Effect of Antiretroviral Therapy on Risk of Sexual Transmission of HIV Infection and Superinfection

Background

The past decade has seen substantial advances in the development of antiretroviral therapy (ART)—medications used in combination to reduce the replication of HIV virus and treat HIV-infected persons. Because of these medications, many HIV-infected persons are able to reduce levels of virus in the bloodstream (plasma viral load) to undetectable levels. Data suggest that HIV-infected persons with undetectable viral load are less infectious, and may be less likely to transmit HIV via sexual contact. This fact sheet summarizes the implications of these data to individual couples and to the potential impact of ART in the prevention of HIV transmission within populations.

Prevention of Sexual Transmission of HIV: Individual Couples vs. Populations

Evidence from observational studies among heterosexual populations [1-4] and men who have sex with men (MSM) [5] suggests that effective ART may greatly reduce the likelihood of sexual transmission from infected individuals to their sexual partners. A study of heterosexual couples in Uganda in which one partner was infected revealed that infected persons who did transmit virus to their partners had significantly higher mean viral load than those who did not transmit (90,254 copies/mL vs. 38,029 copies/mL); no transmissions occurred among couples in which the infected partners viral load was under 1500 copies/mL [1]. Among infected persons at a clinic in Spain, wider availability of effective ART was associated with an 80% decrease in sexual transmission of HIV [2]. While fewer data are available regarding the impact of ART on transmission among MSM (the most affected population in the United States), transmission rates observed among a population of MSM in San Francisco declined with the availability of ART despite increases in risk behavior, associated with an estimated 60% decrease in per-act infectivity [5]. Mathematical modeling studies suggest that successful use of ART by enough infected individuals could substantially reduce the spread of HIV within a population [6-7]. ART thus holds promise as an important prevention tool. However, it is important to note that this potential reduction in HIV transmission within a population does not translate to elimination of transmission risk within individual couples.

What is the Risk of Sexual HIV Transmission for HIV-infected Persons With Undetectable Viral Load?

ART is considered effective when it consistently suppresses plasma viral load to undetectable levels. However, sexual transmission of HIV from an infected partner who

was on ART with a repeatedly undetectable plasma viral load has been documented [8]. An infected partner's genital (seminal or vaginal) fluid viral load may play a greater role than plasma viral load when evaluating the risk of sexual transmission of HIV. The likelihood of HIV transmission in the setting of ART is influenced by a number of factors, several of which are described below.

The Meaning of "Undetectable" Viral Load: Persistence of Virus in Plasma and Seminal Fluid

Periodic blood plasma viral load monitoring is used to measure ART effectiveness. The goal of effective ART is the long-term suppression of plasma viral load, usually defined as the maintenance of a level of HIV virus that is below the threshold detectable by available tests. While plasma viral load tests are reliable, they have limitations: virus levels below a minimum concentration may not be detected. Studies have shown that persistent virus is found in peripheral blood mononuclear cells [9, 10] even when individuals have sustained undetectable plasma viral load levels.

Genital fluid viral loads are not routinely measured in persons on ART. Although ART reduces concentration of virus in seminal fluid [11], virus persists within cells present in seminal fluid of some men who are on ART with undetectable plasma viral load [12-13]. ART also is associated with decrease in cervicovaginal fluid viral load; however, 'breakthrough' shedding has been observed in some studies [14-17]. Therefore, the potential for transmission exists despite sustaining undetectable viral load while on effective ART.

Transient Increases ("Blips") in Viral Load

Several studies have observed that individuals on effective ART who achieve long-term suppression of viral load to undetectable levels may exhibit periodic temporary increases in plasma viral load (blips). These are generally small increases (between approximately 50 and 1000 copies/mL), and are estimated to last for short periods (<3 weeks) [18-20]. Because they are transient in nature, they may be missed on routine viral load testing. Currently, there are insufficient data to make statements regarding the magnitude of transmission risk related to viral load blips. However, it is conceivable that transient increases might correlate with increases in genital fluid viral load, and with enhanced sexual transmission risk.

Correlation Between Plasma and Genital Fluid Viral Load and Resistance to ART

Although ART reduces viral load in both plasma and seminal fluid, undetectable plasma viral load may not always predict undetectable seminal fluid viral load. A recent review of 19 studies, which compared plasma and seminal fluid viral loads, indicates that while blood and genital fluid viral load are often correlated, this is not always the case [21]. Thus, a person with an undetectable plasma viral load may still shed virus in genital fluid at higher levels, which poses risk for transmission.

Several additional factors may affect genital fluid viral load. For example, sexually transmitted infections (STIs) such as gonorrhea and chlamydia have been shown to transiently increase viral load in genital fluids [22-23]. Individuals with active STIs may

therefore be more infectious, despite a low or undetectable plasma viral load. Moreover, as individuals with STIs may not have any symptoms, it may be impossible for either partner to be aware of this increased risk.

Some of the variation in genital fluid viral load may be due to differences in the degree to which different ART medications enter genital fluid. Recently developed research methods allow for measurement of drug concentrations in seminal and vaginal fluids, which can then be compared to drug levels measured in blood. This research has found that some ART medications achieve higher concentrations in genital fluids than others [24-27]. For instance, nucleoside/tide reverse transcriptase inhibitors (NRTIs) penetrate to a greater extent in male and female genital secretions than do protease inhibitors (PIs). Further work of this type may eventually aid in selection of antiretroviral medications in order to reduce sexual transmission. However, more data collected via these methods and better understanding of the degree to which this approach might be effective is needed before specific recommendations can be made.

In addition to differences in viral load between plasma and genital fluids, there may also be differences in the resistance characteristics of virus in these two locations. HIV may become resistant to ART medications through mutations that occur during replication and through exposure to insufficient or inconsistent levels of HIV medications. This may happen when ART medications are not taken according to the prescribed schedule or doses are skipped. In addition, drugs which do not enter the genital fluid as well may help promote the development of resistance in the genital fluid specifically. Some researchers have noted that within an individual, the resistance characteristics of virus isolated from genital fluid may differ from those of virus isolated from plasma [28-30].

In summary, for couples in which one member is HIV-infected, treatment of the infected partner with effective ART and suppression of viral load to undetectable levels should greatly reduce the risk of transmission to the uninfected partner. However, this risk is not eliminated and it may not be maximally reduced at all times due to some of the factors discussed above. Moreover, the likelihood of transmission may be expected to increase with repeated exposures over time. In a model which estimated transmission risk in the setting of suppressed viral load (<50 copies/mL) without intercurrent STIs, the number of expected transmission events occurring within a population of 10,000 serodiscordant couples over 10 years was estimated to be 215 for female-to-male transmission, 425 for male-to-female transmission, and 3,524 for male-to male transmissions [31]. A meta-analysis of data from 11 cohorts including 5,021 heterosexual couples observed no transmissions among persons receiving ART with a viral load of <400 copies/mL; however, analysis of the data was compatible with the possibility of one event per 70 person-years [32]. For this reason, it is important that individual couples recognize the risk, and use additional preventive methods (e.g., condoms) in order to further minimize the chance of transmission.

ART as a Prevention Tool for Sexual Transmission of HIV

While it cannot be assumed that effective ART will eliminate transmission within individual exposures, evidence from several cohort, observational, and mathematical modeling studies suggests that effective ART may be a promising way to reduce sexual HIV transmission within populations. Potential limitations to this approach include availability of ART and appropriate monitoring, willingness of individuals to take medications, and potential offset of benefit though accompanying increases in risk behavior.

One study of the effectiveness of ART in reducing heterosexual transmission of HIV involved analysis of 393 serodiscordant heterosexual couples from 1991-2003. The authors noted that heterosexual transmission was reduced by 80% when the positive partner was treated with ART. Despite this significant reduction, the investigators cautioned against continued possible risk of transmission because of HIV levels in genital secretions of patients on ART [1]. Among 193 discordant couples identified in the Rakai Cohort in which the infected partner had a CD4 counts under 250 cells/μL, no transmission events were observed among 20 couples in which the infected partner was on ART [3]. A study of 2993 discordant couples in Rwanda and Zambia demonstrated that ART use was associated with reduced (but not eliminated) rates of HIV transmission and reduction in unprotected sex [4].

Regarding potential reduction of risk within MSM populations, analysis of data from the San Francisco Young Men's Health Study evaluated transmission events among 534 MSM. The investigators found a 60% decrease in HIV transmission after the introduction of ART. The reduction occurred despite the increases in reported number of risky sexual behaviors [5].

Other information regarding the potential population-level benefit of ART on transmission comes from mathematical modeling studies. Mathematical models involve the development of equations to explain the relationship between the potential effects of ART on viral load and the likelihood of HIV transmission. Modeling can help predict population-level outcomes such as rate of drug resistance, rate of HIV infection or prevalence of infection, and effects of HIV treatment and prevention programs in various settings [33]. Modeling methods are useful tools, but are limited by the fact that models reflect current understanding of how HIV is transmitted [34], as well as the validity of the assumptions and data used in model construction.

The potential impact of changes in risk behavior is one important determinant of the possible effect of ART in preventing transmission within a population. A model of ART use among MSM in a resource-rich setting [6] indicated that if treatment rates are high, transmission is likely to be significantly reduced; however, the rate of infection will be strongly influenced by changes in risk behavior, such that transmission could rise despite the increase in number treated. In a meta-analysis reviewing results of 25 studies of the impact on sexual risk behavior of ART and beliefs regarding transmissibility [35], being on ART or achieving an undetectable viral load was not associated with increased risky

sexual behavior. However, beliefs about HIV transmission and reduced concerns about unsafe sex were associated with a greater likelihood of risky behavior.

Modeling of infectiousness of HIV-infected persons at different stages of disease suggests that persons with high viral loads associated with acute infection and end-stage disease are highly infectious; however, those with asymptomatic infection will contribute most to transmission within a population because of the longer duration of this stage [36]. This suggests that early identification and therapy of infected persons may be an important aspect of the effectiveness of ART as a prevention tool. In a model (designed to reflect South African transmission dynamics) of a program to control heterosexual transmission which included universal voluntary HIV testing and immediate initiation of therapy in those found to be infected [7], incidence of new HIV cases was reduced to less than one per 1000 persons per year within a decade, and estimated deaths occurring through 2050 were estimated to be halved when compared to the current approach of waiting to start ART until a specific CD4 count is reached.

For HIV-infected individuals who are ART-naïve and who have no history of AIDS-defining illness, current U.S. treatment guidelines recommend initiating ART when the CD4 count falls below 350 cells/μL in most cases [37]. Exceptions (for whom treatment should be initiated regardless of CD4 count) include pregnant women, persons with HIV-associated nephropathy, and those co-infected with hepatitis B requiring treatment; the guidance also cites decreasing the risk of HIV transmission to others as a potential benefit to early therapy. The use of 350 cells/μL as a minimum threshold is supported by analyses from a subgroup of participants from the Strategies for management of Antiretroviral Therapy (SMART) study, which noted that among persons with CD4 counts of >350 cells/μL, those who were randomized to deferral of ART until the CD4 count dropped to <250 cells/μL had substantially higher risk of opportunistic diseases and serious non-AIDS events relative to those who initiated ART immediately [38]. A meta-analysis of 18 cohort studies also supports counts of 350 cells/μL as a minimum threshold [39]. Optimally, the decision to institute initiation of ART at a higher CD4 threshold on a widespread level would be based upon data from controlled studies. Recent studies indicate that initiating ART earlier than the currently recommended CD4 threshold of 350 cells/μL may confer benefits on survival [40] and immune function [41], without necessarily increasing risk of adverse events such as peripheral neuropathy, anemia, and renal insufficiency [42]. An ongoing randomized controlled study, HIV Prevention Trials Network (HPTN) 052, will compare the effectiveness of two treatment strategies in preventing the sexual transmission for HIV. Discordant couples will be randomized to either immediate ART for the infected partner, or deferral of ART until the CD4 count falls to between 200-250 cells/μL [43].

When Both Partners are Infected: What is the Significance of Superinfection in HIV Transmission?

Superinfection is defined as infection by a second strain of HIV after initial infection by a primary strain has been established [44]. The frequency and timing of superinfection may vary depending upon the population under study and the method of detection. Follow-up of 78 newly infected individuals (none of whom initiated ART while under study) in one clinic revealed that 4 (5%) had acquired a superinfecting strain within 6 to 12 months of initial infection [45]. In a cohort of 36 high-risk Kenyan women screened for HIV-1 superinfection over a 5-year period beginning at primary infection, seven cases of superinfection were detected [46]. In this study superinfection occurred throughout the course of the first infection: during acute infection in two cases, between 1-2 years after infection in three cases, and as late as 5 years after infection in two cases. The clinical consequences of superinfection for an individual vary, but may include accelerated disease progression and the acquisition of drug resistance [47]. The public health consequences of HIV superinfections are unclear. While superinfection can result in recombination between genetically different viruses, and a number of circulating recombinant forms (CRFs) are prevalent in certain geographic areas [48], it has not been demonstrated that such recombination results in the establishment of more transmissible or virulent viruses. There is also evidence that superinfection occurs only rarely in HIV-infected individuals on effective ART [49, 50].

CDC Guidance on ART and its Effect on Sexual Transmission of HIV

- Use of ART may be a promising tool for slowing the transmission of HIV within populations if prevention benefits are not offset by increases in risk behavior. Success of such a program will depend critically upon 1) widespread testing and early identification of infected persons, 2) ongoing counseling to support maintenance of safer sexual behaviors [51], 3) adequate clinical follow-up to monitor for adverse effects of ART, and 4) geographic and financial accessibility of treatment for affected persons.

- In accordance with U.S. Department of Health and Human Services guidelines [37], clinicians may consider the potential benefit of decreased risk of HIV transmission to others in deciding whether to initiate ART in infected patients (even at CD4 counts of >350 cells/μL).

- The risk of sexual HIV transmission is substantially reduced for individual couples in which the infected partner is on effective ART and has achieved undetectable plasma HIV viral load, but is not completely eliminated. Sexual transmission of HIV may still occur when the infected partner is on effective ART. In February 2008, CDC issued a statement reiterating its previous recommendations [51] that people living with HIV who are sexually active use condoms consistently and correctly with all sexual partners [52].

- For couples in which both partners are infected, the potential implications of superinfection are unclear. Use of condoms is recommended in this setting as well.

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