

Promote HIV Chemoprophylaxis Research, Don't Prevent It

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HIV infects more than 40 million people worldwide, and there are 14,000 new infections per day (1). No preventive vaccine is yet in sight (2). Even as available and proven prevention interventions are used, the HIV pandemic will not be stopped solely by talking to those at risk (3). Chemoprophylaxis with antiretroviral agents is a promising new approach (4). Clinical trials of daily oral antiretroviral dosing as preexposure prophylaxis (PrEP) have been initiated in Africa, Asia, and the United States and are planned in Latin America. Unfortunately, these trials have become controversial.

The first PrEP trials were set up to determine whether administration of tenofovir disoproxil fumarate (TDF) might safely protect high-risk, uninfected individuals from HIV infection. TDF has a long intracellular half-life, which allows once-daily dosing and the possibility of protection even if some doses are missed (5). The lack of drug interactions with hormonal contraceptives, tuberculosis therapy, or opiates makes TDF easier to use in those at highest risk. TDF-resistant strains are not generated easily.

TDF has an excellent safety record, with minimal effects on mitochondrial DNA polymerases that underlie some of the long-term toxicity observed with other antiretroviral drugs (6). The safety profile of TDF has

been established in HIV-infected populations (7), and TDF was well tolerated in small-scale studies of uninfected persons (8). To confirm safety in diverse populations and to protect individual participants, monitoring of biomedical parameters is planned in all PrEP trials. The trials also involve frequent testing for HIV infection to allow the study drug to be stopped before there is a substantial chance of drug resistance occurring (9). Safety is of paramount importance for PrEP, because tolerability standards must be extremely high for any drug that is administered to uninfected individuals.

TDF can partially prevent infection of macaques by simian immunodeficiency virus (SIV) when administered at and after viral challenge (10, 11, 12). This effect may be overcome by repeated exposures to virus (13). Given the limitations of animal models, only clinical trials can determine the safety and efficacy of PrEP for humans.

Concerns about PrEP trials first came to international attention at the 2004 International AIDS Conference in Bangkok, when activists destroyed an exhibition booth of the drug developer that was donating drug and placebo for the trials (14). Shortly afterward, the Cambodian prime minister spoke against PrEP trials, and preparations for a trial in Cambodia were suspended (15). In February of 2005, the Cameroon government suspended administration of a study drug after a PrEP trial had full enrollment in that country. Reporting of these events and the underlying issues has been inconsistent and sometimes inaccurate, which contributed further to the controversy (16).

It is not the idea of PrEP itself, but how the research should be carried out, that is most controversial. How can participants be assured provision of the best preventive practices in a way that allows detection of additional protective effects by PrEP? Which populations are most appropriate for trials? How should community organizations be involved? How can treatment be

provided during and after the trial, including treatment for HIV-1 infections that may occur? How should research populations be assured access to PrEP if it is shown to be useful? The importance of these issues was highlighted at a recent meeting organized by the International AIDS Society, which brought together sponsors, investigators, and community leaders from North and South to discuss solutions (17). There was a clear commitment to candid dialog that addresses these issues.

All participants receive standard prevention measures and are counseled that they should not feel protected by the "pill." The relevant research question is whether addition of daily oral TDF provides protection in addition to what can be achieved by known prevention strategies, including counseling, condoms (male and female), clean needles (18), and management of sexually transmitted diseases. Provision of these prevention measures is expected to decrease risk behavior during the trial (19) but has never eliminated it completely. The trials are designed to recruit large numbers of participants so that any additional protective benefit of PrEP can be discerned.

Investigators use several procedures to assure adequate counseling and to detect and remedy false optimism. Whether such "pill optimism" can be completely eliminated with counseling is being evaluated in PrEP trials, most directly in San Francisco and Atlanta. The risks of overoptimism are especially important if efficacy is modest or is promoted immodestly in communities. Alternatively, efficacy of PrEP may be high, which could empower a vision for an HIV/AIDS-free life and reinforce healthy behaviors. The challenges are not unique to PrEP and are inherent to HIV treatment programs and vaccine development.

Many prospective participants in Africa, Asia, and Latin America are especially vulnerable to HIV and a wide range of other harms, because they reside in some of the poorest parts of the planet, because they are women, or because their lack of legal status can lead to discrimination, extortion, summary judgment, or even execution. Community and governmental organizations often struggle with very limited resources and with international political forces beyond their control. Yet vulnerable populations are also those in most need of safe and effective ways to protect themselves from HIV infection, providing the ethical basis for studies in such groups.

Research in vulnerable populations is essential to evaluate the safety and efficacy of the intervention in those populations.

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