The impact of male circumcision on HIV incidence and cost per infection prevented: a stochastic simulation model from Rakai, Uganda

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Objectives: To estimate the impact of male circumcision on HIV incidence, the number of procedures per HIV infection averted, and costs per infection averted.

Methods: A stochastic simulation model with empirically derived parameters from a cohort in Rakai, Uganda was used to estimate HIV incidence, assuming that male circumcision reduced the risks of HIV acquisition with rate ratios (RR) ranging from 0.3 to 0.6 in men, their female partners, and in both sexes combined, with circumcision coverage 0–100%. The reproductive number (R_0) was also estimated. The number of HIV infections averted per circumcision was estimated from the incident cases in the absence of surgery minus the projected number of incident cases over 10 years following circumcision. The cost per procedure ($69.00) was used to estimate the cost per HIV infection averted.

Results: Baseline HIV incidence was 1.2/100 person-years. Male circumcision could markedly reduce HIV incidence in this population, particularly if there was preventative efficacy in both sexes. Under many scenarios, with RR ≤ 0.5, circumcision could reduce R_0 to < 1.0 and potentially abort the epidemic. The number of surgeries per infection averted over 10 years was 19–58, and the costs per infection averted was $1269–3911, depending on the efficacy of circumcision for either or both sexes, assuming 75% service coverage. However, behavioral disinhibition could offset any benefits of circumcision.

Conclusion: Male circumcision could have substantial impact on the HIV epidemic and provide a cost-effective prevention strategy if benefits are not countered by behavioral disinhibition.

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Introduction

Male circumcision has been associated with reduced risk of male HIV acquisition in several observational studies [1–5] and in one randomized trial [6]. Two ongoing trials in Kisumu, Kenya and Rakai, Uganda will be completed in 2007. One observational study of male-to-female HIV transmission in HIV-discordant couples has suggested that male circumcision may reduce female HIV acquisition if the infected male's viral load was < 50 000 copies/ml [2],

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and a trial to assess the efficacy of male circumcision for prevention of female HIV infection is ongoing in Rakai, Uganda.

On the basis of the evidence that circumcision may reduce male HIV risk, consideration is now being given to the provision of male circumcision as a means of HIV prevention. To assess the potential public health impact of circumcision, a stochastic simulation model was used to estimate the population-level incidence of HIV as a function of the possible efficacy of male circumcision for males and females, and the coverage of circumcision services. We used these estimates to calculate the number of surgeries required per HIV infection averted and the possible cost per infection prevented.

Methods

Details of a stochastic simulation model, based on empirical data derived from a cohort study in Rakai, Uganda, have been previously published [7]. In brief, the model simulated HIV transmission from an HIV-positive person to a negative partner within an HIV-discordant relationship. The parameters used in the simulation are listed in Table 1. The probability of transmission per sex act was computed first by stage of disease in the HIV-positive individuals (acute infection/early disease, latency, and advanced disease/AIDS) [8], by age (15–24, 25–29, 30–34, and 35+ years), and by gender. Gender-specific rates of partner change were based on data from the Rakai cohort, with approximately 8% of HIV-positive women and 53% of HIV-positive men reporting multiple partnerships in a given year [7]. Interview information on sexual networks was used to generate distributions of multiple partnerships, non-marital relationships, coital frequencies, and durations of relationships; on the basis of these distributions, HIV-positive individuals were randomly assigned a probability of such relationships. In this setting, virtually all multiple partnerships were concurrent [9]. To estimate sexual contacts of infected persons with HIV-negative partners, the number of reported sexual partners in the model was randomly reduced by 0.14, since 14% of the infected population in Rakai was in a concordant HIV-positive relationship. (Details of model parameters can be provided on request.)

Each coital act was then simulated to determine whether the HIV-negative partner seroconverted, based on the transmission probability per sex act and characteristics of the couple. Partners who remained uninfected were recycled into the pool of uninfected persons and exposed to risk in subsequent replications. New seroconverters generated by the simulation were recycled into the pool of HIV-infected persons, and transmissions to their subsequent HIV-negative partners were simulated as described above. Simulations were run using SAS (version 8; SAS Institute, Cary North Carolina, USA) with 500 replications.

The total number of seroconversions and total person-years at risk among HIV-negative persons were obtained from the simulation for calculation of average HIV incidence rates per 100 person-years in the Rakai population. To assess the simulated effect of circumcision on the future course of the HIV epidemic, the approximate basic reproductive number (R_0) was estimated using the equation $R_0 = \gamma D c$ [7], where γ is the probability of HIV transmission per sex act, D is the total number of coital acts during the infectious period (approximately 10 years, with an average of 106.8 acts of intercourse per year per couple), and c is the average number of HIV-negative partners for each infected individual (the mean value of c in Rakai is 1.25 HIV-negative partners per HIV-positive individual per year for both sexes combined).

Table 1. Summary of observational data used as parameters in the stochastic model simulations.

Parameter	Empirical estimates of parameter values: Transmission probability/coital act	Sex acts/month
Stage of disease in HIV-positive partner		
Acute infection/early disease ~5 months post-infection	0.0082	10.6
Latent disease	0.0007	10.3
Advanced disease/AIDS	0.0031	6.9
Quartile of age (years)		
15–24	0.0013	10.0
25–29	0.0017	9.0
30–34	0.0006	9.1
35–59	0.0009	7.4
Transmission direction		
Female-to-male	0.0013	9.7
Male-to-female	0.0009	8.3
Mean No. HIV-negative sex partners/year		
HIV-positive female	1.08	
HIV-positive male	1.53	
Assumed HIV incidence rate ratio in circumcised versus uncircumcised	0.3, 0.4, 0.5, 0.6	
Assumed circumcision coverage	0, 25%, 50%, 75%, 100%	

To estimate the possible effects of male circumcision, it was assumed that circumcision might reduce the incidence of HIV with incidence rate ratios (IRR) varying from 0.3 to 0.6 in either males or females alone, or both sexes combined. Efficacy, the reduced incidence of HIV afforded by circumcision, was estimated from $1 - \text{IRR}$. These ranges of potential IRR and efficacy are comparable to those reported in the literature [1–6]. It was assumed that the coverage of circumcision services might vary from 0 to 100% of HIV-negative uncircumcised men, and simulations were run for quartiles of program coverage (25%, 50%, 75%, and 100%). Uncircumcised men constitute 84% of the Rakai male population, so coverage only pertained to this proportion. From Rakai data in male HIV-positive/female HIV-negative couples, a non-significant decreased risk of female HIV acquisition was previously observed, with a rate ratio of 0.4, comparable to the South African trial effects in men [2]; however, in an updated analysis, the HIV IRR in uninfected females with circumcised versus uncircumcised HIV-positive male partners was 0.7 [10]. Therefore, a scenario was also simulated in which the male rate ratio was 0.4 (comparable to the South African trial), and the female IRR was 0.7.

The number of HIV infections potentially averted by each surgery was calculated from the total number of incident cases expected in the population in the absence of a circumcision program minus the number of incident cases estimated with varying circumcision efficacies. To simplify presentation, it was assumed that program coverage was 75% of eligible uncircumcised men. The cost per surgery in the Rakai trial was $69.0, including postoperative care. This was used to estimate the cost per HIV infection averted by circumcision over a period of 10 years.

If circumcision reduces HIV risk, it is possible that individuals will develop exaggerated beliefs in the protective effects and increase sexual risk behaviors. Such disinhibition has been observed following the availability of antiretroviral therapy [11]. Therefore, models were constructed in which number of sexual partners per individual was randomly increased, so that the average number of partners increased by 25%, 50%, or 100% in the population. The impact on HIV incidence was then compared with that estimated from the observed number of partners in the Rakai population.

Results

In the absence of a circumcision program, the HIV incidence in the general population was 1.24/100 person-years, and the approximate reproductive rate was 1.44. Table 2 shows the estimated HIV incidence in the total population, and the IRR at which R_0 would decline to < 1, with assumed circumcision efficacy in males or females separately, and in both sexes combined. With $\geq 60\%$ efficacy and 100% program coverage, circumcision could reduce incidence sufficiently to interrupt the epidemic. At all levels of assumed efficacy and program coverage, the reduction in HIV acquisition among women associated with circumcision was more pronounced than comparable circumcision effects in males. This is because incidence rates are higher in women than men in this population; therefore, factors reducing female

Table 2. Simulation of HIV incidence and transmission probabilities per act associated with male circumcision in men, women, and both sexes.

Efficacy and IRR of HIV in circumcised versus uncircumcised and program coverage (%)	Circumcision effects on HIV acquisition: population incidence/100 person years ($R_0 < 1.0$)		
	Male acquisition	Female acquisition	Both sexes acquisition
Coverage (%) at efficacy 70% (IRR, 0.3)			
25	1.08	1.04	0.90
50	1.00	0.94	0.73 ($R_0 = 0.79$)
75	0.94	0.86 ($R_0 = 0.95$)	0.58 ($R_0 = 0.61$)
100	0.83 ($R_0 = 0.90$)	0.61 ($R_0 = 0.84$)	0.42 ($R_0 = 0.43$)
Coverage (%) at efficacy 60% (IRR, 0.4)			
25	1.11	1.06	0.95
50	1.00	0.98	0.81 ($R_0 = 0.89$)
75	0.96	0.92	0.67 ($R_0 = 0.72$)
100	0.90 ($R_0 = 0.99$)	0.68 ($R_0 = 0.94$)	0.54 ($R_0 = 0.57$)
Coverage (%) at efficacy 50% (IRR, 0.5)			
25	1.1	1.09	1.00
50	1.08	1.03	0.88
75	1.02	0.97	0.77 ($R_0 = 0.84$)
100	1.00 ($R_0 > 1.0$)	0.73 ($R_0 > 1.0$)	0.66 ($R_0 = 0.71$)
Coverage (%) at efficacy 40% (IRR, 0.6)			
25	1.12	1.11	1.04
50	1.11	1.07	0.95
75	1.06	1.02	0.86 ($R_0 = 0.96$)
100	1.02 ($R_0 > 1.0$)	0.79 ($R_0 > 1.0$)	0.78 ($R_0 = 0.0.86$)

IRR, incidence rate ratio.

Table 3. The number of HIV infections averted and cost per infection averted over 10 years.

	Circumcision effects on male HIV acquisition		Circumcision effects on female HIV acquisition		Circumcision effects on HIV acquisition in both sexes	
Circumcision efficacy (%)	Surgeries per infection averted	Cost per infection averted ($)	Surgeries per infection averted	Cost per infection averted ($)	Surgeries per infection averted	Cost per infection averted ($)
60	39	2631	33	2208	19	1269
50	46	3136	38	2579	22	1485
40	58	3911	46	3136	27	1806

acquisition have a greater population-level impact. If circumcision conferred reduced risk of HIV acquisition in both sexes, the impact on population incidence would be most profound (e.g., R_0 could be reduced to 0.79 with only 50% coverage and an IRR of 0.3). Even at lower levels of circumcision efficacy, if the procedure reduced HIV risks in both sexes, it would be theoretically possible to abort the epidemic. Finally, it was assumed that circumcision might have an IRR of 0.4 for male acquisition, as observed in the South African trial [6], and an IRR of 0.7 for females, as suggested by our most recent observational analyses [10]. Under this scenario, given 75% program coverage, the estimated incidence was 0.82/100 person-years and R_0 was 0.89. Thus, the potential public health impact of circumcision is highly dependent on protective efficacy in both sexes.

Table 3 shows the estimated number of HIV infections averted over a decade with varying efficacy of circumcision, assuming 75% coverage of a program. Also shown is the cost per infection averted assuming a unit cost of $69.00 per procedure. This assumes the population is stable over time, and that annual immigration approximately balances emigration, as has been shown to be the case in the Rakai cohort [12]. Because the potential effects of circumcision are likely to persist for many years, the number of surgeries required to prevent one infection over 10 years is relatively few (range, 19–58), even at low circumcision efficacies, and the estimated costs per HIV infection averted ranged from $1269 up to $3911.

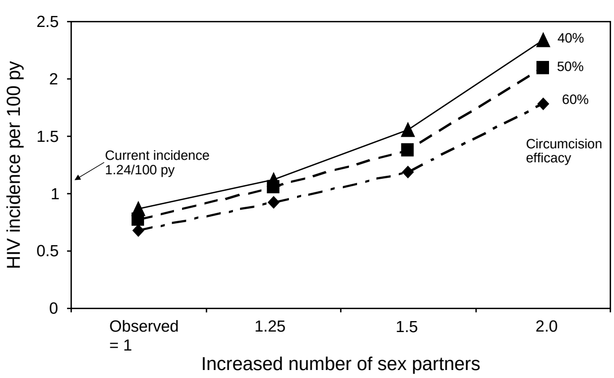

Fig. 1. Population-level HIV incidence with an increase in number of sexual partners and varying degrees of circumcision efficacy for HIV prevention, assuming 75% program coverage. py, person-years.

To assess the impact of behavioral disinhibition if circumcision leads to risk compensation, HIV incidence was simulated assuming an increase in the mean number of sexual partners per year from the observed level up to a doubling of partners. To simplify presentation, it was assumed that the circumcision program coverage was 75%. As shown in Fig. 1, irrespective of the possible efficacy of circumcision, behavioral disinhibition could completely offset any declines in HIV incidence owing to circumcision and potentially could increase incidence above the rates observed in the absence of a circumcision program.

Discussion

If the one completed trial [6] and the two ongoing circumcision trials in Kenya and Uganda demonstrate reduction in HIV risk in men, and if the current Rakai trial shows reduced risks of HIV infection in women, then there will be a compelling argument to provide male circumcision as a means of HIV prevention in those areas where circumcision is not now widely practiced but where HIV prevalence and incidence are high. This includes many countries in east, central and southern Africa. This simulation suggests that male circumcision could reduce HIV incidence in the general population, potentially to a point where the reproductive number could decline to < 1.0 and the epidemic would wane (Table 2). Moreover, since the possible protective effects of circumcision are probably long lasting, even lifelong [13], this is likely to be a cost-effective intervention (Table 3), comparable with other proven preventive strategies such as provision of nevirapine for prevention of mother-to-child HIV transmission [14]. Nevertheless, as indicated in Fig. 1, if circumcised men and their partners develop a false sense of security and increase their risk behaviors, disinhibition could offset any benefits afforded by circumcision, emphasizing the need to maintain intensive risk reduction efforts.

Other model estimates of the impact of circumcision have been recently been published. Williams *et al.* [15] used a dynamic simulation model based on country-level prevalence of circumcision and HIV and estimated that the procedure could avert 2.0 million new infections and 300 000 deaths in sub-Saharan Africa over 10 years. Also, a model based on Soweto suggested substantial potential impact in that setting [16]. Using the results of the South African trial [17], Kahn *et al.* [18] estimated that the cost per HIV infection averted over 20 years could range from $181 with a HIV prevalence of 25%, to $550 with lower HIV prevalence levels. This is substantially lower than the costs estimated for Rakai (Table 3).

There are limitations to this simulation model. First, it is based on parameters derived from empirical studies in rural Rakai, which has a mature generalized epidemic with a current HIV incidence of 1.24/100 person-years, and prevalence of 11%. Therefore, we do not know whether our findings apply to early rapidly expanding epidemics, to the high-intensity generalized epidemics observed in southern Africa, or to urban settings. Nevertheless, if circumcision is as efficacious as suggested by the South African trial [6], it is likely to be beneficial in many contexts. A second limitation is that this simulation pertains to adult circumcision, but if the trials suggest efficacy in adults, it would be prudent also to provide neonatal circumcision services because the surgery is simpler, cheaper, and safer in infants. However, the impact of neonatal circumcision on the epidemic would be delayed for many years until these infants reached the age of sexual maturity, and such long-term projections are likely to be highly speculative and unreliable. A third potential limitation is whether the model accurately reflects the HIV epidemic in Rakai, and whether the assumptions about circumcision efficacy in either or both sexes are realistic. We have shown that the model closely approximates to the observed epidemic dynamics in this population [7], and all model parameters (e.g., rates of transmission per coital act by stage of infection, number of acts and partner change etc.) are based on empirical findings requiring minimal assumptions [7,8]. Consequently, we believe the model reasonably reflects the HIV epidemiology in Rakai. With regard to the efficacy of circumcision for HIV prevention, the range of IRR values used here encompass those reported in observational studies and the one completed trial [1–6], but ultimately the results from ongoing trials will be needed to assess whether these assumptions of efficacy are plausible. It must be noted that observational data suggest that circumcision may be more efficacious in individuals with repeated HIV exposures such as HIV-discordant couples [2], patients with sexually transmitted diseases [3], or truck drivers [4,5], so one can anticipate that the effects are likely to vary within and between populations, depending on the levels of HIV exposure [1,15]. This could also affect efficacy estimates derived from trials.

Male circumcision offers the prospect of an innovative approach to HIV prevention and constitutes a unique public health intervention in that a surgical procedure would be used to confer long-term protection from an infectious disease. The challenges are great, and the experience with tubectomy and vasectomy programs in India provides a sobering precedent for what can go wrong when surgery is used to promote public health. These Indian sterilization programs suffered from poor-quality services, substantial surgical complications, and evidence of coercion [19–21], which ultimately led to the collapse of the programs and the downfall of the Indira Ghandi government [22]. If circumcision becomes part of the HIV prevention armamentarium, we need to ensure that high standards of surgical and postoperative care are provided during scale up to prevent potential complications that could undermine the initiative.

References

1. Weiss HA, Quigley MA, Hayes RJ. **Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis**. *AIDS* 2000; 14: 2361–2370. Review.
2. Gray RH, Kiwanuka N, Quinn TC, Sewankambo NK, Serwadda D, Mangen FW, *et al.* **Male circumcision and HIV acquisition and transmission: cohort studies in Rakai, Uganda.** *AIDS* 2000; **14**:2371–2381.
3. Reynolds SJ, Shepherd ME, Risbud AR, Gangakhedkar RR, Brookmeyer RS, Divekar AD, *et al.* **Male circumcision and risk of HIV-1 and other sexually transmitted infections in India.** *Lancet* 2004; **363**:1039–1040.
4. Lavreys L, Rakwar JP, Thompson ML, Jackson DJ, Mandaliya K, Chohan BH, *et al.* **Effect of circumcision on incidence of human immunodeficiency virus type 1 and other sexually transmitted diseases: a prospective cohort study of trucking company employees in Kenya.** *J Infect Dis* 1999; **180**:330–336.
5. Baeten JM, Richardson BA, Lavreys L, Rakwar JP, Mandaliya K, Bwayo JJ, *et al.* **Female-to-male infectivity of HIV-1 among circumcised and uncircumcised Kenyan men.** *J Infect Dis* 2005; **191**:546–553.
6. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. **Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial**. *PLoS Med* 2005:e298. Epub 2005
7. Gray RH, Li X, Wawer MJ, Gange SJ, Serwadda D, Sewankambo N, *et al.* **Stochastic simulation of the impact of antiretroviral therapy and HIV vaccines on HIV transmission; Rakai, Uganda.** *AIDS* 2003; **17**:1941–1951.
8. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, *et al.* **Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda.** *J Infect Dis* 2005; **191**:1403–1409.
9. Kelly RJ, Gray RH, Sewankambo NK, Serwadda D, Wabwire-Mangen F, Lutalo T, *et al.* **Age differences in sexual partners and risk of HIV-1 infection in rural Uganda.** *J AIDS* 2003; **32**:446–451.
10. Gray RH, Wawer MJ, Thoma M, Serwadda D, Nalugoda F, Li X, *et al.* **Male circumcison and the risks of female HIV and sexually transmitted infections in Rakai, Uganda.** *13th Conference on Retroviruses and Opportunistic Infections*. Denver, February 2006 [abstract 128].
11. Crepaz N, Hart TA, Marks G. **Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review.** *JAMA* 2004; **292**:224–236.
12. Wawer MJ, Serwadda D, Gray RH, Sewankambo NK, Li C, Nalugoda F, *et al.* **Trends in HIV-1 prevalence may not reflect trends in incidence in mature epidemics: data from the Rakai population-based cohort, Uganda.** *AIDS* 1997; **11**:1023–1030.
13. Kelly RK, Kiwanuka N, Wawer MJ, Serwadda D, Sewankambo NK, Wabwire-Mangen F, *et al.* **Age of male circumcision and risk of prevalent HIV infection in rural Uganda.** *AIDS* 1999; **13**:399–405.
14. Sweat MD, O'Reilly KR, Schmid GP, Denison J, de Zoysa I. **Cost-effectiveness of nevirapine to prevent mother-to-child HIV transmission in eight African countries.** *AIDS* 2004; **18**: 1661–1671.

15. Wawer MJ, Reynolds SJ, Serwadda D, Kigozi G, Kiwanuka N, Gray RH. **Might male circumcision be more protective in the highly exposed? An immunological hypothesis.** *AIDS* 2005; **19**:2181–2182.
16. Williams BG, Loyd-Smith JO, Gouw E, Hankins C, Getz WM, Hargrove J, *et al*. **The potential impact of male circumcison on HIV in sub-Saharan Africa.** *PLos Med* 2006; **3**:1–9.
17. Mesesan K, Owens DK, Paltiel AD. **The potential benefits of expanded male circumcison programs in Africa; predicting the population-level impact on heterosexual HIV transmission in Soweto**. *XVI International Conference on AIDS*. Toronto, July 2006 [abstract TUC0203].
18. Kahn JG, Marseille E, Auvert B. Cost-effectiveness of male circumcison in sub-Saharan Africa. XVI International Conference on AIDS. Toronto, July 2006 [abstract TUC0204].
19. Bhatt RV. **Camp laparoscopic sterilization deaths in Gujarat State, India, 1978–1980.** *Asia Oceanic J Obstet Gynaecol* 1991; **17**:297–301.
20. Kabira SG, Narayan R. **Sterilization camps in India.** *Lancet* 1990; **335**:225–235.
21. Kumar S. **Health-care camps for the poor provide mass sterilization quota.** *Lancet* 1999; **353**:1251.
22. Anon. The issue that inflamed India. Time Magazine 1977; 109:38–9.