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The Promise of Antiretrovirals for HIV Prevention

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Abstract

With an estimated 2.6 million new HIV infections diagnosed annually, the world needs new prevention strategies to partner with condom use, harm reduction approaches for injection drug users, and male circumcision. Antiretrovirals can reduce the risk of mother-to-child HIV transmission and limit HIV acquisition after occupational exposure. Macaque models and clinical trials demonstrate efficacy of oral or topical antiretrovirals used prior to HIV exposure to prevent HIV transmission, ie pre-exposure prophylaxis (PrEP). Early initiation of effective HIV treatment in serodiscordant couples results in a 96% decrease in HIV transmission. HIV testing to determine serostatus and identify undiagnosed persons is foundational to these approaches. The relative efficacy of different approaches, adherence, cost and long-term safety will affect uptake and impact of these strategies. Ongoing research will help characterize the role for oral and topical formulations and help quantify potential benefits in sub-populations at risk for HIV acquisition.

Keywords

HIV prevention; Pre-exposure prophylaxis; Microbicide; Tenofovir; Emtricitabine

Introduction

In the 30 years since the advent of AIDS, HIV prevention strategies have focused on behavior modification, condom use, harm reduction for injection drug users, and blood supply screening [1, 2]. Antiretroviral medications used primarily for HIV treatment are now being studied for prevention. Researchers have posited that expanded access to testing and early initiation of highly active antiretroviral therapy (ART) among HIV infected individuals can arrest the global HIV pandemic, decreasing incidence by as much as 95% within 10 years [3]. A recent study has corroborated this model, demonstrating that suppressing HIV-infected persons' HIV RNA decreases the risk of transmission to

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uninfected sexual partners by 96% [4••]. This supports the hope that expanded treatment may decrease HIV incidence on a population level. Post-exposure prophylaxis (PEP) first utilized in occupational settings [5] and then in non-occupational settings [6, 7] suggest that drugs developed for treatment could be used to prevent HIV infection after a likely exposure. Similarly, the use of antiretrovirals to prevent mother-to-child transmission demonstrated that antiretrovirals could be used for prevention [8]. A new prevention strategy has emerged supporting the use of oral and topical antiretrovirals before sexual exposure (known as pre-exposure prophylaxis (PrEP)) to prevent HIV acquisition among high-risk people. We aim to present the rationale for PrEP, current efficacy data, and key considerations for implementation as part of a comprehensive HIV prevention strategy.

Current Prevention Strategies

Sexual intercourse contributes disproportionately to HIV transmission worldwide [9]. However, the estimated rate of sexual transmission varies from 0.04% risk from a female to a male per episode of unprotected sexual intercourse [10] to 1.4% per episode of unprotected anal intercourse [11]. Estimates are influenced by mode of exposure, viral load of the infected partner and male circumcision status [12-15]. Until recently, evidence-based behavior modification strategies focused on condoms [16] which when used consistently provide an 80%–95% reduction in risk of HIV transmission [17, 18]. However particularly for high risk populations many barriers to condom use exist. Among HIV-infected men who have sex with men (MSM), treatment optimism, challenges communicating with partners, and concerns about stigmatization following sero-status disclosure have been associated with decreased condom use [19]. Among African-American heterosexual men, negative attitudes toward condom use and partner related barriers exist [20]. Among women, there is less condom use with regular partners [21] driven by fear of partner resistance to condom use [22], and for some, personal perception of being low-risk [23], history of domestic violence [24] and desire to conceive [25]. Among drugusing women, barriers include fear of being perceived as unfaithful [26], lower socio-economic status [26], sexual non-assertiveness because of economic dependence on male partners and other power dynamics [27].

Complementary HIV prevention strategies include male circumcision [28], increased HIV testing and linkage to medical care [29, 30] access to sterile syringes and other harm reduction approaches [31] which target disproportionately affected groups — partners of people living with HIV, gay and bisexual men, women, and people in need of substance abuse treatment [1, 2]. Early initiation of treatment of HIV-infected individuals may have a population benefit as it lowers community viral load, a population-level measure of virologic suppression within a given geographic or socio-demographic community, and may decrease rates of HIV transmission [32•, 33]. With about 50,000 new cases of HIV occurring in the U.S. annually and approximately 2.6 million new cases worldwide [2] additional prevention strategies are needed, motivating studies exploring the efficacy of earlier initiation of antiretroviral treatment and of oral and topical antiretroviral chemoprophylaxis for high-risk uninfected persons.

Treatment as Prevention

One approach to the use of ART for prevention focuses on initiating treatment of infected people earlier in the course of their disease to decrease their viral burden, minimizing risk of transmission to sexual partners [34]. To test this strategy, the HIV Prevention Trials Network study (HPTN 052) enrolled 1763 HIV serodiscordant couples in 8 countries in sub-Saharan Africa, Asia and the Americas. The infected partners were randomized to early initiation of ART, at CD4 counts between 350 and 550 cells/mm³ or to delayed therapy,

after a decline in CD4 count to less than 250 cells/mm³. The data revealed that early initiation of ART among HIV infected partners yielded a 96% reduction in the risk of transmission to their uninfected partners [4•]. The prevention benefit achieved by treatment of the infected partner, though impressive has limitations. In HPTN 052, genetic studies of transmitted viral strains demonstrated that 11 of 39 uninfected participants who seroconverted during the study acquired HIV from partners outside of their partnership [4•], suggesting that treating infected partners may not provide complete protection against HIV acquisition for members of discordant couples who have other sexual partners.

Despite the demonstrated efficacy of early treatment initiation for prevention, one mathematical model of HIV serodiscordant heterosexual couples suggested that early treatment of the infected partner was less cost effective than administering PrEP to the HIV-uninfected partners, assuming PrEP costs less than 40% of the annual cost of ART [35]. In addition, several studies have suggested that many HIV infections occur in the context of acute HIV [36] when a person may not be aware that they have been infected, and may continue to engage in behaviors that are likely to transmit HIV to others. In the United States (U.S.) the 21% of HIV-infected people unaware of their status account for 3.5 times as many new transmissions as those aware of their HIV-infected status [37]. Since PrEP may provide protection to persons who have contact with newlyinfected persons unaware of their HIV status, PrEP and early initiation of ART could offer complementary HIV prevention strategies.

Perinatal Prevention

The success of ART in preventing mother-to-child HIV transmission supports the rationale of using ART to prevent HIV transmission [38, 39]. U.S. recommendations for reduction of perinatal transmission from HIV-infected mothers to their infants include combination ART administered to the mother antepartum and intrapartum to lower her viral burden and as transplacental pre-exposure prophylaxis to the infant coupled with postpartum antiretroviral post-exposure prophylaxis for the infant [38]. The peripartum use of antiretrovirals as pre and post-exposure prophylaxis has decreased the rate of perinatally transmitted HIV infections from 23% to less than 2% in the U.S. [39].

Post-Exposure Prophylaxis

The prevention of perinatal transmission is not the only setting in which post-exposure prophylaxis (PEP) has been used for HIV prevention. In a case-control study, health care workers who had an occupational exposure to HIV who were prescribed zidovudine as PEP for up to 4 weeks experienced an 81% reduction in their risk of HIV acquisition [5]. Multiple observational trials of PEP after non-occupational (ie, sexual) exposures suggest a protective benefit; however, none have been sufficiently large or randomized to demonstrate a definitive benefit [40]. One study of PEP use among Brazilian MSM suggested that individuals may inaccurately gauge their exposure risk, missing opportunities to benefit from PEP [7]. Given this potential limitation of PEP, ie that risk may not be readily assessed, PrEP may provide more reliable protection.

Macaque Models of Pre-Exposure Prophylaxis

In macaque models, subcutaneous administration of tenofovir, a nucleotide reverse transcriptase inhibitor (NRTI), as a single agent for PrEP decreased rates of simian retroviral infection after repeat rectal exposures [41]. However, an oral NRTI combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) provided better protection. No transmissions occurred with subcutaneous FTC-TDF administered a few hours prior to exposure and then within 24 h after exposure [41, 42]. Macaque models have also shown

that 1% tenofovir vaginal microbicide gel provided 100% protection against retroviral challenge demonstrated in six macaques [43].

Human Trials: Topical PrEP

Prior to recent successes using antiretroviral microbicides, topical agents with non-specific mechanisms of action did not demonstrate efficacy. Nonoxonyl-9, a surfactant, and BufferGel, which maintained an acidic vaginal pH, were not protective [44, 45]. Subsequent studies evaluated large polyanionic topical microbicides: Carraguard [46], PRO 2000 gel [45, 47], or Cellulose Sulfate [48], to prevent HIV binding in vitro [49]. Despite proven efficacy in macaque models, none of these agents were found to protect women against HIV.

Current data now demonstrate the success of topical chemoprophylaxis. The Centre for the AIDS Program of Research in South Africa (CAPRISA), in a double-blind, randomized controlled clinical trial (RCT) of peri-coitally-administered 1% tenofovir vaginal gel in 889 South African women, demonstrated a 39% decrease in new HIV infections [50••]. This study had 72% reported adherence to two peri-coital doses of gel [50••]. With increased adherence (at least 80% of coital episodes), there was a 54% decrease in HIV incidence [50••]. Interim data review of the VOICE trial discovered the study would not be able to prove efficacy of the topical tenofovir microbicide arm and closed that arm of the study [51]. The reasons for the disparate findings in CAPRISA 004 and VOICE regarding topical tenofovir gel effectiveness are under study and could relate to the regimen (peri-coital vs daily dosing), differences in participant adherence patterns, risk behaviors and genital tract environment (e.g., STDs, personal hygiene practices). Topical therapy allows high drug concentrations in the genital tract with limited systemic absorption, which may yield a better safety profile [52]. Macaque pharmacokinetic data suggest that intravaginal tenofovir microbicide gel may yield significant concentrations in the rectal mucosa within 15 min of vaginal administration [53]. More studies are needed; however, this suggests intravaginal use may protect women from HIV transmission due to anal sex. Novel permutations of topical delivery systems undergoing evaluation include: use of other antiretrovirals such as dapivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), as a single agent or coformulated with maraviroc, a CCR5 inhibitor approved for oral treatment [54, 55]; MIV-150 a poorly absorbable NNRTI [56]; and a variety of other binding and integrase inhibitors [57]. Alternate delivery systems such as a microbicide ring may offer enhanced adherence, acceptability, and/or pharmacokinetic properties (Table 1) [58].

Rectal Microbicides

In the developed world, the largest number of new HIV infections are among MSM [59], and increasingly, MSM transmission has been documented as a driver of the epidemic in developing nations in Africa, Asia, and Latin America [60]. The majority of MSM HIV transmission has been due to receptive anal intercourse, which is more efficient than vaginal intercourse [13]. A recent study found that the rectal administration of the 1% tenofovir gel formulated for vaginal use was not well tolerated, likely due to a glycerin component that can promote peristalsis [61]. A new rectal formulation with decreased glycerin is under study in men and women, as 5%-20% of at-risk women in the US and Africa engage in anal intercourse [62]. A rectal microbicide formulation of an NNRTI, UC 781, with limited systemic bioavailability has shown safety and acceptability in Phase I trials, however solubility problems halted further development, and no efficacy trials are underway [63].

Human Trials: Oral PrEP

Three clinical trials have demonstrated that oral PrEP effectively decreases sexual transmission of HIV. The Pre-exposure Prophylaxis Initiative Trial (iPrEx) randomized approximately 2500 gay or bisexual men and transgender women to once-daily FTC-TDF or placebo and found a 44% reduction in HIV incidence in the intervention group [64••]. A case-control sub-group analysis found that patients with detectable levels of free FTC or TDF or their intracellular metabolites had a 92% decreased risk of becoming infected when compared to study participants in whom no detectable study drug was found [64••], linking the prophylactic effect of the antiretrovirals to adherence.

Despite the efficacy of PrEP among at-risk MSM demonstrated in iPrEx, the potential efficacy of PrEP for heterosexual women has been questioned. An interim data assessment of the FEM-PrEP trial, an RCT of daily oral PrEP with FTC-TDF compared to placebo among high risk African women, revealed no difference in the rate of new HIV infections in the intervention group [65], and the trial was stopped. Nonetheless, two subsequent trials have demonstrated efficacy of daily oral PrEP in heterosexual populations. TDF2, an RCT of daily FTC-TDF among approximately 1200 healthy heterosexual men and women in Botswana yielded a 63% reduction in the risk of HIV acquisition [66]. Likewise, Partners PrEP, a phase 3 trial of 4758 heterosexual, HIV serodiscordant couples in Kenya and Uganda, demonstrated 62% fewer infections than placebo among HIV-uninfected partners randomized to take TDF alone and 73% fewer HIV infections than placebo among those randomized to take FTC-TDF [67]. The VOICE trial enrolled 5000 women in several countries in Sub-Saharan Africa to evaluate the relative protection of oral TDF, FTC-TDF or topical TDF compared to gel or pill placebos, but discontinued its oral TDF arm, because the Data Safety Monitoring Board determined that arm would not be able to demonstrate enhanced protection compared to placebo [69]. The discrepancies in trials which showed that oral chemoprophylaxis protected women (Partners PrEP and TDF2) and the results of FEM-PrEP and the oral tenofovir arm of VOICE are still being evaluated. The cervicovaginal tissue concentrations of tenofovir after oral administration may not be as protective as those achieved by vaginal gel application [68].

Implementation Considerations

The roles of adjunct prevention strategies, optimal dosing strategies, potential emergence of drug resistance, long term drug safety considerations and acceptability will need further elucidation before PrEP is widely utilized. In each PrEP trial, participants were offered risk reduction counseling, free condoms and testing and treatment for HIV and other sexually transmitted infections diagnosed during the studies; so demonstrated efficacy was not in real world clinical settings. Intermittent chemoprophylaxis dosing has decreased retroviral transmission in macaque models, and is under study in clinical trials; however, preliminary data from an East African trial hints at adherence challenges for a post-coital PrEP dose, with 25% adherence among MSM and female sex workers and 50% adherence among serodiscordant couples [70].

Safety Concerns

Because no human PrEP trial has demonstrated 100% efficacy, continued medication use could select for drug-resistant virus after breakthrough infections. Tenofovir and emtricitabine predominate PrEP trials because of their long half lives and high mucosal concentrations [71] and compose the backbone of first line ART [72]. If drug resistance emerges among significant numbers of PrEP users resistance could create challenges for HIV treatment [73]. In macaque studies, most breakthrough infections occur with wild type virus; however, in one investigation the M184 signature mutation for emtricitabine

resistance emerged in 33% of breakthrough infections [41]. A subsequent macaque model of rectal HIV transmission demonstrated that daily FTC-TDF successfully prevented transmission of an emtricitabine resistant virus bearing the M184V mutation. In iPrEx, of 10 participants already HIV-infected at the time of enrollment in the window period of acute HIV, 3 demonstrated emtricitabine resistance on genotypic analyses. FTC resistance in the participants randomized to receive placebo likely reflects primary acquisition of a resistant viral strain. However, for the 2 participants randomized to FTC-TDF, the drug-resistant virus could represent either transmitted or newly-evolved resistance in the presence of drug [64•], highlighting the critical importance of ruling out HIV infection prior to initiating PrEP. Population models exploring emergence of drug resistance in the context of antiretroviral selection pressure suggest that increasing use of antiretrovirals for treatment would likely contribute more to the emergence of drug resistance than antiretrovirals used for PrEP, if PrEP implementation involves rigorous pre-initiation HIV screening coupled with frequent periodic screening during use [74, 75].

Although the side-effect profile for many of the drugs being considered for PrEP is well defined for HIV-infected people, less is known about how their side effects among non-infected people. In iPrEx, serious adverse events were rare, and nausea and mild inadvertent weight loss (in about 1-2% of the study participants) were the only statistically significant adverse events. Despite a non-significant trend towards elevated creatinine among the intervention group, all but one participant who stopped study drug because of creatinine elevations resumed without incident [64•]. TDF has been associated with renal injury for some patients when used for HIV treatment [76]. To date, no clinically significant nephrotoxicity has been shown among men or women using daily TDF prescribed as PrEP, whether oral or topical [77, 78]. Nonetheless, each of the PrEP trials excluded participants with pre-existing renal problems, and many participants were non-adherent to their PrEP regimens, so clinicians will still need to monitor PrEP users carefully.

TDF used as ART is also associated with bone mineral density (BMD) loss [79]. A study of daily oral PrEP among MSM found 1% BMD loss at the total hip and femoral neck compared to placebo among the men randomized to TDF, though the rate of bone fractures was no different [80]. An iPrEx sub-study evaluating changes in BMD in the FTC-TDF group also revealed small but statistically significant changes of up to 1% BMD loss [81] with no corresponding difference in fractures, though follow-up was variable and limited. Although BMD was not measured in CAPRISA, rates of fractures did not differ between those randomized to tenofovir gel or to placebo [50•]. Longer term studies of BMD with chronic PrEP use are needed to understand whether the small, but statistically significant, changes increase over time or plateau, and assess future clinical relevance.

Population Specific Issues

Heterosexuals in hyperendemic developing regions, MSM with multiple partners, at-risk women whose local community has a large number of HIV-infected men and injection drug users who do not avail themselves of harm reduction techniques could be key candidates for PrEP. Additional data regarding PrEP efficacy among at-risk women is forth-coming from on-going trials of topical and oral PrEP in South Africa and for injection drug users participating in a study of oral tenofovir in Thailand. As efficacy data emerges attention should focus on ensuring access to PrEP among populations facing barriers to preventive interventions, with messages framed in culturally acceptable contexts.

Acceptability of New HIV Prevention Strategies

These new data engender many questions of how to best tailor early ART and chemoprophylaxis to sustainably decrease HIV incidence. At-risk sub-populations have

different motivators and barriers to PrEP use, including efficacy concerns, cost, and delivery mechanism. U.S. women found taking a daily preventive pill more acceptable than using a gel, whereas women from 3 African sites found both to be equally acceptable and noted the gel enhanced sexual pleasure [82]. Peruvian female sex workers viewed a daily pill to prevent HIV as acceptable in the context of their occupation, while MSM and transgendered individuals found daily use impractical and not aligned with their lifestyle habits. Female sex workers and transgendered individuals expressed concerns about stigmatization by health care workers yet still preferred product dissemination in a health care setting to facilitate privacy. Cost was the single greatest indicator of acceptability followed by efficacy and presence of side effects [83]. At-risk Boston-area men who reported unprotected anal sex with men in the prior year with low educational attainment and moderate income level indicated a higher likelihood of using PrEP than more educated and affluent MSM, though their interest was sensitive to the presence of side effects and cost [84]. Indian heterosexual couples focused on issues of trust, sexual pleasure, efficacy and safety as key for acceptability of a microbicide gel [85]. 97% of CAPRISA participants reported that they would use the microbicide if it was found to be efficacious [50••].

Implementing PrEP in Clinical Settings

The CDC published provisional guidelines on the use of oral PrEP for MSM, based on the iPrEx results [86•]. Topical PrEP is not yet available in clinical settings as it is not FDA-approved or commercially manufactured, though confirmation of the efficacy of TDF 1% gel in ongoing studies, such as the FACTS trial, could facilitate the FDA-approval process. Rapid uptake of oral PrEP with FTC-TDF could occur because these drugs are already FDA-approved for treatment indications. Many at-risk people may not be engaged in care, creating a challenge of who will prescribe and monitor the use of PrEP, particularly if administered systemically. Finally, present uncertainty about ideal dosing strategy limits the ability to accurately calculate cost-effectiveness, with one model estimating a cost of \$298,000 per quality adjusted life year gained among high risk MSM [87] and another estimating a range from \$200 to \$4900 per quality adjusted life year among serodiscordant South African couples depending on efficacy and risk profile, when using generic medication [88]. The success of PrEP programs will be contingent upon addressing potential structural barriers, eg cost and challenges in accessing health services.

Conclusions

Since the peak of the HIV epidemic in 1999, a 19% global decrease in HIV incidence has occurred. Targeted efforts to treat HIV-infected patients in many high prevalence regions have been associated with a 25% regional decrease in HIV incidence over the past decade [2]. Despite this progress, over 2.6 million new HIV infections are diagnosed each year world-wide [89]. In the U.S., where antiretrovirals have been widely available since early in the epidemic, HIV incidence has remained stable at an estimated 48,000 new infections per year since 2006 [90]. However, a recent CDC data release highlights the 48% rise in incidence of HIV infections among MSM most notably in the African-American community and underscores the need for new prevention approaches [90].

Early initiation of HIV treatment and PrEP are promising elements of a multifaceted HIV prevention strategy incorporating behavior modification strategies, condom use, male circumcision and access to clean needles. HIV testing prior to PrEP initiation will identify undiagnosed cases of HIV, another important aspect of epidemic control as earlier treatment can decrease HIV incidence, but entails increased medication and monitoring costs [35]. From a cost-effectiveness and risk mitigation perspective, focusing on high risk populations identified through regional behavioral and demographic data may be a useful approach

given the heterogeneity of the global HIV pandemic. If ongoing research shows intermittent oral and/or topical PrEP to be as effective as daily use, this approach would limit cost and exposure to potential adverse effects making PrEP a more appealing strategy. The use of antiretroviral agents for prevention should be seen as important new adjuncts to existing prevention interventions, but also an area that will continue to evolve as new data emerge.

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Table 1**Current Antiretroviral Topical Microbicide Trials [91]**

Candidates	Study	Population	Status
Tenofovir vaginal gel vs.placebo	FACTS 001 [91]	2200 HIV-uninfected women with Hepatitis B in South Africa	Phase III - Ongoing
Tenofovir gel vs. placebo; Oral Tenofovir vs. Tenofovir- Emtricitabine vs. oral placebo	VOICE (Microbicide Trials Network 003) [91]	5000 heterosexual women in Malawi, South Africa, Uganda and Zimbabwe	Phase IIb - Ongoing (Oral Tenofovir arm discontinued) [69] (Tenofovir gel arm discontinued) [92]
Tenofovir rectal gel	Microbicide Trials Network 007 [91]	63 US men and women	Phase I - ongoing
Tenofovir rectal gel	Project Gel [91]	240 MSM in the US and Puerto Rico	Phase I - Ongoing
Dapivirine vaginal gel	International Partnership for Microbicides 014B [91]	320 women in South Africa	Phase I/II – Analysis
Dapivirine vaginal gel	International Partnership For Microbicides 020 [91]	180 US women	Phase I/II - Ongoing
Dapivirine vaginal gel	International Partnership For Microbicides 014 [91]	320 women in South Africa, Kenya, Malawi, and Rwanda	Phase I/II - Ongoing
Dapivirine vaginal gel	International Partnership For Microbicides 015 [91]	280 women in South Africa, Kenya, Malawi, Rwanda, Tanzania	Phase I/II - Ongoing
Dapivirine vaginal ring	International Partnership For Microbicides 013 [92]	48 women in Belgium	Phase I - Completed
Dapivirine ring; dapivirine- maraviroc ring	Microbicide Trials Network-013/ International Partnership for Microbicides 026 [92]	48 US women	Phase I - Enrolling