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Circumcision and HIV Prevention Among Men Who Have Sex With Men

No Final Word

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IN THE LATE 1980S, AN ECOLOGICAL ASSOCIATION BETWEEN high rates of male circumcision and low human immunodeficiency virus (HIV) prevalence in Africa was noted from epidemiologic, geographic, and ethnographic data.¹ A meta-analysis of epidemiological studies published prior to 2000 suggested a statistically significant protective association between circumcision and HIV infection among African heterosexual men.² A causal relationship between HIV risk reduction and male circumcision seemed likely; there was biological plausibility and consistency between studies. The studies, however, did not confirm that circumcision predated HIV risk reduction or that confounding factors might not explain the association.

One complicating factor in African studies was the Islamic practice of circumcision in the context of polygamy and lower sexual risk, as well as norms against the consumption of alcohol.³ Circumcised Muslim men in Africa may have had multiple partners, but they were also less likely to have sex outside marriage (eg, with commercial sex workers or within extramarital affairs).³ Thus, adult male circumcision might appear to protect individuals from HIV, but the association could be confounded by sexually conservative social and religious norms, lower rates of sexually transmitted infections, and limited sexual networks. An ecological study in 118 developing countries suggested after controlling for the influence of religion, circumcision prevalence was negatively associated with HIV prevalence.⁴ However, a spurious ecological association could not be excluded.

To determine definitively whether male circumcision was a tool for HIV prevention in sub-Saharan Africa, investigators conducted clinical trials that resolved the issue of potential confounding among heterosexual men.⁵⁻⁷ Adult male circumcision reduced HIV acquisition among HIV-

seronegative heterosexual men in South Africa, Kenya, and Uganda with effect sizes that were remarkably consistent and similar to those predicted by the earlier observational studies.^{2,5-7} The biological plausibility of HIV protection resulting from male circumcision has been supported further by immunohistological and histopathological studies indicating the susceptibility of the inner foreskin for virus-target cell contact.^{8,9} Hence, a plausible risk factor (noncircumcised status) was suggested strongly by many epidemiological studies in heterosexual men, and circumcision was determined to protect against HIV in high-quality, well-powered clinical trials in 3 different nations of Africa. Based on the biological, histopathological, epidemiologic, and clinical trials evidence, global health leaders now promote circumcision for reducing HIV risk in heterosexual men.^{10,11}

In this issue of *JAMA*, Millett and colleagues¹² report the results of a meta-analysis evaluating the evidence for male circumcision in reducing risks of HIV and other sexually transmitted infections (STIs) in a group of men who were not well represented in the 3 African clinical trials of heterosexual men, that is, men who have sex with men (MSM). There are at least 4 reasons to assess whether MSM will benefit from circumcision as did at-risk heterosexual men. First, the biological plausibility for HIV protection is diminished by the fact that MSM may practice receptive anal sex, diluting the potential effect of circumcision.¹³ Second, evidence of an HIV protective effect is less consistent in studies of MSM (mostly from the western hemisphere and Europe) than in African studies of heterosexual men.^{2,12} Third, the aggregate HIV protective effect size determined in the study by Millett et al¹² was only an odds risk of 0.86 (95% confidence interval, 0.65-1.13), much lower than protective estimates noted in studies of heterosexual men.^{2,5-7} Fourth, high circumcision rates in North America have not prevented MSM seroprevalence rates of HIV from exceed-

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See also p 1674.

ing rates found among heterosexual men in heavily affected areas of sub-Saharan Africa.

Investigators, peer review groups, and science policy makers will be faced with 3 important questions emerging from the results of this meta-analysis. First, is further research warranted to evaluate the effect of circumcision on HIV incidence in MSM? Most scientists and policy makers will argue a vigorous yes, because MSM continue to be disproportionately overrepresented in new HIV cases, particularly in Asia, Europe, Australia, and the Americas. There is a global need to know whether male circumcision should be considered a tool in the fight against HIV transmission among MSM.

Second, is a randomized clinical trial feasible? Peruvian-Ecuadorian investigators demonstrated strong support for a circumcision trial among MSM in their nations.¹³ Circumcision rates were less than 10% and follow-up rates in Peruvian cohort studies and clinical trials have been high.¹³ In contrast, circumcision rates among MSM in North America are greater than 70% to 80%, making the logistics and costs of a clinical trial much more involved with the need for extensive eligibility screening.^{14,15} Peruvian investigators have documented that even with increased condom use and declining rates of STIs, estimates of HIV seroincidence are likely high enough to support a circumcision trial among MSM in Peru, with HIV conversion as a primary end point.¹⁶

Third, should a randomized, controlled clinical trial of efficacy be conducted with HIV end points? Trial advocates will argue that observational studies will not address the question adequately. Trial skeptics will cite the uninspiring putative 15% protective effect suggested in the meta-analysis by Millett et al¹² (a finding that may have been due to chance based on the nonsignificant *P* value). However, several of the observational studies included in this meta-analysis had methodological limitations that would tend to minimize the strength of an association. For instance, in some studies circumcision status and HIV infection were based on self-report,^{15,17-24} there was low power for stratified analyses in heterogeneous studies that investigated insertive-sex predominance subgroups,^{15,24,25} the temporal relationship of circumcision and HIV infection could not be established in cross-sectional studies,^{15,17,18,21-23,25,26} and substantial effect modifications were likely to have reduced the magnitude of any protective association.^{15,24,25}

Future observational studies without the methodological limitations of earlier descriptive, less hypothesis-driven studies are warranted. However, only randomized clinical trials will determine definitively whether MSM receiving circumcision will reduce HIV risk. Since men who preferentially practice insertive sex are the individuals most likely to derive benefits of circumcision in preventing HIV,¹² their overenrollment would increase an anticipated effect size and increase statistical power in the trial if a trial were to be conducted. Preferential recruitment into a future trial of men practicing insertive sex would contribute equipoise be-

cause individuals practicing receptive sex are less likely to benefit from circumcision.

The Agence Nationale de Recherche sur le SIDA et les Hépatites Virales and the National Institutes of Health provided most of the funds for the circumcision trials in African heterosexual men.⁵⁻⁷ Whether these agencies or other major funders in HIV prevention research (eg, the Bill and Melinda Gates Foundation) will fund a new trial of circumcision in high-risk MSM to assess protection against HIV remains to be determined.

The meta-analysis by Millett et al¹² is likely to be used by both advocates and detractors of clinical trial investment; some will argue the benefit is likely to be too modest to justify a multimillion dollar clinical trial while others will argue that only a clinical trial will answer this important HIV prevention question. Barriers to circumcision among heterosexual men include human rights issues, ethical and legal issues, high cost, fear of pain, safety concerns, availability of surgery services, and sexual risk compensation if men overrate their degree of protection and ongoing risk.^{27,28} As in other HIV prevention trials (eg, HIV vaccines, microbicides, behavior change, opiate addiction treatment, and antiretrovirals for prevention), circumcision would likely be insufficiently efficient to be universally effective in reducing HIV risk, and will have to be combined with other prevention modalities to have a substantial and sustained prevention effect.²⁹⁻³¹ Stigma issues may arise if circumcision promotion campaigns were to be specifically targeted toward MSM. At the same time, MSM might be effectively mobilized by community campaigns, as has been successful before in decreasing high-risk behaviors.

Infant and adult circumcision are recommended in regions with high HIV prevalence as in sub-Saharan Africa.¹⁹ But the question as to whether MSM should be circumcised to reduce their HIV risk, particularly men who preferentially practice insertive sex, is one that only future research can answer.

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