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

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Circumcision Status and Risk of HIV and Sexually Transmitted Infections Among Men Who Have Sex With Men

A Meta-analysis

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Context Randomized controlled trials and meta-analyses have demonstrated that male circumcision reduces men's risk of contracting human immunodeficiency virus (HIV) infection during heterosexual intercourse. Less is known about whether male circumcision provides protection against HIV infection among men who have sex with men (MSM).

Objectives To quantitatively summarize the strength of the association between male circumcision and HIV infection and other sexually transmitted infections (STIs) across observational studies of MSM.

Data Sources Comprehensive search of databases, including MEDLINE, EMBASE, ERIC, Sociofile, PsycINFO, Web of Science, and Google Scholar, and correspondence with researchers, to find published articles, conference proceedings, and unpublished reports through February 2008.

Study Selection Of 18 studies that quantitatively examined the association between male circumcision and HIV/STI among MSM, 15 (83%) met the selection criteria for the meta-analysis.

Data Extraction Independent abstraction was conducted by pairs of reviewers using a standardized abstraction form. Study quality was assessed using the Newcastle-Ottawa Scale.

Data Synthesis A total of 53 567 MSM participants (52% circumcised) were included in the meta-analysis. The odds of being HIV-positive were nonsignificantly lower among MSM who were circumcised than uncircumcised (odds ratio, 0.86; 95% confidence interval, 0.65-1.13; number of independent effect sizes [k]=15). Higher study quality was associated with a reduced odds of HIV infection among circumcised MSM (β, −0.415; P=.01). Among MSM who primarily engaged in insertive anal sex, the association between male circumcision and HIV was protective but not statistically significant (odds ratio, 0.71; 95% confidence interval, 0.23-2.22; k=4). Male circumcision had a protective association with HIV in studies of MSM conducted before the introduction of highly active antiretroviral therapy (odds ratio, 0.47; 95% confidence interval, 0.32-0.69; k=3). Neither the association between male circumcision and other STIs (odds ratio, 1.02; 95% confidence interval, 0.83-1.26; k=8), nor its relationship with study quality was statistically significant (β, 0.265; P=.47).

Conclusions 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.

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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%.[1-3] 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.[4,5] 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).[6,7]

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.[8] 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[7] because unprotected receptive anal intercourse—the riskiest sexual behavior for contracting HIV infection[9]—is inde-

For editorial comment see p 1698.

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pendent 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.[10] Only 1 quantitative review has examined circumcision data from studies of MSM.[11] However, that review included only 2 studies of male circumcision and HIV infection and did not consider unpublished studies or studies of other STIs.[11] 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.

Box. **Methodological Approach for Analysis of Abstracted Data**

1. Only data from circumcised and uncircumcised men who have sex with men were used to calculate effect sizes.
2. Only the most complete data (qualified for computing an odds ratio or data that included an effect size) were abstracted.
3. If bivariate and multivariate data were available in a given study, both were abstracted.
4. Unadjusted data from each study were used to calculate the overall weighted odds for human immunodeficiency infection or other sexually transmitted infection. Data from adjusted analyses were only used from a given study to calculate the weighted odds when bivariate data were unavailable.
5. Each study contributed only 1 effect size per outcome. For example, if a study reported associations between male circumcision and gonorrhea, nongonococcal urethritis, and chlamydial infection, the effects of the 3 sexually transmitted infections were combined into 1 summary effect size.
6. To ensure independence of effects, studies could contribute more than one effect only when data from independent samples were analyzed separately.

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.

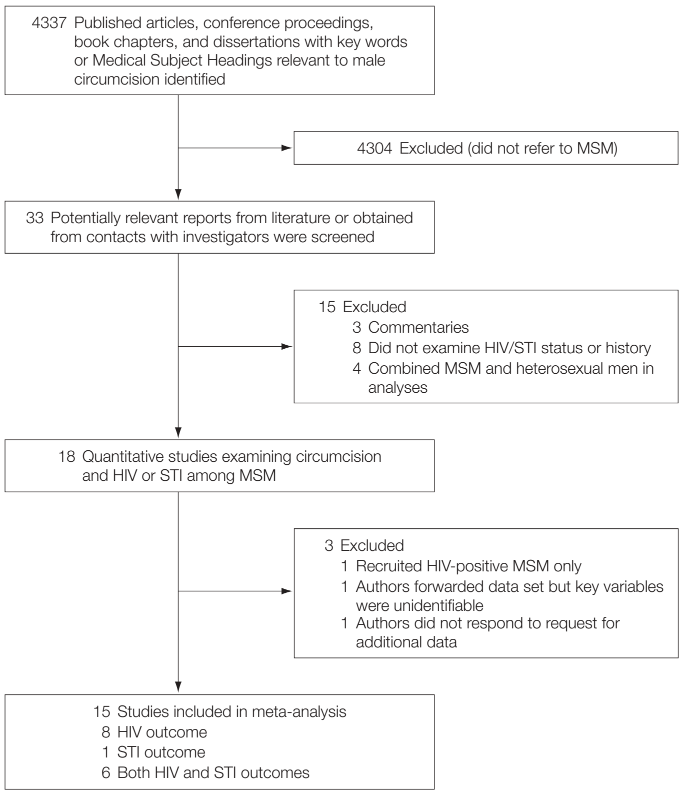
Methodological Approach

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.[12] To estimate the overall effect size, each natural log OR (*ln*OR) was weighted by the inverse of its variance, the weighted *ln*OR summed across samples, and then divided by the sum of the weights.[13] 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)



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.[14] 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.[14] 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.[15,16] Using methods developed by Hedges and Pigott[17] 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 α of .05.

Per recommendations from the Cochrane Collaborative Review Group on HIV Infection and AIDS,[18] the quality of observational studies in this meta-analysis was assessed using the Newcastle-Ottawa Scale.[19] 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,[20] 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.[21] 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[22,23] 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[24] to investigate funnel plot asymmetry. There was no evidence of publication bias among the set of HIV studies in these analyses (β, 0.056; P=.84), but we found evidence of potential publication bias among the set of studies that examined STI (β, 0.824; 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[34] and STI[35]).[22,23,25-41] Seventeen of the 18 studies examined the association between circumcision and

HIV,[22,23,25-31,33,34,36-41] and 7 of the 18 studies examined the association between circumcision and STI.[22,23,27,29,32,33,35]

Of the 17 studies that examined the association between circumcision and HIV infection among MSM, 9 of the original reports[25-28,30,31,33,34,36] found no statistically significant association with HIV, 5 reported[23,37-40] that circumcision had a significant protective association with HIV, 1 reported[22] a nearly significant protective association, 1 reported[41] 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.[29]

Of the 7 studies that examined circumcision and STI among MSM, all except 1 reported data for both HIV and STI.[32] Among the 7 STI studies, 4 of the original reports[22,27,29,33] 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,[23,35] 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,[28,30,38] a final set of 15 studies* were included in the meta-analysis (**TABLE 1**). The 15 studies were conducted between 1989 and 2007. Nine studies[22,23,25-27,32,33,36,37] took place in North America, 9 were conducted[22,23,25,27,32,34-37,41] with primarily white participants, 4 had a prospective cohort design,[26,34-37] 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[29,34-37,40] 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 ($I^2 = 64\%$), 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 country classification (developed vs developing),[42] or racial/ethnic composition of the study sample. However, there was moderately high heterogeneity among studies in each of these stratified analyses (I^2 range, 33%-80%).

In contrast, a statistically significant protective association (OR, 0.47; 95% CI, 0.32-0.69; $k = 3$; $I^2 = 0\%$) 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 ($I^2 = 47\%$). 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; $k = 5$; $I^2 = 53\%$). 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[29,33,34] 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 ($I^2 = 90\%$), too few findings were available for a stratified analysis.

Seven studies[22,23,27,29,32,33,35] contributed 8 findings for the analysis of STIs other than HIV (**FIGURE 3**). All but 1 of the studies[35] were cross-sectional and conducted in North or South America and the analysis included 15 233 circumcised MSM and 11 003 uncircumcised MSM. A study[32] 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 among MSM was not statistically significant (OR, 1.02; 95% CI, 0.83-1.26; $k = 8$). The power for the meta-analysis of STI studies was 0.67 and heterogeneity was moderate ($I^2 = 36\%$). In stratified analyses (**TABLE 3**), circumcision was not significantly asso-

*References 22, 23, 25-27, 29, 31-37, 39-41.

†References 22, 23, 25-27, 29, 31, 33-37, 39-41.

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

Source	Location/ Enrollment Period	Race/ Ethnicity, %[a]	Participant No., Full Sample/ Analytic Sample (HIV or STI)[b]	HIV/STI Assessment	Circumcision Assessment, No./Prevalence, No. (%)	Sample HIV Prevalence, No. (%)[c]	HIV-Positive MSM: No. Circumcised/ Total No. (%)	HIV-Positive MSM: No. Uncircumcised/ Total No. (%)	Study Quality Assessment Criteria, Selection/ Comparability/ Outcome[d]
Cross-sectional study									
Begley et al, 2007[25][e]	7 US cities/ June 2006-October 2006	1 Native American, 2 Asian/Pacific Islander, 5 Latino, 10 other, 25 black, 56 white	880/772 (HIV)	HIV, self-report	Self-report 646/772 (84)	100 (13)	81/646 (13)	19/126 (15)	2/0/0
Kreiss and Hopkins, 1993[23][e]	Seattle, Washington/ April 1989-March 1991	1 Asian/Pacific Islander, 4 black, 4 Latino, 90 white	502/499 (HIV); 502/498 (STI)	HIV, diagnostic test; STI, self-report	Self-report 422/499 (85)	312 (63)	254/422 (60)	59/77 (77)	2/1/1
Kumta et al, 2002[31]	Mumbai, India/ March 2001-July 2002	Not reported	122/122 (HIV)	HIV, diagnostic test	Genital examination 27/122 (22)	21 (17)	2/27 (7)	19/95 (20)	2/0/1
Lafferty et al, 1997[32]	Seattle, Washington/ January 1993-December 1994	6 Latino, 8 other, 9 black, 77 white	1253/899 (STI)	STI, diagnostic test	Genital examination not reported (not reported)	162 (18)	Not applicable	Not applicable	2/1/1
Lai et al, 2004[39][e]	Taipei, Taiwan/ 2003	Not reported	556/556 (HIV)	HIV, diagnostic test	Self-report 154/556 (28)	33 (6)	5/154 (3)	28/402 (7)	2/1/1
Millett et al, 2007[33]	3 US cities/ May 2005-April 2006	49 Latino 51 black	Latino sample: 1091/957 (HIV); 1091/957 (STI) Black sample: 1154/1079 (HIV); 1154/1079 (STI)	HIV, diagnostic test; STI, self-report	Self-report Latino 317/957 (33) Self-report black 794/1079 (74)	Latino 348 (36) Black 563 (52)	Latino 116/317 (37) Black 425/794 (54)	Latino 232/640 (36) Black 138/285 (48)	2/1/1
Mor, 2007[22][e]	San Francisco, California/ January 1996-December 2005	1 Other, 7 black, 10 Asian/Pacific Islander, 16 Latino, 66 white	20 832/20 832 (HIV); 20 832/20 832 (STI)	HIV, diagnostic test; STI, diagnostic test	Genital examination 15 207/20 832 (73)	14902 (72)	8942/12 577 (71)[f]	5960/8255 (72)[f]	3/0/1
Reid et al, 2001[41]	England and Wales/ May 2001-September 2001	1 Black, 2 mixed, 3 Asian, 93 white	14 616/13 851 (HIV)	HIV, self-report	Self-report 3089/13 851 (22)	726 (5)	188/3089 (6)	538/762 (5)	1/0/0
Sanchez, 2007[29][e]	Peru (3 cities) and Ecuador (1 city)/ February 2006-June 2006	Not reported	2884/2884 (HIV); 2284/1308 (STI)	HIV, diagnostic test; STI, diagnostic test	Genital examination 123/2884 (4)	314 (11)	13/123 (11)	301/2761 (11)	3/1/1
Tabet et al, 2002[40][e]	Lima, Peru/ 1996	Not reported	451/440 (HIV)	HIV, diagnostic test	Genital examination 36/440 (8)	84 (19)	Not reported	Not reported	3/1/1
Prospective study (6 mo follow-up)									
Bartholow et al, 2006[36][e]	United States, Canada, the Netherlands/ June 1998-November 1999[j]	2 Asian/Pacific Islander, 2 other, 4 black, 6 Latino, 86 white	5095/5090 (HIV)	HIV, diagnostic test	Self-report 4381/5090 (86)	2.8/100 Person-years 362 (7)	315/4381 (7)	47/709 (7)	3/0/2
Buchbinder et al, 2005[37]	6 US cities/ April 1995-May 1997	5 Asian/Pacific Islander, 7 black, 12 Latino, 76 white	3257/3257 (HIV)	HIV, diagnostic test	Self-report 2866/3257 (88)	1.55/100 Person-years	Not reported	Not reported	3/1/2
Buchbinder, 2007[26]	14 US cities/ December 2004-March 2007	6 Other, 10 black, 10 Latino, 25 multiracial, 50 white	1836/1787 (HIV)	HIV, diagnostic test	Self-report 999/ 1787 (56)	80 (5)	52/999 (5)	28/788 (4)	2/0/2

(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)

Source	Location/ Enrollment Period	Race/ Ethnicity, %[a]	Participant No., Full Sample/ Analytic Sample (HIV or STI)[b]	HIV/STI Assessment	Circumcision Assessment, No./Prevalence, No. (%)	Sample HIV Prevalence, No. (%)[c]	HIV-Positive MSM: No. Circumcised/ Total No. (%)	HIV-Positive MSM: No. Uncircumcised/ Total No. (%)	Study Quality Assessment Criteria, Selection/ Comparability/ Outcome[d]
Prospective study (6 mo. follow-up)									
Templeton et al, 2007[34,35e]	Sydney, Australia/ 2001-2004	2 Middle Eastern, 3 Asian, 4 other, 91 white[g]	1427/1426 (HIV); 1427/1397 (STI)	HIV, diagnostic test; STI, self-report/ diagnostic test[h]	Self-report and genital examination 938/1426 (66)[i]	0.8/100 Person-years 42 (3)	29/938 (3)	13/488 (3)	4/1/3
Retrospective case/control study									
Calzavara et al, 2007[27e]	Ontario, Canada/ 2001-2005	2 Native American, 4 Latino, 9 other, 85 white	165/15 (HIV); 165/165 (STI)	HIV, diagnostic test; STI, self-report	Self-report 11/15 (73%)	Not applicable	2/11 (18)	2/4 (50)	Not applicable

Abbreviations: HIV, human immunodeficiency virus; MSM, men who have sex with men; STI, sexually transmitted infection.
[a] Percentages in the race/ethnicity column may not sum to 100% due to rounding.
[b] Analytic 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.
[c] Sample HIV reported as incidence per 100 person-years for Buchbinder,[37] Templeton,[34,35] and Bartholow.[36]
[d] Study quality assessment based upon Newcastle-Ottawa Scale.[19] Four criteria evaluate study sample selection, 1 criterion assesses comparability, and 3 criteria examine the assessment of the study outcome. One study[27] 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.
[e] Additional data were obtained from authors, co-authors, or principal investigators on these studies.
[f] Based on number of clinic visits.
[g] Racial breakdown reported only for circumcised MSM in sample.
[h] Participants given the option of either self-report or diagnostic tests for STIs.
[i] Subset of 247 men given confirmatory genital examinations.
[j] Of the 61 study sites, 57 were in the United States, 3 in Canada, and 1 in the Netherlands.

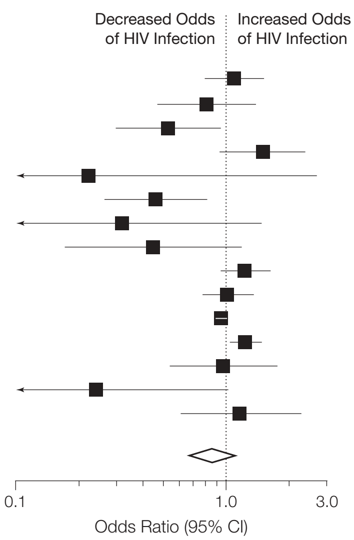
ciated with STIs (bacterial or viral) generally, with specific STIs (ie, syphilis, herpes simplex virus) or with any of the other study or sample characteristics in Table 3. There was also no statistically significant association between study quality, based upon the Newcastle-Ottawa Scale, and the effect sizes of the STI studies (β, 0.265; $P = .47$).

COMMENT

In this meta-analysis of 15 observational studies of the association of circumcision status and HIV infection among 53 567 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.

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

Source	No. of Participants	Odds Ratio (95% CI)
Bartholow et al,[36] 2006	5090	1.09 (0.79-1.50)
Begley et al,[25] 2007	772	0.81 (0.47-1.39)
Buchbinder et al,[37] 2005	3257	0.53 (0.30-0.94)
Buchbinder et al,[26] 2007	1787	1.49 (0.93-2.38)
Calzavara et al,[27] 2007	15	0.22 (0.02-2.67)
Kreiss and Hopkins,[23] 1993	499	0.46 (0.26-0.81)
Kumta et al,[31] 2002	122	0.32 (0.07-1.47)
Lai et al,[39] 2004[a]	556	0.45 (0.17-1.18)
Millett et al,[33] 2007[b]	1079	1.23 (0.94-1.61)
Millett et al,[33] 2007[c]	957	1.01 (0.77-1.34)
Mor et al,[22] 2007	20 832	0.95 (0.89-1.01)
Reid et al,[41] 2002	13 851	1.23 (1.04-1.46)
Sanchez,[29] 2007	2884	0.97 (0.54-1.74)
Tabet et al,[40] 2002	440	0.24 (0.06-1.02)
Templeton et al,[34] 2007	1426	1.17 (0.60-2.26)
Combined (random-effects model)		0.86 (0.65-1.13)



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.
[a] Additional data were obtained from authors, co-authors, or principal investigators.
[b] Denotes black participants.
[c] Denotes Latino participants.

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,[43] and that the era since the advent of HAART has been defined by higher rates of sexual risk behaviors among MSM,[44-48] outbreaks of STIs,[49-51] and increasing rates of HIV infection.[52-56] 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.[37]

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 2. Odds of HIV Infection Among Circumcised vs Uncircumcised Men Who Have Sex With Men by Study and Design Characteristics

Stratified Variable	No. Circumcised	No. Uncircumcised	k[a]	OR (95% CI)[b]	I^2, %[c]	$1-\beta$[d]
≤50% participants HIV positive[e]	8563	15 337	10	0.84 (0.58-1.21)	58	.86
>50% participants HIV positive	13 793	8617	3	0.85 (0.46-1.54)	80	.92
≤50% participants circumcised	4182	14 628	6	0.76 (0.45-1.28)	59	.91
>50% participants circumcised	23 634	11 123	9	0.90 (0.63-1.27)	60	.85
Male circumcision determined by self-report	14 617	14 672	11	0.89 (0.64-1.26)	61	.84
Male circumcision determined by genital examination	13 199	11 079	4	0.68 (0.35-1.33)	44	.92
HIV status determined by self-report	3735	10 888	2	1.03 (0.51-2.06)	53	.93
HIV status determined by diagnostic test	24 070	14 859	12	0.84 (0.62-1.14)	58	.82
Prospective studies	9184	2376	4	1.01 (0.55-1.84)	61	.92
Cross-sectional studies	18 632	23 375	11	0.80 (0.58-1.11)	64	.84
Bivariate analyses[f]	27 651	25 345	13	0.90 (0.68-1.19)	63	.79
Multivariate analyses[f]	4553	1795	5	0.72 (0.39-1.33)	68	.92
Published data	17 380	9684	6	0.75 (0.49-1.17)	71	.89
Unpublished data	10 436	16 067	9	0.93 (0.68-1.36)	33	.85
US studies	23 002	11 271	8	0.91 (0.66-1.27)	62	.84
Non-US studies	4814	14 480	7	0.69 (0.38-1.26)	55	.92
Developed countries (US data included)	27 194	22 927	12	0.91 (0.68-1.21)	64	.80
Developed countries (US data excluded)	4192	11 656	4	0.85 (0.41-1.75)	48	.93
Developing countries	622	2824	3	0.49 (0.16-1.50)	53	.94
>50% White MSM	24 930	20 812	8	0.84 (0.58-1.21)	68	.86
>50% MSM of color[g]	1887	4151	6	0.75 (0.45-1.27)	53	.91
100% Latino MSM	844	3437	3	0.78 (0.38-1.62)	46	.93
Data collected before HAART	3692	504	3	0.47 (0.32-0.69)	0	.87
Data collected after the advent of HAART	24 124	25 247	12	1.00 (0.77-1.30)	47	.77
Higher-quality studies[h]	8712	4385	5	0.79 (0.44-1.40)	53	.91
Lower-quality studies[i]	19 093	21 362	9	0.90 (0.65-1.26)	69	.84
Moderate (22%-66%) male circumcision prevalence	5592	13 107	6	1.00 (0.66-1.53)	44	.88
Large samples[j]	25 767	24 439	8	1.06 (0.77-1.44)	62	.79
Male circumcision determined by genital examination and HIV by diagnostic test[k]	13 199	11 079	4	0.68 (0.35-1.33)	44	.92

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; MSM, men who have sex with men; OR, odds ratio.
[a] k, Denotes the number of individual effect sizes in aggregated analysis. It also denotes the number of studies except Millett et al[33] (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 $1-\beta$ power to detect an association based upon 15% reduction in the odds of HIV infection among circumcised men.
[e] Includes Buchbinder.[37] Only person-years were reported, but HIV prevalence was less than 50%.
[f] Three studies[23,33,37] provided both bivariate and multivariate data.
[g] Four studies[29,31,39,40] 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.
[h] Studies that fulfilled 5 or more of the 8 total criteria in the Newcastle-Ottawa Scale[19] for quality assessment of observational studies.
[i] Studies that fulfilled 4 or fewer of the 8 total criteria in the Newcastle-Ottawa Scale[19] for quality assessment of observational studies.
[j] Analytical samples that included more than 1000 participants.
[k] 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),[57-61] 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.

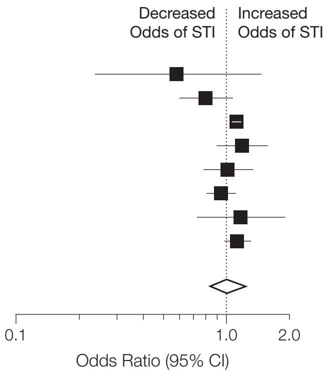
Some patterns in the stratified HIV analyses are of interest as they point to the potentially protective role of circumcision among MSM. Although not statistically significant, circumcision had a stronger protective association with HIV infection in study samples in which circumcision prevalence was 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,[62] 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[63] (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 genital examination, HIV 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[1-3] and a previously published meta-analysis of heterosexual African men.[64]

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[23,29,33,37] 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

Figure 3. Overall Effect Size Estimates for Male Circumcision and STI (Other Than HIV) Among Men Who Have Sex With Men (7 Studies; 8 Findings)

Source	No. of Participants	Odds Ratio (95% CI)
Calzavara et al,[27] 2007	165	0.58 (0.24-1.47)
Kreiss and Hopkins,[23] 1993	498	0.80 (0.60-1.07)
Lafferty et al,[32] 1997	899	1.12 (1.06-1.18)
Millett et al,[33] 2007[a]	1079	1.19 (0.90-1.58)
Millett et al,[33] 2007[b]	957	1.02 (0.78-1.34)
Mor et al,[22] 2007	20 832	0.95 (0.81-1.11)
Sanchez,[29] 2007	1308	1.18 (0.73-1.91)
Templeton et al,[35] 2007	1397	1.13 (0.98-1.31)
Combined (random-effects model)		1.02 (0.83-1.26)



HIV denotes human immunodeficiency virus; CI, confidence interval; and STI, sexually transmitted infection. 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 STI among circumcised men who have sex with men.
[a]Denotes black participants.
[b]Denotes Latino 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).[65] 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)[66] 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.[10]

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

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

Stratified Variable	No. Circumcised[a]	No. Uncircumcised[a]	k[b]	OR (95% CI)[c]	I^2, %[d]	1−β[e]
Any bacterial STI	15 024	9725	6	0.97 (0.70-1.34)	58	.84
Any viral STI	1409	1767	3	1.08 (0.97-1.26)	0	.31
Syphilis	15 024	9725	5	0.93 (0.63-1.37)	39	.87
Herpes simplex	1409	1767	3	1.11 (0.95-1.30)	0	.47
STI determined by self-report[f]	2572	1524	5	0.98 (0.70-1.37)	40	.84
STI determined by diagnostic test[f]	12 661	9479	3	1.06 (0.75-1.51)	49	.85
Bivariate analyses[g]	15 233	11 003	8	1.01 (0.81-1.25)	35	.70
Multivariate analyses[g]	1343	552	3	0.68 (0.23-2.05)	92	.94
Published data	14 109	9257	5	1.01 (0.76-1.35)	54	.80
Unpublished data	1124	1746	3	1.12 (0.98-1.28)	0	.35
Male circumcision determined by self-report	2572	1524	5	0.98 (0.70-1.37)	40	.84
Male circumcision determined by genital examination	12 661	9479	3	1.06 (0.75-1.51)	49	.06
>50% White MSM	14 038	8854	5	0.96 (0.71-1.30)	61	.83
>50% MSM of color[h]	1195	2149	3	1.10 (0.91-1.34)	0	.63
100% Latino MSM	401	1864	2	1.02 (0.78-1.34)	0	.79
Data collected before HAART	421	77	2	0.95 (0.50-1.83)	79	.92
Data collected after the advent of HAART	14 812	10 926	6	1.05 (0.95-1.15)	2	.07
Higher-quality studies[i]	1006	1699	2	1.14 (0.99-1.30)	0	.36
Lower-quality studies[j]	14 110	9257	5	1.01 (0.76-1.35)	54	.80
Moderate (22%-66%) male circumcision prevalence	1239	1115	2	1.11 (0.98-1.26)	0	.29
Large samples[k]	14 393	10 252	4	1.07 (0.97-1.18)	0	.09

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.
[a] One study[32] provided relevant effect sizes but did not report the number for circumcised and uncircumcised men. Any aggregated analyses that include this study underreport the number of participants by circumcision status (eg, any bacterial STI).
[b] k, Denotes the number of individual effect sizes in aggregated analysis. It also denotes the number of studies except Millett et al[33] (2 separate effect sizes for independent samples [black vs Latino men]).
[c] Odds ratios of less than 1 indicate decreased odds of STI among circumcised MSM.
[d] 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%.
[e] Denotes 1−β power to detect an association based upon 15% reduction in the odds of STI among circumcised men.
[f] The studies in this stratified analysis are the same set of studies in the stratified analyses of male circumcision determined by self-report vs genital examination.
[g] Three studies[23,32,35] provided both bivariate and multivariate data.
[h] One study did not report race/ethnicity, but because it was conducted in Ecuador and Peru the data were included in the analysis of MSM of color.
[i] Studies that fulfilled 5 or more of the 8 total criteria in the Newcastle-Ottawa Scale[19] for quality assessment of observational studies.
[j] Studies that fulfilled 4 or fewer of the 8 total criteria in the Newcastle-Ottawa Scale[19] for quality assessment of observational studies.
[k] Analytical samples that included more than 1000 participants.

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.[44-48] Additional studies are necessary to elucidate further the relationship between circumcision status and HIV infection or STIs among MSM.

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Study concept and design: Millett, Flores.
Acquisition of data: Millett.
Analysis 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.
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