

PrEP for HIV Prevention: Two PrEP trials at CROI show an 86% reduced risk of HIV transmission in MSMs. One trial shows a 96% reduced rate of HIV transmission in discordant heterosexual couples.

By Lynda Dee

CROI 2015 (Conference on Retroviruses and Opportunistic Infections) was held in Seattle, WA from February 23 to 26. Arguably, the most exciting news this year involves three exciting pre-exposure prophylaxis (PrEP) studies.

First, let's discuss what PrEP is and the relevant issues. The FDA has approved Truvada for both PrEP and HIV treatment. Currently, Truvada is the only FDA approved drug for PrEP. Truvada actually contains a combination of two HIV drugs in one pill, Viread and Emtriva, and is what is known as a fixed dose combination (FDC). Truvada for PrEP is dosed at one pill once per day. Condom use is also recommended by the Centers for Disease Control (CDC) while using PrEP.

Truvada is also used for HIV treatment in combination with other HIV antiretroviral (ARV) medications. Truvada plus a number of other HIV ARVs are necessary to treat people with HIV in order for the drugs to remain effective against HIV, thereby preventing HIV drug resistance.

There are a number of PrEP related issues, some of which have already been answered, that should be noted before we begin:

Will once daily Truvada most effectively prevent HIV infection?

Will Truvada taken less than once a day prevent HIV infection?

Will real life adherence be the same as during study participation?

Will all populations take their medication as required?

Will PrEP be effective in all MSM communities?

Will PrEP be effective in the heterosexual community?

Will PrEP users who become HIV+ develop resistance to Truvada?

Will PrEP users develop serious side effects?

Will people use condoms if they are using PrEP?

Will people have more sexual partners if they are using PrEP?

Will recreational drug use affect PrEP adherence?

Will other strategies be important in preventing HIV infection?

Keeping these issues in mind, let's review the PrEP studies presented at CROI. The PROUD Study was conducted in the United Kingdom among men who have sex with men (MSMs) with a high risk of HIV infection. PROUD showed that daily oral PrEP administered at existing sexually transmitted disease clinics reduced the risk of HIV infection by 86%.

There were a total of 545 participants in the PROUD study.

Approximately half of the participants started Truvada immediately.

The other half waited 12 months before taking Truvada, and are known as the deferred arm. The researchers wanted to learn whether participants receiving Truvada in a real life situation was as effective as in a clinical trial setting, and whether people would use condoms if they knew they were receiving Truvada.

Because the effectiveness of Truvada was so high in the group receiving immediate treatment, the independent review group monitoring the study recommended that the study be stopped early and that all study participants be given Truvada immediately. Infection rates were so much higher in the deferred group that it would no longer be ethical to continue this group on no treatment. The rate of HIV infection in the Truvada treatment group was 1.3% while the incidence of HIV in the

deferred group was 8.9%. Twenty-two people became HIV infected in the deferred arm and only three people seroconverted in the Truvada treatment arm, resulting in an 86% reduction in HIV infections.

As many as 56% of participants took 100% of their medication. Only three of the six participants who ended up being HIV positive developed resistance and had resistance only to Emtriva and not Viread.

There were no surprise side effects in the PROUD study. Side effects were similar to those seen in other PrEP studies. Only 13 of the 30 people who stopped Truvada did so because of side effects. Eleven of the 13 were able to restart Truvada without issues.

Prior to enrolling in the study, participants self-reported that on average, they had 10 sexual partners within the previous 90 days, and that they had both condomless insertive and receptive sex. While there was no increase in the number of sexual partners or behavior differences between the two study arms, there was an increase in the number of participants who had high numbers of condomless sexual partners during the study. Researchers will need further data to ascertain whether this has clinical significance.

Nearly 60% of study participants were also diagnosed with a sexually transmitted infection (STI) during the study which is also evidence of condomless sex. The use of recreational drugs did not interfere with PrEP adherence.

The other important MSM PrEP study reported at CROI is known as IPERGAY. This study was conducted in six sites in France and one in Canada and looked at intermittent use of PrEP tied to sexual activity (event-driven dosing) rather than the once daily dose of Truvada. The purpose of this study was to determine if adherence which is closely

tied to the effectiveness of Truvada for HIV prevention would be better if taken during periods of sexual activity (on demand), instead of the currently FDA recommended daily dosing. The cost-effectiveness of only using Truvada for PrEP for three days per week rather than daily was also an important study concern.

Most of the 400 IPERGAY high risk MSM study participants took either two Truvada pills or a placebo which is a pill containing no medication between two and 24 hours before having sex, one pill 24 hours after having sex and one pill 48 hours after the last pre-sex dose, instead of one pill once a day. Truvada dosing continued as long as sex continued. The overall study data suggests that participants were taking Truvada an average of three to four days per week. But some study participants who were more sexually active were actually taking Truvada daily.

Once again, Truvada was much more effective than placebo, reducing the risk of HIV infection by 86%. Fourteen people in the placebo arm became HIV infected while only two people in the Truvada arm seroconverted. This equals a rate of 6.75% new infections per 100 people in the placebo arm compared to 0.94% in the Truvada arm which amounts to an 86% reduction of HIV infection.

This study was also stopped early because the rates of HIV infection were so much higher in the placebo patients, proving the superiority of PrEP over no treatment. This is also the first study that shows that an event-driven regimen is effective in high risk MSMs who have frequent sex at a potentially lower cost.

Again, side effects were again similar to those seen in other PrEP studies and those in the placebo arm of this study. Most side effects were mild and consisted of mainly nausea, diarrhea and stomach pain. Only one person taking Truvada discontinued Truvada because of side effects.

IPEGAY participants engaged in high risk sexual behavior prior to the study. The average number of acts two months prior to study enrollment was 10. This number remained the same throughout the study in both the treatment and placebo arms with no increases.

Approximately 1/3 of study participants were diagnosed with an STI during the study, including gonorrhea and syphilis. Eight people were also diagnosed with hepatitis C (HCV) infection, providing more evidence that HCV can be a sexually transmitted disease.

The results from both PROUD and IPEGAY are similar to the results of the IPREX MSM PrEP open label study (all participants receive Truvada) that included 1603 people from the United States, Brazil, Peru, Ecuador, South Africa and Thailand. IPREX results were reported in Melbourne, Australia at the International AIDS Society Conference in July of 2014. In the IPREX study which also included 70 transgender women, the efficacy of PrEP was 84% in people who took two to three doses per week and there were no HIV infections in people who took at least four does per week.

After statistical adjustments, this 100% efficacy translates into a minimum efficacy of 86%, once again confirming that when taken with even moderate consistency, PrEP is highly effective. It is also important to note that recreational drug use did not appear to affect adherence and risk behavior was no higher during the study than previous to study participation.

IPREX also highlighted adherence issues in this study where everyone knew they were receiving Truvada. Only one third of IPREX study participants actually took four doses of Truvada per week. Participants at the highest risk had the best adherence rates. But there was also a substantial drop out rate, especially among younger participants who were still at high risk of HIV infection.

It is important to note that the IPERGAY on demand dosing schedule is still being investigated, and that the CDC PrEP Guidelines still recommend daily PrEP dosing and condom use. Further, although both the PROUD and IPERGAY studies have amended their original study designs so that all participants are now receiving PrEP, both are still ongoing studies. Both studies have released only preliminary data. It will be months before we have a full data analysis of both studies.

There was also a heterosexual PrEP study presented at CROI by researchers from the University of Washington called the Partners Demonstration Project. This study was conducted in Kenya and Uganda in discordant couples (one person is HIV+ and the other person is not). The purpose of this study is to prevent the HIV- partner from becoming infected while attempting to suppress the viral load of the infected partner with ARVs. Although the data in this study is also preliminary, this two-fold HIV prevention strategy reduced the risk of HIV infection by 96%.

Clearly, the promise of PrEP is very exciting. The more data we have, the better it looks. Once again there has been confirmation that if people actually take their medication, very high rates of HIV prevention occur with people on PrEP. So, where do we go from here? At this juncture, we need to investigate what PrEP dosing strategies and interventions are the most effective. Further, we need to investigate behavioral issues in different populations. Will real PrEP adherence be as high as adherence in study participants? Will different PrEP strategies work better in different people? For example, will daily dosing versus dosing on demand be most effective? Personal choice will probably be the best prevention method. It makes perfect sense that what works best for each individual will be the best way to prevent HIV infection.

For more PrEP information, please see the following links:

<http://www.cdc.gov/hiv/prevention/research/prep/>

<http://www.cdc.gov/nchstp/newsroom/2015/IPERGAY-2015-Media-Statement.html>

<http://www.avac.org/event/croi-2015>