During the past 2 years, several pivotal clinical trials have proven that the use of antiretrovirals by HIV-infected and at-risk uninfected persons can decrease the probability of HIV being transmitted sexually. The initial chemoprophylaxis studies evaluated tenofovir administered topically or orally (with or without emtricitabine). However, several questions remain. Some subsequent primary prevention studies did not replicate the results of the initial studies, raising questions about differences in the behaviors of participants in each study (in particular about medication adherence), as well as whether pharmacologic or local mucosal factors might explain the variable efficacy estimates. Other antiretrovirals and delivery systems are being evaluated to maximize the efficacy of primary chemoprophylactic approaches. At present, increasing access to antiretroviral treatment globally is a priority, because expanding access to medication that can prevent morbidity and mortality is itself an important public health goal and may reasonably be expected to decrease HIV incidence. However, for treatment as prevention to be maximally effective, increases in HIV testing, health care workers, and infrastructure are needed, in addition to medications and laboratory support for clinical monitoring. A combination of approaches is needed to most quickly decrease the current trends in HIV incidence, including early diagnosis and initiation of treatment for HIV-infected persons. These approaches can be coupled with appropriately tailored interventions for populations at greatest risk for infection (for example, men who have sex with men and sex workers), including male circumcision, behavioral interventions, and chemoprophylaxis. However, a substantial gap exists between current expenditures and unmet needs, which suggests that mobilization of political will is needed for this combination approach to be successful.

For more than a decade, clinical researchers have established the foundation for the belief that antiretroviral treatment made HIV-infected persons less infectious and that prophylactic use of the same drugs could protect exposed, uninfected persons. In the summer of 2010, the CAPRISA (Centre for the AIDS Programme of Research in South Africa) 004 trial showed that South African women at high risk for HIV infection who applied a topical vaginal gel pericoitally had a 39% decrease in HIV incidence compared with those who used a placebo gel (1). Soon after this important observation, the iPrEx (Preexposure Prophylaxis Initiative) study, which enrolled at-risk men who have sex with men in 6 countries, found a 44% decrease in HIV incidence in participants randomly assigned to receive a coformulated daily dosage of tenofovir–emtricitabine compared with placebo (2). Both studies demonstrated the Achilles’ heel of chemoprevention—that it correlates highly with medication adherence—and nonadherence was common in both studies (1, 2).

Results of the HPTN (HIV Prevention Trials Network) 052 trial announced last summer validated another approach to using antiretrovirals for prevention: HIV-infected persons in serodiscordant couples who initiated antiretroviral therapy at higher CD4 cell counts (that is, between 0.35 and 0.55 \times 10^9 cells/L) were 96% less likely to transmit HIV to their partners than untreated patients with CD4 cell counts in the same range (3). These findings also focused on how antiretrovirals should be most strategically used to arrest the AIDS epidemic. Would it be best to expand treatment only for infected individuals with CD4 cell counts higher than most national guidelines recommend, or could the adjunctive, selective use of chemoprophylaxis for individuals at highest risk for HIV infection augment prevention efforts?

Some modeling studies support the idea that expanded treatment and selective chemoprophylaxis for high-risk populations (for example, men who have sex with men and sex workers) could more rapidly curtail the epidemic than either approach alone (4, 5). However, the large, unmet treatment needs of persons living with advanced HIV infection suggest that expanded access to medication remains a priority.

Additional questions about the benefits of primary chemoprophylaxis have emerged in the past few months, as subsequent trials did not consistently show protective benefits. The FEM-PrEP (Preexposure Prophylaxis) study, in which at-risk southern African women were randomly assigned to receive oral tenofovir–emtricitabine or placebo, was discontinued early because of lack of efficacy (6). However, 2 subsequent trials, the Partners PrEP study (7) and the Centers for Disease Control and Prevention–Botswana TDF (Tenofovir Disoproxil Fumurate)-2 study (8), found that antiretroviral chemoprophylaxis was effective in decreasing HIV transmission among at-risk African heterosexual men and women.

More recently, the VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial discontinued 2 of its active treatment groups: oral tenofovir and topical tenofovir gel (9). Why there were differences between this study and several other trials that enrolled at-risk women, which showed that oral or topical chemoprophylaxis was protective, is not yet understood. Some reasons could include the relatively lower cervicovaginal concentrations of oral tenofovir compared with mucosal levels achieved after application of the topical gel (10), differing patterns of adherence.
in some populations, and the attenuation of chemoprophylactic benefit when concomitant sexually transmitted infections or other causes of inflammation of the genital tract are present.

Studies are under way to address the contribution of these possibilities to the range of results noted in recent trials. Enhanced understanding of how much drug exposure provides adequate protection (11), in conjunction with improved assessments of and interventions to promote chemoprophylactic medication adherence, is needed.

So, where does this leave the field? Several other chemophrophylaxis studies are under way to try to tease out the reasons for the inconsistent findings in these recent trials. The FACTS (Follow-on African Consortium for Tenofovir Studies) 001 trial in South Africa is evaluating pericoital tenofovir vaginal gel use in high-risk women, which is similar to the CAPRISA 004 regimen. This trial may help to determine the relative efficacy of the use of topical tenofovir gel by corroborating the results of either CAPRISA 004 or VOICE (12).

Other studies evaluating at-risk women and oral chemophrophylaxis include the continuing oral tenofovir–emtricitabine treatment group of VOICE, a chemophrophylaxis study of injection drug users in Thailand, and earlier-phase studies of rectally administered microbicides and other classes of antiretrovirals (for example, maraviroc and dapivirine) in oral or gel formulations. Intermittent dosing schedules (either fewer fixed doses per week or pericoital dosing) are being evaluated to determine whether they might be more acceptable, be safer, and result in greater adherence, with similar or greater protection.

While we await the next set of results, the operational focus of HIV chemoprevention is on how to most efficiently expand treatment options for HIV-infected women and men in areas where the epidemic is expanding most rapidly, which has the added benefit of decreasing morbidity and mortality. Although increasing the number of persons receiving treatment may seem straightforward, it involves a series of structural interventions that have not been fully scaled-up in the developing world, or even in the United States.

The full rollout of “treatment as prevention” includes routine HIV testing in all communities where HIV is prevalent and repeated testing for individuals who have some level of new risk after initial negative test results. The development and implementation of point-of-care tests that can identify acutely infected individuals, who will have negative conventional antibody test results for up to several months, are also urgently needed so that at-risk persons can be accurately triaged to treatment or preventive services. Once individuals are newly identified as infected, they must be engaged in care and, after establishing contact with a provider or care team, must be educated and encouraged to initiate antiretroviral therapy and provided support to adhere to the regimen and decrease behaviors that might transmit HIV to others.

Relying on treatment alone to stop the AIDS epidemic is a utopian goal, but residual challenges exist because, in many parts of the world, the scaling-up of testing, linkage to care, providing stable access to treatment, and maintaining medication adherence remain daunting. The recent announcement by the Obama administration to expand treatment for 2 million additional people living with HIV (13) helps to address a great unmet need but will still leave most people living with HIV untreated. Thus, barring a major infusion of resources from other donors, the ability of “test and treat” to stop the epidemic immediately is limited; however, over the longer term, it will ultimately prevent millions of new infections.

Meanwhile, subpopulations who may particularly benefit from chemophrophylaxis include men who have sex with men, injection drug users, and sex workers. Thus, a nuanced approach that addresses judicious use of antiretrovirals for disease prevention in diverse, specific settings is needed.

Despite the lack of efficacy seen in some recent primary prevention trials, the positive findings in others suggest that for some at-risk populations, chemophrophylaxis is a viable strategy that can, and should, be optimized. Future success of antiretroviral therapy for prevention may entail development of new combination medications that are particularly active at genital and rectal mucosal sites and of formulations that are longer-acting and thus not dependent on daily or pericoital administration. Studies are also under way to evaluate new antiretrovirals that may have particularly favorable features for mucosal chemoprotection. Development of chemophrophylaxis against HIV infection is similar to that of another public health challenge, prevention of unwanted pregnancy, and will require a thorough understanding of community norms and the acceptability of different approaches. Chemophrophylaxis is also similar to contraception in that clinicians will need to screen sexually active persons for other infections that are not prevented by antiretroviral therapy.

The use of antiretrovirals for primary and secondary HIV prevention remains a promising approach that should have a major effect on slowing the spread of the epidemic globally. Coupled with expanding HIV testing, treatment, and care, the selective use of chemophrophylaxis, in conjunction with other evidence-based prevention approaches (such as male circumcision and harm reduction for injection drug users), may create the “tipping point” at which the current number of more than 2.5 million new HIV infections annually can finally be substantially curtailed (14). The past few years have provided glimmers of hope while reminding clinical researchers that the accrual of knowledge and the implementation of best practices are incremental processes that require curiosity, humility, tenacity, and political will.

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