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Response to Ronald Gray *et al.*, Male circumcision and HIV acquisition and transmission: cohort studies in Rakai, Uganda (*AIDS* 2000, 14:2371–2381).

[CORRESPONDENCE]

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The renewed interest in the potential role of male circumcision for HIV prevention in regions severely affected by heterosexual HIV transmission [1–14] was further stimulated by recent findings from Uganda. The Rakai Project researchers, who had previously reported that none out of 50 HIV-negative circumcised men in serodiscordant relationships seroconverted after nearly 2 years of exposure (versus 40 seroconversions among 137 uncircumcised men) [15], now conclude that the protective effect of circumcision may be lower or negligible among certain sub-populations such as non-Muslims, adolescents, and never-married men. We are concerned that this conclusion is based on analysis of small sub-groups containing insufficient numbers to be informative, and should not be used to negate the more than 35 studies from 10 other countries, including six previous cohort investigations [1–4,8,9,12,14], which found a protective effect of circumcision among mainly non-Muslim men.

Gray *et al.* found overall a statistically significant protective effect of circumcision on HIV incidence in a population of rural Ugandan men [adjusted rate ratio (RR) 0.53, 95% confidence interval (CI) 0.33–0.87].

Circumcision status was, however, highly associated with religion in this population (99% of Muslims were circumcised compared with 3.7% of non-Muslims), and we agree with the authors that other characteristics associated with Muslim religion (i.e. post-coital cleansing, abstinence from alcohol, polygamous marriage) may influence the risk of HIV. Yet their conclusion that the latest Rakai findings 'suggest that the protective effect of circumcision may be lower or negligible among ... non-Muslims' has several problems: (i) The observed difference in incidence between Muslim and non-Muslim circumcised men was, in fact, not significant (RR 0.63, 95% CI 0.21–2.07), and could have occurred by chance. (ii) Whereas virtually all Muslims were circumcised for religious/cultural reasons, 75% of non-Muslims who were circumcised post-pubertally reported that the procedure was performed for health reasons, typically involving sexually transmitted diseases (STD) or other genital/foreskin infections. This fundamental difference in the reasons for undergoing circumcision clearly confounds the interpretation of data on men circumcised post-pubertally, because such infections increase the risk of HIV acquisition, and are also more frequent among higher-risk individuals. If analysis is restricted to men who were circumcised pre-pubertally, there would be only two incident HIV cases among circumcised non-Muslims, resulting in an RR of 0.71 (95% CI 0.18–2.85) compared with uncircumcised men, but with wide confidence intervals. (iii) Among the HIV-discordant couples analysed in the study, there was also a very strong and significant protective effect of circumcision on the risk of HIV acquisition among the 14 circumcised *non-Muslim* men – regardless of their partners' viral load levels (RR 0, 95% CI 0–0.88). (iv) The confounding between religion and circumcision postulated in Rakai has not been observed in other studies of circumcision and HIV infection. In most other regions where a strong association between the lack of circumcision and HIV risk has been identified, Muslims account for only a minority of circumcised men. For example, contrary to the suggestion of Gray *et al.* that circumcision in Kenya is 'only practised in selected ethnic groups' that may have certain cultural practices that differentially affect the risk of HIV, in fact it is performed by all major ethnic groups except the Luo, who have experienced the country's most severe AIDS epidemic [2,3,6,9,11]. A recent study [3,6] has shown that even among the Luo, circumcision is associated with a strongly significant reduction in the risk of HIV (odds ratio 0.26, 95% CI 0.12–0.56). Fewer than 1% of men in this population were Muslim. In a Kenyan prospective study [12], which found that uncircumcised truck drivers were four times more likely to become HIV infected, just 24% of circumcised men were Muslims, and in a Tanzanian study [16], in which 18% of circumcised men were Muslims, a significant association between the lack of circumcision and HIV infection remained after results were re-analysed excluding Muslims.

Furthermore, there is mounting biological evidence for the protective effect of male circumcision on the risk of HIV. Researchers have found that the highly vascularized inner foreskin tissue contains a much greater density of Langerhans cells than vaginal, rectal, or cervical mucosa, as well as large numbers of CD4 T cells, macrophages, and other HIV immune system targets [7-9,17,18]. A recent in-vitro investigation [9] found the uptake of HIV virus in the inner foreskin mucosa to be many times more efficient than in a control sample of cervical tissue. In addition, a lack of circumcision may increase HIV transmission indirectly through increasing the risk of ulcerative sexually transmitted infections such as chancroid and syphilis [2,4,8,9,14,19], which further exacerbate the risk of HIV infection.

Gray *et al.* conclude by emphasizing the need for randomized controlled trials, and the potential difficulties associated with these. We agree with the authors and others [1,4,5,8,9] that clinical trials would be useful for better establishing the causal relationship between circumcision and HIV infection, but are less pessimistic regarding their feasibility. The primary biological mechanism for the protective effect of male circumcision is now presumed to be the removal of Langerhans and other HIV target cells, and there is no other persuasive biological or epidemiological evidence that circumcision will be more effective among men circumcised pre-pubertally [1,8]. There is thus no reason why clinical trials could not be conducted among consenting men in the general population in their late teens or early-to-mid 20s, which is usually before many African men are infected by HIV (unlike the case in young women) [3,6], thereby avoiding the long follow-up and possible ethical problems involving research on minors raised by Gray *et al.*

It is critical to assess carefully a range of issues including sexual behaviour change, the age of circumcision, complication rates, community support, and cost-effectiveness before and during such studies. Feasibility research and training programmes for introducing safe male circumcision services have been carried out in western Kenya [8,9,11], and preliminary acceptability studies have begun in South Africa [20,21], Botswana [21] (R. Shapiro, Harvard AIDS Institute, unpublished data), Uganda (R. Gray, personal communication), and Zimbabwe (D. Halperin *et al.*, unpublished data). Although most men in these surveys report that they would elect the procedure if it were safely and affordably available, few believe that circumcision can actually prevent AIDS. (The primary reasons for wanting circumcision are related to hygiene and infection/STD prevention, and some also say, e.g. to make condom use easier [22].) This suggests the possibility that if the practice becomes more common in such regions, widespread behavioural 'disinhibition' is unlikely. The first clinical trial of male circumcision, in Kisumu, Kenya, has been approved by ethical review boards and began enrolling participants, aged 18-24 years, in February 2002 [8].

We feel strongly, however, that the improvement and evaluation of male circumcision services must not wait until we know, several years and perhaps millions of new infections hence [22], the results from this or other intervention trials. Growing numbers of young men in many of the eastern and southern African countries most severely affected by HIV/AIDS (including some of the most economically developed nations in the region [23]) are seeking access to safer circumcision services [2,4,5,8-11,19-21,23,24]. The responsible dissemination of information on the risks and benefits of male circumcision and the development of affordable services for safe, voluntary circumcision should be integrated, on a pilot basis in appropriate locales, with existing HIV/STD and reproductive health programmes. Such efforts must commence now, lest the opportunity for a potentially important prevention measure be further delayed.

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