Sub-Saharan African randomised clinical trials into male circumcision and HIV transmission: Methodological, ethical and legal concerns

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In 2007, WHO/UNAIDS recommended male circumcision as an HIV-preventive measure based on three sub-Saharan African randomised clinical trials (RCTs) into female-to-male sexual transmission. A related RCT investigated male-to-female transmission. However, the trials were compromised by inadequate equipoise; selection bias; inadequate blinding; problematic randomisation; trials stopped early with exaggerated treatment effects; and not investigating non-sexual transmission. Several questions remain unanswered. Why were the trials carried out in countries where more intact men were HIV-positive than in those where more circumcised men were HIV-positive? Why were men sampled from specific ethnic subgroups? Why were so many participants lost to follow-up? Why did men in the male circumcision groups receive additional counselling on safe sex practices? While the absolute reduction in HIV transmission associated with male circumcision across the three female-to-male trials was only about 1.3%, relative reduction was reported as 60%, but, after correction for lead-time bias, averaged 49%. In the Kenyan trial, male circumcision appears to have been associated with four new incident infections. In the Ugandan male-to-female trial, there appears to have been a 61% relative increase in HIV infection among female partners of HIV-positive circumcised men. Since male circumcision diverts resources from known preventive measures and increases risk-taking behaviours, any long-term benefit in reducing HIV transmission remains uncertain.

BACKGROUND

A number of observational studies suggested that male circumcision is associated with reduced sexual transmission of HIV, while many other studies reported no such relationship.[1] Since observational studies may be confounded by uncontrolled factors, the evidence was judged to be insufficiently clear for policy implementation. Accordingly, three randomised clinical trials (RCTs) tested the efficacy of male circumcision to reduce female-to-male sexual transmission of HIV in South Africa, Kenya and Uganda.[2] At the time these trials were approved, admittedly more observational studies had reported an association with HIV than not. Consequently, this evidence led to the ethical approval of these RCTs, as it was deemed that the trials were needed to test the hypothesis that adult male circumcision would lead to a decreased risk of HIV acquisition among men. The risk-benefit ratio was judged

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[1] See Appendix below.

[2] Auvert B, Taljaard D, Lagarde E et al, "Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial" (2005) 2(11) PLoS Med e298; Bailey RC, Moses S, Parker CB et al, "Male Circumcision for HIV Prevention in Young Men in Kisumu, Kenya: A Randomised Controlled Trial" (2007) 369(9562) *Lancet* 643; Gray RH, Kigozi G, Serwadda D et al, "Male Circumcision for HIV Prevention in Men in Rakai, Uganda: A Randomised Trial" (2007) 369(9562) *Lancet* 657.

acceptable by all institutional review boards involved, and men were allowed to (and many did) decline participation. It was reported that male circumcision reduces female-to-male sexual transmission of HIV.

In contrast, a parallel RCT into male-to-female sexual transmission of HIV in Uganda demonstrated that male circumcision *increases* male-to-female transmission of HIV.[3] In the male-to-female trial, women were unwittingly exposed to HIV infection since male sexual partners subjected to male circumcision were already HIV-positive. Several women subsequently became HIV-positive following their participation in the trial, raising concerns about informed consent. While male circumcision has not been recommended for HIV-positive men, in real-life settings HIV testing cannot be assured and does not always occur prior to the circumcision intervention. The present critique raises several methodological, ethical and legal concerns with these trials, suggesting that the decision by WHO/UNAIDS to recommend male circumcision as a prophylactic HIV-preventive measure in sub-Saharan Africa was unwarranted.

While the "gold standard" for medical trials is the randomised, double-blind, placebo-controlled trial,[4] the African trials suffered design and sampling problems, including problematic randomisation and selection bias, inadequate blinding, lack of placebo-control (male circumcision could not be concealed), inadequate equipoise, experimenter bias, attrition (673 drop-outs in female-to-male trials), not investigating male circumcision as a vector for HIV transmission, not investigating non-sexual HIV transmission, as well as lead-time bias, supportive bias (circumcised men received additional counselling sessions), participant expectation bias, and time-out discrepancy (restraint from sexual activity only by circumcised men). Men were randomised either to immediate or delayed male circumcision groups, thereby obfuscating long-term effectiveness. The number of crossovers and participants lost to follow-up differed between groups in all three female-to-male trials, and in the South African and Ugandan female-to-male trials group sizes were somewhat discrepant.

Despite large sample sizes, the actual number of HIV-positive circumcised versus intact men was small, but almost identical across the female-to-male trials ((20, 22, 22) versus (49, 47, 45)), raising questions as to whether these were three separate trials, or three arms of the same trial. The Ugandan trial which tested whether male circumcision could reduce male-to-female transmission of HIV was stopped early because 25 (17 in male circumcision group) previously uninfected women became HIV-positive. It appears that male circumcision was associated with a 61% *increase* in HIV transmission,[5] leading Wawer et al to caution that "Condom use after male circumcision is essential for HIV prevention".[6] What is the purpose of male circumcision, if condom use is still needed to prevent sexual transmission of HIV?

Although Siegfried et al stated that no further studies into male circumcision and HIV sexual transmission are needed,[7] in fact, only epidemiological data can provide definitive evidence of effectiveness (as opposed to mere efficacy) of male circumcision within a given population. Examination of the epidemiological data shows that male circumcision does not provide protection against HIV sexual transmission in several sub-Saharan African countries, including Cameroon, Ghana, Lesotho, Malawi, Rwanda, Swaziland and Tanzania, all of which have a higher prevalence of

[3] 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 Randomised Controlled Trial" (2009) 374 *Lancet* 229.

[4] Sussman JB and Hayward RA, "An IV for the RCT: Using Instrumental Variables to Adjust for Treatment Contamination in Randomised Controlled Trials" (2010) 340 BMJ c2073; Padian NS, McCoy SI, Balkus JE et al, "Weighing the Gold in the Gold Standard: Challenges in HIV Prevention Research" (2010) 24(5) *AIDS* 621.

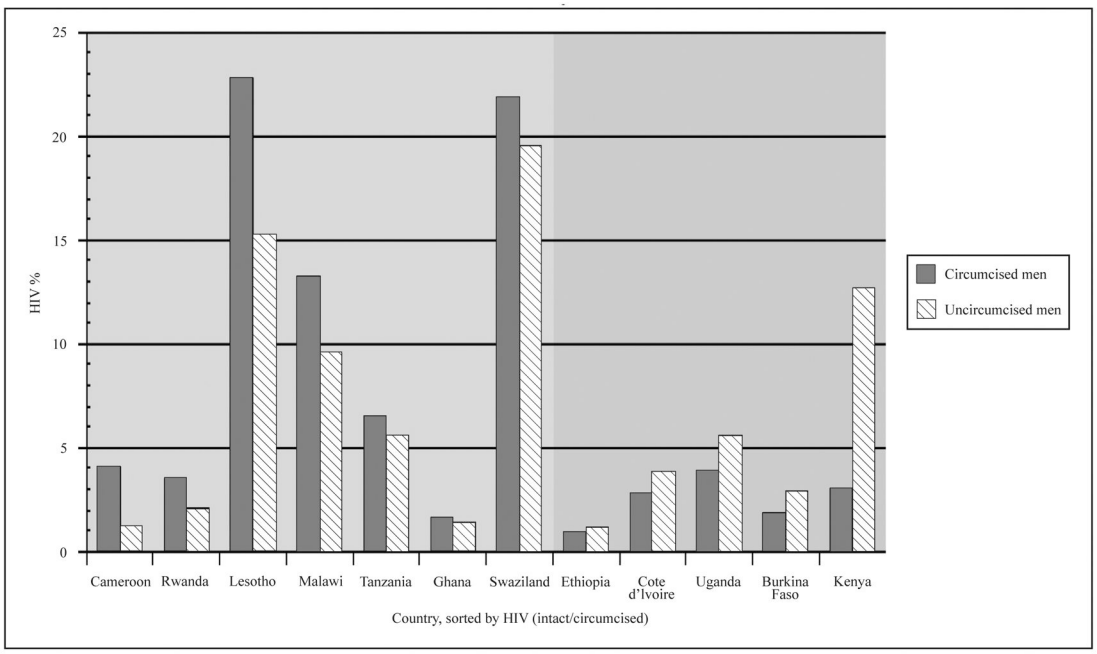
[5] Wawer, Makumbi, Kigozi et al, n 3.

[6] Wawer, Makumbi, Kigozi et al, n 3 at 229.

[7] Siegfried N, Muller M, Deeks JJ et al, "Male Circumcision for Prevention of Heterosexual Acquisition of HIV in Men", *Cochrane Database of Systematic Reviews* (2009) 2 (CD003362), http://www.onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD003362/frame.html viewed 18 October 2011.

HIV infection among circumcised men.[8] This contradictory population-based evidence does not support the WHO/UNAIDS decision to recommend the circumcision of up to possibly 38 million African men as an alleged HIV-preventive measure.

FIGURE 1 Does circumcision protect?



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METHODOLOGICAL CONCERNS

Factors jeopardising internal validity

Several factors may jeopardise the internal validity of RCTs, including:

- researcher expectation bias;
- participant expectation bias;
- inadequate double blinding;
- lead-time bias;
- selection and sampling bias;
- experimental mortality; and
- early termination.

Treatment effects are exaggerated when problems occur with allocation of participants (eg allocation concealment; allocation schedule), exclusion from analyses of certain participants, and early termination of trials. Inadequately concealed trials may exaggerate odds ratios (ORs) by 41% (plus additional 17% if lack of double-blinding).[9] While these internal validity problems were not highlighted in the RCT reports, they are discussed below in relation to each of the four trials.

[8] Young H, "False Assumptions" (2010) 10 *BMC Public Health* 209, http://www.circumstitions.com/HIV.html viewed 20 October 2011; Gisselquist D, *Points to Consider: Responses to HIV/AIDS in Africa, Asia, and the Caribbean* (Adonis & Abbey, London, 2007).

[9] Schulz KF, Chalmers I, Hayes RJ et al, "Empirical Evidence of Bias. Dimensions of Methodological Quality Associated with Estimates of Treatment Effects in Controlled Trials" (1995) 273 JAMA 408.

Researcher expectation bias

The principal investigators had a history of co-authoring papers promoting male circumcision (eg Gray and Wawer have co-authored more than 100 joint papers) indicating their close collaboration.[10] The names of no fewer than 14 co-authors appeared on the reports of both Ugandan trials,[11] suggesting the two trials were not independent. Analysis of the references cited in common across the four trials also reveals substantial overlap.[12]

Claims by Auvert et al as to "the protective effect of MC (male circumcision)" when the trials were terminated prematurely, and that, "If women are aware of the protective effect of MC, this awareness could … [encourage] males to become circumcised" suggest a lack of equipoise. Siegfried et al warned that "researchers' personal biases and the dominant circumcision practices of their respective countries may influence their interpretation of findings".[13] The RCT lead investigators were all documented circumcision advocates who collaborated closely and concurred in recommending the mass circumcision of millions of African men.

Equipoise is essential in order to avoid biased findings.[14] "Under the principle of equipoise, a participant should be enrolled in a randomised controlled trial only if there is substantial uncertainty about which intervention will likely benefit the participant."[15] It is incumbent upon researchers to start from a position of neutrality and balance. In order to quantitatively measure equipoise, an empirical analysis of references cited in each of the four published reports was undertaken based on content deemed pro-circumcision (male circumcision recommended as beneficial), neutral (eg articles pertaining to statistical procedures), or anti-circumcision (male circumcision not recommended), respectively. As Table 1 shows, each of the RCT reports cited observational studies suggesting a benefit of male circumcision, but none of the observational studies showing either no effect of male circumcision on HIV transmission (13 studies), or a higher incidence of HIV among circumcised men (4 studies) were cited.[16] Omission of contradictory evidence prevented a more balanced consideration of the issues and suggests that the trials lacked equipoise from the outset.

TABLE 1 Analysis of cited references

	Auvert et al (South Africa)	Bailey et al (Kenya)	Gray et al (Uganda)	Wawer et al (Uganda)
Pro-male circumcision	24 (70.6%)	36 (72%)	19 (70.4%)	12 (67%)
Anti-male circumcision	2 (5.9%)	1 (2%)	0 (0%)	0 (0%)
Neutral	8 (23.5%)	13 (26%)	8 (29.6%)	6 (33%)
Total	34	50	27	18

Chi-square analyses (with Yates' correction) of the number of cited references deemed to be pro-male circumcision versus anti-male circumcision (chi-squares for pro-male circumcision versus

[10] Mehta SD, Gray RH, Auvert B et al, "Does Sex in the Early Period After Circumcision Increase HIV-Seroconversion Risk? Pooled Analysis of Adult Male Circumcision Clinical Trials" (2009) 23(12) *AIDS* 1557.

[11] Gray, Kigozi, Serwadda et al, n 2; Wawer, Makumbi, Kigozi et al, n 3.

[12] Auvert: 17 out of 34 (50%); Bailey: 19 out of 50 (38%); Gray: 17 out of 27 (63%); Wawer: 7 out of 18 (39%).

[13] Siegfried N, Muller M, Volmink J et al, "Male Circumcision for Prevention of Heterosexual Acquisition of HIV in Men (Cochrane Review)" in *The Cochrane Library*, Issue 3 (Update Software, Oxford, 2003), http://www.cirp.org/library/disease/HIV/cochrane2003 viewed 18 October 2011.

[14] Freedman B, "Equipoise and the Ethics of Clinical Research" (1987) 317(3) NEJM 141.

[15] Karlberg JPE and Speers MA (eds), *Reviewing Clinical Trials: A Guide for the Ethics Committee* (Karlberg JPE, Hong Kong, March 2010).

[16] Young, n 8.

neutral versus anti-male circumcision shown in parentheses) for each of the four trials provide evidence of pre-existing pro-circumcision bias:

Auvert et al: χ^2 = 16.96 (1df), p<.001 (χ^2 = 20.66 (2df), p<.001)
Bailey et al: χ^2 = 31.24 (1df), p<.001 (χ^2 = 35.60 (2df), p<.001)
Gray et al: χ^2 = 17.06 (1df), p<.001 (χ^2 = 18.33 (2df), p<.001)
Wawer et al: χ^2 = 10.08 (1df), p<.001 (χ^2 = 10.13 (2df), p<.01)

In the South African report, two anti-male circumcision references were mis-cited either as neutral[17] or as pro-circumcision[18] so that 25 out of 34 (74%) of the references were cited in support of male circumcision. In the Kenyan report, only one anti-male circumcision reference was cited, but incorrectly as being a neutral reference.[19] In both Ugandan reports, no references opposing male circumcision were cited. In none of the reports was even a single reference cited opposing male circumcision, in contrast to the more than 70% of citations supporting male circumcision. Not acknowledging the published evidence showing no prophylactic benefit of male circumcision is problematic. When the RCTs received scientific and ethical approval, admittedly more observational studies had reported an association between male circumcision and reduced HIV transmission, but not acknowledging the contradictory evidence suggests *confirmation bias*. Admittedly, investigator bias in favour of the hypothesis probably was not the only factor that led to these trials, given the growing desperation to stem the HIV/AIDS epidemic in sub-Saharan Africa.

Participant expectation bias

Participants were informed that previous studies suggested a potential benefit of male circumcision. Presumably the trial authors would argue that this was a requirement of disclosure, but why did they not also inform participants that other observational studies had shown no benefit of male circumcision? Why was this contradictory evidence withheld from the prospective participants? Asking leading questions may have influenced the men's decisions to participate. Indeed, Auvert et al remarked that "59% … of uncircumcised men said that they would be circumcised if it reduced their chance of acquiring HIV and STDs".[20] Did the researchers help create a demand for male circumcision by implying that it would help to protect men against HIV and STDs?[21]

Inadequate double blinding

Although double blinding reduces observer bias and placebo effects, this was not possible in the African trials, since male circumcision cannot be concealed.[22] As Wawer et al conceded, "In view of the surgical nature of the intervention, neither participants nor study clinicians could be masked to assignment group".[23] Also, some researchers had access to the data. In the South African trial, "BA analysed the data with RS, with inputs from JST" and "at each visit to the centre the nurse completed a questionnaire after the genital examination".[24] In the Kenyan trial, "some participants divulged their circumcision status".[25] Knowing men's circumcision status may have influenced responses on the questionnaires. Admittedly, such surgical trials are a tough challenge methodologically and difficult to conduct in situ. It is not possible to conduct such trials to the same standards as a double-blind placebo-controlled trial taking place in a highly controlled laboratory environment.

[17] Siegfried N, Muller M, Deeks et al, "HIV and Male Circumcision – A Systematic Review with Assessment of the Quality of Studies" (2005) 5 Lancet Infect Dis 165.

[18] Kim DS, Lee JY and Pang MG, "Male Circumcision: A South Korean Perspective" (1999) 83 BJU Int 28.

[19] Magoha GA, "Circumcision in Various Nigerian and Kenyan Hospitals" (1999) 76 East Afr Med J 583.

[20] Auvert et al, n 2 at 2.

[21] Dowsett GW and Couch M, "Male Circumcision and HIV Prevention: Is There Really Enough of the Right Kind of Evidence?" (2007) 15(29) Reprod Health Matters 33.

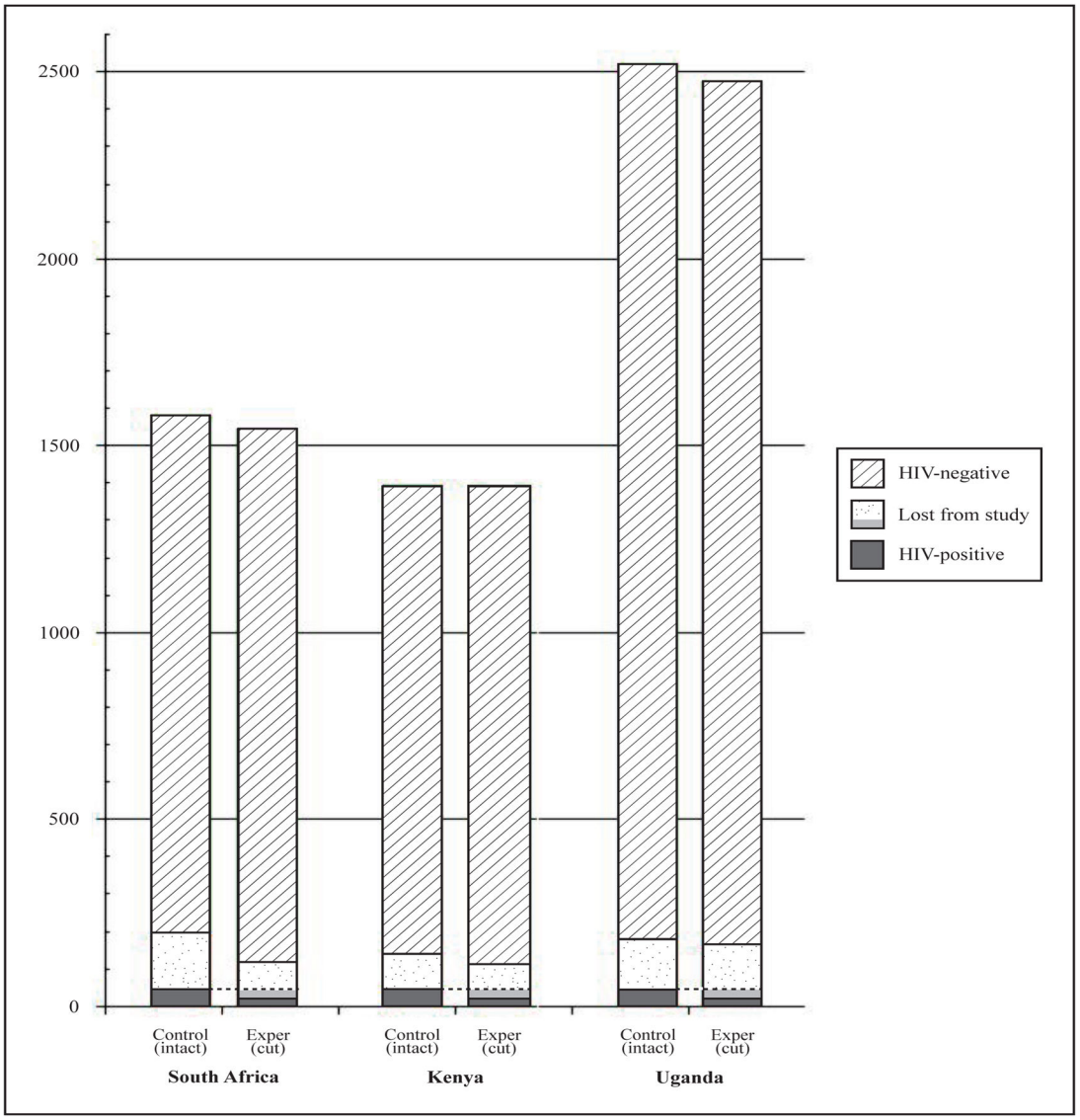
[22] Schulz, Chalmers, Hayes et al, n 9.

[23] Wawer, Makumbi, Kigozi et al, n 3 at 230.

[24] Auvert, Taljaard, Lagarde et al, n 2 at 1.

[25] Bailey, Moses, Parker et al, n 2.

FIGURE 2 Loss from study



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All three trials had significant numbers "lost from study", their HIV status unknown (spotted and light-shaded bars in Figure 2): 100 circumcised men (6.5%) in South Africa, 87 (10%) in Kenya and 140 (3.5%) in Uganda. (The figures are presented confusingly in the published reports because the men did not all enter the trials together, but each trial was stopped at a stroke.)

Those figures are high enough in themselves to cast doubt on the validity of the results, but circumcised men who found they had HIV would be disillusioned with the trials and less likely to return. It would take only 25, 25 and 23 such men respectively to completely nullify the trials, and fewer to render the results non-significant.

The light-shaded part of each of the three right-hand bars (below the dotted lines) represents the much-hyped ″60% protection″ conferred by circumcision. If just those men, whose HIV status is

unknown, proved, in fact, to be HIV-positive (dark-shaded), *circumcision would certainly have no protective effect whatever*, but it would not take all of them to reduce the effect below statistical significance.

(One objection to this argument is that approximately equal numbers of non-circumcised control-group members dropped out. The answer to that is that a major and very likely motivation for them to drop out would be completely different and inapplicable to the experimental group – to avoid getting circumcised. Thus what needs explaining is why nearly equal numbers of circumcised men dropped out, and an HIV-positive diagnosis could be an answer in a significant number of cases.)

Lead-time bias

Men in the intervention group had less time to become HIV-infected since effectively they were out of the trials for up to two months while their circumcision wounds (portals for HIV transmission) healed. This occurred early in the trials, thereby amplifying lead-time bias. Rate ratios (RRs) adjusted for lead-time bias of two months have been calculated using SAS (Version 8.2; SAS Institute, Cary, North Carolina).[26] Auvert et al's RR of 0.40 after adjustment was found to be 0.46;[27] Bailey et al's RR of 0.47 after adjustment was found to be 0.52;[28] while Gray et al's RR of 0.49 after adjustment was found to be 0.56.[29] Thus, the relative protection against HIV (1-RR) decreased to a mean 49%, showing that the claimed 60% protective effect of male circumcision is an overstatement. That the very small *absolute* reduction of about 1.3% was not statistically significant (relevant from a policy implementation perspective) has been overlooked in the RCT reports, where only the *relative* reduction in HIV transmission has been highlighted.

Selection and sampling bias

Pre-screening and participant self-selection may have produced non-equivalent comparison groups and undermined internal validity. Volunteers were not a population-based random sample since religious or ethnic groups already circumcised necessarily were excluded. Presumably, the trials were located in areas where male circumcision was uncommon in order to recruit adequate sample sizes. Since the mostly unemployed men were financially rewarded for participating, it is likely that samples were skewed towards men from lower socio-economic backgrounds.

There were more at-risk men in the delayed circumcision (control) groups in the South African (+36) and Ugandan (+48) female-to-male trials, raising questions about the allocation of participants. In the South African trial, the two groups differed significantly on background variables including age,[30] religious affiliation[31] and ethnic group.[32] There was also a significant between-group difference for ethnic group[33] in the Kenyan trial, suggesting that in both trials, participants from different tribal backgrounds were differentially admitted into the comparison groups. In the Ugandan female-to-male trial, participants allocated to the male circumcision group received significantly more counselling.[34]

In both the South African and Ugandan female-to-male trials, a higher prevalence of STDs and genital disorders was reported within the control groups. Since HIV is more likely to co-occur with other STDs,[35] it is likely that the control groups were at greater risk of acquiring new HIV infections, irrespective of any preventive effect of male circumcision. Why were there significant between-group

[26] Van Howe RS, *Analysis of the Circumcision/HIV Randomised Clinical Trials* (unpublished manuscript, 31 August 2010).

[27] 95% CI 0.23%-0.77%; p =0. 003.

[28] 95% CI 0.31%-0.87%; p = 0.01.

[29] 95% CI 0.34-0.93; p = 0.03.

[30] χ^2 = 4.58 (1df), p<.05

[31] χ^2 = 9.36 (2df), p<.01

[32] χ^2 = 12.84 (2df), p<.01

[33] χ^2 = 12.84 (2df), p<.01

[34] χ^2 = 6.02 (1df), p<.02

[35] Fleming DT and Wasserheit JN, "From Epidemiological Synergy to Public Health Policy and Practice: The Contribution of Other Sexually Transmitted Diseases to Sexual Transmission of HIV Infection" (1999) 75(1) Sex Transm Infect 3.

differences in these background variables? In the South African trial, only men who produced three positive Enzyme-Linked Immunosorbent Assay (ELISA) tests were classified as HIV-positive. The screening approach which comprised one ELISA test and two confirmatory ELISA tests using different testing approaches, represents WHO's current testing strategy for low to middle income countries. Since men with one or two positive ELISA tests were regarded as HIV-negative, how many false negatives (HIV-positive men) were assigned to the respective groups? However, even if some HIV-positive men were erroneously considered to be HIV-negative, it would only affect the study results if the majority of these men were randomised to the delayed circumcision arm.

Experimental mortality

Participant loss (missing data) was considerably greater than the number of new HIV infections.[36] While losses exceeded incident cases, it appears that losses were relatively comparable between study arms. However, it remains unclear whether there was a high proportion of new incident HIV-positive cases among those lost to follow-up in the male circumcision group. Men who submitted to male circumcision but who subsequently became HIV-positive may have become disillusioned and dropped out, differing significantly from those who completed follow-up evaluations. Which participants were not followed up and their HIV status not reported?

Early termination

While it would be unethical to continue trials if efficacy was demonstrated at an interim analysis, the fact remains that truncated RCTs produce exaggerated effect sizes,[37] and amplify lead-time bias.[38] Even though Gray et al acknowledged that "trials that are stopped early could overestimate efficacy when compared with subsequent studies",[39] all the trials still were stopped early, thereby exaggerating any effects, especially since there was only a small number of HIV-positive incident events in the intervention versus control groups, respectively. In addition, Auvert et al conceded that "adjustment cannot fully account for the confounding effect associated with partial follow-up".[40] Claims based on trials stopped early for benefit should be viewed with caution. Subsequently, Bailey et al reported that the "protective effect" of male circumcision in the Kenyan trial had been sustained over 4.5 years.[41] This assertion is difficult to evaluate since it was based on the analysis of incomplete observational data.

Factors jeopardising external validity

The RCT reports provided inadequate information about external validity, including methodological flaws in experimental design and procedures, non-representative sampling (eg sampling from mostly poorly educated, impoverished African men), reporting of *relative* rather than the *absolute* efficacy of male circumcision, and inadequately investigating confounding factors (eg non-sexual transmission of HIV via skin piercing procedures such as injections, transfusion, etc). Also, the reports of the female-to-male trials failed to acknowledge adverse effects of the circumcision interventions (eg four new incident HIV infections related to male circumcision in the Kenyan trial).[42]

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[36] South Africa: 151 versus 49 intact men; 100 versus 20 circumcised men; Kenya: 92 versus 47 intact men; 87 versus 22 circumcised men; Uganda: 133 versus 45 intact men; 140 versus 22 circumcised men.

[37] Montori VM, Devereaux PJ, Adhikari NK et al, "Randomized Trials Stopped Early for Benefit: A Systematic Review" (2005) 294 JAMA 2203; Mills E and Siegfried N, "Cautious Optimism for New HIV/AIDS Prevention Strategies" (2006) 368 *Lancet* 1236; Bassler D, Briel M, Montori VM et al, "Stopping Randomized Trials Early for Benefit and Estimation of Treatment Effects: Systematic Review and Meta-regression Analysis" (2010) 303(12) JAMA 1180.

[38] Pocock S and White I, "Trials Stopped Early: Too Good to be True?" (1999) 353 *Lancet* 943.

[39] Gray, Kigozi, Serwadda et al, n 2 at 666.

[40] Auvert et al, n 2 at 9.

[41] Bailey RC et al, "The Protective Effect of Adult Male Circumcision Against HIV Acquisition is Sustained for at Least 54 Months: Results from the Kisumu, Kenya Trial", Abstract, International AIDS Conference, Vienna, 2010, http://www.pag.aids2010.org/Abstracts.aspx?AID=17707 viewed 20 October 2011.

[42] Gisselquist, n 8; Rothwell PM, "External Validity of Randomised Controlled Trials: 'To Whom do the Results of This Trial Apply?'" (2005) 365 *Lancet* 82; Van Spall HG, Toren A, Kiss A et al, "Eligibility Criteria of Randomized Controlled Trials Published in High-impact General Medical Journals: A Systematic Sampling Review" (2007) 297(11) JAMA 1233; Moher D,

Many problems in generalising results from the trials to the real-world context have been documented.[43] Since the participants enrolled in the trials were not representative of the respective populations at large (at least in the South African and Kenyan trials, where data were provided), it is difficult to generalise the findings. Certain ethnic subgroups were disproportionately represented in the male circumcision and control groups.[44] Green et al concluded:[45]

> Effectiveness in real-world settings rarely achieves the efficacy levels found in controlled trials, making predictions of subsequent cost-effectiveness and population-health benefits less reliable … Recommending mass circumcision by generalizing from the particular RCTs to the diverse populations of Africa highlights problems of external validity identified in several areas of preventive medicine and public health research.

Furthermore, there has been problematic reporting of the trials in the medical literature.[46] Fox and Thomson stated:

> Our concern is that such partial reporting of the trials will impact on the role that circumcision is perceived to play in HIV prevention … in perpetuating erroneous beliefs … that circumcision offers immunity to AIDS … If the contexts of the African trials can be so poorly represented in the medical literature, it is no surprise that accounts in the popular press are still more misleading.[47]

Participants in the immediate male circumcision groups also received two years of free medical treatment plus supportive counselling and safe-sex advice, difficult to provide in any large-scale "roll out" of male circumcision in sub-Saharan Africa. WHO had specifically cautioned that the female-to-male Kenyan and Ugandan findings might not generalise to real-world settings.[48] The RCTs were premised on the untested assumption that men who have sex with men are extremely rare in Africa and that the HIV epidemic is primarily heterosexual in nature. Evidence suggests this is not the case,[49] weakening the findings of the RCTs since male circumcision is not effective in preventing HIV transmission among men who have sex with men, as the United States epidemiological evidence clearly demonstrates.[50] The assumption of heterosexuality is problematic with the African trials. Participants were deemed heterosexual because they *said* they were. In sub-Saharan Africa, capital punishment has been advocated for sodomy, making it unlikely that men would willingly admit to homosexual or bisexual activity. Not controlling for men who have sex with men confounded the RCT

Hopewell S, Schulz KF et al, "CONSORT 2010 Explanation and Elaboration: Updated Guidelines for Reporting Parallel Group Randomised Trials" (2010) 340 BMJ c869; Gisselquist D, "HIV Infections as Unanticipated Problems During Medical Research in Africa" (2009) 16 Accountability in Res 199.

[43] Green LW, McAllister RG, Peterson KW et al, "Male Circumcision is Not the HIV 'Vaccine' We have been Waiting For!" (2008) 2(3) Fut HIV Ther 293; Green LW, Travis JW, McAllister RG et al, "Male Circumcision and HIV Prevention: Insufficient Evidence and Neglected External Validity" (2010) 39(5) Am J Prev Med 479; McAllister RG, Travis JW, Bollinger D et al, "The Cost to Circumcise Africa" (2008) 7(3) Int J Men's Health 307.

[44] South Africa: Sotho 49.0% and 47.3%, Zulu 32.8% and 38.1%; Kenya: Luo 98% and 99%; Uganda: no ethnicity data provided. In South Africa, the major ethnic groups consist of Zulu (21%), Xhosa (17%) and Sotho (15%), so the Xhosa were under-represented. In Kenya the main ethnic groups are Kikuyu (22%), Luhya (14%), Luo (13%), Kalenjin (12%) and Kamba (11%), so the Luo were over-represented.

[45] Green, Travis, McAllister et al, n 43 at 479-481.

[46] For example, by Peter Piot, former UNAIDS Head, in the *Lancet* and by Helen Epstein in the BMJ: see Fox M and Thomson M, "HIV/AIDS and Circumcision: Lost in Translation" (2010) 36 J Med Ethics 798 at 799.

[47] Fox and Thomson, n 46 at 799.

[48] *Statement on Kenyan and Ugandan Trial Findings Regarding Male Circumcision and HIV* (WHO, Geneva, 13 December 2006), http://www.who.int/mediacentre/news/statements/2006/s18/en/index.html viewed 15 October 2010.

[49] Beyrer C, Trapence G, Motimedi F et al, "Bisexual Concurrency, Bisexual Partnerships, and HIV Among Southern African Men Who have Sex with Men (MSM)" (2009) 86(4) Sex Transm Infect 323; Brody S and Potteratt JJ, "Assessing the Role of Anal Intercourse in the Epidemiology of AIDS in Africa" (2003) 14 Int J STD & AIDS 431; Roehr B, "How Homophobia is Fuelling Africa's HIV Epidemic" (2010) 340 BMJ c2245; Wakabi W, "Homophobia is Fuelling the AIDS Epidemic in Africa" (2007) 177(9) CMAJ 1017.

[50] Millet GA, Ding H, Lauby J et al, "Circumcision Status and HIV Infection Among Black and Latino Men Who have Sex with Men in 3 US Cities" (2007) 46(5) J Acquir Immune Defic Syndr 643; Millet GA, Flores SA, Marks G et al, "Circumcision Status and Risk of HIV and Sexually Transmitted Infections Among Men Who have Sex with Men: A Meta-analysis" (2008) 300(14) JAMA 1674.

findings. The American doctors conducting these trials were offering perhaps the only medical attention many of these men were ever likely to receive, making it unlikely that they would admit to homosexual activity if it meant being denied this medical attention. With their multiple flaws, these circumcision trials could not be described as the "gold standard".[51]

Despite these multiple flaws, at the time of writing, the Centers for Disease Control and Prevention (CDC) are considering a recommendation for *routine infant* male circumcision as a putative HIV-preventive measure in the United States (where homosexual activity is the predominant mode of HIV transmission), seemingly ignoring the fact that the African RCTs only investigated HIV transmission among heterosexual adults.

> Recognition of the potential pitfalls in the transition from clinical trials to effective public health policy is particularly crucial given the attempts … by the [CDC] to extrapolate from the three African trials to inform US domestic policy, notwithstanding how typical modes of HIV transmission in the USA are radically different from the model of sexual transmission assumed in the African trials.[52]

The WHO/UNAIDS recommendation to implement mass circumcision programs in Africa also failed to heed Siegfried et al[53] who noted that, notwithstanding the possible personal harm of circumcision, further research is required to assess the feasibility, desirability and cost-effectiveness of male circumcision implementation within local contexts (ie external validity and effectiveness in real-life settings rather than mere efficacy in the contrived experimental settings under which the African RCTs were carried out).

ETHICAL AND LEGAL CONCERNS

Circumcision as a cause of HIV infection

One of the major problems with scaling up these trials is that quality control on a large scale is not feasible, particularly in relation to male circumcision itself being a possible cause of HIV transmission.[54]

> Possible paths for HIV transmission during circumcision include skin-piercing instruments reused without sterilization, and multidose vials of local anesthetic contaminated with HIV from a previous patient … [which] might have infected participants with HIV in Kenya.[55]

Auvert et al acknowledged "the possible impact of surgery on HIV acquisition as a result of sexual activity during the healing phase following circumcision or contamination during surgery"[56] and subsequently, all the lead investigators cautioned that following male circumcision, "men should delay intercourse to limit the potential for increased HIV risk until complete wound healing".[57]

In the Ugandan male-to-female trial, Wawer et al cautioned:

> Female acquisition of HIV … occurred in a higher proportion of couples who resumed sex early … strict adherence to sexual abstinence during wound healing and consistent condom use thereafter must be strongly promoted …[58]

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[51] Young, n 8.

[52] Fox and Thomson, n 46 at 800.

[53] Siegfried, Muller, Deeks et al, n 7.

[54] Brewer D, Potterat JJ, Robert JM et al, "Male and Female Circumcision Associated with Prevalent HIV Infection in Virgins and Adolescents in Kenya, Lesotho, and Tanzania" (2007) 17 Ann Epidemiol 217; Zulu K, Bulawo ND and Zulu W, "Circumcision Razor a Preventative Tool or a Strategic Vector in the Transmission of HIV? – A Case of Zambia", Poster presented at XVI International AIDS Conference, Toronto, Canada, 13-18 August 2006.

[55] Gisselquist D, "Double Standards in Research Ethics, Health-care Safety, and Scientific Rigour Allowed Africa's HIV/AIDS Epidemic Disasters" (2009) 20(12) Int J STD AIDS 839.

[56] Auvert, Taljaard, Lagarde et al, n 2 at 2.

[57] Mehta, Gray, Auvert et al, n 10 at 1557.

[58] Wawer, Makumbi, Kigozi et al, n 3 at 234-235.

Wawer et al acknowledged that "circumcision of HIV-infected men did not reduce transmission of the virus to uninfected female partners".[59] Male circumcision was associated with a relative 61% increased transmission of HIV to female sexual partners. During the six-month follow-up, 25 new incident HIV infections occurred among female partners (17 in male circumcision group). However, in an apparent example of irrational *motivated* reasoning,[60] Wawer et al concluded that, "Male circumcision programmes … confer an overall benefit to women".[61] This dissonance suggests a preconceived bias in favour of male circumcision. Becoming infected with HIV cannot be viewed as a "benefit to women". Why weren't the women informed that their male partners were HIV-positive so that they could take steps to protect themselves? Under any reasonable interpretation of ethical principles, not informing women that they were at risk of HIV infection would seem unethical. It is regrettable that Wawer et al, the institutional review boards, and institutions involved did not investigate this issue, since previously uninfected women actually became HIV-positive following their participation in the trial.

Non-sexual transmission of HIV

The trials did not report on non-sexual transmission of HIV from use of non-sterile surgical and other skin-piercing instruments such as re-use of contaminated scalpels, contaminated injection syringes, contaminated blood transfusions (or other blood exposures from contaminated multi-use vials, etc), likely to occur in any real-life scaling up of male circumcision.[62]

> In the South African trial, 23 (of 69) incident infections occurred in men who reported no unprotected sex … in Uganda, 16 (of 67) infections occurred in men who reported no sex partners (6 infections) or 100 percent condom use (10 infections).[63]

Clearly, "the authors did not control for other sources of HIV transmission, such as exposure through blood transfusions or infected needles … circumcision may not be as effective at decreasing HIV transmission as the article suggests".[64] Since some men acquired HIV without reporting unprotected sexual exposures, the RCT authors had a duty of care to investigate such non-sexual transmission. "These studies, with their ignored evidence (on sexual exposures) and missing evidence (on blood exposures and on HIV status of sexual partners), launched programs to circumcise millions of African men."[65]

Contradictory evidence

What does the frequently cited "60% *relative* reduction" in HIV infections actually mean? Across all three female-to-male trials, of the 5,411 men subjected to male circumcision, 64 (1.18%) became HIV-positive. Among the 5,497 controls, 137 (2.49%) became HIV-positive, so the *absolute* decrease in HIV infection was only 1.31%, which is not statistically significant.

Furthermore, the claimed efficacy of male circumcision in reducing HIV transmission has been contradicted by at least 17 observational studies.[66] To take just one example, Mor et al in an epidemiological study of 58,598 men found no relationship between male circumcision and HIV

[59] Wawer, Makumbi, Kigozi et al, n 3 at 235.

[60] Kunda Z, "The Case for Motivated Reasoning" (1990) 108(3) Psych Bull 480.

[61] Wawer, Makumbi, Kigozi et al, n 3 at 236.

[62] Gisselquist D, "Denialism Undermines AIDS Prevention in Sub-Saharan Africa" (2008) 19 Int J STD & AIDS 649; Gisselquist D, Potterat JJ and Brody S, "Running on Empty: Sexual Co-factors are Insufficient to Fuel Africa's Turbocharged HIV Epidemic" (2004) 15 Int J STD & AIDS 442; Gisselquist D, Rothenberg R, Potterat J et al, "HIV Infections in Sub-Saharan Africa not Explained by Sexual or Vertical Transmission" (2002) 13 Int J STD & AIDS 657.

[63] Gisselquist, n 8, p 136.

[64] Vines J, "Major Potential Confounder Not Addressed" (2006) 3(1) PLoS Med e63 at 136.

[65] Gisselquist, n 8, p 137.

[66] Green, McAllister, Peterson et al, n 43; Green, Travis, McAllister et al, n 43; Thomas AG, Bakhireva LN, Brodine SK et al, "Prevalence of Male Circumcision and Its Association with HIV and Sexually Transmitted Infections in a US Navy Population",

transmission.[67] In at least Cameroon, Ghana, Lesotho, Malawi, Rwanda, Swaziland and Tanzania, HIV is more prevalent among circumcised men.[68] In Malawi, the HIV rate is 13.2% among circumcised men (9.5% among intact men), while in Cameroon the HIV rate is 5.1% among circumcised men (1.5% among intact men). If male circumcision reduces HIV transmission as the RCT authors would have us believe, then why is HIV prevalence much higher in the United States (where most men are circumcised) than in developed countries where most men are intact (eg Europe, Scandinavia, United Kingdom)?[69]

Viral load and genital ulcers are predictors of the risk of heterosexual transmission of HIV.[70] Langerhans cells in the foreskin produce Langerin, which blocks transmission of HIV.[71] Moreover, "Langerhans cells occur in the clitoris, the labia and in other parts of both male and female genitals, and no one is talking of removing these in the name of HIV prevention".[72] Indeed, "[a] lowered risk of HIV infection among [5,297] circumcised women" has even been reported.[73] Why weren't trials also undertaken into the alleged HIV-preventive efficacy of female circumcision to test how randomly allocating women to immediate versus delayed female circumcision groups could "benefit" women by showing that female circumcision is an effective HIV preventive measure?

Auvert et al speculated that "Male circumcision provides a degree of protection against acquiring HIV infection, equivalent to … a vaccine of high efficacy … widespread male circumcision could lead to a strong reduction of the spread of HIV".[74] In contrast, in Thailand, a vaccine provided about six times the protection against HIV as that claimed for male circumcision (across all modalities of transmission, not just sexual), and for both males and females, not just for sexually active men.[75] Also, 1% Tenofovir microbicide gel applied to the genital mucosa (using mucosal immunity) was found to result in a 37-45% reduction in actual risk of HIV infection.[76] Ironically, circumcised men may not benefit from Tenofovir treatment because their preputial mucosa has been excised. Since there was no test of the efficacy of male circumcision versus a vaccine of high efficacy, the claims by Auvert et al were entirely speculative. Thus,

> [A] 60% reduction … among circumcised men … does not mean that those men are really "protected" against HIV … the choice is either using condoms consistently, with extremely low risk of becoming infected, or being circumcised, with relatively high risk of becoming infected … Concluding that "male

presented at the XV International AIDS Conference, Bangkok, Thailand, 11-16 July 2004 (Abstract no TuPeC4861); Mor Z, Kent CK, Kohn RP et al, "Declining Rates in Male Circumcision Amidst Increasing Evidence of Its Public Health Benefit" (2007) 2(9) PLoS One e861.

[67] Mor, Kent, Kohn et al, n 66.

[68] Young, n 8; Gisselquist, n 8; Chao A, Bulterys M, Musanganire F et al, "Risk Factors Associated with Prevalent HIV-1 Infection Among Pregnant Women in Rwanda. National University of Rwanda – Johns Hopkins University AIDS Research Team" (1994) 23(2) Int J Epidemiol 371; Urassa M, Todd J, Boerra JT et al, "Male Circumcision and Susceptibility to HIV Infection Among Men in Tanzania" (1997) 11 *AIDS* 73.

[69] Boyle GJ and Hill G, "The Case for Boosting Infant Male Circumcision in the Face of Rising Heterosexual Transmission of HIV … and Now the Case Against" (2011) 194(2) MJA 99.

[70] Quinn TC, Wawer MJ, Sewankambo N et al, "Viral Load and Heterosexual Transmission of Human Immunodeficiency Virus Type 1. Rakai Project Study Group" (2000) 342(13) NEJM 921.

[71] de Witte L, Nabatov A, Pion M et al, "Langerin is a Natural Barrier to HIV-1 Transmission by Langerhans Cells" (2007) 13 Nat Med 361.

[72] Dowsett and Couch, n 21 at 36.

[73] Stallings RY and Karugendo E, "Female Circumcision and HIV Infection in Tanzania: For Better or for Worse?", Third IAS Conference on HIV Pathogenesis and Treatment, Rio de Janeiro, Brazil, 24-27 July 2005.

[74] Auvert, Taljaard, Lagarde et al, n 2 at 9.

[75] Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S et al, "Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand" (2009) 361(23) NEJM 2209.

[76] Karim QA, Karim SA. Frohlich JA et al, "Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women" (2010) 329(5996) *Science* 1168.

> circumcision should be regarded as an important public health intervention for preventing the spread of HIV" appears overstated … it is unlikely to have a major public health impact.[77]

Lack of fully informed consent

Researchers controlled the information available to men so that provision of fully informed consent may have been compromised. In Uganda, the Kampala *Monitor* reported men as saying, "I have heard that if you get circumcised, you cannot catch HIV/AIDS. I don't have to use a condom".[78] A Brazilian Health Ministry official (Simao) stated:

> [T]he WHO and UN HIV/AIDS program … gives a message of "false protection" because men might think that being circumcised means that they can have sex without condoms without any risk, which "is untrue".[79]

Ugandan President Museveni denounced claims that male circumcision could reduce HIV transmission, saying that it sends out a misleading and dangerous message that "if you are circumcised, you are less likely to catch AIDS even if you behave recklessly. Now what sort of message is that?"[80] Behavioural risk compensation following male circumcision has been demonstrated in large-scale empirical studies.[81] Having being stopped early, the RCTs gave inflated estimates of efficacy which unduly influenced the subsequent advocacy of mass circumcision programs in sub-Saharan Africa. Indeed,

> risk compensation by HIV-infected circumcised men will substantially increase the risk of transmission to their sex partners … the failure of models to account for increased STI risk due to risk compensation likely inflates estimates of averted HIV infections.[82]

Was it ethical to give men a false sense of security?

Participant inducement

As most participants were unemployed, the fact that they were paid and provided with two years of free medical care amounted to a substantial inducement. Inducing impoverished men to submit to amputation of a normal functional sexual body part in the absence of any pre-existing pathology is unethical.[83] "Financial inducements are equivalent to coercion … If benefits to the patient are so self evident, why are payments or gifts thought to be necessary?"[84] The prepuce is a highly erogenous part of the penis.[85] All four RCTs failed to acknowledge the significant bodily injury caused by the

[77] Garenne M, "Male Circumcision and HIV Control in Africa" (2006) 3(1) PLoS Med 143 at 143-145 e 78. DOI: 10.1371/journal.pmed.0030078.

[78] Ajwang J, "Uganda: HIV – Circumcision Isn't Enough", *Monitor* (Kampala) (10 April 2007), http://www.allafrica.com/stories/200704091186.html viewed 22 October 2011.

[79] "Brazil Says No to Circumcision", *VivirLatino* (3 April 2007), http://www.circumcisionandhiv.com/2007/04/brazil_rejects_.html viewed 26 December 2010.

[80] Cocks T, "Ugandan President Rejects Circumcision Study", *Independent Online* (22 December 2006) http://www.iol.co.za/index.php?set_id=1&click_id=3016&art_id=qw1166790421634B225 viewed 26 December 2010.

[81] Laumann EO, Masi CM and Zuckerman EW, "Circumcision in the United States: Prevalence, Prophylactic Effects, and Sexual Practice" (1997) 277 JAMA 1052; Pinkerton SD. "Sexual Risk Compensation and HIV/STD Transmission: Empirical Evidence and Theoretical Considerations" (2001) 21 *Risk Analysis* 727.

[82] Kalichman S, Eaton L and Pinkerton S. "Circumcision for HIV Prevention: Failure to Fully Account for Behavioral Risk Compensation" (2007) 4(3) PloS Med e138 at 597.

[83] Price C, "Male Circumcision: An Ethical and Legal Affront" (1997) 128 Bull Med Ethics 13; Boyle GJ, Goldman R, Svoboda JS et al, "Male Circumcision: Pain, Trauma and Psychosexual Sequelae" (2002) 7 J Health Psychol 329; Todd C, "Research Participation and Financial Inducements" (2001) 1(2) Amer J Bioethics 60.

[84] Raffle AE and Morgan K, "Enhancing Patients' Compliance: Financial Inducements are Equivalent to Coercion" (1998) 316(7128) BMJ 394 at 394.

[85] Sorrells ML, Snyder JL, Reiss MD et al, "Fine-touch Pressure Thresholds in the Adult Penis" (2007) 99 BJU Int 864; Taylor JR, Lockwood AP and Taylor AJ, "The Prepuce: Specialized Mucosa of the Penis and Its Loss to Circumcision" (1996) 77 Br J Urol 291; Cold CJ and Taylor JR, "The Prepuce" (1999) 83(Suppl 1) BJU Int 34.

irreversible amputation and the resultant possible long-term adverse psychosexual effects.[86] The African RCTs inflicted bodily harm in the absence of pathology, violating the first tenet of ethical medical conduct: "primum non nocere" (first do no harm), which may be tantamount to criminal assault.[87]

Do institutional review boards have lower standards when considering experiments in African countries than they have in the United States? "Double standards exist within developed and developing countries, depending on illness conditions, social status of participants, national health priorities."[88] Does the United States medical establishment regard poor, black African men as an expendable resource to be exploited?[89]

> Participants from developing countries may have little or no alternative means of treatment other than that offered through clinical trials … Poverty, limited or no education … may question the validity of the informed consent procedure in this group of patients.[90]

Men were enrolled in the trials even if they did not want to know their HIV status. Although all participants were alleged to have been HIV-negative prior to the female-to-male trials, Bailey et al admitted, "We cannot exclude the possibility that any of these individuals were actually HIV-positive at baseline, and that their [HIV] infection was not detected."[91] Auvert et al stated that it was "unethical to inform participants of their HIV status without their permission … [and] … unethical to deter from participating in the study potentially at-risk men who did not want to know their HIV status".[92] In the single male-to-female trial, Wawer et al reported that "Participants could be enrolled in the trial even if they declined to receive their HIV results".[93] But, how could any reputable institutional review board consider it ethical to withhold information about HIV status since, as a result, some HIV-positive men unknowingly would have infected their female sexual partners?[94] In the United States, individuals are not permitted to participate in such trials without being willing to know their HIV test results. In the sub-Saharan African trials, however, it beggars belief that the investigators did not always warn the female sexual partners of HIV-infected men.[95]

Furthermore, why was there such a brief "cooling off" period for men allocated to the male circumcision group? The surgery was carried out almost immediately after randomisation, ensuring that participants had little time to change their minds. Bailey et al stated that "886 (64%) had their procedures on the day of randomisation".[96] Why were the circumcisions carried out with such undue haste? The lack of an adequate "cooling off" period would seem unethical. Fully informed consent required that men be made aware that male circumcision might not have any prophylactic benefit. Did the RCT investigators make this explicit to the participants?

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[86] Boyle, Goldman, Svoboda et al, n 83; Johnson M, "Male Genital Mutilation: Beyond the Tolerable?" (2010) 10(2) *Ethnicities* 181.

[87] Boyle GJ, Svoboda JS, Price CP et al, "Circumcision of Healthy Boys: Criminal Assault?" (2000) 7 JLM 301.

[88] Wassenaar D, *Double Standards in Research Ethics. Case-studies: Informed Consent and Vaccine to Treat Rotavirus* (EU Forum on Ethics, Research and Globalisation, Brussels, May 2007) p 12.

[89] Wakabi, n 49.

[90] Verástegui EL, "Consenting of the Vulnerable: The Informed Consent Procedure in Advanced Cancer Patients in Mexico" (2006) 7 *BMC Medical Ethics* 13.

[91] Bailey, Moses, Parker et al, n 2 at 651.

[92] Auvert, Taljaard, Lagarde et al, n 2 at 3.

[93] Wawer, Makumbi, Kigozi et al, n 3 at 230, and at 233: "Over the 24-month follow-up period, the cumulative probability of female acquisition of HIV was 21.7% … in the intervention group and 13.4% … in the control group."

[94] Wawer, Makumbi, Kigozi et al, n 3 at 230.

[95] Siegfried N, "Does Male Circumcision Prevent HIV Infection?" (2005) 2(11) PLoS Med e393, DOI:10.1371/journal.pmed.0020393; cf Edwards et al re ethical concerns: Edwards SJL, Lilford RJ and Hewison J, "The Ethics of Randomised Controlled Trials from the Perspectives of Patients, the Public, and Healthcare Professionals" (1998) 317(7167) BMJ 1209.

[96] Bailey, Moses, Parker et al, n 2 at 648.

DISCUSSION

Assertions by Auvert et al that male circumcision "prevented six out of ten potential infections"[97] mask a much smaller, non-significant *absolute* reduction in risk (about 1.3%). Male circumcision is not a cost-effective means of reducing HIV transmission,[98] and any long-term effectiveness in sub-Saharan Africa will not be known for many years.[99] Is it "right to circumcise a whole population or a considerable part of it, when many will not benefit from the intervention, eg because they do not engage in risky sexual behavior"?[100] While the RCT investigators advocated mass circumcision of African men,

> many of their assertions are reminiscent of statements made by fervent proponents of routine neonatal circumcision … exaggerating the alleged advantages, ignoring potential harms, and giving the impression that circumcision is no more than a simple intervention comparable to a vaccination.[101]

Mass circumcision programs inevitably result in complications not generally acknowledged.[102]

> There are always concerns about the safety of MC in sub-Saharan African health systems. Mattson et al reported on the feasibility of performing MC in health facilities in Kenya. The lack of basic instruments and inadequate supplies were identified as crucial limitations in facilitating provision of safe MC.[103]

Why was a "roll-out" of mass circumcision recommended by WHO/UNAIDS when it was known that the RCT findings were exaggerated due to early termination? Overstating the effectiveness of male circumcision in preventing HIV transmission can only result in public health efforts being misdirected.[104] For example, Auvert et al claimed that

> Our study is also the first experimental study demonstrating that surgery can be used to prevent an infectious disease … this finding is an a posteriori proof of the use of MC to improve hygiene.[105]

However, as the United States epidemiological experience illustrates, circumcised men will still acquire HIV, transmit HIV to their sexual partners, and die from AIDS. It is inevitable that mass circumcision programs will result in new HIV infections associated with the surgery itself.[106] Provision of free medical care and sanitary settings would be well nigh impossible to implement in mass circumcision programs. What counselling and compensation will be provided for men who undergo male circumcision but who subsequently become HIV-positive? The evidence suggests that mass circumcision programs may exacerbate the HIV epidemic among women.[107] Under these circumstances, it would be irresponsible and unethical to advocate mass circumcision programs in sub-Saharan Africa.[108] Since HIV transmission in sub-Saharan Africa is largely by non-sexual means, including blood exposures, use of non-sterile surgical instruments and contaminated injection

[97] Auvert, Taljaard, Lagarde et al, n 2 at 5

[98] McAllister, Travis, Bollinger et al, n 43.

[99] Garenne M, "Long-term Population Effect of Male Circumcision in Generalised HIV Epidemics in Sub-Saharan Africa" (2008) 7(1) Afr J AIDS Res 1.

[100] Dekkers W, "Routine (Non-religious) Neonatal Circumcision and Bodily Integrity: A Transatlantic Dialogue" (2009) 19(2) Kennedy Inst Ethics J 125 at 130.

[101] Dekkers, n 100 at 129.

[102] Muula AS, Prozesky HW, Mataya RH et al, "Prevalence of Complications of Male Circumcision in Anglophone Africa: A Systematic Review" (2007) 7 BMC Urol 4, http://www.biomedcentral.com/1471-2490/7/4 viewed 23 October 2011.

[103] Muula et al, n 102; Mattson CL, Muga R, Poulussen R, Onyango T and Bailey RC, "Feasibility of Medical Male Circumcision in Nyanza Province, Kenya" (2004) 81 East Afr Med J 320.

[104] Boyle GJ, "The Introduction of Circumcision into a Non-circumcising Society" (2003) 79 Sex Transm Infect 427; Boyle GJ, "Male Circumcision and Risk of HIV-1 Infection" (2004) 363 *Lancet* 1997.

[105] Auvert, Taljaard, Lagarde et al, n 2 at 9.

[106] Brewer, Potterat, Robert et al, n 54; Zulu, Bulawo and Zulu, n 54.

[107] Wawer, Makumbi, Kigozi et al, n 3.

[108] Green, Travis, McAllister et al, n 43.

syringes,[109] overstating the efficacy of male circumcision can only result in public health efforts being misdirected. It is inevitable that mass circumcision programs will cause new HIV incident infections due to the unnecessary circumcision surgery itself.

The trials failed to acknowledge that safe sex practices, provision of free medical care, payment of participants, use of non-representative samples, and sanitary settings are not generally available in mass circumcision programs.[110] Men who become HIV-positive after undergoing male circumcision would likely become disillusioned and angry. What counselling and compensation will be provided for such men who submit to male circumcision thinking that they will be protected from HIV infection? Mass circumcision programs in sub-Saharan Africa are likely to exacerbate the HIV/AIDS epidemic among women.[111] Wasting scarce resources on male circumcision is unethical, when more effective preventive measures devoid of surgical risks are available. Antiretroviral drugs can reduce HIV transmission by 92%.[112] Another promising approach may be the use of FDA-approved drugs found to destroy the HIV virus via "lethal mutagenesis": "a combination of two clinically approved drugs, decitabine and gemcitabine, reduced HIV infectivity by 73% …. increased mutation frequency decreases infectivity through lethal mutagenesis."[113] These drugs do not merely reduce viral levels (like antiretroviral drugs), but actually eliminate the HIV virus from the body.[114] Now that these FDA-approved drugs can be added to antiretroviral drugs, use of condoms, abstinence, and more sanitary health care provision, the promotion of male circumcision is even less ethical.[115]

Several countries (eg Uganda, Brazil, Rwanda, Thailand) have reduced their HIV rates without recourse to male circumcision.[116] However, according to Gray et al, "We estimate that about 67 circumcisions are needed to prevent one HIV infection".[117] Extrapolating from this Number Needed to Treat (NNT), if the target is to circumcise 38 million men in Africa, then male circumcision would have no HIV-preventive effect for 66/67 × 38,000,000 = 37,432,834 men. Even accepting the exaggerated female-to-male effect sizes reported by the RCT investigators, for every 100 men circumcised, it appears that 66/67 = 98.5 men would receive no HIV-preventive benefit. In countries where HIV prevalence is lower than in Uganda, the NNT would even be higher. Thus, it appears that almost 37.5 million men are to be circumcised for no HIV-preventive gain whatsoever. Furthermore, how can mass circumcision programs be justified if circumcised men still need to use a condom and practice safe sex to prevent HIV infection and other STDs?

CONCLUSIONS

The RCT lead authors all held pre-existing beliefs as to the "benefits" of male circumcision and cited articles that supported their pro-male circumcision opinions.[118] There is a risk that contradictory evidence was also omitted in their institutional review board submissions. When undertaking research

[109] Gisselquist, n 8; Gisselquist, Rothenberg, Potterat et al, n 62.

[110] Edwards, Lilford and Hewison, n 95.

[111] Wawer, Makumbi, Kigozi et al, n 3.

[112] Bernstein HB, Kinter AL, Jackson R et al, "Neonatal Natural Killer Cells Produce Chemokines and Suppress HIV Replication in Vitro" (2004) 20(11) AIDS Res Hum Retroviruses 1189.

[113] Clouser CL, Patterson SE and Mansky LM, "Exploiting Drug Repositioning for Discovery of a Novel HIV Combination Therapy" (2010) 84(18) J Virol 9301 at 9301.

[114] Weinstein RS, Weinstein MM, Alibek K et al, "Significantly Reduced CCR5-tropic HIV-1 Replication in Vitro in Cells from Subjects Previously Immunized with Vaccinia Virus" (2010) 11 *BMC Immunology* 23; cf *HIV Virus Neutralised with New Antibodies* (9 July 2010), http://www.news.ninemsn.com.au/article.aspx?id=7926291 viewed 23 October 2011.

[115] Weller SC and Davis-Beaty K, "Condom Effectiveness in Reducing Heterosexual HIV Transmission" (2002) 1 *Cochrane Database of Systematic Reviews* Art No CD003255.

[116] *The "ABCs" of HIV Prevention: Report of a USAID Technical Meeting on Behavior Change Approaches to Primary Prevention of HIV/AIDS* (17 September 2002). Also see http://www.docstoc.com/docs/92529515/1-MALE-CIRCUMCISION-AND-HIV-PLAYING-RUSSIAN-ROULETTE viewed 23 October 2011.

[117] Gray, Kigozi, Serwadda et al, n 2 at 665.

[118] Gifford F, "Community-equipoise and the Ethics of Randomized Clinical Trials" (1995) 9(2) *Bioethics* 127.

into male circumcision, full disclosure of personal beliefs indicative of likely biases should include professional, religious, political and cultural affiliations, as well as one's own circumcision status.[119] Making unwarranted recommendations in relation to circumcision policy raises the vista of future litigation.[120] WHO/UNAIDS have uncritically accepted the African female-to-male reports as conclusive and have recommended male circumcision as an HIV-preventive measure despite substantial contradictory evidence, including the Wawer et al RCT itself which appears to have shown a 61% relative increase in HIV transmission from circumcised men to their female sexual partners some of whom were not informed that their male partners were HIV-positive. Even though 25 previously uninfected women became HIV-positive, incongruously, Wawer et al still recommended mass circumcision of African men as a putative HIV-prevention measure. Under any reasonable interpretation of ethical principles, the Wawer et al trial appears to have been unethical in not warning all the female sexual partners of HIV-positive men that they were at risk of HIV infection.

All four RCTs failed to adhere to the first tenet of ethical medical conduct, "primum non nocere" (first do no harm), since men were subjected to amputation of a normal, functional body part (a significant sexual injury).[121] None of these trials would have been granted institutional review board clearance in developed countries such as the United States, suggesting ethical double standards.[122] Research that directly harms participants by inflicting a destructive amputation of a normal, healthy, functional body part with potential psychosexual adverse effects[123] and/or by exposing participants and their sexual partners to a potentially life-threatening disease such as HIV is unethical. In light of the problems with clinical equipoise, methodology, male circumcision itself as a cause of HIV nosocomial infection, non-sexual transmission of HIV, unethical procedures, and lack of external validity, the African RCTs appear to have been of limited utility in evaluating the HIV-preventive effectiveness of male circumcision.[124] Accordingly,

> the understandable haste to find a solution to the HIV pandemic means that the promise offered by preliminary and specific research studies may be overstated. This may mean that ethical concerns are marginalised. Such haste may also obscure the need to be attentive to local cultural sensitivities, which vary from one African region to another, in formulating policy concerning circumcision.[125]

Mass circumcision programs in sub-Saharan Africa may translate into a worse plight for women, and because of risk compensation, also a greater risk to circumcised men. WHO/UNAIDS have uncritically accepted the reports of female-to-male trials as conclusive and has recommended male circumcision despite contradictory evidence, including the Ugandan RCT which appears to have shown a *61% relative increase* in male-to-female transmission of HIV.[126] In light of the many methodological, ethical and legal flaws in the trials, the WHO/UNAIDS recommendation to roll out mass circumcision programs in sub-Saharan African countries was not justified.

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[119] Goldman R, "Circumcision Policy: A Psychosocial Perspective" (2004) 9(9) Paediatr Child Health 630.

[120] Giannetti M, "Circumcision and the American Academy of Pediatrics: Should Scientific Misconduct Result in Trade Association Liability?" (2000) 85 Iowa L Rev 1507.

[121] Bensley GA and Boyle GJ, "Physical, Sexual, and Psychological Impact of Male Infant Circumcision: An Exploratory Study" in Denniston GC et al (eds), *Understanding Circumcision: A Multi-disciplinary Approach to a Multi-dimensional Problem* (Kluwer/Plenum, NY, 2001); Bensley GA and Boyle GJ, "Effects of Male Circumcision on Female Arousal and Orgasm" (2003) 116 NZMJ 595; Sorrells, Snyder, Reiss et al, n 85; Taylor, Lockwood and Taylor, n 85; Cold and Taylor, n 85.

[122] Gisselquist, n 55.

[123] Boyle, Goldman, Svoboda et al, n 83.

[124] Benson K and Hartz AJ, "A Comparison of Observational Studies and Randomized, Controlled Trials" (2000) 342(25) NEJM 1878; Concato J, Shah N and Horwitz RI, "Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs" (2000) 342(25) NEJM 1887; Sanson-Fisher RW, Bonevski B, Green LW et al, "Limitations of the Randomized Controlled Trial in Evaluating Population-based Health Interventions" (2007) 33(2) Am J Prev Med 155; Van Spall HG, Toren A, Kiss A et al, "Eligibility Criteria of Randomized Controlled Trials Published in High-impact General Medical Journals: A Systematic Sampling Review" (2007) 297(11) JAMA 1233; Vandenbroucke JP, "Observational Research, Randomised Trials, and Two Views of Medical Science" (2008) 5(3) PLoS Med e67; Dekkers M, von Elm E, Algra A et al, "How to Assess the External Validity of Therapeutic Trials: A Conceptual Approach" (2010) 39 Int J Epidemiol 89.

[125] Fox and Thomson, n 46 at 798.

[126] Wawer, Makumbi, Kigozi et al, n 3 at 233.

Male circumcision is a dangerous distraction and waste of scarce resources that should be used for known preventive measures (eg condoms have an 80% effectiveness).[127] As Karlberg, Director of the Clinical Trials Research Centre at the University of Hong Kong, stated:

> In my view the main problem with such trials is that it will be difficult to understand/study the sexual behavior of the participants; any group difference in the occurrence of HIV can thus be due to this confounding factor. If such a trial confirms that circumcision has a significant but still small effect on the HIV rate the message will be that "we do not need to protect ourselves". But safe sex should instead be promoted whatever the trial outcome is. For those reasons I do believe that such trials are neither scientifically nor ethically sound.[128]

A further serious oversight is that the low public health gains and possible short-term and long-term harms arising from implementing mass circumcision programs in sub-Saharan Africa have not been addressed by the trial investigators.[129] As Altman posited:

> What then, should we think about researchers who … misinterpret their results, report their results selectively, cite the literature selectively, and draw unjustified conclusions? We should be appalled.[130]

APPENDIX

The following studies either show no relationship between HIV infection and circumcision status or a higher risk of HIV infection in circumcised men.

No relationship beween HIV infection and circumcision status

1. Hira SK, Kamanga J, Mcuacua R et al, "Genital Ulcers and Male Circumcision as Risk Factors for Acquiring HIV-1 in Zambia" (1990) 161 J Infect Dis 584.
2. Pépin J, Quigley M, Todd J et al, "Association between HIV-2 Infection and Genital Ulcer Diseases Among Male Sexually Transmitted Disease Patients in The Gambia" (1992) 6 *AIDS* 489.
3. Bollinger RC, Brookmeyer RS, Mehendale SM et al, "Risk Factors and Clinical Presentation of Acute Primary HIV Infection in India" (1997) 278 JAMA 2085.
4. Chiasson M, Stoneburner RL, Hildebrandt DS et al, "Heterosexual Transmission of HIV-1 Associated with Use of Smokable Freebase Cocaine (Crack)" (1991) 5 *AIDS* 1121.
5. Carael M, Van De Perre PH, Lepage PH et al, "Human Immunodeficiency Virus Transmission Among Heterosexual Couples in Africa" (1988) 2 *AIDS* 201.
6. Moss GB, Clemerson D, D'Costa L et al, "Association of Cervical Ectopy with Heterosexual Transmission of Human Immunodeficency Virus: Results of a Study of Couples in Nairobi, Kenya" (1991) 164 J Infect Dis 588.
7. Allen S, Lindan C, Serufilira A et al, "Human Immunodeficiency Virus Infection in Urban Rwanda: Demographic and Behavioral Correlate in a Representative Sample of Childbearing Women" (1991) 266 JAMA 1657.
8. Seidlin M, Vogler M, Lee E et al, "Heterosexual Transmission of HIV in a Cohort of Couples in New York City" (1993) 7 *AIDS* 1247.
9. Konde-Lule JK, Bergley SF and Downing R, "Knowledge Attitudes and Practices Concerning AIDS in Ugandans" (1989) 3 *AIDS* 513.
10. Van de Perre P, Clumeck N, Steens M et al, "Seroepidemiological Study on Sexually Transmitted Diseases and Hepatitis B in African Promiscuous Heterosexuals in Relation to HTLV-III Infection" (1987) 3 Eur J Epidemiol 14.
11. Quigley M, Munguti K, Grosskurth H et al, "Sexual Behavior Patterns and Other Risk Factors for HIV Infection in rural Tanzania: A Case Control Study" (1997) 11 *AIDS* 237.

[127] Weller SC and Davis-Beaty K, "Condom Effectiveness in Reducing Heterosexual HIV Transmission" (2002) 1 *Cochrane Database of Systematic Reviews* Art No CD003255.

[128] Karlberg JPE: Personal communication (5 August 2010).

[129] Lie RK and Miller FG, "What Counts as Reliable Evidence for Public Health Policy: The Case of Circumcision for Preventing HIV Infection" (2011) 11 *BMC Medical Research Methodology* 34.

[130] Altman D, "The Scandal of Poor Medical Research" (1994) 308 BMJ 383 at 383.

12. Hudson CP, Hennis AJM, Kataaha P et al, "Risk Factors for the Spread of AIDS in Rural Africa, Hepatitis B and Syphilis in Southwestern Uganda" (1988) 2 *AIDS* 255.
13. Laumann EO, Masi CM and Zuckerman EW, "Circumcision in the United States: Prevalence, Prophylactic Effects, and Sexual Practice" (1997) 277 JAMA 1052.

A higher risk of HIV infection in circumcised men

1. Barongo LR, Borgdorff W, Mosha FF et al, "The Epidemiology of HIV-1 Infection in Rural Areas, Roadside Settlements and Rural Villages in Mwanza Region, Tanzania" (1992) 6 *AIDS* 1521.
2. Grosskurth H, Mosha F, Todd J et al, "A Community Trial of the Impact of Improved Sexually Transmitted Disease Treatment on the HIV Epidemic in Rural Tanzania: 2. Baseline Survey Results" (1995) 9 *AIDS* 927.
3. Chao A, Bulterys M, Musanganire F et al, "Risk Factors Associated with Prevalent HIV-1 Infection Among Pregnant Women in Rwanda National University of Rwanda-Johns Hopkins University AIDS Research Team" (1994) 23 Int J Epidemiol 371.
4. Urassa M, Todd J, Boerra JT et al, "Male Circumcision and Susceptibility to HIV Infection Among Men in Tanzania" (1997) 11 *AIDS* 73.