Antiretroviral Therapy as HIV Prevention: Status and Prospects

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As antiretroviral treatment of HIV infection has become increasingly accessible, attention has focused on whether these drugs can used for prevention because of increased tolerability of newer medications, decreased cost, and the limitations of other approaches. We review the status of antiretroviral HIV prevention, including chemoprophylaxis, as well as the effects of treatment of infected individuals on prevention. It is possible that the life-saving agents that have transformed the natural history of AIDS can be a critical component of HIV prevention efforts, but their ultimate role in affecting HIV transmission dynamics remains to be defined. (*Am J Public Health.* 2010;100:1867–1876. doi:10.2105/AJPH.2009.184796)

HIV continues to spread rapidly, with more than 2.5 million new infections each year.[1] Efficacious behavioral interventions, when scaled up to achieve sufficient coverage in many populations, have not resulted in durable declines in HIV incidence, and it will take years to demonstrate the efficacy of highly effective HIV-preventive vaccines.[2–4] For more than a decade, increasingly well-tolerated highly active antiretroviral therapy (HAART, which incorporates 3 or more antiretroviral therapy [ART] medications) has dramatically changed HIV-associated morbidity and mortality and has improved the quality of life of HIV-infected individuals.[5,6] Increasing attention has therefore focused on whether available antiretroviral drugs could be used to slow the epidemic. Recent global initiatives have concentrated on expanding access to HIV treatment in resource-limited settings[7]; by the end of 2010, more than 5 million people were receiving HAART.[8]

A growing group of researchers and public officials have suggested that 1 or more ART drugs may be useful not only in clinical benefits to individuals, but also in decreasing HIV transmission globally.[9,10] ART has already dramatically decreased mother-to-child HIV transmission[11] and could conceivably be used to prevent the sexual transmission of HIV via reductions in genital tract HIV concentrations in individuals who are already infected,[12,13] or as pre- or postexposure prophylaxis for uninfected people exposed to HIV (Figure 1).[14]

Despite increasing drug availability, however, the effectiveness of ART for prevention may be limited by concurrent sexually transmitted infections (STIs) that increase infectiousness and susceptibility, nonadherence to therapy, drug-related toxicities, viral resistance, treatment costs, and risk compensation. The effects of HAART initiation can manifest differently in diverse social settings because sexual behavior involves concerns over pleasure and procreation. Although early data from the developed world suggested that HAART could be associated with increased sexual risk,[15–18] more recent data from sub-Saharan Africa has suggested that wider access to HAART is not associated with increased sexual risk-taking behaviors.[19–21] The potential uses of ART for HIV prevention are shown in Figure 2.
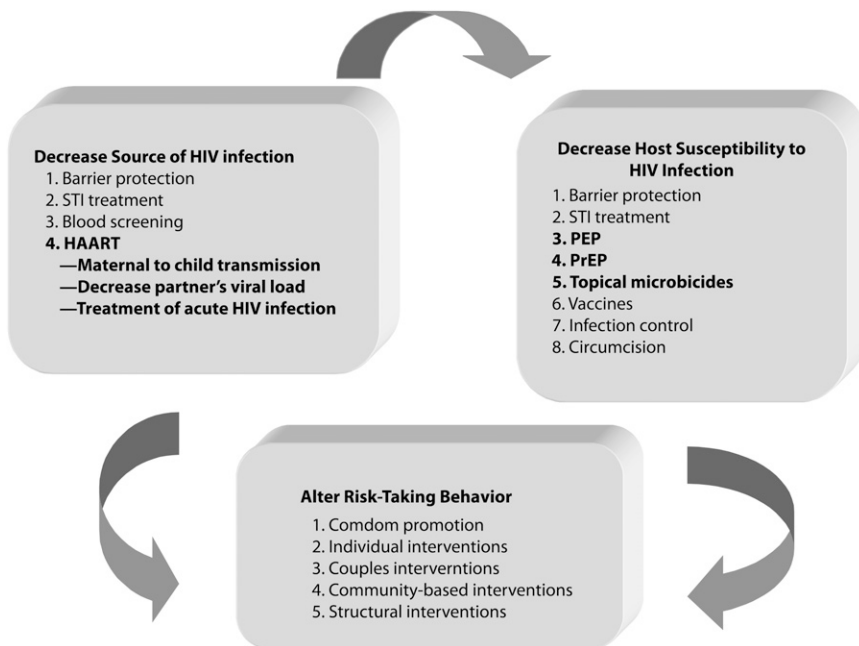
SLOWING THE SPREAD OF HIV

HIV transmission remains a low-probability but high-consequence event occurring in fewer than 1 in 100 contacts on average,[22–24] but the global pandemic is driven by the ubiquity of sexual intercourse and by factors that amplify infectiousness and susceptibility in specific settings. The per-contact calculation is based on composite data, and transmission probabilities vary considerably during the course of the disease, with higher transmission probability in the acute and late phases of HIV infection, when plasma and genital HIV concentrations are higher.[25–29]

The first empirical data about how viral suppression could lead to decreased HIV sexual transmission comes from the Rakai study of Ugandan serodiscordant couples,[30] although this study was completed before generic ART had become widely accessible in Uganda. HIV was not transmitted in discordant couples when the infected partner had a plasma HIV RNA level of less than 400 copies per milliliter.[30] This association between viral load and the risk of HIV transmission among serodiscordant couples was confirmed in subsequent studies in Zambia and Thailand in the pre-HAART era,[31,32] and more recent data showed that HIV-infected partners in discordant relationships were substantially less likely to transmit HIV to their partners if they were on HAART.[33] Another recent African study of serodiscordant couples found that HIV-infected partners who were on HAART were 92% less likely to transmit HIV to their uninfected partners.[33a]

However, other variables besides systemic HIV burden may affect genital tract HIV. Mucosal HIV transmission is complex: animal models suggest that either cell-free or cell-infected virus can replicate in a variety of host cells.[34–36] The minimum inoculum of HIV that can cause human infection remains unclear.[37] Although some studies have documented HIV-preferential binding to cervical and foreskin tissues through dendritic cells,[38,39] women who have undergone hysterectomy and circumcised men can also become infected with HIV,[12,40] suggesting that other urogenital cells can support HIV replication. The temporal window of opportunity for halting transmission through host defenses is very limited, because submucosal viral replication occurs within hours of exposure.[41]

In the first study examining the relationship between treatment and the detection of genital tract HIV, the virus was more readily cultured from seminal plasma and leukocytes in participants with leukocytospermia or advanced disease stage and less likely to be detected in semen among men taking zidovudine.[42] Subsequent semen studies found that genital white blood cells were a significant source of viral burden.[43,44] These data suggest that
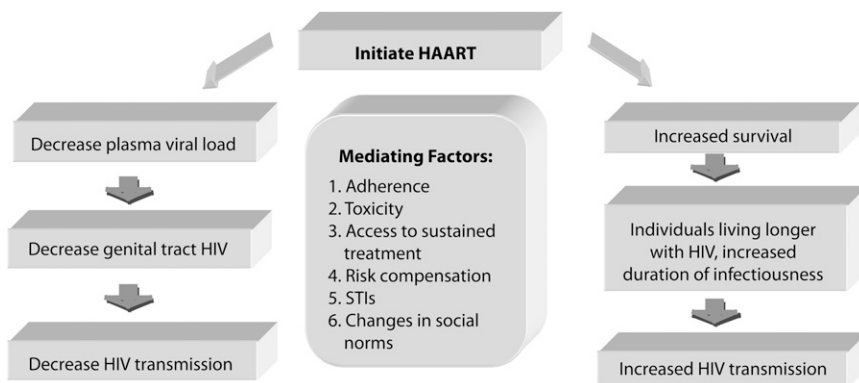
Note. HAART = highly active antiretroviral therapy; PEP = postexposure prophylaxis; PrEP = preexposure prophylaxis; STI = sexually transmitted infection. Bolded items are those that use antiretroviral agents.

FIGURE 1—Potential approaches to prevent HIV transmission.

factors that increase genital tract inflammation may promote infectiousness and that ART could decrease infectiousness, presumably by decreasing viral burden.

Several studies have demonstrated that HAART suppresses viral replication not only in the blood and lymphoid tissues but also in the male and female genital tract.[12,13,45,46] Although treatment generally suppresses cell-free virus in the semen, many treated individuals can still harbor proviral CD4 cells in their semen.[44,47] A further complication is that various HAART drug combinations may not be equally effective in suppressing HIV in genital tissues and systemically.[12,48] Differential penetration of ART drugs in genital tissues may be a function of protein binding and other pharmacodynamic properties.[49] Highly protein-bound

drugs, such as protease inhibitors, achieve lower concentrations in genital tract secretions than in blood plasma.[14,50] Nucleoside analogs and nonnucleoside reverse transcriptase inhibitors achieve higher concentrations in genital tract secretions than in blood plasma,[51–53] which might make them particularly effective in decreasing sexual transmission of HIV.

These findings have led to questions about the optimal timing for HAART initiation if a primary goal is to decrease infectiousness among those who could transmit HIV to others. One key period for treatment could be the acute phase of HIV infection, when patients have elevated viremia for about 3 weeks, until host defenses suppress replication, creating a viral set point.[29,54,55] When viral replication is unimpeded during acute HIV infection, individuals may have more than 1 million copies of virus per milliliter of blood,[56] with the potential to infect many individuals.[54,57] Studies from North America and Africa found that between 40% and 50% of new transmissions came from recently infected patients.[54,57] In Malawi, discordant HIV rapid test results and RNA pooling detected acute HIV infection in almost 2% of STI clinic patients.[58]

Promptly identifying microepidemics, or hot spots, of newly infected persons may present an opportunity for early ART and behavioral interventions to slow the spread of HIV in high-risk settings.[59,60] Studies are under way to determine whether early identification and treatment of acutely infected individuals can have a public health impact on local epidemics, but other questions will take more time to address, such as whether treatment can be discontinued without detriment to the patient if it is initiated in the setting of acute HIV infection. Some public health challenges to identifying patients with acute infection are the very short duration of this infection period, lack of clinical detection because patients and providers often do not recognize the symptoms of acute HIV infection, and the expense of performing RNA pooling in an era of constrained health resources.

Acute HIV infection is followed by a longer period of chronic viral homeostasis in which an infected person may be asymptomatic, with good systemic virological control. This period can be interrupted by STI infections, which may override the suppressive effects of ART in

Note. HAART = highly active antiretroviral therapy; STI = sexually transmitted infection.

FIGURE 2—Potential effects of highly active antiretroviral therapy on HIV transmission.

the genital tract by causing inflammation, facilitating local HIV replication.[27] The acute- and late-stage infection periods are relatively short, so the prolonged asymptomatic period, which can last more than a decade, may be when many transmission events occur.[61–63] An analysis from sub-Saharan Africa suggests that acutely infected persons play a major role in HIV transmission during early, highly concentrated epidemics and that the contribution of chronically infected persons becomes more prominent during advanced and stabilized epidemics.[61] A recent projection suggested that annual HIV testing followed by immediate initiation of ART for all HIV-infected patients regardless of CD4 cell count could have a major impact by reducing the number of new HIV infections.[64]

Can HAART effectively suppress genital tract HIV over a sufficiently long period to stop HIV sexual transmission?[65] Studies from Taiwan and British Columbia have documented a greater than 50% reduction in anticipated number of incident HIV cases following the free provision of ART in 1997.[9,66] A study among 393 couples in the pre- and post-HAART eras in Spain observed an 80% reduction in HIV transmission following the introduction of HAART.[67] A recent observational study of sero-discordant African couples showed substantially lower rates of HIV transmission when the partner with HIV was receiving HAART, but these individuals were more likely to practice safer sex than were persons who remained untreated.[33]

To better understand the preventive effects of therapy in serodiscordant couples, the HIV Prevention Trials Network of the National Institutes of Health is conducting a randomized controlled trial to assess the impact of HAART on transmission among 1750 serodiscordant couples in 8 countries.[68] HIV-infected partners in serodiscordant, monogamous relationships who have CD4 counts that would not warrant immediate initiation of HAART according to current guidelines (i.e., >350 cells/μL) are being randomized to initiate HAART right away or to be clinically monitored until their immunological or clinical status warrants treatment. This study is fully enrolled and should provide important information in the near future.

As more individuals live longer with HIV because of HAART, the pool of persons who could transmit the infection will grow if HAART is not fully suppressive and if

infected individuals increase risk-taking behavior. Studies on the effect of ART on sexual behavior among HIV-infected individuals have been inconsistent, and it is not clear whether the provision of ART may be associated with high-risk sexual behavior in some subpopulations.[69,70] Although data from injection drug users and men who have sex with men (MSM) in the developed world suggest that high-risk behavior can increase with ART,[17,71] studies from resource-limited settings to date have not shown that the provision of ART increases HIV risk-taking behaviors.[72]

Interest in evaluating test-and-treat strategies is growing, but other genital tract factors could mitigate the public health impact of early initiation of HAART. For example, concurrent STIs can raise the probability of HIV transmission[73] by attracting CD4 T lymphocytes and releasing cytokines (e.g., TNF-α, IL-1) that enhance HIV transmission.[37] Bacterial STIs can increase genital tract HIV concentrations,[74] and interventions that provide treatment of these infections can decrease viral shedding.[27,75–77] In the Rakai study, HSV-2-antibody–negative participants with viral loads greater than 38 500 copies per milliliter and HSV-2-antibody–positive participants with viral loads lower than 1700 copies per milliliter had a similar probability of transmitting HIV to their uninfected partner.[78] Unfortunately, in many settings HSV-2 seroprevalence in young adult populations exceeds 50%,[79] and 2 studies have documented that thymidine–kinase inhibitor chemoprophylaxis does not decrease HIV transmission to uninfected partners.[80,81] It is possible that the removal of a pathogen that initiated a genitourinary inflammatory response is insufficient to restore the local cellular milieu.

Another concern about the wider use of ART for prevention is the potential for the development and transmission of antiretroviral resistance if healthy individuals are expected to be fully adherent over many years. Multiple reports have documented that resistant HIV has been sexually transmitted.[82] Although ART resistance has been demonstrated with increased frequency in newly diagnosed and treatment-naive patients over time,[83,84] recent findings suggest that ART-resistant HIV strains may have lower viral transmisability.[85] Thus, public health systems around the world will need to track some of the potential unintended consequences

of earlier initiation of antiretroviral therapy for prevention, such as risk compensation, trends in STI coepidemics, and the prevalence and incidence of transmitted ART-resistant HIV, to fully understand the costs, as well as the benefits, of treatment as prevention.

POSTEXPOSURE PROPHYLAXIS

The evidence that suggests that ART can prevent HIV acquisition comes from the success of efforts to prevent mother-to-child HIV transmission,[86] animal studies,[87,88] and a case–control study of postexposure prophylaxis (PEP) following needle stick injury in health care settings.[89] The Centers for Disease Control and Prevention registry documented that individuals who took zidovudine monotherapy following occupational exposure were one fifth as likely to be HIV infected as were those who did not take medication.[89,90] Data from the rhesus macaque model have suggested that 28 days of ART is needed for effective postexposure prophylaxis.[88]

Concerns have been raised that the use of PEP in nonoccupational settings might result in increased risk taking in some populations, such as among MSM. In a Brazilian MSM study, high-risk participants in a behavioral risk reduction study were educated about PEP while being counseled about safer sex, and were given 4-day starter packs of zidovudine and lamivudine. They were told that if they engaged in risky behavior and began to take the medication, they needed to come back to the study site as soon as possible, so they could get the rest of the 28-day course that they would be expected to take. About one third of the 200 high-risk men who were followed for 24 months (68 men) used PEP, a total of 109 times,[91] another one third engaged in risky behavior but did not use PEP, and the remainder heeded the counseling messages and did not engage in risky behavior. The overall HIV incidence in the cohort was 2.9 per 100 person-years; 10 infections occurred among men who did not use PEP and only 1 occurred among the men who used PEP. Although HIV risk-taking behavior may not be constant over time,[92] most studies of PEP after sexual exposure have not demonstrated increases in risk-taking behavior after PEP, and some have included effective counseling so that PEP could

provide an entry for intensified risk-reduction interventions.[91,93,94]

A major impediment to the wider use of PEP in the past was the relative intolerability of some of the first-line recommended drugs, such as Azidothymidine GlaxoSmithKline (Brentford, UK) and protease inhibitors.[95] However, the use of newer drugs, such as tenofovir, seems to be associated with increased tolerability and completion rates, although randomized controlled trials have not compared PEP regimens head-to-head because of logistical issues, such as the huge sample size needed to compare 2 effective regimens. Tenofovir has many features that are desirable in a chemoprophylactic agent, such as long intracellular half-life, activity in macrophages, and high concentrations in genital tissues.[96] A case–control study found that men who took dual therapy with tenofovir and emtricitabine were more likely to complete a 28-day PEP regimen than were historical control participants taking 2 drug regimens containing zidovudine.[97]

It is still not known whether it is preferable to use 2 drugs or 3 for PEP; the argument for 2 is increased tolerability and completion rates,[98] whereas the argument for 3 is that for a person already exposed to HIV, more drugs provide extra protection against drug-selected or spontaneous mutant strains. Other, newer drugs may offer opportunities for novel PEP strategies, because they are well tolerated (e.g., Atazanavir [Bristol-Myers Squibb; New York, NY] or Raltegravir [Merck; Whitehouse Station, NJ])[99] or achieve high genital tract concentrations (e.g., maraviroc [Pfizer; New York, NY]).[100] Although several lines of data suggest that PEP may decrease the likelihood of HIV transmission, in many settings it may be underused because of clinician concerns about risk compensation and cost and because many at-risk individuals are unfamiliar with its potential or with how to access chemoprophylactic treatment.

PREEXPOSURE PROPHYLAXIS

In situations when the likelihood of exposure to HIV can be foreseen, ART preexposure prophylaxis (PrEP), delivered either as oral therapy or as topical microbicide, could be a logical method of primary prevention. In the field of infectious disease preventive care, patients are routinely provided with prophylaxis

prior to exposure when the risk of infection is imminent—examples include antituberculosis therapy and antimalarials. Data from simian studies suggests that tenofovir-containing regimens protect against infection, with rapid drug absorption and high drug levels remaining in intracellular genital tissues[101] and with the possibility of intermittent dosing.[102] Over the past decade, animal studies have provided the basis for clinical PrEP research,[103] although concerns about access to optimal preventive services and medical treatment of vulnerable populations has impeded initial PrEP research.[104] Some concerns about PrEP are possible behavioral disinhibition, ART cost, acquisition of resistant viral strains, treatment adherence, and chronic medication toxicities.

A phase II, randomized, double-blinded, placebo-controlled trial, completed 3 years ago in Cameroon, Nigeria, and Ghana, demonstrated the safety of daily oral tenofovir for HIV prevention among high-risk women also receiving HIV testing, counseling, and condoms.[105] After enrollment, 8 seroconversions occurred, in 2 women who took tenofovir and 6 who received the placebo. Although this difference was not statistically significant, the trend was in the expected direction, and both groups of women reduced their behavioral risk during the course of the study. The number of sexual partners went down, and the proportion of participants reporting condom use increased over time (52% at baseline to 95% at 12 months).[105,106] Despite concerns that PrEP could lead to behavioral disinhibition, an important finding in this study was that risk behavior decreased over time after initiating PrEP.

These reassuring data have encouraged public health researchers to study PrEP in efficacy trials in several high-risk populations around the world. Over the next few years, data will become available about whether oral tenofovir by itself, oral tenofovir coformulated with emtricitabine, or topical tenofovir gel is more effective than are placebos 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. At the recent International AIDS Society (IAS) meetings in Vienna, data were presented that found that oral tenofovir for PrEP was safe, well-tolerated, and was not associated with increases in sexual

risk behavior among 400 US men who have sex with men.[107]

Previous studies demonstrated that topical tenofovir gel is safe and well tolerated; however in more than half of the women in a pharmacokinetic substudy, systemic levels of tenofovir were detected when the drug was administered topically to low-risk women.[107a] For some, this is good news, because systemic absorption means that significant genital tissue levels were achieved, but low concentrations might be less likely to be associated with clinical toxicities. Others have expressed concern because the levels were very low compared with the systemic levels obtained by a 300-mg oral dose, resulting in subinhibitory concentrations. The most significant chemoprophylaxis results were presented recently at the IAS Meetings in Vienna. The CAPRISA 004 study demonstrated the efficacy of topical 1% tenofovir gel in decreasing HIV incidence by 39% in high risk South African women who used the gel before and after sexual intercourse. The protective effect exceeded 50% among women who used the product at least 80% of the time.[107b]

Post-CAPRISA, major questions are how best to deliver chemoprophylaxis and which drugs to use. The ability of topical 1% tenofovir gel to deliver high drug levels to the genital tissues but with lower systematic drug levels[108] led to the VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial, the first study to compare daily use of 1% tenofovir gel versus oral tenofovir and emtricitabine.[109,110] Studies are underway to assess other topical antiretroviral agents. Assessment of the relative merits and limitations of oral versus topical PrEP agents will require, in addition to clinical trials, careful anthropological work to elucidate whether one approach is associated with more sexual pleasure, fewer systemic side effects, and perceptions of efficacy among people in different cultures.

One broad area of concern is the development of drug resistance through the continued use of PrEP after becoming infected because of a resistant virus, suboptimal adherence, or failure of the prophylactic regimen. In an early-phase study of therapeutic uses of tenofovir, when HIV-infected patients initiated therapy with tenofovir alone, no resistance was detected after 28 days.[111] In a nonhuman primate study, after exposure to drug-resistant viral challenge, drug-resistant minor variants were

detected in monkeys, although tenofovir PEP was still partially effective in protecting monkeys from becoming infected.[112] One study observed no tenofovir resistance after tenofovir or tenofovir–emtricitabine failure,[113] and another detected intermittent emtricitabine resistance.[114] When the virus develops tenofovir and emtricitabine resistance, it is hypersusceptible to zidovudine, but the activity of other nucleoside reverse transcriptase inhibitors is diminished; no effect on other classes of drugs has been found.

Two potential concerns about tenofovir prophylaxis have been mentioned in light of current treatment regimens. First, in resource-limited settings, stavudine has been often used as part of first-line drug treatment because it is inexpensive. Of concern is that the HIV subtype C virus that is most prevalent in these settings may preferentially select for a genetic mutation known as K65R. This resistance mutation may occur after exposure to stavudine-containing HAART, which could create tenofovir resistance.[115,116] Thus, wider stavudine use may be selecting for a larger pool of circulating strains with K65R, which could result in failure of tenofovir prophylaxis.

Another worry is that individuals on tenofovir PrEP will develop tenofovir resistance after becoming infected. Mathematical modeling of HIV prophylaxis for primary prevention suggests that fewer than 1% of the predicted seroconversions would acquire or develop a tenofovir-resistant strain,[117] but in a world where tenofovir is increasingly used for first-line antiretroviral therapy, continued monitoring to assess the potential ecological effects of PrEP is warranted. In clinical trials, participants receive frequent HIV antibody testing; patients in clinical settings will also require ongoing HIV testing to avoid substandard therapy should they become HIV infected. In either of these situations, individuals with tenofovir-resistant virus could compromise their own available treatment choices and spread resistant virus to their partners.

Clinical trials of PrEP are under way at multiple sites that will enroll more than 20 000 HIV-uninfected men and women in Asia, South and North America, and Africa and will address the role of continuous versus intermittent PrEP, topical versus oral PrEP, selection of specific drugs, and the influence of PrEP on risk practices.[118] Some of the first PrEP

efficacy data may be available within the next 2 years, so public health officials and clinicians will need to consider how to train providers to make the medications available to at-risk populations and provide careful monitoring and how to use PrEP to create educable moments that facilitate HIV prevention if PrEP works. Partial efficacy and potential toxicity management issues (e.g., what if tenofovir PrEP decreases the likelihood of HIV acquisition by 50%, but a few participants develop renal failure?) are examples of challenges that will arise in the development of clear and succinct messages as clinical trial data matures. One community-based organization, the AIDS Vaccine Advocacy Coalition (http://www.avac.org) has developed a PrEPWatch feature that provides continuously updated information about the status of the clinical trials.

Many clinical questions will arise regardless of the results of the first-generation PrEP studies; an overview of such studies is shown in Table 1. Other antiviral drugs are being considered for chemoprophylaxis, ranging from the oral CCR5 antagonist maraviroc, which achieves high genital tract levels, to UC-781 and TMC-120, which are poorly absorbable nonnucleoside reverse transcriptase agents and thus are being developed as topical microbicides. Injectable agents and compounds that can be delivered through a slow release ring may alleviate the adherence issues associated with stringent daily regimens. Some agents, such as lamivudine and emtricitabine, may be considered to be optimal parts of PrEP regimens because the virus that is resistant to these drugs has decreased viral fitness.[119,120] Thus, individuals who become infected with this less virulent viral stain would be less likely to transmit to their partners. Because of the long intracellular half-life of drugs such as tenofovir, intermittent dosing strategies may make sense.

A challenge for the use of ART for prevention is the possibility that at-risk persons might obtain off-label drugs even in advance of any efficacy data becoming available. One study suggested that ART was being sold at clubs and self-administered prior to high-risk sexual activity,[121] but other reports from San Francisco and Boston found minimal use among MSM in the past 2 years.[122,123] Clearly, the potential for widespread and unregulated use is great, and the environment could change quickly once data showing a beneficial effect from

antiretroviral PrEP are released. Early work suggests that context matters: interest in using PrEP was substantially affected by perceived efficacy, side effects, and cost.[122] Public health authorities, led by the Centers for Disease Control and Prevention in the United States and by the World Health Organization globally, have begun to meet regularly to anticipate community responses and will be mobilized to work with clinicians, national governments, and representatives of high-risk communities, once efficacy data become available.[124]

OPERATIONAL ISSUES

After nearly 2 decades of experience with HAART, clinicians and public health officials must consider how to optimally use this resource to reduce the number of new infections. Operational research into long-term safety, adherence, benefits of different modes of drug delivery and dosing, and selection of resistant virus is required. Some of these issues will be addressed in the context of phase IV expanded safety studies; others will require the strengthening of public health monitoring systems. Efforts are under way to monitor the emergence of acquired antiretroviral drug resistance in resource-limited settings via the World Health Organization's global network HIVResNet (resistance network), which provides standardized tools, training, technical assistance, laboratory quality assurance, analysis of results, and recommendations for guidelines and public health action.[125]

The recent expansion of World Health Organization treatment guidelines to initiate treatment at a CD4 cell count of 350 cells per microliter—rather than at 200 cells per microliter—will mean that a larger pool of HIV-infected patients will be in need of treatment.[126] Recent curtailment in the US President's Emergency Plan for AIDS Relief for HIV treatment could raise further ethical concerns if providing life-saving medicine to persons already infected with HIV has to compete with efforts to prevent future HIV infections.[127] Moreover, many resource-limited nations may have limited budgets for HIV treatment, and thus will have to carefully decide how to make the best use of limited resources to also decrease the number of new infections.

TABLE 1—Current Studies of Preexposure Prophylaxis Against HIV

Trial name	Population	Location	Drug	Means of Administration	Sample Size	Expected Results
Daily PrEP						
US Extended Safety Trial (CDC 4323)	Gay men; MSM	United States	TDF	Daily oral	400	Study completed 2009; TDF PrEP was safe and well-tolerated.
iPrEX	Gay men; MSM	Brazil; Ecuador; Peru; South Africa; Thailand; United States	TDF/FTC	Daily oral	2500	Fully enrolled 2009; results probable early 2011 or late 2010
Bangkok Tenofovir Study (CDC 4370)	Injection drug users	Thailand	TDF	Daily oral	2400	Completed enrollment 2010; possible results 2010 or early 2011
Caprisa 004	Heterosexual women	South Africa	TFV	Coitally dependent topical vaginal gel	1000	1% TFV decreased HIV incidence by 39%
TDF2 (CDC 4940)	Heterosexual men and women	Botswana	TDF/FTC	Daily oral	1200	Enrollment stopped 2009; safety data probable 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
Intermittent PrEP						
IAVI E001 and E002	Serodiscordant couples; 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	Full enrollment expected 2010
HPTN 067	High-risk women and MSM	Thailand; South Africa	TDF/FTC	Fixed interval versus coitally dependent	360	In planning stages
ATN 082	High-risk young MSM	United States	TDF/FTC	Daily; with or without a behaviorial intervention	100	2011 or 2012

Note. ATN = Adolescent Trials Network; CDC = Centers for Disease Control and Prevention; FEM-PrEP = Study to Assess the Role of Truvada in Preventing HIV Acquisition in Women; FTC = emtricitabine; HPTN = HIV Prevention Trials Network; IAVI = International AIDS Vaccine Initiative; MSM = men who have sex with men; MTN = Microbicide Trials Network; PrEP = preexposure prophylaxis; TDF = tenofovir difurmate; TFV = tenofovir 1% gel; VOICE = Vaginal and Oral Interventions to Control the Epidemic.

FUTURE OF ANTIRETROVIRALS FOR HIV PREVENTION

The degree of public health benefits reaped through the use of ART for prevention will depend on the number of HIV-infected individuals treated, the ability to effectively engage individuals most likely to transmit HIV, the relative stage of a given epidemic, the efficacy of specific ART regimens to reduce viral load in the genital tract, the development of drug-resistant viral strains, and changes in risk-taking behaviors that could compromise the protective effects of ART. Although targeting ART

preventive therapy to infectious individuals or individuals at greatest risk of acquiring HIV can be a major challenge, no consensus has yet emerged about the preventive benefits of widespread administration of ART for the general population. Mathematical models have suggested that widespread provision of ART could substantially reduce HIV incidence, but this benefit could be undermined by behavioral disinhibition.[128,129]

The use of ART to reduce HIV transmission has moved to the forefront of public health approaches to HIV prevention because of the increased tolerability of the medications,

decreased cost, expanded formulary, and limitations of other approaches. Clinical data indicate that earlier initiation of ART for infected individuals is warranted; optimizing the benefits will require attention to adherence, sustained access, behavioral risk reduction, and STI diagnosis and treatment. Although the use of ART for uninfected individuals holds great promise, public health authorities will need to assess the potential of local decreases in HIV infection relative to financial costs and ecological impact, if efficacy trial data show benefit. The field is at an early stage, with major questions remaining, such as what is the least

amount of medication that can be effective with pre- and postcoital dosing and what are the optimal routes of drug delivery (e.g., topical, oral, and injectable).

It is conceivable that in the future the ART formulary will consist of drugs targeted to specific preventive and therapeutic interventions, such as topical agents for stopping viral entry. An effective HIV vaccine is still years away,[3] and the utility of antiretroviral medicines for prevention will be tempered by the fact that these agents are not likely to be 100% effective in the real world. Further studies in pharmacology, virology, and behavioral science will be needed to best understand the intended, and unintended, clinical consequences of widespread ART.

ART may prove to be a critical weapon in HIV prevention, but it will need to be part of a larger arsenal aimed at reducing the number of new infections globally, including circumcision, prevention of mother-to-child HIV transmission, behavioral change, and treatment of STIs. It is possible that the life-saving agents that have transformed the natural history of HIV and the quality of life of infected patients may become part of HAARP (highly active antiretroviral prevention),[130] but their ultimate potential in preventing HIV transmission remains to be fully defined. ∎

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This article was accepted February 19, 2010.

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K. H. Mayer originated the study. Both authors synthesized analyses and wrote the article.

Human Participant Protection

No protocol approval was required because only secondary data were used.

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