Preexposure Prophylaxis for HIV: An Emerging Preventive Strategy to End Ongoing Pandemic

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Abstract
HIV/AIDS continues to have an extraordinary public health impact. Although the HIV/AIDS epidemic on the whole is plateauing, it is spreading rapidly among certain populations.

We enumerate here some HIV preventive modalities that have been demonstrated to be effective in various target populations if properly implemented and adhered to. Some other new strategies are also showing promise in clinical trials.

Epidemiology
HIV infection/AIDS is a global pandemic, with cases reported from virtually every country. At the end of year 2009, an estimated 33.3 million individuals were living with HIV infection according to the Joint United Nations Programme on HIV/AIDS (UNAIDS). More than 95% of people living with HIV/AIDS reside in low and middle income countries, 50% are female, and 2.5 million are children <15 years.

The estimated number of people living with HIV—i.e., the global prevalence—has increased fourfold since 1990, reflecting the combined effects of continued high rates of new HIV infections and the beneficial (life-prolonging) impact of antiretroviral therapy.[Joint united nations programme on HIV/AIDS (UNAIDS)].

In 2009, there were an estimated 2.6 million new cases of HIV infection worldwide, including 370,000 in children <15 years (UNAIDS).

Among high-risk individuals (e.g., commercial sex workers, patients attending STD clinics) who live in urban areas of sub-Saharan Africa, seroprevalence is now >50% in some countries. Heterosexual exposure is the primary mode of HIV transmission in sub-Saharan Africa, with women and girls disproportionately affected, accounting for 60% of all HIV infections in that region. In east, south, and southeast Asia, an estimated 4.9 million people were living with HIV at the end of 2009.

Data for HIV prevalence in couples is available from national surveys in 12 of the 16 countries in Africa and Asia with the largest number of HIV infections. In these 12 countries, the median proportion of HIV-positive women aged between 20 and 29 years, who live with HIV-negative partners, is 54%, and for women aged between 30 and 39 years, it is 49%.

HIV/AIDS continues to have an extraordinary public health impact in the United States. As of January 1, 2010, an estimated 1,108,611 cases of AIDS had been diagnosed in the United States. Out of them, 21% are unaware of their infection, according to recent analysis. Approximately 65% of individuals living with HIV/AIDS were nonwhite and nearly half (48%) were men who have sex with men.

The estimated HIV seroprevalence rate among individuals age 13 years or older in the United States is 0.5%.

The estimated percentage of AIDS diagnoses attributed to injection drug use increased from 20% to 31% during 1985–1994 and then decreased, now it is accounting for 15% of diagnoses in 2009. The estimated percentage of AIDS diagnoses attributed to heterosexual contact increased from 3% in 1985 to 31% in 2009.

As of January 1, 2010, an estimated 9448 cases of AIDS in children <13 years old had been diagnosed in the United States.

Although the HIV/AIDS epidemic on the whole is plateauing in the United States, it is spreading rapidly among certain populations. Similar to other STDs, HIV infection will not spread homogeneously throughout the population of the United States. However, it is clear that anyone who practices high-risk behavior is at risk for HIV infection. In addition, recent increase in HIV infections and AIDS cases among young men who have sex with men.
as well as the spread in pockets of poverty in both urban and rural regions (particularly among underserved minority populations in the southern United States with inadequate access to health care) testify that the epidemic of HIV infection in the United States remains a public health problem of major proportions. It is clear that in order to control and ultimately end the AIDS pandemic, effective prevention of HIV transmission is essential. Following are some HIV preventive modalities that have been demonstrated to be effective in various target populations if properly implemented and adhered to, and several others that are showing promise in clinical trials.

Modalities for Preventing HIV Transmission

Use of condoms can markedly decrease the chance of HIV transmission. It should be remembered that condoms are not 100% effective in preventing transmission of HIV infection. In 2010, a topical microbicide composed of 1% tenofovir in a gel was demonstrated in a clinical trial in South Africa to be 39% effective in preventing acquisition of HIV infection in women engaging in vaginal intercourse. Three clinical trials of heterosexual men in South Africa, Uganda, and Kenya have shown that adult male circumcision results in a 50% to 65% reduction in HIV acquisition in the circumcised subjects. The most effective way to prevent transmission of HIV infection among injectable drug users (IDU) is to stop the use of injectable drugs. Unfortunately, that is extremely difficult to accomplish. The avoidance of sharing of needles and other paraphernalia (“equipments require to do a particular work”) is the next best way to avoid transmission of infection. Furthermore, paraphernalia should be cleaned after each usage with a virucidal solution, such as undiluted sodium hypochlorite (household bleach). Data from a number of studies have indicated that programs that provide sterile needles to addicts in exchange for used needles, have resulted in a decrease in HIV transmission. However, the cultural and social factors that contribute to the sharing of paraphernalia are complex and difficult to overcome.

Transmission of HIV via transfused blood or blood products has been decreased dramatically by a combination of screening of all blood donors for HIV infection by assays for both HIV antibody and nucleic acid. Treatment of an HIV-infected mother with antiretroviral therapy during pregnancy and the infant during the first weeks following birth has proved very effective in dramatically decreasing mother-to-child transmission of HIV. It is becoming appreciated that 5–15% of infants who were born of HIV-infected mothers and who were fortunate enough not to have been infected intrapartum or peripartum become infected via breast-feeding. Therefore, breast-feeding from an infected mother should be avoided if at all possible. Unfortunately, health authorities in most developing countries continue to recommend breast-feeding despite it being the potential way for HIV transmission. In this regard, the most effective way to avoid mother-to-child transmission of HIV is to treat the infected mother throughout the entire pregnancy and to continue therapy during breast-feeding and beyond if the mother’s clinical status warrants such treatment.

The last but very effective modality i.e Antiretroviral preexposure prophylaxis (PrEP) is a promising approach for preventing human immunodeficiency virus type 1 (HIV-1) infection in heterosexual populations, and is proved by various animal and human clinical trials and studies as follows.

Preexposure Prophylaxis for HIV (PrEP)

Animal Studies

In 2010, Cong M, et al and Garcia-Lerma JG et al reported that intermittent oral prophylaxis with tenofovir/emtricitabine (Truvada) protected all 5 macaques exposed to emtricitabine (FTC)-resistant SHIV (a simian immunodeficiency virus with an HIV coat) in a Centers for Disease Control (CDC) trial. The preventive advantages of the tenofovir– emtricitabine combination in the rectal transmission model in rhesus macaques has led to reconsideration of the therapies used in the planned or ongoing human preexposure prophylaxis trials, and some trials have replaced tenofovir with the tenofovir and emtricitabine combination.

In perinatal transmission studies and animal models, the protective benefits of antiretroviral prophylaxis were maximized when the antiretroviral medication was administered both before and after HIV exposure. Studies in animal models suggest that TDF–FTC provides greater protection against HIV-1 than TDF alone. Studies in nonhuman primates provide strong evidence that systemic ART administered before exposure can prevent infection.

Human Studies

The use of antiretroviral medications for the prevention of HIV type 1 (HIV-1) transmission is a promising strategy for reducing the spread of HIV-1. Antiretroviral treatment for persons infected with HIV-1 provides important clinical benefits and substantially reduces infectiousness. Antiretroviral prophylaxis is a potential HIV-1 prevention strategy for those not yet
infected with HIV-1, administered either as postexposure prophylaxis after high-risk occupational or nonoccupational exposure or as preexposure prophylaxis in those with ongoing HIV-1 exposure.2

The efficacy of PrEP for HIV-1 protection in humans has been evaluated for tenofovir, in the form of a vaginal gel or as oral tenofovir disoproxil fumarate (TDF) or oral TDF coformulated with emtricitabine (TDF–FTC).2

In 2010, Eyawo O et al published a systematic review and meta-analysis wherein the possibility of differential efficacy, safety, and cost suggested that TDF and TDF–FTC could be compared as potential PrEP agents. Persons at ongoing risk for HIV-1 acquisition in whom PrEP could be studied and found to be effective in persons who are HIV-1–seronegative but are in a partnership with a person already infected with HIV-1 (an HIV-1–serodiscordant partnership).6

PrEP with antiretroviral drugs is gaining considerable attention as a possible biomedical intervention strategy to prevent sexual transmission of HIV. PrEP is a proven concept for other infectious diseases like malaria. Mathematical models estimate that over the next 10 years an effective PrEP program could prevent 2.7 to 3.2 million new HIV-1 infections in sub-Saharan Africa.7

Jorge Del Romero et al in 2010 reported a possibility of heterosexual transmission from people with HIV taking combined antiretroviral treatment was low.8

In 2010, a study of pre-exposure prophylaxis using two drugs (tenofovir plus emtricitabine) on a daily basis in uninfected men who have sex with men and transgender women demonstrated a 44% efficacy. When participants had a high level of adherence to the regimen, the level of protection rose to 73%.9–11

In 2007 Cohen et al reported the study which was powered to detect a 35% reduction in HIV transmission to sexual partners because the HIV-infected individuals received ART.5

In 2012, Baeten et al observed in their study that heterosexual men and women with a partner known to have HIV-1 infection, once-daily oral TDF and TDF–FTC were associated with risk reductions of 67% and 75%, respectively, against HIV-1 infection when provided in conjunction with other HIV-1 prevention services. Both TDF and TDF–FTC showed significant, and a similar magnitude of, HIV-1 protection for both women and men.2

Women with HIV-1 infection who were breast-feeding infants were enrolled in a randomized, phase 3 trial in Blantyre, Malawi. Extended prophylaxis with nevirapine or with nevirapine and zidovudine for the first 14 weeks of life significantly reduced postnatal HIV-1 infection in 9-month-old infants. (ClinicalTrials.gov number, NCT00115648).12

Transmission of HIV

Transmission of HIV depends on the infectiousness of the host and the susceptibility of the sexual partner. Sexual transmission of HIV has been most closely linked to blood viral burden in the infected host, which probably serves as a surrogate for HIV concentration in the genital tract. In a landmark study Quinn TC et al studied 415 serodiscordant couples in Uganda, reported that probability of HIV transmission increased directly with blood HIV RNA concentrations. Increased transmission was not observed when HIV RNA level was less than 1500 copies/mL.5

Antiretroviral therapy can be expected to reduce HIV RNA concentrations in blood and seminal plasma, female genital tract secretions, and rectal secretions.5

Penetration of antiviral agents into genital tract secretions is dictated by the degree of protein binding and by a drug’s affinity for albumin and alpha-1-acid glycoprotein. Most nucleoside and nucleotide reverse transcriptase inhibitors, which have limited protein binding, attain genital tract concentrations that are 2- to 6-fold greater than plasma concentrations.5

Side Effects

When used for HIV-1 treatment, TDF is known to cause small decreases in glomerular filtration that are of uncertain clinical significance. In their population of HIV-1–seronegative participants without preexisting renal impairment, Mugo NR et al and Rehle TM et al found no evidence of clinically significant elevations in serum creatinine and suggested the need of additional studies of proximal renal tubular function, bone mineral density, and other aspects of long-term safety of TDF-based preexposure prophylaxis, as well as safety in pregnant, breast-feeding, or adolescent women, among whom HIV-1 rates are high.2

Resistance

Among the 8 participants in the TDF and TDF–FTC groups who were found to have been infected at randomization, HIV-1 with resistance to the study medications developed in 2 participants: 1 in the TDF group had a TDF-resistant virus (K65R mutation), and 1 in the TDF–FTC group had an FTC-resistant virus (M184V mutation).2

Factors for Drug Efficacy

Why the results of efficacy of drugs differ across the various studies reported to date is unclear. However, important considerations include (a) the populations studied; (b) likely routes of HIV transmission (vaginal vs. anal mucosa); (c) sexual behaviors, (d) susceptibility to HIV and most important and (e) medication adherence by study participants.13
**Adherence**

Adherence to drug is assessed by measurement of antiretroviral concentration in blood plasma as a biomarker of adherence. Van Damme L et al showed that self-reported pill usage and pill counts can be unreliable measures of adherence and decreased efficacy for prevention was associated with the absence of the antiretroviral drug or drugs in the blood plasma.\(^\text{13}\)

The data highlight the importance of objective measures of adherence and the substantive challenge, even in a research setting, of daily medication for the prevention of HIV in a healthy population.\(^\text{13}\)

**Indications for PrEP**

PrEP should be considered for commercial sex workers, young women aged about 20 to 25 years, men-who-have-sex with men, or intravenous drug users, but only where the incidence of HIV is high.\(^\text{13}\)

**Approval by FDA**

On the basis of these studies reported by Grant RM et al and Peterson L et al and earlier findings, a Food and Drug Administration panel recently recommended approval of the TDF–FTC antiretroviral combination for preexposure prophylaxis.\(^\text{13}\)

**Challenges**

If PrEP is started, how and when will it be stopped? What messages should the health care worker provide to the patient? And how should PrEP be monitored for adherence and safety? Providing a daily medication to healthy, HIV-uninfected persons demands an extraordinarily high degree of safety. There is substantial clinical experience with the TDF–FTC combination in the treatment of people with HIV infection, and no major safety concerns have been identified. However, the drugs have the potential to affect kidney function and liver function and to reduce bone density. The current studies were time-limited (about 1 to 2 years), so the long-term safety of TDF–FTC in healthy persons must be monitored, because the implied use maybe for many years.\(^\text{13}\)

HIV acquired during PrEP has the potential to develop resistance to the antiviral agents used (TDF–FTC), jeopardizing the therapeutic use of these drugs both for the patient in his or her subsequent treatment and for the community at large if resistance to the agents spreads more broadly.\(^\text{13}\)

**Future Strategies**

Further research is needed to identify the highest-risk populations, the preferred dosing strategy (daily or less frequent). We also need to better define the medical risks of the long-term use of these agents in a healthy population, to determine the costs, and to understand the effect on the induction and amplification of antiretroviral resistance.\(^\text{13}\)

**Conclusion**

In the United States, HIV infection is spreading rapidly among certain populations, due to practice of high-risk behavior and young men who have sex with men. Hence it remains a public health problem of major proportions in the United States. Mathematical models estimate that over the next 10 y, an effective PrEP program could prevent 2.7 to 3.2 million new HIV-1 infections in sub-Saharan Africa. The prevention of HIV infection is a critical global public health priority. PrEP is emerging as part of an integrated HIV prevention strategy to end pandemic. Various systemic review and meta-analysis of differential efficacy, safety, and cost of TDF and TDF–FTC have shown that they could be compared as potential PrEP agents. So, PrEP is emerging as one of the important tools for controlling this pandemic. Due to PrEP there can occur a danger of resistance to these drugs in future, but for controlling it PrEP provides the best option.

**References**

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