

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

*An independent monitoring committee overseeing the trial of a vaginal gel aimed at reducing the spread of HIV has recommended the continuation of the trial but the closure of one arm.*

The Microbicides Development Programme (MDP) is an international partnership to develop vaginal microbicides for the prevention of HIV transmission. The MDP301 trial is studying the candidate microbicide PRO 2000/5. There are three arms to the MDP301 trial: women receive a standard prevention package plus one of three gels: 2% PRO 2000/5; 0.5% PRO 2000/5; or placebo gel.

The Independent Data Monitoring Committee (IDMC) for the Microbicides Development Programme (MDP) met on 8<sup>th</sup> February 2008 to examine the data on safety and efficacy collected to date on the MDP301 trial of the candidate microbicide PRO 2000/5.

The IDMC recommended that the 0.5% PRO 2000/5 and placebo gel arms should continue. However, as there is no more than a small chance of showing protection against HIV infection from 2% PRO 2000/5 compared to placebo gel, they recommended no further gel should be prescribed to women allocated to the 2% PRO 2000/5 arm of the trial.

The MDP Trial Steering Committee (TSC) met on 11<sup>th</sup> February 2008 and accepted the recommendations of the IDMC. They noted 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 recruitment to 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 in protecting women against HIV infection.

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 participants to the 0.5% and placebo 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.

The IDMC will continue to monitor the trial carefully until its planned completion in late 2009.

### **Notes to editors**

1. 61% of the 22.5 million HIV-infected people in sub-Saharan Africa are female. The highest incidence of new infections is among women. The reasons why HIV is spreading so rapidly among women are complex; they are rooted in the social, cultural and economic context of women's everyday lives and circumstances; and in situations in which women frequently do not have control over sexual relations. Women are also biologically more susceptible to HIV infection than men. Women's vulnerability to HIV infection is increased in conditions of poverty. Microbicides could contribute substantially to efforts to provide women with more choice in methods to protect themselves and to reduce rates of HIV infection.

2. The scale of the global epidemic of HIV remains staggering. An estimated 33 million people worldwide currently live with the virus. New infections continue and in 2007 alone there were an estimated 2.5 million new infections – i.e. over 6800 persons infected every day (UNAIDS, 2007). HIV infection is still the leading cause of death in Sub-Saharan Africa with 1.6 million deaths last year. In the absence of a viable vaccine there is a need to intensify efforts in other areas and vaginal microbicides are a promising bio-medical intervention for the prevention of HIV infection.

3. The Microbicides Development Programme (MDP) is a partnership to develop vaginal microbicides for the prevention of HIV transmission. MDP partners include 14 research institutions or clinical sites in Europe and Africa. The clinical sites are in South Africa, Tanzania, Uganda, Zambia and Mozambique. Principal Investigator details are listed at the end of this document. The MDP is coordinated jointly by Imperial College, London, and the Clinical Trials Unit of the UK Medical Research Council. The 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. The Programme is funded by the UK Department for International Development (DFID) and the Medical Research Council (MRC) and is currently running a large Phase III trial of a particular microbicide, PRO 2000/5, which is believed to block the entry of sexually transmitted disease pathogens into human cells.

4. Microbicides are substances, formulated as gels or creams, which are being developed to offer protection against HIV and other sexually transmitted infections (STIs) when applied to the vagina or rectum before intercourse (although the current PRO 2000/5 gel formulation is designed for intravaginal use only). The compounds being tested as microbicides work in a number of ways: by killing or otherwise immobilizing the virus; by interfering with the initial infection process (PRO 2000/5 would work in this way); or by preventing the infection from taking hold after it has entered the body. Ideally, an eventual microbicide would combine these mechanisms for extra effectiveness.

5. The various microbicides currently being tested differ from each other in terms of their active ingredients, formulation, and mechanisms of action. Hence, the results of any one particular microbicide cannot be extrapolated to other microbicides.

Furthermore, it is biologically plausible that a microbicide such as PRO 2000/5 may show no protective effect against HIV infection at a higher concentration (e.g. 2% PRO 2000/5), whilst there is still a possibility that the same product may demonstrate 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.

6. 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. 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. On 8th February 2008, they reviewed the data collected on 7,735 women available by 15th January by treatment group (high strength, low strength, placebo). None of the MDP investigators apart from the Trial Statistician has seen the data by treatment group, since this could jeopardise the integrity of the ongoing comparison of the 0.5% and placebo arms of the trial.

7. 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. Website: [www.imperial.ac.uk](http://www.imperial.ac.uk)

8. The Medical Research Council 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 all.  
[www.mrc.ac.uk](http://www.mrc.ac.uk)

9. 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 will also undertake research in areas such as rheumatoid arthritis, respiratory disorders, infectious diseases, geriatrics, complementary medicine, mental health and surgery.

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