Male circumcision for prevention of STI

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Randomised controlled trials of male circumcision to reduce HIV infection

Rakai, Uganda (Gray et al. 2007)
4996 HIV- men aged 15-49
900 HIV+ men and female partners

Kisumu, Kenya (Bailey et al. 2007)
2784 men aged 18-24

Orange Farm, South Africa
(Auvert et al. 2005)
3274 men aged 18-24

Source: 2006 Report on the global AIDS epidemic
(UNAIDS, May 2006)
Circumcision

- Reduced risk of GUD and other STI
- Direct effect - removal of HIV target cells
- Additional co-factor effect
How the foreskin increases risk of infection

Thinly keratinized mucosal layer of inner foreskin
- susceptible to minor trauma and abrasion
- can facilitate entry of pathogens

Area under foreskin is warm, moist environment, suitable for pathogen replication

Circumcision less likely to affect STIs which directly infect the urethra

McCoombe & Short, AIDS 2006 20:1491-1495
Male circumcision and HSV-2 incidence: Evidence from RCTs

Sobngwi-Tambekou et al, JID 2009 199:958-64
Tobian et al, NEJM 2009;360:1298-309
Male circumcision and HSV-2 incidence: Evidence from RCTs

Sobngwi-Tambekou et al, JID 2009 199:958-64
Tobian et al, NEJM 2009;360:1298-309
Meta-analysis of observational data found a small effect of HSV-2 prevalence (RR=0.88, 95%CI 0.77-1.01) (Weiss et al, STI 2006)

Preliminary data from Kisumu find no effect on HSV-2 incidence (RR=0.99, 95%CI 0.67-1.46) (Bailey, IAS 2007)

Smaller protective effect of MC on HSV-2 than on HIV?
- HSV-2 is shed more widely than HIV and is more transmissible
- HSV-2 does not depend so specifically on infecting target cells in the foreskin
Male circumcision and syphilis

- No effect on acquisition of T. pallidum in Ugandan trial, or from preliminary data in other two trials
  
  Tobian et al, NEJM 2009;360:129; Bailey IAS 207

- Among men who seroconverted in Rakai, intervention arm men were less likely to report GUD symptoms prior to seroconversion (RR=0.33, 95%CI 0.16-0.69)

  Ron Gray, personal communication

- Meta-analysis of observational data shows some protective effect on serological evidence of syphilis (RR=0.67, 95%CI 0.54-0.83)

  Weiss et al, STI 2006; 82:101-110
Male circumcision reduces GUD prevalence: Evidence from RCTs

Gray, CROI 2009; Bailey IAS 2007
Male circumcision reduces risk of GUD: Evidence from RCTs

- **Uganda HIV neg**: RR = 0.54, CI: 0.46-0.66
- **Uganda HIV pos**: RR = 0.63, CI: 0.5-0.8
- **Kenya HIV neg**: RR = 0.53

Gray, CROI 2009; Bailey IAS 2007
Which type of GUD does circumcision protect against?

In Rakai, ulcer swabs were taken and tested for H. ducreyi, T. pallidum, HSV-1 and HSV-2 using real-time multiplex PCR

<table>
<thead>
<tr>
<th></th>
<th>Intervention arm (n=25)</th>
<th>Control arm (n=56)</th>
<th>P-value for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-2</td>
<td>48%</td>
<td>39%</td>
<td>0.62</td>
</tr>
<tr>
<td>T. Pallidum</td>
<td>0%</td>
<td>10%</td>
<td>0.09</td>
</tr>
<tr>
<td>H ducreyi</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>HSV-1</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>Unknown aetiology</td>
<td>52%</td>
<td>61%</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Ron Gray personal communication
Male circumcision and prevalence of high risk HPV genotypes: Evidence from RCTs

Auvert et al, JID 2009; 199:14-19
Tobian et al, NEJM 2009;360:1298-309
Limitations include
- method & site of HPV detection
- no baseline data in South African trial

Previous meta-analysis of 9 observational studies found significant protective effect on penile HPV (OR=0.52, 95%CI 0.33-0.82)

* Xavier Bosch et al, J FPRHC 2009 35(1): 5-7 *

Biological mechanism unclear – HPV infects basal cells of epidermis, and circumcision removes vulnerable foreskin tissue
Male circumcision reduces HPV prevalence

- Is impact on acquisition or clearance of HPV?

- Lu et al showed increased clearance of high risk HPV among circumcised men (adjusted hazard ratio=6.5, 95%CI 1.2-19.8), but no impact on acquisition
  
  Lu et al, JID 2009 199:362-371

- Preliminary data from Ugandan RCT show impact on HPV incidence (RR=0.58, 95%CI 0.40-0.83)

  Ron Gray, Nature Reviews Urology 2009 6:
Male circumcision & N.gonorrhoea: No effect

Results of a non-systematic review of observational studies & RCT

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reynolds</td>
<td>0.78 (0.35, 1.74)</td>
</tr>
<tr>
<td>Dave</td>
<td>1.31 (0.67, 2.56)</td>
</tr>
<tr>
<td>Laumann</td>
<td>0.70 (0.39, 1.26)</td>
</tr>
<tr>
<td>Parker</td>
<td>0.44 (0.19, 1.02)</td>
</tr>
<tr>
<td>Diseker</td>
<td>0.62 (0.38, 1.01)</td>
</tr>
<tr>
<td>Hand</td>
<td>0.65 (0.50, 0.84)</td>
</tr>
<tr>
<td>Cook</td>
<td>0.63 (0.45, 0.87)</td>
</tr>
<tr>
<td>Lavreys</td>
<td>0.90 (0.48, 1.69)</td>
</tr>
<tr>
<td>Hooper</td>
<td>0.88 (0.71, 1.09)</td>
</tr>
<tr>
<td>Taylor</td>
<td>1.00 (0.48, 2.08)</td>
</tr>
<tr>
<td>Smith</td>
<td>0.91 (0.71, 1.17)</td>
</tr>
<tr>
<td>South Africa RCT</td>
<td>0.94 (0.69, 1.28)</td>
</tr>
<tr>
<td>Kenya RCT</td>
<td>0.95 (0.68, 1.33)</td>
</tr>
</tbody>
</table>

Relative risk
Kenya trial:
- As-treated analysis: Rate ratio = 0.87, 95% CI 0.65-1.16

South Africa trial:
- Intention-to-treat analysis: adjusted OR = 0.56, 95% CI 0.32-1.00
- As-treated analysis: adjusted OR = 0.75, 95% CI 0.42-1.32

Mehta et al, JID 2009
Sobngwi-Tambekou et al, STI 2009
Kenya trial:
- As-treated analysis: Rate ratio = 0.77, 95%CI 0.44-1.36

South Africa trial:
- Intention-to-treat analysis: adjusted OR = 0.54, 95%CI 0.28-1.02
- As-treated analysis: adjusted OR = 0.47, 95%CI 0.25-0.92

Mehta et al, JID 2009
Sobngwi-Tambekou et al, STI 2009
# Impact of male circumcision on STIs in women

<table>
<thead>
<tr>
<th>Study</th>
<th>STI</th>
<th>RR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rakai RCT</td>
<td>Trichomonas vaginalis prevalence</td>
<td>0.52</td>
<td>0.05-0.98</td>
</tr>
<tr>
<td></td>
<td>Bacterial vaginosis prevalence</td>
<td>0.60</td>
<td>0.38-0.94</td>
</tr>
<tr>
<td></td>
<td>Genital ulceration prevalence</td>
<td>0.78</td>
<td>0.63-0.97</td>
</tr>
<tr>
<td>Multi-country case-control study</td>
<td>HPV prevalence</td>
<td>0.75</td>
<td>0.49-1.14</td>
</tr>
<tr>
<td></td>
<td>Chlamydia trachomatis prevalence</td>
<td>0.18</td>
<td>0.05-0.58</td>
</tr>
</tbody>
</table>

How much of the impact of MC on HIV can be explained through other STI?

- In Rakai, an estimated 11% (95%CI 5-38%) of incident HIV can be explained by the reduction in GUD
  
  *Ron Gray, personal communication*

- Modelling of the trial data indicates that no more than 10-20% of the HIV cases prevented by circumcision were mediated through a reduction in STI
  
  *Boily et al, ETE 2006*
Circumcision provides
- partial protection against GUD and viral infections (HPV and possibly HSV-2)
- Little protection against urethral infections
- Some evidence of a protection against vaginal infections in women

The effect of circumcision on HIV in men is largely independent of the impact on STI

Results from trials not always consistent - further data on impact of circumcision on STI in different settings needed as scale-up of circumcision continues
Acknowledgments

- Research teams for the 3 randomised controlled trials for male circumcision (PIs Ron Gray, Maria Wawer, Bob Bailey, Bertran Auvert)

- World Health Organization for funding
Male circumcision & chancroid/H. Ducreyi: Meta-analysis of observational studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. ducreyi serostatus</td>
<td>1.11 (0.50, 2.46)</td>
</tr>
<tr>
<td>Asymptomatic controls</td>
<td>0.06 (0.01, 0.36)</td>
</tr>
<tr>
<td>Asymptomatic controls</td>
<td>0.12 (0.06, 0.24)</td>
</tr>
<tr>
<td>Asymptomatic controls</td>
<td>0.43 (0.06, 3.08)</td>
</tr>
<tr>
<td>Urethritis controls</td>
<td>0.66 (0.35, 1.24)</td>
</tr>
<tr>
<td>Urethritis controls</td>
<td>0.62 (0.50, 0.77)</td>
</tr>
<tr>
<td>STD patients</td>
<td>0.20 (0.13, 0.31)</td>
</tr>
</tbody>
</table>

Weiss et al, STI 2006; 82:101-110