# AIDS BRIEFS

## MICROBICIDES – WHY DO WE NEED THEM?

Microbicides are topical chemical agents used in the vagina to prevent infection by HIV and other sexually transmitted pathogens. Prototype microbicides are designed to be inserted before each act of intercourse. There are several proof-of-principle phase III trials of candidate microbicides currently in progress or about to start. A definitive answer to their efficacy and safety is expected by 2008. Why do we need to develop chemical barriers against HIV? In the absence of an effective vaccine against HIV, novel biochemical methods for preventing the transmission of HIV are necessary. Condoms are known to be effective, but these remain almost exclusively under the control of men. A woman-controlled method of preventing or reducing the risk of HIV transmission is needed. However, microbicides still need to prove effective in phase III trials, have to be non-toxic, well tolerated, odourless, colourless, easy to use and cheap to manufacture.

## FIRST-GENERATION MICROBICIDES – SURFACTANTS

The first vaginal microbicide to be studied was nonxynol-9 (N9) – with *in vitro* antiviral activity. However, it was associated with vaginal ulceration and it showed no clear reduction in the transmission of HIV. Recently, however, the company Biosyn has developed a new surfactant microbicide, SAVVY, thought to be far less toxic than N9 while still having antiviral activity. This is currently in phase III trials in sites in West Africa.

## SECOND-GENERATION MICROBICIDES – BLOCKING HIV BINDING

Agents that block the binding of HIV are less toxic to the vagina. Candidate agents include several high molecular weight anionically charged sulphated polymers such as PRO 2000, carageen and cellulose sulphate. These have potent anti-HIV activity *in vitro* against the 2 major classes of HVI-1 isolates using both the CCR5 and CXCR4 co-receptors. They have very low toxicity and their therapeutic index is above 10 000. All are, or shortly will be, in phase III trials in women at risk of HIV infection in Africa.

## MICROBICIDE COMPOUNDS

There is some evidence that maintaining a healthy vaginal milieu may protect against infection with HIV and other sexually transmitted infections. All current microbicides are buffered to pH 4.5 and all have been investigated for their ability to sustain vaginal lactobacilli *in vivo*. One candidate vaginal microbicide, 'BufferGel', has a mechanism of action specifically based on the maintenance of low vaginal pH. This is being assessed in parrallel with PRO 2000 in a phase IIb trial.

## THIRD-GENERATION MICROBICIDES – TOPICAL ANTIRETROVIRALS

Tenofovir, a nucleotide analogue reverse transcriptase inhibitor, has a long half-life and is a successful oral anti-HIV agent. A gel formulation has been developed for vaginal use. A multicentre phase II trial of this gel is planned for 2005. Non-nucleotide reverse transcriptase inhibitors (NNRTI) such as UC781 and TMC120 are being formulated and developed as vaginal gels, with the aim of entering phase III trials in 2006 or 2007.

There have been recent reports on the prevention of simian-human immunodeficiency virus transmission in the macaque vaginal challenge model by use of monoclonal antibodies to HIV-1 and by a topical small-molecule CCR5 inhibitor, PSC-RANTES. In both cases, the quantity of the agent needed to prevent transmission *in vivo* was far more than that required *in vitro*. These highly specific agents could possibly be used with second- or third-generation microbicides, but it is unlikely that monoclonal antibodies and peptides alone will be manufactured cheaply enough.

## PHASE III TRIALS OF VAGINAL MICROBICIDES

Clinical trials of microbicides present many problems. Trial populations must have an incidence of HIV of at least 2%. This high level of HIV transmission, however, means that there must be vigorous counselling, screening for and treatment of sexually transmitted infections and provision of condoms and public health education. Adherence is necessary and the microbicide must be used for every risky act of intercourse. Trials designed to test efficacy need to be as short as possible. Non-vaginal exposure to HIV, through anal intercourse or intravenous drug use, will further poten-

tially dilute the effect of the tested microbicide, so behavioural data will be needed for the results of these trials to be fully interpreted. The end result is that these trials need to be large and long, requiring multiple sites in high-incidence regions, and will be expensive. Large pharmaceutical companies are not interested in these agents and the cost of these trials will have to be borne by charities and the public. At the moment, most new agents are being produced in academic centres, which, although slow, is highly cost effective. A product development public-private partnership has been established, the International Partnership for Microbicides, which is establishing clinical trial sites and is developing TMC120. Other advocacy groups include the Global Campaign for Microbicides and the Alliance for Microbicides, which ensure that the pressure is maintained to continue the funding necessary to develop an effective microbicide.

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## SINGLE SUTURE

### KILLER ASPIRIN

A research study that modelled the impact of aspirin on a theoretical population of 20 000 men and women aged at least 70 using a new technique for combining information from many small trials and population surveys, found that a daily dose of aspirin in the over-70s may kill as many people through intestinal bleeding as it saves from heart disease. The results of the study show that between 165 and 528 fewer people would die of heart disease if they took low-dose aspirin, but that between 86 and 238 more would die from a major gastrointestinal bleed. The overall death rate from the 2 causes was not significantly different. The author of this study urged proper clinical trials of the use of aspirin in elderly people.

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