

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

Bertran Auvert, INSERM, UVSQ, AP-HP, France

Adrian Puren, NICD, South Africa

Dirk Taljaard, Progressus, South Africa

Emmanuel Lagarde, INSERM, France

Joëlle Tambekou-Sobngwi, INSERM, France

Rémi Sitta, INSERM, France

NICD (South African National Institute for Communicable Diseases)

ANRS (sponsor) (French National Agency for AIDS Research)

INSERM (French National Institute for medical research)

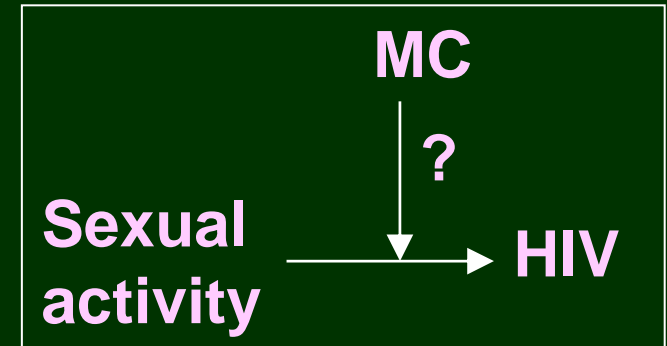
UVSQ (University of Versailles – Saint-Quentin)

AP-HP (Paris – Hospitals)

Why study : HIV  $\leftrightarrow$  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

## 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

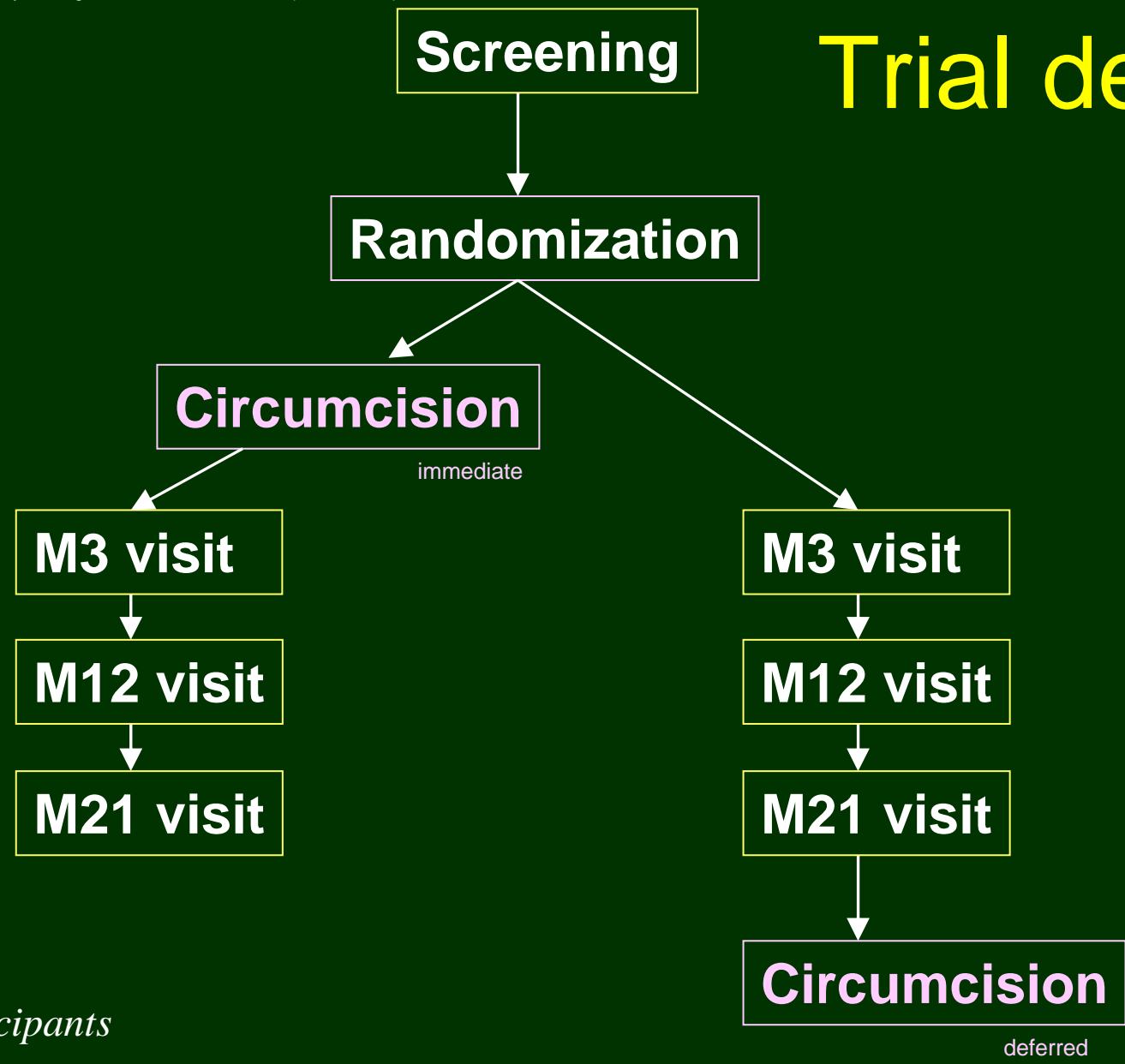
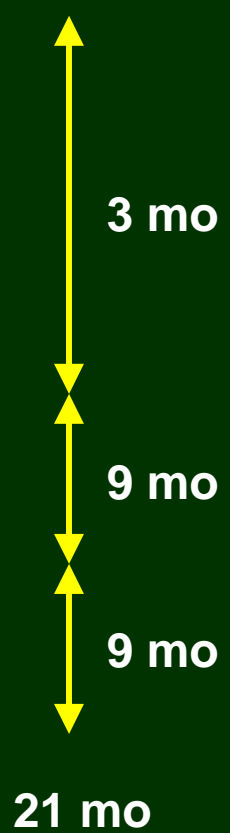
Living in the area

Accept the randomization

Sign informed consent



# Trial design



*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)

HIV+ (inclusion): 4.5%

Among HIV-1 - :

# Baseline

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

# 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%)

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

# Results 2/3

Incident cases :

	<u>M0-M3</u>	M4-M12	M13-M21	Total
Intervention	2	7	9	<b>18</b>
Control	9	15	27	<b>51</b>
Total	11	22	36	<b>69</b>

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<sub>0</sub> : 0.35 (0.20-0.60) Protection : 65% (40-80)

## Adjusted RR

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

RR<sub>1</sub> : 0.33 (0.19-0.57) Protection : 67% (43-81)

## Adjusted RR

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

RR<sub>2</sub> : 0.34 (0.20-0.59) Protection : 66% (41-81)

## Per protocol unadjusted RR (no dilution effect due to cross-over)

RR<sub>3</sub> : 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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