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Integrating HIV Prevention with Care: Antiretroviral Treatment for Prevention

This evidence review is part of a series on HIV prevention and control produced by the National Collaborating Centre for Infectious Diseases. It is intended to inform public health practitioners and community-based workers and guide their practice.

Antiretroviral Therapy and HIV Prevention

HIV transmission depends on infectivity (ability to infect others), susceptibility and the risk of exposure, each of which can be targeted by prevention strategies (1–3). Antiretroviral therapy (ART) can reduce both infectivity and susceptibility to the virus. Pre-exposure and post-exposure prophylaxis may reduce the virus' capability of establishing an ongoing infection regardless of exposure, thereby reducing an individual's susceptibility. This paper will focus on the role of ART, especially highly active antiretroviral treatment (HAART), in lowering infectivity and reducing sexual transmission in individuals in clinical care.

Does Viral Load Influence HIV Transmission?

The connection between higher viral load and HIV transmission was first noted in mother-to-child transmission (3). In 2000, Quinn and colleagues (4) found increased viral load directly related to increased sexual transmission. Among the 415 serodiscordant, heterosexual couples recruited in rural Uganda and followed for a mean of 30 months, overall transmission to uninfected partners was 11.8 per 100 person years. The transmission rate for infected male to female partner (in 228 couples the male partner was diagnosed with HIV at baseline) was not significantly different

Highlights

- ART can effectively reduce sexual transmission of HIV to partners by markedly lowering viral levels in blood as well as genital and rectal secretions.
- Expansion of ART use beyond current guidelines is not recommended at this time, outside of research initiatives but well designed population based studies need to be a carried out.
- Early identification of HIV infection through frequent testing opportunities is necessary to ensure diagnosis before individuals present with advanced HIV/AIDS. Reducing barriers to treatment access and keeping individuals in care is essential to alter transmission risks and health care providers have the major role in both these domains.

than that of female to HIV-negative male partner. In this study transmission did not occur if the infected partner's viral load was less than 1,500 copies/ml. The transmission risk increased 12 fold from 2.2 per 100 person years to 23 per 100 person years when plasma concentration increased from 3,500 copies/ml to greater than 150,000 copies/ml. In this retrospective study, occurring before HAART was widely available in Uganda, one of the participants was receiving ART.

In Thailand 493 heterosexual couples, in which the HIV positive individual was male, were followed for one year. No transmission occurred from the 16 HIV positive men receiving HAART, with viral loads less than 1,094 copies/ml at baseline. Increased baseline viral load was associated with higher infection rates among female partners and with plasma viral load exceeding 500,000 copies/ml, three of the five uninfected partners seroconverted (5).

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Does Antiretroviral Treatment Reduce Viral Load in Genital and Rectal Secretions?

ART has proven efficacy in reducing viral load (6–8) and could contribute to HIV prevention by decreasing the amount of virus present in genital and rectal secretions (genital shedding) (1,6,9). While levels of virus in genital secretions usually decrease to levels lower than blood HIV RNA with ART, this is not always the case (2,10–12). Virus is found in the semen of almost 4% of men with undetectable viral loads, while genital shedding can occur intermittently in the cervicovaginal secretions of up to a third of women with undetectable blood levels (6,11–13). The amount of virus in genital secretions can also be influenced by other factors such as the presence of sexually transmitted infections (STIs) or acute HIV infection. Menstruation, pregnancy and the use of hormonal contraceptives may increase virus in the female genital tract, although this requires further study, particularly in the context of modern HAART (3,5). This makes an absolute prediction of viral load in any individual's genital secretion impossible (1).

The absorption of antiretroviral drugs into the genital tract and secretions also plays an important role in genital shedding. Genital pharmokinetics of ART varies between individuals and between genders and contributes to variable genital HIV shedding (1,10). For example the concentrations of protease inhibitors (PIs) in the male and female genital tract are less than 10% and 50% of that in plasma, respectively (1). A recent study by Neely and colleagues (14) of 290 women, found genital shedding to increase with illicit drug use and non-nucleoside reverse transcriptase inhibitors (NNRTI) regimens, as opposed to PI based regimens (OR, CI: 2.24, 1.13 to 4.45). Shedding was observed in 13% of the PI treated women, compared to 19% of NNRTI treated women.

Could Antiretroviral Treatment Reduce the Risk of Sexual HIV Transmission?

Findings of serodiscordant couples studies provide support for using antiretroviral treatment to reduce sexual transmission, although there is limited direct evidence for the efficacy of ART in reducing HIV transmission.

An Italian study of 463 couples (15) conducted before the widespread use of HAART, found a 50% reduction in HIV transmission with zidovudine treatment of seropositive men. A more recent study from Uganda reported a 98% decrease in transmission associated with HAART, although only half of the sample was followed to six months (16). Castilla and colleagues (8) conducted a study with 393 serodiscordant couples in Spain and compared HIV-incidence among non-infected partners for the period prior to HAART (1991 to 1995), early HAART (1996 to1998) and late HAART (1999 to 2003). Incidence declined from 10.3% during the pre-HAART era to 1.9% in the late HAART period. No transmission occurred if the infected partner was receiving HAART. An 86% reduction in HIV transmission was independently associated with HAART.

A cohort study of men who have sex with men (MSM) in San Francisco (17), attributed a 60% decline in infectivity to the introduction of HAART. Analysis of Taiwan's national HIV surveillance data ascribed a 53% reduction in expected HIV cases to HAART (18). Montaner and colleagues (7) reported similar results for British Columbia, Canada. They estimated that HAART use averted 400 new infections during 2005 and was instrumental in the 50% decrease in HIV incidence from 1995 to1998.

Two ecological studies among MSM did not find the same reduction in HIV incidence. In San Francisco no decrease in HIV incidence with anonymous HIV testing occurred despite the widespread use of HAART (19). HIV incidence for MSM attending sexually transmitted infection (STI) clinics in Amsterdam increased from 1991 to 2001 (20). As pointed out by Cohen and colleagues, STI rates for both these populations were high, indicating continued and increasing risk behaviour (1). Similarly, Porco and colleagues reported an increase in unprotected sexual activity in San Francisco and other American cities following the introduction of HAART (17).

A limitation of observational studies is the mixing of effects of HAART with changes in behaviour, while the ecological studies cannot connect patients receiving therapy to overall

prevalence (1). In response to the lack of controlled data, the U.S. National Institute of Health prevention trial network is funding a randomized control trial (RCT) which will follow 1,750 serodiscordant couples in which the HIV positive individual is receiving HAART for five years.

What are the Challenges for Using Antiretroviral Treatment in Prevention?

The efficacy of HAART in preventing further transmission depends on many factors, including the proportion of the HIV infected population accessed and treated (1). Recently, Montaner and colleagues (7) presented the results of a theoretical demographic model evaluating the potential impact of expanding HAART to treat 100% of PHA. Their results suggest that full expansion of HAART coverage can dramatically decrease transmission of HIV over a short period of time, which in turn can decrease HIV incidence and prevalence over several years. In this hypothetical model, 100% coverage with HAART could be shown to dramatically curb the growth of the epidemic over several decades. While the theoretical approach presented is neither feasible nor realistic, the authors used this model to argue for the rapid expansion of HAART programs throughout the world, based on the proven benefits of HAART on AIDS-related morbidity and mortality and the potential preventive benefit.

Current treatment guidelines support the use of HAART only after there is evidence of clinical or laboratory progression of the disease (8,21). Many individuals in Western countries and over 90% in developing countries only learn of their HIV status late in disease progression. Even then, among those individuals who meet objective criteria to initiate life saving HAART, only a fraction of eligible individuals are on treatment due to multiple barriers. These include high cost of treatment, limited access to services and drugs, as well as a variety of medical (mental illness, injection drug use), social (poverty, homelessness) and cultural factors (reliance on traditional medicine) (22). These factors have been shown to be prevalent in both the developed and the developing world. It is important to recognize that in Canada and the developed world HAART programs fail to capture 25% to 40% of eligible individuals. The situation is worse in the developing world where over 90% of eligible individuals go without treatment in some countries. Similarly, it would be highly desirable that HIV incidence and prevalence be adequately monitored as the role of HAART evolves.

Transmission of drug resistant strains is also of concern (1,21,23). ART resistant strains of HIV account for 5% to15% of new infections (24). From 1997 to 2005, the cumulative incidence of primary resistance to one drug was 9.1% and 1.1% for more than one drug (25). Recent findings suggest, however, that ART resistance in Canada decreased from 13% to 4% between 1997 and 2003 (26). Some evidence also suggests that resistant strains may be less readily transmitted (1,24).

Belief about the effectiveness of HAART may lead to increased risk behaviour (1,6,8,21). Treatment optimism may have contributed to the increase in unprotected sex of MSM in Amsterdam and the U.S. (17,21). According to mathematical models a 10% increase in sexual risk behaviour may be enough to counteract HIV treatment's role in prevention. Unprotected sex increases the incidence of other STIs, which may increase HIV susceptibility and infectiousness (3,9,10,27).

Research Gaps

Additional studies on genital ART pharmokinetics and HIV viral levels in genital secretions are needed. More studies of treatment optimism are needed in the Canadian context. Further study is also required to determine the risk of HIV transmission by PHAs on ART with undetectable viral loads.

The efficacy of HAART in preventing further transmission depends on many factors, including the proportion of the HIV infected population accessed and treated. Current treatment guidelines support the use of HAART only after there is evidence of clinical or laboratory progression of the disease.

What can we Conclude about the Role of HAART in Prevention?

HAART can effectively reduce sexual transmission of HIV by markedly lowering viral levels in blood as well as genital and rectal secretions. HIV transmission from PHAs on HAART with an undetectable viral load remains a possibility, however, and requires further study to estimate its frequency and determinants. Expansion of HAART use beyond current recommendations is not recommended at this time, outside of research initiatives. Challenges to the use of HAART as a prevention strategy include the proportion of PHAs effectively treated, adherence issues, the possibility of transmission of drug resistant virus and the concern about an increase in risky behaviour in some infected individuals. ART does, however, have the potential to add substantially to the prevention strategies available. Further well designed studies to operationalize this outcome should be a priority.

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