

## **Microbicides Development Programme Congratulates Microbicide Trials Network on Completion of Trial HPTN 035**

The Microbicides Development Programme (MDP) congratulates the Microbicide Trials Network (MTN) on its February 9<sup>th</sup> announcement that 0.5% PRO 2000 vaginal gel has demonstrated signs of success in preventing HIV infection in a recently concluded Phase II/IIb clinical trial. The trial, involving 3099 women, compared each of two experimental vaginal microbicides, 0.5% PRO 2000 and BufferGel, with placebo and with no gel. The results, although not conclusive, are encouraging. HPTN 035 is the first human clinical study to find that a vaginal microbicide may prevent male-to-female sexual transmission of HIV infection. Both products were shown to be safe as tested. It was also a major achievement that 94% of participants in the MTN trial were motivated to complete the trial. We extend our thanks to all the women in the trial for their contribution to clinical research.

MDP's Phase III trial of PRO 2000, involving 9389 women and currently testing 0.5% PRO 2000 gel against placebo only, is due to complete follow-up in August and announce results toward the end of 2009. Together, clinical information from these two trials will give a more robust estimate of the true impact PRO 2000 could have on the transmission of HIV infection.

We are committed to a research programme to find a safe and effective microbicide for women and thank participants in the MDP trial for their ongoing support.

### **Notes to Editors**

1. The scale of the global epidemic of HIV remains staggering. An estimated 33 million people worldwide currently live with the virus, of whom 22.5 million live in sub-Saharan Africa. As of 2007, 13.7 million (61%) of the 22.5 million were female and the highest incidence of new infections was among women. Globally, there were an estimated 2.5 million new infections in 2007. HIV infection is still the leading cause of death in Sub-Saharan Africa, with 1.6 million deaths in 2007.
2. A vaginal microbicide is a product originally designed to prevent HIV in women. The intention is that a woman could use a microbicide to protect herself without making demands on her partner. All existing microbicides are still experimental. The potential microbicide involved in both the MDP and MTN trials is a vaginal gel called PRO 2000, being developed by Indevus Pharmaceuticals Inc. of Lexington, Massachusetts, USA.
3. The MDP trial (known as MDP301) aims to determine whether an 0.5% concentration of PRO 2000 gel can help protect women against HIV infection. The MTN trial (known as HPTN 035) tested 0.5% PRO 2000 gel against a placebo gel and against no gel. It also tested a second active gel, BufferGel, and compared this to placebo and to no gel. MDP 301 is testing PRO 2000 gel against placebo only. All women in both trials receive free condoms and are counselled to use them. One MDP site is testing the gel in 840 couples and all sites have carried out in-depth interviews with groups of male partners.

4. MDP301 has enrolled 9389 women. The HPTN 035 trial involved 3099 women. For the specific purpose of comparing 0.5% PRO 2000 gel with placebo, the MDP trial is approximately three times the size of HPTN 035. The vast majority of participants in MDP301 are followed up for 12 months but the site testing gel in couples is following participants for up to 24 months. Participants in HPTN 035 trial were followed up for 12-30 months, depending on when they entered the study.

5. In MDP301, behavioural research is integrated to a unique degree into the way women's use of gel is measured. This may help scientists to interpret the clinical outcome. For example, a microbicide can only work if women use it consistently, and self-reported use may differ from actual use.

6. MDP301 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. Its most recent review took place in December 2008 and resulted in a recommendation that MDP 301 should continue. 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.

7. MDP is an African-European partnership to develop vaginal microbicides for the prevention of HIV transmission. The partnership is coordinated jointly by Imperial College, London, and the Clinical Trials Unit of the UK Medical Research Council. Partner institutions in Africa are University Teaching Hospital, Lusaka, Zambia; Medical Research Council Uganda Virus Research Institute, Entebbe; African Medical and Research Foundation and National Institute for Medical Research, Mwanza, Tanzania; the Africa Centre for Health and Population Studies, KwaZulu Natal, South Africa; South African Medical Research Council, Durban; the Reproductive Health and HIV Research Unit, Department of Obstetrics and Gynaecology, University of Witwatersrand, Johannesburg, South Africa; and Contract Lab Services (CLS), South Africa. In Mozambique, there are two new MDP sites, at the rural Manhiça Health Research Centre and at Mavalane Hospital in the urban capital of Maputo. European partners include the London School of Hygiene and Tropical Medicine, St. George's Hospital, London, and the Universities of York, Southampton and Barcelona. The aim of the partnership is to identify candidate microbicides that perform well in laboratory assessments and take them into human clinical trials from Phase I to Phase III, and on to licensing, where appropriate. Another major objective of MDP is to develop the capacity of African researchers and research institutions.

8. MDP301 is funded by the UK Department for International Development ([www.dfid.gov.uk](http://www.dfid.gov.uk)) and the UK Medical Research Council ([www.mrc.ac.uk](http://www.mrc.ac.uk)). The trial is taking place at 13 clinics, located in Mtubatuba, Durban and Johannesburg, South Africa; Mwanza, Tanzania; Masaka, Uganda; Mazabuka, Zambia.

9. MDP has built a vigorous multicultural and multidisciplinary research network ready to undertake future work of comparable importance and complexity. Years of working collegially have built cohesiveness, efficiency and mutual trust among the scientists, clinical staff, data managers, and other professionals and support staff comprising this Afro-European and pan-African clinical trial network, as well as sound relationships with surrounding communities. MDP has also achieved significant improvements in African laboratory capacity and other research infrastructure, as well as upgrading and reinforcement of professional capacity at its African research sites.

10. Imperial College London - rated the world's fifth best university in the 2007 Times Higher Education Supplement University Rankings - is a science-based institution with a reputation

for excellence in teaching and research that attracts 12,000 students and 6,000 staff of the highest international quality. Innovative research at the College explores the interface between science, medicine, engineering and business, delivering practical solutions that improve quality of life and the environment - underpinned by a dynamic enterprise culture. See [www.imperial.ac.uk](http://www.imperial.ac.uk)

11. The Medical Research Council (MRC) supports the best scientific research to improve human health. Its work ranges from molecular level science to public health medicine and has led to pioneering discoveries in our understanding of the human body and the diseases which affect us.

12. The MRC Clinical Trials Unit was formed by the amalgamation of the MRC HIV Clinical Trials Centre and MRC Cancer Trials Office and supports trials in a wide range of specialties. While maintaining a portfolio of high-quality research in cancer and HIV trials, it also undertakes research in areas such as rheumatoid arthritis, respiratory disorders and infectious diseases.

**For more information about the HPTN 035 clinical study, visit:**

[http://www.hptn.org/research\\_studies/hptn035.asp](http://www.hptn.org/research_studies/hptn035.asp)

**For more information about the MDP 301 clinical study please call:**

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## FREQUENTLY ASKED QUESTIONS

### **What are the MDP 301 and HPTN 035 trials?**

Both trials aimed to find out if PRO 2000 gel could help protect women against HIV.

The HPTN 035 trial involved 3099 women and tested a low concentration (0.5%) of PRO 2000 gel against a placebo gel and against no gel. This trial also tested a second active gel, BufferGel, and compared this to placebo and to no gel. All women in the trial were also counselled to use condoms.

The MDP 301 trial has enrolled 9389 women and will complete follow-up in August 2009. It is testing the same low concentration of PRO 2000 gel, but against a placebo only, and all women in the trial are counselled to use condoms in addition to gel. Behavioural research is an integral part of this trial and may help scientists interpret the clinical outcome. For example, a microbicide can only work if women use it consistently. One MDP site is testing the gel in 840 couples and all sites have carried out in-depth interviews with groups of male partners.

### **Who sponsored these trials and where did they take place?**

The HPTN 035 trial was funded by the U.S. National Institutes of Health and took place at seven trial sites in Africa (South Africa, Malawi, Zimbabwe and Zambia) and a site in the United States. The MDP 301 trial, which is still ongoing, is funded by the UK Department for International Development and UK Medical Research Council. It is being carried out by an African-European partnership of 14 research institutions. Six of the African partners are running 13 clinics, located in South Africa, Tanzania, Uganda and Zambia. A seventh partner, in South Africa, runs the reference laboratory for the trial and an eighth partner, in Mozambique, is preparing for future microbicide trials.

For more details, please see the notes below.

### **What is the design of each trial?**

Participants in the HPTN 035 trial were randomly assigned to one of four study arms (0.5% PRO 2000, BufferGel, placebo, or no gel) and were followed up for 12-30 months, depending on when they entered the study.

Current participants in the MDP301 trial have been randomly assigned to 0.5% PRO 2000 or placebo gel. The vast majority are followed up for 12 months but the site testing gel in couples is following participants for up to 24 months.

For further details, please see the notes below.

**What was done to protect the women in these two trials?**

Protecting the women is our highest priority. Both trials were conducted according to the highest ethical standards. Local Ethics Committees gave permission for the trial to take place at each clinical site. The objectives and procedures of each trial were thoroughly explained to all participants in their local language before they agreed to take part, and were explained again during follow-up. All participants provided written, informed consent.

Women in both studies received regular, voluntary, HIV counselling and testing, HIV education, intensive risk-reduction counselling, free condoms, and condom counselling in order to lower their overall risk of HIV infection. They also received regular medical checks, and any problems found were dealt with promptly. This included prompt treatment of other sexually transmitted infections.

Both trials were regularly reviewed by a number of local, national, and international oversight committees. For each trial, this includes regular monitoring by a committee of independent senior scientists. These experts compare ongoing results in all arms of the trial. If the results indicate that a product is either unsafe or unlikely to be effective, they will recommend that the product be withdrawn from the trial.

**What happens to women who get HIV while participating in MDP301?**

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

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

The aim is to prevent as many new infections as possible and, currently, the majority of new HIV cases, especially among women, occur in sub-Saharan Africa. It is best to test a drug among people that 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 answer the scientific question more rapidly.

**Why are you counselling women to use condoms whenever they have sex? Surely, if they do this, you will not be able to find out if microbicides work.**

We want to protect women against HIV. This is the whole purpose of our research. We urge women to use condoms because we know that condoms will protect them. If our counselling helped all women to use condoms all the time, then we wouldn't need microbicides at all and would be happy with this achievement. Yet many women who would like their partners to use condoms cannot persuade them to do so every time, so if we see fewer new infections in the 0.5% PRO 2000 arm than in the placebo arm, this will mean that the microbicide is probably having an effect.

**What if women in the 0.5% PRO 2000 arm use condoms more consistently than women in the placebo arm?**

All women in both arms of 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. However, we will be able to analyse this after our trial completes follow-up in August 2009.

**How can scientists tell if a microbicide works?**

The rate at which new HIV infections occur in the group on the microbicide is compared with that in the group on 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 do the HPTN 035 results mean for the MDP trial?** The HPTN 035 trial is the first human clinical study to find that a vaginal microbicide may prevent male-to-female sexual transmission of HIV infection. This is an encouraging development for the entire field of HIV-prevention. MDP301 will complete follow-up in August 2009, as planned. If both trials show consistent results, and if the effect is large enough to be clinically useful, then the product has a chance of being licensed.

**Since the HPTN 035 trial has shown that 0.5% PRO 2000 gel may be effective, why do you have to continue with the MDP trial?**

The HPTN 035 trial suggests that 0.5% PRO 2000 might be effective – and this is certainly good news - but it has not given us definite proof. The result was not robust enough to lead to licensing for HIV prevention. A larger trial could provide the evidence required for this. For the purpose of comparing 0.5% PRO 2000 gel with placebo, MDP301 is approximately three times the size of HPTN 035, so our results will help to interpret and better understand the outcome of this trial.

Furthermore, behavioural research is a large part of MDP301 and is integrated to a unique degree into the way we measure gel use. MDP social scientists are investigating many important questions, including factors which influence women to use gel and condoms consistently (or not). Answers to these questions will help ensure that PRO 2000, if found effective, will eventually be made available in ways that encourage people to use it.

**Would it be possible to get a different result in the MDP trial and, if so, which result would be correct?**

This is entirely possible and we mustn't get our hopes up too high. Additional evidence is needed to confirm that this result was not just due to chance. If the MDP trial produces similar or more convincing results, then there is a possibility that 0.5% PRO 2000 could be licensed. We should also remember that a microbicide can only work if women use it, and usage patterns may differ between the two trials. It is especially important that women in the MDP trial remain motivated to complete the trial and use gel consistently. We are very grateful for their ongoing support and dedication.

**The scientists have announced that 0.5% PRO 2000 has achieved a promising reduction in HIV, yet the gel will not be available following the trial. Why not?**

Although any reduction is promising, this result could still be due to chance. It is not considered convincing enough or sufficiently robust for government agencies to license the gel. Most licensing authorities require more than one trial showing the same effect. It is particularly important that we complete MDP301 as this larger trial will provide a much more reliable estimate of the true impact, if any, that 0.5% PRO 2000 could have on the transmission of HIV infection.

**They're saying that the microbicide was effective. Yet some women who used it still got HIV. How do you explain this?**

There are many possible explanations. First of all, for any product to prevent HIV infection, it has to be used consistently. Some women may have been unable to use gel every time they had sex. Some other possibilities are that the microbicide is only partially effective or that it works better for some women than others. We will know more when we get results from the larger MDP trial at the end of this year.

It is important to remember that, even if effectiveness is confirmed, 0.5% PRO 2000 gel will not replace condoms as an HIV prevention option. At best, it would provide some protection to women who cannot use condoms, or offer added protection when used together with condoms.

**When will 0.5% PRO 2000 be available to the general public?**

The findings of the HPTN 035 trial have to be confirmed by another trial. The MDP trial will continue to gather data until end of August 2009 and will announce results toward the end of this year. If the results confirm those of the HPTN035 trial, the international and local regulatory authorities will review them and, if they accept the data from both trials, the product then has to be licensed in each country. This is a long, careful process and can take several years. For now, we have to wait and see if MDP301 shows that 0.5% PRO 2000 can reduce the risk of HIV infection.

## **Notes**

### **Trial design**

The Microbicides Development Programme (MDP) 301 trial set out to determine whether 0.5% or 2% concentrations of the experimental vaginal microbicide gel PRO 2000 could prevent HIV infection more effectively than a placebo gel. The 2% PRO 2000 intervention was stopped in February 2008, when an interim analysis found that the trial had no more than a small chance of showing a protective effect at this strength. The 0.5% arm is scheduled to complete follow-up in August of this year, with results to be announced in late 2009.

The HPTN 035 trial investigated whether 0.5% PRO 2000 or another microbicide called BufferGel could prevent HIV infection more effectively than a placebo or no gel.

3099 women participated in the HPTN 035 trial, whereas 9389 are enrolled in MDP 301. For the specific purpose of comparing 0.5% PRO 2000 gel with placebo, the MDP trial is approximately three times the size of HPTN 035.

Participants in HPTN 035 were followed up for 12-30 months. In MDP 301, the vast majority of participants were followed up for 12 months but one site followed participants for up to 24 months.

All participants in both trials received a standard HIV prevention package of free male condoms, risk reduction counselling, and treatment of sexually transmitted infections.

### **Sponsors and sites**

The HPTN 035 trial was sponsored by the National Institute of Allergy and Infectious Disease (NIAID) Division of AIDS of the US National Institutes of Health and took place at trial sites in Durban and Hlabisa, South Africa; Blantyre and Lilongwe, Malawi; Harare and Chitungwiza, Zimbabwe; Lusaka, Zambia; and Philadelphia, USA.

MDP301 is sponsored by the UK Medical Research Council. The overall programme is funded by the UK Department of International Development (DFID) and the UK Medical Research Council and is a partnership of 14 African and European research institutions. African partners are managing 15 research clinics in Mtubatuba, Durban and Johannesburg, South Africa; Mwanza, Tanzania; Masaka, Uganda; Mazabuka, Zambia; and Manhiça and Maputo, Mozambique.

For more information about the HPTN 035 clinical study, please visit:

[http://www.hptn.org/research\\_studies/hptn035.asp](http://www.hptn.org/research_studies/hptn035.asp)