of ART adherence: association with 3-day self-report and adherence barriers. *Journal of acquired immune deficiency syndromes* (1999). Aug 1; 2006 42(4):455–459. [PubMed: 16810111]
 40. Oyugi JH, Byakika-Tusiime J, Charlebois ED, et al. Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting. *Journal of acquired immune deficiency syndromes* (1999). Aug 15; 2004 36(5):1100–1102. [PubMed: 15247564]
 41. Walsh JC, Mandalia S, Gazzard BG. Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. *AIDS* (London, England). Jan 25; 2002 16(2):269–277.
 42. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care*. Jan; 1986 24(1):67–74. [PubMed: 3945130]
 43. Berg KM, Wilson IB, Li X, Arnsten JH. Comparison of antiretroviral adherence questions. *AIDS Behav*. Feb; 2012 16(2):461–468. [PubMed: 21181252]
 44. Vanhove GF, Schapiro JM, Winters MA, Merigan TC, Blaschke TF. Patient compliance and drug failure in protease inhibitor monotherapy. *JAMA*. Dec 25; 1996 276(24):1955–1956. [PubMed: 8971062]
 45. Belknap R, Weis S, Brookens A, et al. Feasibility of an ingestible sensor-based system for monitoring adherence to tuberculosis therapy. *PloS one*. 2013; 8(1):e53373. [PubMed: 23308203]
 46. Emtriva. Package insert. Foster City, CA: Gilead; Revised July 2012
 47. Viread. Package Insert. Foster City, CA: Gilead; Revised July 2012
 48. Back DJ, Burger DM, Flexner CW, Gerber JG. The pharmacology of antiretroviral nucleoside and nucleotide reverse transcriptase inhibitors: implications for once-daily dosing. *Journal of acquired immune deficiency syndromes* (1999). Aug 1; 2005 39(Suppl 1):S1–23. quiz S24–25. [PubMed: 15990598]
 49. Mannheimer S, Friedland G, Matts J, Child C, Chesney M. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clin Infect Dis*. Apr 15; 2002 34(8):1115–1121. [PubMed: 11915001]
 50. Edelbroek PM, van der Heijden J, Stolk LM. Dried blood spot methods in therapeutic drug monitoring: methods, assays, and pitfalls. *Ther Drug Monit*. Jun; 2009 31(3):327–336. [PubMed: 19349929]
 51. Koal T, Burhenne H, Romling R, Svoboda M, Resch K, Kaever V. Quantification of antiretroviral drugs in dried blood spot samples by means of liquid chromatography/tandem mass spectrometry. *Rapid Commun Mass Spectrom*. 2005; 19(21):2995–3001. [PubMed: 16193530]
 52. Meesters RJ, van Kampen JJ, Reedijk ML, et al. Ultrafast and high-throughput mass spectrometric assay for therapeutic drug monitoring of antiretroviral drugs in pediatric HIV-1 infection applying dried blood spots. *Anal Bioanal Chem*. Sep; 2010 398(1):319–328. [PubMed: 20632164]
 53. Kromdijk W, Mulder JW, Rosing H, Smit PM, Beijnen JH, Huitema AD. Use of dried blood spots for the determination of plasma concentrations of nevirapine and efavirenz. *The Journal of antimicrobial chemotherapy*. May; 2012 67(5):1211–1216. [PubMed: 22302563]
 54. Anderson, P.; Liu, A.; Buchbinder, S., et al. Intracellular Tenofovir-DP Concentrations Associated with PrEP Efficacy in MSM from iPrEx. Paper presented at: Nineteenth Conference on Retroviruses and Opportunistic Infections; 2012; Seattle, WA. #31:B
 55. California Collaborative Treatment, Group. [Accessed April 8, 2013] CCTG 595: Text Messaging Intervention to Improve Adherence to PrEP in High-risk MSM. 2013. <http://clinicaltrials.gov/show/NCT01761643>
 56. Castillo-Mancilla JR, Zheng JH, Rower JE, et al. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. *AIDS Res Hum Retroviruses*. Feb; 2013 29(2):384–390. [PubMed: 22935078]
 57. Liu, A.; Gandhi, M.; Bacchetti, P., et al. Validating Hair as a Biological Marker of TFV Drug Exposure in HIV PrEP. Paper presented at: 18th Conference on Retroviruses and Opportunistic Infections; 2011; Boston, MA. Paper # 995

58. Adams JL, Sykes C, Menezes P, et al. Tenofovir Diphosphate and Emtricitabine Triphosphate Concentrations in Blood Cells Compared with Isolated Peripheral Blood Mononuclear Cells: A New Measure of Antiretroviral Adherence? *Journal of acquired immune deficiency syndromes* (1999). Jan 17.2013
59. Morey TE, Wasdo S, Wishin J, et al. Feasibility of a breath test for monitoring adherence to vaginal administration of antiretroviral microbicide gels. *Journal of clinical pharmacology*. Jan; 2013 53(1):103–111. [PubMed: 23400750]
60. Van Damme, LCA.; Ahmed, K., et al. The FEM-PrEP trial of emtricitabine/tenofovir disoproxil fumarate (Truvada) among African women. 19th Conference on Retroviruses and Opportunistic Infections; 2012; Seattle, WA.

Key points

- Antiretroviral agents are now being used prophylactically with the goal to decrease the risk of HIV infection in uninfected individuals who are at high risk of acquiring HIV.
- Various antiretroviral medications have been selected as putative PrEP agents based on their pharmacodynamic properties.
- Oral agents already FDA approved for treatment including maraviroc and raltegravir or new and promising long-acting investigation agents including long-acting rilpivirine, S/GSK1265744, ibalizumab and dapivirine may serve as alternate PrEP agents.
- Findings in several randomized controlled trials have emphasized the importance of medication adherence for efficacy.
- Adherence is difficult to measure but newer approaches, including dried blood spots, have been developed that are more objective and may better approximate actual medication use.