Circumcision Status and Risk of HIV and Sexually Transmitted Infections Among Men Who Have Sex With Men: A Meta-analysis

Gregorio A. Millett; Stephen A. Flores; Gary Marks; et al.


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A Meta-analysis

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Randomized controlled trials (RCTs) conducted with men in Africa have shown that male circumcision reduces the likelihood of female-to-male transmission of human immunodeficiency virus (HIV) infection by 50% to 60%. Observational studies also suggest that male circumcision may protect heterosexual men against acquisition of other sexually transmitted infections (STI), such as syphilis, chlamydial infection, or genital ulcer disease. The protective effect of circumcision among heterosexual men has generated discussion about the potential role of circumcision in reducing the transmission of HIV and other STIs among men who have sex with men (MSM).

Several factors may influence the protective effect of circumcision among MSM. Male circumcision may be most effective as an HIV prevention strategy in countries where HIV/STI prevalence is high and circumcision prevalence is low. Apart from HIV/STI and male circumcision prevalence, sexual position also plays an important role in the degree to which circumcision protects against disease acquisition among MSM. Circumcision among MSM may protect against HIV infection only among those who primarily or exclusively take the insertive role during unprotected anal intercourse because unprotected receptive anal intercourse—the riskiest sexual behavior for contracting HIV infection—is inde-

CONCLUSION

Pooled analyses of available observational studies of MSM revealed insufficient evidence that male circumcision protects against HIV infection or other STIs. However, the comparable protective effect of male circumcision in MSM studies conducted before the era of highly active antiretroviral therapy, as in the recent male circumcision trials of heterosexual African men, supports further investigation of male circumcision for HIV prevention among MSM.

For editorial comment see p 1698.

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dependent of any protective effect afforded by circumcision.

An expert panel convened by the US Centers for Disease Control and Prevention (CDC) for a consultation on male circumcision and HIV infection recommended that evidence from existing observational studies be systematically reviewed before determining the usefulness of an RCT of male circumcision among MSM. Only 1 quantitative review has examined circumcision data from studies of MSM. However, that review included only 2 studies of male circumcision and HIV infection and did not consider unpublished studies or studies of other STIs. Given the increasing interest in circumcision as an HIV prevention strategy, a more thorough synthesis of available data on circumcision and HIV/STI risk among MSM is critical.

We systematically searched the scientific literature and performed a meta-analysis to examine the strength of the association of circumcision status with HIV infection and other STIs among MSM.

METHODS
Study Selection
We searched widely used databases (ie, MEDLINE, ERIC, Sociofile, PsycINFO, EMBASE, Web of Science, Google Scholar) for relevant reports from the beginning of indexing for each database through February 2008. Searching key words and Medical Subject Headings (US National Library of Medicine) relevant to circumcision (ie, circumcision, circumcised, and uncircumcised), we cross-referenced the male circumcision citations and citations pertinent to homosexual men (ie, homosexual, bisexual, men who have sex with men, MSM, and gay). In addition, we searched the Web sites of HIV/STI–related conferences (ie, International Society for Sexually Transmitted Diseases Research, Conference on Retroviruses and Opportunistic Infections, International AIDS Conference, National HIV Prevention Conference) for relevant abstracts dating back to 1989. Last, we checked the reference lists of pertinent articles for additional citations and contacted investigators of published reports and conference abstracts to identify other possible sources.

Studies that met each of the following criteria were included in the review: (1) recruited MSM as part of the study; (2) included male circumcision as a study variable; and (3) reported quantitative data (either bivariate percentages or results of statistical tests) reflecting the association of circumcision status and HIV or STI prevalence among MSM. When necessary, study authors were contacted to obtain additional information or additional data to calculate effect sizes.

Data Extraction
Pairs of reviewers independently abstracted data from eligible articles. The study team used standardized abstraction sheets for recording study authors, publication year, enrollment period, study location, overall sample size of MSM, sample size of circumcised and uncircumcised MSM, racial/ethnic composition of the sample, study design (cross-sectional vs prospective), determination of circumcision status (self-report vs genital examination), data source (published vs unpublished), and type of analysis (univariate and/or multivariate). Although infrequent, disagreements between reviewers during the abstraction process were resolved by discussion.

Methodological Approach
Abstracted data were entered into a spreadsheet by one investigator and reviewed by a separate investigator. Several decision rules regarding participant characteristics and thoroughness of the data guided the preparation of data for analyses (Box).

Analytic Methods
Odds ratios (ORs) were used to estimate effect sizes. Abstracted data for circumcised MSM and uncircumcised MSM were converted, when necessary, into percentages that represented yes vs no for a given outcome. Standard meta-analytic methods were used to aggregate effects across studies. To estimate the overall effect size, each natural log OR (lnOR) was weighted by the inverse of its variance, the weighted lnOR summed across samples, and then divided by the sum of the weights. For the purpose of presentation and ease of interpretation, we converted effect sizes and 95% confidence intervals (CIs) back to ORs. An OR of less than 1 indicates a decreased odds of HIV infection or STI among circumcised compared with uncircumcised MSM. We used the $I^2$ in-
Figure 1. Selection Process for Study Inclusion in the Meta-analysis of Male Circumcision and HIV/STI Among Men Who Have Sex With Men (MSM)

- 4337 Published articles, conference proceedings, book chapters, and dissertations with key words or Medical Subject Headings relevant to male circumcision identified
- 4304 Excluded (did not refer to MSM)
- 33 Potentially relevant reports from literature or obtained from contacts with investigators were screened
- 15 Excluded
  - 3 Commentaries
  - 8 Did not examine HIV/STI status or history
  - 4 Combined MSM and heterosexual men in analyses
- 18 Quantitative studies examining circumcision and HIV or STI among MSM
- 3 Excluded
  - 1 Recruited HIV-positive MSM only
  - 1 Authors forwarded data set but key variables were unidentifiable
  - 1 Authors did not respond to request for additional data
- 15 Studies included in meta-analysis
  - 8 HIV outcome
  - 1 STI outcome
  - 6 Both HIV and STI outcomes

HIV denotes human immunodeficiency virus; and STI, sexually transmitted infection.

dex to examine heterogeneity of individual effect sizes in the overall aggregations for HIV and STI and in stratified analyses. According to Higgins et al, $I^2$ values of near or less than 25% indicate low heterogeneity, values near 50% indicate moderate heterogeneity, and values near 75% or higher indicate high heterogeneity. Under conditions of low heterogeneity ($I^2 \leq 25\%$), we used fixed-effects models and under conditions of higher heterogeneity ($I^2 > 25\%$) we used random-effects models. Using methods developed by Hedges and Pigott to calculate the statistical power of our meta-analysis, we specified a small effect size (15% relative reduction in odds of HIV infection among circumcised vs uncircumcised MSM) as an estimate of the true population value for the overall and stratified aggregations. Power was calculated using variance components derived from the primary studies, a 2-tailed test, and $\alpha = .05$.

Per recommendations from the Cochrane Collaborative Review Group on HIV Infection and AIDS, the quality of observational studies in this meta-analysis was assessed using the Newcastle-Ottawa Scale. This instrument assesses the quality of nonrandomized studies in 3 broad categories (patient selection [4 criteria], comparability of study groups [1 criterion], and assessment of the outcome [3 criteria]). Following quality assessment standards of previous meta-analyses, studies in our meta-analysis that met 5 or more of the Newcastle-Ottawa Scale criteria were considered to be of higher quality. The aggregated effect size of the higher-quality studies were compared with the aggregated effect size of all other studies. We also examined the association of the Newcastle-Ottawa Scale (sum score across the 3 categories) for each study with the respective effect sizes using a weighted generalized least squares meta-regression model. Study quality was examined further by focusing on a subset of studies with moderate (22%-66%) circumcision prevalence because studies with very high or very low male circumcision rates may not have had enough variability to detect an association with HIV and STI. Last, we assessed study quality by limiting analyses to studies with large analytical samples (>1000 participants), and studies that determined circumcision by genital examination and also used diagnostic tests to assess HIV status.

The effect of potential outliers was examined by comparing the aggregated effect size with estimates obtained after iterations using $k-1$ findings ($k$ = the number of independent effect sizes). Sensitivity analyses of the HIV results indicated that there was no evidence of an outlier among the studies. Sensitivity analyses of the STI results indicated that 2 studies may be outliers, but we did not treat either study as a statistical outlier because each of the $k-1$ estimates produced a 95% CI that overlapped with the 95% CI of the full STI sample. To evaluate the presence of publication bias, we used linear regression methods proposed by Sterne and Egger to investigate funnel plot asymmetry. There was no evidence of publication bias among the set of HIV studies in these analyses ($P = .84$), but we found evidence of potential publication bias among the set of studies that examined STI ($P = .01$).

RESULTS

We identified 4337 citations of which 33 were considered relevant and obtained for further screening (Figure 1). Of these 33 studies, 18 quantitatively examined the association between male circumcision status and HIV or STI among MSM (number of studies and count of reference citations may not sum because Templeton et al has separate citations for HIV and STI). Seventeen of the 18 studies examined the association between circumcision and...
studies were conducted between 1989 and 2002. Of the 18 studies examined the association between circumcision and HIV among MSM, 9 of the original reports found no statistically significant association with HIV, 5 reported that circumcision had a significant protective association with HIV, 1 reported a nearly significant protective association, and 1 reported that circumcised MSM had a significantly greater odds of HIV infection, and 1 reported no statistically significant association in the overall sample but found a significantly protective effect among men who only engaged in insertive anal sex.20

Of the 7 studies that examined circumcision and STI among MSM, all except 1 reported data for both HIV and STI.23 Among the 7 STI studies, 4 of the original reports found no statistically significant association between male circumcision and STIs, 2 reported a significantly protective effect for syphilis and no statistically significant association for other STIs, and 1 reported no association for most STIs but a significantly greater odds of nonchlamydial nongonococcal urethritis.32

After excluding 3 of the 18 total studies due to insufficient data, 20,30,38 a final set of 15 studies were included in the meta-analysis (Table 1). The 15 studies were conducted between 1989 and 2007. Nine studies22,23,25-27,32,33,36,37 took place in North America, 9 were conducted with primarily white participants, 4 had a prospective cohort design, and 9 were unpublished abstracts or reports or previously unreported circumcision data.25-27,29,31,34-36,39,41 The average quality of the studies, based upon the Newcastle-Ottawa Scale, was moderate (Table 1). Five studies that met 5 or more study quality criteria were considered the highest quality; the remaining studies fulfilled fewer than 5 of the scale’s 8 study criteria. Across all studies, the prevalence of male circumcision ranged from 4% to 88% (median = 60%). A total of 53,567 MSM were included in our analytical sample, 52% of whom were circumcised.

Fourteen studies contributed 15 findings for the association of circumcision and HIV infection (Figure 2). Our analysis included a total of 27,816 circumcised MSM and 25,751 uncircumcised MSM. The weighted overall effect size reflecting the association between circumcision and HIV infection among MSM was protective, but statistically nonsignificant (OR, 0.86; 95% CI, 0.65-1.13; k = 15). The power for the overall meta-analysis of HIV outcome studies was 0.78. There was moderate to high heterogeneity among the 15 findings (I² = 64%), which warranted further examination via stratified analyses. Most of the stratified analyses revealed associations that were moderately protective, but not statistically significant (Table 2). Circumcision was not significantly associated with HIV infection when stratified by prevalence of HIV among study samples, prevalence of male circumcision among study samples, method used to determine either circumcision or HIV status, cross-sectional or prospective studies, bivariate or multivariate analysis, published or unpublished data, country in which the study was conducted (United States vs non United States), World Bank income classification (developed vs developing), or racial/ethnic composition of the study sample. However, there was moderately high heterogeneity among studies in each of these stratified analyses (I² range, 33%–80%).

In contrast, a statistically significant protective association (OR, 0.47; 95% CI, 0.32-0.69; k = 3; I² = 0%) of circumcision with HIV infection was found for MSM studies conducted prior to the introduction of highly active antiretroviral therapy (HAART) in 1996. Of studies conducted after HAART, the association of circumcision and HIV infection was not statistically significant and heterogeneity among those studies was much higher (I² = 47%). We also found statistically nonsignificant results when we examined studies with moderate circumcision prevalence (22%-66%) and studies with large analytical samples (>1000 participants), but slightly more protective results for studies that used both a genital examination to determine circumcision status and a diagnostic test to determine HIV infection. The association between circumcision and HIV infection among the subset of higher-quality studies (determined by the Newcastle-Ottawa Scale) was protective, but statistically nonsignificant (OR, 0.79; 95% CI, 0.44-1.40; k = 5; I² = 53%). However, in the meta-regression, being circumcised was associated with a reduced odds of HIV infection as study quality scores increased (β = −0.415; P = .01).

A separate analysis (not shown in Table 2) of 4 findings from 3 studies reporting HIV infection and circumcision status for MSM who engaged exclusively or primarily in insertive anal intercourse (n = 2238) was protective, but not statistically significant (OR, 0.71; 95% CI, 0.23-2.22; k = 4). The power for this analysis was 0.94. Although there was high heterogeneity among these 4 findings (I² = 90%), too few findings were available for a stratified analysis.

Seven studies22,23,27,29,32,33,35 contributed 8 findings for the analysis of STIs other than HIV (Figure 3). All but 1 of the studies35 were cross-sectional and conducted in North or South America and the analysis included 15,233 circumcised MSM and 11,003 uncircumcised MSM. A study32 of 899 MSM that provided an effect size for the association between circumcision status and STI, but did not provide the prevalence of circumcised and uncircumcised MSM, was also included in the analytical sample. The weighted overall effect size for the association between circumcision status and STI, but did not provide the prevalence of circumcised and uncircumcised MSM, was also included in the analytical sample. The weighted overall effect size for the association between circumcision status and STI, but did not provide the prevalence of circumcised and uncircumcised MSM, was also included in the analytical sample. The weighted overall effect size for the association between circumcision status and STI, but did not provide the prevalence of circumcised and uncircumcised MSM, was also included in the analytical sample. The weighted overall effect size for the association between circumcision status and STI, but did not provide the prevalence of circumcised and uncircumcised MSM, was also included in the analytical sample. The weighted overall effect size for the association between circumcision status and STI, but did not provide the prevalence of circumcised and uncircumcised MSM, was also included in the analytical sample. The weighted overall effect size for the association between circumcision status and STI, but did not provide the prevalence of circumcised and uncircumcised MSM, was also included in the analytical sample. The weighted overall effect size for the association between circumcision status and STI, but did not provide the prevalence of circumcised and uncircumcised MSM, was also included in the analytical sample. The weighted overall effect size for the association between circumcision status and STI, but did not provide the prevalence of circumcised and uncircumcised MSM, was also included in the analytical sample. The weighted overall effect size for the association between circumcision status and STI, but did not provide the prevalence of circumcised and uncircumcised MSM, was also included in the analytical sample.
<table>
<thead>
<tr>
<th>Source</th>
<th>Location/Enrollment Period</th>
<th>Race/Ethnicity, %</th>
<th>N, Full Sample/Analytic Sample (HIV or STI)</th>
<th>HIV/STI Assessment</th>
<th>Circumcision Assessment, N/Prevalence, No. (%)</th>
<th>Sample HIV Prevalence, No. (%)</th>
<th>No. Circumcised/Total No. (%)</th>
<th>No. Uncircumcised/Total No. (%)</th>
<th>Study Quality Assessment Criteria/Selection/Comparability/Outcome (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Begley et al, 2007</td>
<td>7 US cities/ June to October 2006</td>
<td>1 Native American, 2 Asian/Pacific Islander, 5 Latino, 10 other, 25 black, 55 white</td>
<td>880/772 (HIV)</td>
<td>HIV, self-report</td>
<td>Self-report 646/772 (84)</td>
<td>100 (13)</td>
<td>81/646 (13)</td>
<td>19/126 (15)</td>
<td>2/0/0</td>
</tr>
<tr>
<td>Krieger and Hopkins, 1993</td>
<td>Seattle, Washington/ April 1999 to March 1991</td>
<td>1 Asian/Pacific Islander, 4 black, 4 Latino, 90 white</td>
<td>502/499 (HIV); 502/498 (STI)</td>
<td>HIV, diagnostic test; STI, self-report</td>
<td>Self-report 422/499 (85)</td>
<td>312 (63)</td>
<td>254/422 (60)</td>
<td>59/77 (77)</td>
<td>2/1/1</td>
</tr>
<tr>
<td>Kuma et al, 2006</td>
<td>Not reported</td>
<td>6 Latino, 8 other, 9 black, 77 white</td>
<td>1253/899 (STI)</td>
<td>STI, diagnostic test</td>
<td>Not reported</td>
<td>21 (17)</td>
<td>2/27 (7)</td>
<td>19/95 (20)</td>
<td>2/0/1</td>
</tr>
<tr>
<td>Lafferty et al, 2006</td>
<td>Seattle, Washington/ January 1992 to December 1994</td>
<td>1 Asian/Pacific Islander, 4 black, 4 Latino, 90 white</td>
<td>506/556 (HIV)</td>
<td>HIV, diagnostic test</td>
<td>Self-report 154/556 (28)</td>
<td>33 (6)</td>
<td>5/154 (3)</td>
<td>28/402 (7)</td>
<td>2/1/1</td>
</tr>
<tr>
<td>Lai et al, 2007</td>
<td>Taipei, Taiwan/ May 1992 to December 1994</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>4/0/0</td>
<td></td>
</tr>
<tr>
<td>Millet et al, 2007</td>
<td>3 US cities/ May to October 2006</td>
<td>49 Latino</td>
<td>20932/20832 (HIV); 20932/20832 (STI)</td>
<td>HIV, diagnostic test; STI, diagnostic test</td>
<td>Self-report 317/957 (33)</td>
<td>Latino 348 (36)</td>
<td>Latino 516/317 (37)</td>
<td>Latino 232/640 (36)</td>
<td>2/1/1</td>
</tr>
<tr>
<td>Mor, 2007</td>
<td>San Francisco, California/ January 1996 to December 1994</td>
<td>1 Other, 7 black, 10 Asian/Pacific Islander, 16 Latino, 66 white</td>
<td>14 616/13 851 (HIV)</td>
<td>HIV, self-report</td>
<td>Self-report 3089/13 851 (22)</td>
<td>762 (5)</td>
<td>188/3088 (6)</td>
<td>538/762 (5)</td>
<td>1/0/0</td>
</tr>
<tr>
<td>Reid et al, 2001</td>
<td>England and Wales/ May 2001 to September 2001</td>
<td>1 Black, 2 mixed, 3 Asian, 93 white</td>
<td>2884/2384 (HIV); 2284/1308 (STI)</td>
<td>HIV, diagnostic test; STI, diagnostic test</td>
<td>Self-report 123/2384 (4)</td>
<td>314 (11)</td>
<td>13/123 (11)</td>
<td>301/2761 (11)</td>
<td>3/1/1</td>
</tr>
<tr>
<td>Sanchez, 2007</td>
<td>Peru (3 cities) and Ecuador (1 city)/ February, 2006- June 2007</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>3/1/1</td>
<td></td>
</tr>
<tr>
<td>Tabet et al, 2002</td>
<td>Lima, Peru/ 1996</td>
<td>Not reported</td>
<td>451/440 (HIV)</td>
<td>HIV, diagnostic test</td>
<td>Genital examination 36/440 (8)</td>
<td>84 (19)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>3/1/1</td>
</tr>
<tr>
<td>Bartholow et al, 2006</td>
<td>United States, Canada, the Netherlands/ June 1998- November 1999</td>
<td>2 Asian/Pacific Islander, 2 other, 4 black, 6 Latino, 86 white</td>
<td>5096/5090 (HIV)</td>
<td>HIV, diagnostic test</td>
<td>Self-report 4381/5090 (86)</td>
<td>2.8/100 Perion-years 362 (7)</td>
<td>315/4381 (7)</td>
<td>47/709 (7)</td>
<td>3/0/2</td>
</tr>
<tr>
<td>Buchbinder et al, 2005</td>
<td>6 US cities/ 1995- May 1997</td>
<td>5 Asian/Pacific Islander, 7 black, 12 Latino, 76 white</td>
<td>3257/3257 (HIV)</td>
<td>HIV, diagnostic test</td>
<td>Self-report 2866/3257 (88)</td>
<td>1.65/100 Perion-years Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>3/1/2</td>
</tr>
<tr>
<td>Buchbinder, 2007</td>
<td>14 US cities/ December 2004- March 2007</td>
<td>6 Other, 10 black, 10 Latino, 25 multiracial, 50 white</td>
<td>1836/1787 (HIV)</td>
<td>HIV, diagnostic test</td>
<td>Self-report 998/1787 (56)</td>
<td>80 (5)</td>
<td>52/999 (5)</td>
<td>28/788 (4)</td>
<td>2/0/2</td>
</tr>
</tbody>
</table>

(Continued)
Table 1. Summary of Studies in Meta-analysis of Male Circumcision Status and HIV/STI Risk Among Men Who Have Sex With Men (cont)

<table>
<thead>
<tr>
<th>Source</th>
<th>Location/Enrollment Period</th>
<th>Race/Ethnicity, %a</th>
<th>Participants</th>
<th>HIV/STI Assessment</th>
<th>Circumcision Assessment, No./Prevalence, No. (%)</th>
<th>Sample HIV Prevalence, No. (%)</th>
<th>Sample HIV Positive, No. (%)</th>
<th>HIV-Positive MSM</th>
<th>Study Quality Assessment Criteria, Selection/Comparability/Outcomeb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Templeton et al, 2007</td>
<td>Sydney, Australia/2001-2004</td>
<td>2 Middle Eastern, 3 Asian, 4 other, 91 white</td>
<td>1427/1428 (HIV); 1427/1397 (STI)</td>
<td>HIV, diagnostic test; STI, self-report/diagnostic test</td>
<td>Self-report and genital examination 938/1426 (66)</td>
<td>0.8/100 Person-years</td>
<td>29/938 (3)</td>
<td>13/488 (3)</td>
<td>4/1/3</td>
</tr>
<tr>
<td>Calzavara et al, 2007a</td>
<td>Ontario, Canada/2001-2005</td>
<td>2 Native American, 4 Latino, 9 other, 85 white</td>
<td>165/15 (HIV); 165/165 (STI)</td>
<td>HIV, diagnostic test; STI, self-report</td>
<td>Self-report 11/15 (73%)</td>
<td>Not applicable</td>
<td>2/11 (18)</td>
<td>2/4 (50)</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men; STI, sexually transmitted infection.

aPercentages in the race/ethnicity column may not sum to 100% due to rounding.
bAnalytic and full samples were taken directly from the original reports. The HIV analytic sample was used as the denominator in calculating male circumcision and HIV prevalence.

Discrepancies between analytic and full samples were due to missing data.

Sample HIV reported as incidence per 100 person-years for Buchbinder, Templeton, and Bartholow.

Study quality assessment based upon Newcastle-Ottawa Scale. Four criteria evaluate study sample selection, 1 criterion assesses comparability, and 3 criteria examine the assessment of the study outcome. One study was not included in the quality assessment because the scale's criteria for case-control studies differ from the criteria for cross-sectional and prospective studies.

Additional data were obtained from authors, co-authors, or principal investigators on these studies.

Based on number of clinic visits.

Racial breakdown reported only for circumcised MSM in sample.

Participants given the option of either self-report or diagnostic tests for STIs.

Subset of 247 men given confirmatory genital examinations.

Of the 61 study sites, 57 were in the United States, 3 in Canada, and 1 in the Netherlands.

Figure 2. Overall Effect Size Estimates for Male Circumcision and HIV Infection Among Men Who Have Sex With Men (14 Studies; 15 Findings)

HIV denotes human immunodeficiency virus, and CI, confidence interval. Odds ratios are from reconstructed 2 × 2 tables and may differ from those in original reports. Odds ratios of less than 1 indicate decreased odds of HIV infection among circumcised men who have sex with men.

aAdditional data were obtained from authors, co-authors, or principal investigators.

bDenotes black participants.

cDenotes Latino participants.

COMMENT

In this meta-analysis of 15 observational studies of the association of circumcision status and HIV infection among 33,567 MSM, the odds of being HIV positive were 14% lower among MSM who were circumcised than among MSM who were uncircumcised, but the difference was not statistically significant. When we restricted the analysis to studies of MSM who reported primarily engaging in insertive anal sex, the aggregated findings also were statistically nonsignificant. The STI analyses similarly revealed no statistically significant association by circumcision status among MSM. Additionally, we had sufficient power for the HIV analyses and adequate power for most STI analyses. Taken together, these findings indicate insufficient evidence among available observational studies conducted with MSM of an association between circumcision and HIV infection or other STIs.

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Several important findings emerge from the results of our meta-analysis. First, we found a statistically significant protective association for circumcision among MSM in studies conducted before the advent of HAART, but a statistically nonsignificant association for studies conducted after HAART. A possible explanation for this difference may be related to an increase in the sexual risk behaviors of MSM after HAART. It has been well documented that beliefs that HAART limits HIV transmissibility are associated with increases in sexual risk behavior among MSM, and that the era since the advent of HAART has been defined by higher rates of sexual risk behaviors among MSM, outbreaks of STIs, and increasing rates of HIV infection. Higher rates of sexual risk behavior among MSM since the availability of HAART may diminish the relative effectiveness of male circumcision, and is supported by studies of MSM that report that behavioral risk factors (eg, unprotected anal sex) contribute comparatively more to HIV seroconversion than circumcision status.

Second, circumcision was not associated with STI in the overall or the stratified analyses of study and sample characteristics but the power for several STI analyses was low. Stratified analyses among higher-quality studies and among studies with moderate

<table>
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<tr>
<th>Table 2. Odds of HIV Infection Among Circumcised vs Uncircumcised Men Who Have Sex With Men by Study and Design Characteristics</th>
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<tbody>
<tr>
<td>Stratified Variable</td>
</tr>
<tr>
<td>≤50% participants HIV positive ( g )</td>
</tr>
<tr>
<td>&gt;50% participants HIV positive</td>
</tr>
<tr>
<td>≤50% participants circumcised</td>
</tr>
<tr>
<td>&gt;50% participants circumcised</td>
</tr>
<tr>
<td>Male circumcision determined by self-report</td>
</tr>
<tr>
<td>Male circumcision determined by genital examination</td>
</tr>
<tr>
<td>HIV status determined by self-report</td>
</tr>
<tr>
<td>HIV status determined by diagnostic test</td>
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<tr>
<td>Prospective studies</td>
</tr>
<tr>
<td>Cross-sectional studies</td>
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<tr>
<td>Bivariate analyses ( l )</td>
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<tr>
<td>Multivariate analyses ( l )</td>
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<tr>
<td>Published data</td>
</tr>
<tr>
<td>Unpublished data</td>
</tr>
<tr>
<td>US studies</td>
</tr>
<tr>
<td>Non-US studies</td>
</tr>
<tr>
<td>Developed countries (US data included)</td>
</tr>
<tr>
<td>Developed countries (US data excluded)</td>
</tr>
<tr>
<td>Developing countries</td>
</tr>
<tr>
<td>&gt;50% White MSM</td>
</tr>
<tr>
<td>&gt;50% MSM of color ( g )</td>
</tr>
<tr>
<td>100% Latino MSM</td>
</tr>
<tr>
<td>Data collected before HAART</td>
</tr>
<tr>
<td>Data collected after the advent of HAART</td>
</tr>
<tr>
<td>Higher-quality studies ( l )</td>
</tr>
<tr>
<td>Lower-quality studies ( l )</td>
</tr>
<tr>
<td>Moderate (22%-66%) male circumcision prevalence</td>
</tr>
<tr>
<td>Large samples ( l )</td>
</tr>
<tr>
<td>Male circumcision determined by genital examination</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; MSM, men who have sex with men; OR, odds ratio. \( a \), Denotes the number of individual effect sizes in aggregated analysis. It also denotes the number of studies except Millett et al \( a \) (2 separate effect sizes for independent samples [black vs Latino men]). \( b \), Odds ratios of less than 1 indicate decreased odds of HIV infection among circumcised MSM. \( c \), Fixed-effects models were used to aggregate effect sizes within strata when \( I^2 \) was 25% or less, and random-effects models were used when \( I^2 \) was greater than 25%. \( d \), Denotes 1−/H9252 power to detect an association based upon 15% reduction in the odds of HIV infection among circumcised men. \( e \), Denotes 1−/H9252 power to detect a decrease in HIV prevalence by 15% reduction in the odds of HIV infection among circumcised men. \( f \), Includes Buchbinder et al \( f \) only year persons were reported, but HIV prevalence was less than 50%. \( g \), Three studies \( g \) provided both bivariate and multivariate data. \( h \), Four studies \( h \) did not report race/ethnicity, but were included in the analysis of MSM of color because the studies were conducted in Taiwan, India, Ecuador, and Peru. \( i \), Studies that fulfilled 5 or more of the 8 total criteria in the Newcastle-Ottawa Scale \( j \) for quality assessment of observational studies. \( j \), Studies that fulfilled 4 or fewer of the 8 total criteria in the Newcastle-Ottawa Scale \( j \) for quality assessment of observational studies. \( k \), Analytical samples that included more than 1000 participants. \( l \), The studies in this stratified analysis are the same set of studies in the stratified analysis of male circumcision determined by genital examination.
circumcision prevalence indicated that circumcision was associated with a nearly significant greater odds of acquiring STI, but caution should be undertaken in interpreting these results because only 2 studies were included in each stratified analysis. Further, these findings may be the result of uncontrolled confounding since STIs can be transmitted through routes other than insertive penile intercourse (ie, oral, digital-anal, skin-to-skin, receptive anal sex), thus bypassing any effect associated with circumcision status.

Third, our review indicates that the available scientific literature examining circumcision status and HIV/STI among MSM are of varied methodological quality. Studies in our meta-analysis may not have been designed specifically to examine HIV/STI in relation to male circumcision and our statistically nonsignificant findings may be due to variability among studies and not the absence of an effect. Nearly two-thirds of the reports in our meta-analysis did not have sufficiently high methodological quality, the point estimates as well as the widths of the CIs included a wide range of values, and between-study heterogeneity was moderate to high in the overall and stratified analyses. A separate analysis of HIV outcome studies with the highest methodological quality revealed a protective but statistically nonsignificant association between circumcision and HIV infection. However, we found that being circumcised was associated with a reduced odds of HIV infection as study quality increased.

Some patterns in the stratified HIV analyses are of interest as they point to the potentially protective role of circumcision among MSM. Although not statistically significant, circumcision had a stronger protective association with HIV infection in study samples in which circumcision prevalence was 50% or lower compared with samples with a greater than 50% circumcision prevalence. A similar pattern was apparent in stratified analyses by country. The aggregated US studies, where circumcision prevalence is relatively high, had a 9% reduction in odds of HIV infection among circumcised MSM. By contrast, the reduction in odds was higher in countries with lower adult circumcision rates than the United States (15% reduction in studies conducted in other developed countries and 51% reduction in developing countries). We also found a comparatively stronger, albeit nonsignificant, protective association of circumcision with HIV infection in MSM studies in which circumcision status was determined by diagnostic test, multivariate analyses adjusted for confounders, and samples were limited to MSM who primarily engaged in insertive anal sex. Moreover, we found a 53% reduction in the odds of HIV infection among circumcised MSM during the era before HAART, which is comparable with the 50% to 60% reduction in the odds of HIV infection among circumcised heterosexual men in the 3 African RCTs and a previously published meta-analysis of heterosexual African men.

Our meta-analysis has several strengths. First, it is the most comprehensive meta-analysis of male circumcision and HIV or STI risk among MSM. Second, we stratified the data by several study design and sample characteristics to gauge the presence or absence of an association. Third, half of our analytical sample (over 26 000 MSM participants) was derived from unpublished data, minimizing concern over publication bias. Fourth, our meta-analysis includes domestic and international studies of MSM, including studies from developed and developing countries. Last, our conclusions are informed by power analyses, by analyses of heterogeneity of the aggregated findings, and by analyses that stratified studies according to methodological quality.

There are also several limitations to our review. The studies in our meta-analysis are observational and most did not control for potentially confounding variables. However, 4 studies did provide multivariate findings that controlled for age and HIV risk behaviors, and these aggregated analyses were statistically nonsignificant. Another limitation is that a substantial proportion of the studies in our meta-analyses were cross-sectional, which limits inferences of HIV or STI incidence. Similarly, the analyses of MSM who engaged in insertive anal intercourse were derived from cross-sectional studies and likely include MSM who engaged in receptive anal sex during their lifetime, which may bias the association between circumcision...
Table 3. Odds of Sexually Transmitted Infections (Other Than HIV) Among Circumcised vs Uncircumcised Men Who Have Sex With Men by Study and Design Characteristics

<table>
<thead>
<tr>
<th>Stratified Variable</th>
<th>Circumcised</th>
<th>Uncircumcised</th>
<th>k</th>
<th>OR (95% CI)</th>
<th>I²</th>
<th>%d</th>
<th>1−β²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any bacterial STI</td>
<td>15,024</td>
<td>9,725</td>
<td>6</td>
<td>0.97 (0.70-1.34)</td>
<td>58</td>
<td>.84</td>
<td></td>
</tr>
<tr>
<td>Any viral STI</td>
<td>1,409</td>
<td>1,767</td>
<td>3</td>
<td>1.08 (0.97-1.26)</td>
<td>0</td>
<td>.31</td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>15,024</td>
<td>9,725</td>
<td>5</td>
<td>0.93 (0.63-1.37)</td>
<td>39</td>
<td>.97</td>
<td></td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>1,409</td>
<td>1,767</td>
<td>3</td>
<td>1.11 (0.95-1.30)</td>
<td>0</td>
<td>.47</td>
<td></td>
</tr>
<tr>
<td>STI determined by self-report¹</td>
<td>2,572</td>
<td>1,524</td>
<td>5</td>
<td>0.98 (0.70-1.37)</td>
<td>40</td>
<td>.84</td>
<td></td>
</tr>
<tr>
<td>STI determined by diagnostic test⁷</td>
<td>12,661</td>
<td>9,479</td>
<td>3</td>
<td>1.06 (0.75-1.51)</td>
<td>49</td>
<td>.85</td>
<td></td>
</tr>
<tr>
<td>Bivariate analyses³</td>
<td>15,233</td>
<td>11,003</td>
<td>8</td>
<td>1.01 (0.81-1.25)</td>
<td>35</td>
<td>.70</td>
<td></td>
</tr>
<tr>
<td>Multivariate analyses⁹</td>
<td>1,343</td>
<td>562</td>
<td>3</td>
<td>0.68 (0.23-2.05)</td>
<td>92</td>
<td>.94</td>
<td></td>
</tr>
<tr>
<td>Published data</td>
<td>14,109</td>
<td>9,257</td>
<td>5</td>
<td>1.01 (0.76-1.35)</td>
<td>54</td>
<td>.80</td>
<td></td>
</tr>
<tr>
<td>Unpublished data</td>
<td>1,124</td>
<td>1,746</td>
<td>3</td>
<td>1.12 (0.98-1.28)</td>
<td>0</td>
<td>.35</td>
<td></td>
</tr>
<tr>
<td>Male circumcision determined by self-report</td>
<td>2,572</td>
<td>1,524</td>
<td>5</td>
<td>0.98 (0.70-1.37)</td>
<td>40</td>
<td>.84</td>
<td></td>
</tr>
<tr>
<td>Male circumcision determined by genital examination</td>
<td>12,661</td>
<td>9,479</td>
<td>3</td>
<td>1.06 (0.75-1.51)</td>
<td>49</td>
<td>.96</td>
<td></td>
</tr>
<tr>
<td>&gt;50% White MSM</td>
<td>14,038</td>
<td>8,854</td>
<td>3</td>
<td>0.96 (0.71-1.30)</td>
<td>61</td>
<td>.83</td>
<td></td>
</tr>
<tr>
<td>&gt;50% MSM of color⁵</td>
<td>1,195</td>
<td>2149</td>
<td>3</td>
<td>1.10 (0.91-1.34)</td>
<td>0</td>
<td>.63</td>
<td></td>
</tr>
<tr>
<td>100% Latino MSM</td>
<td>401</td>
<td>1,864</td>
<td>2</td>
<td>1.02 (0.78-1.34)</td>
<td>0</td>
<td>.79</td>
<td></td>
</tr>
<tr>
<td>Data collected before HAART</td>
<td>421</td>
<td>77</td>
<td>2</td>
<td>0.95 (0.50-1.83)</td>
<td>79</td>
<td>.92</td>
<td></td>
</tr>
<tr>
<td>Data collected after the advent of HAART</td>
<td>14,812</td>
<td>10,926</td>
<td>6</td>
<td>1.05 (0.95-1.15)</td>
<td>2</td>
<td>.07</td>
<td></td>
</tr>
<tr>
<td>Higher-quality studies¹</td>
<td>1,006</td>
<td>1,699</td>
<td>2</td>
<td>1.14 (0.99-1.30)</td>
<td>0</td>
<td>.36</td>
<td></td>
</tr>
<tr>
<td>Lower-quality studies¹</td>
<td>14,110</td>
<td>9,257</td>
<td>5</td>
<td>1.01 (0.76-1.35)</td>
<td>54</td>
<td>.80</td>
<td></td>
</tr>
<tr>
<td>Moderate (22%-66%) male circumcision prevalence</td>
<td>1,239</td>
<td>1,115</td>
<td>2</td>
<td>1.11 (0.88-1.26)</td>
<td>0</td>
<td>.29</td>
<td></td>
</tr>
<tr>
<td>Large samples⁸</td>
<td>14,393</td>
<td>10,252</td>
<td>4</td>
<td>1.07 (0.97-1.18)</td>
<td>0</td>
<td>.09</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; MSM, men who have sex with men; OR, odds ratio; STI, sexually transmitted infection.

¹Denotes the number of individual effect sizes in aggregated analysis. It also denotes the number of studies except Millett et al (2 separate effect sizes for independent samples [black vs Latino men]).
²ORs of less than 1 indicate decreased odds of STI among circumcised MSM.
³Fixed-effects models were used to aggregate effect sizes within strata when I² was 25% or less, and random-effects models were used when I² was greater than 25%.
⁴Denotes 1−β power to detect an association based upon 15% reduction in the odds of STI among circumcised men.
⁵Studies that fulfilled 5 or more of the 8 total criteria in the Newcastle-Ottawa Scale for quality assessment of observational studies.
⁶Studies that fulfilled 4 or fewer of the 8 total criteria in the Newcastle-Ottawa Scale for quality assessment of observational studies.
⁷Analitical samples that included more than 1000 participants.

and HIV infection toward the null. An additional limitation is that moderate to high heterogeneity between studies remained in many of our stratified analyses. There were also not enough data to examine STIs separately, aside from syphilis and herpes simplex virus, and aggregating all STI data in our analyses possibly diluted our ability to detect any effects. Last, we found evidence of publication bias in the STI data. However, 3 of the 7 (43%) STI studies were unpublished studies and aggregated analyses revealed no statistically significant associations between circumcision and STI for published or unpublished data.

Considerable gaps remain in the available literature of male circumcision among MSM. Additional prospective studies of MSM need to be conducted that meet high quality assessment criteria (eg, genital examinations, diagnostic tests for HIV/STI, multivariate analyses). There also needs to be more data on the proportion of MSM who only engage in insertive anal sex, whether such proportions differ by race/ethnicity, age, geography, cultural context or other factors, and the population-level impact of new HIV infections possibly averted by circumcising these men. Further research studies should also examine sexual behavior differences between circumcised and uncircumcised MSM and how these differences may be related to HIV transmission. In addition, future research should compare the relative effectiveness of current HIV prevention strategies (eg, behavioral interventions targeting MSM) with mathematical models of male circumcision and HIV infection among MSM. Last, it is unknown whether differences exist in viral shedding in the anus vs the vagina, and how potential differences in viral load in either cavity may affect the likelihood of HIV transmission to an uncircumcised, seronegative, insertive male partner per act of unprotected intercourse.

Serious consideration should be given to conducting an RCT under conditions that would be optimal (ie, high acceptability of circumcision, high HIV prevalence, low circumcision prevalence) to evaluate the potential prevention implications of circumcision among MSM.
MSM. The association between circumcision and HIV infection may not be uniform across all groups of MSM and any proposed trial might consider enrolling HIV-negative MSM who primarily engage in insertive anal sex and/or reside in resource-deprived settings without HAART access. However, recruitment challenges and ethical considerations need to be thoroughly addressed before initiating any RCT with MSM.

We found a protective, albeit statistically nonsignificant, association of circumcision with HIV infection in our meta-analysis of MSM observational studies, and a statistically nonsignificant association between circumcision status and STI. Our data revealed that male circumcision conferred a significant protective effect from HIV infection among MSM in studies conducted before HAART but not after, possibly due to documented increases in sexual risk behavior during the era since the availability of HAART. Additional studies are necessary to elucidate further the relationship between circumcision status and HIV infection or STIs among MSM.

Author Contributions: Mr Millett had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Millett, Flores. Acquisition and interpretation of data: Millett, Flores, Marks, Reed, Herbst.

Drafting of the manuscript: Millett, Flores, Marks, Reed, Herbst.

Critical revision of the manuscript for important intellectual content: Millett, Flores, Marks, Reed, Herbst.

Statistical analysis: Flores.

Administrative, technical, or material support: Millett, Flores, Marks, Reed, Herbst.

Study supervision: Millett.

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CIRCUMCISION AND RISK OF HIV AND SEXUALLY TRANSMITTED INFECTIONS

Abstract presented at: XIV International AIDS Conference; July 7–12, 2002; Barcelona, Spain.


