



FOR GENERAL DISTRIBUTION

Results of the iPrEx Pre-Exposure Prophylaxis trial

Background

The results of a large clinical trial of daily oral dosing of Truvada to prevent acquisition of HIV were published in the 25 November issue of the *New England Journal of Medicine*.

Truvada is a fixed-dose combination of two antiretroviral drugs, called tenofovir and emtricitabine. Truvada is already licensed for the treatment of HIV infection in humans.

These results demonstrate that Truvada is effective in reducing sexual acquisition of HIV among men who have sex with men (MSM).

The study was called *iPrEx*, which stands for Pre-Exposure Prophylaxis Initiative.

This is the first human study to show that pre-exposure prophylaxis (PrEP) is effective in reducing sexual transmission of HIV.

The study

A total of 2,499 participants were enrolled the study. All were born male but 29 (1%) reported their current gender as female. Participants were recruited at sites in a number of countries: Peru (55%); Ecuador (12%); USA (9%); Thailand (5%); Brazil (5%); and South Africa (4%).

This was a randomised, double-blind, placebo-controlled study. Participants were randomised to receive either Truvada or placebo. Neither the participants nor the researchers knew which participants were on the Truvada arm and which participants were on the placebo arm of the study.

Participants were men at high risk for acquiring HIV. A total of 4,905 men were screened and 410 (8.3%) of these were excluded because they were already HIV positive. Another 10 men were found to be HIV infected at enrolment. Participants received counselling throughout the trial, and were also provided with condoms, STI testing and treatment, and hepatitis vaccinations. Participants from the USA and South Africa were also offered post-exposure prophylaxis.

The enrolment period was from July 2007 to December 2009. The first participants started taking the study drug in June 2008 and all participants had stopped taking the study drug by August 2010.

Participants were followed for a median of 1.2 years (maximum 2.8 years), which represents a total of 3,324 person years follow up. The participant retention rate was 85–92%.

Participants were monitored for:

- HIV infections
- Risk behaviours
- Adherence to the daily dosing regimen
- Sexually transmissible infections (STIs)
- Adverse events (especially renal and liver related)
- Hepatitis B flares (among participants who were reactive to hepatitis antigens)
- Drug levels

All participants were followed for at least 8 weeks after they stopped taking the study drug.

Participants reactive to hepatitis antigens will be followed for hepatitis flares for 16 additional weeks, for a total of 24 weeks after stopping the study drug.

Participants enrolled in the optional sub study of bone mineral density, fat distribution, and fasting lipids will be asked to return for one additional visit 24 weeks after stopping the study drug.

Participants who HIV seroconvert during their participation in the study will also be followed until the end of study drug follow-up, and for at least 24 weeks after study participants stop taking the study drug.

The study was funded by the US National Institutes of Health (NIH) and the Bill & Melinda Gates Foundation.

The findings

HIV infections were 44% lower among participants in the Truvada group compared to the control group who received the placebo. In total, 100 people became infected during the trial—36 in the Truvada group and 64 in the placebo group.

An increase in protection from HIV infection was associated with increased adherence. Among those in the Truvada group who took more than 50% of their drugs (as measured by self-report and returned pills) efficacy was 50%, and among those who took more than 90% of drugs, efficacy was 73%.

Efficacy was greater in those who had detectable blood levels of the study drugs. In fact of the 34 men taking the study drugs who seroconverted, only 3 (9%) actually had detectable levels of tenofovir or emtricitabine.

Efficacy was also greater among those men who reported any unprotected receptive anal intercourse at the time of enrolling in the study, compared to those who didn't.

There was no difference in efficacy based on region, race or ethnic group, age education level, circumcision, or alcohol use.

Risk behaviour did not increase among participants during the trial.

Risk behaviour for HIV did not increase among participants during the trial. In fact, the proportion of participants who used condoms *increased* after enrolment. Also the total number of receptive anal intercourse partners decreased.

Overall, Truvada was found to be safe and well-tolerated with the main side effects being elevations in creatinine levels, nausea and weight loss.

No tenofovir or emtricitabine resistance was found in any of the 100 participants from either study arm who seroconverted during the trial.

Implications of these findings

The implications of these findings require considerably more detailed analysis and the calm, careful consideration of where Truvada may fit within the repertoire of HIV transmission prevention strategies.

The trial results indicate that, at best, pre-exposure prophylaxis with Truvada may complement the consistent use of condoms and other risk reduction strategies, rather than replacing them. This trial took place within the context of existing well-established prevention strategies (enhanced condom and lubricant availability, peer support and community mobilisation, counselling, etc).

The results also indicate that even under clinical trial conditions it will be difficult to achieve the adherence levels required to ensure high efficacy.

Nonetheless, initial analysis does suggest that the suitability of Truvada prophylaxis for some individuals or groups at very high-risk of HIV infection, for example, sero-discordant couples who have trouble with maintaining consistent condom use, should be thoroughly investigated and considered.

The trial was in place for less than two years; the issues of adherence over the long-term and of possible side-effects from long-term use of Truvada, will need further consideration and study in assessing desirability of taking up Truvada prophylaxis on both an individual and a population basis.

Next steps

AFAO is hosting a workshop to consider the implications of the trial results on 7 December 2010 in Sydney.

As a result of this trial's findings, the manufacturer of Truvada, Gilead Sciences, may choose to file for a licence for the use of Truvada in preventing HIV infection. This application would be made to the Food and Drugs Administration in the United States, and to regulatory authorities in other countries. The company may choose to wait for results of other ongoing trials before making such an application.

These results will affect the design of future studies. Once-daily dosing of Truvada will be the likely control arm for future PrEP trials testing other agents and dosing strategies. Other studies that are either planned or currently underway will examine intermittent and event-based dosing of PrEP which may be more practical and cost-effective approaches.

Informal use

AFAO cautions people against self-prescribing PrEP for several reasons:

- Before taking PrEP, individuals would need to ensure that they are HIV negative;
- Regular monitoring for side-effects of Truvada and regular HIV testing thereafter is required;
- This study of daily dosing of Truvada cannot be extrapolated directly to intermittent or occasion use.

Other studies

There are a number of PrEP studies taking place using either Truvada or tenofovir. These trials are being conducted among different populations (such as injecting drug users, women, and young men who have sex with men), different dosing strategies (daily, intermittent and event-based dosing) and different approaches (oral dosing or topical microbicides).

References

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