

Studies of the Association Between Circumcision and HIV Acquisition in Men

- 4 ecological studies
- 33 cross-sectional studies
- 13 prospective studies
- The adjusted relative risk of HIV infection for circumcised men found in the prospective studies is 0.52 – 0.18

Rakai Study

Quinn et al. NEJM 2000; 342:921-929

Study of 415 discordant couples

- 40 infections in 137 uncircumcised men
- 0 infections in 50 circumcised men
- Seroincidence of 16.7 per 100 person-yrs in uncircumcised men.

Orange Farm Trial Results

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

HIV seroconversions				
	M0–M3	M4–M12	M12–M21	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

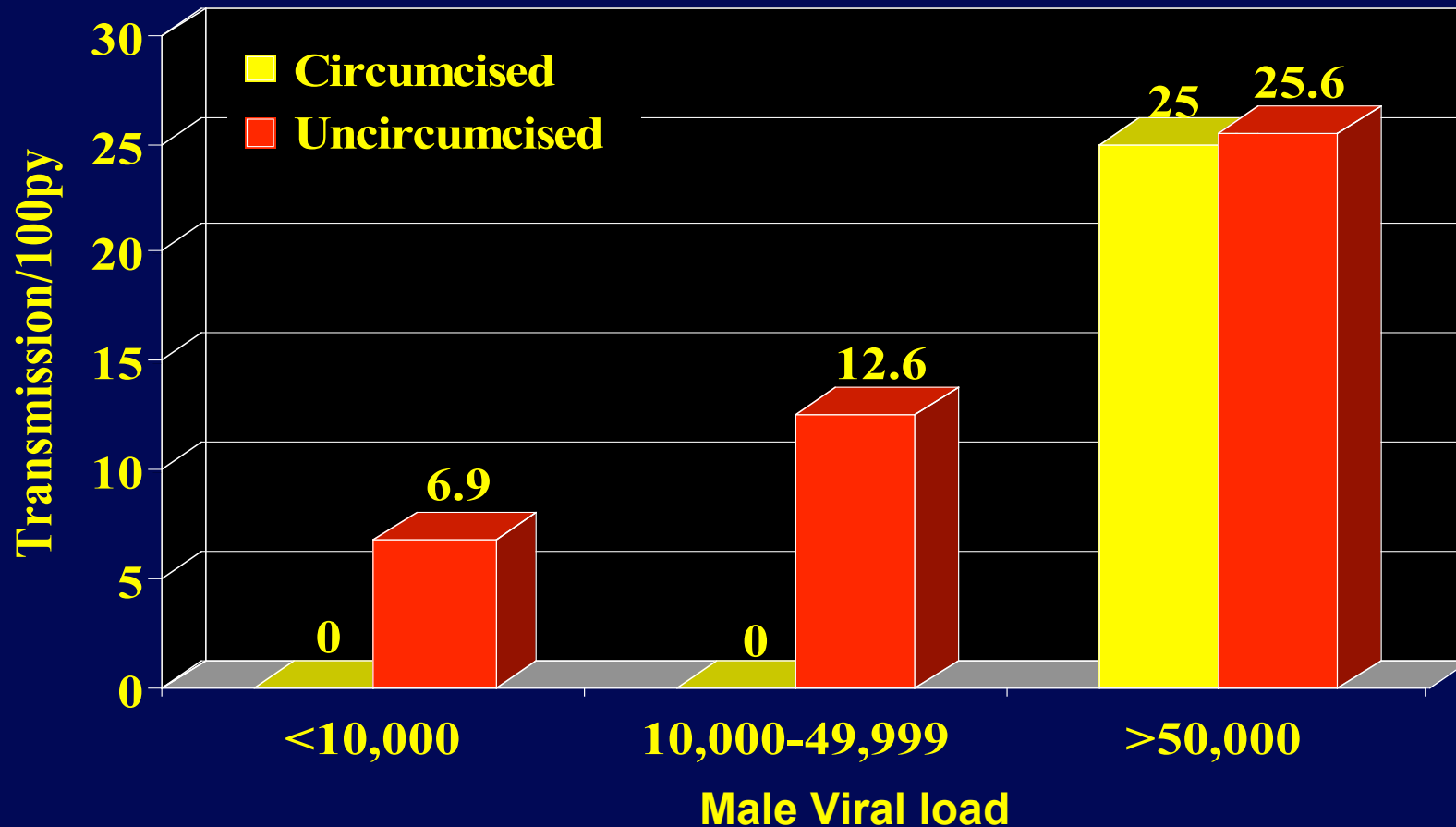
Per protocol RR: 0.24 (0.14-0.46)

Controlling for behavioral factors: RR=0.39

Features of Three Clinical Trials

	Orange Farm	Rakai	Kisumu
Population	Semi-urban	Rural	Urban
MC Rate	20%	16%	10%
HIV Incidence	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 Analysis	Nov, 2004	Dec, 2006	Dec, 2006

Circumcision Status and HIV Transmission to Women



Of 47 couples in which circumcised *male partner* was HIV+ AND whose viral load was <50,000 particles, 0 of female partners were infected after two years, vs. 26 of 143 female partners of uncircumcised HIV+ men (9.6/100 py) ($p = 0.02$).

Quinn et al NEJM 2000

Other Benefits of Circumcision

- Circumcision likely has protective effect against
 - Urinary tract infections in infants
 - 12 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
 - HSV-2
 - 30% reduction in circumcised 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
 - 0.18 – 0.50 in women with circumcised partners

Benefits of Circumcision?

- Circumcision may have no protective effect against:
 - Chlamydia
 - Gonorrhea
 - Genital herpes (HSV-2)

Susceptibility of Human Foreskin Tissue to HIV Infection

- Foreskin mucosa contains higher proportions of CD4+ T cells, macrophages and Langerhans' cells than cervical mucosa but approximately the same proportions as in the glans penis, frenulum and the outer surface of the foreskin.
- The outer surface of the foreskin and the glans is protected by a thick layer of keratin.
- In explant culture, the inner surface of the foreskin had nine times more HIV-DNA than in infected cervical tissue, and no HIV-DNA was detected in tissue from the outer surface of the foreskin.

Patterson et al. American J of Pathology 2002

McCoombe and Short. AIDS 2006

Modeling 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.

Cost-effectiveness Models

- Kahn et al, 2006
 - Cost is \$181 per HIV infection averted over 20 years in Guateng, SA. With 25.6% prevalence.
 - Cost-effectiveness is sensitive to HIV prevalence, cost of MC, and RR of MC.
 - If HIV prevalence is 8%, cost per infection averted is \$550.
- Other models, unpublished
 - Cost per infection avoided ranges from \$450 - \$2500.
 - Cost per infection avoided for PMCT is \$2517.

Main Barriers and Facilitators for Acceptability of MC

Results of 13 studies from 10 countries in sub-Saharan Africa

Barriers:

- Cost
- Fear of pain
- Concern for safety

Facilitators:

- Hygiene
- Reduced STIs
- Attractiveness

Westercamp and Bailey, in press

Behavioral Disinhibition/ Risk Compensation

- If MC is promoted as being protective against HIV infection, will circumcised men be more likely to engage in higher risk behaviors?
- Orange Farm Trial Results
 - Sexual behavior factors higher in circumcised men
 - Mean # sexual contacts higher in circumcised men
 - Behavioral factors had no influence on effect of MC
- Agot et al., 2006
 - No difference in sexual risk behaviors of men circumcised and controls in Siaya, Kenya

Complications from Circumcision in Africa

- One study in Nigerian and Kenyan Hospitals
 - Complication rate about 12%
- Kisumu UNIM randomized controlled trial (ages 18-24yrs)
 - Complication rate of 1.7%
- Orange Farm Trial (ages 18-24yrs)
 - Complication rate of 3.8%
- Bungoma, Kenya
 - 17.5 % complication rate in medical settings
 - 35% complication rate in traditional settings

Key Research Questions

- Biological mechanisms
 - Studies that include circumcised controls
 - Studies of the healing and keratinization process
- Impact of MC on HIV prevalence
 - Modeling
 - Intervention studies
 - Quasi-experimental design

Operations Research

- Needs assessments
 - Training, equipment, supplies
- Integration of MC services with VCT, STI treatment, behavioral counseling, and male reproductive services
- Acceptability
 - Barriers and facilitators
 - Uptake by age, education, residence, gender
- Acceptability outside Africa
 - India, China, Caribbean
- Safety – evaluation of AEs in medical and traditional settings
- Scaling up from demonstration to national programs
- Trials of sutureless procedures for adults
 - Mogen, Gomco clamps, Plastibell, other

Key Research Question

- What will be the impact on other prevention trials?
 - Do we simply counsel participants about the benefits and risks of MC?
 - Must we offer MC to all participants (or their partners)?
 - Require controls to be circumcised?
 - Stratify enrollment by MC status?
 - By how much will MC effect our power?

Barriers to Moving Forward

- MC: the abandoned child of HIV prevention
 - Opposition by activists
 - Concern that this is another male-only intervention
 - Lack of researchers with interest and experience
 - Lack of knowledge in non-circumcising communities
- “Wait and see” policy of normative agencies and donors
 - Prevents operational research that is needed now

“All scientific work is incomplete whether it is observational or experimental. That does not confer upon us a freedom to ignore the knowledge we already have or to postpone the action that it appears to demand at a given time.”

Bradford Hill, 1965