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Chemoprophylaxis for HIV Prevention: New Opportunities and New Questions

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Abstract

Growing data suggest that antiretrovirals can be used as an effective means of HIV prevention. This paper reviews the current status and future clinical prospects of utilizing antiretroviral chemoprophylaxis before and after high-risk HIV exposure to prevent HIV transmission. The discussion about using antiretrovirals as a means of primary HIV prevention has moved to the forefront of public health discourse because of a growing evidence base, the increased tolerability of the medications, the decreased cost, the ever expanding formulary, and the limitations of other approaches.

Keywords

HIV; AIDS; primary prevention; ART; preexposure prophylaxis; postexposure prophylaxis; topical microbicides

WHY ANTIRETROVIRALS FOR PRIMARY HIV PREVENTION?

With more than 2.5 million new HIV infections annually1, HIV prevention is at a crucial juncture, since most biomedical interventions have failed to effectively decrease HIV acquisition,2 an effective HIV preventive vaccine remains years away,3 and many behavioral strategies have not led to durable reductions in the number of new HIV infections.4 Growing observational and modeling data suggest that antiretrovirals (ARVs) can be used as an effective means of HIV prevention.[5] Antiretroviral therapy (ART) for prevention includes not only prompt initiation of HIV-infected individuals on treatment to decrease the risk of transmission6,7 *(see* El-Sadr in this Supplement) but also ART prophylaxis for at-risk uninfected individuals.8 Numerous animal model studies have demonstrated that ART administered parenterally, orally, or topically before or just after retroviral challenge was protective against HIV acquisition.9,[10] Historically, treatment as prevention, or chemoprophylaxis, has been routinely used for other infectious diseases, including malaria, tuberculosis, and sexually transmitted infections (STIs),[11,12] but the

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duration of administration is generally days to months rather than many years, as may be the case with HIV medications.

Antiretroviral postexposure prophylaxis (PEP) to prevent HIV acquisition was first recommended for use in occupational settings more than a decade ago.[13] Subsequent studies have led to recommendations for its use in nonoccupational settings, and research is underway to examine whether ART preexposure prophylaxis (PrEP) could be an effective method of primary prevention for individuals who have ongoing risks for becoming HIV-infected.9,14. This paper reviews the current status and future clinical prospects of utilizing antiretroviral chemoprophylaxis before and after high-risk HIV exposure to prevent HIV transmission.

POSTEXPOSURE PROPHYLAXIS

The best proof of concept for the relationship between ARVs and HIV transmission comes from studies of the prevention of mother-to-child transmission (PMTCT)15,16 and a case-control study of postexposure prophylaxis (PEP) following needle stick injury in health care settings.17 The Centers for Disease Control and Prevention (CDC) registry documented that health care workers who took zidovudine (AZT) monotherapy following occupational exposure were one fifth as likely to become HIV-infected as those who did not take treatment.13,17 The rhesus macaque SIV challenge model has suggested that 28 days of ART is needed for optimally effective PEP18 and has been the basis for the recommendation of a 4-week course for humans exposed to HIV. In the past, a major impediment to wider implementation of PEP utilization was the relative intolerability of first-line agents, such as azidothymidine and protease inhibitors (PIs).19 A study examining PEP uptake in several European emergency departments found that almost half of the individuals did not complete the full 28-day PEP course because of decreased tolerability of regimens, including zidovudine/lamivudine and either ritonavir-boosted lopinavir or atazanavir.20 A subsequent case-control study of nonoccupational PEP found that men who took tenofovir–emtricitabine were more likely to complete a 28-day course of PEP than historical controls taking 2-drug AZT-based regimens.21 Other newer drugs may also offer opportunities for novel PEP strategies due to improved tolerability and novel mechanisms of action (eg, raltegravir)22 and/or high genital tract concentrations (eg, maraviroc).23 It remains to be fully elucidated whether 2 would be preferable to 3 for PEP. A 2-drug regimen would decrease regimen complexity (eg, 1 to 3 coformulated pills a day), increasing tolerability and completion rates, but alternatively, if the individual has been exposed to a treatment-experienced HIV-infected source, more drugs could provide extra protection against the selection for drug resistant virus.24

Though PEP has not been widely utilized outside occupational healthcare settings, concerns have been raised by some that wider utilization may be counterproductive among individuals at increased risk for HIV by decreasing their protective behaviors.. A study of MSM in Brazil did not demonstrate increases in risk-taking behaviors after PEP, and HIV incidence was significantly lower in PEP users.[25] Because this was not a randomized controlled trial, unintended biases could have been present (eg, PEP users being generally less risky, etc). Other studies have included prevention counseling to increase the intervention's long-term efficacy, to optimize the educable moment when at-risk individuals are seeking to protect themselves from infection.[25,26] Despite efforts to use the PEP clinical encounter as a means to help people decrease risk-taking behavior, the San Francisco Health Department STD Clinic found that 1.3% of PEP users became HIV-infected within 6 months after completing their medication course, underscoring the need for sustained behavioral interventions for those at increased risk in addition to the provision of drugs.27

PREEXPOSURE PROPHYLAXIS

In situations where the likelihood of HIV exposure can be anticipated ahead of time, ARVs delivered in either oral or topical formulations could be a logical mode of primary prevention. The groundwork for current clinical PrEP research has been provided by animal studies over the past decade.[10] The most widely studied antiretroviral for PrEP, tenofovir, has many features that are desirable in a chemoprophylactic agent, including long intracellular half-life, activity in monocyte/macrophages and other cells that may transmit HIV in genital secretions, and high concentrations in genital tissues.[28] Preclinical nonhuman primate studies that evaluated the efficacy of tenofovir-based PreP found that the drug could protect against HIV acquisition when used topically or systemically.[29] Subsequent macaque studies suggested possibility of intermittent dosing, given the high rates of protection found as long as animals received at least one dose preexposure, and another about 2 hours after the viral challenge.[30,31]

The ideal PrEP agent would have a long half-life, achieve high concentrations in target tissues, have a high barrier to the development of drug resistance, and be safe and inexpensive (Figure 1). Although all current clinical trials of PrEP involve tenofovir plus or minus emtricitabine, concerns have been raised about reliance on these drugs for chemoprophylaxis because they are mainstays of treatment. In the worst case scenario, individuals might use chemoprophylaxis intermittently, and if they did not undergo frequent HIV screening, they could select for, and then transmit, drug-resistant strains. Thus, other ARVs have been suggested as promising candidates for a multidrug PrEP regimen. Lamivudine and emtricitabine may be optimal for use as PrEP because of their great tolerability and long safety record, and strains that become resistant to these drugs almost invariably develop the M184V mutation, conferring decreased viral fitness,[32] minimizing the risk of onward transmission to sex partners. Other well-studied antiretroviral agents may not be optimal for PrEP because they do not penetrate genital tissues in adequate concentrations,[33] which is a function of relative protein binding and other pharmacodynamic properties.[34] Protease inhibitors are highly protein-bound, achieving lower concentrations in the genital tract, compared to nucleoside analogues and nonnucleoside reverse transcriptase inhibitors.[35,36] The oral CCR5 coreceptor antagonist maraviroc achieves high genital tract and rectal concentrations[37] and could be effective as PrEP.[37] If the initial tenofovir-based PrEP trials demonstrate efficacy, future studies may focus on the evaluation of other drugs with novel mechanisms of action and/or different pathways of resistance.

CURRENT STATUS OF PrEP CLINICAL TRIALS

Multiple clinical PrEP trials are underway among different communities globally to examine the impact of oral and/or vaginal tenofovir or emtricitabine/tenofovir on HIV acquisition (Table 1). These trials will enroll more than 20,000 HIV-uninfected men and women to address a variety of questions, including proof of concept, and if effective, then whether intermittent PrEP can be used, whether topical or oral PrEP is more effective, and whether drug resistance emerges as a clinical problem because of extensive use of these medications for chemoprophylaxis. All of these studies are examining the influence of PrEP on risk-taking behaviors.[38] These studies are occurring among MSM in the Americas, Thailand, and South Africa; among at-risk women in sub-Saharan Africa; among HIV-discordant couples in Africa; and among Thai injection drug users. Most of these trials are evaluating daily dosing; a few will also include intermittent dosing strategies.[39] A community-based organization, the AIDS Vaccine Advocacy Coalition (www.avac.org), has developed a PrEPWatch feature that provides continuously updated information about the status of clinical trials currently underway.

The results of the first human PrEP study, a phase II, randomized double-blinded placebo controlled trial, was completed in 2007 and demonstrated the safety of daily oral tenofovir compared to a placebo for HIV prevention among high-risk West African women who received HIV testing, counseling, and condoms.[40] Women in the intervention arm had fewer seroconversions than women in the control arm (8 vs 2), but this difference was not statistically significant.40›41 Importantly, both groups of women reduced their behavioral risk during the course of the study. Initial data suggests that efficient recruitment and implementation of large-scale phase III PrEP trials is possible with motivated participants and community engagement.42 One earlier planned PrEP study among Cambodian female sex workers never began enrollment because of community concerns, which led to extensive discussions among researchers, public officials, and other key stakeholders in order to anticipate concerns that might be raised in different communities—for example, regarding access to medication after trial completion.43 Over the next few years, data will become available to address whether oral tenofovir by itself, oral tenofovir coformulated with emtricitabine, or topical tenofovir gel (ie, a microbicide) will be more effective relative to placebo.[44]

An area of concern has been the development of drug resistance through the continued use of PrEP if participants unknowingly become HIV-infected, either by exposure to a drug-resistant virus, suboptimal adherence, or failure of the regimen (eg, inadequate tissue penetration). Individuals who had 2 weeks of tenofovir monotherapy (as a run-in to a study of a 3-drug-regimen) did not develop tenofovir resistance.[45] In monkeys who were challenged with tenofovir-resistant SHIV, the use of tenofovir as PEP prevented HIV infection.46 Mathematical models of HIV prophylaxis have suggested that less than 1% of the predicted serconversions would develop a tenofovir-resistant strain.47 Due to the increasing use of tenofovir as part of first-line treatment regimens, continued monitoring to assess the effects of PrEP is warranted.

Data from oral and topical PrEP studies were presented at the International AIDS Society meetings in Vienna in July 2010. A study of 400 at-risk MSM, recruited in 3 US cities, compared the use of oral tenofovir to a placebo and found no evidence of increased clinical toxicities (particularly no increased renal insufficiency, bone demineralization, or other side effects) or increased sexual risk taking among the men assigned to tenofovir compared to those who received the placebo.48 Although this safety study was not powered to demonstrate drug efficacy, no new HIV infections were detected among the men who received the tenofovir. Another very important study, CAPRISA 004, studied tenofovir gel in high-risk women in KwaZulu-Natal, South Africa, and found that the women assigned to the tenofovir gel were significantly less likely to become HIV infected than those who used placebo gel49). Although the route of administration is different than oral chemoprophylaxis, the finding of a significant level of protection by a topical antiretroviral medication is a key observation, raising the hope that oral PrEP studies will also demonstrate a protective effect. Ultimately, it will be important to determine which route of administration is most effective for each specific population, since local anatomy (eg, vaginal versus rectal mucosa) and tissue pharmacology may determine the relative advantages of one approach over another. The VOICE trial being conducted by the NIH-funded Microbicide Trials Network (www.mtnstophiv.org) will be the first to evaluate an antiretroviral gel compared to oral medication, and may be a harbinger of future studies to determine the optimal chemoprophylactic strategies.

The success of the CAPRISA 004 study is important to prevention science, as the first demonstration of the ability of chemoprophylaxis to decrease HIV incidence and as the first proof of the protective effects of a topical microbicide. Future microbicide trials will evaluate other topical antiretroviral drugs, including dapivirine, a nonnucleoside reverse

transcriptase agent, as well as other targets of the HIV life cycle, such as entry and integrase inhibitors. Future human studies will also assess whether other delivery mechanisms, ranging from vaginal rings to injectable compounds, might enhance product efficacy by decreasing the challenges of daily or coitally dependent adherence. More current information can be found on the Microbicide Trials Network website (www.mtnstopshiv.org) and the AIDS Vaccine Advocacy Coalition website (www.avac.org).

IMPLEMENTATION OF ANTIRETROVIRAL CHEMOPROPHYLAXIS

If PrEP is found to be an effective mode for HIV prevention, concerns about wider utilization include risk compensation, cost (ie, who will pay?), acquisition of resistant virus, adherence, and drug-related toxicities. The CDC and the World Health Organization have begun to meet regularly to anticipate community responses and to work with clinicians, national governments, and representatives of at-risk communities, as efficacy data becomes available.[50] Providing ART to uninfected individuals will also need to be balanced with the imperative to provide prompt treatment access to HIV-infected individuals meeting guidelines for treatment initiation. However, it is possible that PrEP could be a cost-effective means of HIV prevention for younger and high-risk populations in the United States,51 given the high cost of treating new HIV infections over the life course.

If PrEP is found to be effective, questions will arise as to who should prescribe these drugs and how best to train providers. ART as PrEP will require researchers and clinicians to optimally utilize these agents in a focused manner to reduce the number of new HIV infections. Identifying individuals at high risk for HIV infection and then initiating them on PrEP could be a major challenge, given continued stigma associated with behaviors that put individuals at increased risk of acquiring HIV. Major areas that will require further clinical research include monitoring long-term safety, development of adherence strategies, assessing methods of optimal drug delivery and dosing, and minimizing selection of resistant viruses. Addressing these questions will require expanded safety and effectiveness trials as well as the development of public surveillance systems to monitor HIV incidence, risk compensation, and resistant virus evolution. Patients in clinical settings will require ongoing and regular HIV testing to avoid substandard therapy in the case of becoming HIV infected. Individuals with tenofovir-resistant virus could compromise their own treatment options and could spread resistant virus to their sex partners or offspring.

Potential risk compensation among individuals using PrEP may also compromise its effectiveness.[52] It is possible that individuals could obtain off-label access to drugs in advance of efficacy data becoming available. Reports of ART being sold at clubs and of self administration prior to high-risk sexual activity have emerged,[53,54] but studies from urban US centers have found minimal off-label PrEP use to date.[55,56] However, the potential for widespread and unregulated use persists, and the demand could quickly change, based on when data becomes available to suggest a beneficial effect of PrEP.[53] In order to ensure that PrEP does not lead to risk compensation and to provide PrEP as part of a risk reduction strategy, optimal prevention counseling packages will need to be developed.[57]

CONCLUSIONS: FUTURE OF ART FOR PRIMARY PREVENTION

The promise of ART chemoprophylaxis for uninfected individuals is great, but the field is still in an early stage, and major questions remain.. The discussion about using ART as a means of primary HIV prevention has moved to the forefront of public health discourse because of the increased tolerability of the medications, the decreased cost, the ever expanding formulary, and the limitations of other behavioral and biomedical approaches.

Optimizing the use of antiretroviral agents for HIV prevention will require careful consideration of adherence, sustained access, behavioral risk reduction, and STI diagnosis and treatment. The ability to implement ART for primary prevention in the United States will depend on effectively engaging at risk individuals and educating their providers, as well as decreasing the economic impediments to optimal use.

It is conceivable that in the future certain drugs may be reserved for specific preventive and therapeutic interventions. Further research in pharmacology, virology, behavioral science, and health care service delivery will be needed to better understand the intended and unintended consequences of widely using ART for prevention. PEP and PrEP will likely be part of a larger HIV prevention toolbox that will be used to reduce the number of new infections, a toolbox that would also include behavioral risk reduction strategies, expanded HIV testing, male circumcision, prevention of mother-to-child transmission, and possibly STI treatment.[4, 58] The search for an effective HIV vaccine must continue as well. But in the mean time, the use of multiple partially effective interventions could significantly slow the epidemic.

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Figure 1.
PrEP delivered as a pill vs gel.

Table 1

Current Clinical Trials of PrEP

Trial Name	Population	Location	Drug	Means of Administration	Sample Size	Expected Results
US Extended Safety Trial (CDC* 4323)	Gay men; MSM	United States	TDF	Daily oral	400	TDF is safe and well-tolerated as PrEP for MSM
iPrEX	Gay men; MSM	Brazil, Ecuador, Peru, South Africa, Thailand, United States	TDF/FTC	Daily oral	2500	Fully enrolled 2009; results probable by late 2010
Bangkok Tenofovir Study (CDC 4370)	Injecting drug users	Thailand	TDF	Daily oral	2400	Completed enrollment 2010; possible results 2010/early 2011
CAPRISA 004	Heterosexual women	South Africa	TDF	Coitally dependent topical vaginal gel	1000	First demonstration of the efficacy of tenofovir gel
TDF2 (CDC 4940)	Heterosexual men and women	Botswana	TDF/FTC	Daily oral	1200	Enrollment stopped 2009; safety data likely 2010
Partners PrEP	Serodiscordant heterosexual couples	Kenya, Uganda	TDF and TDF/FTC	Daily oral	3900	Enrolling; data expected 2012
FEM-PrEP	Heterosexual women	Kenya, Malawi, South Africa, Tanzania, Zambia	TDF/FTC	Daily oral	3900	Enrolling; data expected 2013
VOICE (MTN 003)	Heterosexual women	South Africa, Uganda, Zambia, Zimbabwe; additional sites to be determined	TDF; TDF/FTC	Daily oral (TDF, TDF/FTC) Daily topical vaginal gel (TDF)	5000	Enrolling; data expected 2013
ATN 082	High-risk young MSM	United States	TDF/FTC	Daily dosing with or without a behavioral intervention	100	Enrolling; results in 2011 or 2012
Studies Involving Intermittent PrEP (i-PrEP)						
IAVI E001 and E002	Serodiscordant couples and at-risk men and women	Kenya, Uganda	TDF/FTC	Daily oral; intermittent oral (twice weekly + coital dosing)	150	Full enrollment expected 2010
HPTN 066	Low-risk men and women	United States	TDF/FTC	Different dosing strategies planned	48	Intense pharmacokinetic study; full enrollment expected 2010
HPTN 067	High-risk women and MSM	Thailand, South Africa	TDF/FTC	Fixed interval vs coitally dependent	360	In planning stages

*CDC denotes Centers for Disease Control and Prevention; FTC, emtricitabine; MSM, men who have sex with men; TDF, tenofovir; IAVI, the International AIDS Vaccine Initiative; and HPTN, the HIV Prevention Trials Network.