

Male circumcision to cut HIV risk in the general population

In today's *Lancet*, results from two randomised trials show considerable benefit of male circumcision in reducing HIV incidence in men,^{1,2} confirming findings from an earlier trial in South Africa.³ The recent focus on antiretroviral treatment—although necessary and appropriate—has made primary prevention a secondary issue. Renewed interest in HIV prevention is welcome.

The South African trial was done in a periurban setting near Johannesburg,³ in 3274 men aged 18–24 years randomised to immediate (n=1617) or later (n=1657) circumcision. The trial was stopped after a planned interim analysis showed a significant 60% relative reduction in HIV risk associated with circumcision. The participants were from the general population and loss to follow-up was low, supporting the generalisability of the findings. However, concern was expressed about the randomisation procedures, the slight imbalance in baseline characteristics between groups, and potential selection bias. WHO and other UN agencies issued a supportive statement,⁴ but urged restraint while awaiting the results of two ongoing trials, presented today.

Robert Bailey and colleagues' trial¹ in Kisumu, Kenya, was also done in men aged 18–24 years, randomly assigned to circumcision (n=1391) or delayed circumcision (n=1393).¹ The trial was stopped after an unscheduled interim analysis in December, 2006, when evidence emerged of a significant benefit from circumcision. The HIV incidence rate was high, at 1.1 per 100 person-years in the circumcised men and 2.1 per 100 person-years in the control group (or 2.1% and 4.2%, respectively, over 2 years). There was an estimated 53% (unadjusted modified intention-to-treat analysis) to 60% (as-treated analysis) reduction in relative risk of HIV infection associated with male circumcision.

Ronald Gray and co-workers' study² in Rakai, Uganda, included 4996 men aged 15–49 years; 2474 were randomised to immediate and 2522 to delayed circumcision. As with the trial in Kenya, this trial was stopped early after an interim analysis showed significant efficacy. HIV incidence was 0.66 per 100 person-years in the circumcision group and 1.33 per 100 person-years in the control

group.² The estimated reduction in the relative risk of infection with HIV was 51% (unadjusted modified intention-to-treat analysis) to 55% (as-treated analysis). Both trials were methodologically and analytically sound.

Thus three randomised trials now provide firm evidence that the risk of acquiring HIV is halved by male circumcision. Applying the circumcision efficacy² to the age-specific HIV incidence rates from a large population-based longitudinal HIV survey⁵ in rural KwaZulu-Natal, South Africa, we find that circumcision would prevent an estimated 35 000 new HIV infections in 2007 alone in the 2.5 million mostly uncircumcised men in the province (figure 1).⁶

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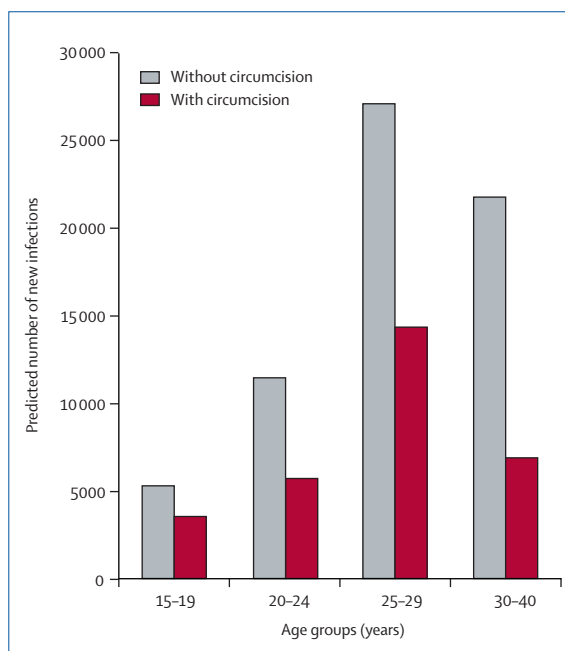


Figure 1: Predicted numbers of new HIV infections in KwaZulu-Natal, 2007
Effect of circumcision by age from reference 2, age-specific incidence from unpublished data, HIV prevalence updated from reference 5, and the KwaZulu-Natal mid-year population of males from reference 6.

However, male circumcision does not provide 100% protection, and condoms remain an important part of HIV prevention. With the acknowledgment that consistent condom use is difficult and rare, the finding of considerable benefit of circumcision with inconsistent condom use is noteworthy.² Will circumcision reduce condom use and increase risk taking? Although in the trials presented today there

was no evidence of increased risky sexual behaviour associated with circumcision, such findings need cautious interpretation, because the declining incidence in the control group in Rakai—which, although not statistically significant, reduces the difference between the groups—possibly suggests an effect of counselling and education in this setting.²

Acceptance of the clinical evidence that male circumcision is effective in preventing transmission of HIV does not automatically imply that governments and international organisations should strive to start circumcision programmes. Before male circumcision can become a health policy, countries need to develop capacity to educate and counsel people about the operation. The challenge will be to learn how to convey the public-health message that, although circumcision reduces the risk of HIV, it is nevertheless necessary to always use condoms because circumcised individuals can still become infected. Also needed are studies to investigate whether male circumcision will be accepted, and whether traditional circumcision rites could be integrated into a general policy. Evidence seems to indicate that the acceptability of circumcision in Africa is high;^{7,8} 80% of eligible control participants in the Ugandan trial had agreed to be circumcised by the time the study was closed.² However, acceptability could vary greatly across African communities,^{7,8} and could be different in other populations with a high burden of HIV—eg, in southeast Asia. In South Africa, dozens of boys and young men are injured or die every year after traditional circumcisions.⁹ Can traditional practices be adapted to maintain their cultural meaning while ensuring the safety of the circumcised, or can clinical circumcision take on the cultural function (figure 2)?

Operational studies are needed to compare different technologies and health-systems approaches to scale up male circumcision and establish safety and cost-effectiveness. Although safe adult male circumcisions can be delivered in resource-poor settings, health workers that can do circumcision without much further training are likely to be scarce.¹⁰ Circumcisions should be done by individuals with primary-care surgical skills in facilities that can guarantee the sterility of the operation and appropriate wound dressing to ensure low rates of adverse events similar to those seen in the trials.^{1-3,10}



Figure 2: Dogon boys, in Mali, in circumcision dress

Still Pictures

The printed journal includes an image merely for illustration

The ethics of mass circumcisions to reduce HIV transmission need to be addressed. Is it ethical to circumcise everybody even if many will not benefit from the intervention—eg, people who do not engage in risky sexual behaviour or are HIV positive? Whether circumcised men who are infected with HIV are also less likely to transmit the infection to their uninfected partners is not known; a trial studying the male-to-female preventive effect of circumcision is in progress. Is it ethical to circumcise infants and young children who cannot consent to the procedure? A recent law in South Africa banning circumcision under the age of 16 years is an example of an effort to protect children from unsafe circumcision.¹¹

We now have proof of a permanent intervention that can reduce the risk of HIV infection in men, which is positive news about prevention after past and current disappointments.^{12,13} The excitement that the results of these trials will surely generate should not cause us to forgo due diligence in investigating whether and how the clinical evidence can be translated into routine practice. Otherwise, a historic opportunity to save lives could be squandered.

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We declare that we have no conflict of interest.

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Thrombosis: the last frontier of coronary stenting?

In 1991, Serruys and colleagues¹ reported a 24% incidence of thrombotic stent occlusion 6 months after implantation into human coronary arteries. At the time, many cardiologists thought that bare-metal stents would soon disappear from clinical use. However, 2–3 years later, improved antiplatelet regimens, better stents, and better implantation techniques came into use. The incidence of stent thrombosis dropped to about 1.2% and, despite the rare but poorly quantified occurrence of late stent thrombosis (figure), overall the problem was thought to be solved.

15 years later, an intense debate has resurfaced, which questions whether current drug-eluting stents (with their potent antirestenotic effect and potential for delayed local vascular healing) are associated with an excess of thrombotic problems. In today's *Lancet*, Joost Daemen and colleagues² report the risk of early and late stent thrombosis after implantation of coronary drug-eluting stents in clinical practice. The researchers followed up a cohort of 8146 patients, who were treated in two large academic hospitals (in Rotterdam, the Netherlands, and Bern, Switzerland), for a mean 1.7 years. The incidence of early stent thrombosis (ie, occurring \leq 30 days after implantation) was 1.1%, as recorded by angiography.

More importantly, the incidence of late stent thrombosis (ie, $>$ 30 days after implantation) was a steady 0.6% of patients a year.

Daemen and colleagues' decision to focus on angiographically proven events can only have underestimated the true incidence of stent thrombosis, and

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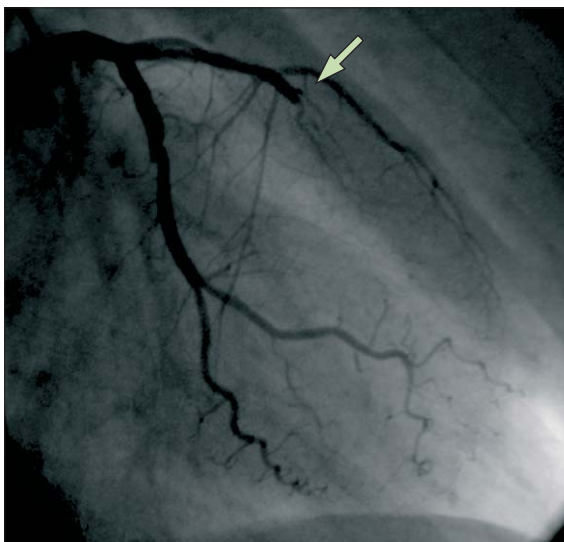


Figure: Stent thrombosis (arrow) of left anterior descending coronary artery 3 years after implantation of bare-metal device