La recherche VIH dans les pays du Sud: l’exemple des études circoncision

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DESC maladies infectieuses, 9 octobre 2014, Paris-Descartes
Estimated number of adults and children newly infected with HIV in 2012

- **Western & Central Europe**: 29 000 [25 000 – 35 000]
- **Middle East & North Africa**: 32 000 [22 000 – 47 000]
- **Sub-Saharan Africa**: 1.6 million [1.4 million – 1.8 million]
- **Eastern Europe & Central Asia**: 130 000 [89 000 – 190 000]
- **South & South-East Asia**: 270 000 [160 000 – 440 000]
- **North America**: 48 000 [15 000 – 100 000]
- **Caribbean**: 12 000 [9400 – 14 000]
- **Latin America**: 86 000 [57 000 – 150 000]
- **East Asia**: 81 000 [34 000 – 160 000]
- **Oceania**: 2100 [1500 – 2700]

**Total**: 2.3 million [1.9 million – 2.7 million]

1981: First AIDS case
1983: HIV discovery

70%: Africa
HIV in Africa

Heterogeneity
60%: Southern and Eastern Africa
Why?

Transmission:
heterosexual
mother-to-child

HIV prevalence: 5%-28% in Southern and Eastern Africa

High HIV prevalence: Zambia (Ndola)  Kenya (Kisumu)
Lower HIV prevalence: Cameroon (Yaoundé)  Benin (Cotonou)

Comparison: cross-sectional survey in each site
questionnaire
biological samples

<table>
<thead>
<tr>
<th></th>
<th>Cotonou (Benin)</th>
<th>Yaoundé (Cameroon)</th>
<th>Kisumu (Kenya)</th>
<th>Ndola (Zambie)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex partners (Men Women)</td>
<td>5 2</td>
<td>10 3</td>
<td>5 2</td>
<td>5 2</td>
</tr>
<tr>
<td>Circumcision (%)</td>
<td>99</td>
<td>99</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>HIV (%) (Men-Women)</td>
<td>3.9 – 4.0</td>
<td>4.4 – 8.4</td>
<td>21.1 – 31.6</td>
<td>25.4 – 35.1</td>
</tr>
</tbody>
</table>

Kenya (Kisumu): Odds ratio: 0.25 (0.12-0.52)

Results: key factors
Community level: **Male circumcision, HSV-2**
Individual level: Sexual behavior, **Male circumcision, HSV-2**

Auvert et al. AIDS, 2001
Orange Farm randomized controlled trial (ANRS-1265)

Semi-urban township established in 1989
Gauteng province: 40km South-East of Johannesburg
110,000 adults
Estimated HIV prevalence (%) among antenatal clinic attendees in 2002: 31.6%

2002-2005
n = 3 274 uncircumcised men aged 18-24 y
Follow-up: 18 months
Result of the first MC RCT

**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**: 0.85 (0.55 - 1.32) /100 py
- **Control**: 2.1 (1.6 - 2.8) /100 py
- **Total**: 1.5 (1.2 – 1.9) /100 py

**Unadjusted RR**: 0.40 (0.24 – 0.68) p=0.00059

**Protection (1-RR)**: 60% (32% - 76%) ↔ 1 / 2.5

The intervention prevented 6 out of 10 potential HIV infections!

First surgical intervention to prevent an infectious disease!

Bertran Auvert –Orange Farm Intervention Trial (ANRS 1265)
Impact of MC on HIV acquisition among men: Evidence from observational studies and RCTs

In the years 2000, three randomized controlled trials were conducted in South Africa, Kenya and Uganda (Auvert et al., PLoS Med 2005; Bailey et al., Lancet 2007; Gray et al., Lancet 2007).

In all three trials, circumcised men had a risk of HIV acquisition reduced by approximately 60% compared to uncircumcised men.

**Causal link**
MC and HIV acquisition: Biological Plausibility

Inner foreskin mucosa is a major gateway to viral entry
Prone to inflammation, micro lesions and abrasions
(Anderson et al, Reproductive Immunology 2011)
Rich in HIV target cells (Morris et al. Int J STD AIDS, 2012; Hirbod et al.,
American Journal of Pathology 2010; McCoombe et al., AIDS 2006)
Sub-preputial space prone to viral survival and replication (Anderson et al., Reproductive
Immunology 2011)

Uncircumcised penis

Infected cells form synapses with Langerhans cells, leading to its migration and transmission to T-cells in lower mucosal layers

McCoombe et al., AIDS 2006

Fox et al., Antiviral Research 2010
History of the association of MC with HIV

In 1986, first mention of a possible link between MC and HIV (Alcena, NY State Journal of Medicine 1986)

In 1989-90, two articles highlighted a geographical inverse correlation between rates of MC and HIV prevalence among men and women at country level (Bongaarts, AIDS 1989; Moses, International Journal of Epidemiology 1990)

Between 1990 and 2000, numerous observational epidemiological studies showed that in Africa, circumcised men are in general less infected with HIV (Weiss, AIDS 2000)

Heterogeneity of HIV prevalence in Africa is mainly explained by MC
La circoncision doit maintenant être reconnue comme une mesure efficace de prévention du VIH ... dans les pays de forte prévalence du VIH et de faible prévalence de la circoncision.
MC reducing effect against other STIs and genital cancers

No evidence of an increasing effect of MC on STIs or genital cancers

**HSV-2** among men *(Tobian et al., NEJM 2009; Sobngwi-Tambekou, J., et al, JID, 2009)*

**HPV** acquisition:

- among men *(Tobian et al., NEJM 2009; Auvert et al., JID, 2009; Tobian et al., Fut Micro, 2011; Tobian et al., AIDS 2012; Gray et al., JID, 2011; Wilson et al. STI, 2012; Tarnaud et al., Infect Dis Obstet Gynecol, 2011)*

- among female partners *(Wawer et al., Lancet, 2011; Tobian et al., Fut Micro, 2011; Davis et al., Int J Cancer. 2013)*


**Bacterial vaginosis** among female partners *(Gray et al., Am J, Obst Gyn, 2009)*

**Mycoplasma genitalium** among men *(Mehta et al. STD, 2012)*

**Genital ulcers** among men *(Gray et al., Plos Med, 2009)* and women *(Gray et al., Am J, Obst Gyn, 2009)*

**Genital cancers** among men and women *(Larke NL et al., Cancer Causes Control 2011; Castellsague, X., et al., N Engl J Med, 2002)*

**Syphilis** among men and women *(Pintye et al, 20th Int. AIDS Conf 2014)*
2/3 des Africains sont circoncis. 25 millions d’adultes sont non circoncis.
The Orange Farm
Bophelo Pele project (ANRS12126)

Phase 4 study implemented in 2008 in Orange Farm
3 years after the end of the MC trial
Population: 110,000 adults
HIV prevalence among adults: 25%
Male circumcision prevalence about 12% in 2002

Mortality: Age-adjusted population attributable fraction* to HIV positivity
Women 36.2% (23.6% to 43.8%)  * Miettinen formula
Men 18.5% (5.3% to 43.8%)

Provision of MC to all male residents aged 15+
Feasibility of a mass VMMC* intervention?
MC uptake?
Short-term impact on HIV and other STIs? (men and women)
Impact on risky sexual behavior? (men and women)

Budget: 3 millions of Euros

*VMMC: Voluntary male medical circumcision
Bophelo Pele project

Communication
Radio
Information sessions for ♀ and ♂
Mobile speaker system
School and clinic talks
Household visits
Distribution of brochures

Recruitment
Fixed and mobile recruitment points
Information visits
Individual counseling for ♀ and ♂
HCT
STI treatment
Condom distribution

MMC Surgery
Disposable surgical kits
Local anesthesia
3 teams of 1 medical circumcisers and 5 nurses
Task-sharing

Laboratory testing
HIV, HSV-2, HPV testing
Methods

Independent biomedical cross sectional surveys

Survey-3a: 2012  3293 men 18+  3473 women 18+

Cohort study

Follow-up of Survey-3a (24 months) → Survey-3b (Jan 2014)

Data collection and testing

Face-to-face questionnaire
Blood: HIV (Elisas), HSV-2 (IgG Elisa), ARVs, BED
Genital examination and swab: HPV shedding by PCR

Statistical analysis

Univariate and multivariate analysis of prevalence data
Double robust analysis (propensity weighted and adjusted)
→ Weighted* Prevalence Rate Ratio (wPRR)

Mathematical modeling of prevalence data by age
→ HIV & HSV-2 Incidence Rate Ratio (IRR)

* The weights are the inverse of the propensity score, which was estimated from the basic covariates using logistic regression (age group, ethnic group, religion, having at least a child, occupation, age at first sexual intercourse, alcohol consumption, education level, and having ever been married).
Mathematical modelling

\[ \text{Natural mortality} \longrightarrow S_{\text{age}} \longrightarrow \text{Natural & AIDS mortality} \longrightarrow I_{\text{age}} \]

\[
dS = -mSdt - iSdt
\]
\[
dI = -mIdt + iSdt - sdt
\]
\[
s_t = \int_{q}^{t} i_u S_u W_{t-u} \exp(-\int_{u}^{t} m_a da) du
\]
\[
\text{Prevalence} = 1 - \frac{\exp(\int_{q}^{t} i_u dv)}{1 - \int_{q}^{t} i_u \exp(-\int_{0}^{u} i_v dv) \left( \int_{0}^{t} W_v dv \right) du}
\]

From
- observed HIV prevalence by age and by MC status
- age at circumcision of each individual

Assuming a static environment

Using a parametrical HIV incidence (i) rate by age (Weibull distribution) and wMLE

We obtained
- Age-specific HIV incidence by MC status
- HIV incidence rate ratio (IRR)

Modelling was adapted
- For women to obtained HIV incidence rate ratio
  (women having had only circumcised partners versus other women)
- For HSV2
1 Uptake of VMMC

25,000 VMMC (no death, 1 permanent scar of 1cm)

In 3 years. Survey-2 (2010-11)

15-49 years:

11.9% (10.3% to 13.6%) → 53.1% (51.3 to 55.0)

15-24 years:

→ 58.0% (56.3 to 59.9)
2 Effect of MC status on HIV prevalence & incidence among men (surveys-2)

HIV prevalence (N = 3 338)

Circumcised men: 6.6% (5.3% to 8.1%)
Uncircumcised men: 18.8% (16.3% to 21.3%)
wPRR* = 0.52 (0.40 to 0.67) => Reduction of 48% (23% to 60%)

Without these VMMCs, HIV prevalence rate in 2010–2011 would have been 19% higher (12% to 26%) among men aged 15 to 49 y.

* Adjusted for survey, age group, ethnic group, religion, alcohol consumption, education level, occupation, having ever been married, age at first sexual intercourse, number of lifetime sexual partners, consistent condom use).
## Effect of MC on sexual behavior (survey-2)

### Reported by men: Two or more non spousal partners in the last 12 months

<table>
<thead>
<tr>
<th>Group</th>
<th>Circumcised</th>
<th>Uncircumcised</th>
<th>Weighted prevalence rate ratio</th>
<th>All men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumcised</td>
<td>50.4%</td>
<td>44.2%</td>
<td>(47.9% to 52.9%)</td>
<td></td>
</tr>
<tr>
<td>Uncircumcised</td>
<td>47.5%</td>
<td></td>
<td>(45.7% to 49.3%)</td>
<td></td>
</tr>
<tr>
<td>Weighted prevalence rate ratio*</td>
<td>1.03</td>
<td>(0.95 to 1.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All men</td>
<td>47.5%</td>
<td></td>
<td>(45.7% to 49.3%)</td>
<td>N=1771</td>
</tr>
</tbody>
</table>

### Reported by men: Consistent condom use with all non spousal partners

<table>
<thead>
<tr>
<th>Group</th>
<th>Circumcised</th>
<th>Uncircumcised</th>
<th>Weighted prevalence rate ratio*</th>
<th>All men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumcised</td>
<td>44.0%</td>
<td>45.4%</td>
<td>(41.7% to 46.5%)</td>
<td></td>
</tr>
<tr>
<td>Uncircumcised</td>
<td>44.6%</td>
<td></td>
<td>(42.6% to 46.6%)</td>
<td></td>
</tr>
<tr>
<td>Weighted prevalence rate ratio*</td>
<td>0.94</td>
<td>(0.85 to 1.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All men</td>
<td>44.6%</td>
<td></td>
<td>(42.6% to 46.6%)</td>
<td>N=1399</td>
</tr>
</tbody>
</table>

### Non-spousal partnerships always protected by condoms

<table>
<thead>
<tr>
<th>Group</th>
<th>Consistent condom use with all non spousal partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among circumcised men</td>
<td>= 63.9% (2671 / 4177)</td>
</tr>
<tr>
<td>Among uncircumcised men</td>
<td>= 61.3% (3287 / 5362) aPRR = 1.00 (0.96 to 1.05)</td>
</tr>
</tbody>
</table>

Auvert et al. Plos Med Sep 03, 2013 DOI: 10.1371/journal.pmed.1001509
Figthing HIV in Africa: current available tools

**Group level: real life:**
- **ARVs**
  - To prevent mother to child transmission
  - To prevent dying of HIV

**Male circumcision**
- To prevent (2.5) HIV acquisition of by men

**ARV to all HIV-pos for prevention**

**ARV to high-risk HIV-neg**

**Structural interventions**

**Condoms**
- To reduce (95%) the transmission of HIV

**Sexual behavior change** (abstinence, faithfulness)
- To reduce the transmission of HIV

**HCT**
- Compulsory entry point for ARVs

**Efficiency**
- **Efficacy** and **Efficiency**

**Group level: Clinical trial:**
- **Efficacy**

**Individual level:**
- **Efficiency**
- **Efficacy** and **Efficiency**
- **Efficacy**
- **Efficacy** (efficiency under study)
- **Efficacy**
- **Efficacy**
- **Individual effect**
- **Individual effect**
MC as an HIV prevention strategy for men in Eastern and Southern Africa

Advantages

- MC already widely practiced in sub-Saharan Africa
- **Efficiency** proven (Auvert et al., PloS Med 2013)
- **Unique, simple, permanent, and cheap procedure**
- Proven reducing effect on common STIs such as HSV-2 and HPV
- Recommended by major international health organizations *(WHO and UNAIDS, 2007)*
- May reduce the HIV epidemic in Eastern and southern Africa to the levels observed in other parts of sub-Saharan Africa
- Can complement other prevention strategies: condom use, risk reduction counseling, ARVs, etc.

Disavantages

- Uptake of intervention in non-circumcising communities unknown: Can an 80% MC coverage be achieved?
- Implementation constraints (financial and human resources, logistical capabilities, community ownership and political leadership)
- **No proven direct effect on women**
- **Risk of the surgery**
Roll-out of VMMC in Africa among adults and youth

High potential impact: potential reduction by >25% of the global epidemic

Target: MC prevalence of 80% in 14 priority settings (Southern and Eastern Africa)
Botswana, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe

Activity:
Number of adult VMMC needed: 20 000 000
Number done (end of 2013): 6 000 000 (30% of the target)
Number of HIV infections averted in the next 20 years*: 1-2 000 000

Cost:
Estimated total: US$ 1-2 billion
Already spent: US$ 300 000 000
Cost per VMMC: US$ 50
Donors: PEPFAR, the Global Fund and the BMGF

Children: Programs are starting

In South Africa
Target: 6 000 000
Done in MC clinics: 2 000 000 (33% of the target)
50 clinics based on the Orange Farm clinic
GP (reimbursed by PEPFAR or health insurances)

*3 to 5 MC to prevent 1 HIV infection in the following 20 years (Kahn, Marseille, Auvert, Plos Med, 2006)
Conclusion

- Exemple d’étude multidisciplinaire:
  Épidémiologie quantitative, biologie, économie de la santé, épidémiologie sociale, biomathématiques
- Meilleure compréhension de l’épidémie VIH en Afrique
- Intervention chez les adultes et les enfants (hommes)
- Effet potentiel majeur sur l’épidémie avec une technique millénaire

1986: 1ère publication
2001: Étude observationnelle multisite
2005: 1er essai randomisé (Orange Farm)
2007: Recommandations OMS
2012: 1ère phase 4 (Orange Farm)
2011-2018: Généralisation: succès ?
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The community of Orange Farm
Thank you for your attention 😊