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Review Article

Male Circumcision and HIV/AIDS Risk – Analysis of the Scientific Evidence

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ABSTRACT

Objective: The aim of this review was to evaluate the scientific evidence supporting the hypothesis that male circumcision reduces the risk of HIV infection and consequently the incidence of acquired immunodeficiency syndrome (AIDS).

Patients and Methods: We performed a literature search of the major databases (Medline, Embase, Cochrane Library, Biosis and Science Citation Index) for papers published in the period 1999 to 2008, using the terms "male circumcision", "HIV infection" and "sexually transmitted infection," plus the combination of the search terms "foreskin" and "HIV receptor" to identify 1,048 articles. We reviewed the abstracts to identify 278 articles meriting detailed review. This detailed review considered how well individual studies were designed and carried out, using a standard checklist to provide a systematic quality rating for individual studies. This process identified a total of 80 papers, which were rated following the level of evidence and grade of recommendation scales modified from the Oxford Center for Evidence-Based Medicine.

Results: Detailed analysis of the selected articles on male circumcision and HIV infection risk revealed the following. Systematic reviews, meta-analyses and modeling studies: there were 11 papers, 10 positive (favoring circumcision) and 1 negative; of the 10 positive studies, 4 were level 3 evidence, 5 were level 2 and 1 was level 1 evidence. Randomized controlled trials: there were 3 studies, all positive with level 1 evidence. Non-randomized cohort studies: there were 6 papers, 5 were positive (2 level 3 and 3 level 2 evidence) and 1 was negative (level 3 evidence). Case-control studies: there were 12 studies, 11 positive (all level 3) and 1 negative (level 3 evidence). Case series: there were 2 studies, both positive (level 3 evidence). Expert opinion: there were 34 studies, 30 positive (15 level 4, 15 level 3 evidence), 2 negative (both level 4) and 2 neutral (both level 4 evidence). Cost-effectiveness studies: there were 3 studies, all positive, all level 2 evidence. Pertinent biological studies: there were 3 studies, all positive, all level 4 evidence. The three large, exceptionally well-done randomized, controlled trials of adult male circumcision among consenting, healthy men in three African countries enrolled a total of 10,908 uncircumcised, HIV-negative adult men. The cumulative HIV infection risk estimated using intention-to-treat Kaplan-Meier analysis showed an overall rate ratio (RR) of 0.42 (95% confidence interval (CI) 0.31-0.57), corresponding to a protective effect of 58% (95% CI 43-69%). Meta-analysis of the "as-treated" results of the three trials showed even stronger protection against HIV infection in the circumcision group (summary RR 0.35, 95% CI 0.24-0.54).

Conclusions: Rigorous analysis of the available scientific evidence clearly supports a positive recommendation that male circumcision should be actively promoted in populations at high risk of HIV infection. There is a need to provide safe male circumcision services for high-risk populations, because this is one of very few proven HIV prevention strategies. Male circumcision provides a much-needed addition to the limited HIV prevention armamentarium. The challenges to implementation must now be faced.

Keywords : male circumcision, HIV/AIDS

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INTRODUCTION

During the past two decades there has been considerable controversy regarding the question whether male circumcision reduces the risk of human immunodeficiency virus type 1 (HIV) infection and, consequently, the incidence of the acquired immunodeficiency syndrome (AIDS).

An increased risk of uncircumcised men acquiring HIV or other sexually transmitted infections (STIs) may be explained by a number of plausible biological mechanisms. These include an increased rate of inflammatory conditions, susceptibility of the mucosal surface of the prepuce to trauma, and the longer survival of pathogens in the warm, moist subpreputial space. The lack of keratinization and the high density of HIV target cells make the inner foreskin especially susceptible to HIV infection, compared with the keratinized surface of the outer foreskin and glans[1-4].

The possibility that male circumcision may protect against HIV infection was first suggested in 1986[5]. Ecological studies in areas with low prevalence of male circumcision and high HIV prevalence in sub-Saharan Africa and in developing countries elsewhere have supported this hypothesis[6,7]. Further evidence comes from systematic reviews of observational study data comparing HIV infection rates in circumcised and uncircumcised men[1,8]. A meta-analysis of 15 studies adjusted for potential confounders found the reduced risk of HIV infection in circumcised men to be large and highly significant (adjusted risk ratio (RR) 0.42, 95% confidence interval (CI) 0.34-0.54)[1]. Subsequent studies have reported similar findings[9].

Three randomized clinical trials of adult male circumcision in South Africa, Kenya, and Uganda have reported highly significant decreases in HIV infection risk among participants randomly assigned to circumcision[10-12]. Nonetheless, the controversy about male circumcision and HIV/AIDS transmission has not been laid to rest completely.

The aim of this review was to evaluate the scientific evidence supporting the hypothesis that male circumcision reduces the risk of HIV infection and consequently the incidence of AIDS.

PATIENTS AND METHODS

We performed a literature search for papers published or accepted for publication in peer reviewed journals, and excluded papers published in non-peer reviewed supplements. The search included the last 10 years of data in the major databases (Medline, Embase, Cochrane Library, Biosis, and Science Citation Index).

For inclusion in the final analysis, we required papers that either contained original data or original data analyses, such as systematic reviews or meta-analyses. We also included relevant articles on possible biological mechanisms and articles that reviewed selected data and opinions. The search strategy used the term “male circumcision” combined with the terms “HIV infection,” “complications,” “acceptability,” and “sexually transmitted infection,” plus the combination of the search terms “foreskin” and “HIV receptor” to identify 1,048 articles.

Included papers were rated according to levels of evidence. The hierarchy of study types was: systematic reviews and meta-analysis or modeling, randomized controlled trials, non-randomized cohort studies, case-control studies, case series, and expert opinion (as the lowest level). In addition, we included other relevant biological studies and cost-effectiveness studies. We reviewed the titles and abstracts of the articles identified in the initial search to identify 278 articles meriting detailed review.

Table 1: Summary of randomized controlled clinical trials of male circumcision to prevent HIV infection in three African countries.

	South Africa[10]	Kenya[11]	Uganda[12]
Participants			
Control	1,582	1,393	2,522
Circumcision	1,546	1.391	2,474
Age range (years)	18-24	18-24	15-49
Setting	Peri-urban	Urban	Rural
Circumcision method	Forceps-guided by local general practitioners, Monopolar cautery	Forceps-guided by study clinicians, No cautery	Sleeve method by study clinicians Bipolar cautery
Visit schedule (months)	3, 12 and 21	1, 3, 6, 12. 18 and 24	6, 12 and 24
Retention rate	92% at 21 months	86% at 24 months	90% at 24 months
Person-years of follow-up	4,693	4,428	6,744
HIV infections (circumcision:control)	20:49	19:46	22:45
Risk ratio (95% CI)	0.41 (0.24-0.69)	0.41 (0.24-0.70)	0.43 (0.24-0.75)
Summary risk ratio for all three trials (95% CI)		0.42 (0.31-0.57)	

CI = confidence interval. Modified from Weiss, et al.[9]

This detailed review considered how well individual studies were designed and carried out using a standard checklist to assure that a consistent approach was used in the methodological assessment of the evidence. The objective of the checklist was to provide a systematic quality rating for individual studies. This process identified a total of 80 papers, representing every study type category.

Papers were rated following the level of evidence scale modified from the Oxford Center for Evidence-Based Medicine (http://minerva.minervation.com/cebm/docs/levels.html.) Levels of evidence were assigned as either positive (circumcision reduces HIV infection risk) or negative (circumcision does not reduce HIV infection risk). A level of evidence was given to each individual study.

- **Level 1 evidence:** meta-analysis of randomized controlled trials (RCTs) or a good quality RCT, or 'all or none' studies in which no treatment is not an option.
- **Level 2 evidence:** "low quality" RCTs (e.g. < 80% follow-up) or meta-analysis (with homogeneity) of good quality prospective 'cohort studies'.
- **Level 3 evidence:** good quality retrospective 'case-control studies' or good quality 'case series', or high-quality systematic reviews of available data that did not incorporate meta-analyses or evaluation of the original data.
- **Level 4 evidence:** expert opinion where the opinion is based not on evidence but on 'first principles' (e.g. physiological or anatomical) or bench research.

As with levels of evidence, the grades of recommendation may apply either positively (do the procedure) or negatively (do not do the procedure). There are four grades of recommendation.

- **Grade A recommendation** usually depends on consistent level 1 evidence and often means that the recommendation is

effectively mandatory and placed within a clinical care pathway. However, there will be occasions where excellent evidence (level 1) does not lead to a Grade A recommendation, for example, if the therapy is prohibitively expensive, dangerous or unethical.

- **Grade B recommendation** usually depends on consistent level 2 and/or 3 studies, or 'majority evidence' from randomized clinical trials (RCT's).

- **Grade C recommendation** usually depends on level 4 studies or 'majority evidence' from level 2/3 studies.

- **Grade D ("no recommendation possible")** is used where the evidence is inadequate or conflicting and when expert opinion is delivered without a formal analytical process.

RESULTS

Detailed review and analysis of the selected articles on studies of male circumcision and HIV infection risk in the period 1999 to 2008 revealed the following.

- **Systematic reviews, meta-analyses and modeling studies**[1,7-9,13-20]: There were 11 papers, 10 positive (favoring circumcision) and 1 negative; of the 10 positive studies, 4 were level 3 evidence, 5 were level 2 and 1 was level 1 evidence.

- **Randomized controlled trials**[10-12]: There were 3 studies, all positive with level 1 evidence.

- **Non-randomized cohort studies**[21-26]: There were 6 papers, 5 were positive (2 level 3 and 3 level 2 evidence) and 1 was negative (level 3 evidence).

- **Case-control studies**[27-39]: There were 12 studies, 11 positive (all level 3) and 1 negative (level 3 evidence).

- **Case series**[40-41]: There were 2 studies, both positive (level 3 evidence).

- **Expert opinion**[6,42-76]: There were 34 studies, 30 positive (15 level 4, 15 level 3 evidence), 2 negative (both level 4) and 2 neutral (both level 4 evidence).

- **Cost-effectiveness studies**[77-79]: There were 3 studies, all positive, all level 2 evidence.

- **Pertinent biological studies**[2-4]: There were 3 studies, all positive, all level 4 evidence.

Therefore, during the last 10 years, the great preponderance of evidence, at all four levels, has been positive, i.e. supporting the hypothesis that male circumcision reduces the risk of HIV infection.

The three large, exceptionally well-done RCTs of adult male circumcision among consenting, healthy men in three African countries enrolled a total of 10,908 uncircumcised, HIV-negative adult men[10-12]. Participants were randomly assigned to circumcision or control arms, then followed for up to 2 years. Retention rates were high (86-92%).

Table 1 shows the cumulative HIV infection risk among men estimated using intention-to-treat Kaplan-Meier analysis. The overall rate ratio (RR) was 0.42 (95% confidence interval (CI) 0.31-0.57), corresponding to a protective effect of 58% (95% CI 43-69%).

The true protection provided by male circumcision may be better estimated by an "as-treated" analysis, assigning outcomes according to the actual circumcision status of participants. All participants did not adhere to the arm they were randomly assigned to. Meta-analysis of the "as-treated" results of the three trials shows even stronger protection against HIV infection in the circumcision group (summary RR 0.35, 95% CI 0.24-0.54)[9].

DISCUSSION

While observational studies showing a statistically significant risk of HIV infection among circumcised men provide provocative

and compelling evidence, they cannot prove causality. However, the three randomized, controlled clinical trials of adult male circumcision conducted in South Africa, Kenya and Uganda do provide compelling evidence that circumcision substantially reduces the risk of female-to-male HIV transmission[10-12].

Comparing the adverse event rates in the three RCTs is complicated because the studies had different visit schedules, adverse event definitions and criteria. In the Kenyan trial, adverse events possibly, probably or definitely related to circumcision occurred in 23 of 1334 circumcised participants (1.7%)[80-81]. All adverse events were mild or moderate and resolved quickly. In the South African trial, the adverse event rate was 54 per 1495 (3.6%) men[10]. In the Ugandan trial, the surgery-related adverse event rate was 7.6% (178/2328)[12]. The risk of moderate adverse events related to surgery was 3% in the Uganda trial, including five severe adverse events (0.2%). All of these events were managed successfully.

Detailed analyses of the African trials indicate that male circumcision is likely to be very cost-effective[77]. The South African trial estimated that the cost per HIV infection averted was about US$ 181, with net savings of US$ 2.4 million over 20 years (cost savings of US$ 2,631 per circumcision). The Kenyan trial estimated the cost as $200 per HIV infection averted[9]. Costs were higher in Uganda, where 39 circumcisions would be needed to prevent one HIV infection over 10 years at a cost of US$ 2,631 per HIV infection averted over 10 years[78]. Because benefits of circumcision are life-long, male circumcision is likely to prove very cost-effective in high-risk African settings.

Several controversial issues remain, including the cultural acceptability of male circumcision in non-circumcising African communities, socio-cultural and economic issues of expanding male circumcision services, and the relevance of the findings for other populations.

The RCT data indicate that adult male circumcision can be safe in limited-resource settings when performed by experienced, well-trained providers. However, when male circumcision is undertaken in septic conditions by inexperienced providers or with poor aftercare, serious complications or even death can result. Thus, implementation of safe adult male circumcision in many African settings will require considerable effort and national policies.

The potential for an increase in unsafe sex practices (known as, 'risk compensation' or 'behavioral disinhibition') after circumcision could potentially offset the protective effect of male circumcision. The Ugandan trial found no difference in sexual behaviors during the trial by circumcision status[12]. The South African trial showed a significantly increased mean number of sex acts between 4 and 21 months among men in the circumcision arm, but no increase in the number of sexual partners or a change in condom use[10]. The Kenyan trial reported a decrease in reported risk-taking behaviors during the 24 months of follow-up in both study arms[11].

The RCT findings are reassuring, but these data may not be generalizable. The trials provided the highest standards of preventative care, with intensive individual counseling. Furthermore, participants did not know that circumcision reduced their risk of HIV infection. The challenges of expanding services within already overstretched health systems include the need to provide adequate counseling to convey the message that male circumcision is a risk-reduction strategy that provides partial protection only.

Nevertheless, the positive findings in the male circumcision RCTs are in stark contrast to recent negative reports of other HIV prevention interventions, including: microbicides, the female diaphragm and gel, treatment to suppress genital herpes infections and, most recently, an adenovirus-based HIV vaccine.

In conclusion rigorous analysis of the available scientific evidence clearly supports a Grade A positive recommendation that

male circumcision should be actively promoted in populations at high risk of HIV infection. There is a need to provide safe male circumcision services for high-risk populations, because this is one of very few proven HIV prevention strategies. In addition to other health benefits, male circumcision provides a much-needed addition to the limited HIV prevention armamentarium. The challenges to implementation must now be faced.

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