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Microbicides: stopping HIV at the gate

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For 4 days in April, 2006, 1300 scientists, funders, policymakers, and activists from all over the world attended the Microbicides 2006 Conference in Cape Town, South Africa, to discuss the latest research findings, exchange information, and consider future directions in developing microbicides for preventing the sexual transmission of HIV.[1] This conference was the largest such gathering ever, and the conference location in sub-Saharan Africa, which has seen 77% of the world's AIDS deaths and is home to some two-thirds of all people living with HIV,[2] vividly reminded participants of the misery and devastation wrought by this virus.

The global HIV/AIDS epidemic continues largely unchecked[2] and hopes of developing a preventive vaccine in the near future look increasingly remote. Condoms can provide a high level of protection against the sexual transmission of HIV if used correctly and consistently, but the truth is that many women lack the social or economic power to persuade their partners to use them. These facts have highlighted the importance of efforts to develop other approaches to prevention, especially female-controlled measures, including microbicides.

Microbicides are antimicrobial medications formulated for vaginal administration to prevent the transmission of

***Panel 1:* Examples of microbicides under development**

Inactivate HIV by destabilising or damaging viral structures

Savvy*=C31G (surfactant; disintegrates virus' lipid envelope)

Cyclodextrin (alters envelope structure)

BufferGel* and Acidform (acid-buffering agents)

Lactobacillus suppositories (bacteria secrete lactic acid and hydrogen peroxide)

Prevent HIV from docking properly with target cells (various classes of lymphocyte that bear on their surface the virus' primary receptor, CD4, and co-receptor, CCR5 or CXCR4)

Negatively charged polymers

Carraguard* (carrageenan product derived from seaweed)

PRO 2000* (naphthalene sulphonate polymer)

Ushercell* (cellulose sulphate)

CAP (cellulose acetate 1,2-benzenedicarboxylate)

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*Protective benefits currently being assessed in large-scale clinical trials.

VivaGel (negatively charged dendrimer)

Anti-HIV proteins

Cyanovirin-N (originally from cyanobacteria, now from recombinant organisms)

Monoclonal antibodies against components of docking mechanism

Antiretroviral drugs (prevent HIV from replicating inside target cells)

Tenofovir (nucleoside reverse-transcriptase inhibitor)

TMC-120, UC-781, MIV-150 (non-nucleoside reverse-transcriptase inhibitors)

Combination products with more than one mechanism of action (provide protection against broader range of pathogens and reduce risk of transmitting drug-resistant HIV strains)

PC-815 (Carraguard combined with MIV-150)

CAP combined with UC-781

Microbicides combined with cervical barriers

HIV. Ideally, they will also protect against other sexually transmitted infections, such as gonorrhoea, chlamydia, and genital herpes.[3] Although no microbicide has yet been proven to block the sexual transmission of HIV in humans, many promising candidates prevent infection in the laboratory and a dozen or so are in advanced stages of development. The protective effectiveness and long-term safety of five of these drugs are now being assessed in large-scale clinical trials in communities at high risk of HIV infection in Africa and other regions.[4] Many other candidate products are waiting in the wings at the preclinical stage. Microbicides have several different mechanisms of action against HIV (panel 1). Some are also spermicidal (eg, Savvy, BufferGel, Ushercell); others are not (eg, Carraguard, antiretroviral drugs). Combination products are also being investigated.[5-7]

Microbicides based on antiretrovirals originally developed as therapeutic drugs are currently being intensively investigated.[8,9] Because of their specific mechanism of action they offer the hope that a woman could conceive safely even if her partner is HIV positive. However, with these microbicides, questions arise about potential problems of drug resistance. As the availability of antiretroviral drugs for treating HIV-positive patients becomes greater in regions severely hit by the epidemic, will they remain effective once drug-resistant HIV strains begin to circulate in the community? Although the amounts of antiretroviral drug used in microbicides are low compared with the doses used for therapy, and resultant systemic drug levels are also low, could their frequent use by HIV-positive women result in the emergence of drug-resistant variants, which might then be transmitted to their partners and beyond? The situation will need to be carefully monitored once these products are on the market.

Most of the microbicides in late-stage development are formulated as vaginal gels, inserted with an applicator before each act of intercourse (coital dependency). However, some are also being tested in intravaginal rings, which could remain in place for several weeks while the active agent diffuses into the vaginal epithelial cells, in principle providing continuous protection.[10] Other ways of delivering microbicides are being developed, including suppositories which would not necessarily require the provision of an applicator. One of the more innovative approaches exploits commensal bacteria that naturally colonise the human vagina, genetically engineered to secrete specific anti-HIV proteins.[11,12]

Three important general conclusions emerged from the Cape Town conference. First, the need for safe, effective, affordable, and acceptable microbicides is more urgent than ever, especially

given the worsening epidemics in populous countries such as India and China. Second, impressive progress has been made since the previous such conference, in London in 2004. Third, the field still faces some major challenges, which are coming more into focus. Ideas about the design of phase III trials to assess microbicide effectiveness, and

Panel 2: **Major challenges in microbicide research and development**

- Need to devise reliable ways of selecting most promising candidates and formulations for clinical evaluation, on basis of more detailed knowledge of factors that govern mucosal transmission of HIV and of steps at which microbicides can intervene. Biomarkers predictive of safety and efficacy need to be identified and validated.
- Shortage of trial sites with suitable populations, necessary expertise, and infrastructure.
- Clinical trials to assess microbicide efficacy need to be of more efficient and cost-effective design, and provide participants with appropriate standard of care.
- Need to overcome twin problems of enhancing level of adherence to trial protocol and of obtaining reliable feedback about sexual behaviour, condom use, and product use.
- Regulatory requirements for microbicide registration require clarification.
- Total annual funding needed to support high-priority microbicide research and development activities estimated to be around $280 million, about twice current level of funding.
- Need for major drug companies to make substantial investments in microbicide development, large-scale manufacture, and commercialisation.

contingent regulatory and ethical issues, are becoming more sophisticated and complex.[13,14]

The question of providing trial participants with an appropriate standard of care is a moving target, differing from one location to another and evolving over time as perceptions and realities change as to what is feasible, such as the provision of expensive drugs. Dealing equitably with such difficulties requires a committed and trusting relation between researchers, trial participants, and the broader community. There are also challenges in preclinical development, product formulation, scale-up, manufacture, commercialisation, and access (panel 2). To start to address these challenges, an exercise undertaken during the past year, sponsored by many of the organisations responsible for funding microbicide research, has culminated in a document called *The Microbicide Development Strategy*, which identifies the main obstacles holding back progress in this field and recommends ways and means of overcoming them. This strategy will be released during the XVI International AIDS Conference in Toronto, and will provide a broad strategic framework intended to assist funders, researchers, and product developers in their shared task of accelerating the pace of the microbicide agenda.

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