



MICROBICIDES DEVELOPMENT PROGRAMME

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Preparing for rollout of tenofovir 1% gel in 2015

An estimated 7,400 new HIV infections occurred EVERY DAY in 2008, the majority in women of child bearing age.

The South African CAPRISA 004 microbicide trial reported:

- 39% reduction in HIV in women using tenofovir vaginal gel compared to placebo gel
- 51% reduction in genital herpes (HSV2)
- 54% reduction in HIV when gel was used as instructed for 80% or more of the sex acts

The instructions were complicated requiring TWO doses per sex act, but NO MORE THAN TWO in one day.

CAPRISA 004 was a good result for HIV prevention, and a good result for microbicides as a method of delivery, but did not answer the following questions:

- will ONE dose of gel prior to sex provide protection (it protects 100% of monkeys)?
- will a dose of gel EVERY DAY provide better protection (a regime that might tolerate missed doses)?
- could other methods of delivery such as rings, depo injections or tablets provide greater protection?
- will resistant virus emerge if HIV testing is less frequent?
- will tenofovir gel be safe in broader study populations including younger women aged 16-17, and pregnant women?

In 2013 the VOICE trial will report on the safety and effectiveness of using tenofovir gel EVERY DAY in broader populations, and the relative benefits of gel and tablets. The US Food and Drug Administration (FDA) have stated that this trial should be sufficient to support a licensure application for tenofovir gel.

The FACTS trial will repeat the TWO dose strategy used in CAPRISA 004, which informally the South African Medicine Controls Council (MCC) have indicated a preference for, in order to support licensure in South Africa.

The International Partnership for Microbicides plans to test the dapivirine ring which releases constant drug against placebo in two trials 2011-14. This will appeal to many women, but may not suit women having infrequent sex.

In 2015, we should have licensed tenofovir gel, but we will not know if ONE dose of gel per sex act will protect women

ONE dose would be simpler and cheaper to implement, but it may not work well enough to justify roll-out.

Assessing ONE dose against placebo will give a more precise measure of effectiveness, and be quicker and cheaper than comparing it to TWO doses in roll-out.

The proposed MDP302 trial

- Will assess ONE dose per sex act compared to placebo with 90% power to detect a 50% reduction in HIV
- Will assess ONE dose per sex act compared to placebo with 80% power to detect a 50% reduction in HSV2
- Will assess TWO doses per sex act compared to placebo as a 'positive' standard in a smaller number of women
- Will have 90% power to detect a 5% difference in adherence between ONE dose and TWO doses **within each centre**
- Will reduce the frequency of HIV testing to 3m (and 6m if no resistance half way through the trial)
- Will assess safety in 16-17 year olds, and pregnant women (subject to national approvals)
- Will build on established clinic, laboratory and community infrastructure in Mozambique, Uganda, Tanzania and Zambia – 3 of these countries have no current experience of tenofovir gel

CAPRISA 004 broke new ground, opening the door to a new technology that women can use to protect themselves against HIV, and still have children. ONE dose per sex act with less frequent HIV tests would lead to a net saving of \$3,542 per HIV infection averted, which could be invested back into the programme to increase the number of women that can be given a choice in 2015.

Europe invested €202M in microbicide research in the last decade - €22M more over the next 4 years would build on this investment and tell us whether ONE dose per sex act protects in time to inform implementation once the gel is licensed.

This is a small additional investment for a large return – millions of women and their children would benefit.



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MDP302 Summary

A randomised placebo-controlled trial to assess the effectiveness of a single dose of 1% tenofovir vaginal gel, in relation to BAT24 dosing, in preventing acquisition of HIV and HSV2, and to compare adherence between the two regimens

Participating sites and capacity

Partner institution	Target	Population	Incidence/100py (95% CI), source	Condom use (last sex act)
MRC/UVRI Uganda Unit in Entebbe and Masaka, Uganda	1000	Sero-discordant couples	4.8 (3.7-6.4), MDP301 data	86%
Mwanza Intervention Trials Unit in Geita and Mwanza, Tanzania	1000	High risk young women in bars	4.4 (3.1-6.1), EDCTP cohort data	31%
University of Zambia in Mazabuka, Zambia	800	General population	4.2 (3.2-5.6), MDP301 data	19%
CISM in Manhica and Maputo, Mozambique	800	General population	5.0 (3.1-8.0), EDCTP cohort data	40%

Main objectives and outcomes

- Effectiveness of a single dose applied before sex, or failing that as soon as possible afterwards
 - in preventing acquisition of HIV at or before 76 week endpoint
 - in preventing acquisition of HSV2 at or before 76 week endpoint
 - in relation to the effectiveness of BAT24 in the same populations
- Safety including
 - Adolescents
 - **Pregnant women**
- The extent to which differences in **triangulated adherence** explains the differences in effect (single dose compared to BAT24) **within each country**

Design and sample size

Participants will be randomised as described in the figure below, with 2400 participants randomised to single dose and 1200 to BAT24. The sample size is comfortably sufficient, with 90% power, to detect a reduction in HIV incidence of at least 50% in the single dose TFV arm versus placebo. This assumes a conservative 4.0/100 py incidence in the placebo arm.

