

# Male circumcision for prevention of heterosexual acquisition of HIV in men – a Cochrane review

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## Background

Male circumcision is defined as surgical removal of all or part of the foreskin of the penis, practiced as part of a religious ritual usually conducted shortly after birth or in childhood; as a medical procedure related to infections, injury or anomalies of the foreskin; or as part of a traditional ritual as an initiation into manhood.<sup>1</sup> For over a decade observational studies have suggested an association between male circumcision and HIV infection in males, most suggesting a protective effect of male circumcision on HIV acquisition in men.

Six reviews<sup>2-7</sup> and one meta-analysis<sup>6</sup> of these observational studies have been published, reaching different conclusions on the association between male circumcision and HIV infection. In this Cochrane review [see Box 1] we assess the likelihood that use of circumcision as an intervention will reduce transmission of HIV infection to men. This review thus differs in aim from previous reviews, which concentrated on assessing evidence of the association between circumcision and HIV.

Circumcision itself may be a proxy measure of the knowledge and behaviour learnt during initiation, when young men are taught about traditional sexual practices, including monogamy and penile hygiene. Circumcision practices are largely culturally determined, so there are strong beliefs and opinions surrounding them. It is important to acknowledge that researchers' personal biases and dominant circumcision practices of their respective countries may influence interpretation of findings. In addition, viral load is increasingly considered to be crucial in HIV transmission,<sup>8</sup> and may be both an important confounder and an effect modifier.

## Objective

To assess the evidence of an interventional effect of male circumcision for preventing acquisition of HIV-1 and HIV-2 by men through heterosexual intercourse.

## Methods

### Search strategy

We searched online for published and unpublished studies in *The Cochrane Library* (issue 2, 2002), MEDLINE (April 2002), EMBASE (February 2002) and AIDSLINE (August 2001). We also searched databases listing conference abstracts, scanned reference lists of articles, and contacted authors of included studies and researchers working in the field to source unpublished studies. The search was not limited by language.

### Selection criteria

We searched for randomised and quasi-randomised controlled trials of male circumcision or, in their absence, observational studies that compared rates of HIV-1 and HIV-2 infection in circumcised and uncircumcised heterosexual men.

### Data collection and analysis

Independent reviewers selected studies, assessed study quality and extracted data. We stratified studies based on study design and whether they included participants from the general population or high-risk groups (such as patients treated for sexually transmitted infections). We expressed findings as crude and adjusted odds ratios (OR) together with their 95% confidence intervals (CI) and conducted a sensitivity analysis to explore the effect of adjustment on study results.

## Box1

### What is a Cochrane review?

A Cochrane systematic review differs from a traditional narrative review in that it is systematic, attempts to reduce bias by extensive searches, is explicit in its methods, is current and is regularly updated, and uses meta-analysis when appropriate. Each review undergoes two stages of peer review and completed reviews are published by the Cochrane Collaboration in an electronic database, The Cochrane Library, produced quarterly.



## Results

We identified no completed randomised controlled trials (RCTs). Three RCTs are currently under way or commencing shortly. We found 35 observational studies: 16 conducted in the general population and 19 in high-risk populations. Meta-analysis was not performed as many of the studies had a high likelihood of bias and heterogeneous results (Box 2), suggesting that any overall summary statistic is likely to be misleading. Synthesis focused on describing the direction and consistency of effect, assessing the likelihood of bias, and investigating factors that may explain differences between the results of studies.

### Box 2 What is heterogeneity?

Heterogeneity refers to the variability between studies: it can be methodological, clinical or statistical. When there is excessive heterogeneity in the results of studies, we call it statistically significant. This would suggest that the studies are too different from each other to combine into one outcome in a meta-analysis

### Methodological quality of included studies

Overall study quality was highly variable. **Performance bias** (misclassification of exposure) may be present in all studies where circumcision status was obtained by self-report rather than direct observation; 15 studies assessed circumcision status by self-report and 20 by direct observation. **Detection bias** (misclassification of outcome) was rare as nearly all studies ( $N = 33$ ) used blinded methods for assessing and confirming HIV status.

All 5 cohort studies included were susceptible to **attrition bias** as loss-to-follow-up was either greater than 20%,<sup>9,10</sup> unequal between circumcised and uncircumcised groups,<sup>11</sup> or unclear.<sup>12,13</sup>

**Selection bias** was problematic in all studies, and results were potentially confounded by other risk factors for transmission of HIV such as sexual behaviour and religion. Circumcised and uncircumcised groups (in cohort and cross-sectional studies) and HIV-positive and HIV-negative groups (in case-control studies) were seldom balanced for all or most of the 10 risk factors that we identified as potential confounders prior to quality assessment (see Box 3). Statistical adjustments for measured confounding factors were made in 14 of the 35 included studies. Adjusted confounders differed across studies in number and type.

## General population study results

We identified 1 cohort study, 14 cross-sectional studies and 1 case-control study conducted in the general population. The unadjusted results are graphically depicted in Figure 1.

The single cohort study<sup>3</sup> ( $N = 5516$ ) showed a significant difference in HIV transmission rates between circumcised and uncircumcised men [OR = 0.58; 95% CI: 0.36 to 0.96]. The adjusted OR was 0.53 (95% CI: 0.33 to 0.87).

The 14 cross-sectional studies<sup>14–24</sup> had inconsistent findings. Eight were in the direction of benefit while 6 were in the direction of harm, with point estimates of ORs ranging between 0.28 and 1.73. Six studies had statistically significant results, 4 in the direction of benefit and 2 in the direction of harm. The test for heterogeneity (see Box 3) was highly significant ( $P < 0.00001$ ); 86% of variability between studies was attributable to between-study differences and not random variation. Nine studies reported adjusted ORs, with 8 in the direction of benefit, ranging from 0.26 to 0.80. Use of adjusted results tended to show stronger evidence of an association, although they remained heterogeneous ( $P < 0.00001$ ); 83% of variability in adjusted results not being explainable by chance alone.

Only 1 case-control in a general population was included.<sup>25</sup> This study was small ( $N = 51$ ) and found no significant difference in HIV transmission rates between circumcised and uncircumcised men [OR = 1.90; 95% CI: 0.50 to 7.20].

### Box 3 The 10 potentially important confounders

- Age
- Sexual behaviour
- Location of trial
- Religion
- Education, occupation, socio-economic status
- Sexual behaviour – measured by age at first intercourse, number of sexual partners, contact with sex workers
- Any sexually transmitted infections
- Condom use
- Migration status, travel to different countries
- Other possible exposures, e.g. injection, blood transfusions

Figure 1

Review: Male circumcision for prevention of heterosexual acquisition of HIV in men  
Comparison: 01 Circumcision versus No circumcision  
Outcome: 01 HIV status in General Population groups

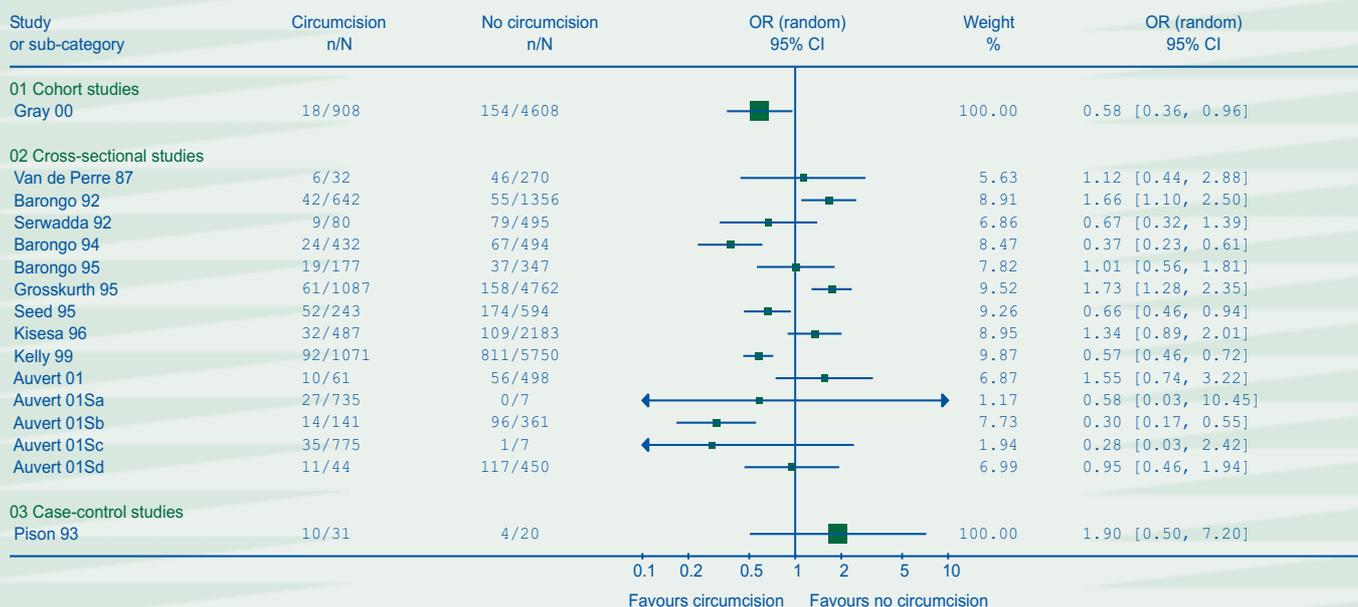
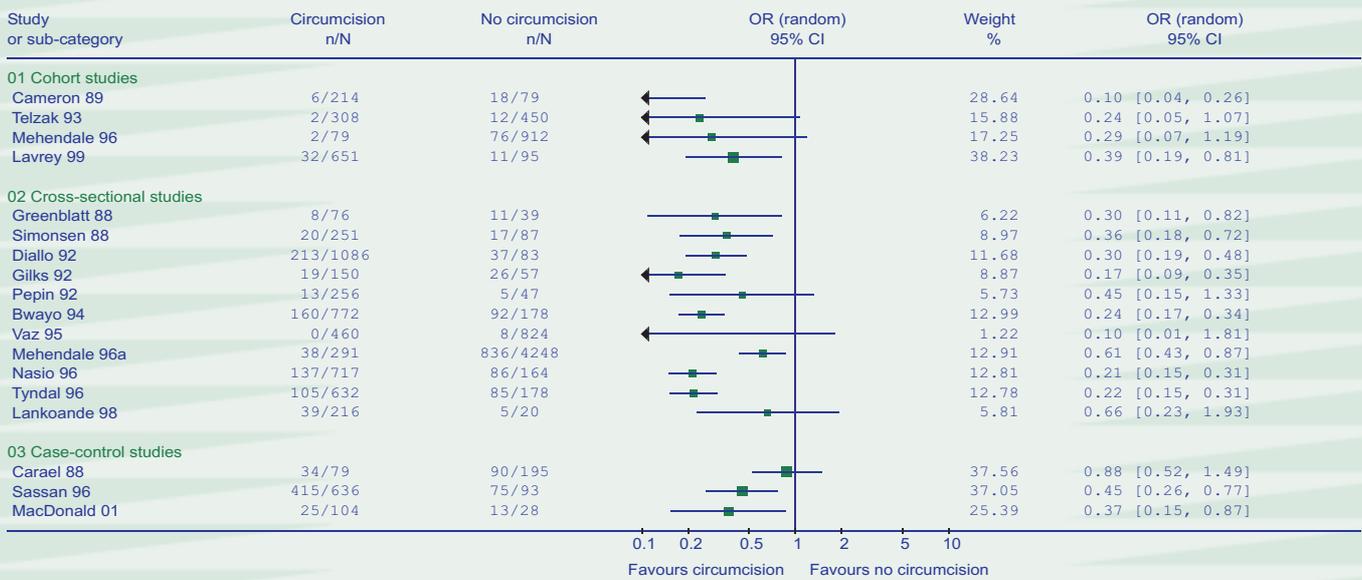


Figure 2

Review: Male circumcision for prevention of heterosexual acquisition of HIV in men  
 Comparison: 01 Circumcision versus No circumcision  
 Outcome: 02 HIV status in High Risk groups



### High-risk group study results

We identified 4 cohort studies, 12 cross-sectional studies and 3 case-control studies conducted in high-risk groups. The unadjusted results are graphically depicted in Figure 2.

The 4 cohort studies<sup>9-12</sup> were all in the direction of benefit from circumcision, and 2 had statistically significant results. Point estimates varied from odds ratios of 0.10 to 0.39. Between-study heterogeneity was not significant; however, 42% of the variability in results was not explicable by chance. The studies were clinically diverse: 2 conducted in Kenya, 1 in truck drivers<sup>10</sup> and the other in a sexually transmitted infections (STI) clinic<sup>11</sup>; the third conducted in a STI clinic in India<sup>9</sup> and the fourth in a STI clinic in New York City.<sup>12</sup>

Unadjusted results from 11 cross-sectional studies<sup>9, 26-35</sup> were in the direction of benefit, 8 being statistically significant. Estimates of effect varied from ORs of 0.10 to 0.66. Between-study heterogeneity was significant ( $P = 0.0009$ ); 66% of variability in results was not explicable by chance. Four of the cross-sectional studies report adjusted ORs ranging from 0.20 to 0.59, and all were significant. One additional study<sup>36</sup> only reported an adjusted OR in the direction of benefit which was statistically significant.

Three case-control studies<sup>37-39</sup> met inclusion criteria and were all in the direction of a protective effect of circumcision on HIV status, 2 being statistically significant. The test for between-study heterogeneity was marginal; 54% of variation in results could not be explained by the play of chance. One study<sup>38</sup> reported an adjusted OR of 0.50 (95% CI: 0.30 to 0.77).

### Sensitivity analysis

Seventeen studies reported both crude and adjusted effects. In general, adjustment made little difference to size, direction or significance of effects in 11 studies. The 6 studies with substantial differences between crude and adjusted results all changed in favour of a protective effect of circumcision, one adjusted OR being significant. All these studies were cross-sectional studies in the general population. Use of adjusted results where available made little difference in the observed degree of heterogeneity.

### Discussion

There are currently no RCTs assessing effectiveness of male circumcision in preventing HIV acquisition in heterosexual men. However, three large trials are currently under way in Kenya ( $N = 2776$ ), Uganda ( $N = 5000$ ) and South

Africa ( $N=3500$ ), scheduled for completion in 2005/6. Properly conducted RCTs are regarded as the best method of assessing effectiveness of health care interventions as they generate comparable intervention and non-intervention groups, the only differences between groups being attributable to the effect of the intervention, or chance.

Due to the lack of RCT evidence, and prompted by publication of other reviews reporting that male circumcision provides a protective effect on HIV acquisition in heterosexual men, we assessed the evidence of the benefits of circumcision available from observational studies. Observational studies differ in two important ways from RCTs. First, the intervention (circumcision) did not occur as part of the study, nor was it likely that it occurred directly for reason of possible HIV prevention. Most study participants were likely to be circumcised for cultural or religious reasons. In addition, age of circumcision was not reported in most studies and could have an influence on results. If circumcision was conducted after HIV acquisition, a potential protective effect could be missed. Secondly, the studies were not designed to have comparable circumcised and non-circumcised groups. As HIV is related to sexual behaviour, which may in turn be partly determined by culture and religion, strong confounding factors in these studies seem likely.

In assessing the quality of the observational studies we identified 10 potentially important confounders that studies would need to ensure were either balanced between circumcised and uncircumcised groups or, if unbalanced, that were adequately adjusted for (see Box 2). Many studies either did not measure these variables or, if reported, were either not balanced between groups or not adjusted for. It is important to note that observational studies, unlike RCTs, can only adjust for known confounders, and only then if they are measured without error. The effect of unknown confounders may well be operating in either direction within and across all of the included studies.

The studies from high-risk groups included in this review do report a powerful protective effect of circumcision, measured by both unadjusted and adjusted odds ratios. More mixed results were reported for the general population. As all the observed results could be explained by likely confounding, RCTs are essential before circumcision is implemented as a public health intervention. Implementation of circumcision will encounter cost, both financial and in terms of potential personal harm; **no adverse effects are reported in this review only because none of the observational studies investigated them.** Feasibility issues of implementation are beyond the scope of this review but need to be carefully considered. ■■■■➔

## Implications for practice and policy

Despite the positive results of a number of observational studies, there are not yet sufficient grounds to conclude that male circumcision, as a preventive strategy for HIV infection, does more good than harm. The results of current ongoing RCTs will need to be carefully considered before circumcision is implemented as a public health intervention for prevention of sexually transmitted HIV.

## Implications for consumers

It would be prudent for consumers to await the findings of ongoing randomised trials before deciding on the balance between benefits and risks of male circumcision in the context of HIV infection.

## Implications for research

Randomised trials assessing the effects of male circumcision across diverse cultural and religious groups are urgently needed. Short-term trials will need to be conducted on sexually active adults and longer trials on pre-adolescents to adequately assess the effect on HIV acquisition. Trials must measure sexual practices, especially any changes from pre-circumcision behaviour, to evaluate whether the benefit of circumcision occurs through changed sexual behaviour or the absence of the foreskin.

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