Oral pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention strategy that can be used by HIV-negative people to reduce their risk of getting HIV. Oral PrEP typically involves taking prescription pills every day, and good adherence is necessary for this strategy to be effective. Ongoing research on oral PrEP is evaluating its long-term effectiveness and safety, patient experiences, and alternative dosing schedules, such as an on-demand regimen. There is also research investigating different forms of PrEP, such as long-acting injectable formulations.


Long-term follow-up from the PROUD study

New data from the PROUD study continued to show that PrEP reduces the risk for HIV, and has psychosocial benefits for participants under long-term follow-up.

The PROUD study, which was conducted at 13 sexual health clinics in England, began in November 2012 and first reported results in February 2015. This study enrolled 544 HIV-negative gay men and other men and transgender women who have sex with men who reported having anal sex without a condom in the past three months. Participants were randomly assigned to either begin taking daily PrEP immediately (the immediate group) or to delay PrEP use for one year (the deferred group). The first phase of PROUD was stopped early because of the high level of effectiveness observed – participants in the immediate group had an 86% reduced risk of getting HIV compared to those in the deferred group.

In November 2014, all participants were offered PrEP, regardless of the group they started in, and 449 people continued follow-up in this second phase. There was no significant difference in the rate of HIV infection between the two original groups during the second phase.

However, the deferred PrEP group experienced a dramatic drop in the rate of HIV infection in the second phase (one HIV infection occurred in 206 participants) compared to the first phase (21 out of 255 participants acquired HIV). This data confirms PrEP’s long-term effectiveness and underscores the ability of participants to have high adherence to PrEP. The researchers stated that the HIV infections that occurred during this study most likely happened in people who were not adherent to PrEP when they were exposed to HIV.

In the last six months of follow-up, 368 people had a clinic visit, and 89% of those had at least one PrEP prescription. After four years of study follow-up (range two to four years), 60% of the original participants continue to take PrEP.

The incidence of rectal sexually transmitted infections (STIs) was high in both groups through both phases. This indicates that participants remained at high risk for HIV, and confirms the need for PrEP in this population. It also underscores the importance of regular STI testing and treatment while on PrEP.

The PROUD study investigators also reported on the results of a qualitative study that explored 41 participants’ perspectives on PrEP as an HIV risk reduction strategy. They found that most viewed PrEP as one of many risk reduction strategies that they used to reduce the risk of HIV, including the use of condoms, strategic positioning
and serosorting. Participants perceived that PrEP provided additional protection from HIV. The many psychosocial benefits of PrEP that participants described included reduced fear and anxiety of acquiring HIV, increased control over personal risk, and greater intimacy.

**IPERGAY confirms on-demand PrEP is highly effective for MSM, even when having infrequent sex**

In an effort to provide a non-daily option for people who want to take PrEP, the IPERGAY study evaluated the effectiveness of an intermittent, or on-demand, PrEP strategy in gay men and other men who have sex with men (MSM) at six sites in France and one site in Montreal. The on-demand strategy involves taking two pills two to 24 hours before sexual activity, followed by one pill taken daily until 48 hours after the last sexual activity.

*The first phase of IPERGAY* was a randomized controlled trial (RCT) that was stopped early when the strategy was found to be effective—there was an 86% reduced risk of getting HIV in men given PrEP compared to those given placebo pills. After the RCT phase ended, all participants were offered intermittent PrEP and 361 people continued to be followed in the open-label phase.

The original IPERGAY results found that men in the study were having sex frequently and taking a median of 16 pills per month. This led the researchers to question whether an on-demand strategy may not work as well for MSM having sex less frequently.

At the IAS conference, IPERGAY investigators presented results on a sub-study aiming to find out if men having sex less often were still protected by an on-demand PrEP strategy. The sub-study looked at time periods during which participants used 15 or fewer pills per month and said they used PrEP “systematically or often and not “from time to time or never.” Patterns of PrEP use varied over time for individuals and between participants. Overall, 269 participants had this pattern of PrEP use at some point during the study. In total, these 269 participants accumulated 134 person years of follow-up (equivalent to following 134 people for a year).

During these periods of lower PrEP use, participants used a median 9.5 pills per month, had sex a median of five times per month, and no HIV infections occurred. All participants who acquired HIV during these follow-up periods were in the placebo group and were not taking PrEP. The study investigators concluded that an on-demand PrEP strategy remains highly effective in MSM even when they have infrequent sex.

**Long-acting injectable cabotegravir**

Cabotegravir is an experimental antiretroviral drug that is being investigated as a potential new form of PrEP. A long-acting formulation of cabotegravir, given by injection every two to three months, could provide an alternative option for people who may have trouble adhering to a daily or on-demand oral PrEP regimen.

*An earlier study (called ECLAIR)* first looked at the safety and tolerability of injectable cabotegravir. The study found that 800mg of cabotegravir given by injection every 12 weeks was generally safe and did not cause serious long-term side effects. However, this dosing frequency was not optimal because drug levels did not remain high for as long as expected.

A follow-up study (called HPTN 077) was designed to further evaluate the safety and acceptability of a new dosing regimen (600mg of cabotegravir given by injection every eight weeks) and the original regimen (800mg every 12 weeks), while also measuring drug levels in the blood.

Researchers enrolled 199 participants at low risk for HIV infection, since the study was designed to assess safety and tolerability, not effectiveness. Unlike the ECLAIR study that only enrolled men, two-thirds of the participants in HPTN 077 were women. One trans woman and six trans men were also included. Participants were recruited from eight sites in four countries (South Africa, Malawi, Brazil and the United States).

Participants were randomly assigned to one of the following four groups, receiving:

- 800mg cabotegravir injections every 12 weeks (82 participants)
- placebo injections every 12 weeks (28 participants)
- 600mg cabotegravir injections every eight weeks (69 participants)
placebo injections every eight weeks (20 participants)

All participants were given oral cabotegravir (or placebo) pills for four weeks to ensure safety before receiving the long-acting injection. The total dosing period was 41 weeks. The 18-month follow-up period is ongoing, and will be completed in the summer of 2018.

Most participants experienced temporary reactions at the injection site, however the vast majority of reactions were mild to moderate. While 90% of participants experienced a reaction after their first cabotegravir injection, the proportion decreased to 60% by the fifth injection in the participants who received 600 mg injections. Only one of the 199 participants dropped out of the study because of an injection site reaction.

The researchers estimated a target threshold above which drug levels should remain for injectable PrEP to be able to prevent HIV acquisition. Men and women appeared to process the drug differently, and not all participants maintained target drug levels throughout the period between injections with the 12-week dosing regimen. However, drug levels remained consistently above target levels for both men and women using the eight-week dosing regimen. Another study is underway to evaluate the efficacy of long-acting cabotegravir injected at eight-week intervals.

**Dutch study explores motivations for choosing daily PrEP versus on-demand PrEP among MSM**

An ongoing demonstration project called the Amsterdam PrEP Project (AMPrEP) enrolled 376 HIV-negative MSM between June 2015 and February 2017, offering them a choice between taking PrEP daily or on-demand. As part of this study, AMPrEP researchers wanted to investigate the reasons men chose one dosing regimen over the other. Participants were interviewed at baseline about their reasons for choosing daily or on-demand PrEP, and were interviewed again at follow-up visits (every three months) if they decided to switch from one to the other, or decided to stop taking PrEP.

At enrolment, 273 men (73%) chose to take PrEP daily and 103 (27%) started on-demand PrEP. As of February 2017, 44 participants had switched to daily PrEP, and 39 had switched to the on-demand regimen. Participants provided a variety of motives for choosing and switching between regimens, based on expectations (before starting) and actual experiences once on PrEP. Note that participants were able to give more than one reason for their decision.

At baseline, reasons for **choosing daily PrEP** included the following:

- Need for daily structure (32%)
- Anticipated adherence issues with taking PrEP on-demand (31%)
- Expecting to have unplanned and/or frequent sex (19%)
- To have or maintain more sexual freedom (4%)
- Wanting to try out the daily regimen (3%)
- Fear of side effects related to on-demand PrEP use (1%)
- Fear of developing drug resistance with on-demand PrEP (<1%)

Reasons given for **switching to daily PrEP** (after starting on-demand) included the following:

- Increasing sexual risk behaviour (26%)
- Having unplanned sex (24%)
- Desire for more structured adherence (17%)
- Experiencing side effects from on-demand PrEP (15%)
- Already taking many pills with on-demand strategy (11%)
- To gain more sexual freedom (4%)
- Doubts about the efficacy of on-demand PrEP (4%)

At baseline, reasons for **choosing on-demand PrEP** included the following:

- Mostly having planned sex (42%)
- Only having risky sex occasionally (28%)
• Concerns about the toxicity and burden of taking medication daily (19%)
• Anticipated adherence issues with daily PrEP (10%)
• Wanting to try out the on-demand regimen (<1%)
• To stop or control sexual risk episodes (<1%)

Reasons given for **switching to on-demand PrEP** (after starting daily PrEP) included the following:

• Having less sex than anticipated (30%)
• Aversion to taking daily medication (25%)
• Experiencing side effects from daily PrEP (20%)
• Seeking a better match with current sexual risk behaviour (13%)
• To stop or control sexual risk episodes (4%)
• Experiencing adherence problems with daily PrEP (4%)
• Wanting to experiment with a different regimen (3%)

As of February 2017, 18 participants had stopped PrEP completely. Participants gave the following reasons for stopping PrEP use completely:

• Experiencing unacceptable side effects (eight participants)
• Reduced sexual risk (six participants)
• Changed life circumstances (two participants)
• Preference for exclusive condom use (one participant)
• PrEP provoked extreme sexual risk taking (one participant)

This research highlights that people have different preferences for the way they want to take PrEP, and that these preferences can change based on experiences and life circumstances. The study researchers recommend that individuals taking PrEP should be able to choose and switch between PrEP regimens that work best for them, based on their changing personal risk and adherence strategies.

**Resources**

- CATIE statement on the use of oral pre-exposure prophylaxis (PrEP) as a highly effective strategy to prevent the sexual transmission of HIV
- Pre-exposure prophylaxis (PrEP) resources
- Oral pre-exposure prophylaxis (PrEP) – fact sheet

—Camille Arkell

**References**

with mean (MSM) in the Netherlands: motives to choose for, switch to, or stop with daily or event-driven PrEP.
Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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