The kindest cut: Male circumcision for HIV and STI prevention in men and women

A relief on the tomb of Ankh-Mahor
Overview

- Ecological and observational studies
- Biological Plausibility
- Randomized clinical trials
- Safety and Acceptability
- Future Considerations as a Preventative Measure
HIV prevalence in adults in sub-Saharan Africa, 2001

- 20 – 39%
- 10 – 20%
- 5 – 10%
- 1 – 5%
- 0 – 1%
- Trend data unavailable
- Outside region
Ecologic Relationship Between HIV and Male Circumcision

HIV Seroprevalence (%) vs. % Circumcised males

Bongaarts AIDS 1989

Caldwell; Sci Am; 1996
Meta-analysis of circumcision and male HIV acquisition

Weiss et al AIDS 2000
### HIV Prevalence and age

*Kelly et al AIDS 1999, PhD Dissertation 2001*

<table>
<thead>
<tr>
<th>Current Male age</th>
<th>Circumcised HIV (%)</th>
<th>Uncircumcised HIV (%)</th>
<th>PRR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td>0.8</td>
<td>3.5</td>
<td>0.22 (0.07-0.70)</td>
</tr>
<tr>
<td>25-34</td>
<td>14.6</td>
<td>26.2</td>
<td>0.56 (0.41-0.76)</td>
</tr>
<tr>
<td>35+</td>
<td>9.1</td>
<td>19.2</td>
<td>0.47 (0.30-0.94)</td>
</tr>
</tbody>
</table>

**Effects of MC appear long lasting**
Meta-analysis circumcision and male HIV acquisition by risk groups (Weiss Geneva 05)

<table>
<thead>
<tr>
<th>Population-based</th>
<th>N</th>
<th>RR</th>
<th>95% CI</th>
<th>p-het</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>0.57</td>
<td>0.47-0.70</td>
<td>0.23</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High risk groups</th>
<th>N</th>
<th>RR</th>
<th>95% CI</th>
<th>p-het</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>0.31</td>
<td>0.23-0.42</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>
HIV Acquisition among HIV- Male Partners of HIV+ Female Partners By Circumcision Status In Rakai

Quinn et al NEJM 2000, Gray et al AIDS 2001
Limits to observational studies

- Circumcised men are selected:
  - Religion (Islam, Judaism). Affects risk behaviors, alcohol use etc.
  - Traditional/tribal, puberty rituals
  - Medical indications (phimosis, GUD)

- Possible confounding between reasons for circumcision and potential HIV effects
Age at circumcision

- Infancy or childhood (usually religious in Africa)
- Puberty (ritual and sexual initiation)
- Adult (often for medical indications)
Biological Rationale for circumcision & HIV

- Biological plausibility
  - Inner mucosa of foreskin is rich in HIV target cells (9x cervix)
  - External foreskin/shaft keratinized and not vulnerable
  - After circumcision, only vulnerable mucosa is meatus

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

- Intact foreskin associated with infections
  - GUD
  - Balanitis/phimosis
  - Possible increase HIV entry or shedding
Possible circumcision protective mechanisms

Circumcision

Anatomic effect by removal of foreskin

- Reduced Target cells for HIV
- Reduced GUD, reduced cofactor effects
COMPARISON OF KERATIN THICKNESS ON THE EXTERNAL AND INTERNAL MUCOSAL SURFACES OF HUMAN FORESKIN

Patterson et al. Am J Pathol 2002

External Surface

Mucosal Surface

Patterson et al. Am J Pathol 2002
HUMAN FORESKIN INFECTED WITH HIV-1\textsubscript{Bal} IN EXPLANT CULTURE

Mucosal Surface
- Red-uninfected cells
- Green-infected T-cells
- Yellow-HIV-1 bound to Langerhan’s cells

External Surface

Patterson et al. Am J Path 2002
Circumcision and male GUD and STIs
Meta-analysis of circumcision and symptomatic male GUD

M Thoma R Gray 2006
Meta-analysis of circumcision and male ulcerative STIs (Weiss et al STIs 2006)

- HSV-2  RR = 0.9 (0.8-1.0)
- Syphilis RR = 0.7 (0.5-0.8)
- H.ducreyi RR = 0.06-1.1 (no summary estimate)
- Considerable heterogeneity between studies
Prospective studies of circumcision and male STIs

<table>
<thead>
<tr>
<th></th>
<th>Puna India (Reynolds et al Lancet 2004) RR (CI)</th>
<th>Rakai, Uganda (Gray et al AIDS 2004) RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-2</td>
<td>0.9 (0.5-1.6)</td>
<td>0.9 (0.8-1.0)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>0.6 (0.3-1.3)</td>
<td>1.2 (1.0-1.4)</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>0.8 (0.4-1.8)</td>
<td>0.7 (0.9-2.1)</td>
</tr>
<tr>
<td>Chlamydia</td>
<td></td>
<td>1.7 (0.9-2.9)</td>
</tr>
<tr>
<td>GUD</td>
<td></td>
<td>0.8 (0.7-1.1)</td>
</tr>
</tbody>
</table>
Circumcision and HPV
(Castellsague et al NEJM 2002)

- Multinational case-control study

- Male HPV infection circumcised vs uncircumcised
  OR = 0.37, CI 0.16-0.85

- Monogamous women whose husband’s had 6+ partners. Cervical cancer associated with circumcision
  OR = 0.42, CI 0.23-0.79
Male circumcision and female HIV acquisition

- Observational data of M+/F- discordant couples in Rakai (Gray et al AIDS 2000)
  - Reduced male-to-female transmission if HIV+ male was circumcised: IRR ~ 0.41
  - If HIV+ male viral load < 50,000 cps/mL
    - Male circumcised: No transmission
    - Male uncircumcised: Transmission 9.6/100 py (p = 0.02)
Of 47 couples in which circumcised male partner was HIV+ AND whose viral load was <50,000 particles, 0 of female partners were infected after two years, vs. 26 of 143 female partners of uncircumcised HIV+ men (9.6/100 py) (p = 0.02).

Quinn et al NEJM 2000, Gray et al AIDS 2000
Circumcision and **Male-to-Female** HIV & STI Transmission in Rakai

<table>
<thead>
<tr>
<th>Female Infection</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent HIV</td>
<td>0.76 (0.62-0.92)*</td>
</tr>
<tr>
<td>HSV-2</td>
<td>0.75 (0.54-1.03)*</td>
</tr>
<tr>
<td>BV</td>
<td>0.79 (0.69-0.91)*</td>
</tr>
<tr>
<td>Trichomonas</td>
<td>0.65 (0.55-0.77)*</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>1.06 (0.61-1.84)</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>1.19 (0.51-2.79)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>0.93 (0.76-1.13)</td>
</tr>
<tr>
<td>HPV</td>
<td>0.72 (0.46-1.12)</td>
</tr>
</tbody>
</table>

(Gray et al CROI 2006)  

*P<0.05
Randomized trials of male circumcision for HIV prevention in men

- Three trials:
  - South Africa (ANRS),
  - Kenya (NIH),
  - Uganda (NIH)

- Similar designs:
  - Enroll HIV- uncircumcised men, randomize to:
    - Immediate circumcision (Intervention)
    - Circumcision delayed 21-24 months (Control)
  - Endpoints:
    - HIV incidence
    - Safety
    - Behavioral disinhibition
    - STIs
Rakai Two Circumcision Trials

- NIH sponsored trial:
  - 5000 HIV- men
  - Endpoints: Male HIV incidence, safety, behaviors

- Gates sponsored trial
  - ~ 800 HIV+ men
  - ~ 7000 women
  - Endpoints: HIV incidence in women, STI incidence in men & women, safety in HIV+, behaviors
South African ANRS 1265 Trial

- Trial stopped in Nov, 2004 due to evidence of efficacy at interim analysis
- Intervention n= 1538, Control n= 1590
- Enrollment comparability good
- Cross-over: Intervention 4.8%, Control 8.4%
- Loss to follow up: Intervention 6.8%, Control 9.7%

## South African ANRS Trial

### Incident cases

<table>
<thead>
<tr>
<th></th>
<th>M0-M3</th>
<th>M4-M12</th>
<th>M13-M21</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
<td>2</td>
<td>7</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>9</td>
<td>15</td>
<td>25</td>
<td>49</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>11</td>
<td>22</td>
<td>36</td>
<td>69</td>
</tr>
</tbody>
</table>

### Incidence rates:

- **Intervention**: 0.9 (0.6 - 1.3) /100 py
- **Control**: 2.1 (1.6 - 2.8) /100 py

### Unadjusted RR:

- 0.40 (0.24 – 0.68)  
  
  p=0.00059

### Protection (1-RR):

- 60% (32% - 76%)

### Per Protocol analysis RR:

- 0.25 (.14-.46)  or 75% protection

---

*Auvert et al PLoS Med 2005*
Discussion

- First RCT demonstrating a strong protective effect of on HIV acquisition in men
  - Trials stopped early often overestimate efficacy
  - Partial protection; Short term effect
  - Consistent with expectation

- Public health response (NIH, UNAIDS)
  - Completion of NIH trials before deciding on policy
  - Make safe circumcision available to men who request it, but do not promote circumcision for HIV prevention

Interim analyses of Kenyan and Ugandan trials June 27
Potential impact of male circumcision: Stochastic simulation model

What is the potential effect of circumcision on:

- HIV incidence in the population?
- Course of the HIV epidemic (reproductive rate $R_0 < 1.0$)
- Number of circumcisions needed to avert HIV infection
- Cost per HIV infection averted
Population HIV incidence by circumcision reduction in male HIV acquisition, and program coverage

Stochastic Simulation Model
(Gray et al IAS 2005)
Population HIV incidence by circumcision reduction in female HIV acquisition, and program coverage

(Gray et al IAS 2005)
Population HIV incidence by combined male and female circumcision efficacy, and program coverage

Maximum impact on incidence if circumcision reduces risk in men and women

(Gray et al IAS 2005)
Number of circumcisions to prevent one incident HIV infection over 10 years, with 75% program coverage

<table>
<thead>
<tr>
<th>RR</th>
<th>Acquisition in males</th>
<th>Acquisition in females</th>
<th>Acquisition in both sexes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Surgeries per infection averted</td>
<td>No. Surgeries per infection averted</td>
<td>No. Surgeries per infection averted</td>
</tr>
<tr>
<td>0.3</td>
<td>31</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td>0.5</td>
<td>46</td>
<td>38</td>
<td>22</td>
</tr>
<tr>
<td>0.6</td>
<td>58</td>
<td>46</td>
<td>27</td>
</tr>
</tbody>
</table>
Cost-effectiveness of male circumcision for HIV prevention

Rakai: Cost per circumcision ~ $69.0
Research study using physicians and fully equipped theaters.
Program costs are likely to be lower
## Cost per HIV infection averted over 10 years

<table>
<thead>
<tr>
<th>RR</th>
<th>Acquisition in males</th>
<th>Acquisition in females</th>
<th>Acquisition in both sexes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cost per infection averted ($)</td>
<td>Cost per infection averted ($)</td>
<td>Cost per infection averted ($)</td>
</tr>
<tr>
<td>0.3</td>
<td>2125</td>
<td>1836</td>
<td>1052</td>
</tr>
<tr>
<td>0.5</td>
<td>3136</td>
<td>2579</td>
<td>1485</td>
</tr>
<tr>
<td>0.6</td>
<td>3911</td>
<td>3136</td>
<td>1806</td>
</tr>
</tbody>
</table>

- Circumcision is likely to be cost-effective if RR ≤ 0.6, especially if protection occurs in both sexes. If circumcision reduces acquisition and subsequent transmission of HIV, GUD, bacterial vaginosis and other STDs (?HPV), the public health impact and cost benefit will be great.

- Longer duration of efficacy increases cost-effectiveness

- Nevirapine $2,517 per infection averted (Sweat *AIDS* 2004)
Effect of disinhibition on HIV incidence, by circumcision
IRR in both sexes combined and 75% coverage

Behavioral disinhibition can offset all benefit, even at high circumcision efficacy
Surgery and risks

- “Forceps guided” method or clamp: Draw foreskin over the glans, clamp and cut (South Africa, Kenya trials)
  - Simpler procedure
  - More bleeding
  - Leaves more residual foreskin

- “Sleeve circumcision”: Dissect the foreskin and remove all foreskin tissue (Rakai)
  - More complex procedure
  - Less bleeding

Fig. 1. Classification of four types of male prepuce. A, foreskin completely covers the glans; B, foreskin covers one half of the glans; C, foreskin beyond sulcus but can be extended to cover one-half of the glans without compressing it; D, foreskin completely absent. From Cancer, Vol. 13, No.3, 1960:444. Copyright 1960 American Cancer Society. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. (Ref. 21).
Dorsal nerve block

- Mixture of bupivacaine 0.25% and lignocaine 0.5% is used.
- Usually 5-6 mls is sufficient to infiltrate the left and right dorsal nerves.
Proximal incision
Lateral view of proximal and distal incisions

Sleeve of foreskin
Remove sleeve of foreskin
Approximation of skin edges and suturing
Wound closure
Inner dressing
Outer dressing
Time to wound healing and resumption of sex: Rakai Trial

- Median time to certified wound healing 28 days
- Median time to resumption of sex 43 days
- Only 11% of men resumed sex before complete wound healing
Safety of circumcision

- Trial complication rates still being determined:
  - Problems of comparability between trials in follow up schedules, observers and definitions
  - Frequency of all moderate or severe complications requiring treatment ~ 2-4% in trials
  - Infections, bleeding, hematoma, wound dehiscence, inadequate skin removal

Rate of wound healing in men With and without complications
Risks of traditional circumcision

- Traditional circumcision complications:
  - ~10% or more??
Acceptability

- Studies in Kenya, South Africa, Uganda, Botswana, Haiti, Tanzania, Zambia and Zimbabwe report acceptability rates of 48-85%. (Rakia ~ 69%)

- Perceived improved hygiene, decreased susceptibility to HIV, and easier condom use.

- Concerns include:
  - Fear of pain
  - Reduced sexual pleasure
  - Limited access to health facilities should complications occur
  - Stigma, religious identity (Islam)
Male circumcision could have a major impact on the HIV epidemic and can be cost-effective, especially if protective in both sexes and over a prolonged period.

Other benefits might include decreased STIs, balanitis and phimosis in men.

Potentially reduced HIV and STIs in female partners.

Possible reduced penile cancer, and cervical cancer among female partners.

Behavioral disinhibition could offset benefits, and intensive risk reduction and integration with other prevention programs will be required.
Programmatic issues

- Scale up to provide safe adult circumcision (training, equipment, supplies/medications etc.)

- Specialized surgical centers to maximize quality of surgery and postoperative care

- Discourage traditional practitioners or poorly trained private practitioners

- Provide neonatal circumcision?

- Prevent behavioral disinhibition and maintain HIV prevention efforts
Acknowledgments

Rakai Health Sciences
- Maria Wawer
- David Serwadda
- Godfrey Kigozi
- Fred Nalugoda
- Stephen Watya

JHU
- Ton Quinn
- Xianbin Li
- Michael Chen

U of Versailles
- Bertran Auvert

U of Illinois
- Robert Bailey

NIH
- Melanie Bacon, Carlie Williams

Gates Foundation
- Renee Ridson