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Preexposure Prophylaxis for HIV Prevention

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Abstract

Reducing the incidence of HIV remains one of our greatest public health challenges. However, there is growing optimism that preexposure prophylaxis (PrEP) could have a major impact on preventing incident HIV infection. Recently presented data on the use of oral PrEP in men who have sex with men (MSM) have provided proof-of-principle for this strategy. Additional clinical trials are evaluating whether PrEP provides similar protection to risk groups other than MSM, such as heterosexual persons and injection drug users. Still unanswered questions include optimal dosing strategies, long-term safety, maximizing adherence and minimizing costs, addressing drug resistance in the face of PrEP failure, optimizing access, and assessing effects on risk behavior. Future implementation will be guided by the results of clinical trials in progress. This article provides a review of the data on the potential strengths and limitations of PrEP as an HIV prevention strategy, identifies challenges to implementation of this approach, and outlines knowledge gaps.

Keywords

Preexposure prophylaxis; HIV; Antiretrovirals

Introduction

The HIV/AIDS pandemic remains among our greatest public health challenges. Estimates project that as many as 60 million new HIV infections could occur during the theoretical 15 to 20 year wait for an effective preventive vaccine [1]. There is an urgent need for novel and effective HIV prevention strategies which could be deployed immediately. Male condoms are highly effective for HIV prevention, but consistent use is hindered by issues of consumer dissatisfaction, adherence, slippage/breakage, and lack of receptive-partner control. Other interventions including treatment of sexually transmitted infections (STIs) [2•], male circumcision [2•], and use of a tenofovir (TFV) 1% microbicide vaginal gel [3•] have shown clinical efficacy in reducing HIV acquisition. On the other hand, treatment of herpes simplex virus-2 (HSV-2) [4], diaphragms [4], non-antiretroviral-based vaginal microbicides [4], and preventive vaccines [5] have all failed to demonstrate protection against HIV infection and, in some instances, may have even increased transmission rates [3•].

It is becoming clear that no single prevention strategy will be 100% effective, nor acceptable and applicable to all populations. Therefore, novel tools in the HIV prevention armamentarium and innovative ways of combining effective strategies to maximize impact are desperately needed. Antiretroviral therapy (ART) has been shown to reduce morbidity and mortality in persons chronically infected with HIV [1]. Accordingly, there is strong interest in exploring the potential use of ART in a prevention capacity in three domains: 1) to reduce infectiousness among HIV-positive persons, 2) to prevent infection among HIV-negative persons when used as postexposure prophylaxis (PEP) after occupational or nonoccupational exposure to HIV-infected blood or fluids [1], and 3) to prevent infection in high-risk HIV-seronegative populations when given as preexposure prophylaxis (PrEP) [6, 7]. In this review, we summarize available literature on oral PrEP use, which has recently gained international attention following efficacy results reported in the *Iniciativa Profilaxis Pre-exposición* (iPrEx) trial [8••].

Definition of PrEP

Preexposure prophylaxis involves the use of ART in anticipation of potential HIV exposure from known or unknown sources with the aim of preventing HIV acquisition or, at least, altering the natural course of infection to attenuate disease progression, reduce morbidity, and/or decrease infectiousness. The fundamental concept of using antimicrobials to prevent infections is not new—a notable example being the use of chloroquine to prevent malaria. The use of oral contraceptive pills (OCPs) to prevent pregnancy, while an imperfect analogy, is another similar structural concept. Ideal drug characteristics for PrEP treatment would include low pill burden with no more than once-daily dosing, long intracellular and extracellular half-life, favorable pharmacokinetic properties such as the ability to rapidly reach and accumulate in genital and rectal tissues, good tolerability and safety, high potency, low cost, contraceptive and anti-sexually transmitted infection activity, and a high barrier to resistance [6, 9].

Antiretroviral Drugs for Oral PrEP

PrEP strategies that have been evaluated for efficacy have used the nucleos(t)ide reverse transcriptase inhibitor (NRTI) tenofovir disoproxil fumarate (TDF or Viread) alone or in combination with emtricitabine (FTC), including a co-formulation of FTC/TDF in a once-daily pill (Truvada) [10]. Agents active at the pre-integration stage of viral replication that may prevent the establishment of HIV-infected cells are thought to be more suitable than post-integration drugs like protease inhibitors (PIs), although data to support this supposition are limited [9]. In contrast to NRTIs, nonnucleoside RT inhibitors (NNRTIs) and PIs generally achieve lower drug concentrations in the genital tracts of males and females as compared to blood plasma; a potential liability when attempting to reduce genital tissue susceptibility to infection [11]. The availability of new drugs such as those that block viral DNA integration or entry through CCR5 are mechanistically attractive; however, comparative trials of different agents for PrEP have yet to be performed, and the optimal correlates of protection have yet to be defined [12].

Developing Support for PrEP

The goal of PrEP would be to achieve protective concentrations of a biologically active agent in the target cells at the time exposure occurs, and to block the establishment of founder populations of infected cells [9]. This end point is based on observations that mucosal HIV infection may be prevented by a rapid and efficient host immune response or by limiting the size of founder populations of infected cells to a theoretical threshold under which infection cannot be established [9].

To date, PrEP efficacy has been shown only in men who have sex with men (MSM) in the multinational iPrEx study [13]. However, differences in the early events of mucosal versus parenteral infection, dissemination kinetics between rectal and vaginal HIV transmission [13, 14], and different pharmacokinetics of antiretroviral drugs in genital secretions versus blood plasma necessitate confirmation of PrEP efficacy in different populations and via distinct modes of viral inoculation. Exploring the questions raised by iPrEx is the foundation of this review, with the goals of presenting current animal and human research, examining theoretical models, and laying the groundwork for future research of PrEP.

The developing conversation about PrEP is laden with questions about acute and longer term toxicity and safety, efficacy and effectiveness, risk reduction, and implementation. The sections below provide an overview of current research on these topics, as well as formulate a case for future PrEP studies.

Pharmacokinetics

A comprehensive understanding of the pharmacology of antiretroviral drugs in genital secretions and tissues is essential to define the most appropriate drug candidates and dosing strategies for PrEP. Correlating drug levels, drug dosing (including route and dose amount), and protective efficacy are critical parameters which remain to be defined. Recent findings from animal studies suggest that the high level of protection by preexposure dosing strategies may be related to the long persistence of tenofovir diphosphate (TFV-DP) and emtricitabine triphosphate (FTC-TP) in mononuclear cells. The rapid FTC distribution in tissues and the long intracellular TFV persistence complement each other to maximize PrEP efficacy [15•]. However, the threshold levels of TFV-DP and FTC-TP that result in protection have not been defined, and protective drug levels may differ according to the type of exposure. The intracellular assay used in the iPrEx study was sensitive enough to detect drug for approximately 14 days after the last dose taken, based on TFV-DP half-life extrapolation, assuming the half-lives of 39 h and 150 h for FTC-TP and TFV-DP, respectively [13]. Detectable plasma concentrations of FTC and TFV, with half-lives of 10 to 14 h, would be expected to last for approximately 2 to 3 days after dosing [16]. The incorporation of methods for inexpensively measuring long-term drug exposure, such as that afforded by analysis of hair, may be helpful since long-term drug exposure has been a strong predictor of virologic suppression in treatment trials [17].

An increased understanding of pharmacokinetics will aid in the development of studies to define the advisability of intermittent PrEP (the non-daily dosing of ART as prevention in HIV seronegative patients), which is likely to be more practical to implement, improve cost-effectiveness, reduce the risk of drug toxicities, and improve acceptability. The clinical efficacy of short-course (single dose) prophylaxis with nevirapine in preventing mother-to-child transmission of HIV [18] is an analogy for this concept in the HIV prevention literature. This rationale is supported by the high FTC and TFV concentrations achieved in the male and female genital tract after oral administration [11], their long intracellular half-lives in humans [19], and the relatively small size of founder virus populations that initiate an HIV infection in the mucosa after sexual or transmucosal exposures [20]. Data from animal models support the efficacy of intermittent drug dosing with TDF or FTC/TDF where an extended window of protection was attributed to the long intracellular persistence of FTC and TFV in PBMCs [15•, 21]. In humans, it was additionally shown that protection could be achieved with only pre-coital and post-coital dosing of a TFV 1% vaginal gel [3•]. These data support further study of intermittent PrEP strategies, especially in light of concerns regarding intermittent dosing strategies, which center on the concept that subtherapeutic levels of drug in intermittent strategies may provide suboptimal protection, and may facilitate development of drug-resistant virus. Detailed pharmacokinetic analyses

from simultaneous sampling of blood plasma and rectal tissue homogenates after single and multiple doses of oral TDF and topical 1% TFV gel suggest that local administration provides optimal tissue levels local to the rectum, and correlates well with an ex vivo infection model [22]. Further study is needed in order to understand the dosing and formulation options for maximizing PrEP efficacy.

Efficacy of PrEP

Multiple lines of evidence including data from animal studies [6, 23], clinical trials in humans [8], and mathematical models [24•] suggest that PrEP might be an effective strategy for preventing HIV among high-risk populations.

Preclinical Research in Animal Models

The use of ART for HIV prophylaxis has been studied extensively in non-human primate models of mucosal and parenteral transmission of simian immunodeficiency virus (SIV) or simian-human immunodeficiency virus (SHIV; Table 1). Macaque studies have shown that PrEP can be highly effective in preventing infection after intravenous, oral, rectal, or vaginal exposure in a dose-dependent manner [23, 25–27]. A repeat-low-dose exposure macaque model of rectal and vaginal SHIV transmission showed that higher drug doses and combination treatments might be more effective in preventing SHIV transmission than single drugs or lower doses [23, 27]. FTC/TDF additionally provided robust protection against HIV infection in a humanized mouse model using vaginal HIV repeat challenges [28].

The finding that daily PrEP using a combination of FTC and TDF was more robust in macaques than single-drug PrEP prompted some of the clinical trials (notably the Botswana heterosexual transmission study; Table 2) to be modified mid-study to evaluate safety/efficacy of FTC/TDF instead of TDF alone. Upcoming human clinical trials (the Partners PrEP study and VOICE; Table 2) will directly compare oral TDF to oral FTC/TDF, and will provide critical information on incremental benefits and/or toxicities of these specific two-drug versus single-drug regimens.

Human Clinical Trials

ART has been shown to be effective in suppressing HIV replication in chronically infected individuals, with dramatic reductions in morbidity and mortality [13]. Human evidence to support the testing of ART for PrEP comes from two sources: clinical trial data on the efficacy of ART in preventing mother-to-child transmission of HIV (PMTCT) [29]; and observational data concerning ART used as postexposure prophylaxis [1, 30]. The first clinical reports of PrEP came from a phase 2 trial of TDF in West Africa (n=936 women, exposed to HIV primarily through vaginal sex), which found eight seroconversions over 476 person-years of HIV testing, of which six occurred in the placebo group and two in the group taking daily oral TDF [31]. The study was not sufficiently powered to examine efficacy, owing to the premature closure of two study sites and lower-than-expected HIV incidence in the study population [31]. In 2010, the CAPRISA 004 study showed that a vaginal gel containing 1% TFV reduced HIV infection by approximately 39% overall and 54% among women with high adherence (> 80% adherence by self-report) to product use [3•]. In the recently reported iPrEx trial, once-daily oral FTC/TDF provided 44% additional protection from HIV among MSM compared to intensive risk reduction counseling including condom provision and education alone [8••]. Although self-reported pill adherence was high, drug exposure that was measured objectively based on both plasma levels and an intracellular assay suggested significantly lower levels of daily medication adherence [8••]. Analyses of data on ART levels as a measure of adherence demonstrated that greater

adherence to daily medication dosing predicted improved levels of protection against seroconversion [8••].

Additional PrEP trials are in various stages of completion (Table 2). The at-risk populations in these studies are MSM, heterosexual men and women, and intravenous drug users (IDUs). All trials are using TDF-containing products—comprising TDF alone or in combination with FTC—and all are evaluating daily use with the exception of one pilot study of intermittent dosing. A phase 2 study of novel PrEP regimens in MSM is in advanced stages of development by the HPTN (HIV Prevention Trials Network). Further, adolescent MSM are being studied in an ongoing clinical trial of PrEP developed by the ATN (Adolescent Trials Network) [32].

Mathematical Models

If currently enrolling trials support the efficacy demonstrated by the iPrEx study, mathematical modeling suggests that there could be a substantial public health benefit of widespread implementation. In fact, there is the possibility of up to a 74% decline in cumulative HIV infections in 10 years from a product with 90% efficacy and with 75% coverage of the general population [33]. Despite a 44% efficacy estimate, the iPrEx pharmacokinetic nested case–control cohort suggests that efficacy levels >90% may be possible if adherence can be optimized along with safer sex behaviors [8••]. Several population-level models have suggested that PrEP could have a substantial impact in the United States [24•] and in resource-limited settings [33], including Africa and India [34]. However, these mathematical models are limited by their inability to accurately estimate changes in sexual risk behavior, since even small changes in sexual risk behavior could change drastically the predicted effectiveness of these models, and potentially entirely abrogate the primary drug effect [34].

Effect of PrEP on Viral Load

Mathematical models have also been used to determine the effect of PrEP on viral load [33]. These models suggest that a reduction in the magnitude of acute viremia associated with primary HIV infection during PrEP treatment could reduce infectivity and therefore secondary transmission [23]. Substantial reductions in viral load during seroconversion could also reduce CD4⁺ T-cell depletion, help preserve immune function, and attenuate the course of HIV infection [35]. Although some small studies suggest that being on PrEP when an HIV infection occurs is associated with low virologic set point [23, 35], the iPrEx study did not confirm these findings: the viral loads after seroconversion were not different among FTC/TDF recipients compared with placebo recipients [13].

Seroconversion Despite the use of PrEP

Not surprisingly, PrEP is an imperfect prevention strategy, and failures of PrEP have been described in human and animal studies. In animals, these have been variably attributed to residual virus replication in cells not protected by drugs, development of resistance to FTC (in preference to TDF), and suboptimal drug absorption [15•]. In humans, medication nonadherence is likely an additional major contributor.

The studies of FTC/TDF-based PrEP in macaques have shown that when seroconversion despite PrEP does occur after challenges with wild-type strains, population-level resistance testing demonstrates either no resistance, or a treatment-emergent FTC resistance mutation (M184V/I), and not the TDF-associated K65R mutation [23, 36].

Concerns about PrEP and PrEP failures increasing rates of transmitted resistance have yet to be borne out; however, in a mathematical model, Supervie et al. [37] predicted PrEP interventions could substantially reduce population-level transmission but significantly increase the proportion of new infections caused by resistant strains. The results of clinical studies completed thus far have been provocative: in the West Africa trial, where TDF monotherapy was studied as PrEP in heterosexual women, two seroconversions were diagnosed in participants randomized to TDF. Genotypic analysis of one of these two participant's specimens revealed no evidence of TDF-related resistance mutations (the other isolate was not able to be amplified for genotyping) [31]. In a phase 2 trial of 1% TFV gel (HPTN 050), no new resistance mutations were detected in plasma and cervicovaginal lavage after 14 days of product use in HIV-infected women [38]. In the iPrEx study, two subjects in the FTC/TDF group who were undergoing acute seroconversion at enrollment were found to have FTC-resistant viruses (M184V/I) at 4 weeks of follow-up; one clearly treatment emergent [13]. The absence of detectable resistance mutations in those who seroconverted despite being randomized to FTC/TDF in iPrEx should be interpreted as evidence of poor adherence to drug therapy, rather than exonerating resistance as a "collateral harm" of PrEP seroconversion [8•, 39, 40].

These observations have prompted the US Centers for Disease Control and Prevention (CDC), as part of guidance for clinicians on the use of PrEP as a prevention strategy in MSM, to recommend a baseline nucleic acid amplification test (NAAT) or viral load testing for anyone initiating PrEP who might have symptoms compatible with an acute seroconversion syndrome. Many prevention experts argue that anyone at sufficient risk for seroconversion to warrant PrEP use might benefit from baseline viral load, NAAT, or recently FDA-approved fourth-generation antibody/antigen "sandwich" ELISA testing to help exonerate asymptomatic acute HIV infection at baseline [30]. Although using multiple ART agents for PrEP may minimize the development of resistance [9], larger cohorts and more widespread use will be needed to clarify the resistance, virologic, and immunologic sequelae of seroconversion despite the use of PrEP.

Safety of PrEP

Even if PrEP is highly effective, the known toxicity risks of ART in HIV-infected patients raise concerns for toxicity in HIV-uninfected individuals prescribed preventive ART. When medication is taken by healthy asymptomatic individuals, even mild side effects may compromise adherence [8•]. Also, healthy individuals with intact immune systems may develop side effects not previously reported such as the experience with nevirapine. iPrEx demonstrated that the initiation of FTC/TDF PrEP can be associated with early treatment symptoms of nausea and weight loss [9, 41]. Based on longer-term exposure in HIV-infected populations, the side effects of TDF or FTC/TDF include potential for kidney injury, loss of bone mineral density, gastrointestinal effects, and flares of hepatitis B after discontinuing use, and serious adverse event rates are in the 1% to 3% range [9, 41]. Reassuringly, less than 5% of HIV-uninfected patients using either TDF or TFV gel in clinical trials had serious drug-related adverse events, and decreases in renal function were the most common drug-related serious adverse events [3•, 8•, 31]. In the MSM population of the iPrEx study, there were trends toward more creatinine elevations (most were self-limited, and all resolved with medication discontinuation) in the FTC/TDF group than in the placebo group [13]. However, although there were no differences in serious adverse events or grade 3 or 4 laboratory abnormalities between the two groups in this study [13], the ability to detect safety outcomes may have been decreased by lower-than-expected drug exposure. With only a median of 1.2 years of follow-up in iPrEx, ongoing drug safety surveillance will need to be a component of plans for future trials, as well as large-scale rollout of PrEP. Recently presented data on reductions in bone mineral density (BMD) in both TDF and FTC/TDF-

based PrEP trials, although statistically significant, are of unclear clinical significance [42, 43].

Implementation of PrEP

The implementation of PrEP is likely to be limited, at least initially, to high-risk persons who have access to monitoring services. However, the literature on implementation strategies to prevent HIV infection is sparse and centers largely on the replication of evidence-based interventions to reduce sexual risk behavior [24•]. Implementation and scale-up of PrEP has numerous unique challenges including the safety of administering ART to healthy asymptomatic people, optimizing adherence to tablets or topical formulations for long periods, costs (including who will pay for medication supplies and monitoring), development of resistant virus for those who acquire HIV while on PrEP treatment (and the subsequent implications on future response to ART once infected), optimal frequency of testing and safety monitoring, and possible behavioral risk compensation [3•], [9].

Adherence

Poor adherence may lead not only to suboptimal protection efficacy but may also impact drug resistance. Although high levels of adherence to ART are feasible in infected populations [30, 31], it is unclear if the same is true in HIV-uninfected populations, and the iPrEx study corroborates this concern [13]. Some of the most striking observations from iPrEx were the disconnection between participant self-report of medication adherence and observed drug levels, and the dose–response relationship between adherence (by any measure) and efficacy. Optimization of adherence to PrEP is going to be a critical, but extremely challenging, need for future investigation.

Costs and Other Resource and Infrastructure Challenges

The rollout of PrEP programs will have to deal with substantial logistical and financial challenges. The cost of providing PrEP to the 100,000 most at-risk people in the US could exceed \$1 billion each year at current retail prices, which would exceed the CDC's current HIV prevention budget just with this intervention alone [24•]. In a recent study, Paltiel et al. [24•] showed that price reductions and/or increases in efficacy could make PrEP a cost-effective option in younger populations or those at highest risk of infection. If PrEP is determined effective for use, new strategies for financing PrEP delivery as part of a comprehensive strategy of prevention services to at-risk individuals will be imperative [9].

Implementation challenges will be heightened in resource-limited settings, such as human resource short-ages, limited health services utilization by at-risk individuals, ongoing stigma, disease co-morbidity, health literacy, and insufficient protections against involuntary status disclosure or discrimination [30]. As an integrated strategy, PrEP needs to be considered a true combination approach whose success is likely to be critically dependent on co-implementation with behavioral, biomedical, and structural elements such as HIV testing, safety screening, drug abuse treatment, mental health services, human rights, partner services and basic medical care, behavioral interventions to support adherence and reduce risk behaviors, treatment of side effects, and linkages to HIV care and services in the event of PrEP failure [6, 30].

Risk Compensation

A critical concern in evaluating the effectiveness of PrEP, regardless of its efficacy, is whether individuals taking PrEP feel protected against infection and consequently increase their transmission-risk behavior [44]. Mathematical modeling suggests that the impact of PrEP may be diminished or even entirely abrogated by behavioral change [34].

Reassuringly, the results from the Ghana PrEP study showed that sexual risk behavior did not increase during the trial [30, 31]. Although in the CAPRISA 004 trial there were no changes in risk behavior during the trial, there is a suggestion that observed rates of unprotected sex in both arms may be higher than the general population back-ground rate [3•]. The iPrEx study also showed that high-risk MSM can be mobilized to increase condom use and reduce number of sexual partners [13]. Behavioral changes during future open-label use of PrEP may differ because of lack of a placebo arm, and an increased expectation of benefits. Optimal PrEP use will require co-locating behavioral interventions to maximize drug adherence and minimize risk compensation behaviors by PrEP users [13] since both behavioral parameters (adherence and sexual risk) will be critical for maximizing PrEP's public health impacts [13].

Next Steps in PrEP Research

Although animal research has provided valuable information and can guide the next steps in the research and practice of PrEP, and human trials will ultimately determine if oral PrEP can prevent HIV transmission, there are many unresolved issues that deserve further investigation. Firstly, the iPrEx study in MSM may not be generalizable to other populations, such as heterosexual men and women and injection drug users, who are being evaluated in other PrEP studies. Other unanswered questions regarding PrEP include the optimal choice of agents, interval and duration of PrEP treatment, intervals for HIV testing and safety monitoring, and strategies for discontinuation of PrEP. Moreover, strategies for combining PrEP with other HIV prevention approaches—such as STI treatment or circumcision, immunotherapies such as vaccines, and topically applied preparations—are areas for future development, which will expand as new biomedical strategies emerge [6, 30]. These are especially important since there is likely to be a synergistic benefit when combining the increasing arsenal of known partially effective HIV prevention interventions. Further research is necessary to ascertain how PrEP may be integrated into other services needed by populations at risk for HIV, such as non-HIV-identified primary care (to minimize stigma), substance abuse treatment, mental health services, and basic health care needs.

Research efforts should also identify ways to maximize PrEP's acceptability to potential users, since PrEP's public health impact will depend in part on uptake [13]. Acceptability may depend on perceived efficacy, side effects, and cost [30] and will likely also be complicated by attitudes toward medical providers, pill-taking, vaginal or rectal products, ART, PEP, and other psychosocial factors including societal norms, poverty, and social stigma. There is much to learn about how to implement PrEP strategies acceptably, which may include packaging PrEP pills discreetly and addressing PrEP in stigma reduction campaigns. Specific attention will need to be devoted to safety, efficacy, and acceptability in adolescent populations, pregnant or breastfeeding women, and those with comorbidities such as hepatitis and/or renal dysfunction. Finally, implementation will depend on the development of guidelines for PrEP use in practice settings [45••]. Guidelines must specify the types of settings in which PrEP may be delivered safely and effectively and the necessary personnel qualifications to prescribe PrEP, conduct safety screening, and provide supportive services. According to interim guidelines from the CDC, until the safety and efficacy of PrEP is determined in trials now under way with populations at high risk for HIV acquisition by other routes of transmission (e.g., injection drug users), PrEP should be considered only for MSM [45••]. However, guidelines are likely to change rapidly as new data is deployed in the coming months. Despite the current early stage of available data on PrEP, ongoing research efforts will mature the understanding of many of these issues and set the basis for development of guidelines on PrEP that will be a valuable aid for clinicians.

How to Deploy ART for Prevention: Treatment of HIV-Positives at Higher CD4 Cell Counts or for PrEP?

In a scenario of ever-more-limited financial resources, there is a burgeoning tension as to where to invest these prevention resources: in test-and-treat strategies (i.e., finding undiagnosed HIV infection and initiating ART to reduce infectivity of positive persons), or in PrEP (reducing the susceptibility of negative but at-risk persons). Data from an observational cohort in Africa suggest that initiation of ART reduces the likelihood that an HIV-negative sexual partner will become HIV-infected by 92% [46]. These data, in concert with the above presented data on the efficacy of ART use in HIV-negative individuals, have caused some to forge allegiances to one strategy; these both will likely need to be used in combination to effectively combat the epidemic, and should be looked at as a synergy, rather than competing interests.

Conclusions

Antiretroviral PrEP is a promising HIV-prevention approach. Early events of mucosal infection represent a window of high virus vulnerability, potentially enabling antiretroviral drugs to block the establishment of a persistent infection. Research in animal models of mucosal and parenteral transmission has provided evidence for the efficacy of PrEP, and has formed the basis for the design of human clinical trials. Ongoing trials will answer many of the outstanding questions about the effects of PrEP drugs, including optimal dosing schedule, route of administration, and efficacy for different types of HIV exposure. If PrEP is confirmed to be safe and effective, implementation programs will require substantial resources with extensive community education about the indications, availability, and effectiveness of the intervention while emphasizing the concomitant use of other proven prevention strategies.

Responsible use of PrEP and understanding of limitations of the data are critical. There are several areas that will require further research and ongoing surveillance if PrEP is to become part of an HIV prevention program. This includes optimization of types and routes of prophylactic agents and monitoring for HIV infection and toxicity. A multicomponent approach that includes behavioral, structural, and biomedical interventions will likely be essential to curb the HIV epidemic. Such mutually reinforced frameworks are needed to protect diverse communities from the spread of HIV and other diseases.

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Table 1

Animal studies of preexposure prophylaxis (PrEP)

Animal	Macaques [15, 23, 25–27, 47–55]									
Virus	SHIV [15, 23, 27, 47, 49, 50, 53]									
Challenge	PR [15, 23, 27]									
PrEP agent	FTC/TDF [15, 23]	FTC [23]	TDF [27]	FTC/TDF [50]	TDF [50]	CCR5 inhibitor [47, 49, 53]	Other entry inhibitor [53]			
Route of PrEP	PO [15, 23]	SQ [23]	PO [27]	V [50]	V [50]	PO [47]	V [49, 53]	V [53]		
Dosing Regimen	I/D	I/D	I/D	x 1	x 1	D	x 1	x 1		
Timing of first dose before challenge	≤ 24 hrs vs 7 days	< 24 hrs	< 24 hrs	< 24 hrs	< 24 hrs	< 24 hrs	< 24 hrs	< 24 hrs		
% Protection from infection [†]	50%–83% (s) [15] 67% (s) [23]	100% (s)	NR (ns)	83.3% (s)	100% (s)	45%–56% (s)	75%–86% (s) [49] 66%–100% (s) [53]	66%–100% (s)		

Animal	Macaques [15, 23, 25–27, 47–55]									
Virus	SIV [25, 26, 48, 51, 52]					Simian-tropic (st) HIV-1 [54]				
Challenge	PR [52]	PO [25, 26, 48]	IV [51]	IV [54]	IV [56]	PR [56]	IV [56]	V [28]		
PrEP agent	TDF [52]	TDF [25, 26, 48]	TDF [51]	EFV/FTC/TDF [54]	FTC/TDF [56]	FTC/TDF [56]	FTC/TDF [56]	CCR5 inhibitor [28]		
Route of PrEP	PR [52]	PO [25]	SQ [48]	SQ [54]	IP [56]	IP [56]	IP [56]	IP [28]		
Dosing regimen	x 1	D	Perinatal	D	D	D	D	D		
Timing of first dose before challenge	< 24 hrs	< 24 hrs	< 24 hrs vs 2 days	7 days	3 days	3 days	3 days	3 days		
% Protection from infection [†]	89% (s)	0%–83% (ns)	100% (s)	100% (only 2 animals)	63% (s)	88% (s)	88% (s)	88% (s)		

D daily, EFV efavirenz, FTC emtricitabine, I intermittent, IP intraperitoneal, IV intravenous, (ns) not significant, PO oral, PR rectal, (s) statistically significant, SIV simian immunodeficiency virus, SHIV simian-HIV, SQ subcutaneous, TDF tenofovir, V vaginal, x 1 administered once on the day of challenge

[†] Summary of data, heterogeneous populations/study methods, and multiple statistical methods used in parent studies

Table 2

Ongoing and planned preexposure prophylaxis (PrEP) trials [32]

Study	Location	Sponsor/founder	Population	PrEP strategies being tested	Status/expected completion
US Extended TDF Safety Trial	United States	CDC	400 MSM	Daily oral TDF	Enrollment started in 2005 Fully enrolled/2010 Fully enrolled/ongoing
Bangkok TDF Study	Thailand	CDC	2400 injecting drug users	Daily oral TD	Enrollment started in 2005 Fully enrolled/2012
TDF-2	Botswana	CDC	1200 heterosexual men and women	Daily oral FTC/TDF (switched from TDF in 2007)	Enrollment started in 2007 Fully enrolled/2011 Enrolling/2011
Partners PrEP	Uganda, Kenya (Partners PrEP study)	BMGF	4700 serodiscordant heterosexual couples	Daily oral TDF vs daily oral FTC/TDF	Enrollment started in 2008 Enrolling/2013
FEM-PrEP	Kenya, Malawi, South Africa, Tanzania, Zambia (FEMPrEP)	FHI/USAID	3900 high-risk women	Daily oral FTC/TDF	Enrollment started in 2009 Enrolling/2013
IAVI E001, E002 Phase 1/2	Kenya, Uganda	IAVI	150 high-risk women and men	Daily oral FTC/TDF vs intermittent oral FTC/TDF	Enrollment started in 2009 Completed 2010
VOICE, MTN003	South Africa, Uganda, Zambia, Zimbabwe (VOICE study)	NIH/MTN	5000 sexually active women	Daily oral TDF vs daily oral FTC/TDF or daily topical 1% TFV gel	Enrollment started in 2009 Enrolling/2013 Completed/2011
MTN 001 Phase 2, Adherence	South Africa, Uganda, United States	CONRAD, DAIDS/NIAD, Gilead, MTN	144 heterosexual women	Daily 1% topical TFV gel vs daily oral TDF	Enrolling/2011
PrEP in YMSM (ATN 082) Phase 2, Safety, Acceptability, Feasibility	United States	ATN, NICHD	99 young men who have sex with men (YMSM)	Daily oral FTC/TDF	Enrolling/2011
PrEP Using TMC278LA Phase 1/2, Safety and Pharmacokinetics	United Kingdom	St. Stephens AIDS Trust	100 men and women (vaginal and penile/rectal)	TMC278LA injected intramuscularly	Enrolling/2011
iPrEx Open-Label Extension	Brazil, Ecuador, Peru, South Africa, Thailand, United States	NIH	iPrEx trial participants (2499) are offered the opportunity to enroll in this open-label extension	HIV-negative participants offered daily FTC/TDF; HIV-positive participants offered continued monitoring and risk reduction services	2011 enrollment begins/2013

ATN Adolescent Trial Network, *BMGF* Bill & Melinda Gates Foundation, *CDC* US Centers for Disease Control and Prevention, *FHI* Family Health International, *FTC* entricitabine, *IAVI* International AIDS Vaccine Initiative, *MSM* men who have sex with men, *MTN* Microbicide Trials Network, *NIH* US National Institutes of Health, *TDF* tenofovir, *USAID* United States Agency for International Development

Table 2 is an amalgamation of the currently accessed AVAC web page (reference 32, accessed March 2, 2011) and AVAC web page as assessed on January 25, 2011. The US Extended TDF Safety Trial and MTN 001 Phase 2 adherence trials have recently been completed but have not been published. These trials are not included in the current AVAC web page (reference 32, accessed March 2, 2011)