

Factsheet

CAPRISA 004 and Adherence to Study Product

Summary

- The CAPRISA 004 trial had good adherence—on average 72.2 percent of reported sex acts were covered by two doses of tenofovir gel.
- Although adherence is challenging to measure, accurate assessment of adherence is important because it influences the level of protection observed in a study.
- CAPRISA 004 measured adherence based on monthly self-reports and counts of used and unused gel applicators returned by the participants.
- Women who followed the prescribed regimen of two doses of tenofovir gel for more than 80 percent of their sex acts had a 54 percent lower risk of acquiring HIV.
- CAPRISA 004 used innovative methods to support adherence, including motivational interviewing techniques, to increase adherence to gel use.
- Future trials will need to place greater emphasis on enhancing and objectively measuring adherence in light of its substantial influence on the trial outcome.

Importance of adherence to study product

Adherence is the degree to which a participant uses a study drug as directed to ensure that the correct dose of the product is being administered and available when needed. Adherence is a major issue in HIV prevention trials as non-adherence may decrease the potential effectiveness of the study drug and skew the safety profile of the study product. Even a highly effective drug will appear to be ineffective if enough participants fail to follow the prescribed drug regimen. So non-adherence threatens a study's validity, and complicates the scientists' ability to derive scientific conclusions. Poor adherence may be responsible for the lack of success in recent microbicide trials, some of which had drug adherence as low as 44 percent—low enough to mask the true effectiveness of a study drug.

The support and measurement of adherence are important components of a clinical trial. Because CAPRISA 004 was designed as a double-blind study—neither the researchers nor the participants knew which participants received the active gel—adherence support was provided to all participants. Similarly, the adherence levels had to be measured among all of the participants, regardless of whether they received the active ingredient or the placebo.

Dosing regimen and adherence

CAPRISA 004 set out to evaluate the safety and effectiveness of using two doses of the study gel every day a woman had sexual intercourse. Each participant was asked to apply a first dose of the assigned study gel within 12 hours before anticipated sexual intercourse, to insert a second dose as soon as possible after intercourse and no more than two doses of gel in a 24-hour period. Hence the dosing strategy is referred to as *BAT24*. For example, if a woman only has intercourse

(or coitus) on one Saturday evening in a two week-period, she would apply only two doses of the gel on that Saturday—once before sex, and once after, for that two week-period. This approach is known as *coitally related dosing* or *episodic dosing*. It differs from two other approaches known as *daily dosing* (where study participants are requested to apply the study gel once every day) and *intermittent dosing* (where study participants are requested to apply the study gel at regular intervals, such as once every week).

The relationship between microbicide dosing regimens and drug adherence is controversial. Some people argue that a strategy that instructs a woman to use the gel every day, regardless of whether she has sex, may be associated with higher adherence because they believe that it is easier to remember something if it becomes part of one's daily routine. Others argue that a strategy that instructs a woman to apply the gel when she is having sex may be associated with higher adherence because they believe that it is easier to remember to use a vaginal gel if it is associated with the sex act. Both opinions are probably correct to some extent as some women may find coitally related use easier to remember, whereas others may find daily use easier to remember. It is therefore critical to use the dosing strategy most likely to achieve high adherence based on information from behavioural studies in the specific population of women where the study is being conducted.

How did CAPRISA 004 try to achieve high drug adherence?

The CAPRISA 004 researchers conducted preliminary studies of women in the rural and urban study populations before the clinical trial began to obtain detailed information on their sexual behaviour patterns, their potential adherence to the medication, their risks of being infected by HIV, and the rates of new HIV infections. The researchers also talked to women at the urban and rural clinics about the possible approaches that would best suit them and enable them to maintain high levels of adherence.

Various approaches were devised based on this pre-trial information, on information based on monkey studies, and on studies of the drug nevirapine, which is used to prevent the mother-to-child transmission of HIV. The community representatives who served on the study advisory committees at each site then provided detailed input on the strengths and weaknesses of each approach. These consultations were critical to the selection of BAT24 as the preferred dosing regimen for CAPRISA 004.

An important consideration in CAPRISA 004 was the way in which sexual frequency is linked to migrant labour, especially among the rural women. In this group, sex is largely restricted to times when husbands and partners return from the cities—usually once or twice a month. Coitally related dosing was therefore preferred in this setting.

For the study, the CAPRISA 004 researchers developed a customized program to improve adherence to the dosing regimen, including innovative counselling aids such as checklists, teaching aids, and personal diaries. Participants were trained on the use of the gel applicator during enrolment and at follow-up visits. They also received personalized support and counselling during the trial. CAPRISA researchers also introduced a participant-centered and interviewer-driven technique, called *motivational interviewing*. This constructive approach helps participants devise their own strategies to achieve high adherence. For example, instead of telling the participant when to use the gel, the interviewer and the participant discuss how to

incorporate the use of the gel into the participant's patterns of sexual activity. The rationale being that participants are more likely to act on self-devised and self-motivating solutions to past problems experienced in achieving high adherence.

Methods used to measure drug adherence in the CAPRISA 004 trial

The CAPRISA 004 researchers assessed each participant's adherence to the study gel based on self-reports by the participants and counts of returned gel applicators. Every month, each participant was asked to report the frequency of sexual activity during the last 30 days and adherence to the product-use regimen for the last sex act. The researchers also counted the number of used and unused applicators that were returned every month by each participant.

This information was used to create three measures of adherence: (1) self-reports of adherence to the product-use regimen for the last sex act; (2) the number of used applicators returned per month; and (3) dividing the number of reported sex acts per month by half the number of used applicators that were returned. The limitation of measure (1) is that it is based on data on the last sex act only, which may not be representative of the entire month. The limitation of measure (2) is that it does not take into account the frequency of sex. Since each woman was asked to apply the study gel according to the BAT24 regimen (described above), the last measure (3) was used as the primary measure of adherence in the study.

It should be noted that adherence is intrinsically difficult to measure accurately and there is no gold standard of measuring adherence. The use of applicator counts to calculate adherence for every participant each month and the use of this information for motivational interviewing was an important step forward in linking real-time adherence measurement to adherence support in the CAPRISA 004 trial.

Gel adherence in CAPRISA 004

Adherence to the BAT24 dosing regimen was good in the CAPRISA 004 trial. The adherence levels of each measure listed above are:

1. Self-reported adherence to the BAT24 dosing regimen was on average 82.4 percent during the last sex act.
2. Each month, study participants returned an average of 6.0 used applicators.
3. Applicator returns indicate that, on average, 72.2 percent of reported sex acts were covered by two doses of tenofovir gel.

The differences between the average self-reported adherence of 82.4 percent and the average applicator-based adherence of 72.2 percent probably reflects reporting variability and/or slightly higher adherence in the last sex act prior to a study visit compared to the rest of the month. These adherence numbers take on greater meaning when compared to the measured effectiveness of the tenofovir gel (see below).

Adherence and effectiveness of tenofovir gel

Researchers found that the participants who adhered most closely to the dosing regimen were the least likely to acquire HIV—suggesting that the effectiveness of the tenofovir gel increased with increasing adherence to the BAT24 regimen.

Tenofovir gel was 54 percent effective among women who adhered to the BAT24 regimen for at least 80 percent of sex acts; 38 percent effective among women who adhered to the regimen for 50 percent to 80 percent of sex acts; and 28 percent effective among women who adhered to the regimen for less than 50 percent of sex acts.

The CAPRISA 004 scientists found that some participants became less inclined to follow the dosing regimen after the first 18 months of gel use in the study. This decline in BAT24 adherence paralleled a decline in estimates of the effectiveness of the gel. The parallel trend suggests that the effectiveness of the gel is closely linked to adherence.

The researchers also found that motivational interviewing increased the BAT24 adherence rates and, in turn, the effectiveness of the tenofovir gel. Motivational interviewing included one-on-one consultations that identified and addressed the challenges being faced by each participant. The interviews were conducted in a supportive environment and ultimately led to customized goals that helped each participant overcome her particular challenges. The attainment of these goals substantially enhanced adherence during the study.

Future analysis of adherence in CAPRISA 004

The CAPRISA scientists are continuing to study the data that were collected on adherence. In the future, we hope to (1) analyze the trends in adherence observed during the course of the study; (2) compare the adherence measures described here with more detailed measures from case-controlled data; (3) validate adherence measures using a biological marker of the participant's tenofovir levels; and (4) identify predictors of adherence from our data that will help us to develop interventions to increase adherence in future trials.