

Q & A

Microbicides Development Programme (MDP) update: MDP301 Phase III trial continues but one arm closes

1. What is the MDP301 trial?

The MDP301 study, also known as the Microbicides Development Programme phase III trial of PRO 2000/5 microbicide candidate gel, is a clinical trial to evaluate the safety and efficacy of a potential vaginal microbicide product. A microbicide is a gel or cream applied in the vagina or rectum to prevent HIV infection and other sexually transmitted infections (STI). The MDP301 trial is evaluating two doses of PRO 2000/5 gel compared to placebo gel: 0.5% PRO 2000/5 strength product and 2% PRO 2000/5, which is four times stronger than 0.5% PRO 2000/5.

2. Who sponsors and conducts this trial?

The UK Medical Research Council is the sponsor for the MDP301 trial. It is jointly funded by MRC and the UK government's Department for International Development (DFID). It is conducted by the Microbicides Development Programme, a partnership of African and European researchers working together to fight HIV.

3. When did the MDP301 trial begin?

The MDP301 trial began enrolling volunteers in Uganda and Johannesburg in October 2005, in Durban in December 2005, Tanzania in February 06, Africa Centre, KwaZulu Natal in April 06 and Zambia in July 06.

4. How many participants are involved and where is the study being conducted?

By 15th January, 7,735 women had been enrolled across the following six trial sites:

- University Teaching Hospital, Lusaka, Zambia. Trial participants are employees of the Zambia Sugar Plantation as well as women from the local town of Mazabuka.
- Medical Research Council Uganda Virus Research Institute, Entebbe. Trial volunteers are drawn from 25 rural villages and most are couples in which the male partner sometimes has HIV and sometimes does not.
- African Medical and Research Foundation and National Institute for Medical Research, Mwanza, Tanzania. Most participants are women working in food and recreational facilities in 10 administrative wards of Mwanza City.
- The Africa Centre for Health and Population Studies, KwaZulu Natal, South Africa. Recruits to the study come mainly from a rural population of 80,000 people in the Centre's demographic study area.
- South African Medical Research Council, Durban. MDP works at Medical Research Council clinics in three semi-urban districts, Tongaat, Verulam and Isipingo. The clinics offer primary health care, and trial participants have been drawn from women who come for family planning and post-natal care.
- Reproductive Health and HIV Research Unit (RHRU), Department of Obstetrics and Gynaecology, University of Witwatersrand, Johannesburg,

South Africa. Here, MDP has two trial sites, one within the grounds of a tertiary referral hospital in Soweto and the other at Orange Farm, a township 30 km to the south. Trial volunteers come from a large urban population spread over 31 districts.

The trial intended to enroll 9,590 women in total, but the early closure of the 2% PRO 2000/5 arm means fewer volunteers could now be required. MDP301 is still on track for a late 2009 trial result for the efficacy and safety of the 0.5% PRO 2000/5 arm.

5. What is the investigational product being tested?

PRO 2000/5 (naphthalene sulphonate polymer) is an entry and fusion inhibitor that binds to viruses and bacteria to prevent them from binding to and infecting healthy cells. PRO 2000/5 is a synthetic long-chain molecule made of repeating units of naphthalene sulphonate. For vaginal use, it is formulated as a water-based gel.

6. What is the design of MDP301?

MDP301 is a Phase 3 trial, designed as a 3 arm study for two formulations (0.5% and 2%) of PRO 2000/5. The three arms are:

1. standard prevention package + placebo gel
2. standard prevention package + PRO 2000/5 0.5%
3. standard prevention package + PRO 2000/5 2%

7. What is an Independent Data Monitoring Committee (IDMC) and how does it monitor the study?

The MDP Phase III clinical trial of PRO 2000/5 is overseen by an Independent Data Monitoring Committee whose members have no involvement in running the trial and no financial interest in its outcome. The Committee meets routinely to review data emerging from the trial and monitor the safety of participants. Usually, an IDMC recommends that the trial should continue as planned. However they may decide to stop the trial (or one of the arms) if there is strong evidence of efficacy or of serious toxicity. Occasionally, as here for one arm, they may decide to stop for reasons of futility if there is no more than a small chance of showing benefit.

The Committee is chaired by Professor Sir Alasdair Breckenridge, an expert on safety of medicines and Chairman of the UK Medicines and Healthcare products Regulatory Agency. Other members are Professor Catherine Hill, Head of Department, Service of Biostatistics and Epidemiology, Institute Gustave-Roussy, France; Professor Florence Mirembe, Former Head of Obstetrics and Gynaecology at Mulago Hospital, Kampala, Uganda; and Dr Isaac Malonza, Deputy Country Director (Kenya) of JHPIEGO, an international health organization affiliated with The Johns Hopkins University in Baltimore, Maryland USA, and former Head of the Microbicides Desk of the World Health Organisation. In 2007, the Committee met on 10 January, 12 March, 18 June and 29 November.

8. What were the results of the 8th February 2008 IDMC?

On the 8th February 2008 the IDMC reviewed the safety and efficacy data from 7,735 women in the MDP301 trial enrolled across all six participating sites and recommended that the 0.5% PRO 2000/5 and placebo gel arms should continue.

However, they recommended that no further gel should be prescribed to women allocated to the 2% PRO 2000/5 arm of MDP301, as there is no more than a small chance of showing protection against HIV infection from 2% PRO 2000/5 compared to placebo gel.

The MDP Trial Steering Committee (TSC) met on 11th February 2008 and accepted the recommendations of the IDMC. In particular they were reassured that the reason for discontinuing the 2% PRO 2000/5 gel arm was because it was unlikely to show benefit rather than because of harm. The TSC considered that it was important to continue with the 0.5% PRO 2000/5 and placebo arms, as it is still possible that 0.5% PRO 2000/5 will prove to be effective and help to protect women against HIV infection. Recruitment of new trial participants to these arms will continue.

9. How can a stronger dose of product be less effective than a weaker dose?

We don't know the answer to that but are planning to investigate further. It is biologically plausible that a product may show no protective effect against HIV infection at a concentration of 2%, but show a protective effect at a lower concentration (0.5%). There are a number of possible explanations for this, one being that any beneficial effect against HIV could be partly outweighed by a local effect on the vaginal lining related to the higher concentration product. In other words, the weaker dose may be gentler on the vagina.

10. Does that mean that the stronger dose (2%) may have caused harm to the women who received it?

The reason given by the DMC for their recommendation to discontinue the 2% PRO 2000/5 arm was that there was no more than a small chance of it showing protection. This indicates that there was no conclusive evidence of harm or increased risk of infection in those women who had received 2% PRO 2000/5.

11. What is happening to the volunteers enrolled in the MDP301 trial?

All women in the 0.5% PRO 2000/5 and placebo gel arms will be asked to continue to use their gel and attend the clinic according to their planned schedule. Recruitment of new trial participants to these arms will continue.

Women in the 2% PRO 2000/5 gel arm are being contacted and asked to return to their study site as soon as practically possible, bringing with them any unused 2% PRO 2000/5 gel supplies. They will be invited to attend the clinic every three months until they have completed their week 52 visit. At these clinic visits, they will be counselled, tested for HIV, other STIs and pregnancy as per the existing trial protocol. Study staff will provide referrals for further medical care if needed.

All MDP clinical sites have procedures in place for the care of women who become HIV positive. Any women who become HIV positive during the trial will continue to receive counselling and referral to local health care providers for their ongoing care. Where local services are overburdened MDP clinics are offering additional services to facilitate the transfer of care.

12. Where can I find more information on microbicides and HIV prevention clinical trials?

The following weblinks are good sources of additional information:

Microbicides Development Programme	http://www.mdp.mrc.ac.uk/
Global Campaign for Microbicides (GCM)	http://www.global-campaign.org/
GCM factsheets	http://www.global-campaign.org/EngDownload.htm
GCM brief on understanding safety in microbicides trials:	
	http://www.global-campaign.org/clientfiles/Safety%20Evaluation-Fundamentals.pdf
Alliance for Microbicides Development	http://www.microbicide.org/
International Partnership for Microbicides	http://www.ipm-microbicides.org
Microbicides 2008	http://www.microbicides2008.com/
HIV Prevention Trials Network	http://www.hptn.org/index.htm
Population Council	http://www.popcouncil.org/microbicides/index.html

Alternatively, for further information please call:

1. Press contacts:

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2. Clinical Site contacts:

Zambia

University Teaching Hospital, Lusaka, Zambia.
Principal Investigator: Dr Maureen Chisembele, (tel +260 (966) 439910, email: pintmini@yahoo.com).

Uganda

Medical Research Council Uganda Virus Research Institute, Entebbe.
Principal Investigator: Dr Anatoli Kamali (tel +256 772 422765, email: Anatoli.Kamali@mrcuganda.org).

Tanzania

African Medical and Research Foundation and National Institute for Medical Research, Mwanza, Tanzania.
Principal Investigator : Dr Claire Moffat (tel +255 786 960018, email: claire.moffat@lshtm.ac.uk).

South Africa

Principal Investigator for RHRU and Country PI: Professor Helen Rees (tel +27 82 5722057, email: h.rees@rhrujh.co.za)

1. The Africa Centre for Health and Population Studies, KwaZulu Natal, South Africa
2. South African Medical Research Council, Durban
3. Reproductive Health and HIV Research Unit (RHRU), Department of Obstetrics and Gynaecology, University of Witwatersrand, Johannesburg, South Africa.