



MICROBICIDES DEVELOPMENT PROGRAMME

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Microbicides Development Programme 302 Clinical Trial Design

MDP302: Summary

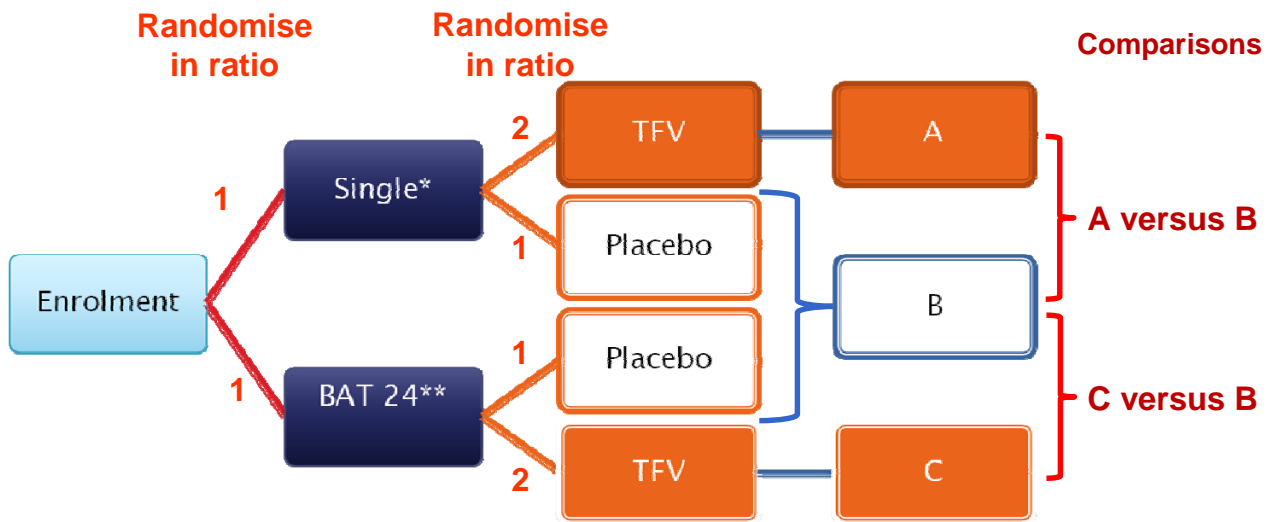
MDP302 is a placebo-controlled efficacy trial of 1% tenofovir (TFV) gel, applied as a single dose (before or immediately after sex) or as two doses (before and after sex, known as BAT24), to prevent vaginally acquired HIV infection.

Trial design

Participants will be randomised as described in Figure 1 to the following groups:

- BAT24 dose vaginal administration of 1% TFV gel
- BAT24 dose vaginal administration of placebo gel
- Single dose vaginal administration of placebo gel
- Single dose vaginal administration of 1% TFV gel

Figure 1: MDP302 Trial Design



* Single dose before (or immediately after) sex
 **Two doses, before and after sex and no more within 24 hours

Inclusion criteria: Women aged 16 years and above at enrolment in Uganda and in Tanzania or aged 18 years and above in other sites; reporting to be sexually active at entry and expecting to remain so during follow-up; willing to undergo HIV testing and informed of the result at screening, follow-up visits, and any other visit that may be required; HIV negative at screening according to local HIV testing algorithm; willing to use gel as instructed; willing to undergo regular speculum examinations, blood draws for routine laboratory parameters and genital infection screening; willing to have regular pregnancy tests; willing to receive health education about condoms; willing to be followed up after the end of trial participation in the event of seroconversion during the trial and willing and able to give informed consent.

Exclusion Criteria: Women that are unable or unwilling to provide a reliable method of contact for the field team; are likely to move permanently out of the area within the next year; are using spermicides regularly; are pregnant; have grade 3 clinical or laboratory abnormalities which are considered by the clinician or the trial management group to make enrolment inadvisable; require referral for assessment of a clinically suspicious lesion; have had an infection or a surgical intervention of the cervix, or to the womb through the cervix, within 30 days of enrolment; have known latex allergy; are participating, or have participated within 30 days of enrolment in a clinical trial of a vaginal product, e.g. of a microbicide, barrier method or any other intervention likely to impact on the outcome of this trial; and women who are considered unlikely to be able to comply with the protocol.



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Primary outcome and assessment

Acquisition of HIV infection before or at the 52 week time point (or at 72 weeks in Uganda) confirmed by a central reference laboratory, in participants confirmed to be HIV negative at enrolment. HIV status will be determined according to site specific algorithms using FDA and WHO approved assays. All rapid results that are positive or discordant at or after enrolment will be confirmed by the central reference laboratory.

Sample size, assumptions and statistical power

The placebo arms will be combined for the primary analysis: pair-wise comparisons of each TFV dosing strategy versus combined placebo group. The study will be powered for each pair-wise comparison at 83% (with 5% significance, 2-sided) to detect a minimum 50% reduction in HIV incidence compared to placebo. This is based on accumulating a total of 3915 woman-years of follow-up and 78 HIV infections for each two group comparison; an HIV incidence of 4.0 per 100 woman-years in the control group and a 10% loss of woman-years by end of follow-up. The statistical power depends on the HIV incidence in the control arm (as this determines the number of expected HIV infections). Based on current estimates of HIV incidence in these trial populations, 4 per 100 women years remains a conservative assumption (See Table 1).

Site capacity

We are aiming to enrol 3750 HIV negative women to MDP302 from a range of general, high risk and sero-discordant couple populations in sub-Saharan Africa. The participating institutions will recruit women from the different communities as shown in Table 1.

Table 1: Site capacity and trial populations

Partner institution	# in 18m	Population	Incidence/100py (95% CI), source
MRC/UVRI Uganda Unit in Entebbe and Masaka, Uganda	1200	Sero-discordant couples	4.8 (3.7-6.4), MDP301
Mwanza Intervention Trials Unit in Geita and Mwanza, Tanzania	700	High risk young women in bars	4.4 (3.1-6.1), EDCTP cohort
University of Zambia in Mazabuka, Zambia	750	General population	4.2 (3.2-5.6), MDP301
CISM in Manhica and Maputo, Mozambique	600	General population	5.0 (3.1-8.0), EDCTP cohort
MRC HIV Prevention Research Unit, Durban, South Africa	500	General population	6.4 (5.4-7.5), MDP301

Follow-up, assessments and gel adherence

Participants will be followed for 60 weeks (76 weeks in Uganda). The full schedule of visits and assessments is provided in the Appendix. All participants will be asked to keep simple daily gel diaries to record gel use and sex acts, and return them at each 4 week visit. Applicator returns, gel diary entries and gel adherence as reported in the behavioural interview will be compared and differences discussed with the participant at each long clinical visit, resulting in a final 'reconciled' estimate of adherence.

Primary Analysis

A time-to-event approach will be used for the analysis of the primary efficacy outcome of acquisition of HIV for each TFV versus combined placebo comparison. This will take the form of a modified intent-to-treat (MITT) analysis whereby women subsequently found to be HIV positive at enrolment will be excluded from analysis. Product efficacy will be expressed as 1 minus the hazard ratio comparing TFV versus placebo, estimated from a Cox proportional hazards model, stratified by centre.

We do not plan to formally compare the efficacy of TFV between dosing schedules as we anticipate any difference would be small and could largely reflect differences in adherence. However we will perform post randomisation subgroup analyses of pre-defined groups of consistent and inconsistent gel users within each dosing schedule and the relative effects will inform prescribing practice and roll-out (should TFV prove to be effective).



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Figure 1: Summary of visit schedule for MDP302 participants

