MALE CIRCUMCISION FOR STI PREVENTION: HOW WELL DOES IT WORK AND HOW IS IT DONE?

Kawango Agot Impact Research & Development Organization Kisumu, Kenya

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Presentation Outline

PART 1:
- Introduction
- Association of male circumcision with:
  - Human papillomavirus
  - Genital Ulcer Disease
  - Herpes Simplex Virus Type 2
  - Syphilis
  - Gonorrhoea, Chlamydia and Trichomoniasis
- Conclusions

PART 2:
- Current status of male circumcision devices for adolescents and adults
  - PrePex™
  - Shang Ring™
- Conclusions and recommendations

INTRODUCTION TO PART 1

1855: Review of venereal disease patients

<table>
<thead>
<tr>
<th></th>
<th>Jews (n=58)</th>
<th>Non-Jews (n=272)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis</td>
<td>11 (19%)</td>
<td>165 (61%)</td>
</tr>
<tr>
<td>Gonorrhoea</td>
<td>47 (81%)</td>
<td>107 (39%)</td>
</tr>
</tbody>
</table>

Author’s interpretation: “The circumcised Jew is, then, very much less likely to contract syphilis than an uncircumcised person”

MC/STI Association Revisited

- In the 1980s and 1990s, observational studies indicated that male circumcision (MC) was potentially effective against HIV acquisition
- Evidence also emerged that MC could confer protection to non-HIV STIs
- In 2005-2006, three randomized controlled trials (RCTs) demonstrated that MMC reduces by 51-60% the risk of acquiring HIV in African men
- The RCTs also evaluated the effect of MMC on other non-HIV STIs
- Since the RCTs, additional studies, systematic reviews and meta-analyses have explored the association between MMC and various STIs
### Human Papillomavirus

**Association between MC and HPV: S. Africa & Kenya RCTs**

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Author</th>
<th>Population</th>
<th>Effect size (95% CI)</th>
<th>Other Info</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of MC on the prevalence of high-risk HPV in young men: Results of a RCT in Orange Farm, South Africa</td>
<td>Auvert et al; J Infect Dis 2009</td>
<td>South Africa Young men (n=3274)</td>
<td>PRR 0.66 (0.51-0.86)</td>
<td>Incidence in high risk HPV</td>
</tr>
<tr>
<td>Association of Low-Risk HPV Infection with MC in Young Men: Results from a Longitudinal Study Conducted in Orange Farm, South Africa</td>
<td>Tarnaud et al; Infect Dis 2011</td>
<td>South Africa Young men (n=1,264)</td>
<td>aPRR 0.53 (0.40-0.70)</td>
<td>Incidence in low risk HPV</td>
</tr>
<tr>
<td>Acquisition and persistence of HPV-16 and HPV-18 among men with high HPV and low infections in a circumcision trial in Kisumu, Kenya</td>
<td>Sankoh et al; J Infect Dis 2012, Butukw et al, Int J Cancer; 2012</td>
<td>Kenya: Young men (n=2,920)</td>
<td>HR 0.32 (0.20-0.49) HR 0.34 (0.21-0.54)</td>
<td>Persistence of HPV-16 Incidence of HPV-16</td>
</tr>
<tr>
<td>HR 0.46 (0.38-0.54)</td>
<td>Persistence of HPV-18</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Genital Ulcer Disease

**Association between MC and HPV: Non-RCT Data**

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Author</th>
<th>Population</th>
<th>Effect size (95% CI)</th>
<th>Other Info</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence, incidence, and risk factors for HPV in a community in southern Tanzania</td>
<td>Phuphan et al; Sex Transm Dis 2013</td>
<td>Men age 16-39 from Dar es Salaam (n=13419)</td>
<td>AOR 0.75 (0.57-0.99)</td>
<td>Any HPV type</td>
</tr>
<tr>
<td>MC and prevalence of genital HPV infection in men</td>
<td>Poynter et al; J Infect Dis 2012</td>
<td>Healthy Men in USA (n=8033)</td>
<td>aIRR 0.89 (0.69-1.15)</td>
<td>Clearance for any HPV</td>
</tr>
<tr>
<td>MC and prevalence of genital HPV in a systematic review and meta-analysis</td>
<td>Albers et al; Sex Transm Dis 2012</td>
<td>Meta-analysis of 21 studies (1,071,030)</td>
<td>OR 0.70 (0.52-0.95)</td>
<td>HPV prevalence</td>
</tr>
<tr>
<td>MC and the incidence and clearance of genital HPV infection in men</td>
<td>Larke et al; J Infect Dis 2010</td>
<td>Men (n=1,264)</td>
<td>RR 1.01 (0.66 - 1.55)</td>
<td>HPV incidence</td>
</tr>
<tr>
<td>MC and HPV clearance among HIV-positive men</td>
<td>Serwadda et al; Lancet Infect Dis 2010</td>
<td>HIV-positive men (n=200)</td>
<td>RR 0.33 (0.22-0.60)</td>
<td>Incidence of multiple high-risk HPV</td>
</tr>
<tr>
<td>HPV incidence and clearance among HIV+ and HIV-men</td>
<td>Tabor et al; AIDS 2012</td>
<td>HIV+ &amp; HIV-negative men (n=669)</td>
<td>OR 0.30 (0.15-0.79)</td>
<td>HPV incidence</td>
</tr>
<tr>
<td>Effect of MC of HIV-negative men on transmission of HPV to HIV-negative women</td>
<td>Weaver et al; Int J Cancer; 2011</td>
<td>Concordant HIV-negative couples (n=1245)</td>
<td>HR 0.77 (0.49-0.93)</td>
<td>Incidence of high-risk HPV in women</td>
</tr>
</tbody>
</table>

### Circumcision Reduces GUD: Results from the 3 RTCs

![Circumcision Reduces GUD: Results from the 3 RTCs](image)

*Association may be spurious given relationship between MMC and HIV in MSM not clear*
Herpes Simplex Virus Type 2

Evidence from the 3 RCTs: South Africa and Uganda Trials

- Orange Farm Trial
  - Circumcision had borderline impact on incident HSV-2 in intention to treat analysis (IRR 0.66; CI 0.39-1.12) but was significantly protective in as treated analysis (IRR 0.55; CI 0.32-0.94) [1]

- Rakai Trial
  - At 24 months follow up, incident HSV-2 was lower in circumcision group (aHR 0.72; CI 0.56-0.92) [2]
  - Contrary to findings in men, circumcision of partner did not affect HSV-2 acquisition among females with HSV-2-positive partners (RR 0.85; CI 0.44-1.67) [3]


Evidence from the 3 RCTs: The Kenya Trial

- Kisumu Trial:
  - Overall, the incidence of HSV-2 did not differ by MC status (RR 0.94; CI 0.7-1.25) [1]
  - Blood samples from HIV seronegative men were tested for HSV-2 using HerpeSelect HSV-2 ELISA (n=120), Kalon HSV-2 ELISA (n=120), U of Washington Western blot (n=101) and a recombinant inhibition test (n=90) [2]
  - Compared to Western blot, HerpeSelect had 100% specificity but only 40% sensitivity; while Kalon had 92% sensitivity and 79% specificity
  - Relative to recombinant inhibition test, Kalon test had 80% sensitivity and 82% specificity
  - Using the recombinant inhibition test, sensitivity of Western blot was low, at 49%
  - Overall, the Kalon HSV-2 ELISA performed better than HerpeSelect


Mixed results on association between MC and HSV-2

Evidence from a Systematic Review/Meta-analysis and RCTs

- In 2006, a systematic review and meta-analysis of 26 published articles indicated significant reduction in syphilis in circumcised men (RR 0.67; CI 0.54-0.83) [1]

- Kisumu Trial:
  - Incident syphilis did not differ by MC status (RR 1.23; CI 0.41-3.61) [2]

- Rakai Trial:
  - Incident syphilis did not differ by MC status (aHR 1.10; CI 0.75-1.61) [3]


Syphilis
Association between Male Circumcision and the Incidence of Syphilis among Men and Women: A Prospective Study in HIV-1 Serodiscordant Heterosexual African Couples


Recent Evidence

Rationale, Objectives and Methods

- **Objectives**: Assess the association between MC and incident syphilis among HIV-infected and -uninfected men and women enrolled in the Partners PrEP Study

- **Population**: Participants in Kenya and Uganda HIV-1 serodiscordant heterosexual couples in the Partners PrEP Study

- **Methods**: Analysis of prospective data covering 2.75 years of follow-up

Results

- Data obtained from 4,716 HIV-1 heterosexual serodiscordant couples

- 221 incident syphilis infections were identified (122 men and 99 women)

- Circumcised men had a 42% overall reduction in risk of acquiring syphilis overall (AHR 0.58; CI 0.37-0.91), and:
  - A 62% significant reduction among HIV-infected men (AHR 0.38; CI 0.18-0.81)
  - A 36% non-significant reduction among HIV-uninfected men (AHR 0.64; CI 0.36-1.11)

- Partners of circumcised men had a 59% reduction in risk of acquiring syphilis overall (AHR 0.41; CI 0.25-0.69), and:
  - A 48% reduction among HIV-infected women (AHR 0.52; CI 0.27-0.97)
  - A 75% reduction among HIV-uninfected women (AHR 0.25; CI 0.08-0.76)

Does MC protect against Ng, Ct and Tv?

- **Kenya Trial**: The incidence of *N. gonorrhoea*, *C. trachomatis* and *T. vaginalis*, combined or individually, did not differ by circumcision status.

- **Uganda Trial**: MC did not protect against genital discharge (PRR 0.84; CI 0.63-1.11) or Dysuria (PRR 0.77-1.21)

- Among female partners, circumcision reduced symptoms of *Tv* (PRR 0.52; CI 0.05-0.98), any *Bv* (PRR 0.60; CI 0.38-0.94) and severe *Bv* (PRR 0.39; CI 0.24-0.64)

- **South Africa Trial**: The prevalence of *Ng*, *Ct* and *Tv* did not vary by MC status in intention-to-treat analysis *(Ng*: OR 0.97; p = 0.84; *Ct*: OR 0.58; p = 0.065; *Tv*: OR 0.54; p = 0.06); however, in the as-treated analysis, circumcision protected men against *Tv* (AHR 0.41, p = 0.03)

Neisseria Gonorrhoeae, Chlamydia Trachomatis and Trichomonas Vaginalis

Circumcision does not protect against Gonorrhea

![Observational studies and RCTs](image)

Slide, courtesy of Supriya Mehta, UIC

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reynolds</td>
<td>0.78 (0.51, 1.24)</td>
</tr>
<tr>
<td>Dave</td>
<td>1.36 (0.67, 2.76)</td>
</tr>
<tr>
<td>Lothman</td>
<td>1.50 (0.39, 5.82)</td>
</tr>
<tr>
<td>Packer</td>
<td>0.61 (0.39, 0.95)</td>
</tr>
<tr>
<td>Hand</td>
<td>0.58 (0.35, 0.94)</td>
</tr>
<tr>
<td>Cook</td>
<td>0.60 (0.28, 1.29)</td>
</tr>
<tr>
<td>Lermay</td>
<td>0.50 (0.08, 2.57)</td>
</tr>
<tr>
<td>Hepner</td>
<td>0.88 (0.37, 2.18)</td>
</tr>
<tr>
<td>Taylor</td>
<td>1.00 (0.48, 2.20)</td>
</tr>
<tr>
<td>Smith</td>
<td>0.95 (0.75, 1.17)</td>
</tr>
<tr>
<td>South Africa RCT</td>
<td>0.94 (0.59, 1.49)</td>
</tr>
<tr>
<td>Kenya RCT</td>
<td>0.95 (0.68, 1.32)</td>
</tr>
</tbody>
</table>

RR (Relative Risk)
Conclusions (1/2)
- Interest in the association between MC and STIs has spanned over 160 years
- HPV prevalence, incidence and clearance lower in HIV-uninfected circumcised men
- Site of sample collection matters!
- Incidence of high risk HPV also lower in female partners of circumcised men
- MC reduces genital ulcer disease in both HIV-uninfected and HIV-infected men
- Testing method matters!
- In the Uganda trial, MC lowered HPV risk in female partners but had no effect on their acquisition of HSV-2

Conclusions (2/2)
- MC had no effect on syphilis in the Uganda and Kenya trials, but:
  - A recent analysis of among PrEP participants, MC reduced incident syphilis among HIV-infected men and female partners of both infected and uninfected men
- MC had no effect on Ng, CT and Tv among men in the trials, except in as treated analysis in South Africa
  - Ugandan women with circumcised partners has lower symptoms of Tv and Bv

Introduction to Part 2
- Long term follow up of circumcised men in the randomized controlled trials showed sustained reduction in HIV acquisition: 73% in Uganda after 5 years and 58% in Kenya after 7 years (1)
- In South Africa, VMMC rollout led to significant reduction in HIV incidence by 57-61% (3)
- WHO/UNAIDS estimate that 20.8m circumcisions are needed to achieve 80% coverage in 14 priority countries in Africa and avert 3.4m infections by 2025
- About 9.1m circumcisions were performed in these countries between 2008 and 2014
- A key obstacle to rapid rollout of VMMC is the technical difficulty of surgical techniques recommended by WHO/UNAIDS: forceps guided, sleeve resection and dorsal slit
  - These techniques take around 15-30 minutes, and require highly trained providers (physicians in a number of counties) and relatively sterile environments
- Simplified VMMC methods, such as devices, could greatly facilitate rollout.
- Two adult VMMC devices have been prequalified by WHO: PrePex, in 2013 and Shang Ring, in 2015.

PART 2: MALE CIRCUMCISION DEVICES

PREPEX MALE CIRCUMCISION SYSTEM
(Circ MedTech Ltd, Tartola, British Virgin Islands)
PrePex™ - Background

- **PrePex™** is a single use, disposable device consisting of an inner ring, elastic outer ring, placement ring, verification thread and sizing accessory
- Works by compressing the foreskin and cutting off circulation, leading to necrotic foreskin which is then removed after 7 days
- Requires no sutures, no injectable anesthesia (uses anesthetic cream), no sterile (but clean) settings, and no bleeding during placement or removal
- Easily used by trained lower cadre health care providers
- Prequalified by WHO on 13/May/2013 following 8 studies of 2,417 men in Rwanda, Uganda and Zimbabwe

How does PrePex work: Placement

How does PrePex work: Removal

Results from Comparative Trials: Pre-Pex & Conventional Surgical Methods

<table>
<thead>
<tr>
<th>Study (Type)</th>
<th>Location</th>
<th>Clients</th>
<th>Type of providers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety study</td>
<td>Rwanda</td>
<td>55 healthy, HIV-negative clients</td>
<td>Physicians and Nurses</td>
</tr>
<tr>
<td>Randomized comparison with surgery</td>
<td>Rwanda</td>
<td>146 PrePex, 73 surgery (dorsal slit)</td>
<td>Physicians and Nurses</td>
</tr>
<tr>
<td>Field study</td>
<td>Rwanda</td>
<td>666 generally healthy men (5 positive)</td>
<td>Lower cadre Nurses</td>
</tr>
<tr>
<td>Safety Study</td>
<td>Zimbabwe</td>
<td>53 HIV-negative men</td>
<td>Physicians and Nurse Assistants</td>
</tr>
<tr>
<td>Randomized comparison with surgery</td>
<td>Zimbabwe</td>
<td>246 HIV-negative men</td>
<td>Physicians and Nurse Assistants</td>
</tr>
<tr>
<td>Field Study</td>
<td>Zimbabwe</td>
<td>641 HIV-negative men</td>
<td>Nurses, with physician back-up</td>
</tr>
<tr>
<td>Two field studies</td>
<td>Uganda (IHK)</td>
<td>634 healthy men</td>
<td>Surgeons, Medical Officers, Clinical Officers, Nurses</td>
</tr>
<tr>
<td>Safety/acceptability study</td>
<td>Uganda (IHK)</td>
<td>477 HIV-negative men</td>
<td>Clinical Officers and Nurses</td>
</tr>
<tr>
<td>Safety/acceptability study</td>
<td>Kenya</td>
<td>977 HIV-negative men</td>
<td>Clinical Officers and Nurses</td>
</tr>
<tr>
<td>Safety/acceptability study</td>
<td>Kenya</td>
<td>977 HIV-positive men (ongoing)</td>
<td>Clinical Officers and Nurses</td>
</tr>
<tr>
<td>Active surveillance study</td>
<td>Kenya</td>
<td>16,000 HIV-negative men (ongoing)</td>
<td>Clinical Officers and Nurses</td>
</tr>
</tbody>
</table>

| Results of Comparative Trials: Pre-Pex & Conventional Surgical Methods |
|-----------------------------|---------------|---------------|
|                         | PrePex         | Surgery       |
| Total placement and removal time | 5.7 min. | 19.2 min. |
| Adverse events: Mild/Moderate/Severe | 0.4% | <1% |
| Satisfaction with cosmetic result | 99% | “similar” |
| Pain (on Visual Analog Scale of 0-10) | Placement: 0.5 Removal: 0.1 Ischemia: 2.2 | Intense at removal, but fleeting and returns to 1.5 soon after |
| Preference | 88% Uganda | 86% Uganda |
| Successful placement /removal | 92.6% / 99.5% | N/A |

SHANG RING MALE CIRCUMCISION DEVICE
(Wu Hu SNNDA Medical Treatment Appliance Technology Co. Ltd, Wu Hu City, China)
Shang Ring – Background

- Shang Ring is a sterile, single use, disposable device consisting of 2 concentric plastic rings – inner and outer rings – that interlock; remains in place for 5-7 days and requires no suturing
- Comes in 32 sizes (for all ages, from neonates to adults); approved for sale and use in EU & USA
- Over 600,000 circumcisions have been performed in China since 2005 using Shang Ring
- 3 studies in China showed that Shang Ring is safe, acceptable and easy to use
- 5 studies have been conducted in Kenya, Uganda and Zambia and confirmed safety, ease of use and acceptability profiles observed in China
- Following these studies, the device was prequalification by WHO in May 2015

Shang Ring is a sterile, single use, disposable device consisting of 2 concentric plastic rings – inner and outer rings – that interlock; remains in place for 5-7 days and requires no suturing.

How does Shang Ring Work: Placement

How does Shang Ring Work: Removal

Clinical Evaluation of Shang Ring in Adult African Men

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Reference</th>
<th>Location</th>
<th>Year</th>
<th>Number and type of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety Study (case series)</td>
<td>Barone M, Ndede F, Li PS et al.</td>
<td>Kenya</td>
<td>2009</td>
<td>40 healthy HIV-negative men &gt;18 years old</td>
</tr>
<tr>
<td>Spontaneous Detachment Study</td>
<td>Barone M, Ndede F, Li PS et al.</td>
<td>Kenya</td>
<td>2010/11</td>
<td>50 healthy HIV-negative men &gt;18 years old</td>
</tr>
<tr>
<td>Field Study (field study)</td>
<td>Kigozi G, Musoke R, Watya S, et al.</td>
<td>Uganda</td>
<td>2011/12</td>
<td>1211 healthy men &gt;18 years old</td>
</tr>
</tbody>
</table>

Results from Comparative Surgical Trials: Shang Ring & Conventional Surgical Methods

<table>
<thead>
<tr>
<th>Location</th>
<th>Mean duration of procedure</th>
<th>Pain 1 hour post-op**</th>
<th>Men's preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya &amp; Zambia</td>
<td>7 min, 20 min, 6 min, 18 min</td>
<td>3.6, 3.6</td>
<td>98.4%</td>
</tr>
<tr>
<td>Uganda</td>
<td>8 min, 20 min, 8 min, 18 min</td>
<td>3.4, 3.4</td>
<td>98.2%</td>
</tr>
</tbody>
</table>

Shang Ring: ongoing studies:
- Spontaneous detachment; use of topical cream instead of injectable lidocaine (Kenya)
- Using every other size so that the number of sizes that one could need to stock can be reduced (Zambia)
- ShangRing has received registration for use in clinical practice in Kenya (June 2015)

PrePex – new developments with programmatic implications:
- Many adolescents ineligible – due to phimosis and adhesions
  - WHO lists 53% for 13 year olds, 40% for 14 year olds, and 29% for 15 year olds ineligible
  - Risk of tetanus infections in PrePex – need for TT vaccination prior to placement.
- ??? Use in remote settings: Early displacements/self-removals after the onset of necrosis and before all circulation to the distal foreskin has stopped.
Conclusions

- VMMC devices are safe and highly acceptable among African adults, hence a viable option for scaling up of MMC in sub-Saharan Africa
  - Shang Ring most suitable for adolescents
- Both clients and providers preferred devices to conventional surgical methods
- Performed efficiently by non-clinicians thus can address human resource shortfalls
- No need for sterile setting hence availability of theater space not huge limitation
  - However,
  - Train service providers on surgical procedures as well to serve those ineligible for device placement or address AEs.

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