Chapter 15
Critique of African RCTs into Male Circumcision and HIV Sexual Transmission

Gregory J. Boyle

Abstract On the basis of three seriously flawed sub-Saharan African randomized clinical trials into female-to-male (FTM) sexual transmission of HIV, in 2007 WHO/UNAIDS recommended circumcision (MC) of millions of African men as an HIV preventive measure, despite the trials being compromised by irrational motivated reasoning, inadequate equipoise, selection bias, inadequate blinding, problematic randomization, trials stopped early with exaggerated treatment effects, and failure to investigate non-sexual transmission. Several questions remain unanswered. Why were the trials carried out in countries where more intact men were HIV+ than in those where more circumcised men were HIV+? Why were men sampled from specific ethnic subgroups? Why were so many men lost to follow-up? Why did men in the intervention group receive additional counselling on safe sex practices? The *absolute reduction* in HIV transmission associated with MC was only 1.3 % (without even adjusting for known sources of error bias). *Relative reduction* was reported as 60 %, but after correction for lead-time bias alone averaged 49 %. In a related Ugandan RCT into male-to-female (MTF) transmission, there was a 61 % *relative increase* (6 % *absolute increase*) in HIV infection among female partners of circumcised men, some of whom were not informed that their male partners were HIV+ (also some of the men were not informed by the researchers that they were HIV+). It appears that the number of circumcisions needed to infect a woman (Number Needed to Harm) was 16.7, with one woman becoming infected for every 17 circumcisions performed. As the trial was stopped early for "futility," the increase in HIV infections was not statistically significant, although clinically significant. In the Kenyan trial, MC was

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associated with at least four new incident infections. Since MC diverts resources from known preventive measures and increases risk-taking behaviors, any long-term benefit in reducing HIV transmission remains dubious.

Keywords Randomized clinical trials • HIV/AIDS • Sexual transmission • Male to female transmission • Female to male transmission • Researcher bias • External validity

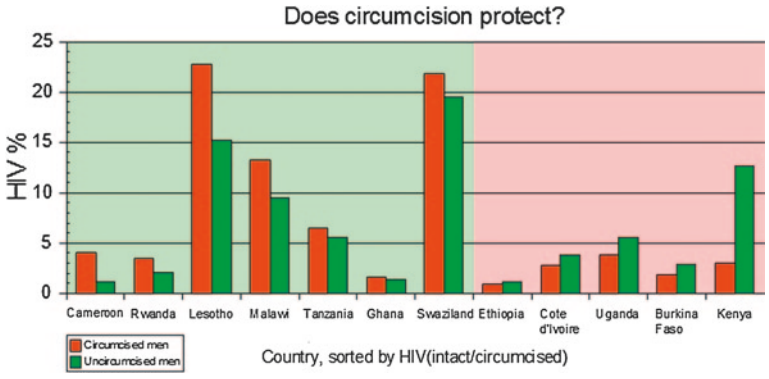
15.1 Background

Three randomized clinical trials (RCTs) tested the efficacy of male circumcision (MC) to reduce female-to-male (FTM) sexual transmission of HIV in South Africa, Kenya, and Uganda. (Auvert et al. 2005; Bailey et al. 2007; Gray et al. 2007) At the time when these trials were approved, it was deemed that they were needed to test the hypothesis that MC would lead to a decreased risk of HIV acquisition among men. The risk–benefit ratio was judged acceptable by all Institutional Review Boards (IRBs) involved, and men were allowed to (and many did) decline participation. It was reported that MC reduces FTM sexual transmission of HIV. Evidence from a parallel RCT into male-to-female (MTF) sexual transmission of HIV in Uganda suggested that MC *increases* MTF transmission of HIV. Alarmingly, this evidence appears to have been ignored by WHO/UNAIDS in recommending the promotion of MC (Wawer et al. 2009). In the MTF trial, women were unwittingly exposed to HIV infection since male sexual partners who submitted to MC were already HIV+. Several women subsequently became HIV+, raising concerns about informed consent. In real-life settings, HIV testing cannot be assured and will 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 MC as an HIV-preventive measure was unwarranted.

While the "gold standard" for medical trials is the randomized, double-blind placebo-controlled trial (RCT), (Sussman and Hayward 2010; Padian et al. 2010) the African trials suffered design and sampling problems, including problematic randomization and selection bias, inadequate blinding, lack of placebo-control (MC could not be concealed), inadequate equipoise, experimenter bias, attrition (673 drop-outs in FTM trials), not investigating MC as a cause of HIV transmission, not investigating non-sexual HIV transmission, as well as lead-time bias, supportive bias (circumcised men provided additional counselling sessions), participant expectation bias, and time-out discrepancy (restraint from sexual activity only by circumcised men). Men were randomized either to immediate or delayed MC groups, obfuscating long-term effectiveness. The number of crossovers and participants lost to follow-up differed between groups in all three FTM trials, and in the South African and Ugandan FTM trials group sizes were somewhat discrepant.

Despite excessively large sample sizes (producing statistically significant effects that were trivial), the actual number of HIV+ circumcised vs. intact men was small, but almost identical across the FTM 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 MTF trial was stopped early after 25 (17 *in MC group*) *previously uninfected women became HIV+*. MC was associated with a 61 *% relative increase* (6 *% absolute increase*) in HIV transmission, (Wawer et al. 2009) leading Wawer et al. to caution that, *Condom use after male circumcision is essential for HIV prevention* (Wawer et al. 2009). What is the purpose of MC if condom use is still needed to prevent sexual transmission of HIV?

Although the Cochrane review asserted that no further studies into MC and HIV sexual transmission are needed, (Siegfried et al. 2009) the epidemiological evidence shows that MC does not reduce HIV sexual transmission in several sub-Saharan African countries, including Cameroon, Rwanda, Lesotho, Malawi, Tanzania, Ghana, and Swaziland, all of which have a higher prevalence of HIV infection among circumcised men (Young 2010; Gisselquist 2007). Clearly, much epidemiological evidence does not support the WHO/UNAIDS decision to recommend the genital cutting of millions of African men as a putative HIV preventive measure.



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15.2 Methodological Concerns

15.2.1 Factors Jeopardizing Internal Validity

Several factors may jeopardise internal validity of RCTs, including (1) researcher expectation bias, (2) participant expectation bias, (3) inadequate double blinding, (4) lead-time bias, (5) selection and sampling bias, (6) experimental mortality, and (7) premature termination. Treatment effects are exaggerated when there are

problems with participant allocation (e.g., allocation concealment; allocation schedule), exclusion of certain participants from analyses, and early termination of trials. Inadequately concealed trials may exaggerate ORs by 41 % (plus additional 17 % if lack of double-blinding) (Schulz et al. 1995). These internal validity problems are discussed below in relation to each of the four trials.

1. Researcher expectation bias

The principal investigators had a history of co-authoring papers promoting MC (e.g., Gray and Wawer have co-authored more than 100 joint papers) indicating their close collaboration (Mehta et al. 2009). The names of no fewer than 14 co-authors appeared on the reports of both Ugandan trials, (Gray et al. 2007; Wawer et al. 2009) suggesting the two trials were not independent. Analysis of the references cited in common across the four trials also reveals substantial overlap (Auvert: 17 out of 34 = 50 %; Bailey: 19 out of 50 = 38 %; Gray: 17 out of 27 = 63 %; Wawer: 7 out of 18 = 39 %).

Claims by Auvert et al. (2005) as to *the long-term protective effect of MC* 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. A Cochrane Review warned, *researchers' personal biases and the dominant circumcision practices of their respective countries may influence their interpretation of findings* (Siegfried et al. 2003). The lead investigators of the RCTs were all established pro-circumcision advocates who collaborated closely and concurred in recommending the mass circumcision of millions of African men.

Equipoise is essential. (Freedman 1987) *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*… (Karlberg and Speers 2010). 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 (MC recommended as beneficial), neutral (e.g., articles pertaining to statistical procedures), or anti-circumcision (MC not recommended), respectively. As Table 15.1 shows, each of the RCT reports cited observational studies suggesting a benefit of MC, but not even one of the observational studies showing either no effect of MC on HIV transmission (13 studies) or a higher incidence of HIV among circumcised men (4 studies) were cited (Young 2010). Omission of contradictory evidence prevented a balanced

Table 15.1 Analysis of cited references

	Auvert	Bailey	Gray	Wawer
Pro-MC	24 (70.6 %)	36 (72 %)	19 (70.4 %)	12 (67 %)
Anti-MC	2 (5.9 %)	1 (2 %)	0 (0 %)	0
Neutral	8 (23.5 %)	13 (26 %)	8 (29.6 %)	6 (33 %)
Total	34	50	27	18

consideration of the available empirical evidence, suggesting the trials lacked equipoise and were biased from the very outset.

Chi square analyses (with Yates' correction) of the number of cited references deemed to be pro-MC versus. anti-MC (Chi squares for Pro-MC versus Neutral vs. Anti-MC shown in parentheses) for each of the four trials provide evidence of pre-existing pro-circumcision bias.

Auvert $\chi^2 = 16.96(1df), p < 0.001$ ($\chi^2 = 20.66(2df), p < 0.001$)
Bailey $\chi^2 = 31.24(1df), p < 0.001$ $\left(\chi^2 = 35.60\,(2df), p < 0.001\right)$
Gray $\chi^2 = 17.06(1df), p < 0.001$ $\left(\chi^2 = 18.33(2df), p < 0.001\right)$
Wawer $\chi^2 = 10.08(1df), p < 0.001$ $\left(\chi^2 = 10.13(2df), p < 0.01\right)$

In the South African report, two anti-MC references were mis-cited either as neutral (Siegfried et al. 2005) or as pro-MC (Kim et al. 1999) so that 25/34 (74 %) of the references were cited in support of MC. In the Kenyan report, only one anti-MC reference was cited, but incorrectly as being neutral (Magoha 1999). In both Ugandan reports, no references opposing MC were cited. In none of the reports was even a single reference cited as opposing MC, in contrast to the more than 70 % of citations supporting MC. Not acknowledging the published evidence showing no prophylactic benefit of MC suggests selective reporting and *confirmation bias*. Admittedly, investigator bias in favor of the hypothesis probably was not the only factor that led to these trials given the growing desperation to stem the terrible HIV/AIDS epidemic in sub-Saharan Africa.

2. Participant expectation bias

Participants were informed that previous studies suggested a potential benefit of MC. 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 MC? 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*. Did the researchers help create a demand for MC by implying that it would help to protect men against HIV and STIs? (Dowsett and Couch 2007).

3. Inadequate double blinding

Since MC cannot be concealed, double blinding, which reduces observer bias and placebo effects, was not possible in the African trials (Schulz et al. 1995). 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* (Wawer et al. 2009). 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*… (Auvert et al. 2005). In the Kenyan trial, …*some participants divulged their circumcision status*… (Bailey et al. 2007). Knowing men's circumcision status may

have influenced their questionnaire responses. Clearly, it is not possible to conduct such trials to the same standards as a double-blind placebo-controlled trial taking place in a laboratory setting.

4. 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 infection) healed. This occurred early in the trials, thereby amplifying lead-time bias. HIV incidence rate ratios (RRs) adjusted for lead-time bias of two months have been calculated using SAS (Version 8.2; SAS Institute, Cary, North Carolina) (Van Howe 2010). Auvert's RR of 0.40 after adjustment was found to be 0.46 (95 % CI 0.23–0.77 %; $p = 0.003$), Bailey's RR of 0.47 after adjustment was found to be 0.52 (95 % CI 0.31–0.87 %; $p = 0.012$), while Gray's RR of 0.49 after adjustment was found to be 0.56 (95 % CI 0.34–0.93 %; $p = 0.026$). Thus, the relative protection against HIV (1-RR) across the three trials decreased to a mean of 49 %, showing that the claimed 60 % protective effect of MC is an overstatement. That the *absolute* reduction of 1.3 % was statistically but not clinically 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. The statistical significance was most likely an artifact due to the excessively large sample sizes in the two comparison groups (5,411 men circumcised; 5,497 controls) wherein the studies were overpowered thereby producing a statistical effect when the absolute effect was unimportant.

5. 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 MC was uncommon in order to recruit adequate sample sizes. Since many unemployed men were financially rewarded for participating, it is likely that samples were skewed towards men from lower SES backgrounds.

There were more at-risk men in the delayed circumcision (control) groups in the South African (+36) and Ugandan (+48) FTM trials, raising questions about the allocation of participants. In the South African trial, the two groups differed significantly on background variables including age ($\chi^2 = 4.58$ (1df), $p < 0.05$), religious affiliation ($\chi^2 = 9.36$ (2df), $p < 0.01$), and ethnic group ($\chi^2 = 12.84$ (2df), $p < 0.01$). There was also a significant between-group difference for ethnic group ($\chi^2 = 12.84$ (2df), $p < 0.01$) in the Kenyan trial, suggesting that, in both trials, participants from different tribal backgrounds were differentially admitted into the comparison groups. In the Ugandan FTM trial, participants allocated to the MC group received significantly more counselling ($\chi^2 = 6.02$ (1df), $p < 0.02$).

In both the South African and Ugandan FTM trials, a higher prevalence of STIs and genital disorders was reported within the control groups. Since HIV is more

likely to co-occur with other STIs, (Fleming and Wasserheit 1999) it is likely that the control groups were at greater risk of acquiring new HIV infections, irrespective of any preventive effect of MC. Why were there significant between-group differences on these background variables? In the South African trial, only men who produced three positive Enzyme-Linked Immunosorbent Assay (ELISA) tests were classified as HIV+. The screening approach, which comprised one ELISA test and two confirmatory ELISA tests using different testing approaches, represents WHOs' current testing strategy for low- to middle-income countries. Since men with one or two positive ELISA tests were regarded as HIV−, how many false negatives (HIV+ men) were assigned to the respective groups? However, even if some HIV+ men were erroneously considered to be HIV−, it would only affect the study results if the majority of these men were randomized to the delayed circumcision arm.

6. Experimental mortality

Participant loss (missing data) was considerably greater than the number of new HIV infections (South Africa: 151 vs. 49 intact men, 100 vs. 20 circumcised men; Kenya: 92 vs. 47 intact men, 87 vs. 22 circumcised men; Uganda: 133 vs. 45 intact men, 140 vs. 22 circumcised men). 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+ infections among those lost to follow-up in the MC group. Men who submitted to MC but who subsequently became HIV+ may have become disillusioned and dropped out, differing from those who completed follow-up evaluations. Which participants were not followed up and their HIV status not reported? *The problem with both the lost-to-follow-up and non-sexual transmission numbers is that they are unknown, thereby creating uncertainty, and reducing confidence in the estimate of the treatment effect* (Van Howe RS, 12 March 2011, "personal communication").

7. Early termination

Truncated RCTs produce exaggerated effect sizes (Montori et al. 2005; Mills and Siegfried 2006; Bassler et al. 2010) and amplify lead-time bias (Pocock and White 1999). Even though Gray et al. acknowledged that *trials that are stopped early could overestimate efficacy when compared with subsequent studies,* (Gray et al. 2007) all three FTM trials were stopped early, thereby exaggerating effects. In addition, Auvert et al. conceded that *adjustment cannot fully account for the confounding effect associated with partial follow-up*. Claims based on trials stopped early for benefit should be viewed with caution. Subsequently, Bailey reported that the "protective effect" of MC in the Kenyan trial had been sustained over 4.5 years (Bailey et al. 2010). This assertion is difficult to evaluate since it was based on the analysis of incomplete *observational data*. As Van Howe (12 March 2012, "personal communication") pointed out, *No one knows the trajectory the data would take in the next 20 years because the studies were stopped prematurely (as soon as they reached statistical significance, although the effect size was inconsequential). The bottom line is that the three African RCTs had a very serious missing data problem, to the point where the results are basically worthless.*

8. Statistical significance versus clinical significance

The three FTM trials, while significant in the statistical sense, were not significant in any clinically important or meaningful real-life sense. The RCT investigators failed to investigate non-sexual sources of HIV infections, they built-in lead-time bias, and may have coerced the largely unemployed participants in the trials with inducements of monetary payments. *Inexplicably, WHO, UNAIDS, and various medical journal editors continue to advocate the circumcision solution even though they know the science is invalid* (Van Howe RS, 10 March 2011, "personal communication"). In the RCT reports, why was the relative reduction highlighted rather than the absolute reduction, thereby giving the misleading impression that MC could actually reduce HIV sexual transmission, wen the evidence actually indicated that MC resulted in a negligible risk reduction (ARR)? The trials found nothing of any clinical significance and after adjusting for sources of error bias, any statistically significant effect would have disappeared entirely.

While the results of the RCTs were "statistically" significant, the Absolute Risk Reduction (ARR) was so small as to be almost meaningless. The studies all had nearly identical methods and shared the same built-in forms of bias, all of which increased the estimated treatment effect. As Van Howe pointed out (10 March 2012, "personal communication"),

> *The first big problem was that half of the men did not get HIV from sexual contact, so that would reduce the absolute risk reduction from 1.3 to 0.65 %. The lead-time bias would reduce the ARR by another 17–0.54 %. Early stoppage of studies is associated with an over estimate of treatment effect by 30 %, so the ARR becomes 0.38 %. There is also the expectation bias in both the researchers and participants and the Hawthorn effect this produced. This could have reduced the treatment effect by another 10 % at least, so the ARR is now 0.34 %.*

Van Howe further commented (12 March 2011, "personal communication") that,

> *This does not even account for the missing data problem in which there were several men lost to follow-up for every man who became infected. The accepted approach to missing data is to calculate the extremes and note that the truth lies within that range. If one assumes that all the men in the control group lost to follow-up became HIV+ and none of the intervention group became infected, the RRs in the three studies would be: Auvert: 0.10, 95 % CI = 0.07–0.16; Gray: 0.07, 95 % CI = 0.04–0.11; Bailey: 0.14, 95 % CI = 0.09–0.2. If all the men in the intervention group lost to follow-up became HIV infected and none of the men lost to follow in the control group were to become infected relative risks would be: Auvert: 2.52, 95 % CI = 1.81–3.51; Gray: 5.60, 95 % CI = 4.33–7.71; Bailey: 3.13, 95 % CI = 2.25–4.35. For the Ugandan FTM trial (Gray et al.) the relative risk ranged from 0.07 to 5.60. This is a huge range, suggesting that the number lost to follow-up was excessive and what happened to these men (what we don't know) could easily increase the reported risk estimates. The bottom line is these studies have a very serious missing data problem, to the point where the results are basically worthless.*

The NNT for the unadjusted 1.3 % is 1/0.013 or 76.9, so that 77 men would gain no benefit whatsoever from circumcision. If we use the adjusted ARR estimate of 0.34, then the NNT is 294.1, so it is obvious that the vast majority of African men submitting to circumcision would receive absolutely no

HIV-preventive benefit whatsoever. Thus, for every HIV infection (theoretically) averted, 294 men would have a highly sensitive part of their penis destroyed and suffer the consequences of short-term and/or long-term complications, including reduced sexual sensitivity/function, as well as possible life-long psychological distress (PTSD).

The Ugandan MTF trial was stopped prematurely as soon as it became apparent that the absolute increase in risk was 6 %. The number of circumcisions needed to infect a female partner (Number Needed to Harm) suggests that for every 17 male circumcisions performed, another female partner became infected with HIV. Why has this clinically important finding apparently been overlooked by WHO/UNAIDS in their recommending mass circumcision programs? *Considering that there are more effective methods of prevention available that do not remove body parts and increase the risk to female partners, why is circumcision even part of the discussion? The money could be better spent on clean medical equipment and needles, condoms, and secondary prevention with ARTs* (Van Howe RS, 12 March 2011, "personal communication").

15.3 Factors Jeopardizing External Validity

The RCT reports provided inadequate information about external validity, including methodological flaws in experimental design and procedures, non-representative sampling (e.g., sampling from mostly poorly educated, impoverished African men), reporting of *relative* rather than the *absolute* efficacy of MC, and inadequately investigating confounding factors (e.g., non-sexual transmission of HIV via skin piercing procedures such as injections, transfusion, etc.). Also, the reports of the FTM trials failed to acknowledge adverse effects of the circumcision interventions (e.g., four new incident HIV infections related to MC in the Kenyan trial) (Gisselquist 2007; Rothwell 2005; Van Spall et al. 2007; Moher et al. 2010; Gisselquist 2009).

Many problems in generalizing results from the trials to the real-world context have been documented (Green et al. 2008, 2010; McAllister et al. 2008). Since the men enrolled in the trials were not representative of the respective populations at large (at least in the South African and Kenyan trials, where data was provided), it is difficult to generalize the findings. Certain ethnic sub-groups were disproportionately represented in the MC and control groups (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 that the Xhosa were under-represented. In Kenya, the main ethnic groups are Kikuyu (22 %), Luhya (14 %), Luo (13 %), Kalenjin (12 %), and Kamba (11 %), so that the Luo were over-represented. Green et al. (2010) concluded that *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.

Furthermore, there has been inaccurate and irresponsible reporting of the trials in the medical literature (e.g., by Peter Piot, former UNAIDS Head in the *Lancet* and by Helen Epstein in the *BMJ*) (Fox and Thomson 2010). Fox and Thomson stated that *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* (Fox and Thomson 2010).

Men enrolled in the immediate MC groups received two years free medical treatment plus supportive counselling and safe-sex advice, difficult to provide in any large-scale "roll out" of MC in sub-Saharan Africa. WHO had specifically cautioned that the FTM Kenyan and Ugandan findings might not generalize to real world settings (Statement on Kenyan 2006). The RCTs were premised on the untested assumption that men who have sex with men (MSM) are extremely rare in Africa and that the HIV epidemic is primarily heterosexual in nature. Evidence suggests this is not the case, (Beyrer et al. 2009; Brody and Potteratt 2003; Roehr 2010; Wakabi 2007) weakening the findings of the RCTs since MC is not effective in preventing HIV transmission among MSM, as the USA epidemiological evidence clearly demonstrates (Millet et al. 2007, 2008). 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 activity. Not controlling for MSM confounded the RCT 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" (Young 2010).

Alarmingly, the United States Centers for Disease Control and Prevention (CDC) recently has been considering a recommendation for *routine infant* MC as an HIV-preventive measure in the USA (where homosexual activity is the predominant mode of HIV transmission), ignoring the fact that the 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 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* (Fox and Thomson 2010).

The WHO/UNAIDS recommendation also failed to heed the Cochrane Review, (Siegfried et al. 2009) which noted that further research is required to assess the feasibility, desirability, and cost-effectiveness of MC implementation within local contexts (i.e., external validity and effectiveness in real-life settings, rather than the contrived experimental settings under which the RCTs were carried out).

15.4 Ethical and Legal Concerns

15.4.1 Circumcision as a Cause of HIV Infection

One of the major problems with scaling up these trials is that quality control is not feasible, particularly in relation to MC itself being a possible cause of HIV transmission (Brewer et al. 2007; Zulu et al. 2006). *Possible paths for HIV transmission during circumcision include skin-piercing instruments reused without sterilization, and multidose vials of local anaesthetic contaminated with HIV from a previous patient… [which] might have infected participants with HIV in Kenya* (Gisselquist 2009). Auvert et al. acknowledged *the possible impact of surgery on HIV acquisition as a result of sexual activity during the healing phase following circumcision*…. (Auvert et al. 2005) and subsequently, all the lead investigators cautioned that following MC, …*men should delay intercourse to limit the potential for increased HIV risk until complete wound healing* (Mehta et al. 2009). In the Ugandan MTF trial, Wawer et al. cautioned that, *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…* (Wawer et al. 2009).

Wawer et al. acknowledged that …*circumcision of HIV-infected men did not reduce transmission of HIV to female partners…* MC was associated with a relative 61 % increased transmission of HIV to female sexual partners. During the 6 month follow-up, 25 new-incident HIV infections occurred among female partners (17 in MC group). However, in an apparent example of irrational *motivated* reasoning, (Kunda 1990). Wawer et al. concluded that *Male circumcision programmes…confer an overall benefit to women* (Wawer et al. 2009). This dissonance suggests a preconceived bias in favour of MC. How can becoming infected with HIV be viewed as a "benefit to women"? Why weren't the women informed that their male partners were HIV+ so that they could take steps to protect themselves? Not informing women that they were at risk of HIV infection would seem unethical. It is regrettable that Wawer et al. the IRBs, and institutions involved did not investigate (which would have been legally required if the trial had been conducted in the United States) since previously uninfected women actually became HIV+ following their participation in the trial.

15.4.2 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 MC (Gisselquist 2008; Gisselquist et al. 2004, 2002). *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 % condom use (10 infections)*

(Gisselquist 2007). Clearly, *the authors did not control for other sources of HIV transmission such as blood transfusions or exposure through infected needles… circumcision may not be as effective at decreasing HIV transmission as the article suggests* (Vines 2006). Since some men acquired HIV having reported no 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* (Gisselquist 2007).

15.5 Contradictory Evidence

What does the frequently cited "60 % *relative* reduction" in HIV infections actually mean? Across all three FTM trials, of the 5,411 men subjected to MC, 64 (1.18 %) became HIV+. Among the 5,497 controls, 137 (2.49 %) became HIV+, so the *absolute* decrease in HIV infection was trivial, being only 1.31 %, which was statistically but not clinically significant (see discussion above).

The claimed efficacy of MC in reducing HIV transmission has been contradicted by at least 17 observational studies (Green et al. 2008, 2010; Thomas et al. 2004; Mor et al. 2007). To take just one example, Mor et al. in an epidemiological study of 58,598 men found no relationship between MC and HIV transmission (Mor et al. 2007). In at least Cameroon, Ghana, Lesotho, Malawi, Rwanda, Swaziland, and Tanzania, HIV is more prevalent among circumcised men (Young 2010; Gisselquist 2007; Chao et al. 1994; Urassa et al. 1997). 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 MC reduces HIV transmission, as the RCT authors would have us believe, then why is HIV prevalence much higher in the USA (where most men are circumcised) than in developed countries where most men are intact? (e.g., Europe, Scandinavia, United Kingdom) (Boyle and Hill 2011)

Viral load and genital ulcers are predictors of the risk of heterosexual transmission of HIV (Quinn et al. 2000). Langerhans cells in the foreskin produce Langerin, which blocks transmission of HIV (de Witte et al. 2007). 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* (Dowsett and Couch 2007). Indeed, *A lowered risk of HIV infection among [5297] circumcised women* has been reported (Stallings and Karugendo 2005). Why weren't trials also undertaken into the alleged HIV-preventive efficacy of female circumcision (FC) to test how randomly allocating women to immediate vs. delayed FC groups could "benefit" women by showing that FC 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 MC could lead to a strong reduction of the spread of HIV* (Auvert et al. 2005). In Thailand, a vaccine provided about six times the protection against HIV

as that claimed for MC (across all modalities of transmission, not just sexual), and for both males and females, not just for sexually active men (Rerks-Ngarm et al. 2009). 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 (Karim et al. 2010). 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 MC vs 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 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…* (Garenne 2006).

15.5.1 Lack of Fully Informed Consent

It appears that 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…* (Ajwang 2007). A Brazilian Health Ministry official (Simao) stated, *the 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"* (VivirLatino and April 2007). Ugandan President Museveni denounced claims that MC 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*? (Cocks 2006) Risk compensation following MC has been demonstrated in large-scale empirical studies (Laumann et al. 1997; Pinkerton 2001). Having being stopped early for benefit, 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* (Kalichman et al. 2007). Is it ethical to give men a false sense of security?

15.5.2 Participant Inducement

As most participants were unemployed, paying them and providing two years free medical care was clearly 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. (Price 1997; Boyle et al. 2002; Todd 2001). *Financial inducements are equivalent to coercion… If benefits to the patient are so self evident, why are payments or gifts thought to be necessary*? (Raffle and Morgan 1998) The prepuce is a highly erogenous part of the penis (Sorrells et al. 2007; Taylor et al. 1996; Cold and Taylor 1999). All four RCTs failed to acknowledge the significant bodily injury caused by the irreversible amputation and the resultant possible long-term adverse psychosexual effects (Boyle et al. 2002; Johnson 2010). 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 (Boyle et al. 2000).

Do IRBs have lower standards when considering experiments in Africa as compared with the USA? *Double standards exist within developed and developing countries, depending on illness conditions, social status of participants, national health priorities* (Wassenaar 2007). Does the USA medical establishment regard poor black African men as an expendable resource to be exploited? (Wakabi 2007) *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* (Verástegui 2006).

Although all participants were alleged to have been HIV- prior to the FTM trials, Bailey et al. admitted, *We cannot exclude the possibility that any of these individuals were actually HIV+ at baseline, and that their [HIV] infection was not detected* (Bailey et al. 2007). 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* (Auvert et al. 2005). But, how could any reputable IRB consider it ethical to withhold information about HIV status since some HIV+ men unknowingly infected their female sexual partners? (Wawer et al. 2009) In the USA, individuals are not permitted to participate in a trial without being willing to know their HIV test results. Even when men did hear their HIV results, the investigators did not warn their female sexual partners (Edwards et al. 1998).

Why was there such a brief "cooling off" period for men allocated to the MC group? The surgery was carried out almost immediately after randomization 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…* 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 MC might not have any prophylactic benefit. Did the RCT investigators make this explicit to the participants?

15.6 Discussion

Assertions by Auvert et al. that MC *prevented six out of ten potential infections* Auvert et al. 2005 mask a much smaller, non-significant *absolute* reduction in risk (1.3 %). MC is not a cost effective means of reducing HIV transmission,

(McAllister et al. 2008) and any long-term effectiveness in sub-Saharan Africa will not be known for many years (Garenne 2008). Is it *right to circumcise a whole population or a considerable part of it, when many will not benefit from the intervention, for example, because they do not engage in risky sexual behaviour* (Dekkers 2009). 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* (Dekkers 2009). Mass circumcision programs inevitably result in complications not generally acknowledged (Muula et al. 2007). *There are always concerns about the safety of MC in sub-Saharan African health systems… The lack of basic instruments and inadequate supplies were identified as crucial limitations in facilitating provision of safe MC…* (Mattson et al. 2004).

Why was a "roll-out" of mass circumcision recommended by WHO/UNAIDS when it was known when the RCT findings were exaggerated due to early termination? Overstating the effectiveness of MC in preventing HIV transmission can only result in public health efforts being misdirected (Boyle 2003; Boyle 2004). For example, Auvert et al. made the claim 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…* However, as the USA 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 (Brewer et al. 2007; Zulu et al. 2006). 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 MC but who subsequently become HIV+? The evidence suggests that mass circumcision programs may exacerbate the HIV epidemic among women (Wawer et al. 2009). Under these circumstances, it would be irresponsible and unethical to advocate mass circumcision programs in sub-Saharan Africa (Green et al. 2010). 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 syringes, (Gisselquist 2007; Gisselquist et al. 2002) overstating the efficacy of MC 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 (Edwards et al. 1998). Men who become HIV+ after undergoing MC would likely become disillusioned and angry. What counselling and compensation will be provided for such men who submit to MC 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 (Wawer et al. 2009). Wasting scarce resources

on MC is unethical, when more effective preventive measures devoid of surgical risks are available. Antiretroviral drugs (ART) can reduce HIV transmission by 92 % (Bernstein et al. 2004). 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* (Clouser et al. 2010). These drugs don't merely reduce viral levels (like ART), but actually eliminate the HIV virus from the body (Weinstein et al. 2010),[1] Now that these FDA-approved drugs can be added to the list with ART, use of condoms, abstinence, and more sanitary healthcare provision, the promotion of MC is even less ethical (Weller and Davis-Beaty 2002).

Several countries (e.g., Uganda, Brazil, Rwanda, Thailand) have reduced their HIV rates without recourse to MC.[2, 3] However, according to Gray et al. 2007 *We estimate that about 67 circumcisions are needed to prevent one HIV infection*. Extrapolating from this NNT, if the target is to circumcise 38 million men in Africa, then MC would have no HIV-preventive effect for $66/67 \times 38{,}000{,}000 = 37{,}432{,}834$ men. Even accepting the exaggerated FTM effect sizes reported by the RCT investigators, for every 100 men circumcised, $66/67 = 98.5$ 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?

15.7 Conclusions

The RCT lead authors all held pre-existing beliefs as to the "benefits" of MC and cited articles that supported their pro-MC opinions (Gifford 1995). One wonders whether contradictory evidence was also omitted in their IRB submissions? When undertaking research into MC, 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 (Goldman 2004). Making unwarranted recommendations in relation to circumcision policy raises the vista of future legal litigation (Giannetti 2000). WHO/UNAIDS has uncritically accepted the African FTM reports as conclusive and have recommended MC as an HIV-preventive measure despite substantial contradictory evidence, including the Wawer et al. RCT itself which showed a 61 % relative increase (6 % absolute

[1] HIV virus neutralised with new antibodies http://news.ninemsn.com.au/article.aspx?id=7926291.

[2] The "ABCs" of HIV prevention 2002.

[3] HIV and AIDS can be stopped, World Vision Australia. http://www.worldvision.com.au/wvconnect/content.asp?topicID=19.

increase) in HIV transmission from circumcised men to their female sexual partners, some of whom were not informed that their male partners were HIV+. Even though 25 previously uninfected women became HIV+, incongruously, Wawer et al. still recommend mass circumcision of African men as a putative HIV prevention measure. Under any reasonable interpretation of ethical principles, the Wawer et al. trial was unethical in not telling some of the men that they were HIV+ and not warning some female sexual partners of HIV+ 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) (Bensley and Boyle 2001, 2003). None of these trials would have been granted IRB clearance in developed countries such as the USA, suggesting ethical double standards (Gisselquist 2009). Research that directly harms participants by inflicting a destructive amputation of a normal, healthy, functional body part with potential psychosexual adverse effects (Boyle et al. 2002) 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, MC as a cause of HIV infection, non-sexual transmission of HIV, unethical procedures, and lack of external validity, the African RCTs were of limited utility in evaluating the HIV-preventive effectiveness of MC (Benson and Hartz 2000; Concato et al. 2000; Sanson-Fisher et al. 2007; Van Spall et al. 2007; Vandenbroucke 2008; Dekkers et al. 2010). 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* (Fox and Thomson 2010).

Mass circumcision programs in sub-Saharan Africa may translate into worse plight for women and, because of risk compensation, also a greater risk to circumcised men. WHO/UNAIDS has uncritically and irresponsibly accepted the methodologically flawed reports of FTM trials as conclusive and has recommended MC despite contradictory evidence, including the Ugandan RCT which showed increased MTF transmission of HIV (Wawer et al. 2009). 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.

MC is a dangerous distraction and waste of scarce resources that should be used for known preventive measures (e.g., condoms have an 80 % effectiveness) (Weller and Davis-Beaty 2002). As Professor Johan Karlberg, MD, PhD, 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 in 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 (Karlberg 2010). 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 (Lie and Miller 2011). Also, the serious missing data problem, combined with all the other known sources of error bias discussed above, basically means that these trials are worthless in terms of informing the debate on male circumcision and any putative FTM reduction in HIV sexual transmission (Van Howe and Storms 2011). Alarmingly, the Ugandan MTF trials started to show an increase in HIV infections among the female sexual partners of HIV+ men, which appears to have been ignored by WHO/UNAIDS in recommending that millions of African men should undergo invasive, damaging circumcision. 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* (Altman 1994).

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Appendix

The following studies either show no relationship with circumcision status or a higher risk in circumcised men.

No relationship between HIV infection and circumcision status (13 studies)

1. Hira SK, Kamanga J < Mcuacua R, et al. Genital ulcers and male circumcision as risk factors for acquiring HIV-1 in Zambia. *J Infect Dis* 1990; 161:584–5.
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. *AIDS* 1992; 6:489–93.
3. Bollinger RC, Brookmeyer RS, Mehendale SM, et al. Risk factors and clinical presentation of acute primary HIV infection in India. *JAMA* 1997; 278:2085–9.
4. Chiasson M, Stoneburner RL, Hildebrandt DS, et al. Heterosexual transmission of HIV-1 associated with use of smokable freebase cocaine (crack). *AIDS* 1991; 5:1121.
5. Carael M, Van De Perre, PH, Lepage PH, et al. Human immunodeficiency virus transmission among heterosexual couples in Africa. *AIDS* 1988; 2:201–5.
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. *J Infect Dis* 1991; 164:588–91.
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. *JAMA* 1991; 266:1657–63

8. Seidlin M, Vogler M, Lee E, et al. Heterosexual transmission of HIV in a cohort of couples in New York City. *AIDS* 1993; 7:1247–54.
9. Konde-Lule JK. Bergley SF, Downing R. Knowledge attitudes and practices concerning AIDS in Ugandans. *AIDS* 1989; 3:513–18.
10. Van de Perre P, Clumeck N, Steens M, et al. Seroepidemiological study on sexully transmitted diseases and hepatitis B in African promiscuous heterosexuals in relation to HTLV-III infection. *Eur J Epidemiol* 1987; 3:14–8.
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. *AIDS* 1997; 11:237–48.
12. Hudson CP, Hennis AJM, Kataaha P, et al. Risk factors for the spead of AIDS in rural Africa, hepatitis B and syphilis in southwestern Uganda. *AIDS* 1988; 2:255–60.
13. Laumann EO, Masi CM, Zuckerman EW. Circumcision in the United States: prevalence, prophylactic effects, and sexual practice. *JAMA* 1997; 277:1052–7

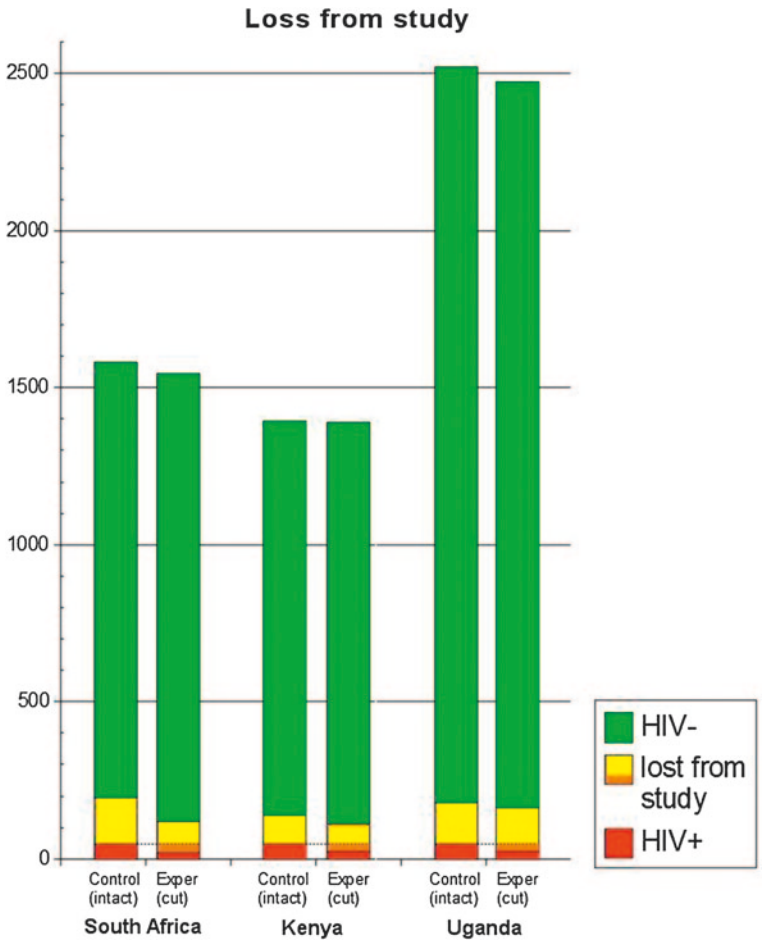
A higher risk of HIV infection in circumcised men (4 studies)

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. *AIDS* 1992; 6:1521–8.
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. *AIDS* 1995; 9:927–34.
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. *Int J Epidemiol* 1994; 23:371–380.
4. Urassa M, Todd J, Boerra JT, et al. Male circumcision and susceptibility to HIV infection among men in Tanzania. *AIDS* 1997; 11:73–80 [study 1].

The orange 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+ (red), circumcision would certainly have no protective effect whatever, but it would not take all of them to reduce the effect below statistical significance.

All three trials had significant numbers "lost from study", their HIV status unknown (yellow + orange bars in the graphs below)—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.



From www.circumcstitions.com (retrieved 4 July 2011; reproduced with permission from the author Hugh Young, email: hugh@buzz.net.nz).

References

Ajwang J (2007) Uganda: HIV—circumcision isn't enough, Monitor (Kampala), 10 April. http://allafrica.com/stories/200704091186.html

Altman D (1994) The scandal of poor medical research. BMJ 308:383–384

Auvert B, Taljaard D, Lagarde E et al (2005) Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial. PLoS Med 2(11):e2

Bailey RC, Moses S, Parker CB et al (2007) Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet 369(9562):643–656

Bailey RC et al. (2010) The protective effect of adult male circumcision against HIV acquisition is sustained for at least 54 months: results from the Kisumu, Kenya trial. IAC, Abstract FRLBC101

Bassler D, Briel M, Montori VM et al (2010) Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. JAMA 303(12):1180–1187

Bensley GA, Boyle GJ (2001) 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

Bensley GA, Boyle GJ (2003) Effects of male circumcision on female arousal and orgasm. New Zealand Med J 116:595–596

Benson K, Hartz AJ (2000) A comparison of observational studies and randomized, controlled trials. N Engl J Med 342(25):1878–1886

Bernstein HB, Kinter AL, Jackson R et al (2004) Neonatal natural killer cells produce chemokines and suppress HIV replication in vitro. AIDS Res Hum Retroviruses 20(11):1189–1195

Beyrer C, Trapence G, Motimedi F et al (2009) Bisexual concurrency, bisexual partnerships, and HIV among Southern African men who have sex with men (MSM). Sex Transm Infect 86(4):323–327

Boyle GJ (2003) Issues associated with the introduction of circumcision into a non-circumcising society. Sex Transm Infect 79:427–428

Boyle GJ (2004) Male circumcision and risk of HIV-1 infection. Lancet 363:1997

Boyle GJ, Hill G (2011) "The case for boosting infant male circumcision in the face of rising heterosexual transmission of HIV"…and now the case against. Med J Aust 194(2):99

Boyle GJ, Svoboda JS, Price CP et al (2000) Circumcision of healthy boys: criminal assault? J Law Med 7:301–310

Boyle GJ, Goldman R, Svoboda JS et al (2002) Male circumcision: pain, trauma and psychosexual sequelae. J Health Psychol 7:329–343

Brazil says no to circumcision (2007) VivirLatino, 3 April 2007. (Retrieved Dec. 26, 2010). URL. http://www.circumcisionandhiv.com/2007/04/brazil_rejects_.html

Brewer D, Potterat JJ, Robert JM et al (2007) Male and female circumcision associated with prevalent HIV infection in virgins and adolescents in Kenya, Lesotho, and Tanzania. Ann Epidemiol 17:217–226

Brody S, Potteratt JJ (2003) Assessing the role of anal intercourse in the epidemiology of AIDS in Africa. Int J STD AIDS 14:431–436

Chao A, Bulterys M, Musanganire F et al (1994) Risk factors associated with prevalent HIV-1 infection among pregnant women in Rwanda. National university of Rwanda-Johns Hopkins university AIDS research team. Int J Epidemiol 23(2):371–380

Clouser CL, Patterson SE, Mansky LM (2010) Exploiting drug repositioning for discovery of a novel HIV combination therapy. J Virol 84(18):9301–9309

Cocks T (2006) Ugandan president rejects circumcision study, Independent Online, 22 Dec, 2006. URL. http://www.iol.co.za/index.php?set_id=1&click_id=3016&art_id=qw1166790421634B225 (Retrieved Dec. 26, 2010)

Cold CJ, Taylor JR (1999) The prepuce. BJU Int 83(Suppl. 1):34–44

Concato J, Shah N, Horwitz RI (2000) Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 342(25):1887–1892

Dowsett GW, Couch M (2007) Male circumcision and HIV prevention: is there really enough of the right kind of evidence? Reprod Health Matters 15(29):33–44

de Witte L, Nabatov A, Pion M et al (2007) Langerin is a natural barrier to HIV-1 transmission by Langerhans cells. Nat Med 13:361–371

Dekkers W (2009) Routine (non-religious) neonatal circumcision and bodily integrity: a transatlantic dialogue. Kennedy Inst Ethics J 19(2):125–146

Dekkers M, von Elm E, Algra A et al (2010) How to assess the external validity of therapeutic trials: a conceptual approach. Int J Epidemiol 39:89–94

Edwards SJL, Lilford RJ, Hewison J (1998) The ethics of randomised controlled trials from the perspectives of patients, the public, and healthcare professionals. Br Med J 317(7167):1209–1212

Fleming DT, Wasserheit JN (1999) From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect 75(1):3–17

Freedman B (1987) Equipoise and the ethics of clinical research. N Eng J Med 317(3):141–145
Fox M, Thomson M (2010) HIV/AIDS and circumcision: lost in translation. J Med Ethics 36:798–801
Garenne M (2006) Male circumcision and HIV control in Africa. PLoS Med 3(1):31
Garenne M (2008) Long-term population effect of male circumcision in generalised HIV epidemics in sub-Saharan Africa. Afr J AIDS Res 7(1):1–8
Giannetti M (2000) Circumcision and the American academy of pediatrics: should scientific misconduct result in trade association liability? Iowa Law Rev 85:1507–1568
Gifford F (1995) Community-equipoise and the ethics of randomized clinical trials. Bioethics 9(2):127–148
Gisselquist D (2007) Points to consider: responses to HIV/AIDS in Africa, Asia, and the Caribbean. Adonis & Abbey, London
Gisselquist D (2008) Denialism undermines AIDS prevention in sub-Saharan Africa. Int J STD AIDS 19:649–654
Gisselquist D (2009a) HIV infections as unanticipated problems during medical research in Africa. Accountability Res 16:199–217
Gisselquist D (2009b) Double standards in research ethics, health-care safety, and scientific rigour allowed Africa's HIV/AIDS epidemic disasters. Int J STD AIDS 20(12):839–845
Gisselquist D, Rothenberg R, Potterat J et al (2002) HIV infections in sub-Saharan Africa not explained by sexual or vertical transmission. Int J STD AIDS 13:657–666
Gisselquist D, Potterat JJ, Brody S (2004) Running on empty: sexual co-factors are insufficient to fuel Africa's turbocharged HIV epidemic. Int J STD AIDS 15:442–452
Goldman R (2004) Circumcision policy: a psychosocial perspective. Paediatr Child Health 9(9):630–633
Gray RH, Kigozi G, Serwadda D et al (2007) Male circumcision for HIV prevention in men in Rakai Uganda: a randomised trial. Lancet 369(9562):657–666
Green LW, McAllister RG, Peterson KW et al (2008) Male circumcision is not the HIV 'vaccine' we have been waiting for! Fut HIV Ther 2(3):293–299
Green LW, Travis JW, McAllister RG et al (2010) Male circumcision and HIV prevention: insufficient evidence and neglected external validity. Am J Prev Med 39(5):479–482
Johnson M (2010) Male genital mutilation: beyond the tolerable? Ethnicities 10(2):181–207
Karlberg JPE (2010) Personal communication (email). University of Hong Kong.
Karlberg JPE, Speers MA (2010) Reviewing clinical trials: a guide for the ethics committee. Karlberg JPE, Hong Kong
Kalichman S, Eaton L, Pinkerton S (2007) Circumcision for HIV prevention: failure to fully account for behavioral risk compensation. PloS Med 4(3):e138
Karim QA, Karim SA, Frohlich JA et al (2010) Effectiveness and safety of Tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science 329(5996):1168–1174
Kim DS, Lee JY and Pang MG (1999) Male circumcision: A South Korean perspective. Brit J Urol Int 83:28
Kunda Z (1990) The case for motivated reasoning. Psych Bull 108(3):480–498
Laumann EO, Masi CM, Zuckerman EW (1997) Circumcision in the United States: prevalence, prophylactic effects, and sexual practice. JAMA 277:1052–1057
Lie RK, Miller FG (2011) What counts as reliable evidence for public health policy: the case of circumcision for preventing HIV infection. BMC Med Res Methodol 11:34
Magoha GA (1999) Circumcision in various Nigerian and Kenyan hospitals. East Afr Med J 76: 583
Mattson CL, Muga R, Poulussen R, Onyango T, Bailey RC (2004) Feasibility of medical male circumcision in Nyanza province. Kenya. East Afr Med J 81:320–335
McAllister RG, Travis JW, Bollinger D et al (2008) The cost to circumcise Africa. Int J Men's Health 7(3):307–316
Mehta SD, Gray RH, Auvert B et al (2009) Does sex in the early period after circumcision increase HIV-seroconversion risk? Pooled analysis of adult male circumcision clinical trials. AIDS 23(12):1557–1564
Mills E, Siegfried N (2006) Cautious optimism for new HIV/AIDS prevention strategies. Lancet 368:1236

Millet GA, Ding H, Lauby J et al (2007) Circumcision status and HIV infection among black and Latino men who have sex with men in three US cities. J Acquir Immune Defic Syndr 46(5):643–650

Millet GA, Flores SA, Marks G et al (2008) Circumcision status and risk of HIV and sexually transmitted infections among men who have sex with men: a meta-analysis. JAMA 300(14):1674–1684

Moher D, Hopewell S, Schulz KF et al (2010) CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Br Med J 340:c869

Mor Z, Kent CK, Kohn RP et al (2007) Declining rates in male circumcision amidst increasing evidence of its public health benefit. PLoS ONE 2(9):e861

Montori VM, Devereaux PJ, Adhikari NK et al (2005) Randomized trials stopped early for benefit: a systematic review. JAMA 294:2203–2209

Muula AS, Prozesky HW, Mataya RH et al (2007) Prevalence of complications of male circumcision in Anglophone Africa: a systematic review. BMC Urol 7:4

Padian NS, McCoy SI, Balkus JE et al (2010) Weighing the gold in the gold standard: challenges in HIV prevention research. AIDS 24(5):621–635

Pinkerton SD (2001) Sexual risk compensation and HIV/STD transmission: empirical evidence and theoretical considerations. Risk Anal 21:727–736

Pocock S, White I (1999) Trials stopped early: too good to be true? Lancet 353:943–944

Price C (1997) Male circumcision: an ethical and legal affront. Bull Med Ethics 128:13–19

Quinn TC, Wawer MJ, Sewankambo N et al (2000) Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai project study group. N Engl J Med 342(13):921–929

Raffle AE, Morgan K (1998) Financial inducements are equivalent to coercion. BMJ 316(7128):394

Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S et al (2009) Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med 361(23):2209–2220

Roehr B (2010) How homophobia is fuelling Africa's HIV epidemic. BMJ 340:c2245

Rothwell PM (2005) External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet 365:82–93

Sanson-Fisher RW, Bonevski B, Green LW et al (2007) Limitations of the randomized controlled trial in evaluating population-based health interventions. Am J Prev Med 33(2):155–161

Schulz KF, Chalmers I, Hayes RJ et al (1995) Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 273:408–412

Siegfried N, Muller M, Volmink J et al. (2003) Male circumcision for prevention of heterosexual acquisition of HIV in men (Cochrane Review). In: The Cochrane Library, Issue 3, Update Software, Oxford

Siegfried N, Muller M, Deeks et al (2005) HIV and male circumcision-A systematic review with assessment of the quality of studies. Lancet Infect Dis 5:165

Siegfried N, Muller M, Deeks JJ et al. (2009) Male circumcision for prevention of heterosexual acquisition of HIV in men. Cochrane Database Syst Rev 2 (CD003362). URL: http://onlinelibrary.wiley.com/o/cochrane/clsysrev/articles/CD003362/frame.html

Sorrells ML, Reiss JL, Snyder MD et al (2007) Fine-touch pressure thresholds in the adult penis. BJU Int 99:864–869

Stallings RY, Karugendo E (2005) Female circumcision and HIV infection in Tanzania: for better or for worse? 3rd IAS conference HIV pathogen and treatment, Rio de Janeiro, Brazil, 24–27 July

Statement on Kenyan and Ugandan trial findings regarding male circumcision and HIV (2006) WHO, Geneva, Switzerland, December 13. http://www.who.int/mediacentre/news/statements/2006/s18/en/index.html (Retrieved Oct. 15, 2010)

Sussman JB, Hayward RA (2010) An IV for the RCT: using instrumental variables to adjust for treatment contamination in randomised controlled trials. BMJ 340:c2073

Taylor JR, Lockwood AP, Taylor AJ (1996) The prepuce: specialized mucosa of the penis and its loss to circumcision. Br J Urol 77:291–295

The "ABCs" of HIV prevention: report of a USAID technical meeting on behavior change approaches to primary prevention of HIV/AIDS (2002) 17 Sept

Thomas AG, Bakhireva LN, Brodine SK et al. (2004) Prevalence of male circumcision and its association with HIV and sexually transmitted infections in a U.S. navy population. Abstract no. TuPeC4861. Presented at the XV international AIDS conference, Bangkok, Thailand, 11–16 July 2004

Todd C (2001) Research participation and financial inducements. Amer J Bioethics 1(2):60–61

Urassa M, Todd J, Boerra JT et al (1997) Male circumcision and susceptibility to HIV infection among men in Tanzania. AIDS 11:73–80

Vandenbroucke JP (2008) Observational research, randomised trials, and two views of medical science. PLoS Med 5(3):e67

Van Howe RS (2010) Analysis of the circumcision/HIV randomised clinical trials. Unpublished manuscript

Van Howe RS, Storms MR (2011) How the circumcision solution in Africa will increase HIV infections. J Pub Health Africa 2:e4. doi:10.4081/jphia.2011.e4

Van Spall HG, Toren A, Kiss A et al (2007) Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA 297(11):1233–1240

Vines J (2006) Major potential confounder not addressed. PLoS Med 3(1):e63

Verástegui EL (2006) Consenting of the vulnerable: the informed consent procedure in advanced cancer patients in Mexico. BMC Med Ethics 7:13

Wakabi W (2007) Homophobia is fuelling the AIDS epidemic in Africa. CMAJ 177(9):1017

Wassenaar D (2007) Double standards in research ethics. Case-studies: informed consent and vaccine to treat rotavirus. EU forum on ethics, research and globalisation. Brussels

Wawer MJ, Makumbi F, Kigozi G et al (2009) Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomised controlled trial. Lancet 374:229–237

Weinstein RS, Weinstein MM, Alibek K et al (2010) Significantly reduced CCR5-tropic HIV-1 replication in vitro in cells from subjects previously immunized with vaccinia virus. BMC Immunol 11:23

Weller SC, Davis-Beaty K (2002) Condom effectiveness in reducing heterosexual HIV transmission. Cochrane Database Syst Rev Issue 1 Art. No. CD003255

Young H (2010) False assumptions. BMC Public Health 10:209. URL: http://www.circumstitions.com/HIV.html (Retrieved Dec. 23, 2010)

Zulu K, Bulawo ND, Zulu W (2006) 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

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