Trials of Male Circumcision for HIV and STI Prevention in Men and Women

Godfrey Kigozi
Both trials were population based

Two circumcision trials
HIV-negative men (NIH funded)
HIV+ men (Gates funded)

Consenting HIV-negative and HIV+Men were enrolled and randomized to circumcision or control arms

Consenting wives of married male participants were enrolled into A follow up study
Trial of Male Circumcision for HIV Prevention in Men

• Enroll HIV-negative uncircumcised men, randomize to:
  • Immediate MC (Intervention n= 2474)
  • MC delayed 24 months (Control n=2522)
  • Follow up at 6, 12 and 24 months

• **Endpoints:**
  • HIV incidence
  • Safety
  • Behavioral disinhibition
  • STIs and STI symptoms
HIV incidence over 24 months by Circumcision Status

<table>
<thead>
<tr>
<th>Intervention HIV Incidence /100 py</th>
<th>Control HIV Incidence /100 py</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.66</td>
<td>1.33</td>
<td>0.40 (0.23-0.70)</td>
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</tbody>
</table>

HIV reduction - 60%

Gray et al Lancet 2007
Meta-analysis: Circumcision
For HIV prevention in HIV-neg men

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational studies</td>
<td>0.42 (0.34,0.54)</td>
</tr>
<tr>
<td>Trials</td>
<td></td>
</tr>
<tr>
<td>South Africa</td>
<td>0.41 (0.24,0.69)</td>
</tr>
<tr>
<td>Auvert et al. Plos Med 2005</td>
<td></td>
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<tr>
<td>Kenya</td>
<td>0.41 (0.24,0.70)</td>
</tr>
<tr>
<td>Bailey et al Lancet 2007</td>
<td></td>
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<tr>
<td>Uganda</td>
<td>0.43 (0.24,0.75)</td>
</tr>
<tr>
<td>Gray et al Lancet 2007</td>
<td></td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>0.42 (0.31,0.57)</td>
</tr>
<tr>
<td><strong>HIV reduction 58%</strong></td>
<td></td>
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</tbody>
</table>
Circumcision and Sexual satisfaction/dysfunction in men and women

- Sexual satisfaction in men was 98.4% in circumcised and 99.9% among controls.

- 57.3% of women partners of circumcised men reported no change and 39.8% an improvement in sexual satisfaction.

*No adverse effects on male and female sexual satisfaction or function* (Kigozi et al Brit J Urol 2008)
Reduction of STIs with Circumcision in Men

• Genital Ulcer Disease (GUD)
  • RR = 0.53 (0.43-0.64)  Gray et al Lancet 2007
• HSV-2
  • RR = 0.72 (0.56-0.92)  Tobian et al NEJM 2009
• HPV
  • RR = 0.67 (0.51-0.82)  Gray et al JID 2010
• Pro-inflammatory anaerobes
  • Marked reduction following circumcision  (Price et al Plos One 2010, Liu et al Mbio 2013)
HIV Incidence higher with larger foreskin surface area: Size matters!

Comparison of pre-MC HIV incidence by foreskin surface area measured after circumcision

HIV Incidence by Foreskin Surface Area

<table>
<thead>
<tr>
<th>Quartile of Foreskin Area</th>
<th>HIV Incidence/100 py</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25%</td>
<td>0.85</td>
</tr>
<tr>
<td>25-49</td>
<td>1.02</td>
</tr>
<tr>
<td>50-74</td>
<td>1.18</td>
</tr>
<tr>
<td>75+</td>
<td>2.07</td>
</tr>
</tbody>
</table>

IRR = 2.44 CI 1.1-4.8

Kigozi et al, AIDS 2009
The Foreskin Contains HIV Target Cells

CD1A Dendritic cells  CD4 T-cells  CD8 T-cells

Cells for HIV entry in epidermis  Cells for HIV replication and dissemination in dermis

The large the foreskin the more the dendritic and CD4/CD8 T cells

(Johnson, Redd et al JID 2011)
Trial of Circumcision in HIV+ Men

Rationale: Cannot deny MC to HIV+ men
- Stigma in HIV+ men
- Behavioral disinhibition in HIV-neg men

• End points
  • Safety in HIV+ men
  • STI effects in HIV+ men
Surgery-related adverse events in HIV+ compared to HIV-neg men

<table>
<thead>
<tr>
<th></th>
<th>HIV+ men % (N=420)</th>
<th>HIV-neg men % (N=2326)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>3.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>Total</td>
<td>3.1</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Safety is comparable in HIV+ and HIV-neg men

# Genital Ulceration and HPV Infections in HIV+ Men

<table>
<thead>
<tr>
<th></th>
<th>Circumcised HIV+ Men (%)</th>
<th>Uncircumcised HIV+ Men (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital Ulcers</td>
<td>10.0</td>
<td>16.0</td>
<td>0.63 (0.5-0.8)</td>
</tr>
<tr>
<td>HR-HPV Prevalence</td>
<td>55.3</td>
<td>71.7</td>
<td>0.77 (0.62-0.97)</td>
</tr>
</tbody>
</table>

*Circumcision provides benefit to HIV+ men by reducing genital ulceration and HR-HPV infections*

Serwadda et al. JID 2010
Effects of MC on HIV Acquisition in HIV-negative Women

• HIV-negative female partners of HIV+ male circumcision trial participants were invited to be followed up.

• Identified and followed -
  • 93 HIV-ve partners of circumcised men and
  • 70 HIV-ve partners of un-circumcised men

• Followed at 6, 12 and 24 months

• Endpoint:
  • HIV incidence in women
  • STI in Women

(Wawer et al Lancet, 2009)
Female HIV Acquisition by Male HIV+ Circumcision Status

No significant difference in HIV acquisition by partner circumcision status

(Wawer et al. Lancet, 2009)
Female HIV acquisition 0-6 months by resumption of sex and partners’ circumcision wound healing

![Bar chart showing HIV transmission rates](chart)

- **Sex before healing**: 27.8
- **Sex after healing**: 9.5
- **Controls**: 7.9

**P < 0.06**

*Resumption of sex before wound healing increased HIV transmission*
HIV Shedding is Increased After Circumcision of ART Naïve HIV+ men

Shedding was increased for 3 weeks after circumcision especially in ART Naïve HIV+ve men

Tobian et al PLOS Med 2015
Genital Infections in HIV-negative Women by Male Partner’s Circumcision Status

• HIV-negative women with HIV-negative male partners were followed up over 24 months

• Males were randomized to circumcision (n=648) or uncircumcised controls (n=597)

• Women were assessed for vaginal infections and HPV

Wawer et al. Lancet 2011
Vaginal infections and GUD at 24 months by HIV-negative Male Circumcision Status

Partners of circumcised men had lower rates of vaginal infection

(Gray et al Am J Obs Gynecol 2008)
# HR-HPV Infection in HIV-negative Females by Male Partner’s Circumcision Status

<table>
<thead>
<tr>
<th></th>
<th>Male Circumcised</th>
<th>Male Uncircumcised</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR-HPV Prevalence</td>
<td>27.6</td>
<td>38.6</td>
<td>0.71 (0.68-0.85)</td>
</tr>
</tbody>
</table>

*Male circumcision decreased HPV infection in women and could reduce cervical cancer.*

Wawer et al. Lancet 2011
Thanks