The cost-utility analysis of adult male circumcision for prevention of heterosexual acquisition of HIV in men in sub-Saharan Africa: a probabilistic decision model

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ABSTRACT

Objective: The aim of this study was to assess the cost-utility of adult male circumcision (AMC) versus no AMC in the prevention of heterosexual acquisition of HIV in men in sub-Saharan Africa.

Methods: A decision tree was constructed and parameterized using data from published sources. The economic evaluation was conducted from the perspective of government health care payer. Benefits (disability adjusted life years [DALYs]) and costs were discounted at 3%. Costs were assessed in 2008 US dollars. One-way and probabilistic sensitivity analyses were conducted to assess the stability of the base-case results. The uncertainty surrounding the estimates of cost effectiveness was illustrated through a cost-effectiveness acceptability curve and cost-effectiveness plane.

Results: In the base-case analysis, AMC can be regarded as cost saving because it is associated with higher DALYs gained and lower costs than no AMC. The probability that AMC is cost effective is above 0.96 at a threshold value of $150 and remains high over a wide range of threshold values. Thus, there is very little uncertainty surrounding the decision to adopt AMC for prevention of heterosexual acquisition of HIV in men. The results were found to be sensitive to varying any of the following parameters: DALYs averted, discount, and circumcision efficacy.

Conclusions: AMC is found to be cost saving. AMC may be seen as a promising new form of strategy for prevention of heterosexual acquisition of HIV in men, but should never replace other known methods of HIV prevention and should always be considered as part of a comprehensive HIV prevention package.
Introduction

Human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) accounts for about 20% of all deaths and disability adjusted life year (DALY) lost in Africa [1]. The cost of the AIDS epidemic is incurred not only in dollars, but also in the suffering and death of friends, family, and loved ones. The loss to society is untold. The continent has lost productivity and creativity, as well as health and social service dollars. Of the estimated 33 million people infected with HIV worldwide, about half are men, most of whom have become infected through heterosexual intercourse [1]. There is conclusive evidence from observational data [2] and three randomized controlled trials [3–5] that circumcised men have a significantly lower risk of becoming infected with the HIV. There is evidence to support the biological basis for the protective effect of circumcision on HIV transmission. The uncircumcised penis consists of the penile shaft, glans, urethral meatus, inner and outer surface of the foreskin, and the frenulum [6]. Penile shaft and outer surface of the foreskin are covered by a keratinized, stratified squamous epithelium [6]. The inner mucosal surface of the foreskin is not keratinized and is rich in Langerhans’ cells (potential HIV receptors) [7], making it particularly susceptible to the virus. The foreskin is retracted down to the shaft of the penis during heterosexual intercourse and the whole inner surface of the foreskin is exposed to vaginal secretions, providing a substantial area where HIV transmission could take place [6].

New approaches to combat the pandemic are particularly welcome in light of United Nations’ estimates that almost 5 million people become infected with HIV, and more than 2 million people die of AIDS, each year [1]. Innovations in antiretroviral drug treatment have invigorated international efforts to curb the annual burden of AIDS deaths, but preventing new infections remains the key to breaking the back of the epidemic and curtailing the expanding need for treatment [8]. Several innovations demonstrate promise for reducing the efficiency of HIV transmission [9]. However, for any of these approaches to reduce the rate of new infections, they must reach sufficient numbers of people who are likely to transmit or acquire infection, and their protective benefits must not be offset by increased riskier behavior in the targeted community [9,10]. Because population interventions can reach large numbers of at-risk persons inexpensively, they have the potential to be highly cost effective [10]. HIV prevention is still our best hope for fighting the HIV/AIDS epidemic. There is evidence to suggest that adult male circumcision (AMC) can be a cost-effective strategy for prevention of heterosexual acquisition of HIV in men. Several economic evaluations [11–15] have shown that AMC is cost effective, or even cost saving (a cost-saving intervention is one that actually saves society money in the long run by preventing costly medical care) for the prevention of heterosexual acquisition of HIV in men. A preliminary examination of the existing economic evaluations suggests that, studies have tended to focus on population in a limited geographic area, have expressed results in terms of cost per HIV infection averted (HIA), or have not considered DALYs [16]. Most of these studies did not include impact of complications association with AMC in their models [16]. Except for Kahn et al. [15], most of the authors did not consider multivariate sensitivity analysis. Simple series one-way sensitivity analyses cannot provide enough insight into the scale of decision uncertainty [17]. In many models, the uncertainty in the individual parameters may be very unlikely to change a decision. The way to understand the implications for decision uncertainty of imprecisely estimated parameters is to include all of those parameters subject to uncertainty in the sensitivity analysis, and to use the full distributions of those parameters based on all available evidence [17]. This is not possible with simple one-way sensitivity analysis.

To examine these issues further, the present study reports the results of a cost-utility analysis of AMC for the prevention of heterosexual acquisition of HIV in men. The model was populated using data derived from three randomized trials and other sources, and then calibrated probabilistically to represent the joint uncertainty in the input parameters.

Methods

Model structure

We designed a decision-tree model to compare costs and benefits of AMC, which is outlined in Figure 1. The prevention strategy, male circumcision, is compared to a “no-program” option, in which AMC is not offered. The AMC has been described elsewhere. The target population includes all adult male in sub-Saharan Africa. The study assesses the lifetime costs and effects of male circumcision for the prevention of heterosexual acquisition of HIV in men. The time frame is, therefore, lifetime because we estimate there is an expected lifetime of medical care costs for HIV/AIDS. The analytical horizon also includes all of the future benefits, DALY averted associated with each case of HIV infection averted. This anal-

![Fig. 1 - Base-case decision tree for adult male circumcision versus no adult male circumcision.](image-url)
ysis adopts the perspective of a government health-care payer in sub-Saharan Africa. We considered all direct programs and medical costs. Health outcomes and cost accrued beyond 1 year were discounted at 3% for the base-case analysis, 0% and 5% were tested in sensitivity analysis. All cost data were converted to US dollars and inflated to 2008 prices using price inflation index. Results were presented as incremental cost-effectiveness ratio (ICER), mean incremental costs and effects, cost-effectiveness planes (CE-plane), and cost-effectiveness acceptability curves (CEACs). These were chosen to represent the output uncertainty from probabilistic sensitivity analysis (PSA) within the decision-making context [18–19]. CEACs provide a measure of likelihood that a decision to apply a given intervention is correct across a range of “willingness-to-pay” thresholds [18,19]. “Willingness-to-pay” in this context represents the maximum amount a decision maker is prepared to pay for a gain of one DALY averted. The model was developed using the R programming language [20].

Parameters

Parameter estimates were extracted from published data. Table 1 presents the model input parameters and their sources. The prevalence of HIV among uncircumcised male was based on evidence from Demographic and Health Surveys [21]. Only 12 countries with available data on HIV prevalence were included [21]. The rate of complications associated with AMC was estimated from nine published studies [3–5,22–27]. The study considered adverse events related to surgery. The most common adverse events were postoperative bleeding and infections. Other reported adverse events include: wound disruptions, delayed healing, and swelling at the incision site. We calculated the weighted point estimates for prevalence of HIV among uncircumcised male and rate of complication of AMC using meta-analysis. We calculated the prevalence by calculating proportions with 95% confidence intervals (CIs) for each study and then pooled the data to derive a pooled proportion with 95% CI. For the purpose of proportion meta-analysis, the proportions were first turned into a quantity (the Freeman-Tukey variant of the arcsine square root transformed proportion [28]) suitable for the usual fixed and random effects summaries. The pooled proportion was calculated as the back-transform of the weighted mean of the transformed proportions, using DerSimonian weights for the random effects model in the presence of significant heterogeneity [29]. Efficiency of AMC was estimated from three large RCTs [3–5] identified in a recent Cochrane systematic review [30] using fixed and random-effect meta-analysis. The coverage of antiretroviral therapy (ART) was taken from a recent joint United Nations AIDS (UNAIDS) progress report. The cost of AMC and cost of treating complications associated with AMC were taken from the Orange Farm (OF) trial [3]. The lifetime cost of HIV treatment was based on a recent study in South Africa [15]. This study estimated a lifetime cost with ART and without ART. The study did not include non-medical HIV/AIDS costs borne by the patients (e.g., the cost of travel to receive treatment). DALY averted per HIV infections had been previously reported [13].

Sensitivity analysis

To account for uncertainty around model input parameter values, one-way and probabilistic sensitivities were carried out. One way-sensitivity (univariate) analyses were done by varying the parameters according to the ranges in Table 1. Probabilities were varied over the ranges derived from their 95% CIs. Variations in costs, utility, discount, and time horizons were based on estimated minimums and maximums according to the methodology described in recently published work [31]. If not available, standard errors were defined as 25% of the mean, so that a 95% CI would be 50% more or less than mean. Both low and high ICERs were recorded in univariate analyses.

A probabilistic sensitivity analysis (PSA) was performed to demonstrate the robustness of the model against all input assumptions. Using Monte Carlo technique, all model parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Deterministic mean</th>
<th>Range</th>
<th>Distribution</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probabilities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV among uncircumcised males (%)</td>
<td>5.05</td>
<td>2.25–8.89</td>
<td>Beta</td>
<td>(19)</td>
</tr>
<tr>
<td>Effect of male circumcision (OR)</td>
<td>0.43</td>
<td>0.30–0.61</td>
<td>Lognormal</td>
<td>(7–9)</td>
</tr>
<tr>
<td>Rate of complications (%)</td>
<td>10.99</td>
<td>5.62–17.86</td>
<td>Beta</td>
<td>(7–9, 20–25)</td>
</tr>
<tr>
<td>ART coverage (%)</td>
<td>44</td>
<td>41–48</td>
<td>Beta</td>
<td>(48)</td>
</tr>
<tr>
<td>Cost</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male circumcision ($)</td>
<td>65.14</td>
<td>32.58–97.71</td>
<td>Normal</td>
<td>(7)</td>
</tr>
<tr>
<td>Treating complications ($)</td>
<td>15.48</td>
<td>7.74–23.22</td>
<td>Normal</td>
<td>(7)</td>
</tr>
<tr>
<td>Lifetime cost of treating HIV/AIDS</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART ($)</td>
<td>15,410.36</td>
<td>13,045.83–18,757.40</td>
<td>Normal</td>
<td>(34)</td>
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<tr>
<td>No ART ($)</td>
<td>3,465.02</td>
<td>3,050.30–3,905.45</td>
<td>Normal</td>
<td>(34)</td>
</tr>
<tr>
<td>Utilities</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DALY saved per HIV averted</td>
<td>15.50</td>
<td>7.75–23.25</td>
<td>Uniform</td>
<td>(12)</td>
</tr>
<tr>
<td>Discount (%)</td>
<td>3</td>
<td>0–5</td>
<td>Uniform</td>
<td>Assumed</td>
</tr>
<tr>
<td>Time on treatment (years)</td>
<td>15</td>
<td>10–20</td>
<td>Uniform</td>
<td>Assumed</td>
</tr>
</tbody>
</table>

Note: $ - values in 2008 US dollars.
ART, antiretroviral therapy; DALY, disability adjusted life-years; OR, odds ratio.
were varied simultaneously according to pre-specified distributions. Distributions were assigned according to the inherent characteristics of each parameter according to accepted conventions. Beta distribution was used for all probabilities. All costs were assumed to follow a normal distribution. The efficacy of AMC was expressed as odds ratio (OR). We used log-odds ratio, because lognormal distribution asymptotically normalize the skewed OR. Uniform distribution was used for utilities, discount, and time horizon. Results were based on 10,000 Monte Carlo simulations.

Policy makers will wish to identify interventions that are less costly than the comparator and have better health outcomes, called dominant, and rule out those that are more costly and less effective, termed dominated. More costly and more effective interventions may be selected if they are thought to represent good value for money. An intervention was defined as cost effective if it was dominant or had an incremental cost per DALY averted under US$150. The value of US$150 was chosen in the base case, to represent a decision-maker’s valuation of a healthy year of life. This was based on recommendations of the Ad Hoc Committee on Health Research Priorities, which stated that any intervention costing less than US$150 per DALY averted should be considered attractive in low-income countries [32].

Results

Figure 2 shows the odds ratio and 95% CIs from the individual RCTs [3–5] and pooled result. The meta-analysis demonstrated statistically significant superiority of AMC over no AMC in preventing HIV infection (pooled OR = 0.43; 95% CI 0.30 to 0.61); such that participants that underwent AMC were 57% (95% CI 39% to 70%) less likely to be diagnosed with HIV than those without AMC. The pooled effect was identical assuming random or fixed effects. There was no significant statistical heterogeneity between the trial results ($\chi^2 = 0.60; df = 2; P = 0.74$ and $\chi^2 = 0.31; df = 2; P = 0.86$) with the degree of heterogeneity quantified by the $I^2$ as 0% in both analyses. The prevalence of HIV among uncircumcised males ranged from 0% in Senegal to 19% in Lesotho (Fig 3), with the pooled prevalence being 5% (95% CI 2% to 9%). The rate of complications associated with AMC ranged from as low as 2% to as much as 50% (Fig 4), with a pooled complication rate of 11% (95% CI 6% to 18%).

The expected costs and DALYs generated from the model are shown in Table 2. At base-case values of all parameters, the total number of DALY averted by the intervention was 0.28. The base-case was associated with negative net costs (i.e., cost savings) of $91. Thus, AMC dominates no AMC because it is associated with lower cost and higher DALY averted (cost saving). We tested the robustness of the cost-effectiveness results extensively. Figures 5 and 6 depict the results of one-way sensitivity analysis when one parameter value was varied at a time while holding other parameters at their base-case values. AMC was associated with lower cost and higher DALY averted than no AMC for all parameters (dominates). However, incremental cost was most sensitive to the variations in DALY, discount rate, and program effectiveness. DALY averted had the strongest impact on both incremental cost and utility. The incremental cost ranged from minus US$206 to minus $4 when DALY was varied from 7.74 to 23.25. Varying complication rate and ART coverage had little impact on the incremental cost.

Figure 7 presents the 10,000 simulations in terms of incremental costs (y axis) and DALYs (x axis) and takes no AMC into consideration as the reference. A majority (89%) of incremental cost-effect pairs fall in the southeast quadrant of the incremental cost-effectiveness plane, indicating that the AMC is less costly and more effective than the no AMC for the prevention of...
heterosexual transmission of HIV in men. Proportions (11%) of
the points lie in the northeast quadrant, indicating that the AMC
is more costly and also more effective than the no AMC. Figure 8
presents the CEACs for the incremental cost per DALY averted.

As shown in Figure 8, if decision makers were willing to pay
US$150 per DALY, the probability of AMC being cost effective was
0.96. The probability of AMC being cost effective was 100% when
the willing to pay was US$500.

Fig. 3 – Forest plot of the prevalence of HIV among uncircumcised men and 95% confidence intervals (CIs) of individual studies and pooled data.

Fig. 4 – Forest plot of the rate of complications associated with male circumcision and 95% confidence intervals (CIs) of individual studies and pooled data.
Discussion

Main findings

We constructed a decision analytical model to evaluate the cost effectiveness of AMC for the prevention of heterosexual acquisition of HIV in men. The incremental cost effectiveness was conducted from the perspective of the government health-care payer. In the base-case analysis, AMC can be regarded as cost saving because it is associated with higher DALYs gained and lower costs than no AMC. There is also little uncertainty associated with this decision. The probability that AMC is cost effective is above 0.96 at a threshold value of US$150 and remains high over a wide range of threshold values. The sensitivity analyses found that the cost-effective outcomes were not sensitive when varying any of the following parameters: costs of treating complications, rate of AMC-associated complications, and prevalence of HIV among uncircumcised males. The results were found to be sensitive to varying any of the following parameters: DALYs averted, discount, and circumcision efficacy.

Strengths and limitations of the study

This model provided a more favorable cost effectiveness outcome for AMC than the previously published economic evaluations in this area. To the best of our knowledge, this is the first model to incorporate probabilistic sensitivity analysis to give a comprehensive estimate of uncertainty associated with AMC and based results from pooled data from the three large trials. Decision analytical models provided several advantages compared with economic evaluations alongside clinical trials; evidence from multiple sources can be combined and systematic sensitivity analyses done[33]. The prevalence HIV among uncircumcised males and complication rates were based on meta-analysis of several studies from sub-Saharan Africa. This study compared the costs and outcomes of the AMC with what would be expected without any intervention. Comparison with no AMC allows the cost effectiveness of this model of AMC to be compared with any other intervention in health, and not just to be considered as an incremental change to alternative HIV prevention strategies[34]. This method of comparing a health-care intervention with the hypothetical alternative of doing nothing, and using probabilistic sensitiv-

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost</th>
<th>Incremental cost</th>
<th>DALYs</th>
<th>Incremental DALY</th>
<th>ICER ($/DALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deterministic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No male circumcision</td>
<td>282.87</td>
<td>-91.11</td>
<td>9.45</td>
<td>0.28</td>
<td>Dominates*</td>
</tr>
<tr>
<td>Male circumcision</td>
<td>191.76</td>
<td></td>
<td>9.73</td>
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<td></td>
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<tr>
<td>Mean – PSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No male circumcision</td>
<td>266.49</td>
<td>-79.63</td>
<td>10.42</td>
<td>0.31</td>
<td>Dominates*</td>
</tr>
<tr>
<td>Male circumcision</td>
<td>186.86</td>
<td></td>
<td>10.73</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PSA – probabilistic sensitivity analysis

* Dominates- means adult male circumcision is cost-saving as it is associated with higher DALYs gained and lower costs than no circumcision.
ity analyses, follows the WHO health economists’ recommendations for economic evaluation and priority setting [35].

The model adopted a simplistic representation of the risk of acquiring HIV infection among circumcised and uncircumcised adult males. The main limiting assumption of the static model includes the use of non-dynamic process at the level of the risk of each sexual encounter, which could lead to a large underestimate of benefit and cost utility. Similarly, the model could underestimate cost effectiveness of AMC for prevention of HIV, because we assume no direct benefit to the female partners. However, a recent meta-analysis [36] of data from one randomized controlled trial and six longitudinal studies found little evidence that AMC directly reduces risk of HIV in women (pooled risk ratio = 0.80; 95% CI 0.53 to 1.36). The authors of this meta-analysis [36] cautioned that effect male-to-female HIV prevention cannot be ruled out. In addition, the model did not account for the impact of risk compensation that may be associated with AMC. It is not clear how AMC will lead to risk compensation (i.e., circumcised men engaging in riskier sex behavior due to false sense of protection). Several trials found no compelling evidence of increased HIV risk sexual behaviors among circumcised men [4,5,37,38].

Another limitation includes uncertainty in parameter values and the demonstrated sensitivity of the results to changes in some parameter values. All probabilities and utilities used to populate the model are estimates derived from the literature. Each of those estimates carries inherent uncertainty. However, the uncertainty in the evidence base was reflected in the model. To simultaneously assess the implications of uncertainty in all elements of evidence, we used probabilistic analysis to establish the decision uncertainty associated with whether to implement AMC on a large scale [17]. This informs decision makers about the probability of AMC being the most cost effective is conditional on the value that the decision maker places on a unit of health gain. The use of a decision-tree model allowed us to extrapolate clinical outcomes beyond the duration of the existing clinical trials. Models inevitably serve as simplified approximations of the true nature. For simplicity we compared the AMC to no AMC option. In reality, there are other HIV-prevention interventions options. An additional limitation is that the lifetime costs of treating HIV were estimated based upon 2003 cost data [39]. It is possible that significant changes in treatment costs and practices have occurred since then. To address this limitation, we inflated the cost data to 2008 US pricing parity index. We did not include productivity losses due to mortality and morbidity – we assumed that these losses were incorporated in the DALY measures.

**Comparison with other studies**

This analysis supports conclusions of previous economic evaluations [11–15] that AMC would offer a cost-effective approach to
the prevention of heterosexual acquisition of HIV in men. For example, Gray et al. [14] estimated the cost per HIA over 10 years could range from $2808 with 60% circumcision efficacy, to $4173 with 40% circumcision efficacy. Kahn et al. [15] estimated cost per HIA over 20 years at $193, and also reported that the results were sensitive to the cost of AMC, cost of averted HIV treatment, the protective effect of AMC, and HIV prevalence. Auvert et al. [11] found that the estimated costs per HIA over 10 and 20 years were $351 ($271 to $473) and $174 ($138 to $232). The net savings over 20 years was estimated at $2.4 billion (95% percentile interval 1.5 to 3.5). Fieno et al. 2008 [13] estimated the cost per HIV over 20 years at $390. Bollinger et al. [12] estimated cost per HIV and

![Incremental DALY](image)

*Fig. 7 – Incremental cost-effectiveness plane for adult male circumcision versus no adult male circumcision.*

![Cost-effectiveness acceptability curve](image)

*Fig. 8 – Cost-effectiveness acceptability curve for adult male circumcision versus no adult male circumcision.*
net savings over 17 years with 60% circumcision efficacy at $642 and $10,616 respectively.

These findings are comparable with other prevention and treatment strategies in developing countries in terms of economic criteria [40]. Recent reviews of HIV prevention cost effectiveness suggest a range of US$10 to more than $10,000 per HI A [41,42]. South African studies on the cost effectiveness of HIV interventions focus on mother-to-child transmission prevention interventions (with results ranging from cost saving if adjusted for averted medical care cost to $2492 per HI A) [43–46] and the cost effectiveness of ongoing antiretroviral therapy [47,48]. Provision of the female condom to sex workers was found to be cost saving if adjusted for averted medical care costs [49]. A study of rescreening for HIV during late pregnancy found net savings [46], and another study found that targeted sexually-transmitted infection treatment in sex workers costs US$78 per DALY [50].

Conclusion

In conclusion, the results of this analysis suggest that AMC can be regarded as cost saving. There is also little uncertainty associated with this decision. The decision makers can be certain that the probability that AMC is cost effective is above 0.96 at a threshold value of US$150 and remains high over a wide range of threshold values. On these grounds, AMC may be seen as a promising new form of strategy for prevention of heterosexual acquisition of HIV in men. However, our enthusiasm must be tempered by the fact that AMC does not provide complete protection against HIV. In addition, there is no definitive evidence that male circumcision reduces the risk of HIV transmission from men to women [36], or between men who have sex with men [51]. Thus, AMC should never replace other known methods of HIV prevention and should always be considered as part of a comprehensive HIV prevention package, which included: promoting delay in the onset of sexual relations, unprotected penetrative sex, reduction in the number of sexual partners, providing and promoting correct and consistent use of male and female condoms, providing HIV testing and counselling services, and providing services for the treatment of sexually-transmitted infections.

REFERENCES