Reducing HIV-1 transmission through prevention strategies targeting HIV-1-seropositive individuals

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Introduction

The recent international effort to expand access to antiretroviral therapy in resource-limited countries has resulted in increasing numbers of people seeking HIV-1 testing and care. The expanding population of HIV-1-seropositive individuals who are aware of their status provides an opportunity for directing novel prevention strategies towards those who are at risk for transmitting the virus. In addition to behavioural strategies, which will undoubtedly be central to prevention efforts, two broad categories of biomedical interventions could provide important tools for reducing the risk for HIV-1 transmission from seropositive individuals. First, antiretroviral therapy may directly reduce infectivity by decreasing the quantity of virus in plasma and at mucosal surfaces. Second, strategies targeting sexually transmitted diseases (STDs) could reduce HIV-1 transmission risk both among those receiving antiretrovirals and among the larger population of HIV-1-seropositive individuals who will not yet have advanced immunosuppression and thus will not qualify for immediate initiation of antiretroviral therapy. This article will review key data supporting the use of antiretroviral therapy and STD treatment as methods for decreasing HIV-1 infectivity, and will examine current questions and ongoing studies designed to test interventions for decreasing the spread of HIV-1 through prevention in positives.

Keywords: sexually transmitted diseases, antiretroviral therapy, infectivity

Antiretroviral therapy to decrease HIV-1 transmission risk

Several pieces of data provide indirect evidence suggesting that antiretroviral therapy could decrease sexual transmission of HIV-1. Initiation of antiretroviral therapy results in dramatic reductions in plasma HIV-1 viral load, which is a key predictor of transmission risk. The efficacy of antiretrovirals for reducing mother-to-child HIV-1 transmission has been firmly established in clinical trials, but similar controlled data proving the efficacy of antiretroviral therapy for prevention of sexual transmission are not yet available. An observational study of HIV-1-serodiscordant couples, published in 1994, demonstrated a significantly lower rate of male-to-female transmission (by 50%) when the seropositive man was treated with zidovudine. More recently, a cross-sectional study of 393 heterosexual couples found that the prevalence of HIV-1 was significantly lower in the partners of individuals receiving highly-active antiretroviral therapy (8.6% versus 0%, \( P = 0.01 \)). However, the actual magnitude of the effect of antiretroviral therapy on sexual transmission remains unknown, and some caution is warranted when considering this indirect evidence. In particular, it is clear that persistent genital HIV-1 shedding can occur in some men and women despite an undetectable plasma viral load, suggesting that these individuals may remain infectious.
To test the hypothesis that antiretroviral therapy decreases infectivity, an international multicentre randomized trial comparing antiretroviral therapy plus HIV-1 primary care versus HIV-1 primary care alone for prevention of sexual transmission of HIV-1 in serodiscordant couples began enrolling participants in early 2005 [HIV Prevention Trials Network (HPTN) Protocol 052; National Institute of Allergy and Infectious Diseases]. Monogamous couples in which the HIV-1-infected partner has a CD4 lymphocyte count of 300–500 cells/mm³ are being enrolled, as individuals with more advanced immunosuppression would qualify for antiretroviral therapy to delay disease progression and prolong survival. Thus, the aim of this trial is to establish the efficacy of antiretroviral therapy to prevent sexual transmission within serodiscordant couples in which the HIV-1-seropositive partner has modest, but not severe, immunosuppression.

Alternative strategies will be needed to evaluate the potential efficacy of antiretrovirals for decreasing HIV-1 transmission in other settings, such as during acute infection and in the later stages of disease, when infectivity may be significantly enhanced. In addition, the effect of STD co-infections, frequent partner change and other cofactors that may characterize populations other than monogamous serodiscordant couples will be important to explore. A complementary methodology for studying HIV-1 transmission risk is the measurement of genital HIV-1 shedding as a surrogate marker for infectivity. An understanding of the effects of antiretrovirals on HIV-1 infectivity may be gained through studies of the time course, magnitude and durability of genital HIV-1 suppression. In addition, factors such as STDs and hormonal contraceptive use, which influence genital HIV-1 shedding in antiretroviral-naive individuals, may remain important as correlates of HIV-1 infectivity in those receiving antiretrovirals. Novel risk factors for HIV-1 shedding, such as drug adherence and resistance, could emerge as the dominant determinants of infectivity in antiretroviral-treated individuals. Longitudinal genital HIV-1 shedding studies will be able to efficiently examine these risks. Our group and others have embarked on studies to address these questions. Together with the results of the HPTN 052 trial, we anticipate that this research will provide a broader understanding of the potential for reducing HIV-1 transmission using antiretroviral therapy.

STD and HIV-1 transmission: epidemiological synergy

Bidirectional interactions between HIV-1 and other STDs have been recognized since early in the HIV-1 epidemic and are believed to be among the factors leading to the rapid spread of HIV-1 in many resource-limited settings. Numerous longitudinal studies have established the now widely accepted principle that STDs increase the risk for HIV-1 acquisition. In contrast, few studies have examined the reciprocal effect of HIV-1 on STD risk. In a recent publication, we evaluated the influence of HIV-1 infection on acquisition of STDs using data from a 10 year prospective cohort study of female sex workers in Mombasa, Kenya. In multivariate analyses controlling for sexual risk behaviour and demographic factors, HIV-1 was associated with a nearly 3-fold increased risk for genital ulcer disease [GUD; hazard ratio (HR) 2.8, 95% confidence interval (CI) 2.0–3.9], most of which was clinically consistent with genital herpes reactivation. There were also significant increases in the risk of vulvovaginal candidiasis (VVC; HR 1.5, 95% CI 1.3–1.8) and infection with Neisseria gonorrhoeae (HR 1.6, 95% CI 1.1–2.2). The risk of both GUD and VVC increased significantly with progressive levels of immunosuppression. These findings have important public health implications, as they suggest that HIV-1 infection, particularly in the setting of advancing immunosuppression, may lead to an increase in susceptibility to some STDs. It is also important to recognize that regardless of this apparent increase in biological susceptibility, HIV-1-infected individuals often have high rates of STDs, probably because of shared behavioural risk factors that facilitate both HIV-1 and STD transmission.

Several cross-sectional studies in HIV-1-seropositive individuals have demonstrated that bacterial STDs (e.g. Neisseria gonorrhoeae and Chlamydia trachomatis), trichomoniasis and VVC are associated with higher concentrations of HIV-1 in genital mucosal secretions. A smaller number of carefully-conducted prospective studies subsequently showed that treatment of these conditions reduces genital HIV-1 shedding, providing convincing evidence of reduced infectiousness. In one study, treatment of urethritis in men significantly reduced seminal HIV-1 RNA concentrations from $5.1 \log_{10}$ copies/mL at the time of diagnosis to $4.6 \log_{10}$ copies/mL 2 weeks later ($P < 0.001$). Similarly, among women with cervical STDs, HIV-1 RNA concentrations in cervical secretions were reduced from $4.1 \log_{10}$ copies/swab at baseline to $3.2 \log_{10}$ copies/swab 2 weeks after successful treatment ($P = 0.001$). Likewise, vaginal mucosal HIV-1 RNA levels were significantly lower 2 weeks after treatment of VVC ($3.4 \log_{10}$ copies/swab, $P < 0.001$) and trichomoniasis ($3.7 \log_{10}$ copies/swab, $P < 0.001$).

Several strategies should be considered as potential methods for decreasing HIV-1 infectivity in seropositives through improved management of STDs. Syndromic management has been shown to decrease HIV-1 transmission in a community-level trial, an effect that may have been mediated in part through reducing infectivity in HIV-1-seropositive individuals with STDs. However, syndromic management has limited utility for the efficient management of cervical STDs, and further work is needed to determine the efficacy of this intervention for reducing HIV-1 transmission when targeted specifically towards HIV-1-seropositives. An alternative strategy for addressing STDs in HIV-1-seropositive individuals is periodic screening with directed treatment. This approach has the advantage of identifying asymptomatic STDs, but may be limited by the cost and infrastructure required for testing, underscoring the need to develop rapid, accurate and inexpensive tests for STDs. Finally, prophylactic therapy could be provided to HIV-1-seropositive individuals at particularly high risk for infection with STDs. Individual-level trials of prophylactic therapy for prevention of STDs have been almost uniformly successful, although the risk for development of resistance to chemoprophylactic regimens could limit the use of this potentially important strategy.

The special case of herpes simplex virus type-2

Herpes simplex virus type-2 (HSV-2) is highly prevalent in many resource-limited countries. During the past several years, there has been an expanding recognition of HSV-2 as risk factor for HIV-1 acquisition and transmission. There is compelling evidence that HSV-2 infection significantly increases individual-level risk of HIV-1 acquisition, and the prevalence of HSV-2 infection may be a key determinant of HIV-1 rates in populations. There is also evidence that HSV-2 increases the infectiousness of those co-infected with HIV-1. A prospective study of 235 monogamous HIV-1-serodiscordant couples found that the presence of a genital
ulcer in the index partner increased the risk of HIV-1 transmission by ~2-fold,\(^1\) a finding that carries added significance in light of our recent study demonstrating that HIV-1-associated immunosuppression increases the risk for GUD.\(^{13}\) Furthermore, even non-ulcerative HSV-2 reactivation may be associated with increased genital shedding of HIV-1.\(^{22}\) Thus, there has been interest in the effect that anti-HSV-2 therapy might have for reducing HIV-1 infectivity in dually infected individuals.

International multicentre trials are under way to evaluate the efficacy of anti-HSV-2 medications for reducing HIV-1 infectivity. An ongoing clinical trial is testing the efficacy of HSV-2 suppressive therapy for reducing transmission in serodiscordant couples by providing anti-HSV-2 medications to the HIV-1-seropositive/HSV-2-seropositive partner (Partners in Prevention Trial; Bill and Melinda Gates Foundation). Additional studies are being conducted to evaluate the effect of HSV-2 suppressive therapy on genital HIV-1 shedding and to determine whether episodic anti-HSV-2 treatment for symptomatic genital herpes can reduce the quantity of HIV-1 in genital ulcers.\(^{23}\) These studies will provide valuable information about the effect of anti-HSV-2 therapy as a strategy to prevent HIV-1 transmission from those with HIV-1/HSV-2 co-infection.

### Public health and prevention in positives

While the principal goal of prevention strategies targeting seropositive individuals will be to decrease HIV-1 transmission, direct benefits to HIV-1-seropositive individuals might also be expected, including slower HIV-1 progression and decreased STDs. However, interventions such as earlier initiation of antiretroviral therapy and chemoprophylaxis for HSV-2 also carry potential risks, including medication side effects and development of drug resistance. In other words, strategies for prevention in positives may exchange population-level benefits for risks borne primarily by individuals living with HIV-1.

Ethical questions that require seeking a balance between individual and public health interests are not unique to sexual HIV-1 transmission. For example, chemoprophylaxis to prevent mother-to-child HIV-1 transmission requires that mothers assume risks in order to reduce the chances that their infants will be infected. Similar questions are raised by partner notification for individuals diagnosed with STDs, isolation of those with communicable diseases such as tuberculosis, and mandatory vaccination programmes.

No single policy is likely to provide an adequate answer for every population, setting and intervention strategy. At one end of the spectrum, interventions for prevention in positives could simply be made available, leaving patients and providers to develop individualized plans for reducing transmission risk. Indeed, strategies such as expanding access to antiretroviral therapy for those with intermediate levels of immunosuppression (CD4 counts 200–350 cells/mm\(^3\)), might be welcomed and readily taken up by seropositives. At the other end of the spectrum, health officials might seek to mandate certain interventions as part of a public health strategy for reducing HIV-1 transmission. Between these extremes, there exists a continuum of potential implementation strategies.

The possibility that interventions designed to reduce infectivity in seropositives will be counterbalanced by increases in sexual risk behaviour is an issue of great public health importance. A recent systematic review found that both HIV-1-seropositive and -seronegative individuals who believe that being on antiretroviral therapy reduces the risk for HIV-1 transmission may engage in higher risk sexual activity.\(^{24}\) However, there are almost no data from resource-limited countries, and it is not known whether similar behavioural patterns will be observed in these settings.

Regardless of changes in sexual risk taking, interventions for prevention in positives are unlikely to be 100% effective. This information must be incorporated into counselling for seropositive individuals receiving such interventions. Traditional approaches including abstinence, consistent condom use and disclosure of serostatus to sex partners will remain essential. Thus, HIV-1-seropositive individuals will still need to accept a substantial share of the burden of preventing further transmission.

Finally, an early concern raised in reference to the widespread introduction of antiretroviral therapy in resource-limited countries was the potential for poor adherence leading to transmission of resistant HIV-1. However, initial reports suggest that adherence is high in resource-limited settings,\(^{25}\) and the international consensus has been that life-prolonging treatment should not be delayed because of theoretical concerns about transmitted resistance. The use of antiretrovirals and other medications for prevention in positives will require additional consideration of the question of transmitted resistance. As further research into prevention interventions is conducted, data on adherence, development of resistance and transmission of resistant viruses will be essential to inform the development of evidence-based public health policies about the implementation of these strategies.

### Conclusions

The expanding availability of antiretroviral therapy in resource-limited countries has greatly increased the number of individuals seeking HIV-1 testing and care, providing new opportunities to strengthen HIV-1 prevention efforts. Successful strategies for HIV-1 prevention in seropositive individuals should be guided by an appreciation of the interactions between HIV-1 and STDs. With generalized epidemics affecting many resource-limited countries,\(^{26}\) the risk for HIV-1 acquisition has extended far beyond the usual core-transmitter groups. In this context, targeted interventions directed to ‘high-risk’ seronegative individuals may have only a limited impact on HIV-1 rates at the population level. Comprehensive population-wide prevention programmes will need to incorporate both traditional risk reduction approaches for preventing infection in those at risk for HIV-1 acquisition and innovative strategies for reducing infectivity in those who are at risk for transmitting the virus. Further research to develop and test methods for HIV-1 prevention in positives is urgently needed.

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### Transparency declarations

None to declare.

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