

Overview of the current evidence on male circumcision and HIV prevention



Overview of the current evidence on male circumcision and HIV prevention

- Male circumcision in the emerging HIV prevention technology landscape
- Historical and epidemiological perspective
- Known benefits (non-HIV)
- Strength of the evidence for HIV
- Biological rationale
- Other issues: impact, resource needs, acceptability, risk compensation, safety

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Prevention Research Landscape



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Male circumcision: historical perspective

Male circumcision (MC) is associated with various cultural factors:

- traditional or religious practices
- rites of passage into adulthood
- promotion of hygiene

The earliest documentary evidence



for circumcision is from Egypt. Tomb artwork from the Sixth Dynasty (2345-2181 B.C.) shows circumcised men, and one relief from this period (Ankh Mahor) shows the rite being performed on standing adult males

Genesis (17:11) places the origin of the rite among the Jews in the age of Abraham who lived around 2000 B.C.

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Prevalence of Male Circumcision



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Male Circumcision: Background Information

- Globally, approximately 30% of men are circumcised. In Africa, approximately 68%.
- A practice observed mostly for cultural and religious reasons, less often for health reasons.
- A simple procedure that confers benefits.
- A surgical procedure that entails risks
- The benefits of male circumcision must be weighed against the potential harm.

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Benefits of Circumcision

Urinary tract infections in infants

J2 fold increased risk in uncircumcised boys Syphilis

> 1.5-3.0 fold increased risk in uncircumcised men Chancroid

> 2.5 fold increased risk in uncircumcised men Human Papilloma Virus (HPV)

> 63% reduction in circumcised men

Invasive penile cancer in men

> 22 times more frequent in uncircumcised men Cervical cancer in female partners

2.0 - 5.8 times more frequent in women with uncircumcised partners

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Studies of the Association Between Circumcision and HIV Infection

 4 <u>ecological studies</u>: HIV prevalence lower with higher male circumcision prevalence

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MALE CIRCUMCISION AND POPULATION BASED HIV PREVALENCE IN AFRICA



Sources: ORC/MACRO, 2005, USAID, 2002

MALE CIRCUMCISION AND HIV IN ASIA



Sources: UNAIDS, 2004



Studies of the Association Between Circumcision and HIV Infection

- 4 <u>ecological studies</u>: HIV prevalence lower with higher male circumcision prevalence
- 35 <u>cross-sectional studies</u>: meta-analysis
 - Overall Crude OR: 0.52 (95% CI: 0.40 to 0.68)
 - Adjusted OR: 0.42 (95% CI: 0.34 to 0.54)

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Meta-analysis by Weiss et al. AIDS 2000; 14:2361-2370





Studies of the Association Between Circumcision and HIV Infection

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- 35 cross-sectional studies: meta-analysis
 - Overall Crude OR: 0.52 (95% CI: 0.40 to 0.68)
 - Adjusted OR: 0.42 (95% CI: 0.34 to 0.54)
- 14 prospective studies: adjusted relative risk of HIV infection for circumcised men is 0.52 - 0.18 (i.e. at least half the probability of acquiring HIV)

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HIV Acquisition among Male Partners of HIV + Female Partners By Circumcision Status In Rakai



Female viral load

40/137 *uncircumcised* men (16.7/100 py) vs. 0/50 of *circumcised* men became infected after two+ years (p = 0.004).

Quinn et al NEJM 2000



Need for Clinical Trials

- "Randomized clinical trials are needed to determine the utility of circumcision as an HIV preventive measure."
- Reasons:
 - All epidemiological studies had been observational (cannot exclude residual confounding); not all results were consistent
 - Risk of too early resumption of sexual activity after circumcision or subsequent risk compensation could counteract any protective effect
 - Risk of post-surgical complications must be balanced against any protective effect

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Biological Determinants Affecting HIV Sexual Transmission

Infectiousness

Level of Blood Viral Load Genital Viral Load Stage of Infection Lack of circumcision* Genital ulcerations Inflammatory STDs Cervical ectopy Viral Subtype X4/R5 Phenotype Antiretroviral therapy ()

<u>Acquisition</u>

Viral Load in Index Case Lack of circumcision* Genital ulcers Inflammatory STDs Cervical ectopy HLA Haplotype Chemokines/Cytokines

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Biological Rationale for HIV link

- Biological plausibility
 - Inner mucosa of foreskin is rich in HIV target cells
 - External foreskin/shaft keratinized and not vulnerable
 - After circumcision, only vulnerable mucosa is meatus
- Foreskin is retracted over shaft during intercourse
 - Large inner mucosal surface exposure
 - Micro-tears, especially of frenulum
- Intact foreskin associated with infections
 - Genital ulcer disease
 - Balanitis/phimosis
 - Possible increased HIV entry or shedding

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Features of Three Clinical Trials

	Orange Farm	Rakai	Kisumu
Population	Semi-urban	Rural	Urban
MC Rate	20%	16%	10%
HIV incid.	1.6%	1.3%	1.8%
Age Range	18-24 yrs	15-49 yrs	18-24 yrs
Sample size	3,128	5,000	2784
Completion	April, 2005	June, 2007	Sept, 2007
Interim DSMB	Nov, 2004	Dec, 2006	Dec, 2006

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Orange Farm Trial Results

□Follow-up - 4664 person-years, mean 18 months

HIV seroconversions					
	M0-M3	M4-M12	M12-21	Total	
Intervention (<i>n</i> =1538)	2	7	9	18	
Control (<i>n</i> =1590)	9	15	27	51	
TOTAL	11	22	36	69	

Unadjusted RR: 0.40 (0.24–0.68); p=0.00013 Controlling for behavioural factors: RR=0.39 Per protocol RR: 0.24 (0.14–0.46)

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Issues Still to be Addressed

- The impact on HIV prevalence at the population level: modelling studies
- Resource needs (financial, human, facility), cost effectiveness
- Acceptability

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Modelling the Impact of MC on HIV Prevalence & Incidence

Williams et al., 2006

- 100% uptake of MC could avert 2.0 million new infections and 0.3 million deaths over ten years in sub-Saharan Africa
- Could avert 5.7 million new infections over 20 years

Mesesan et al., 2006

 50% uptake of MC could avert 32,000 – 53,000 new infections in Soweto, SA over 20 yrs. Prevalence would decline from 23% to 14%

Nagelkerke et al., submitted

 Prevalence in Nyanza Province, Kenya would decline from 18% to 8% over 30 years with 50% uptake of circumcision over 10 years

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- 13 Acceptability Studies in Non-Circumcising Communities (9 countries) Westercamp and Bailey 2006
 - Perception that MC improves hygiene is nearly universal.
 - Perception that MC reduces risk of STI is widespread
 - Perception that MC reduces risk of HIV is variable
 - Biggest barriers to MC are cost, and concerns about safety (risk of infection or mutilation), and pain
 - Most communities want safe, affordable MC services to be available.

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Issues Still to be Addressed

- The impact on HIV prevalence at the population level: modelling studies
- Resource needs (financial, human, facility), cost effectiveness
- Acceptability
- Operational requirements
- Risk compensation will circumcised men feel they are protected and engage in more risky behaviours? Will women assume they are protected and not negotiate condom use?
- Safety

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Risk Compensation

If male circumcision is promoted as being protective against HIV infection, will circumcised men be more likely to engage in higher risk behaviours?

- > Orange Farm Trial Results
 - Mean # sexual acts higher in circumcised men
 - Behavioural factors had no influence on effect of MC
- > Agot et al., 2006 Siaya, Kenya
 - No difference in sexual risk behaviours of men who became circumcised compared to controls

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Complications Due to Neonatal Male Circumcision in the United States

- One study of 230,632 infants
 - Complication rate of 0.2%
 - Bleeding .13%
 - Infection .06%
- One study of 5,521 infants
 - Complication rate of 2.0%
 - Bleeding 1.0%
 - Infection 0.4%

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Complications from Circumcision in Africa

- In East and southern Africa circumcision primarily of adolescents (ages 8 – 18 years)
- > One study in Nigerian and Kenyan Hospitals: about 12%
- Kisumu UNIM randomized controlled trial (ages 18-24yrs): complication rate of 1.7%
- > Orange Farm Trial (ages 18-24yrs): 3.8%

Many anecdotal reports throughout Africa of bleeding, infection, mutilation and death, especially associated with traditional MC

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Background Study in Bungoma, Kenya Bailey and Egesah 2006

- BaBukusu are an ethnic group that has traditionally practiced MC for many generations.
- Recently, Bukusu families have begun to shift from traditional circumcision rites and rituals toward medicalized circumcision.
- Reasons: <u>cost</u>, time away from school and work, safety, HIV risk, "modernization"
- Presents an ideal natural experiment to assess medical versus traditional MC

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Complications From Traditional Versus Medical Circumcisions in Bungoma District, Kenya (N=1010)

VARI	TRAD	ITION	MED	ICAL	TO	TAL	<u>OR</u>
AE	N ^r	<u>%</u>	Ν	%	Ν	%	
Yes	156	35.2	99	17.7	255	25.4	2 53*
No	287	64.8	460	82.3	747	74.6	2.00
					Bailey &	Egesah, ä	2006
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Most Common Complications Reported

- Profuse bleeding
- Infection requiring antibiotics
- Insufficient foreskin removed: recircumcision required
- Excessive pain
- Erectile dysfunction
- Torsion
- Urinary tract infections

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Adverse Events (AE) By Setting

		NUMBER	
FACILITY	#	AEs	%
Public Facility	111	11	10.1
Private Facility	346	78	22.5
Traditional	426	146	34.3
Total	883	235	26.6

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Summary of Bungoma Complication Study

- Traditional circumcisers and most medical practitioners are not adequately trained
- Most facilities lack proper supplies and instruments
- Many AEs could be avoided if boys and parents are adequately trained in post-operative wound care.
- Most Bukusu would in practice prefer medical circumcision over traditional circumcision, but they fear stigma and disapproval within the community.
- If medical circumcision were actively promoted, with complete and correct information provided, many Bukusu boys and parents would elect to be circumcised by a medical professional.

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Summary



- Evidence of the protective effect of MC on STIs and HIV is compelling: observational, biological, clinical trial
- Modelling indicates that MC could avert millions of new HIV infections in East and southern Africa, and would be highly cost-effective.
- Acceptability of MC in non-circumcising populations is already high and growing.
- > The limited data on safety are alarming.

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- > Safety is feasible, but will take resources.
- > Risk compensation must always be a concern.
- Needs for training and resources are widespread outside of hospitals

