

# Randomized, controlled trials for HIV/AIDS prevention in Africa: learning from unexpected results

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**Evaluation of: Wawer MJ, Makumbi F, Kigozi G *et al.*: Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomized controlled trial. *Lancet* 374, 229–237 (2009).** A randomized, controlled trial (RCT) testing the hypothesis that circumcision in HIV-infected men would reduce HIV transmission to uninfected female sexual partners failed to confirm such findings from observational studies in Africa. Researchers noted no statistically significant differences in incident HIV to partners of circumcised or uncircumcised HIV-infected men. Surprisingly, by the time the trial was terminated because of futility, the trend was toward higher incidence in partners of circumcised men. The trial may have been stopped too early to adequately assess this unexpected trend. Since the investigators focused exclusively on sexual transmission, it is possible, if not likely, that unmeasured nonsexual (unsanitary puncturing) exposures caused some incident HIV infections, thus contaminating their protocol. The history of RCTs for AIDS prevention in Africa has been highlighted by unexpected results. RCTs have almost exclusively focused on sexual transmission, a framework that may be a leading culprit behind unexpected and disappointing outcomes.

The history of randomized, controlled trials (RCTs) for HIV/AIDS prevention in sub-Saharan Africa has often been highlighted by surprising, not to mention disappointing, results. Such is the case with an RCT conducted in the Rakai district of Uganda [1], in which researchers tested the hypothesis that circumcision in HIV-infected men would reduce transmission of HIV and other sexually transmitted infections (STIs) to their uninfected female sexual partners.

Conducted in parallel with the RCT of circumcision in HIV-uninfected men, which indicated that circumcision substantially reduced acquisition of HIV by approximately 50% [2], the hope was that HIV transmission in the other direction (male–female) would be attenuated by male circumcision, a hope distilled from several observational studies [3–5]. Regrettably, this hypothesis failed to be supported by the present RCT, which was terminated early because of futility [1]. Why were findings from observational studies not supported by experimental evaluation of the intervention? Neither the Rakai researchers nor I know; in this article, I briefly review the trial’s assumptions, methods, results and shortcomings to suggest some reasons not considered by the investigators.

## Summary of methods

Beginning in 2003, investigators in the Rakai district screened 7274 men whose HIV prevalence approached 16%, aiming to recruit

uncircumcised HIV-infected men aged 15–49 years with no evidence of major immune suppression (of possible concern when contemplating circumcision). Computer-generated randomization divided the 922 enrolled participants into two groups: 474 men offered immediate circumcision (intervention arm) and 448 offered circumcision after study completion (24 months, control arm). These 922 HIV-infected men were asked to invite their regular sex partners to participate. As the intervention required surgery, neither participants nor study staff could be blinded to the study arm. The primary end point of the RCT was the male–female HIV transmission rate for each arm.

Newly circumcised men were examined at three postsurgery intervals: 24–48 h, 5–9 days and 4–6 weeks, until wound healing could be certified. At each interval, the men were inspected for wound healing and interviewed about sexual exposures. Men in both arms and their women partners were tested for HIV plus two minor STIs, and interviewed about sexual and related health behaviors at 6, 12 and 24 months postenrollment. Sequencing of Gag and gp41 HIV fragments obtained from sera of both index men and their newly infected partners was attempted to evaluate partner-linked HIV sequence concordance.

Women were compensated for their time and travel at US\$3 per visit; compensation for men is not stated. “At every study visit, participating

men and their female partners were provided with intensive education on HIV/STI prevention, including promotion of sexual abstinence, faithfulness and consistent condom use. Additionally, both partners were offered free condoms ... and couples voluntary counseling and testing" [1]. Participants were counseled to refrain from intercourse until healing was complete. Repeated efforts were made to promote HIV disclosure; by self-report, close to three-quarters of HIV-infected men in each arm "disclosed their serostatus to their female partner" [1].

#### Summary of results

Of the 374 regular partners of the 474 men in the intervention arm, 92 HIV-uninfected women were successfully followed, as were 67 HIV-uninfected women among the 348 partners of the 448 men in the control arm. An additional 59 HIV-uninfected women partners, almost equally divided by the study arm, were followed but analyzed separately owing to the nonsynchronous enrollment with their male partner. In the primary analysis, 17 (18.5%) of the 92 HIV-uninfected women partners in the intervention arm and eight of the 67 (11.9%) in the control arm acquired HIV during follow-up, considered to be a nonsignificant result ( $p = 0.36$ ). Secondary analysis of the 59 HIV-negative women partners who enrolled 6 months or more after their man partner demonstrated similar results: 17.4% in the intervention arm and 15.8% among controls ( $p = 0.65$ ). Consistent condom use, although increasing during the trial and (ironically) notably higher in the intervention arm, remained below 50%.

The Kaplan-Meier survival analysis and Cox proportional hazards modeling demonstrated that the cumulative probability of HIV acquisition by women was 21.7% in the intervention arm and 13.4% in the control arm ( $p = 0.287$ ) and that, controlling for differences in enrollment characteristics, the adjusted hazard ratio was 1.49 ( $p = 0.368$ ). Incident HIV was more likely to occur in women who reported resuming sex early after circumcision of their male partner (27.8%) compared with women in the intervention arm, who delayed sex (9.5%), and with women in the control arm (7.9%). Finally, HIV sequence data, although reported for only approximately half (13 of 25) of the couples where the woman acquired HIV, demonstrated that the distance between linked partners was less than 0.5%, indicating "probable HIV acquisition within the partnership" [1]. In summary, this RCT did not demonstrate that circumcision

of HIV-infected men was protective for their women partners; enrollment for the RCT was ceased at the end of 2006, while participant follow-up continued for another 12 months before stopping.

#### Discussion

The criticism that this RCT was probably terminated prematurely has been voiced previously [101]. Wilton noted that there was a clear trend "towards much greater rates of HIV infection among the female partners of circumcised men" and, "Therefore, continued observation to the scheduled completion date of the study could only have yielded more and better data, possibly rising to the level of statistical significance". Wilton speculates that the investigators, committed to circumcision owing to the success of their principal RCT [2], may have been trying to avoid contrary evidence [101].

Whatever the merits of Wilton's view, and while I believe that the investigators conscientiously implemented their RCT, there are also missing (perhaps unreported) data that could have influenced observed outcomes and their validity. It is clear that the investigators focus exclusively on sexual intercourse; their report fails to consider other modes of HIV transmission (note the absence of bloodborne transmission variables). HIV can be transmitted by blood exposures and opportunities for unsanitary puncturing in poor countries abound. It has been reported that, in Uganda, a majority of households have reusable equipment for injecting medication [6], and anyone who has ever visited Uganda's rural areas will be familiar with shortcomings in infrastructure that pose serious impediments to sterilization of syringes and other sharp objects (e.g., razor blades and lancets).

On follow-up visits, participants were queried about sexual, but apparently not blood, exposures. Absence of evidence is not evidence of absence. Participants who acquire HIV are not always infected through sexual contact, but also through blood exposure. For example, the authors state that the HIV sequence assays performed on linked HIV-infected partners indicate "probable HIV acquisition within the partnership" [1]. The default assumption here is that transmission was sexual when, in point of (overlooked) possibility, sharing of medical injection equipment and other shared blood exposures within and outside the household would produce the same results. It is also possible that some of the incident cases were acquired

in the community via other unassessed puncturing exposures. Moreover, it is troubling that, in populations with very high follow-up rates [1], HIV sequencing data were available for only 13 of the 25 couples; this shortfall is not explained. Complete partner-linked HIV sequencing would be especially important in light of a previous report from the same region of Africa where HIV sequencing in “known sexual partners failed to show significantly related sequences” [7].

In addition, the investigators do not mention whether data on anal intercourse were sought; the reader is left to assume that intracouple HIV incidence was a result of heterosexual sex (assumed to be penile–vaginal intercourse). Epidemiologic assessment by such default assumptions undermines confidence in study results. Not only is it becoming increasingly clear that anal intercourse in sub-Saharan Africa is much more common than suspected [8,9], but incident HIV infections to women would be much more efficiently transmitted anally than vaginally, especially since people are less likely to use condoms during anal than vaginal intercourse. Finally, the investigators do not report whether any vaginal sex behaviors were associated with incident infection, nor do they say whether any HIV incident cases occurred in women reporting no sexual partners during the relevant interval.

#### Future perspective

Singular focus on sexual HIV transmission, lack of specificity in modes of sexual transmission, incomplete HIV sequencing on partner-linked pairs, not to mention possibly inappropriate

termination of the RCT, undermine confidence in the validity of the trial’s outcomes. Yet, such unexpected and disappointing results fit within the long lineage of RCTs in sub-Saharan Africa that have, during the last two decades, monochromatically focused on sexual HIV transmission and failed to demonstrate anticipated outcomes. This lineage includes RCTs and population-based surveys to assess the efficacy of treating STI to reduce HIV incidence [10], the impact of sexual concurrency on rapid HIV propagation [11,12], the impact of sexual behavior interventions [13] and the impact of vaginal microbicides [14] or of providing pre-exposure prophylaxis (daily tenofovir [14]). The words ‘paradox’, ‘surprising’ and ‘unexpected’ are commonly used in these reports. The real lesson from disappointing RCTs may be that sexualization of sub-Saharan Africa’s HIV epidemics has deterred researchers from exploring a broad range of blood exposures as contributing factors [15]. Two decades of unexpected and disappointing results argue for a fundamental reassessment of what is being missed by the orthodox assumptions. Is it time to cut the Gordian Knot?

#### Financial & competing interests disclosure

*The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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### Executive summary

#### Introduction

- Randomized controlled trials (RCTs) for HIV/AIDS prevention in Africa have been highlighted by unexpected and disappointing results for two decades; the present RCT in Rakai is, regrettably, no exception.

#### Aims & methods

- The study aimed to assess whether circumcision in HIV-infected men would reduce HIV transmission to their female sex partners.
- Men in the intervention arm were circumcised immediately, while controls waited 24 months postenrollment for surgery.

#### Results

- There was no statistical difference in HIV incidence to the women partners of HIV-infected men in either arm.
- This RCT did not show that circumcision of HIV-infected men was protective for their sex partners.

#### Discussion

- Trial investigators did not assess nonsexual routes of HIV transmission to accurately assess origin (sexual or bloodborne?) of incident cases.
- RCT may have been stopped too early to adequately evaluate the unexpected trend towards greater HIV incidence in women partners of the circumcised men.

#### Future perspective

- RCTs must assess a broad range of both sexual and bloodborne exposures; such an expanded search should clarify reasons for unexpected and disappointing results of RCTs and ameliorate efficacy of prevention efforts in Africa.

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▪▪ of considerable interest

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- **Short and bold critique of Rakai RCT of incident HIV infection from HIV-infected men to their female sexual partners.**

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