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Negligible Risk: Updated results from two studies continue to show that antiretroviral treatment and an undetectable viral load is a highly effective HIV prevention strategy

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Successful antiretroviral treatment (ART) can reduce the amount of HIV in the bodily fluids (the viral load) to below the levels that tests can detect (undetectable). Interim analyses from two important studies—HPTN 052 in 2011 and PARTNER in 2014—clearly demonstrated that ART and an undetectable viral load is a highly effective HIV prevention strategy for heterosexual and gay male serodiscordant couples.

Recently, these two studies released updated findings reaffirming that successful ART can dramatically reduce the risk of HIV transmission through both anal and vaginal sex.

HPTN 052 and PARTNER - basics and summary of their preliminary findings

The HPTN 052 and PARTNER studies were similar, but also different in important ways. The basics of both studies—and their preliminary results—are described below.

HPTN 052 study

Purpose: To determine how much the use of ART can reduce the risk of HIV transmission in serodiscordant couples.

Study population: 1,763 heterosexual serodiscordant couples in which the HIV-positive partner had not yet started ART. Enrollment started in June 2007.

Study type: Randomized controlled trial. Half of the participants were randomized to start ART immediately, while the other half delayed starting ART. All participants received a comprehensive package of healthcare services at study visits (every three months).

Preliminary analysis: The randomized phase of the study was stopped in May 2011, once it became clear that the risk of HIV transmission was 96% lower among couples who were randomized to start ART immediately compared to the couples who were randomized to start ART later. When the study was stopped, all couples were offered ART and the study investigators continued to follow the couples until May 2015.

PARTNER study

Purpose: To determine the risk of HIV transmission when the HIV-positive partner has an undetectable viral load and no condoms are used.

Study population: 485 heterosexual and 282 same-sex male serodiscordant couples in which condoms were not being used and the HIV-positive partner was already on treatment and receiving routine care. Enrollment started in September 2010.

Study type: An observational study in which there was no randomization or a control group of couples that did not have an HIV-positive partner on treatment. The HIV-positive partner was engaged in routine care, and the HIV-negative partner was tested for HIV every six to 12 months.

Preliminary analysis: Initial results presented in 2014 included information on participants followed between September 2010 and November 2013. There were no HIV infections despite over 44,000 condomless sex acts when the viral load was undetectable. The study investigators continued to follow participants after the release of these preliminary results to improve confidence in their findings.

For more information on these studies see [HPTN 052](#) and [PARTNER](#).

If an HIV-negative partner became infected with HIV in these studies, a genetic analysis of their virus was performed. This was done to confirm that their virus was linked to the virus of the HIV-positive partner with whom they enrolled in the study, and was not transmitted by someone outside of the relationship.

Summary of updated findings

HPTN 052

The final updated HPTN 052 analysis presented information on all 1,763 couples, including those who remained in the study after ART was offered to everyone in May 2011. By the end of the study (May 2015), half of the couples had been followed for more than five and a half years. Partners of the HIV-positive participants were followed for 8,509 person-years (equivalent to following 8,509 people for one year).

The interim HPTN 052 analysis found that the risk of HIV transmission was 96% lower in the immediate ART group compared to the delayed ART group. At the time this analysis was conducted, very few of the delayed group participants (21%) had started ART, so this could be interpreted as ART reducing the risk of HIV transmission by 96%. In the final analysis, the risk of HIV transmission was 93% lower in the immediate group compared to the delayed group; a smaller risk reduction. This was expected, as by the end of the study almost all of the participants (96%) in the delayed ART group had started ART. Therefore, this analysis was no longer comparing ART to no ART, and the increased ART use in the delayed group led to the smaller difference in HIV risk between the two groups. Instead of focusing on the difference in risk between the two groups, looking at the total number of HIV transmissions that occurred while the HIV-positive partner was on ART is more useful.

Overall, 78 HIV-negative partners became infected with HIV during the entire study. Genetic analysis of the virus of the previously HIV-negative partners showed that 26 of the 78 (33%) were infected by a sexual partner outside of this relationship, and 46 (59%) came from the HIV-positive partner with whom they enrolled in the study. Genetic analysis could not determine whether or not the viruses were linked for six of the 78 new infections.

Of the 46 HIV infections that originated from the HIV-positive partners that were enrolled in the study, only eight occurred when a partner was on ART. However, it is unlikely that any of these transmissions occurred when the viral load was undetectable (defined in this study as less than 400 copies/ml). Four of the HIV infections occurred within three months of the HIV-positive partner starting ART, likely before the viral load had reached undetectable levels.

The other four infections occurred in couples where ART was not working, also known as virological failure. In this study, virological failure was defined as having a viral load of more than 1,000 copies/ml (as determined by two consecutive viral load tests that were three months apart) any time after taking ART for more than six months. None of these transmissions were due to HIV drug resistance and they may have been due to poor adherence.

HPTN 052 clearly demonstrated that ART can dramatically reduce the risk of HIV transmission through vaginal sex. It is compelling that so few HIV infections occurred while the HIV-positive partner was on ART, and no infections occurred when the partner on ART had an undetectable viral load, despite the long duration of time that couples were followed. However, it is important to note that couples also reported using condoms most of the time (93% of the time in the interim analysis). Theoretically, the high rate of condom use may have partially contributed to the low number of HIV infections during the study, although study participants may have over-reported how often they used condoms. The PARTNER study (described below) specifically explored the risk of HIV transmission when the viral load is undetectable and condoms are not used.

PARTNER

The final PARTNER findings included information from couples followed between September 2010 and May 2014. The final analysis was restricted to periods of time between the HIV-negative partners' HIV tests where the viral load of

the HIV-positive partner was undetectable and no other forms of protection were used. To accomplish this, the analysis excluded time periods where couples used condoms, the HIV-negative partner used post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP), the HIV-positive partner had no viral load test or when the HIV-positive partner had a viral load that was detectable (defined in this study as more than 200 copies/ml).

Information on 888 couples (548 heterosexual men and women and 340 gay men), of whom half had been followed for more than 1.3 years, was analyzed. These couples contributed 1,238 eligible couple-years of follow up (equivalent to following 1,238 couples for one year). During this time, half of heterosexual couples reported having more than 35 condomless sex acts a year and half of gay couples reported having more than 42. Overall, there were a large number of condomless sex acts when the viral load was undetectable—approximately 22,000 among gay couples and 36,000 among heterosexual couples enrolled in the study.

By the end of the study, 11 of the partners had become infected with HIV (10 gay men and one heterosexual person). Genetic analysis of the virus in the previously HIV-negative partners showed that all 11 were infected by a sex partner outside of the relationship, and not the HIV-positive partner with whom they enrolled in the study. This meant that there were no HIV transmissions between the couples enrolled in the study, despite the large number of condomless sex acts between them.

The PARTNER results were particularly compelling with respect to the impact of having an undetectable viral load, since couples were not using condoms (compared to HPTN 052 where 93% reported using condoms in the interim analysis).

While there were no HIV infections when the viral load was undetectable, it was not possible for the study authors to conclude that the risk is zero. Indeed, it is impossible for any research study to ever conclude zero risk, but study investigators can measure the degree of certainty that the risk is zero. In the PARTNER study, there was more uncertainty for receptive anal sex (where the HIV-negative person is the receptive partner during anal sex), as there were fewer of these types of sex acts compared to others. Based on this single study, the authors concluded that when the viral load is undetectable and no condoms are used, “appreciable levels of risk cannot be excluded, particularly for anal sex and when considered from the perspective of a cumulative risk over several years.”

What this means

The results of both HPTN 052 and PARTNER reaffirmed that ART is a highly effective strategy to prevent the sexual transmission of HIV. Both studies found that no HIV transmissions occurred when the partner on ART was undetectable. In HPTN 052, only eight transmissions occurred when the HIV-positive partner was on treatment, and the viral load was likely not undetectable. Importantly, all couples in both studies were engaged in regular care, such as ongoing viral load monitoring, testing for sexually transmitted infections (STIs), and adherence and risk-reduction counselling. These supports likely helped improve the HIV prevention benefit of ART.

The findings from these studies provide insight into the rare circumstances where HIV transmission can occur within the context of a serodiscordant relationship in which the positive partner is on ART. These include the period between starting ART and achieving an undetectable viral load and virological failure.

From these two studies we know that sex with partners outside of the main relationship accounted for a substantial number of HIV transmissions to the HIV-negative partner. In HPTN 052, 33% of all HIV transmissions occurred from outside the main relationship. In PARTNER, 100% of all HIV transmissions occurred from outside the main relationship.

Consensus on the risk of sexual transmission of HIV when the viral load is undetectable

Based on the cumulative evidence to date, community members and leading researchers have endorsed the following [Prevention Access Campaign](#) statement:

“People living with HIV on ART with an undetectable viral load in their blood have a negligible risk of sexual transmission of HIV. Depending on the drugs employed it may take as long as six months for the viral load to become undetectable. Continued and reliable HIV suppression requires selection of appropriate agents and excellent adherence to treatment. HIV viral suppression should be monitored

to assure both personal health and public health benefits.”

Spread the word

It is important that community members—both people living with HIV and those at risk for HIV—be given information and offered counselling about ART and undetectable viral load as a highly effective strategy to prevent the sexual transmission of HIV. The following key messages are important:

- ART is a highly effective HIV prevention strategy (when the viral load is undetectable) regardless of whether condoms are used. However, using condoms as part of a combination HIV prevention strategy can reduce the risk for other STIs, particularly if couples are having sex outside the relationship.
- It is possible for viral load to increase if ART stops working due to poor adherence to medications or drug resistance. Regular adherence to medications and viral load testing is important to ensure that ART is working and an undetectable viral load is maintained.
- It can take up to six months for the viral load to reach undetectable levels once treatment has started and some people may find it more difficult to reach undetectable levels. Guidelines generally recommend that the viral load be undetectable for at least six months (as determined by two consecutive viral load tests) prior to using ART as a prevention strategy.
- In a non-monogamous relationship in which the HIV-positive partner is on successful ART, the main risk of HIV transmission comes from outside the relationship. Couples should be encouraged and supported to discuss their relationship status with each other (for example, monogamous or non-monogamous) and consider using HIV prevention strategies, such as pre-exposure prophylaxis or condoms, with outside sex partners if the relationship is non-monogamous.

References

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2. Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *Journal of the American Medical Association*. 2016;316(2):171–81. Available from: <http://jama.jamanetwork.com/article.aspx?articleid=2533066>

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