

CATIE-News

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Insight into HIV transmission risk when the viral load is undetectable and no condom is used

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The sexual transmission of HIV occurs after an exposure to fluids that contain HIV, such as semen and fluids from the vagina and rectum. The amount of virus in these fluids (also known as viral load) is the most important factor that determines whether an exposure to HIV will lead to infection. Research shows that a higher viral load increases the risk of HIV transmission and that a lower viral load decreases the risk.

The viral load in the *blood* of a person living with HIV is measured regularly to monitor the success of antiretroviral therapy (also called ART). Successful ART can reduce the viral load in the blood and other bodily fluids to undetectable levels, which can reduce the risk of sexual transmission. ART therefore represents an important new HIV prevention tool, which also has the potential to reduce the guilt, blame and anxiety associated with the possibility of transmitting HIV to a partner.

Gaps in the evidence

Several studies released over the past few years have confirmed that ART has HIV prevention benefits. The most well-known study is the randomized-controlled clinical trial known as HPTN 052. In this study, early initiation of ART reduced the risk of HIV transmission by 96% among heterosexual serodiscordant couples. However, the couples who participated in this study reported having mostly vaginal sex, so the reduction in HIV risk for anal sex remained unclear.

While HPTN 052 showed that ART can dramatically *reduce* the risk of HIV transmission through vaginal sex, the *actual* risk of HIV transmission (i.e., what the risk is lowered *to*) when the blood viral load is undetectable remained unknown, particularly for condomless sex.

Fortunately, two ongoing studies are investigating these unanswered questions. The studies are aiming to determine the *actual* risk of HIV transmission (for condomless vaginal and anal sex) when the HIV-positive partner's blood viral load is undetectable. Preliminary results from one of these studies—the PARTNER Study—were released at the recent Conference on Retroviruses and Opportunistic Infections (CROI) held in Boston in March 2014. These results are the first to provide direct evidence that ART can reduce the risk of HIV transmission during anal sex.

The PARTNER study

The PARTNER study is a large observational study that is following serodiscordant couples at over 70 HIV clinics in 14 European countries. All of the couples enrolled:

- are either heterosexual or gay men
- consist of one HIV-negative partner and one HIV-positive partner who is on ART
- do not use condoms regularly

The study began in September 2010 and is ongoing.

Once enrolled, the HIV-positive partner must commit to receiving their HIV care from the study clinic and both partners are required to attend the clinic every six months. At each visit, the HIV-positive partner's viral load is measured, the HIV-negative partner's HIV status is checked, and both partners are asked to complete a

questionnaire about their sexual behaviour in the past six months. The HIV-positive partner also receives additional care, such as STI testing and information on the importance of adherence to ART, and both partners are told about the importance of using condoms to reduce the risk of HIV transmission.

If an HIV-negative partner becomes infected with HIV, a genetic analysis of the virus is performed. This is done to confirm that the virus was transmitted by the HIV-positive partner enrolled in the study and not by someone else outside of the relationship.

Results

The preliminary results presented at CROI are part of a planned interim analysis. They are based on information from couples, followed up until November 2013, that met the following criteria:

- report of condomless sex
- an undetectable viral load in the HIV-positive partner (defined as less than 200 copies per ml of blood)
- no use of PEP or PrEP by the HIV-negative partner

Of the 1,110 couples recruited by November 2013, 767 met the above criteria. This included 282 same-sex male couples, 245 heterosexual couples where the HIV-positive partner was female, and 240 heterosexual couples where the HIV-positive partner was male. Overall, couples contributed a total of 894 couple-years of follow-up (equivalent to following 894 couples for a year).

At the start of the study, the HIV-positive partners had been on ART for an average of 5 years and couples had been having condomless sex for an average of 2 years.

During the preliminary study period, eligible couples reported condomless sex an average of 45 times a year (approximately once a week). This ranged from 16 times a year to 90 times a year. Same-sex male couples had sex more often than heterosexual couples. Same-sex male couples were also more likely to have a partner outside of the relationship (34% vs. 3% for heterosexual couples) and have a sexually transmitted infection (16% vs. 5%).

Between September 2010 and November 2013, the couples reported more than 44,000 condomless sex acts. These included:

- 13,728 receptive vaginal sex acts (the HIV-negative partner receiving the HIV-positive partner's penis into their vagina) with or without ejaculation
- 14,295 insertive vaginal sex acts (the HIV-negative partner inserting their penis into the HIV-positive partner's vagina)
- 7,738 receptive anal sex acts (the HIV-negative partner receiving the HIV-positive partner's penis into their anus) with or without ejaculation
- 11,749 insertive anal sex acts (the HIV-negative partner inserting their penis into the HIV-positive partner's anus)

Despite the large number of condomless sex acts, no HIV transmissions occurred between any of the couples enrolled in the study. However, some of the HIV-negative partners did become infected with HIV by a person outside of the relationship.

Since there was no control group in the PARTNER trial, it is difficult to know how many HIV transmissions would have occurred if the HIV-positive partner was *not* on ART and did *not* have an undetectable viral load. However, using information from previous studies, researchers estimated that 15 HIV infections in heterosexual couples and 86 among same-sex male couples would have occurred if the HIV-positive partner had *not* been on ART.

The PARTNER study represents the first direct evidence that ART can reduce the risk of HIV transmission for same-sex male couples.

Understanding and measuring certainty

The fact that no transmissions occurred in this study is very encouraging. However, as with any research finding, it is important to consider the role that chance may have played. This is particularly important when investigating HIV transmission risk, because the average risk of HIV infection can be relatively low in some cases, regardless of viral

load. The lower the risk, the more difficult it is to measure accurately. In general, the larger the study, the more confident researchers can be that the results are real and did not occur due to chance.

One way of measuring certainty is to use confidence limits. Confidence limits take into account the potential effects of chance and suggest a range of values that likely encompass the “true” risk. In the PARTNER study, investigators calculated upper confidence limits for the risk of HIV transmission per sex act and over time. The “upper confidence limit” provides an estimate of the highest possible transmission risk that is consistent with the study results.

For this study, upper confidence limits can be interpreted as follows:

- It is extremely *likely* that the “true” risk is somewhere between 0% and the upper confidence limit.
- It is extremely *unlikely* that the “true” risk is *above* the upper confidence limit.

The upper confidence limit is particularly important when a study finds zero risk because it gives some indication of how close to zero the “true” risk is likely to be.

Risk per-act of sex

Upper confidence limits were calculated for the risk of HIV transmission per act of condomless sex with an HIV-positive partner:

- Receptive vaginal sex (with or without ejaculation) – 0.028%
- Insertive vaginal sex – 0.027%
- Receptive anal sex (with or without ejaculation) – 0.05%
- Insertive anal sex – 0.033%

For example, the upper confidence limit for *receptive anal sex* can be interpreted as follows:

Given the number of *receptive anal sex* acts that occurred and the fact that no HIV infections were observed, it is extremely *likely* that the “true” risk is somewhere between 0% and 0.05%, and extremely *unlikely* that it is above 0.05%. Although it is still possible that the “true” risk is zero, or only slightly higher than zero, the researchers could not rule out the possibility that the risk is as high as 0.05%.

Despite this uncertainty, this research is still meaningful. Many of the upper confidence limits are lower than the HIV transmission risks that have been estimated for when a person’s viral load is *detectable*. For example, the average per-act transmission risk for receptive anal sex has been estimated to be 1.4% when the viral load is *detectable*. However, the PARTNER study found that this risk is extremely likely to be below 0.05% when the viral load is *undetectable*.

Previous studies have estimated the average risk per condomless sex act when the viral load is *detectable* to be 0.08% for receptive vaginal sex, 0.04% for insertive vaginal sex and 0.06-0.62% for insertive anal sex. Therefore the PARTNER study strongly suggests that ART reduced the risk of HIV transmission for all types of sex.

Risk over time

Upper confidence limits were also calculated for a couple’s 10-year risk of HIV transmission when the HIV-positive partner has an undetectable viral load:

- Receptive vaginal sex (with or without ejaculation) – 11.7%
- Insertive vaginal sex – 11.4%
- Receptive anal sex (with or without ejaculation) – 17.9%
- Insertive anal sex – 12.8%

For example, the upper confidence limit for *receptive anal sex* can be interpreted as follows:

Given that couples were having condomless sex about once a week, it is extremely likely that the 10-year risk of HIV transmission is somewhere between 0 and 17.9% for *receptive anal sex*. While it is still possible that the “true” risk is zero, or only slightly higher than zero, the study could not rule out the possibility that the risk is as high as 17.9%.

It is important to note that the size of the upper confidence limit reflects the effects of chance. Receptive anal sex has the highest upper confidence limits because there were fewer receptive anal sex acts during the study compared to other types of sex. The lower number of sex acts means chance may have played a greater role.

Conclusion

The preliminary results from the PARTNER study provide important and encouraging new insight into the risk of transmitting HIV sexually when a person's viral load is undetectable and no condom is used. These results can help serodiscordant couples assess their HIV risk and make informed decisions.

The investigators of the PARTNER study concluded that the overall risk of HIV transmission through condomless sex for couples in stable serodiscordant relationships (when the HIV-positive partner is on ART, receives regular HIV care, and has an undetectable blood viral load) is "extremely low, but uncertainty over the risk remains, particularly over receptive anal sex. Additional follow-up in MSM (men who have sex with men) is essential to provide more precise estimates for transmission risk given the current assumptions of safety in some communities."

As the PARTNER study continues to follow couples who continue to have sex, the upper confidence limits will become "tighter" and move closer to zero—assuming that no HIV transmissions occur. This will allow the investigators to more confidently conclude that the risk of HIV transmission is "extremely low" for all types of vaginal and anal sex. The PARTNER study will continue to follow heterosexual couples until April 2014. Same-sex male couples will be followed until 2017 and the investigators plan to enroll 450 more gay male couples.

—James Wilton

Resources

[Official Q&A for PARTNER Studies](#)

[HPTN 052: The trial that changed everything](#) - *TreatmentUpdate*

[Undetectable viral load and HIV transmission risk: results of a systematic review](#) - *CATIE News*

[Treatment and viral load: what do we know about their effect on HIV transmission?](#) - *Prevention in Focus*

[Putting a number on it: the risk from an exposure to HIV](#) - *Prevention in Focus*

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