

AIDS briefs

Reduced dose of d4T still effective

KEITH ALCORN

The use of a reduced dose of d4T (stavudine), as recommended by the World Health Organization (WHO), did not reduce the likelihood of viral load suppression after 6 months in a large cohort of South African patients, researchers from the Aurum Institute of Health Research report in the 24 August edition of *AIDS*.

The use of d4T in first-line treatment has been phased out in the developed world owing to toxicity, but in developing countries fixed-dose combinations containing d4T are still widely used owing to the drug's low cost compared with tenofovir or abacavir. In South Africa d4T remains a staple component of first-line treatment in the public health system, despite widespread calls for its use to be phased out.

The key toxicities associated with d4T are lipotrophy (fat loss), hyperlactataemia and lactic acidosis, and peripheral neuropathy.

The drug was originally licensed at a dose of 40 mg twice daily in adults weighing more than 60 kg.

In 2007 the WHO recommended that developing country treatment programmes should use a 30 mg dose of d4T if it was not possible to phase out use of the drug. Their recommendation was based on a number of small studies showing no negative effect of a lower dose in adults weighing more than 60 kg.

Adoption of the 30 mg dose has been slow in some national programmes, and data are still lacking from an African population on the virological effects of initiating therapy with a lower dose of d4T.

Researchers at the Aurum Institute in Johannesburg analysed data from 618 patients enrolled in community-based HIV care programmes in South Africa who initiated treatment containing d4T between January 2006 and January 2008. All patients had been followed up for at least 6 months after starting treatment, and weighed at least 60 kg at baseline.

Of the eligible patients, 110 received a 30 mg dose and 508 received a 40 mg dose. Those receiving a 30 mg dose were

slightly more likely to receive nevirapine than efavirenz and to have WHO stage 4 HIV disease, and had significantly lower baseline CD4 counts (91 v. 115, $p=0.0001$). These differences were not a result of individualisation of treatment, say the investigators, but owing to a change in guidelines during the period under study.

There was no significant difference after 6 months of treatment in the proportion of patients who had a viral load below 400 copies/ml or 50 copies/ml (79% v. 81% and 60% v. 58%, respectively). Multivariate analysis that adjusted for NNRTI agent, baseline viral load and weight showed no effect of dose on viral suppression.

The investigators say their findings provide additional evidence to support the WHO recommendation, but note that evaluation of long-term side-effects according to dose is essential.

Hoffmann CJ, *et al.* HIV suppression with stavudine 30 mg versus 40 mg in adults over 60 kg on antiretroviral therapy in South Africa. *AIDS* 2009; 23 (13): 1784-1786.

Article courtesy of www.aidsmap.com

Circumcision significant in HIV prevention

ROGER PEBODY

In the high HIV-prevalence countries of southern Africa, between 5 and 15 men will need to be circumcised to prevent 1 HIV infection in the 10 following years at a cost of \$150 - \$900 per infection prevented.

These are the conclusions of an expert review of mathematical models of the impact of male circumcision, organised by UNAIDS, WHO and the South African Centre for Epidemiological Analysis, and published in the open access journal *PLoS Medicine*.

The group concluded that even if circumcised men either reduced their use of condoms or resumed sex too soon after the operation, circumcision would remain beneficial on a population level. They also concluded that women will benefit indirectly from circumcision.

Although there is compelling evidence from randomised controlled trials that male circumcision can reduce the risk of men acquiring HIV through heterosexual sex, the longer-term population-level

impact of introducing or expanding male circumcision services remains uncertain. Questions have remained about the cost-effectiveness of male circumcision as an HIV prevention measure in the short, medium, and long term.

A number of different mathematical models have been developed to estimate the likely impact (and several have been previously described on www.aidsmap.com). However, the models have used different baseline assumptions and input variables, and so have sometimes produced slightly different results.

In order to come to a consensus about a number of key questions related to the impact of male circumcision, an expert group was convened to review the findings from 6 previous modelling studies.

Most of the models were based on assumptions from settings where at least 80% of men are not currently circumcised, where HIV is predominantly spread through heterosexual transmission, and where HIV prevalence is greater than 15% of the general population. Prevalence is this high in southern African countries such as Zimbabwe, Zambia, Botswana, Namibia and South Africa, but not elsewhere on the continent.

The published paper does not contain detailed numerical projections of the impact of circumcision in various circumstances, and concentrates on the situation in the highest-prevalence countries. The group used the modelling studies to come to a broad consensus on the answers to the key questions.

What is the expected impact on HIV incidence?

The models predict that, over 10 years, 1 new HIV infection would be averted for every 5 - 15 men circumcised. In some circumstances, if almost all men are circumcised, HIV incidence could be reduced by around 30 - 50% in 10 years.

In countries with a somewhat lower HIV incidence and prevalence, circumcision would have less impact. The group agreed that in such countries, circumcision programmes that focused on specific subpopulations could have a substantial impact. Such groups could be chosen on the basis of their low rates of circumcision or their higher HIV risk (men with HIV-positive partners; men with sexually transmitted infections; soldiers; truck drivers; migrant workers; etc.).

What is the impact on women?

Circumcision does not directly benefit women, and if men resume sex too soon after being circumcised, women are actually at increased risk of HIV infection.

However, the group concluded that women would benefit indirectly because their likelihood of meeting an HIV-positive male partner would decline. Moreover, reductions in sexually transmitted infections in both men and women would reduce women's risk of acquiring HIV.

What is the impact of circumcising HIV-positive men?

Circumcision of an HIV-positive man does not reduce his risk of transmitting the virus. In fact, if a man with HIV resumes sex too soon after circumcision, incomplete healing could lead to an increased risk of HIV transmission. Two models addressed this issue, and concluded that this is unlikely to have an impact on a population level because the post-healing time is relatively short.

Moreover, the group noted that systematic exclusion of men with HIV from circumcision might lead to stigma for all uncircumcised men. One model indicated that targeting circumcision to men with the highest risk of HIV exposure will provide the greatest overall benefit, even though this will also recruit more men with HIV infection.

What is the effect of risk compensation?

If men believe that circumcision protects them fully against infection, there is the possibility of an increase in sexual risk-taking. Three models suggested risk compensation by circumcised men and their partners would only have a 'small effect' at the population level, unless it was to the extent of complete abandonment of condoms.

However, if increases in risk-taking took place across the entire adult population, this would substantially reduce the benefit of circumcision. The group recommend intensive communication campaigns to prevent this occurring.

Do the effects vary by age group of men circumcised?

The models showed that circumcising men who have not started sexual activity leads to the greatest population-level benefit in the long term, but circumcising 25 - 34-year-olds has the greatest benefit in the first 20 years. Circumcising 50-year-old men has little effect on HIV incidence.

The group did not find that circumcising newborn babies would be cost-effective. Although circumcision at this stage is safer and cheaper, the impact on HIV would not be seen for over 20 years.

How do the effects vary with speed of service scale-up?

The group concluded that rapid initial scale-up leads to a greater impact and is more cost-effective, with fewer circumcisions required to avert one infection, at a lower cost.

What are the discounted savings?

The models estimated that each infection that is prevented because of circumcision costs between \$150 and \$900, calculated over a 10-year time period. When calculated over 20 years, the cost per prevented infection is \$100 - \$400. Costs will be higher in lower-prevalence countries.

These costs are based on \$30 - \$60 per adult circumcision, and a life-time treatment cost of \$7 000 per HIV infection (first-line therapy only).

Implementation

Findings from the modelling studies have been used to refine and validate a pragmatic, decision makers' programme planning tool that can model what the scale-up of male circumcision may achieve and cost in specific settings.

UNAIDS/WHO/SACEMA Expert Group. Male circumcision for HIV prevention in high HIV prevalence settings: What can mathematical modelling contribute to informed decision making? *PLoS Med* 6(9): e1000109. doi:10.1371/journal.pmed.1000109

Article courtesy of www.aidsmap.com

BRIDGET FARHAM

*Single suture****The ethics of living and dying***

In the Netherlands, doctors must be convinced of unbearable and hopeless suffering before granting a request for euthanasia. But when non-physical aspects of suffering are central to the issue, GPs, consultants, and euthanasia review committees seem to differ in their judgement. Presented with such a case scenario, GPs were less likely to deem the patient's suffering unbearable than were consultants and committee members. The suffering of patients with dementia and those who were 'tired of living' were least often considered to be unbearable by all three groups.

Rietjens JAC. *J Med Ethics* 2009; 35: 502-507.