Adherence in HIV Prevention Research
A primer for HIV prevention advocates

Products only work if people use them. This is true for aspirin, birth control, condoms and, of course, biomedical HIV prevention strategies like oral PrEP and topical microbicides. One of the challenges for clinical trials of PrEP, microbicides and other strategies is gathering information on trial participants' actual use of these products. Since a pill or a gel is used away from the clinic, it's necessary to gather information about use in various ways. This can include asking participants about use and, in some cases, gathering biological samples. This fact sheet explains some of the approaches being used to gather adherence data today.

Why are adherence data important?

If there is no evidence of benefit from a product in a particular trial, is that because the product isn't effective, or because participants did not use it correctly and consistently? Adherence data can help researchers develop the best possible answer to this question. If a product is effective, adherence data can help researchers draw conclusions about how patterns of use relate to levels of effectiveness.

In the CAPRISA 004 trial of 1% tenofovir gel the data showed the gel reduced womens' risk of HIV by an estimated 39 percent. This number comes from looking at the data from all the women in the trial, regardless of how each participant adhered to the trial regimen. As with every biomedical HIV prevention trial, CAPRISA 004 researchers collected adherence data throughout the study. Using these data (more on the different ways to collect this information below), the CAPRISA 004 trial team was able to group the participants into low, intermediate and high adherers. When looking at the effectiveness data by group, the data showed that in high adherers the gel reduced risk of infection by an estimated 54 percent. This adherence data allowed the researchers to make additional conclusions about the effectiveness of the product.

How is adherence measured in HIV prevention research trials, particularly trials of oral PrEP and topical microbicides?

There are many different ways to measure adherence. Participants can be asked to report on their patterns of pill taking and/or missed doses. This can be done in interviews at the clinic, in pill-taking diaries, via SMS messages that are sent to participants' cell phones, or via computer-assisted self-administered interviews.

This "self-reported" information can be complemented by analysis of biological samples (e.g., blood, tissue and hair samples). For some products, the active drug will appear in the blood, tissue or hair of those participants assigned to the active arm and who are using the product. These samples can be tested to see if the drug is there (i.e., Was the participant using the product?) and, if so, whether the level is consistent with regular use.

Researchers often talk about triangulating between self-report and biological measures to get an estimate of adherence. Other approaches include unannounced home visits to do pill counts and electronic MEMS cap, which is a kind of electronic monitoring system on a pill bottle that records each time it is opened.

What are the strengths and limitations of different approaches?

Self-report, either by a computer-assisted interview or interview with site staff, is one of the least expensive ways to measure adherence and, unlike biological measures, it can detect adherence patterns. This method can also be a way by which researchers uncover some of the challenges participants may be facing when trying to adhere to the study protocol—and while the trial is still ongoing, come up with way to better support participants' adherence. While biologic samples can provide important information, they will never be able to show that a participant is having trouble remembering to take their pill or a partner doesn't like a gel so they can't always use it as directed. There are limits to self-report. It is rarely the only measure of adherence in a trial, given that it can be subject to social desirability bias (participants report what they think site staff want to hear, not what actually transpired) and recall ability, or as one researcher noted, "Remembering what you forgot."

Biological measures are able to tell researchers about drug levels in various tissues and parts of the body (for more on these studies, see AVAC's PK/PD fact sheet for advocates at *www.avac.org/intro*). These measures are more objective as drug levels are not subject to participant recall or social desirability, as self-report can be. Researchers can get a more objective picture of how a participant may or may not be adhering to the regimen. Some limits of these measures can include higher cost, acceptability and the inability to detect patterns of or challenges to adherence (drug levels can't show the exact schedule a participant took a pill, for example).

A recent example of using biological samples to measure adherence and learn more about the effectiveness of a new intervention in a trial was from the iPrEx PrEP trial. This study looked at the safety and effectiveness of once-daily TDF/FTC in gay men and transgender women. In the study, pill-taking was measured in multiple ways, including self-report, pill counts and measurements of drug concentrations in participants' blood and hair. Although self-reported pill use was high across the study, plasma drug level testing indicates that actual pill use and drug exposure among those in the active arm may have been substantially lower. The trial result based on the intent- to-treat analysis (meaning it included all participants enrolled in the study) showed that daily TDF/FTC reduced risk in the study population by an estimated 44 percent. The trial team also conducted a small sub-study that looked at whether participants in the active drug arm (receiving TDF/FTC) had detectable levels of the drug in their blood. This sub-study found that participants receiving TDF/FTC who had detectable drug levels consistent with what one would expect for daily dosing were at significantly lower HIV risk compared to those who had no detectable levels. As in the CAPRISA 004 study, adherence data allowed researchers to get a better understanding of product effectiveness.

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