Can Antiretroviral Therapy Be Used to Prevent Sexual Transmission of Human Immunodeficiency Virus Type 1?

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Approximately 5 million people annually are newly infected with human immunodeficiency virus (HIV). Although education, behavior modification, and promotion of condom use are effective transmission-prevention measures, the severity of the pandemic demands that all possible prevention strategies be explored. Antiretroviral therapy has the potential to decrease sexual transmission of HIV type 1 by reducing levels of HIV RNA and thus decreasing the risk that infected persons will transmit the disease or by its use as preexposure or postexposure prophylaxis. In this article, we explore the rationale for using antiretroviral therapy to prevent sexual transmission of HIV, as well as the limitations of this approach.

At the end of 2001, it was estimated that 40 million individuals worldwide were living with HIV/AIDS and that 5 million new infections occurred each year [1]. The majority of these new infections occur in developing countries, and heterosexual intercourse is the predominant mode of transmission. Although education, behavior modification, and promotion of condom use are effective prevention measures [2], the severity of the pandemic demands that all possible prevention strategies be explored [3].

Antiretroviral medications effectively treat HIV disease, and their role in preventing HIV infection is emerging. Antiretroviral therapy (ART) has the potential to decrease sexual transmission of HIV in 2 ways: (1) by reducing HIV RNA concentrations and thus decreasing the risk that an infected person will transmit the virus and (2) by its use as preexposure prophylaxis or postexposure prophylaxis (PEP). In this article, we explore the rationale for using ART to prevent sexual transmission of HIV, as well as the limitations of this approach.

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USE OF ART TO REDUCE THE RISK OF HIV TRANSMISSION

The proposal that ART be used to reduce the risk that an HIV-infected individual will transmit the virus is based on successful use of these agents to prevent perinatal transmission of HIV type 1 (HIV-1), on the biological and epidemiologic aspects of heterosexual transmission of HIV, and on the pharmacologic properties of ART.

Prevention of mother-to-child transmission of HIV. In mother-infant pairs, the risk of HIV transmission can be directly correlated with maternal plasma HIV RNA levels [4]. Several key trials support the use of ART to prevent mother-to-child transmission (reviewed by Mofenson and McIntyre [5]). In the AIDS Clinical Trials Group Study 076, the first randomized, placebo-controlled study of perinatal transmission, zidovudine was administered orally to pregnant women from week 24 of gestation until the onset of labor, intravenously throughout the delivery, and orally to the infant for 6 weeks after delivery. This resulted in a decrease in the perinatal HIV transmission rate from 25.5% to 8.3% [6]. The finding that

administration of a single dose of nevirapine to the mother at the onset of labor and to the neonate at birth resulted in a 13.1% decrease in the transmission rate [7] was even more promising for developing countries. In developed countries, perinatal transmission of HIV has nearly been eliminated among mother-infant pairs as a result of early identification of HIV infection in pregnant women and use of ART [8]. Furthermore, treatment of pregnant women with zidovudine reduces the immune response to HIV in their offspring.

However, mother-to-child transmission and sexual transmission are not analogous biological events, and the exact mechanism by which ART prevents mother-to-child transmission is not known. Some studies have documented mother-to-child transmission of HIV even when the mother's HIV RNA level was undetectable. In addition, more-complete protection from HIV is observed when the neonate also receives ART [9].

Prevention of sexual transmission of HIV. The biological factors associated with sexual transmission of HIV have been extensively reviewed [10], and it is clear that the level of HIV RNA in the source patient is a critical determinant. In a study of 415 couples in Uganda with discordant HIV status, when the infected partner had a blood plasma HIV RNA concentration <1500 copies/mL, no transmission events occurred [11]. Conversely, HIV-infected study subjects with blood plasma HIV RNA concentrations >50,000 copies/mL were nearly 12 times more likely to transmit HIV than were subjects with blood plasma HIV RNA concentrations <3500 copies/mL. Blood plasma HIV RNA concentrations also were found to be the best predictor of transmission in more-recent, prospective studies by investigators working in Zambia [12] and Thailand (S. Tovanabutra, V. Robison, J. Wongtrakul, S. Sennum, Y. Suriyanon, D. Kingkeow, S. Kawichai, P. Tanan, A. Duerr, and K. E. Nelson, unpublished data).

Deductive reasoning suggests that sexual transmission should also be strongly related to the concentration of virus present in genital fluid, because this represents the infectious inoculum. In some (but not all) investigations, HIV RNA concentrations in blood can be correlated with HIV RNA concentrations in genital fluid [13, 14], and the correlation coefficient increases dramatically in subjects receiving ART [15]. However, local replication of HIV is possible, particularly in the presence of inflammation [16]. Chakraborty et al. [15] have developed a model that predicts the probability of transmission of HIV from men to women as a function of HIV levels in seminal plasma.

ART consistently decreases levels of HIV RNA in genital fluid, often below the limits of detection (<400 copies/mL) [13]. The pharmacologic activity of antiretroviral agents in semen has been extensively studied [17]. Zidovudine and lamivudine concentrate in the seminal plasma and achieve concentrations greater than in blood, whereas some protease inhibitors poorly penetrate into the genital tract [17, 18]. Differential penetration of ART may influence the evolution of virus isolates in the blood and in the genital compartments and, in turn, affect the likelihood of sexual transmission.

The impact of ART on HIV transmission has been addressed in a single observational study of 436 couples in which all men were HIV positive, all women were HIV negative, and some men received zidovudine monotherapy [19]. The incidence of HIV infection among previously HIV-seronegative female sexual partners of all men in this study was 3.7 per 100 person-years. After the analysis was adjusted for symptoms of AIDS, $CD4^+$ cell count, p24 antigen positivity, and condom use, administration of zidovudine monotherapy to the HIV-positive male member of a couple produced a 50% reduction in risk. However, the same study revealed an 80% risk reduction that was associated with condom use.

Mathematical models also suggest that ART will have an impact on the incidence and prevalence of HIV. In a model generated by Gray et al. [20], from the Uganda transmission study, it was predicted that successful ART would reduce the incidence of HIV infection by 80%. Models based on the HIV epidemic in the homosexual communities in San Francisco [21, 22] and Australia [23] also have predicted that increased use of ART could prolong survival for HIV-infected individuals and reduce the incidence of HIV transmission. However, these prevention gains could be partially offset if increases in risk-taking behaviors or viral resistance develop.

LIMITATIONS OF ART IN PREVENTING SEXUAL TRANSMISSION OF HIV

ART can only be used to treat individuals whose HIV status is known and for whom ART is clinically appropriate. This precludes application of this strategy in treatment of patients with primary HIV infection, although some experts believe that primary infection carries the highest risk of transmission, because it is associated with elevated HIV RNA levels and continued sexual activity [24]. Even if use of ART is limited to treatment of individuals with long-standing HIV infection, such people must be identified, and access to affordable and tolerable therapy must be provided to them.

Viral resistance will emerge as ART becomes more widespread, and suboptimal suppression of HIV RNA will promote viral resistance. The degree to which HIV resistance will affect the epidemic is unclear. It has been argued that mutant variants may be less "fit" for transmission [25], although studies of primary infection have clearly demonstrated transmission of resistant virus [26]. Modeling experiments also have been used to gauge the effects of resistance [21]. For example, Blower et al. [22] predict that transmitted resistance is likely to increase gradually, with a doubling time of ~4 years, and estimate that a median of 15.6% (interquartile range, 6.1%–28.1%) of new

HIV infections are likely to be resistant to antiretroviral agents by 2005. Indeed, many ongoing studies suggest that this percentage may be even higher. Paradoxically, these investigators have demonstrated that use of the ARTs that are most effective at suppressing drug-sensitive isolates will lead to an increase in transmitted resistance [22]. However, increases in levels of resistance in a given population can be avoided. In Switzerland, where >80% of prescribed antiretroviral drugs are dispensed by one of the highly experienced Swiss HIV Cohort centers, prevalence of drug-resistant HIV in newly infected individuals has been decreasing since 1996. Clearly, if ART is to be introduced in a country as a measure to reduce the incidence of HIV infection, special attention should be given to optimization of adherence to therapy from the very beginning.

The belief that ART reduces the risk of HIV transmission can lead to increases in sexual risk-taking behavior. The prevalence of sexually transmitted diseases has increased among gay men in Amsterdam [27] and some American cities [28], which suggests that a new lapse in adherence to safer sex practices has occurred. Mathematical models [21–23] suggest that an increase of even 10% in sexual risk-taking behavior could offset the protective effect of ART. In addition, the inflammation caused by sexually transmitted disease can increase the excretion of HIV in the genital tract, even in patients receiving ART (C. Pilcher, personal communication, 2001).

Although ART use is now widespread, the actual effects of such therapy on the incidence of HIV in a population have been difficult to determine. A group of investigators in San Francisco, where a substantial percentage of HIV-infected people are receiving ART, has tried to address this difficult but important question. Those investigators are concurrently measuring the incidence of HIV and of rectal gonorrhea and sexual behavior in several populations. Their work to date supports the idea that use of ART can increase sexual risk-taking behaviors. The data available do not allow conclusions about the effect of ART on the spread of HIV to be drawn, in part because distinct populations are being studied [28].

REDUCING SUSCEPTIBILITY TO HIV WITH ART

The primary evidence for the effectiveness of PEP in preventing sexual transmission of HIV is from animal studies and extrapolation from occupational-exposure data.

Early animal studies that evaluated the effectiveness of PEP were modeled to more closely simulate occupational exposure, by use of an intravenous inoculum [29]. These early studies generally did not demonstrate adequate efficacy for this intervention. However, differences in the viral inoculum, virulence, and medications used make interpretation of the study results difficult [30]. More recently, tenofovir (a nucleoside reverse-transcriptase inhibitor) has shown promise as a highly effective medication for prevention of simian immunodeficiency virus (SIV) in macaques. In a study by Tsai et al. [31], tenofovir treatment was initiated either 48 h before or 4 or 24 h after intravenous inoculation of 10 ID_{50} SIV_{mne} and continued for 28 days. Remarkably, none of the 25 treated macaques became infected. Further investigations by the same group demonstrated that the protective effects of PEP markedly decreased if treatment was initiated 24 h after exposure or if the duration of therapy was less than 28 days [32]. In a model simulating sexual transmission, pigtailed macaques were inoculated vaginally with HIV type 2 (HIV-2). Tenofovir was administered 12 h ($n = 4$), 36 h ($n = 4$), or 72 h ($n = 4$) after this exposure, and treatment continued for 28 days. Three of 4 untreated control animals became infected with HIV-2. All 8 animals that received therapy within 36 h of exposure were protected from HIV-2 infection, and 1 of the 4 animals in which therapy was started at 72 h became infected [33].

Data on humans are limited to data from a single case-control study that evaluated HIV transmission after occupational exposure [34]. This study demonstrated that subjects who received PEP with zidovudine were 81% less likely to seroconvert than individuals who did not receive zidovudine. Deep injury, visible blood, intravessel procedures, and terminal illness in the source patient all posed an increased risk of seroconversion.

This accumulated evidence serves as the basis for the Centers for Disease and Control Prevention policy that advocates the use of ART for PEP after occupational exposure to HIV [35]. A policy for prophylaxis after sexual exposure to HIV that is based on earlier recommendations [36] is in development. The use of PEP to treat individuals after high-risk sexual encounters or sexual assault is unlikely to have appreciable effects on the epidemic, because the risk of transmission from a single unprotected sex act is estimated to be very low.

LIMITATIONS OF PEP IN PREVENTING SEXUAL TRANSMISSION OF HIV

Limitations of PEP include cost, toxicity of agents, potential viral resistance, effect on sexual risk-taking behavior, patient adherence to therapy, and logistics of prompt administration of therapy. Several studies have been conducted that address these limitations. A San Francisco PEP study included 401 individuals who presented within 72 h after exposures related to high-risk sexual behavior or intravenous drug use. Subjects were offered ART, as well as risk-reduction and medication-adherence counseling [37]. Treatment was initiated at a mean of 33 h after exposure, and 78% of the subjects completed the 4-week course of therapy. No seroconversions were documented, but this study was not powered to demonstrate efficacy.

Rather, it documented both the magnitude of demand for PEP and the feasibility of its application.

Investigators in Brazil [38] conducted a investigation of PEP in a group of high-risk homosexual men, using self-administered initiation of therapy. Subjects were provided the initial doses (4 days) of PEP, to be taken immediately after perceived exposure. Subjects deemed to be at significant risk by a clinician in a follow-up examination were offered 24 additional days of therapy. The investigators considered the initiation of PEP to be appropriate in 90% of the cases, and the majority of subjects completed the 28-day course of therapy. The investigators reported reduced risk-taking behavior in the study population.

The results of a relatively conservative cost-effectiveness analysis by Pinkerton et al. [39] suggest that a narrow application of PEP would be most appropriate. Only in the setting of receptive anal intercourse and near-certain HIV infection in the index partner would PEP be considered cost effective.

CONCLUSIONS AND FUTURE OBJECTIVES

ART is a potential tool for use in curbing the AIDS epidemic, one that both decreases the risk that the index patient will transmit the virus and reduces the susceptibility of the uninfected partner. However, if this approach is to be broadly and successfully implemented, a concerted effort to identify all infected individuals must be made, so that counseling and education can proceed, and antiretroviral medications should be made available to infected individuals, including those in developing nations. A more detailed review of this topic is available in [30].

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