Male circumcision and HIV prevention – Protection for the individual or the population?

Tim Farley

Control of Sexually Transmitted Infections
Department of Reproductive Health and Research
World Health Organization
Geneva
Global map of male circumcision prevalence at country level, as of December 2006

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: DHS and other publications

© WHO 2007. All rights reserved

No data
< 20% prevalence
20-80% prevalence
> 80% prevalence
Male Circumcision and HIV Infection

- The evidence: male acquisition
  - Ecological
  - Observational
  - Experimental
  - Biological plausibility
- The evidence: female acquisition
  - Observational
  - Experimental
  - Biological plausibility
- Models for impact of expanding male circumcision in high HIV incidence settings
Male circumcision and HIV infection

Bongaarts, AIDS 1989

![Graph showing the relationship between male circumcision prevalence and HIV prevalence.](image)
HIV and MC Prevalence – Africa
Adapted from Halperin & Bailey, Lancet 1999; 354: 1813

MC Prevalence < 20%
MC Prevalence > 80%
HIV and MC Prevalence – Asia
Adapted from Halperin & Bailey, *Lancet* 1999; 354: 1813

<table>
<thead>
<tr>
<th>Country</th>
<th>MC Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia</td>
<td>2.6</td>
</tr>
<tr>
<td>Thailand</td>
<td>1.5</td>
</tr>
<tr>
<td>Burma</td>
<td>1.2</td>
</tr>
<tr>
<td>India</td>
<td>0.91</td>
</tr>
<tr>
<td>PNG</td>
<td>0.6</td>
</tr>
<tr>
<td>Vietnam</td>
<td>0.3</td>
</tr>
<tr>
<td>China</td>
<td>0.1</td>
</tr>
<tr>
<td>Indonesia</td>
<td>0.1</td>
</tr>
<tr>
<td>Philippines</td>
<td>0.1</td>
</tr>
<tr>
<td>Pakistan</td>
<td>0.1</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>0.0</td>
</tr>
</tbody>
</table>

MC Prevalence < 20%

MC Prevalence > 80%
Population based studies - adjusted risk ratios

Weiss et al AIDS 2000 14:2361-2370
* Additional study - not included in published meta-analysis

Adjusted RR

Barongo-2
Kelly
Quigley
Serwadda
Urassa-2
Urassa-3
*4city-Kis
*4city-Nd
*Kumwende
*Kumwende
Combined

Summary RR=0.57
CI=0.47-0.70
High risk groups - adjusted RR

* Additional study - not included in published meta-analysis

Summary RR=0.31, CI=0.23-0.42
Meta-analysis of prospective studies
Weiss et al. 2000

Overall
- Crude OR: 0.52 (95% CI: 0.40 to 0.68)
- Adjusted OR: 0.42 (95% CI: 0.34 to 0.54)

Population-based studies
- Adjusted* OR: 0.57 (95% CI: 0.47 to 0.70)

High risk groups
- Adjusted* OR: 0.31 (95% CI: 0.23 to 0.42)

*Including additional studies not included in published meta-analysis
Male Circumcision and HIV Infection

The evidence: male acquisition
- Ecological
- Observational
- Experimental
- Biological plausibility

The evidence: female acquisition
- Observational
- Experimental
- Biological plausibility

Models for impact of expanding male circumcision in high HIV incidence settings
Randomised controlled trials of male circumcision to reduce HIV infection

Rakai, Uganda
Gray et. al. (2007)
Lancet; 369: 657 – 66

Kisumu, Kenya
Bailey et. al. (2007)
Lancet; 369: 643 – 56

Orange Farm, South Africa
Auvert et. al. (2005)

Randomized Controlled Trials

All three trials of a similar design

– HIV-ve men randomized to immediate or delayed circumcision
– All men given initial and refresher HIV and STI risk reduction counselling during follow-up
– Followed prospectively and tested for HIV at regular intervals
– Information recorded on sexual behaviour, condom use, incident STIs
## Features of Three RCTs

<table>
<thead>
<tr>
<th></th>
<th>Orange Farm</th>
<th>Rakai</th>
<th>Kisumu</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Semi-urban</td>
<td>Rural</td>
<td>Urban</td>
</tr>
<tr>
<td><strong>MC prevalence</strong></td>
<td>20%</td>
<td>16%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Age range</strong></td>
<td>18-24 yrs</td>
<td>15-49 yrs</td>
<td>18-24 yrs</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>3,128</td>
<td>4,996</td>
<td>2,784</td>
</tr>
<tr>
<td><strong>Schedule (months)</strong></td>
<td>3, 12, 21</td>
<td>6, 12, 24</td>
<td>1, 3, 6, 12, 18, 24</td>
</tr>
<tr>
<td><strong>First results</strong></td>
<td>Jul 05</td>
<td>Dec 06</td>
<td>Dec 06</td>
</tr>
</tbody>
</table>
## Results of RCTs

<table>
<thead>
<tr>
<th></th>
<th>Orange Farm</th>
<th>Rakai</th>
<th>Kisumu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (p-yr)</td>
<td>4664</td>
<td>6,744</td>
<td>?</td>
</tr>
<tr>
<td>HIV infections</td>
<td>69</td>
<td>67</td>
<td>69</td>
</tr>
<tr>
<td>HIV+ control</td>
<td>49</td>
<td>45</td>
<td>47</td>
</tr>
<tr>
<td>HIV incid control (per 100 p-yr)</td>
<td>2.1</td>
<td>1.33</td>
<td>4.2</td>
</tr>
<tr>
<td>HIV+ circumcised</td>
<td>20</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>% reduction</td>
<td>60% (32-76)</td>
<td>51% (22-75)</td>
<td>53% (22-72)</td>
</tr>
<tr>
<td>P-value</td>
<td>P &lt; 0.001</td>
<td>P = 0.006</td>
<td>P = 0.0065</td>
</tr>
</tbody>
</table>
### Impact on HIV incidence:
Evidence from observational studies and RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.42 (0.34, 0.52)</td>
</tr>
<tr>
<td>High-risk groups</td>
<td>0.29 (0.20, 0.42)</td>
</tr>
<tr>
<td>General Population</td>
<td>0.56 (0.44, 0.71)</td>
</tr>
<tr>
<td>South Africa</td>
<td>0.40 (0.24, 0.67)</td>
</tr>
<tr>
<td>Kenya</td>
<td>0.41 (0.24, 0.70)</td>
</tr>
<tr>
<td>Uganda</td>
<td>0.49 (0.28, 0.86)</td>
</tr>
</tbody>
</table>
Kisumu RCT: Cumulative HIV Incidence over 42 Months: Circumcision Group versus Controls

Incidence in circumcision: 2.6%
Incidence in controls: 7.4%
RR = 0.36 [0.23, 0.57]

Bailey et al  AIDS 2008 presentation
Male Circumcision and HIV Infection

The evidence: male acquisition
- Ecological
- Observational
- Experimental
- Biological plausibility

The evidence: female acquisition
- Observational
- Experimental
- Biological plausibility

Models for impact of expanding male circumcision in high HIV incidence settings
Biological Rationale for HIV link

Biological plausibility
- Inner mucosa of foreskin is rich in HIV target cells
- External foreskin/shaft keratinized and less vulnerable
- After circumcision, remaining inner aspect of foreskin quickly keratinizes, density of target cells is reduced and cells are less accessible

Foreskin is retracted over shaft during intercourse
- Large inner mucosal surface exposure
- Vulnerable to micro-tears, especially of frenulum

Intact foreskin associated with infections
- Genital ulcer disease
- Balanitis
- Possible increased HIV entry or shedding
### Foreskin Surface Area and HIV Incidence

965 initially HIV-negative men in Rakai population cohort subsequently enrolled in one of two randomised trials of immediate vs. delayed circumcision and foreskin surface area estimated at time of operation.

<table>
<thead>
<tr>
<th>Foreskin surface area</th>
<th>Follow-up (years)</th>
<th>HIV infections</th>
<th>Incidence (/100 py)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;= 26.3 cm²</td>
<td>994.9</td>
<td>8</td>
<td>0.80</td>
</tr>
<tr>
<td>26.4 – 35.0 cm²</td>
<td>975.3</td>
<td>9</td>
<td>0.92</td>
</tr>
<tr>
<td>35.1 – 45.5 cm²</td>
<td>888.5</td>
<td>8</td>
<td>0.90</td>
</tr>
<tr>
<td>&gt;= 45.6 cm²</td>
<td>926.8</td>
<td>23</td>
<td>2.48 IRR 2.37 (1.05 – 5.31)</td>
</tr>
</tbody>
</table>

Ref: Kigozi et al., *AIDS* 2009 (ePub)
Male Circumcision and HIV Infection

- The evidence: male acquisition
  - Ecological
  - Observational
  - Experimental
  - Biological plausibility

- The evidence: female acquisition
  - Observational
  - Experimental
  - Biological plausibility

- Models for impact of expanding male circumcision in high HIV incidence settings
Of 47 couples in whom circumcised *male partner was HIV+ AND* whose viral load was <50,000 particles, *0 female partners were infected* after two years, compared with 26 of 143 female partners of uncircumcised HIV+ men (9.6/100 py) (p = 0.02)
RCT Female HIV Acquisition
Wawer et al., Lancet 2009; 374: 229-237

- Trial conducted in Rakai in parallel with trial among HIV -ve men
- Men screened for eligibility and willingness to participate in RCT of male circumcision
  - HIV –ve men ➔ enrolled in acquisition RCT
  - HIV +ve men
    - if CD4 count > 350, enrolled in transmission RCT
    - Partners linked through Rakai demographic surveillance programme
    - Consenting HIV –ve partners followed and included
### RCT Female HIV Acquisition

**Wawer et al., Lancet 2009; 374: 229-237**

<table>
<thead>
<tr>
<th></th>
<th>Partners of circumcised men</th>
<th>Partners of un-circumcised men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of women</td>
<td>92</td>
<td>67</td>
</tr>
<tr>
<td>Incident HIV infections</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Cumulative HIV infection rate (24m)</td>
<td>21.7% (12.7-33.4%)</td>
<td>13.4% (6.7–25.8%)</td>
</tr>
<tr>
<td>Risk ratio</td>
<td>1.58 (0.68–3.66); p=0.287</td>
<td></td>
</tr>
</tbody>
</table>

1. Circumcision of HIV-infected men did not reduce HIV transmission to female partners over 24 months
2. Longer-term effects could not be assessed
3. Particular concern of excess risk of M → F transmission if resumption of sex before full wound healing (3x higher risk)
Biological Plausibility for Effects of Circumcision on HIV Acquisition in Women

- Female partners of circumcised men have lower prevalence of bacterial vaginosis (risk factor for HIV acquisition)
- Observational data referred to men circumcised many years previously, but long follow-up in cohort not practical
- Possibility of later protective effect, but cannot be confirmed
- Potential short-term increased risk of HIV transmission
Male Circumcision and HIV Infection

The evidence: male acquisition
- Ecological
- Observational
- Experimental
- Biological plausibility

The evidence: female acquisition
- Observational
- Experimental
- Biological plausibility

Models for impact of expanding male circumcision in high HIV incidence settings
Models to Assess Impact and Cost-Effectiveness

- Population groups
  - Circumcised men
  - Uncircumcised men
  - Women
- Age groups for simulating epidemic
  - Either 5- or 10-year intervals
- Targets for intervention
  - Neonates, men before sexual debut, all men, "high risk" men, ...
- Population structure, HIV prevalence and incidence, sexual mixing, ... typical of high-HIV low-circumcision population
  - e.g. Kisumu (Kenya), Zimbabwe, Botswana, ...
HIV Prevalence by Age and Sex

[Swaziland Demographic and Health Survey 2006]

Focus on men before ages of high HIV incidence

Neonatal circumcision easier and cheaper but need to wait 20 or more years before impact
Model Flow Diagram
Hallett et al., PLoS ONE 2008; 3(5): e2212

Age-specific sexual mixing between HIV +/- men and women
Infectiousness varies according to stage of disease
60% lower HIV incidence in circumcised compared with uncircumcised men
Impact of Circumcision on HIV Incidence

1. Immediate impact on HIV incidence in circumcised men (primary [direct] effect)
2. Delayed and somewhat attenuated impact in women (secondary [indirect] effect)
3. Impact in uncircumcised men (tertiary effect)
4. Additional impact in circumcised men

![Graph showing incidence rate ratio over years since intervention starts]
Risk Compensation
Lower condom use with casual partners by circumcised men

1. Impact of circumcision (both direct and indirect effects) sufficiently large that even 50% reduction in condom use results in minimal dilution of effect
Impact of Circumcision Coverage

Model for Circumcision Service Expansion
[informed by Botswana demographic information]

Adult, 15-year and Neonatal Programme

523,000 males 15-49y (80% coverage within 5y)

Maintain age 15y programme until youngest cohorts sufficiently old

23,700 male births annually (80% coverage within 4y)
Conclusion: Protection for Individual or Population?

- High-level generalised epidemics only seen in populations where few men circumcised
- Strong evidence of large individual level effect of circumcision (60% risk reduction)
- Modelling shows important secondary and tertiary effects as HIV incidence and prevalence drop
- Challenge is to support countries with high HIV incidence and little or no tradition of circumcision to scale up services rapidly