

The Impact of male circumcision on the female-to-male transmission of HIV

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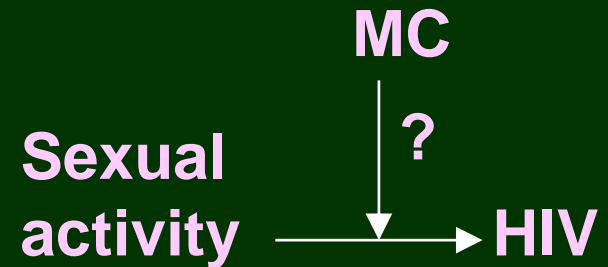
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The question: HIV \leftrightarrow male circumcision (MC) ?

- Spread of HIV
- Prevention ?



Observational studies (1986 →)

Cross-sectional studies

Prospective studies

Africa (India)

Systematic review and meta-analysis

RCT a definitive answer

Objective

Effect of MC on HIV incidence among young males

Location

South Africa

Orange Farm (Urban area close to Johannesburg)

1 centre

Context

Heterosexual spread

High HIV prevalence (ANSUR data: HIV=31.6%)

MC Prevalence : 20%

Median age at MC: 17 years

Acceptability study

Study design

RCT

Orange Farm Trial

Approval

University of the Witwatersrand Human Research Ethics Committee

Local authorization by health authorities

Scientific committee (ANRS)

Recruitment

General population

Males: 18-24 year-old

Uncircumcised

Willing to be circumcised

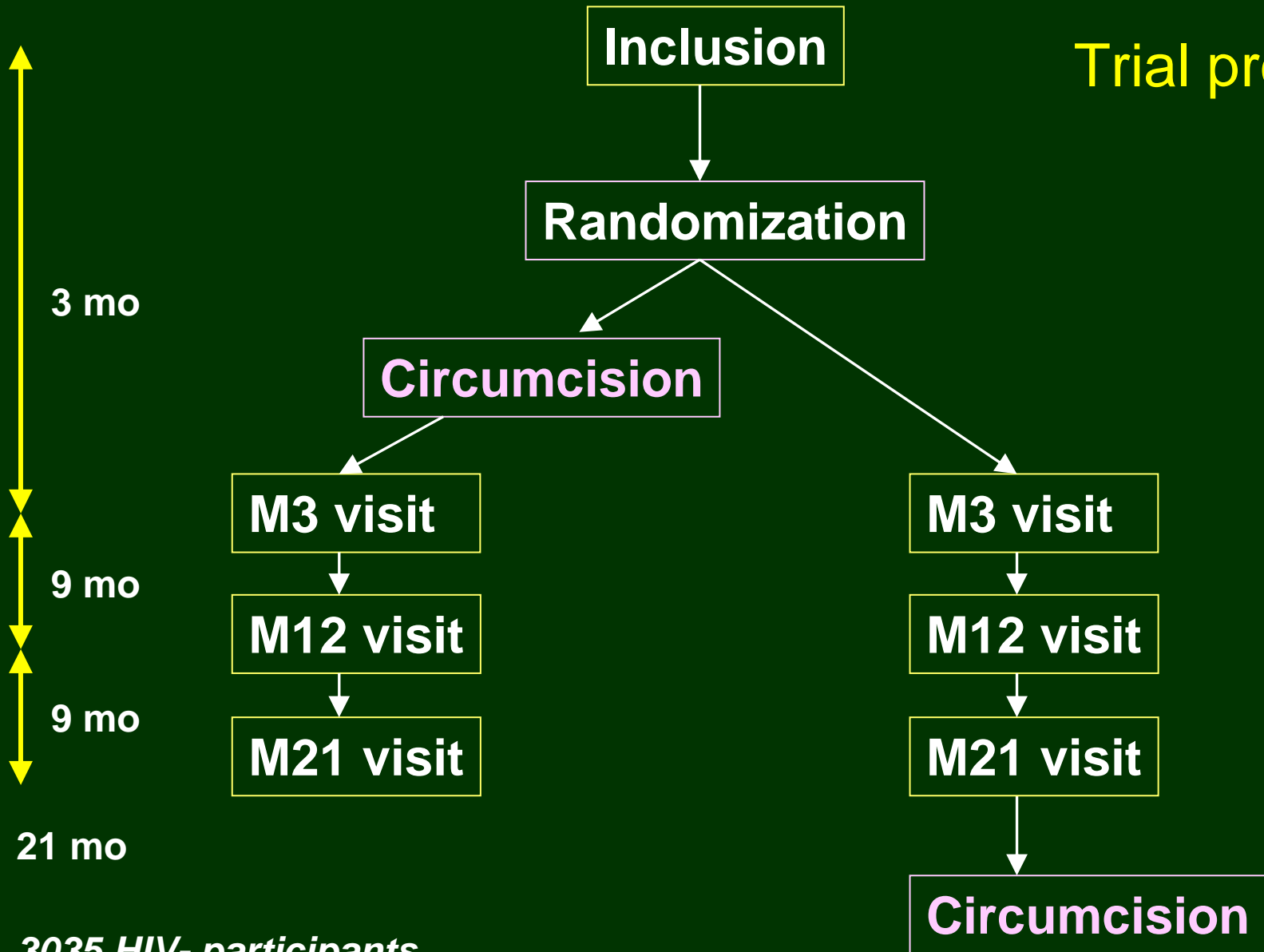
In good health

Living in the area

Accept the randomization

Informed Consent

Trial profile



3035 HIV- participants

Power 80%

Incidence 2% per year

Reduction of HIV incidence by 50%

Interim analysis (all M12 completed)

Orange Farm Trial

Male circumcision

Performed by experienced physicians (GP)
Standard protocol (Wits University, Urology Dept.)
Technique: Forceps-guided method
Local anaesthesia, Post-operative analgesia

Each visit (inclusion, M3, M12, M21)

Counselling (professional counsellor)
Questionnaire (sexual behaviour)
Blood sample tested for HIV (Elisa)
Clinical examination
Treatment of GUD, severe HSV-2 lesions

Prevention of opportunistic infection - ART

Reason of participation: free and medicalized MC

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
- Time independent covariates (background characteristics)
- Time dependant covariates (sexual behaviour, 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)

Interim analysis → interruption of the trial ($p < 0.0095$)

HIV+ (inclusion): 4.5%

Among HIV-1 - :

Baseline

	Control n=1590	Intervention n=1538
<i>Background characteristics</i>		
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%
<i>Reported sexual behaviour</i>		
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%

Follow up

Follow-up:

4664 person-years

mean (IQR) 17.9 mo (12.7–21.0)

Cross-over:

Intervention group : 4.8% (68/1427) not C. at M3

Control group : 8.4% (92/1100) C. at M21

Loss to follow-up:

7.9% (Intervention : 6.8% vs. Control : 9.7%)

AE:

3.8% (60/1582)

HIV-1 incidence cases and rate (95% CI):

69 HIV-1 infections

1.5 (1.2 – 1.9) /100 py

Results 1/2

Incident cases :

	M0-M3	M3-M12	M12-M21	Total
Intervention	2	7	11	20
Control	9	15	25	49
Total	11	22	36	69

Incidence rates:

Intervention: **0.85** (0.55 - 1.32) /100 py

Control: **2.1** (1.6 - 2.8) /100 py

Unadjusted RR : **0.4** (0.24 – 0.68) $p=0.00059$

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

Results 2/2

Unadjusted RR

RR₀ : 0.4 (0.24-0.68)

Adjusted RR

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

RR₁ : 0.38 (0.23-0.65)

Adjusted RR

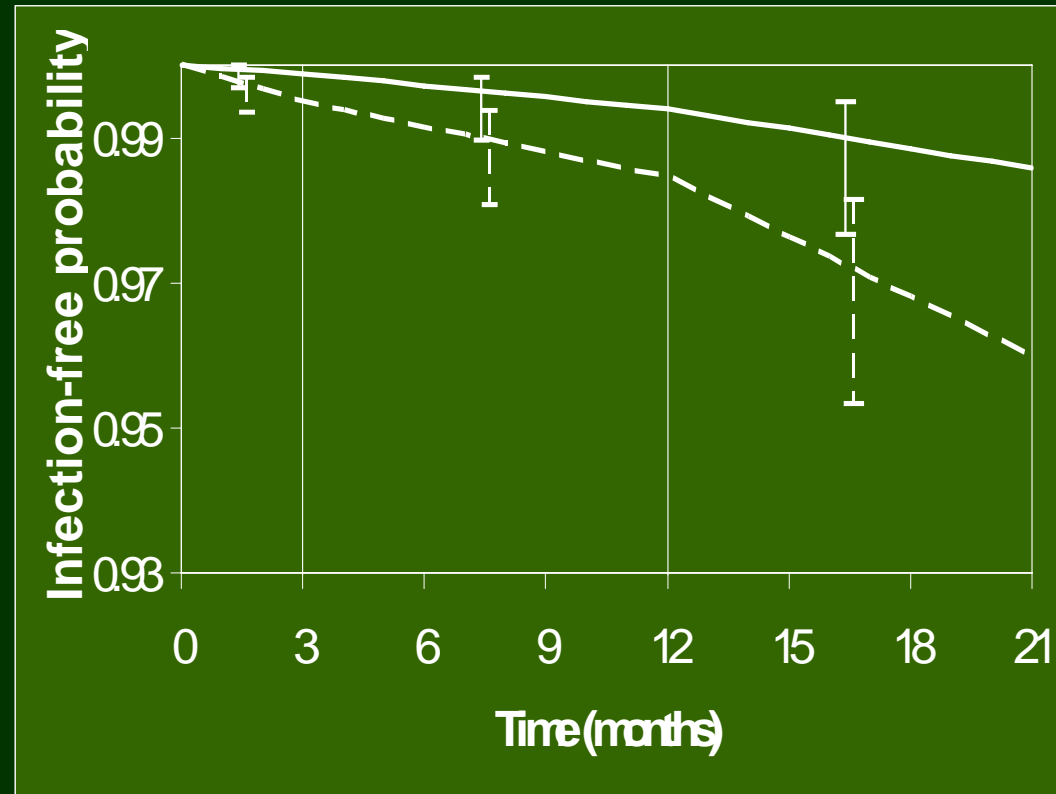
(..., marital status, condom use,
of sexual partners, # of sexual contacts)

RR₂ : 0.39 (0.23-0.66)

Per protocol unadjusted RR

RR : 0.25 (0.14-0.46) : 75% (64-86) protective

All p < 0.0002



Adverse Event	HIV-Negative at Randomization (<i>n</i> = 1,495 MC)	HIV-Positive at Randomization (<i>n</i> = 73 MC)	Total (<i>n</i> = 1,568 MC)
Death	0 (0%)	0 (0%)	0 (0%)
Pain	12 (22.2%)	1 (16.7%)	13 (31.7%)
Excessive bleeding	9 (16.7%)	0 (0%)	9 (15%)
Infection	2 (3.7%)	1 (16.7%)	3 (5%)
Damage to the penis	3 (5.6%)	1 (16.7%)	4 (6.7%)
Swelling or haematoma	9 (16.7%)	1 (16.7%)	10 (16.7%)
Anaesthesia-related events	1 (1.9%)	0 (0%)	1 (1.7%)
Excessive skin removed	0 (0%)	0 (0%)	0 (0%)
Insufficient skin removed	4 (7.4%)	0 (0%)	4 (6.7%)
Delayed wound healing	1 (1.9%)	1 (16.7%)	2 (3.3%)
Problems with urinating	0 (0%)	0 (0%)	0 (0%)
Problems with appearance	8 (14.8%)	1 (16.7%)	9 (15%)
Other cause	5 (9.3%)	0	5 (8.3%)
Total	54 (100%)	6 (100%)	60 (100%)
	[3.6%]	[8.2%]	[3.8%]

Adverse Event	HIV-Negative at Randomization (<i>n</i> = 1,131 M21 visits)
Problem with urinating ^a	3 (27.3%)
Dissatisfied with the appearance of the penis ^a	4 (36.4%)
Mild or moderate erectile dysfunction ^a	4 (36.4%)
Torsion of penis ^b	0 (0%)
Total (%)	11 (100%) [1.0%]

Discussion

- RCT demonstrates a protective effect of male circumcision on HIV acquisition by males
- Partial protection: 60% Protective
- RCT but we cannot avoid all biases:
characteristics of partners \leftrightarrow MC
- Consistent with published studies
- Effect on other STIs: HSV-2
- Public health intervention ?

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