

MICROBICIDES DEVELOPMENT PROGRAMME

Medical Research Council

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The MDP 301 Trial - Q&A

What is the MDP 301 trial?

MDP 301 is a Phase III trial evaluating the safety and effectiveness of the investigational vaginal microbicide PRO 2000 for reducing the risk of HIV infection in women.

What is a microbicide?

A microbicide is a gel or cream which would be applied in the vagina or rectum to reduce the risk of HIV infection and possibly other sexually transmitted diseases. To date, all such products are still experimental in nature. MDP 301 evaluated two strengths (0.5% and 2%) of the experimental microbicide gel PRO 2000, compared to placebo gel. The trial gel was provided to MDP free of charge by Endo Pharmaceuticals Solutions.

Who has sponsored and conducted this trial?

The trial has been conducted by the Microbicides Development Programme, a not-for-profit partnership funded by the UK government through its Department for International Development and the Medical Research Council (MRC). MRC is the trial sponsor.

Where has the study been conducted?

MDP 301 has been conducted at thirteen clinics managed by six partners in four countries in Africa.

- University Teaching Hospital, Lusaka, Zambia. Trial participants were employees of the Zambia Sugar Plantation and women from the local town of Mazabuka.
- Medical Research Council Uganda Virus Research Institute, Entebbe. Trial volunteers were mainly sero-discordant couples drawn from 25 rural villages.
- African Medical and Research Foundation and National Institute for Medical Research, Mwanza, Tanzania. Most participants were women working in food and recreational facilities in 8 administrative wards of Mwanza City.
- The Africa Centre for Health and Population Studies, KwaZulu Natal, South Africa. Recruits to the study came mainly from a rural population of 80,000 people in the Centre's demographic area.
- South African Medical Research Council, Durban. MDP worked at Medical Research Council clinics in three semi-urban districts, Tongaat, Verulam and Isipingo. The clinics offer primary health care, and trial participants were drawn from women who came for family planning and post-natal care.

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- Reproductive Health and HIV Research Unit (RHRU), Department of Obstetrics and Gynaecology, University of The Witwatersrand, Johannesburg, South Africa. Here, MDP 301 had two 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 came from a large urban population spread over 31 districts.

Additionally, Contract Laboratory Services (CLS), a joint venture between the South African National Health Laboratory Service (NHLS) and the Wits Health Consortium (WHC), has served as a central reference laboratory for serology testing and confirmation and provided Good Clinical Laboratory Practice training to nearly 60 laboratory staff at trial sites.

Who are the European partners?

European partners include the London School of Hygiene and Tropical Medicine, St. George's University of London, and the Universities of York, Southampton and Barcelona. The MDP partnership is coordinated jointly by Imperial College London, and the Clinical Trials Unit of the UK Medical Research Council, which has been working on clinical trials with African partners for over 30 years.

Why are such trials carried out in high-risk areas?

Microbicide trials aim to prevent as many new HIV infections as possible and, currently, the majority of new HIV cases worldwide, especially among women, occur in sub-Saharan Africa. It is best to test a drug among the people who need it most because we have to make sure the drug will be safe and acceptable in these populations. Additionally, a trial in a high-risk area is likely to determine more rapidly whether a potential product is safe and effective. Prior to the MDP 301 trial, PRO 2000 was evaluated for safety in women recruited in Europe, the US, India and Africa.

What is PRO 2000?

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

When did the MDP 301 trial begin and when did the last woman exit the trial?

The MDP 301 trial began enrolling volunteers in Uganda and Johannesburg in October 2005, in Durban in December 2005, Tanzania in February 2006, Africa Centre in April 2006 and Zambia in July 2006. Follow-up of the last participant was completed on 18 September 2009.

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What was the study design?

MDP 301 was designed as a randomised, placebo-controlled trial to explore the safety and effectiveness of two concentrations of PRO 2000 gel. Between October 2005 and August 2008, 9385 eligible, sexually active, HIV-uninfected women were enrolled across sites in sub-Saharan Africa.

Until February 2008, participants were randomly assigned to receive either 0.5% or 2% PRO 2000 gel or a placebo (inactive) gel. In February 2008, the trial's Independent Data Monitoring Committee recommended closure of the 2% gel group, following a finding that there was no more than a small chance of demonstrating benefit at that concentration. Recruitment to the 2% gel group then ceased and 2% gel was no longer dispensed, although women previously assigned to this group continued to be followed up. Participants enrolled after 13 February 2008 were randomly assigned to receive either 0.5% PRO 2000 gel or placebo gel.

Participants were instructed to apply a single dose of study gel up to one hour before every act of vaginal intercourse, using a single-use, pre-filled applicator. Participants received free condoms and risk-reduction counselling, regular health checks, testing and treatment for sexually transmitted infections and referral for HIV treatment where appropriate.

Most study participants completed 12 months of follow-up but the couples in Uganda were followed for up to 24 months.

The trial's primary efficacy outcome measure is HIV infection up to 12 months. Secondary efficacy outcomes include HIV infection up to 6 and 9 months, and infection by HSV-2, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis*. Safety is also carefully assessed.

How did the trial structure its data management?

Unlike many other international trials, MDP 301 was structured to ensure that African trial centres owned and controlled their own data. Local data management occurred on site and African investigators have direct access to their own site data for scientific papers. The trial's data-management system included four levels of error detection: Double-data entry picked up discrepancies, automatic checks detected missing data, and data were also checked centrally every two weeks and then analysed statistically.

How was the trial managed?

A trial management group, including senior representatives of all the sites, held monthly teleconferences to monitor enrolment, retention, rates of infection, rates of pregnancy and possible side effects experienced by participants. Senior scientists visited all sites regularly to oversee participants' safety, review treatment decisions and ensure that international clinical standards were being met. Each laboratory was assessed

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annually to ensure that it followed Good Clinical Laboratory Practice and that any difficulties were addressed. On-site training was offered and experts were available round-the-clock by email or phone.

Other MDP bodies, again representing all partners, oversaw programme and financial performance. A high-level Trial Steering Committee, consisting of senior MDP investigators, community members and independent scientists and clinicians, was responsible for scientific decisions including trial modification, continuation or curtailment. The committee is advising the sponsor on interpretation of the findings and making recommendations concerning further research.

Additionally, two groups of eminent scientists have provided independent oversight:

- An International Scientific Advisory Group reviewed MDP 301's scientific strategy at least once a year, in part to ensure that it complemented other major initiatives in the microbicides field. Chair of the Group is Professor Anna Glasier OBE, until recently Director of Sexual and Reproductive Health at the University of Edinburgh and now Director of Family Planning and Well Woman Services as well as Lead Clinician for Sexual Health Services of the Lothian Primary Care NHS Trust, Edinburgh.
- An Independent Data Monitoring Committee. (See next question)

Each country where we work has also provided oversight through ethics and government regulatory committees. Plans and procedures were approved in advance by the ethics committees and any adverse developments were reported to them immediately.

What is the Independent Data Monitoring Committee?

MDP 301 has been overseen by an Independent Data Monitoring Committee (IDMC) whose members had no involvement in running the trial and no financial interest in its outcome. The Committee met routinely to review efficacy and safety data emerging from the trial, monitor the safety of participants and ensure that ethical considerations receive priority. Usually, such committees (which are also known as Data Safety Monitoring Boards) recommend that a trial should continue as planned. However they may recommend curtailing all or part of a trial if there is no more than a small chance of showing benefit, or if evidence of benefit is overwhelming, or, most importantly, if a product is found to be toxic.

Our IDMC 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

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organization affiliated with The Johns Hopkins University in Baltimore, Maryland USA, and former Head of the Microbicides Desk of the World Health Organisation.

Who participated in MDP 301 – and why did people enrol?

Because cultural factors can affect the way a product is used, MDP 301 tested PRO 2000 in a range of environments – from urban townships like Soweto to semi-urban and rural communities in various African countries, and a sugar plantation in Zambia. MDP generally focussed on women in stable relationships. One site focussed on couples, mainly those where one partner was HIV-positive and the other was not.

Women gave various reasons for joining the trial. Some wanted to qualify for the regular health checks, free condoms, counselling and hospital referrals provided by the trial. Some wanted to know their HIV status or valued the chance of added protection. Many had lost family and friends to HIV/AIDS and said they wanted to help find a solution.

What is “informed consent”?

Participants must satisfy staff that they understand the trial and its potential effects on them and they must provide formal agreement to take part. Our study teams used information sheets, visual aids and open-ended questions to ensure that each woman understood the risks and benefits of the study before she agreed to participate. Each time a woman visited the clinic, staff re-checked to be sure she still understood what was happening and agreed to it. Participants were entitled to withdraw their consent at any time.

How were communities involved?

Each trial centre employed liaison staff to ensure that local concerns were understood and addressed by trial teams, that community values and practises were respected, and that messages from the clinic were properly conveyed. Additionally, each centre had the benefit of an advisory board or group, consisting of local community leaders and stakeholders.

What was done for participants’ welfare?

The safety of our volunteers is paramount. We are proud that 90% of our volunteers reported using condoms as often as, or more than, they did before joining the trial. Participants received regular health check-ups, treatment for ordinary infections or ailments and referrals for specialist care as needed. Some women seemed to gain confidence through their participation in the trial and we found a higher proportion of supportive partners than anticipated.

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What happened to women who became pregnant during the trial?

Women who became pregnant during the trial were taken off gel but continued to be followed up, receiving the same health care as other participants. In the second half of 2006, following an amendment to the trial protocol, women were able to resume gel when they were no longer pregnant. The timing of resumption varied among centres.

Do microbicides prevent pregnancy?

To date, all microbicides are experimental, candidate products. PRO 2000 is unlikely to prevent pregnancy but other microbicide candidates may be different

Is PRO 2000 safe for pregnant women?

If MDP finds that 0.5% PRO 2000 vaginal microbicide gel is safe and effective in reducing the risk of HIV infection in women, further tests would be carried out to examine safety in pregnancy.

What happened to women who became HIV-positive during the trial?

These women were able to continue in the trial and so were seen frequently at the MDP clinic, where they received counselling to assist them to come to terms with the diagnosis. During follow-up, their general medical problems were dealt with either in the MDP clinic or through referral. If a woman required antiretroviral drugs at any time during her follow-up, then she was referred immediately for therapy. Other sexually transmitted infections were treated immediately at the MDP clinic, and contraception and condoms continued to be provided. Women who became HIV-infected during the study and who also become pregnant were referred to antenatal clinics for interventions to prevent mother-to-child transmission. When the women finished trial follow-up, they were referred for the best care available under local guidelines.

Why did you counsel women to use condoms whenever they had sex? Surely if they did this, you could not find out if microbicides worked.

We want to protect women against HIV. This is the whole purpose of our research. We urged women to use condoms because we know that condoms will protect them. But women who want to conceive cannot use condoms and our experience tells us that many women who would like their partners to use condoms cannot persuade them to do so every time, in other words, condoms will not have been used consistently by all participants, despite our best efforts. Therefore, if we had seen far fewer new infections in the 0.5% PRO 2000 group than in the placebo group, this would have meant that the microbicide was having an effect.

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How can you know if a microbicide works?

The rate at which new HIV infections occur in the group using the microbicide is compared with the rate in the group using placebo. Statistical tests allow us to tell if any difference detected between the two groups is due to chance. If chance can be confidently excluded, scientists conclude that the difference is likely to reflect a true effect of the microbicide. However, scientists, and more importantly, the authorities that approve new drugs, usually would want to see this in more than one trial. Two trials with a positive result would provide a more reliable answer.

What if women using PRO 2000 gel also use condoms more consistently than women in the placebo group?

All women in the trial are counselled to use condoms every time they have sex. They are not told whether they are using PRO 2000 or a placebo gel, and the gels look alike, so there is no obvious reason why one group would use condoms at a higher rate than the other.

What good will come of this?

Important discoveries can take a long time to materialise. It took almost half a century to discover the cause of polio and develop a vaccine. Sir Almroth Wright worked for over 40 years to discover a vaccine for typhoid fever after the bacterium had been identified. Even when a drug is found not to work, key lessons are learned which contribute to later successes.

MDP 301 has left a positive legacy. New laboratories have been equipped and accredited. Site staff have received experience and training in conducting clinical trials to the highest international standards. Many have been supported to acquire degrees and diplomas which will also advance their careers. Thousands of women have received counselling that will help them practise safe sex and lead healthier lives. They have a new understanding of their rights with respect to health care and know how to make the most of the care they receive. The trial has helped many women to discuss sex and HIV prevention options openly with their partners, and a surprising number report that their relationships have improved as a result.