The Public Health Implications of Pre-Exposure Prophylaxis for HIV Infection in High Risk Individuals

by

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ABSTRACT

Pre-exposure prophylaxis (PrEP) is a novel approach to human immunodeficiency virus (HIV) infection prevention in which antiretroviral medication is used prior to potential HIV exposure to reduce the likelihood of infection. PrEP may be a useful adjunct to current prevention approaches in the absence of an effective HIV vaccine or microbicide. Current and planned clinical trials seek to answer critical questions about the safety and efficacy of PrEP in at-risk populations. While these clinical trials are likely to answer many questions about the role of PrEP in HIV prevention, additional clinical, social, and ethical questions will be raised. In anticipation of the results of these trials, the public health community should act proactively to answer many of the questions surrounding the use of PrEP in populations outside the context of clinical trials. By beginning to answer the myriad of questions likely to arise with this prevention strategy now, the public health system can better prepare themselves and the communities they serve for the implementation of PrEP or other HIV prevention strategies in the future.

INTRODUCTION

Pre-exposure prophylaxis (PrEP) is a novel approach to human immunodeficiency virus (HIV) infection prevention in which antiretroviral medication is used prior to potential HIV exposure to reduce the likelihood of infection. In the absence of an effective vaccine or microbicide, PrEP has gained popularity as a possible adjunct to current prevention strategies. Clinical trials investigating the safety, efficacy and viability of pre-exposure prophylaxis strategies among high-risk populations are now underway in the United States and internationally.

It is not yet known if PrEP will be a safe or effective approach to HIV prevention. The planned and on-going clinical research studies seek to answer questions of safety and effectiveness. If clinical trials do demonstrate safety and efficacy, public health officials will be faced with significant clinical, ethical and logistical challenges related to the implementation of PrEP in their communities. Additional studies will be necessary to help determine how PrEP will be used in clinical and public health practice. Guidelines for use in at-risk populations will need to be developed quickly. Persons at-risk will need to be rapidly identified and appropriate education and outreach initiated.

PrEP should be distinguished from post exposure prophylaxis (PEP), a prevention strategy in which antiretroviral medication is administered closely following a potential HIV exposure. PEP has been extensively studied in prevention of HIV infection following occupational exposures and has recently been expanded for use following high-risk sexual exposures.

This paper will examine the evidence supporting the use of pre-exposure prophylaxis for HIV, starting with a review of other biomedical prevention strategies, with an emphasis on

HIV PEP and strategies for preventing the transmission of HIV infection from mother to child. Additional scientific evidence supporting the use of PrEP will be summarized and the major clinical trials of PrEP currently planned or enrolling will be reviewed. Finally, current and anticipated challenges to the national, regional and local public health systems will be reviewed and recommendations for action provided.

THE HIV EPIDEMIC

In June 1981, the U.S. Center for Disease Control and Prevention (CDC) issued its first warning about a rare form of pneumonia occurring among a small group of young gay men in California. The unusual pneumonia was later included in a case definition of a new syndrome, Acquired Immune Deficiency Syndrome (AIDS), a term established in 1982. In 1983, the U.S. Public Health Service issued recommendations for preventing the transmission of AIDS through sexual conduct and blood transfusion. That same year, female sexual partners of men with AIDS were added as the fifth at-risk group, joining a list of risk factors that already included male homosexuality, intravenous drug abuse, Haitian origin and hemophilia A. In 1984, the agent responsible for AIDS, HIV, was discovered. Also in 1984, the CDC recommended abstinence from intravenous drug use and reduction of needle sharing as the primary strategy to reduce the transmission of the HIV virus among intravenous drug users (IDU).[1] Since that time, over 60 million people have been infected with HIV worldwide, including the approximately 40 million persons estimated to be living with HIV/AIDS today.

Prevention methods that protect against exposure to HIV, such as those recommended by the CDC early in the epidemic: sexual abstinence, monogamy with an uninfected partner,

consistent and correct condom use, avoidance of intravenous drug use and consistent use of sterile equipment by those unable to cease intravenous drug use, remain the most effective prevention measures. The most widely used prevention methods, including abstinence, partner reduction and condom use, have shown efficacy in preventing the transmission of HIV and, in certain settings, these behavioral interventions have been shown to slow the rate of HIV transmission. Unfortunately, behavioral interventions are inconsistently utilized, fail to be universally effective, and therefore have been inadequate to control the HIV pandemic.

Global Outlook

HIV/AIDS cases have been reported in all regions of the world, though the majority of persons of living with HIV/AIDS (95 percent) and the majority of new HIV infections and HIV/AIDS related deaths occur in low- and middle-income countries. The nations of sub-Saharan Africa carry the highest burden of disease with a prevalence rate estimated to be over 20 percent in six sub-Saharan African nations. [2]

UNAIDS/WHO estimates that over 14,000 persons were infected with HIV each day in 2003.[2] Of the new infections, 12,000 occurred in persons aged 15 to 49 years of age, 50 percent of who were 15 to 24 years old. Nearly 2,000 of the new infections occurred in children under 15 years of age.[3]

Women comprise an increasing portion of adults living with HIV/AIDS, comprising nearly half of all AIDS cases at the end of 2004. While this trend is occurring in most regions of the world, it is particularly notable in sub-Saharan Africa where women represent approximately 57 percent of adults living with HIV/AIDS.[2] Gender inequality in social and

economic status and in access to prevention and care services increases the vulnerability of women to HIV.[4]

Global Summary of the HIV/AIDS Epidemic December 2004		
Total Persons Living with HIV/AIDS in 2004		
Total	**39.4 million**	**(35.9-44.3 million)**
Adults	**37.2 million**	**(33.8-41.7 million)**
Women	**17.6 million**	**(16.3-19.5 million)**
Children under 15 years	**2.2 million**	**(2.0-2.6 million)**
Total Persons Infected with HIV in 2004		
Total	**4.9 million**	**(4.3-6.4 million)**
Adults	**4.3 million**	**(3.7-5.7 million)**
Children under 15 years	**640,000**	**(570,000-750,000)**
Death from HIV/AIDS in 2004		
Total	**3.1 million**	**(2.8-3.5 million)**
Adults	**2.6 million**	**(2.3-2.9 million)**
Children under 15 years	**510,000**	**(460,000-600,000)**

Source: UNAIDS/WHO Global Summary of the HIV/AIDS Epidemic[3]

United States

The CDC estimates that there are 850,000 to 950,000 persons in the United States living with HIV, including 180,000 to 280,000 persons who do not know they are infected. From 2000 to 2003, in the 32 states that used confidential, name-based reporting of HIV and AIDS cases for at least the past 4 years, the overall annual rate of diagnosis of HIV/AIDS remained stable. However, racial and gender disparities in HIV/AIDS continue to worsen. For example, rates among non-Hispanic black females were 19 times higher than rates among non-Hispanic white females during the reporting period. The racial disparities seen in HIV/AIDS incidence underscore the need for continued emphasis on programs targeting

females in racial and ethnic minority populations to reduce the number of cases of HIV/AIDS.[5]

North Carolina

Over 2,100 new cases of HIV disease (HIV and AIDS cases) were reported in North Carolina in 2003. The overall infection rate for HIV was 25.2 per 100,000 persons. Rates of HIV/AIDS have remained stable over the past five years, though increases are noted among African Americans and Hispanics. Sexually transmitted infections, including HIV infection, remain disproportionately represented among racial and ethnic minorities. The rate of HIV for Hispanics (25.4 per 100,000) is over two and a half times greater than that for whites and the rate for non-Hispanic blacks (76.6 per 100,000) is eight times greater than that for whites. Also of note, the infection rate for black females (51.9 per 100,000) was over 14 times higher than that for white, non-Hispanic females (3.6 per 100,000).[6]

PREVENTING HIV INFECTION

The trends in infection rates reviewed above highlight the importance of identifying new methods of HIV prevention. With the burden of HIV infection in certain regions of the world, especially sub-Saharan Africa, reaching staggering proportions, the need for effective preventive approaches to halt or reduce the rate of new infections is well recognized. Efforts remain focused on new biomedical interventions, such as vaccines and microbicides to prevent new HIV infection.

HIV Vaccine

There are many scientific challenges to the development of an effective HIV vaccine and, unfortunately, the vaccine candidates currently under investigation appear unable to produce protective immunity. The first phase III HIV/AIDS vaccine trials have shown a complete lack of efficacy. Given the difficult, and currently unresolved, scientific challenges to eliciting antibodies by vaccination that are capable of neutralizing HIV, these negative results were expected by many investigators in the field.[7] Since current vaccine candidates are unlikely to be adequately effective, behavioral interventions remain critical to HIV prevention.

Microbicides

The development of safe and effective vaginal microbicides, chemical compounds that can be applied topically to inactivate HIV, is another focus of current prevention research. Microbicides may be especially important to women, especially in the developing world, when male sex partners are unwilling to use condoms consistently or at all. Current efforts are aimed at developing intravaginal and intrarectal topical formulations that either directly inactivates HIV, stop HIV from attaching or entering, or prevent HIV replication and dissemination. Ideally, an anti-HIV microbicide would act against HIV in multiple ways, combining these approaches. Additionally, a microbicide should ideally act as a contraceptive, preventing unintended pregnancies. To be useful, the microbicide agents will need to be safe and effective following vaginal or rectal administration and cause minimal or no genital symptoms despite repeat use.[8]

A safe and effective anti-HIV microbicide is not yet available; however there are 23 microbicide products in various stages of clinical development. Multicenter phase I/II safety and phase II/III efficacy studies are currently planned or underway in diverse geographic locations. For the majority of these products, no information is available regarding mucosal safety or efficacy following extended vaginal or rectal exposure.[9] The ultimate role of microbicides in HIV prevention efforts remains to be determined and the time course for broad clinical trials of a microbicide suggests that it will be several years before a microbicide is available for widespread clinical use.

BIOMEDICAL PROPHYLAXIS: LESSONS FROM CURRENT STRATEGIES

With an effective HIV vaccine or microbicide still years away, HIV prevention experts have begun to explore alternative biomedical approaches to the prevention of new infection. One approach that has gained significant support in the past 3 years is pre-exposure prophylaxis (PrEP). Animal studies suggest the possible effectiveness of a single agent antiretroviral for the prevention of new infection and clinical researchers are now exploring the use of antiretrovirals as a preventative treatment in HIV negative humans.

The concept of providing a preventive medication prior to exposure to an infectious disease is not a new one. For example, travelers to areas endemic for malaria often receive antimalarial medication to prevent infection in the case of exposure to the malaria parasite. Historically the use of antiretroviral medications to prevent HIV infection has occurred in two settings: following occupational exposure to HIV and in the prevention of mother to child transmission. These two prophylaxis strategies provide supportive evidence for PrEP and

have also raised many important questions that should be considered as PrEP strategies are developed and studied.

HIV Post Exposure Prophylaxis

Medical treatment following exposure is less effective than preventing HIV infection by avoiding exposure.[10] However, post exposure prophylaxis (PEP) is an accepted HIV prevention strategy in a select group of at-risk individuals. PEP has been primarily studied and utilized in occupational exposure settings. PEP was widely accepted after the publication of a retrospective, case-control study of health care workers having occupational, percutaneous exposure to HIV-infected blood. After controlling for other risk factors for HIV transmission, post exposure use of zidovudine (AZT) reduced the odd of acquiring HIV infection by more than 80 percent. [11]

Subsequent studies have examined the use of PEP for non-occupational exposure (for example, sexual or drug use) to HIV. Recent studies have suggested that it is indeed safe, feasible and cost-effective to deliver PEP to reduce the risk of HIV infection in non-occupational exposures. [12,13]

While limited, the available data suggest that the availability of PEP does not increase risk behavior among users. Several trials have suggested that in the setting of intensive counseling on risk reduction, the availability of PEP did not result in a higher rate of high-risk sexual activity.[14-16] Martin and colleagues examined the relationship between PEP and risk behavior in a group of approximately 400 adults who received PEP following high-risk sexual or drug related exposures. The study found that in the 12 months following the exposure and PEP, after 12 months 73 percent of participants reported a decrease in the frequency of risk

behaviors and 83 percent did not request additional PEP.[15] Another study found that PEP was sought and utilized most commonly by individuals who usually practice safe sexual or injection drug practices but experience a lapse. However, the same study also found that it was difficult to deliver PEP in a timely manner following exposure to HIV, perhaps diminishing its efficacy.[12]

A high-risk cohort of 200 HIV negative homosexual males in Brazil received preventive counseling, PEP instruction and 4-day starter packs of two HIV antiretroviral medications to be administered immediately after exposure to blood or semen. Participants reporting any high-risk sexual exposure at baseline and 18 months were 57 and 54 percent respectively. During the study period PEP was initiated 92 times by 65 participants. Men who began taking PEP after a self-identified high-risk exposure were evaluated within 96 hours; 92 percent met the event eligibility criteria (clinician-defined high-risk exposure). Seroincidence was 0.7 per 100 person-years (one seroconversion) among men who took PEP and 4.1 per 100 person-years among men who did not take nPEP (11 seroconversions). After analysis of the trial results, study authors concluded that reported high-risk behaviors declined in the cohort with access to PEP. A lower HIV seroincidence was noted among PEP users, though the limited statistical design and power of the analysis did not allow direct measurement of PEP efficacy.[16] Additional studies, including cohort studies of rape survivors, have suggested a benefit to PEP when initiated within 72-96 hours of possible exposure.[12]

The CDC has issued guidelines for occupational PEP.[17] Additional recommendations for the use of PEP in non-occupational exposures are also available from the CDC, however previously the CDC did not advocate the use of PEP in non-occupational settings.[18]

Guidelines released in February 2005 now include recommendations for the use of a 28 day course of combination antiretroviral therapy for persons who have had non-occupational exposure to blood, genital secretions or other potentially infected body fluids of a person known to be HIV infected, or when the exposure represents a substantial risk for HIV transmission, and when the person seeks care within 72 hours of exposure.[12]

State guidelines for non-occupational PEP have been developed and issued in New York, Rhode Island and California.[19,20,21] Massachusetts has issued a clinical advisory recommending that clinics create protocols to address PEP issues.[22] Recommendations for the use of PEP following sexual assault have been adopted in many states as well. Internationally, many nations, including South Africa, France, Italy, Spain and Australia, have policies recommending the use of PEP for non-occupational exposures.[23]

Overall, PEP for non-occupational exposure was well tolerated. According to the U.S. Non-occupational PEP Surveillance Registry, for 107 high risk exposures for which PEP was taken, the regimen initially prescribed was stopped or modified in 22 percent of cases; modifications or stops were reported because of side effects in half of these instances.[24]

Prevention of Mother to Child Transmission

The use of antiretrovirals to prevent the transmission of HIV from an infected mother to her infant has been one of the most successful HIV prevention strategies to date. Administration of antiretroviral medication to an HIV-infected mother during labor, or earlier in pregnancy, and to the infant postpartum dramatically reduces the rate of peri-natal HIV infection. In 1994, a prospective, randomized controlled trial demonstrated AZT administered to HIV-infected women during pregnancy and labor and to infants for 6 weeks

following delivery reduced peri-natal transmission by 67 percent, from 25.5 percent to 8.3 percent.[25] Similar approaches, using the antiretroviral agent nevirapine or combination antiretroviral therapy combined with elective caesarean section and avoidance of breastfeeding, have reduced transmission rates to 1-2 percent.[26] The mechanisms for these reductions are multi-factorial and are likely to involve both pre- and post exposure effects. Pre-exposure, antiretroviral treatment prevents cross-placental and intrapartum HIV transmission by reducing the viral load of the mother. Antiretroviral medications that cross the placental barrier also offer drug exposure to the fetus. Administration of antiretroviral therapy to the infant following delivery comprises the post exposure prophylactic component.

Information on the safety of the various antiretroviral therapy regimens suggests that short-course regimens are generally well tolerated with mild and rare side effects for the woman and her infant. Concern is greater for women taking antiretroviral therapy for extended periods of time, especially those women who would not otherwise require antiretroviral treatment. Recent studies have focused on the risk of drug resistance with short-course regimens. Drug resistance has been reported for pregnant women and, less commonly, in children. Resistance is known to occur quickly in women and infants exposed to single-dose nevirapine.[27] The clinical consequences of viral resistance following mother to child transmission prophylaxis are unclear.[28] Concerns about resistance must be balanced along with other risks and benefits of MTCT prophylaxis, including the widespread availability, simplicity and practicality of the single-dose NVP regimen. The risk of antiretroviral resistance also must be considered with the use of a single antiretroviral agent for PrEP in a population at high-risk for HIV infection.

Additional Examples of Pre-Exposure Prophylaxis

Prophylactic strategies are utilized in non-HIV settings as well. One of the most widely accepted prophylactic strategies is the use of anti-malarial medications to prevent or attenuate malaria infection in visitors to malaria endemic areas. Additionally, pre-exposure prophylaxis of sexually transmitted infections has demonstrated usefulness in certain populations and during outbreaks.

Malaria Chemoprophylaxis

Malaria is an infectious agent for which chemoprophylaxis is a standard preventive measure. The decision to use anti-malarial prophylaxis requires a careful risk-benefit analysis weighing the risk of acquiring potentially serious malarial infection against the risk of harm from the prophylactic agent. Malaria prevention for travelers to endemic areas combines behavior modifications such as the use of insect repellants and protective clothing and nets with prophylactic medications. Although anti-malarial medications do not prevent infection with the malaria parasite, they help prevent the development of clinical illness. A wide variety of anti-malarial agents are available, but most are associated with significant side effects. In addition, anti-malarial drugs, particularly newer agents, are costly. Despite imperfect protection, toxicity, and high cost, chemoprophylaxis combined with behavioral interventions to reduce mosquito exposure is considered the standard of care for persons traveling to malaria-endemic areas and has made visits to these areas safer.[29]

Mass Treatment of Sexually Transmitted Infections

The epidemiologic approach to the treatment of sexually transmitted infections (STI) involves the administration of antibiotic therapy to a population based on increased risk rather than for symptoms or proven infection. In high-prevalence populations where rates of exposure to STI are high, mass treatment likely works both by preventing and treating infections. Although mass treatment is not standard practice in the United States, the approach has been studied in international setting for the prevention and control of STI including Chlamydia, gonorrhea and syphilis. Additionally several trials have demonstrated that STI treatment can reduce the transmission of HIV.[30,31,32,33] The degree to which this approach may be effective depends on a variety of factors including pathogen and host factors. Problems with mass treatment include the cost of providing treatment, difficulties with adherence, challenges eliciting community support, and the risk of emerging drug resistance.[34] Similar issues arise with the use of antiretrovirals for HIV PrEP.

PRE-EXPOSURE PROPHYLAXIS: SUPPORTING EVIDENCE

As discussed above, antiretrovirals appear to prevent or reduce HIV transmission in post-exposure prophylaxis and in mother-to-child transmission settings. Additional evidence supporting the use of PrEP for HIV prevention comes from animal studies and several small clinical trials.

Animal Studies and Early Trials

The first studies using animal models of pre-exposure prophylaxis were conducted using the antiretroviral agent nevirapine. A variety of animal models demonstrated the effectiveness of nevirapine in preventing or delaying HIV infection.[35]

One of the first reports on the feasibility of PrEP for the prevention of new HIV infection in humans was first presented in 2002 at the XVth International AIDS Conference in Barcelona. This phase I/II trial, known as HIVHOP 101, provided a 200mg tablet of nevirapine once weekly, twice weekly, or every other day to a cohort of men and women in the Baltimore area at high risk for HIV infection. The group included sex partners of HIV-positive persons, gay men and injecting drug users. In this trial, none of the participants reported significant side effects from the medication, though increases in liver function tests were seen more frequently in participants receiving the higher doses of nevirapine.[36] The authors reported that risk-taking did not increase during the study and none of the participants became HIV positive during the course of the trial. However, the trial was designed to assess the safety of the use of antiretroviral medications as PrEP, not to assess the effectiveness of PrEP nor its impact on risk behavior. However, the study was successful as "proof of concept".

While nevirapine appeared promising as a PrEP agent, concerns about liver toxicity, particularly in women with intact immune systems, were raised in other trials. Notably, a study published in the *Journal of Acquired Immune Deficiency Syndromes* in August 2004 found that HIV-negative people appear to have a higher risk of side-effects when exposed to nevirapine, according to a review of case reports and toxicity reports from people exposed to the drug as a component of PEP after potential exposure to HIV. The authors suggest that autoimmunity may be at the root of these toxicities, since when severe adverse reactions have

occurred in HIV-positive people (at a rate of less than 1 percent), they have tended to be when CD4 counts were high. They conclude, "Although precise estimates of the risk for severe hepatotoxicity are not available, the risk appears to be higher than in HIV infected persons.... Therefore, non-HIV infected individuals should not receive PEP or other prophylaxis regimens that include multiple doses of nevirapine."[37] These findings have raised concerns about the safety of using nevirapine in pre-exposure settings. Subsequently, planned clinical trials using nevirapine in HIV negative persons have been discontinued.

Table 1. Ideal Chemoprophylactic Agent for Pre-Exposure Prophylaxis[38]
Blocks infection
Long half-life
High penetration into target tissues
Low toxicity
High tolerability
High barrier to resistance
Inexpensive to produce
Stable in heat and humidity
No food requirement for dosing

Adapted from Grant R. Pre-exposure prophylaxis. Twelfth Conference on Retroviruses and Opportunistic Infections, Boston, abstract 137, 2005.

Tenofovir

Given significant concerns about the safety of nevirapine in HIV negative persons, attention turned to other antiretroviral agents with an excellent safety profile and other features conducive to PrEP. The antiretroviral medication tenofovir has been selected for planned trials of PrEP because of its safety and efficacy. Animal studies with tenofovir have shown that tenofovir, administered before and immediately after a single retroviral exposure, can prevent the transmission of a virus similar to HIV in monkeys and delay and attenuate infection in animals receiving serial exposure.[39,40]

Tenofovir meets many of the requirements for the ideal chemoprophylactic agent (table

1). Approved by the Food and Drug Administration in 2001, experience with tenofovir in the treatment of HIV infection is extensive. Adverse effects with tenofovir are rarely reported with the most common side effects including nausea, decreased appetite and flatulence. Tenofovir can be dosed as one pill taken once daily and reports document excellent adherence.[41] The CDC cites these features when explaining the rationale behind the use of tenofovir in multiple international clinical trials,

> Tenofovir has been selected for investigation as chemoprophylaxis against HIV in high-risk individuals because of its unique pharmacologic profile. In addition to the convenience of being a once-daily single tablet with a safety profile comparable to placebo among HIV-infected persons, it has striking anti-HIV potency and a low potential for selection of resistant viruses. Each of these properties is necessary given the realities of the intended target populations.[42]

OVERVIEW OF PLANNED PRE-EXPOSURE PROPHYLAXIS RESEARCH STUDIES

As of April 2005, there are several major human trials of HIV PrEP underway or in the planning stages. These trials focus on the safety and/or efficacy of PrEP in high-risk women (Cameroon, Ghana, Nigeria), high-risk men (Malawi), sexually active young adults (Botswana), injection drug users (Thailand) and MSM (United States). These planned or ongoing trials are summarized in Table 2. A planned National Institutes of Health trial of PrEP in commercial sex workers in Cambodia has been placed on hold after sex workers, activists and the Cambodian Department of Health raised concerns about the ethics of the trial design. Additionally, activists have opposed trials in Cameroon and Thailand citing concerns about the safety of the trial design and ethical treatment of trial volunteers. These controversies will be discussed further below.

Family Health International/Gates Foundation

Family Health International (FHI) received a grant from the Bill and Melinda Gates Foundation to conduct phase II studies of PrEP in high-risk, HIV-negative adults in Ghana, Nigeria, Cameroon and Malawi. The trials are double-blinded, randomized and placebo-controlled. The trials are anticipated to last approximately 2 years, beginning with a 6 month screening phase followed by a 6 month recruitment phase and 12 months of study drug use for participants. The primary endpoints of the study are safety and efficacy. The safety of tenofovir for PrEP will be determined by adverse event reports and laboratory measurements.

For the FHI trials, efficacy of tenofovir for the prevention of HIV acquisition will be determined by the rate of HIV seroconversion. Trial volunteers will receive counseling that they are participating in a research study and that they may be receiving placebo. Participants will receive counseling in HIV prevention including education on safer sexual practices and be provided with condoms. Overlapping behavioral research is also being conducted to determine the acceptability of the intervention among participants, their partners, and the community. Additionally the barriers and facilitators to the PrEP strategy will be studied to assist in the translation of trial results to HIV prevention program planning. Study completion is scheduled for mid-2006 after which trial results will begin to become available.

CDC Sponsored Trials

The U.S. Centers for Disease Control (CDC) is sponsoring three separate trials to answer important questions about the safety and efficacy of daily oral tenofovir for the prevention of new HIV infection in populations at high risk for infection worldwide. The three trials seek to enroll a total of 3,200 participants from three countries: Botswana, Thailand and the United States. The Botswana and Thailand trials are designed to determine

if once daily tenofovir is safe and effective in reducing HIV transmission among heterosexual and intravenous drug users, respectively. The U.S. trial is designed to assess the tolerability of tenofovir in men who have sex with men (MSM) but is not adequately powered to assess efficacy in this population. Subsequent trials with larger numbers of participants would be required to demonstrate effectiveness in the MSM population.[43]

The CDC studies are also designed to address issues pertinent to the design of future PrEP trials and to the implementation of similar PrEP strategies. These issues include the impact of PrEP on risk behavior, medication adherence and acceptability, and drug resistance.

Volunteer Protections

To ensure the scientific validity and the maintenance of ethical standards, each trial has undergone review and has been approved by institutional review boards (IRBs) at the sponsoring institution and by each host country and study site. Independent data and safety monitoring boards (DSMB) have been established to review data on enrollment, safety and efficacy at standard intervals. The DSMB will review trial findings on an ongoing basis to determine that it is safe to continue the trial. During the phase III portion of the trials, the DSMB will determine at which point the study results are conclusive.

Table 1. Major PrEP Trials, March 2005. Adapted from Szekeres G et al. 2004.[44]

Sponsor	Trial Aims	Study Location	Population	Target Enrollment	Study Duration	Enrollment Schedule	Notes
FHI/Gates Foundation	• Evaluate the safety and efficacy of TDF for PrEP • Determine acceptability of PrEP among participants, their partners and the community • Identify barrier and facilitators to translating study results into effective HIV prevention planning	Ghana	high-risk women	400	2 years	Began summer 2004	Enrollment on hold in Cameroon while government investigates allegations of unethical and unsafe practices from activists.
		Nigeria		400			
		Cameroon		400			
		Malawi	heterosexual men	400		To begin summer 2005	
CDC	• Evaluate biological and behavioral safety of TDF for PrEP	Thailand	IDUs	1,600	30 months	Began fall 2004	Enrollment halted after protesters raised concerns regarding just treatment of volunteers.
	• Evaluate efficacy of TDF for PrEP • Assess adherence to study drug • Evaluated TDF resistance in participants who seroconvert • Bone density, bone metabolism will be evaluated in a subset of participants	Botswana	sexually active adults	1,200	32 months	To begin spring 2005	
		United States	high-risk MSM	400	2 years	Began fall 2004	
NIAID	• Evaluate safety and efficacy of TDF for PrEP • Evaluate safety of TDF in participants with hepatitis B • Assess adherence to study drug • Evaluate changes in risk behavior	Cambodia	female CSW	960	1 year	On hold	Study halted after protestors raised concerns regarding the ethics and safety of trial design.

PrEP Pre-exposure prophylaxis; TDF tenofovir DF; IDUs intravenous drug users; MSM men who have sex with men; CSW commercial sex workers

CLINICAL TRIALS CONTROVERSY

In certain participating countries, the PrEP trials have met significant resistance from HIV/AIDS advocacy groups. These protests illustrate many of the challenges facing researchers and pharmaceutical companies when conducting clinical trials in developing nations. In recent years, the increasingly global nature of health research has highlighted questions regarding the ethics of trial design, conduct and follow-up. While research studies conducted by scientists from more prosperous nations in poorer countries more heavily burdened by disease may reflect efforts to help address a public health problem, these studies may reflect an assessment that a foreign location is more convenient, inexpensive, and efficient. This may impose ethically inappropriate burdens on the host country and on trial participants. This potential for exploitation has lead to an effort to ensure that protections are in place for participants in international clinical trials.

Sponsoring or conducting research in developing countries often poses special challenges arising from cultural differences, such as distinct histories, political, judicial and economic systems. In countries with a significant burden of poverty, primary health care services are often inadequate and a majority of the population cannot access basic health care services. As a result of these adverse conditions, persons in these countries are often vulnerable in situations in which the improved health care is offered, including clinical trials. Further, participants in developing nations may not fully understand the nature of informed consent and may lack adequate funds to obtain health care following trial participation. Groups such as commercial sex workers and intravenous drug users are seen as especially vulnerable because they lack political or economic bargaining power to negotiate the terms of a trial as well as the resources to acquire the necessary treatment or insurance if they contract the virus during the test. [45]

The National Bioethics Advisory Committee (NBAC) issued a report in 2001 titled "Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries."[46] The NBAC report outlines the essential requirements for the ethical conduct of clinical trials. These requirements include both procedural and substantive items and builds on the three basic ethical principles outlined for research involving human participants in the 1979 Belmont Report: respect for persons, beneficence and justice.[47] The expanded recommendations include several principles that are crucial to the design and success of international trials of PrEP. The conflicts over PrEP trials in Cambodia, Cameroon, and Thailand highlight the importance of community involvement, assessment and outreach in trial design and early implementation.

Cambodia

The National Institutes of Health awarded a grant to the University of California-San Francisco to conduct a trial of tenofovir's effectiveness in preventing the transmission of HIV in 960 Cambodian women, the majority of who were commercial sex workers. Cambodian Prime Minister Hun Sen ordered the trial to stop in August 2004, citing possible harmful effects of the study drug on trial participants and inadequate provisions for follow up care for trial participants. In July, representatives of the Women's Network for Unity, an organization of Cambodian commercial sex workers, interrupted a session at the XV International HIV Conference in Bangkok to protest the trial. The group raised concerns about the study design and said they would not participate in the trial unless they were provided with 30 years of health insurance to cover possible adverse consequences of trial participation.

Cameroon

On February 3, 2005, the Ministry of Health of Cameroon announced that it was suspending the FHI sponsored clinical trial of tenofovir for HIV PrEP, citing "failings in…implementation." The trial, which involves HIV-negative commercial sex workers in the city of Douala, came under fire from activist groups, most notably ACT UP/Paris, who alleged that the trial violated ethical norms and called for it to be halted. ACT UP/Paris claims that the study recruited vulnerable participants without providing adequate HIV/AIDS prevention information or treatment. Cameroon's Health Minister, Urbain Awono, stated, "The decision to suspend the trial comes after an audit commission of doctors recently delivered a report on how the trial was being conducted." A spokesperson for FHI denied the accusations. FHI is addressing the health minister's concerns and making progress towards implementing recommendations from the ministry of health including changes in administrative procedures and bolstering partnerships with local HIV prevention organizations to provide better counseling and support services to trial participants. On February 14, 2004, the health ministry did agree to allow the follow-up of participants currently enrolled in the trial.[48]

"Tenofovir makes me vomit." ACT UP activists staged demonstrations against the PrEP trials at the 15th International AIDS Conference. From Science Now, 2005. [49]

Thailand

In December 2004 Thai protesters released a statement to the national press accusing trial organizers of ignoring international ethical standards and exploiting injecting drug users.[50] On March 9, 2005, one day after a proposed trial of 1,600 IDUs in Bangkok received approval from Thailand's ethical review body, Thai AIDS advocacy organizations, lead by the Thai Drug Users' Network (TDN), held a press conference expressing their concerns regarding the planned trial. Patient's rights advocates criticized the failure of trial organizers to supply clean injecting equipment and expressed concern that different standards were being applied to the IDU participants than participants at high-risk because of sexual behavior. "In the African sites, condoms are offered as a matter of course to the trial participants, who are chose for their high risk sexual behavior," said Paisan Suwannawong, Director of the Thai AIDS Treatment Action Group (TTAG). The TDN also expressed concern over the planned management of new HIV infections diagnosed during screening for the trial and for persons who seroconvert during trial

participation. TDN and several other HIV advocacy organizations called on UNAIDS to intervene and postpone the start of the trial in order to allow better community involvement and resolution of perceived trial problems. Seree Jintakanon, chairman of TDN, said,

> We 100 percent support research into new and better options for HIV prevention. But, tenofovir, which would have to be taken every day for the rest of one's life, costs nearly US$500/month. Trial participants would only get it free for one year. We are not hopeful that this method of prevention would be available for IDU or for ANY Thai person for that matter, ever. If IDU and PLWHA were invited to be part of the process from the beginning, however, we might have negotiated better post-trial access.[51]

Community Involvement in Research Design and Implementation

The interruption of the PrEP trials in Cambodia, Cameroon, and Thailand suggest a failure of trial sponsors to adequately assess, involve, and inform the target communities during critical stages of trial development. Over the past three decades, researchers have increasingly involved communities in the design of research. In addition, research participants, health advocates, and other members of the communities from which participants are recruited have requested, and in some cases demanded, involvement in the design of clinical trials. By consulting with the community, researchers often gain insight about whether the research question is relevant and responsive to health needs of the community involved. Further, community consultation can improve the informed consent process and resolve problems that arise due to the use of difficult or unfamiliar concepts. Such discussions can provide insight into whether the balance of benefits and harms in the study is considered acceptable and whether the interventions and follow-up procedures are satisfactory. Community consultation is particularly important when the researcher does not share the culture or customs of the population from which research participants will be recruited. For upcoming and future clinical trials of PrEP

and prior to the implementation of PrEP strategies in local communities, community assessment must be completed and community partnerships formed.

MODELING THE IMPACT OF PRE-EXPOSURE PROPHYLAXIS

PrEP is unlikely to be completely effective in preventing the transmission of HIV infection. Previously developed theoretical models for HIV preventive vaccines can be used to estimate the impact of PrEP efficacy, range of coverage, possible increases in risk behavior, and epidemic control. A model developed by Anderson and Garnett for low-efficacy HIV vaccines identifies several parameters that define the impact of the intervention, vaccine in this case, on the individual and the community.[52] Factors impacting at the individual level include:

- Apparent efficacy of the intervention (vaccine or prophylaxis)
- Duration of protection
- Failure rate (fraction of individuals receiving the intervention who be come infected when exposed to the virus)
- Relative infectiousness of individuals infected while receiving the intervention (vaccine or prophylaxis) compared with that of untreated individuals
- Relative length of incubation period in individuals infected while receiving the intervention compared with that of untreated individuals

Community factors to consider include the changes in sexual behavior after the introduction of the intervention, the partner exchange rate in the population and sex acts per partner.

The authors conclude that for a vaccine with 80 percent efficacy in the setting of no significant behavior change and a life expectancy of 35 years of sexual activity, eradication of HIV infection would not be possible. Similar conclusions could be drawn about PrEP, which is likely to have an even lower efficacy than a vaccine offering partial protection. However, despite imperfect protection, communities can benefit from vaccines of lower efficacy. High population coverage with a vaccine of low efficacy could reduce the incidence and prevalence of

HIV infection. Additionally, with the use of behavioral and other prevention approaches, PrEP may act synergistically to further reduce the burden of HIV disease.

PRE-EXPOSURE PROPHYLAXIS CHALLENGES

Potential risks of antiretroviral PrEP include drug toxicity, reduced utilization of behavioral HIV prevention measures and the acquisition of antiretroviral-resistant HIV strains. Additional challenges exist with ensuring fair and equal access to prevention education and prevention strategies, including PrEP, and with assuring funding for PrEP medication and monitoring.

Drug Toxicity

As discussed above, tenofovir has been selected for the current trials of PrEP because of an excellent safety and tolerability profile. The most significant concerns regarding the safety of tenofovir relate to it's potential for kidney damage. Reports of tenofovir-associated renal toxicity in HIV positive patients receiving combination antiretroviral therapy have increased in the medial literature.[53,54] Also, toxicities described for other nucleoside analogues, a class of HIV medications that includes tenofovir, may apply to tenofovir as well. These toxicities include serious medical conditions such as lactic acidosis and lipodystrophy.[55] The ongoing and planned clinical trials offer 1-2 years of monitoring following trial participation. It is possible that previously unrecognized risks and adverse effects might develop in HIV negative recipients of PrEP. Given that with PrEP antiretroviral agents like tenofovir may be used either continuously or intermittently for prolonged periods of time, ongoing monitoring will be a critical part of clinical studies and of any broader implementation scheme. The frequency and duration of

safety monitoring for PrEP remains to be determined and future trials may be required to determine the optimal monitoring strategy.

Behavior Change

Current and future clinical trials will work to understand the impact of a daily drug regimen on HIV risk behaviors. Further study into the impact of PrEP on risk behaviors will be critical should tenofovir or another agent prove effective in reducing HIV transmission. One of the greatest risks is that persons at risk for HIV infection will reduce use of proven behavioral prevention strategies such as condom use. However, limited data on the use of PEP in high-risk persons suggests there is not an increase in risk-behavior in persons receiving PEP.

Because it is likely that no single prevention strategy will be 100 percent effective against HIV transmission, reducing transmission will require determining how to integrate available prevention strategies, biomedical and behavioral, to optimize benefit.[44] Data collection on beliefs about PrEP and the development of educational strategies based on these findings must be completed prior to adoption of PrEP approaches.

Adherence and Acceptability

If clinical trials demonstrate that daily PrEP is effective and safe, implementation of PrEP strategies in a broader public health context will require that patients be willing to comply with daily dosing of medication. Future research must be aimed at assessing whether persons at risk are willing and able to maintain the daily regimen. Barriers to strict adherence will need to be identified and addressed as part of trial participation and for future use outside of clinical trials.

Drug Resistance

As discussed above, clinical experience with the antiretroviral nevirapine has demonstrated the development of drug resistance in mothers and infants exposed to a single dose of nevirapine. Although resistance to tenofovir is uncommon among HIV infected persons when used in combination with other antiretroviral medications, it is unclear how often resistance may develop if prophylaxis fails and PrEP recipients become infected with HIV while taking tenofovir alone. For PrEP recipients who do develop HIV infection during participation, concern exists that drug resistance may develop to the prophylactic agent, possibly limiting future HIV treatment options for the individual.

Current clinical trials have adopted a strategy of frequent, regular HIV testing to monitor for the development of new HIV infection in trial participants: if study volunteers become infected, study medication will be immediately discontinued. Additionally, resistance testing will be provided to all persons infected during the trial and repeated 12 months after infection is detected. It is hoped that these data will provide important information on the frequency with which resistance occurs and will help guide treatment decisions as infected persons are referred to treatment and care. How to best monitor PrEP recipients outside of trial settings will need to be determined by additional studies. A balance will need to be met between safety, cost, and convenience in the monitoring strategy adopted for broad use.

Access and Economics

Should PrEP be effective in reducing the transmission of HIV infection, strategies for applying the research findings to at-risk populations will need to be developed. Challenges will exist in identifying at-risk individuals, in the provision of medical evaluation, monitoring and

risk reduction counseling and in the provision of medication. Determining how best to cover the costs of PrEP will require collaboration between public health officials, community groups, representatives from the health industry, health insurers, and government officials

RECOMMENDATIONS FOR POLICY ACTION AT THE STATE AND LOCAL PUBLIC HEALTH LEVELS

Important findings on the effectiveness of PrEP strategies for the prevention of HIV infection are likely to become available in the next three years. Safety information will be available as well, though the long-term effect of PrEP will only be determined by more extensive and prolonged follow up. If clinical trials suggest that PrEP is safe and effective, numerous clinical questions will need to be resolved prior to widespread implementation of PrEP strategies at the local public health levels. Since the systems developed within the context of a clinical trial are rarely reproducible in the community, a number of questions will need to be answered prior to implementing PrEP in local communities.

In North Carolina, targeting PrEP interventions to the highest risk persons will require a complete analysis of populations at high risk for HIV infection. The intervention would most likely target HIV negative partners of HIV positive persons, men who have sex with men (MSM), female partners of MSM, and intravenous drug users and their partners. Other individuals who might be considered for PrEP could include commercial sex workers and persons in situations where HIV risk is elevated, such as prisoners. A local assessment of community resources and factors impacting efficacy and safety will be important as well.

Prior to the availability of results from the ongoing and planned clinical trials of PrEP, the North Carolina public health system can begin to prepare for the possibility that the intervention will prove successful. The following recommendations outline important steps in preparation for the adoption of PrEP.

- Convene a panel of key stakeholders to address if and how PrEP programs would be implemented and covered in the state of North Carolina. The panel should include state government officials, representatives from state and local public health systems, HIV clinicians, health insurers, PrEP and prevention researchers, prevention counselors, community leaders and representatives from the communities most impacted by HIV. Issues to be address by the statewide stakeholder panel include:
    - Funding allocations for all aspects of PrEP: behavioral, social and biomedical

- Convene an expert panel of researchers, prevention experts, clinicians and community representatives to develop recommendations for state-specific research that will need to be conducted prior to the implementation of PrEP programs. Specific questions to answer include:

  How to select candidates for PrEP
    - How to screen and counsel PrEP recipients for sexually transmitted diseases including HIV
    - How and by whom prophylactic medications will be provided (primary care physician, public health clinic)
    - How to best monitor patients receiving PrEP
    - How to manage persons that become HIV infected while on PrEP

- Conduct a community assessment in the communities most likely to be impacted by PrEP will need to be performed to answer a number of questions critical to the success of PrEP programs. Issues to address include:

    - Current use of safer sexual practices and other prevention methods
    - Impact of PrEP availability on risk behaviors and use of other prevention methods
    - Determining the extent of pre-existing PEP and PrEP use among at-risk individuals
    - The optimal approach to introducing and marketing PrEP to at-risk populations
    - Issues of access to healthcare services including role of race and gender in access

CONCLUSIONS

PrEP offers a novel approach to HIV prevention that may be a useful adjunct to current prevention approaches in the absence of an effective HIV vaccine or microbicide. Current and planned clinical trials seek to answer critical questions about the safety and efficacy of PrEP in at-risk populations. While these clinical trials are likely to answer many questions about the role of PrEP in HIV prevention, additional clinical, social and ethical questions will be raised. In anticipation of the results of these trials, the public health community should act proactively to answer many of the questions surrounding the use of PrEP in populations outside the context of clinical trials. By beginning to answer the myriad of questions likely to arise with this prevention strategy now, the public health system can better prepare themselves and the communities they serve for the implementation of PrEP or other HIV prevention strategies in the future.

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