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Newer approaches to HIV prevention

The publication of two randomised trials in today's *Lancet* signals a new era for HIV prevention. The studies, in Uganda and Kenya, show that male circumcision halves the risk of adult males contracting HIV through heterosexual intercourse.

This success is extremely welcome news. The results of these trials, along with the findings of a preliminary South African trial published in 2005, now provide a solid evidence-base to inform health policy. Large-scale implementation of male circumcision has the potential to substantially reduce HIV transmission, particularly in sub-Saharan Africa. But, as an accompanying Comment and Viewpoint highlight, this new intervention presents many opportunities but also raises many questions.

One such question is the effect of male circumcision on women. Initially, wide-scale implementation of male circumcision will lower HIV infection in men. But modelling studies suggest that over time women could benefit from an effect similar to the herd immunity seen with mass immunisation. Male circumcision might also directly protect against male-to-female transmission of HIV. A trial to test this hypothesis is under way in Uganda, with results expected in 2008.

In the meantime, new approaches for HIV prevention in women are urgently needed. According to UNAIDS, during the past 2 years, the number of women and girls infected with HIV has increased in every region of the world. Although condoms can provide a high level of protection (80–90%) against sexual transmission of HIV if used consistently and properly, many women are not in a position to persuade partners to use them. The development of new technologies that put HIV prevention in the hands of women is therefore crucial.

Microbicides—vaginally applied antimicrobial medications that can kill, block, or inactivate HIV—are one such intervention. According to a Review of microbicide drug candidates, published online by *The Lancet* on Feb 14, a large number of compounds—more than 60 at the start of 2006—are in the development pipeline. And, at the beginning of this year, five phase III trials testing different formulations were under way.

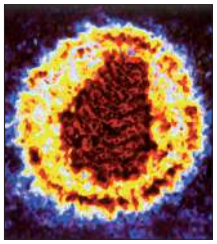
Sadly, however, the microbicide field was hit with bad news on Feb 1, when the International AIDS Society announced that two phase III trials of the candidate microbicide cellulose sulphate had been stopped because preliminary results suggested a potential increased risk for HIV in women who used the compound. At present, there is no explanation as to why cellulose sulphate was associated with a higher risk of HIV infection than placebo.

Although the halting of these trials is a disappointing setback for microbicide research, the investigators deserve praise for acting quickly as soon as an adverse effect became apparent. In the development of any new product, ruling out potential candidates is essential for progress. As for the remaining late-stage microbicide trials, if they prove successful, first-generation products could be available by 2009. If they fail, second-generation products could become available by 2012.

A much more distant hope for HIV prevention is the development of an effective vaccine that can offer long-term protection against the wide spectrum of HIV variants that exist. Despite the fact that there are now more than 30 vaccine candidates in clinical trials, and three of these are in advance stage testing (phase IIb and phase III), many obstacles still lie in the way of the development of a truly effective HIV preventive vaccine.

The genetic diversity of HIV presents an enormous challenge for researchers. And, because the virus has the ability to evade neutralising antibodies produced by natural immunity, the standard vaccine strategy of mimicking natural infection to induce antibodies has so far proved impossible. Strengthening cell-mediated immunity offers another possible route to success. About 90% of candidate HIV vaccines in development use this approach. These products will not prevent infection. But it is hoped that they will lower viral load and therefore progression to AIDS and secondary transmissions. Whether even this will be possible remains to be seen. Some observers believe that a vaccine to prevent HIV will never be achieved.

Ultimately, even if an HIV preventive vaccine or microbicide were to be developed, they are unlikely to be 100% effective. This prospect, together with the knowledge that male circumcision offers only partial protection against HIV infection, means that the future of HIV prevention will involve combining new methods with existing approaches, such as condom use. The emerging truth is that no single approach alone will be able to stem the spread of HIV. ■ *The Lancet*



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