The impact of male circumcision on the female-to-male transmission of HIV: Results of the intervention trial: ANRS 1265

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INSERM (French National Institute for medical research)
UVSQ (University of Versailles – Saint-Quentin)
AP-HP (Paris – Hospitals)
Why study: HIV ↔ male circumcision (MC)?
Can MC be used as a prevention of HIV infection?

First paper (Fink, 1986)

Observational studies (>30)
- Cross-sectional, cohort, case-control studies
- In sub-Saharan Africa (Tanzania, South Africa, Kenya, Uganda...)
- but also India
- Systematic review and meta-analysis by Helen Weiss:
  Reduction of risk of HIV infection by 42% (34 – 54)

Randomized controlled intervention trial evidence was needed

Bertran Auvert – IAS 2005 – 27 July- Orange Farm Intervention Trial (ANRS 1265)
Objective

To assess the effect of MC on HIV incidence among young males

Location

South Africa
Orange Farm (Urban area close to Johannesburg)

Local context

Heterosexual spread of HIV
High HIV prevalence (ANC data: HIV=31.6%)
MC Prevalence : 20%
Median age at MC: 17 years

Acceptability study

(70% of uncircumcised males will accept to be circumcised if MC reduces the risk of getting HIV)
Orange Farm Trial (ANRS 1265)

Study design
Randomized controlled intervention trial

Approval
- University of the Witwatersrand Human research Ethics Committee
- Authorization by health authorities
- Scientific committee (ANRS)

Recruitment
- General population
- Males: 18-24 year-old
- Uncircumcised
- Willing to be circumcised
- In good health
- Living in the area
- Accept the randomization
- Sign informed consent
Trial design

- **Screening**
- **Randomization**
  - **Circumcision**
    - Immediate
      - M3 visit
      - M12 visit
      - M21 visit
    - Deferred
      - M3 visit
      - M12 visit
      - M21 visit

3035 HIV- participants
Power 80%
Incidence 2% per year
Reduction of HIV incidence by 50%

Interim analysis (all M12 completed)
Orange Farm Trial (ANRS 1265)

Male circumcision
- Performed by selected physicians (GP)
- Local anesthesia, Post-operative analgesia
- Technique: Forceps guided method
- Standard protocol (Wits University)

Blind follow-up and evaluation

Each visit (inclusion, M3, M12, M21)
- Counseling (professional counsellor)
- Questionnaire (sexual behavior)
- Blood sample tested for HIV (3 Elisa)
- Clinical examination
- Treatment of GUD

Prevention of opportunistic infection - ART
Statistical analysis

“Intention to treat” and “per protocol”
Grouped censored data (M1-M3, M4-M12, M13-M21)
Time is continuous

→ piecewise exponential proportional hazards model
  - Exact duration of each period for each person
  - Time independent covariates (background characteristics)
  - Time dependant covariates (sexual behavior, treatment of GUD)
  - Rates of infection (/100 person-years ; py)
  - Rate ratios (RR) of HIV incidence (RR with 95%CI)
  - Easy implementation (Poisson log linear model, duration as offset)
### Baseline

**HIV+ (inclusion): 4.5%**

**Among HIV-1:**

<table>
<thead>
<tr>
<th></th>
<th>Control n=1590</th>
<th>Intervention n=1538</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than or equal to 21 years</td>
<td>52.3%</td>
<td>48.7%</td>
</tr>
<tr>
<td>More than 21 years</td>
<td>47.7%</td>
<td>51.3%</td>
</tr>
<tr>
<td>Primary level of education completed</td>
<td>98.4%</td>
<td>98.2%</td>
</tr>
<tr>
<td>Religion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African traditional</td>
<td>47.2%</td>
<td>51.4%</td>
</tr>
<tr>
<td>Protestant or Catholic</td>
<td>11.1%</td>
<td>11.9%</td>
</tr>
<tr>
<td>Other religion</td>
<td>41.6%</td>
<td>36.7%</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sotho</td>
<td>48.0%</td>
<td>48.3%</td>
</tr>
<tr>
<td>Zulu</td>
<td>37.8%</td>
<td>33.0%</td>
</tr>
<tr>
<td>Other</td>
<td>14.2%</td>
<td>18.7%</td>
</tr>
<tr>
<td>Drank alcohol in the past month</td>
<td>41.9%</td>
<td>42.2%</td>
</tr>
<tr>
<td><strong>Reported sexual behaviour</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have had first sexual experience</td>
<td>90.5%</td>
<td>91.7%</td>
</tr>
<tr>
<td>Median (IQR) age at first sex (years) (1)</td>
<td>16.6 (15.1–18.4)</td>
<td>16.8 (15.4–18.5)</td>
</tr>
<tr>
<td>Median (IQR) number of lifetime sex partners (2)</td>
<td>4 (2–7)</td>
<td>4 (3–7)</td>
</tr>
<tr>
<td>Used a condom at first sex (2)</td>
<td>13.3%</td>
<td>15.3%</td>
</tr>
<tr>
<td>Ever used a condom (2)</td>
<td>81.2%</td>
<td>82.3%</td>
</tr>
<tr>
<td>At risk behaviour (3) (4)</td>
<td>46.7%</td>
<td>46.9%</td>
</tr>
<tr>
<td>Married or living as married (4)</td>
<td>1.8%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Mean (IQR) number of non-spousal partners (5)</td>
<td>1.4 (0–2)</td>
<td>1.4 (0–2)</td>
</tr>
<tr>
<td>At least one sexual partnership with only one sexual contact (5)</td>
<td>29.8%</td>
<td>30.7%</td>
</tr>
<tr>
<td>Mean (IQR) number of sexual contacts (5)</td>
<td>8.1 (0–8)</td>
<td>8.7 (1–8)</td>
</tr>
<tr>
<td>Attended a clinic for a health problem related to the genital area (5)</td>
<td>10.1%</td>
<td>9.5%</td>
</tr>
</tbody>
</table>
Results 1/3

Planned interim analysis
  Interruption of the trial (DSMB) (p<0.0095)
  MC proposed to control group

Follow-up:
  4664 person-years
  Mean (IQR) 17.9 mo (12.7–21.0)

Cross-over:
  Intervention group: 4.8% (68/1427) not C.
  Control group: 8.4% (92/1100) C.

Adverse events
  3.8% (60/1582)

Loss to follow-up:
  7.9% (Intervention: 6.8% vs Control: 9.7%)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Total (n=1582 MC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pain</td>
<td>13 (31.7%)</td>
</tr>
<tr>
<td>Excessive bleeding</td>
<td>9 (15%)</td>
</tr>
<tr>
<td>Infection</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Damage to the penis</td>
<td>4 (6.7%)</td>
</tr>
<tr>
<td>Swelling or haematoma</td>
<td>10 (16.7%)</td>
</tr>
<tr>
<td>Anaesthesia-related events</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Excessive skin removed</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Insufficient skin removed</td>
<td>4 (6.7%)</td>
</tr>
<tr>
<td>Delayed wound healing</td>
<td>2 (3.3%)</td>
</tr>
<tr>
<td>Problems with urinating</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Problems with appearance</td>
<td>9 (15%)</td>
</tr>
<tr>
<td>Other cause</td>
<td>5 (8.3%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>60 [3.8%]</strong></td>
</tr>
</tbody>
</table>
Results 2/3

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>Intervention</td>
<td>2</td>
<td>7</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>Control</td>
<td>9</td>
<td>15</td>
<td>27</td>
<td>51</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>22</td>
<td>36</td>
<td>69</td>
</tr>
</tbody>
</table>

Incidence rates:

- Intervention: 0.77 (0.49 - 1.23) /100 py
- Control: 2.2 (1.7 - 2.9) /100 py
- Total: 1.5 (1.2 – 1.9) /100 py

Unadjusted RR: 0.35 (0.20 – 0.60) p=0.00013

Protection (1-RR): 65% (40% - 80%)

The intervention prevented 6 to 7 out of 10 potential HIV infections.
Results 3/3

**Unadjusted RR**

\[ RR_0 : 0.35 \ (0.20-0.60) \] Protection : **65%** (40-80)

**Adjusted RR**

(age, religion, ethnic group, alcohol consumption, recruitment period)

\[ RR_1 : 0.33 \ (0.19-0.57) \] Protection : 67% (43-81)

**Adjusted RR**

(…, marital status, condom use, # of sexual partners, # of sexual contacts)

\[ RR_2 : 0.34 \ (0.20-0.59) \] Protection : 66% (41-81)

**Per protocol unadjusted RR**

(no dilution effect due to cross-over)

\[ RR_3 : 0.25 \ (0.14-0.46) \] Protection: 75% (64-86)

All \( p < 0.0002 \)
Discussion

- First RCT demonstrating a strong protective effect of safe male circumcision on HIV acquisition by males
- Reduction of the female-to-male transmission
- High but partial protection
- Short term effect
- Sub-Saharan context (heterosexual spread)
- Consistent with expectation
- Public health intervention? (where? how? effect?)
Acknowledgements

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