Preventing HIV Transmission in Persons with HIV

Introduction and Background

The availability of widespread effective antiretroviral therapy has transformed HIV from a fatal infection to a manageable chronic disease. Despite major advances in antiretroviral therapy, the incidence of new HIV infections in the United States continues to occur at a significant rate, with approximately 38,000 persons newly infected with HIV each year.[1,2,3] In addition, for persons living with HIV, antiretroviral therapy can dramatically reduce HIV transmission to others.[4,5,6,7] All clinicians providing HIV services should have knowledge and awareness of effective strategies that can play a role in reducing the risk of transmission of HIV from persons living with HIV. This following topic review will focus on behavioral, biomedical, and structural measures related to preventing transmission from persons living with HIV, a topic often referred to in the past as Prevention with Positives and now referred to in global efforts as Positive Health, Dignity, and Prevention.[8]
Antiretroviral Treatment as Prevention

A sentinel study in Rakai, Uganda first reported HIV RNA levels tightly correlated with risk of heterosexual HIV transmission.[9] This study involved 415 serodifferent heterosexual couples not taking antiretroviral therapy and the main finding was that mean serum HIV RNA was significantly higher in subjects whose partners seroconverted than in subjects whose partners remained HIV negative and HIV transmission was considered rare among persons who had an HIV RNA level less than 1,500 copies/mL (Figure 1).[9] This study played a major role in generating and testing the hypothesis that lowering HIV RNA levels with antiretroviral therapy would have a major impact on HIV transmission.

Antiretroviral Therapy in Serodifferent Couples

Convincing data from several studies have shown that antiretroviral treatment taken by individuals with HIV dramatically reduces HIV transmission to their sexual partners.[5,6,10,11]

- **HPTN-052**: The concept of treating persons with HIV infection to prevent transmission to others, often referred to as “treatment as prevention” garnered major support following release of data from the landmark HPTN-052 trial.[5,6] The HPTN-052 trial was a randomized, controlled study that enrolled 1,763 HIV serodifferent, predominantly heterosexual couples from 9 countries. All persons with HIV infection had a CD4 count of 350 to 550 cells/mm$^3$ at enrollment and no HIV-related symptoms. The trial demonstrated that early initiation of antiretroviral therapy (started at the time of enrollment) reduced rates of sexual transmission of HIV to the uninfected partner by 96%, when compared with deferral of antiretroviral therapy (started when the CD4 count decreased to less than 250 cells/mm$^3$ or onset of an AIDS-related event). (Figure 2).[5,6]

- **Observational Trials**: Several observational studies with serodifferent heterosexual couples have similarly demonstrated that treating the partner with HIV with antiretroviral therapy is a potent intervention for preventing sexual transmission of HIV to the uninfected partner.[12] Further, data from a meta-analysis of 5,021 heterosexual serodifferent couples reinforces this finding; no HIV transmissions were reported in patients treated with antiretroviral therapy if the person with HIV infection had an HIV RNA level below 400 copies/mL.[11]

- **PARTNER-1 Study**: In the first phase of the European PARTNER (Partners of People on ART—A New Evaluation of the Risks) study, investigators at 75 sites in 14 European countries evaluated the impact of antiretroviral therapy on HIV transmission risk in 888 HIV-serodifferent couples engaging in condomless sex, including 548 heterosexual couples and 340 gay male couples.[4] The eligibility for enrollment required the partner with HIV infection to be taking antiretroviral therapy and have an HIV RNA level less than 200 copies/mL.[4] Enrollment took place during September 2010 to May 2014 and during this time there were zero phylogenetically linked HIV transmissions that occurred in these couples, with an estimated 58,000 condomless sex acts (22,000 in gay male couples and 36,000 in heterosexual couples).[4] There were 11 new HIV infections during the study period, but none of these were phylogenetically linked.

- **PARTNER-2 Study**: In the second phase of the European PARTNER (Partners of People on ART—A New Evaluation of the Risks) study, investigators at the same 75 sites in 14 European countries continued the PARTNER study, but additional enrollment was only for serodifferent gay men.[13] The enrollment period analyzed for PARTNER-2 was September 2010 to July 31, 2017 and included a total of 972 serodifferent gay male couples.[13] The design to include only serodifferent gay male couples was to make up for some of the imbalance of the predominantly heterosexual serodifferent couples enrolled in the PARTNER-1 trial. As with PARTNER-1, the eligibility for enrollment required the partner with HIV infection to be taking antiretroviral therapy and have an HIV RNA level less than 200 copies/mL. During the study, the serodifferent gay male couples reported condomless anal sex a total of 76,088 times and there were zero phylogenetically-linked transmissions.[13] There were, however, 15 new HIV...
Undetectable Equals Untransmittable

Extensive data from multiple studies strongly support the concept that persons with HIV who consistently take antiretroviral therapy and maintain undetectable HIV RNA levels do not transmit HIV sexually to others, even with condomless sex.[4,13,14] This concept is now commonly referred to as “U=U” (Undetectable equals Untransmittable).[7] The U=U concept is an extremely important message that is now widely endorsed by prominent scientists, clinicians, organizations, and societies.[7] The findings from the studies that serve as the foundation for the U=U concept underscore the tremendous impact that antiretroviral treatment can have in preventing transmission of HIV from persons living with HIV. These findings also emphasize the benefit of routine HIV testing and prompt initiation of antiretroviral therapy for persons who test positive for HIV. For persons living with HIV who are having condomless sex, it is important to perform regular screening for sexually transmitted infections, since antiretroviral therapy does not provide protection against common sexually transmitted infections, such as chlamydia, gonorrhea, and syphilis.

Community Viral Load and Treatment Impact at Population Level

Several groups have also shown that a reduction in community viral load is associated with decreased numbers of new HIV infections in that community, suggesting wide-scale use of antiretroviral therapy in persons living with HIV infection could significantly reduce HIV transmission at the population level. For example, in British Columbia, scale-up of antiretroviral therapy from 1996 to 2009 led to a 52% decline in new HIV infections.[15] A separate study performed in San Francisco found that reductions in mean and total community viral load from 2004 to 2008 were associated with decreased new HIV diagnoses.[16] Furthermore, mapping of mean and total community viral load can identify disparities. For example, a community viral load study in Washington, D.C. revealed highest viral loads in low income areas with low education rates;[17] a similar study in New York City showed that low-income neighborhoods had the highest community viral loads, HIV prevalence, and HIV-related death rates.[18] Mathematical modeling also shows that expanded utilization of antiretroviral therapy is cost-effective due to the number of new infections averted.[19] Nevertheless, there are limitations to use of community viral load as a proxy for measuring ongoing HIV transmission, including selection bias in studies that measure viral load only among those individuals engaged in care, the variability of viral load measurements over time, different prevalence rates in communities that influence the per-contact probability of transmission, and other confounding factors.[20] It is important to note, too, that the benefit of using early antiretroviral therapy for HIV prevention among men who have sex with men is less clear than in heterosexuals; in the HPTN-052 trial, 97% of the couples were heterosexual, and no published randomized studies have specifically focused on treatment as prevention in men who have sex with men.

Expert Recommendations for Treatment as Prevention

Based primarily on the findings from HPTN-052, the Adult and Adolescent ARV Guidelines include prevention of transmission of HIV as one of the main reasons to recommend antiretroviral therapy for all persons living with HIV infection.[21] Among those who initiate antiretroviral therapy, the goal
is to achieve and maintain undetectable HIV RNA levels. Although available data suggest a very low risk of sexual HIV transmission from persons on antiretroviral therapy who achieve and consistently maintain undetectable HIV RNA levels, most experts caution against asserting no risk of HIV transmission exists from persons who maintain an undetectable HIV RNA level. In addition, the type of sexual contact and the presence of concomitant sexually transmitted infections in either partner can potentially impact the risk of sexual HIV transmission. A cohort study of men who have sex with men in Australia showed 53 HIV seroconversions occurred among 1,427 participants in an era (2001 to 2004) when most patients were receiving antiretroviral therapy. Furthermore, discordance can exist between blood and semen HIV RNA levels; one prospective cohort study of 25 men showed that despite effective antiretroviral therapy and undetectable plasma HIV RNA levels, 48% (12 of 25) men had detectable HIV RNA levels in the semen. Accordingly, most experts continue to recommend consistent use of condoms for persons living with HIV, even for those with an undetectable HIV RNA level. The Adult and Adolescent ARV Guidelines do not address antiretroviral treatment as prevention among persons who inject drugs, but theoretically, antiretroviral therapy should decrease blood-borne transmission of HIV; several studies have demonstrated that HIV incidence among persons who inject drugs decreases in parallel with decreasing community viral load.
Knowledge of HIV Status

In 2006, the Centers for Disease Control and Prevention (CDC) led a major initiative for increased HIV screening and diagnosis in the United States.[26,27] The proportion of persons with undiagnosed HIV infection has steadily decreased from an estimated 25% in 2003 to 14.2% in 2016.[28,29,30] Several HIV transmission modeling studies for the United States have concluded that persons who are unaware of their HIV status account for a disproportionately higher number of transmitted HIV infections than persons aware of their HIV diagnosis.[31,32,33] In the 2016 Center for Disease Control and Prevention (CDC) Progression and Transmission of HIV (PATH 2.0) model, investigators estimated that among all persons living with HIV in the United States in 2016, the 14.5% of persons with undiagnosed HIV accounted for 37.5% of new HIV transmissions that year (Figure 3).[33] In addition, studies have shown a relatively high prevalence of sexually transmitted infections among individuals unaware versus aware of their HIV diagnosis—an important finding since STIs increase the likelihood of transmitting HIV to others.[22,34,35] Knowledge of HIV serostatus is the first step toward linking persons to HIV in care whereby they can receive antiretroviral therapy. In a meta-analysis of high-risk sexual behavior of persons in the United States aware and unaware of their HIV infection status, investigators concluded that persons who become aware they are infected with HIV substantially reduce high-risk sexual activity.[36] The National HIV Behavioral Surveillance Project examined the impact of knowledge of HIV status among persons who inject drugs and found that individuals aware of their HIV infection had fewer sexual partners and less frequent unprotected sex when compared with individuals not aware of their HIV status; the study did not find significant differences in drug use behaviors based on knowledge of HIV status.[37]
Behavioral Prevention Interventions for Persons with HIV

Risk Reduction Counseling

Counseling to reduce activities that can increase the risk of HIV transmission to others is an insufficient method for reducing HIV transmission. For persons living with HIV, the impact of consistently taking antiretroviral therapy and maintaining undetectable HIV RNA levels far exceeds the impact of prevention strategies that rely on behavioral interventions. Nevertheless, risk reduction counseling for persons with known HIV infection remains a complementary piece of a comprehensive prevention strategy. The CDC has identified evidence-based risk reduction counseling strategies for people living with HIV. Moreover, older studies have examined the impact of behavioral interventions for people living with HIV and showed a reduction in self-reported condomless sex as well as a decline in the incidence of sexually transmitted infections in persons who received behavioral interventions. Subsequently, a national demonstration project evaluated the effectiveness of prevention programs in HIV clinics and found prevention messages from a primary care provider had a higher impact on patient risk behavior when compared with messages given by health educators or peer educators living with HIV infection. In the current era, however, medical providers often do not see risk reduction counseling as a high priority as they prioritize comprehensive HIV care. Overall, the impact of risk reduction counseling in preventing HIV transmission from persons living with HIV is minor compared with the impact of taking antiretroviral therapy and maintaining undetectable HIV RNA levels.

HIV Status Disclosure and Partner Testing

Partner counseling and referral services is a public health service that helps people living with HIV disclose their HIV status to current or former sexual or injection drug partners. The public health system provides a trained counselor who can work with the person newly diagnosed with HIV to support disclosure to partners, as well as to directly provide partner notification in cases where the person with newly diagnosed HIV infection is not able to disclose their HIV status. Partner notification and testing is a very important because of the high yield in HIV case finding. In two national studies, partner counseling and referral services, including partner notification and HIV testing, effectively identified a substantial number of partners with a new HIV diagnosis; in these studies, 8% of the partners of persons newly diagnosed with HIV tested positive for HIV and these results were consistent across a 10-year period.

Condom Use

Extensive data has shown that persons with HIV who are taking antiretroviral therapy do not transmit HIV sexually to others, even with condomless sex. Accordingly, efforts emphasizing condom use as the primary method for HIV prevention have markedly diminished in recent years. Nevertheless, condoms still have a role for persons living with HIV, especially in persons newly starting on antiretroviral therapy and for persons who do not have consistently suppressed HIV RNA levels. In addition, condoms prevent of acquisition of other sexually transmitted diseases. Consistent, correct condom use markedly reduces the risk of sexual transmission of HIV but it does not completely eliminate the risk. Existing data have estimated that consistent condom use decreases HIV transmission by 70 to 80% among HIV serodifferent heterosexual couples when compared with noncondom users. In a separate analysis of the protective effect of condom use among HIV serodifferent gay male couples who have anal sex, investigators from the CDC estimated consistent condom use reduced the risk of HIV transmission by 70%. One estimate of condom effectiveness was even higher (in the range of 90 to 95%) based on correct and consistent condom use. Correlates of condom failure include improper or inconsistent use of appropriate lubricants, amphetamine use, heavy alcohol use, and lower socioeconomic status; proper use of condom-compatible lubricants improves condom effectiveness by lessening the risk of condom breakage and by reducing rectal or vaginal trauma. Unfortunately, negotiating condom
Serosorting and Seropositioning

The practice of serosorting and seropositioning (strategic positioning), and condom serosorting are self-selected behaviors intended to reduce HIV transmission risk and are referred to as seroadaptive strategies.[56,57] Serosorting describes the practice of choosing sex partners based on concordant HIV status, typically with the practice of selectively using condoms only when sex occurs with persons of serodifferent HIV status. Strict serosorting for gay men usually is in reference to men having sex only with other men who have the same HIV status as themselves. Position serosorting (also called strategic positioning or seropositioning) refers to choosing a different sexual position or practice based on the HIV serostatus of one’s partner; typically, a person with HIV infection will take the receptive role during unprotected anal sex when their partner does not have HIV. Data on the impact of serosorting have been mixed.[57,58,59,60] There are no guidelines in the United States that recommend serosorting as an impactful prevention measure.
Importance of Diagnosing and Treating Acute HIV Infection

At the time of early HIV infection (less than 6 months after HIV acquisition), patients usually have high HIV RNA levels and lack of significant neutralizing antibodies and thus are considered highly infectious. [61, 62, 63] Studies have evaluated the relative likelihood of transmitting HIV during acute or early HIV infection, and estimate a significantly higher risk in acute or early HIV infection than with chronic HIV infection. [64, 65, 66, 67] Using the 2016 Prevention (CDC) Progression and Transmission of HIV (PATH 2.0) model, the Centers for Disease Control and Prevention estimated the highest risk of HIV transmission along the HIV continuum of care occurred in persons with acute HIV who were unaware of their HIV diagnosis (Figure 4). [33] Accordingly, it is important to diagnose individuals with acute and recent (early) HIV infection whenever possible. To this end, the 2014 CDC HIV testing guidelines recommend the use of a fourth-generation antigen-antibody test as an initial screening tool in an effort to improve the diagnosis of persons with acute HIV. [68, 69] In addition, persons diagnosed with acute HIV infection should receive counseling regarding reduction in risk behaviors and ideally start immediate treatment with antiretroviral therapy to prevent forward transmission of HIV infection, as well as to garner potential long-term immunologic benefit from early therapy. [5, 70, 71] The Adult and Adolescent ARV Guidelines recommend initiating antiretroviral therapy in all persons with acute or recent HIV infection. [72]
Treatment of Sexually Transmitted Infections

Sexually transmitted infections (STIs) can facilitate transmission and acquisition of new HIV infection. The 2015 STD Treatment Guidelines and the Adult and Adolescent Opportunistic Infection Guidelines recommend all sexually active persons living with HIV undergo routine screening for sexually transmitted infections at all exposed anatomic sites (e.g. pharynx, rectum, urethra) and that testing include serologic screening for syphilis. Despite these recommendations, several studies suggest there have been low rates of screening at rectal and pharyngeal sites in persons living with HIV. Any identified sexually transmitted infection should be promptly treated along with treatment of the partner. Trends of increasing sexually transmitted infections, particularly syphilis, gonorrhea, and chlamydia, have been reported among men with HIV infection who have sex with men. Noninjection drug use, particularly with methamphetamines, as well as recreational use of erectile-enhancing medications, among men with HIV infection who have sex with men has been implicated in transmission of sexually transmitted infections, including HIV. Available data on herpes simplex virus (HSV) has not shown a convincing reduction in HIV transmission risk with acyclovir suppressive therapy taken by persons with HIV infection, despite clear evidence that acyclovir (and valacyclovir) suppressive therapy taken by persons dually infected with HIV and HSV decreases HIV RNA levels and slows HIV disease progression. Screening, diagnosis, and treatment of sexually transmitted infections in persons living with HIV remains a priority, but, in the current era, the impact on preventing transmission of HIV remains unclear, especially for persons taking suppressive antiretroviral therapy.
Circumcision

Male circumcision studies related to HIV prevention have involved men without HIV infection (as a means to prevent HIV acquisition) and men with HIV (as a means to prevent HIV transmission to others). Three studies conducted in Africa during 2002 to 2006 evaluated more than 10,000 African heterosexual couples and addressed the impact of male circumcision on HIV acquisition among men from their female sex partners; overall, there was a 51 to 60% reduction in HIV incidence among men who were circumcised compared to men who were uncircumcised (Figure 5).[83,84,85,86] Studies have also shown that lack of circumcision increases the risk of genital ulcer diseases, which in turn can increase the risk of HIV transmission and acquisition.[87,88,89] Based on available data, many countries in resource-limited settings have formal circumcision programs in place for males not infected with HIV. A meta-analysis that examined the impact of circumcision on HIV acquisition among men who have sex with men concluded insufficient evidence exists that male circumcision protects against HIV acquisition in this group.[87] In contrast to the benefit of circumcision in heterosexual men without HIV infection, there is no evidence that performing circumcision on males with HIV infection will reduce HIV transmission to their heterosexual or same sex partners. In a large study in Rakai District, Uganda that enrolled 922 uncircumcised heterosexual men with HIV infection who had a CD4 count of at least 350 cells/mm³, investigators randomized the men to receive immediate circumcision or delayed circumcision (24 months later) and circumcision did not reduce HIV transmission to female partners; the investigators stopped the trial early due to futility (Figure 6).[90] In the United States, there are no recommendations to use circumcision as an HIV prevention measure.
Prevention Strategies in Persons with Substance Use

Alcohol and illicit drug use are common among persons living with HIV and are recognized cofactors for HIV transmission.\[91, 92, 93\] In addition, more serious substance use disorders among persons living with HIV are associated with high rates of HIV transmission risk behaviors and low antiretroviral therapy adherence.\[94\] Alcohol use is the most prevalent risk factor for poor HIV medication adherence and low rates of viral suppression.\[95, 96\] Methamphetamine and other amphetamine type stimulant use can be an important factor in HIV transmission.\[97, 98\] Injection of methamphetamines plays a dual role in HIV transmission—through sharing injection equipment and by altering antiretroviral medication adherence and sexual behavior while high on methamphetamine. Prevention efforts utilizing syringe exchange programs can play a key role in preventing HIV transmission from persons with HIV who inject drugs. These prevention efforts led to a major decline in HIV incidence among persons who inject drugs, with an estimated 80% decline from the 1988 to 1990 time period to the 2003 to 2006 period.\[99\] In the United States in 2016, injection drug use was responsible for approximately 5 to 8% of new HIV infections.\[30\]

Harm Reduction Approach

Programs that provide safe injection equipment, HIV prevention education, and opiate substitution therapy are often referred to as following a harm reduction philosophy. In harm reduction programs, syringe services often provide a comprehensive set of services beyond basic needle exchange, including HIV counseling and testing, screening for sexually transmitted infections, screening for tuberculosis, vaccination services, and referral to substance use treatment programs. It is extremely important to remember that persons who inject drugs can also acquire and transmit HIV via sexual contact and should be counseled about sexual risk reduction strategies.\[100\] Many syringe services exchange sites can link interested persons who use drugs to formal education programs; a Cochrane review found that standard educational interventions, rather than multi-session psychosocial interventions, are a cost-effective way to reduce injection and sexual risk behavior.\[101\]

Syringe Services

In the United States, approximately 12% of persons living with HIV infection acquired HIV through injection drug use and another 5% had male-male sexual contact and injection drug use as their risk factor for acquiring HIV infection.\[30\] Thus, persons who inject drugs represent a significant source for potential HIV transmission in the United States. The use of sterile needles and injection equipment with each fix is an effective way for persons who inject drugs to limit their risk of acquiring and transmitting HIV and hepatitis C virus.\[102\] Opponents of syringe services argue that these programs condone and even encourage drug use, especially among youth; an early cohort study showed that a needle exchange program in Montreal was associated with a higher rate of HIV seroconversion, likely due to new social networks formed through the exchange, and this stigma has persisted.\[103\] In contrast, multiple studies and reviews have concluded that providing sterile equipment to persons who inject drugs actually reduces injecting risk behaviors, lowers the risk of HIV and hepatitis C virus infection, and facilitates entry into drug treatment.\[3, 104, 105, 106\]

Use of Federal Funds for Syringe Services Programs

The use of federal funds for needle exchange programs in the United States has been a highly controversial issue.\[107\] Needle exchange programs were initial introduced with great enthusiasm in Amsterdam in 1983 as a public health strategy to limit the spread HIV through injection drug use. The models used in Amsterdam sparked interest in the United States during the mid-1980's, but, in 1988, opponents of this public health strategy passed a law that explicitly banned federal funding for any needle exchange programs.\[107\] The funding ban was in existence until late 2015, except for a brief lift in the ban during during 2010 and 2011. In December 2015, the Consolidation Appropriations Act was signed into law and it modified the existing restrictions on the use of federal
funds for programs that distribute sterile needles or syringes. Although the new law continues to prohibit federal funding to purchase sterile needles or syringes, it does allow use of federal funds for other elements of a syringe service program if it is deemed appropriate by a relevant State or local health department (in consultation with the Centers for Disease Control and Prevention). In 2016 the Department of Health and Human Services issued Guidance to assist state, local, tribal, and territorial health departments for permission requests to use federal funds to support syringe service programs.[108]
Summary Points

- Integrated, evidence-based biomedical, behavioral, and structural interventions can substantially reduce transmission of HIV infection from persons living with HIV in the United States.
- Antiretroviral therapy is recommended for all persons living with HIV to prevent HIV transmission to others.
- Extensive data from multiple studies strongly support the concept that persons with HIV who consistently take antiretroviral therapy and maintain undetectable HIV RNA levels do not transmit HIV sexually to others, even with condomless sex.
- Persons unaware of their HIV status account for a disproportionate number of new HIV infections in the United States. The percentage of persons unaware of their HIV status has declined from 20% in 2008, to 14.2% in 2016.
- Most persons aware of their HIV status have a substantial reduction in activities associated with increased risk of HIV transmission to others.
- For persons newly diagnosed with HIV infection, partner notification and contact HIV testing provides effective HIV case finding and the opportunity to decrease exposure to others.
- Consistent and correct condom use decreases HIV transmission by approximately 80% among serodiscordant heterosexual couples and reduces the per-contact risk of HIV infection by 78% among men who have sex with men who practice receptive anal intercourse.
- Serosorting is commonly referred to as the practice of choosing sex partners based on concordant HIV status or the practice of selectively using condoms when sex occurs with persons of discordant HIV status. The evidence for serosorting as a harm reduction strategy is conflicting.
- Persons with undiagnosed acute (early) HIV infection have the highest relative risk of HIV transmission to others. Diagnosis, counseling, and treatment of persons with acute HIV can substantially reduce new HIV infections.
- Trends of increasing sexually transmitted infections, particularly syphilis, gonorrhea, chlamydia, and hepatitis C, are noted among men with HIV infection who have sex with men, and represent opportunities for treatment and risk reduction counseling.
- Circumcision reduces the risk of acquiring HIV in heterosexual men, but there is no evidence that performing circumcision on males with HIV infection will reduce HIV transmission to their uninfected heterosexual partners. The benefit of circumcision in preventing HIV acquisition or transmission in men who have sex with men is unclear.
- Screening for substance use can help providers identify individuals infected with HIV who could benefit from support to decrease or stop alcohol and illicit drug use. Providing counseling and treatment of substance use, including syringe services programs and opiate substitution therapy when indicated, can reduce injecting and sexual risk behaviors, and promote adherence to antiretroviral therapy.
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**Figures**

**Figure 1 Adjusted Rate Ratio of Heterosexual Transmission of HIV-1 According to Serum HIV-1 RNA Level of the HIV-1 Positive Partner**

In this study, 415 HIV-1 serodifferent couples (one partner HIV-positive and the other HIV-negative) in Rakai Uganda were enrolled and followed prospectively for up to 30 months to evaluate HIV transmission. None of the individuals enrolled in the study were receiving antiretroviral therapy. This graphic illustrates the correlation of risk of HIV transmission and serum HIV-1 levels in the person infected with HIV. No HIV transmissions occurred from persons with HIV who had serum HIV RNA-1 levels less than 1,500 copies/mL.

The HPTN 052 trial enrolled 1,763 HIV serodifferent couples and 97% of the couples were heterosexual.

The HIV-positive participants in the early therapy arm received combination antiretroviral therapy and those in the deferred therapy arm started when their CD4 decreased to less than 250 cells/mm$^3$ or they had an AIDS-related event.

Figure 2 (Image Series) - HPTN 052 and Antiretroviral Therapy for the Prevention of HIV-1 Infection

Image 2C: HPTN 052 Results

This graphic shows linked transmissions in the two study groups. Couples in the early therapy arm had a 96% reduction in new HIV transmission events.

Figure 3 Transmission of HIV and Awareness of HIV Status

This graph shows the estimated percentage of HIV transmissions based on awareness of HIV diagnosis. Persons with undiagnosed have a disproportionately increased number of transmissions. These estimates were based on the 2016 Center for Disease Control and Prevention (CDC) Progression and Transmission of HIV (PATH 2.0) model.

Figure 4 Relative Risk of HIV Transmission Along the HIV Care Continuum

This graph shows the estimated transmission rate based on transmissions per 100,000 person-years. Persons with acute HIV infection who were unaware of their diagnosis had the highest rate of transmission. These estimates were based on the 2016 Center for Disease Control and Prevention (CDC) Progression and Transmission of HIV (PATH 2.0) model.

Figure 5 Risk of Heterosexual Male HIV Acquisition Based on Circumcision Status of Male

These three studies conducted in Africa addressed the risk of heterosexual HIV acquisition in men based on their circumcision status. As shown, the risk of HIV acquisition was significantly lower in men who were circumcised when compared with those who were uncircumcised.

**Figure 6 Risk of Heterosexual Female HIV Acquisition Based on Circumcision Status of Male**

In this study, investigators in Rakai, Uganda enrolled 922 uncircumcised males with HIV infection who were randomized to undergo immediate circumcision or have circumcision delayed for 24 months. The trial was stopped early because of futility and there was no reduction in risk of female HIV acquisition from their male partners who had been circumcised.