

Exposé of misleading claims that male circumcision will increase HIV infections in Africa

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Abstract

Despite over two decades of extensive research showing that male circumcision protects against heterosexual acquisition of HIV in men, and that includes findings from large randomized controlled trials leading to acceptance by the WHO/UNAIDS and the Cochrane Committee, opponents of circumcision continue to generate specious arguments to the contrary. In a recent issue of the *Journal of Public Health in Africa*, Van Howe and Storms claim that male circumcision will increase HIV infections in Africa. Here we review the statements they use in support of their thesis and show that there is no scientific basis to such an assertion. We also evaluate the statistics used and show that when these data are properly analyzed the results lead to a contrary conclusion affirming the major role of male circumcision in protecting against HIV infection in Africa. Researchers, policy makers and the wider community should rely on balanced scholarship when assessing scientific evidence. We trust that our assessment may help refute the claims by Van Howe and Storms, and provide reassurance on the importance of circumcision for HIV prevention.

Introduction

In the face of overwhelming evidence to the

contrary, Van Howe and Storms argue in a recent article in this journal that *there is a lack of scientific evidence, biological plausibility, and epidemiological evidence for male circumcision (MC) as a protection against HIV infection in men*.¹ The article contains, however, unsupported claims, sources that either fail to support or contradict the claims attributed to them, errors in calculations, fallacious reasoning and selective citing of evidence. Previous publications by the first author of the article have been severely criticized.²⁻⁸ In one of these, involving a meta-analysis of sexually transmitted urethritis, a conclusion that MC would increase this category of STIs arose because the data analyzed differed from that in the source publications; when the actual source data were subjected to a valid meta-analysis by others MC it was found not to increase these STIs.⁴

These are serious problems with potential policy implications deleterious to international public health, and for this reason, a detailed, point-by-point analysis of the key arguments in the article is required. After reading our exposé we trust that readers of the journal will be made aware of our concerns.

The article's Introduction

The article begins by levelling criticism at an extensive review in 2007 by the WHO/UNAIDS of the benefits of MC in protection against HIV,⁹ claiming that this contains fundamental flaws that have been glossed over by its proponents within these organizations. We disagree.

Rebuttal of the claim of lack of scientific evidence

The article then criticizes the three randomized controlled trials (RCTs) whose findings on male circumcision in HIV prevention have been endorsed by the WHO/UNAIDS.¹⁰ In support of the article's statement that the trials *had expectation bias (both researcher and participant), selection bias, lead-time bias, attrition bias, duration bias, and early termination that favored the treatment effect the investigators were hoping for* a review in the *Lancet*¹¹ is cited. The latter was, however, published six to eight years before the results of the respective trials were published.¹²⁻¹⁴ The prior observational data suggesting that MC might reduce HIV acquisition in men generated the hypothesis that was tested in the rigorous randomized controlled trials. This cannot be construed as bias. It would be unethical to conduct trials in the absence of a testable hypothesis of potential benefit. The 1999 *Lancet* review remained silent on the subject of such biases in the trials, and its co-author Halperin had no direct involvement with the trials. In the absence of any justification whatsoever, the

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article then claims that *All three studies were overpowered such that the biases alone could have provided a statistically significant difference*. This comment reveals a lack of understanding of predetermined trial stopping rules. The three trials were stopped early because formal interim analyses showed greater efficacy than had been anticipated. Thus, rather than indicative bias, the RCT investigators were conservative in their assumptions.

The article then proceeds to attempt to establish that substantial numbers of men in the trials did not acquire HIV through sexual contact. The arguments used are, however, problematic. First, commenting on the South African trial,¹² the article mistakenly assumes that men who said they had no sexual contact or had always used a condom *became infected through non-sexual means*. This would make sense only if: (i) condoms were completely effective in preventing HIV transmission; and (ii) self-reported data on condom usage were reliable. In fact, self-reported sexual behavior is often unreliable,¹⁵ and a realistic estimation of the effectiveness of consistent condom use is 80%-90%,¹⁶ not *more than 99%* as claimed in the article.

The attempt in the article to then subtract these particular men from the trial data for HIV infections is, therefore, misguided. Secondly, commenting on the Ugandan trial,¹⁴ the article

notes that men who reported no sexual partners during the follow-up interval of seroconversion accounted for 6 infections, but fails to mention that these infections were evenly distributed between the intervention and control arms. Moreover, these 6 men reported being sexually active in other follow-up intervals, suggesting misreporting. On this basis, the article by Van Howe and Storms calculates that *at most 35 of the 67 infections in the Ugandan trial can be attributed to sexual transmission*. The basis for this calculation is not given. It would imply that 32 infections cannot be attributed to sexual transmission. This greatly exceeds the figure of 6 reported in their article, suggesting a serious error in calculation. The article makes the same mistake with data from the Kenyan trial,¹³ where 5 men reported no sexual activity before seroconversion, from which the article calculates that 33 infections cannot be attributed to sexual transmission. Thus, in contrast to the conclusion that *Conservatively for the three trials, 89 of the 205 infections (43.1%) were sexually transmitted*, the corrected figure is 194 (95% of infections), so invalidating the claim.

No large phase III trial is perfect, and minor anomalies may arise by chance among subgroups. But such trials are designed and powered to address a primary hypothesis in the entire population of participants, not in minor subgroups.

The claim of lack of biological plausibility

In this section, a number of the claims are without foundation. The statement that *the mucosa of the inner and outer prepuce have been shown to be of the same thickness* misrepresents the source, which studied the thickness of the keratin layer, not that of the entire foreskin tissue.¹⁷ That study has, moreover, been criticized because the foreskins were from men circumcised for a medical condition that could have affected foreskin histology, the inner mucosa is thicker at the distal end,¹⁸ and the discrepant results may be attributed to the lack of a standardized method to evaluate keratin thickness, as well as effects of age and other factors on keratin thickness.¹⁹ This article is also at odds with other authors who were not cited, who reported lower keratinization of the inner foreskin.¹⁹⁻²² Furthermore, the statement *mucosa of the inner and outer prepuce* contradicts the fact that the outer surface of the prepuce is not mucosal.

The article notes that the foreskin's Langerhans cells act as an entry point for HIV, though it misrepresents this as the speculation of unspecified *proponents*. The article erroneously claims that *research has shown that Langerhans cells are quite efficient in repelling HIV* and [this] *explains why the*

transmission rate of HIV is one per 1,000 unprotected coital acts. In reality, Langerhans cells act as a target for HIV.¹⁹⁻²² Next it is claimed that secretion of the protein langerin by Langerhans cells kills viruses and protect[s] against other sexually transmitted infections. Support for such speculation is not, however, provided. Even if langerin were to be secreted it would not kill viruses. Langerin works by binding HIV after it is sequestered into Langerhans cells, then shunts it to *intracellular granules* for degradation.²³ This mechanism becomes overwhelmed at higher viral loads,^{23,24} thus explaining why lack of a foreskin protects against HIV infection.

The claim in the article that its authors have unpublished data to show that circumcised men are at greater risk for STIs contradicts every reliable meta-analysis that has been published in the literature to date,²⁵ as well as evidence from the African randomized controlled trials showing MC lowers risk of HSV-2 and HPV infection.²⁶⁻³⁰

In an attempt to refute the argument that the sub-preputial space acts as a harbor for sexually transmitted pathogens, the article claims that *Meta-analyses assessing the susceptibility to genital infections with herpes simplex virus and human papilloma virus have not shown an association with circumcision status*. Three sources are cited to support this. The first of these reported reduced risk of HSV-2 infection (of borderline statistical significance), chancroid and syphilis.³¹ The second, by Van Howe,³² led to criticism by international HPV experts in a critique whose title referred to that article as a *biased, inaccurate and misleading meta-analysis*.⁸ A proper meta-analysis of the same source data showed that circumcision had a substantial protective effect,⁸ as found subsequently in an expanded meta-analysis.^{25,33}

The article omits to mention the fact that circumcision changes the flora of the penis,³⁴ and that moistness in the space beneath the prepuce increases risk of HIV infection.³⁵ HIV risk increases with foreskin surface area.³⁶ Far from a lack of biological plausibility there are multiple plausible biological explanations for circumcision's protective effect.^{19,27,37-39}

Lack of consistent epidemiological evidence

The article asserts that *In Africa, there are several countries where circumcised men are more likely to be HIV infected than intact men, including Malawi, Rwanda, Cameroon, Ghana, Zimbabwe, Lesotho, Swaziland, and Tanzania*. This misrepresents the evidence. More correctly, *some* observational cross-sectional studies in these countries have found such results. However, the overwhelming majority of prospective epidemiological studies suggest

that MC is protective.⁴⁰ Additionally, such studies are inherently susceptible to confounding,³⁸ and cannot establish causality since circumcision is often performed for medical reasons (frequently recurrent STIs or genital ulcer disease as a consequence of HIV), and so many circumcised men in the studies were already infected prior to circumcision.⁴¹

It is claimed that *If the national survey data that are available from 19 countries are combined in a meta-analysis (Table 1) the random-effects model summary effect for the risk of a genitally intact man having HIV is an odds ratio of 1.10 (95%CI=0.83-1.46), indicating that on a general population level, circumcision has no association with risk of HIV infection*. Here the article's analysis contradicts previously published analyses of such data. For example, a study of data from 18 studies in sub-Saharan Africa by Gebremedhin found a protective effect of circumcision which was strengthened when adjusted for *number of lifetime partners, sexual behavior, age, place of residence (urban/rural), educational status, marital status, comprehensive knowledge towards HIV/AIDS and frequency of use of mass media* (OR of 4.95, 95% CI 4.57–5.36 for uncircumcised vs. circumcised men).⁴²

The article further asserts that *Among developed nations, the United States has the highest rate of circumcision and the highest rate of heterosexually transmitted HIV*. While it is true that the US has higher HIV prevalence than many developed countries, it is not true that it has the highest.⁴³ HIV left Africa and arrived in the USA, via Haiti,⁴⁴ earlier than the rest of the world, so has had more time to spread. More importantly, between-country comparisons of aggregate data represent one of the weakest of all analyses because of their failure to isolate the effect of the parameter that is being studied, as Van Howe himself acknowledged in 1999.⁴⁵ And even then, for 38 developing countries in which *heterosexual* acquisition is the major mode of HIV infection, UNAIDS data have shown HIV prevalence to be 16% for the 8 countries with low (<20%) MC rates and 3% for the 22 with high (>80%) MC rates.⁴⁶ The US has relatively poor levels of sex education and consequent condom usage,⁴⁷⁻⁵⁰ which might reasonably be expected to act as a confounding factor. Most importantly, in the developed world most HIV infections occur through receptive anal sex and injecting drug use, neither of which is influenced by circumcision status. Interestingly, however, there is evidence to suggest that, when using male-to-female transmission as a baseline, female-to-male transmission (which MC is known to protect against) is far lower in the USA than in Europe.⁵¹

The article goes on to claim that *Within the United States, blacks have the highest rate of*

circumcision and the highest rate of heterosexually transmitted HIV. Four sources are cited in support of the claim regarding circumcision rates by race, and it is instructive to examine them. Two are concerned with neonatal circumcision, not the prevalence of circumcision among adults.^{52,53} Even so, one of the sources cited actually contradicts the authors' claim, reporting that 89.6% of whites were circumcised versus 86.9% of African Americans.⁵³ The latter is not a nationally representative sample, nor is the third source cited.⁵⁴ These thus fail to support the article's claim, as does the only nationally-representative study of adults which found MC prevalence was 88% in non-Hispanic whites, 73% in non-Hispanic blacks, 42% in Mexican Americans, and 50% in others.⁵⁵ Similarly, another nationally-representative study of adults reported that in particular, whites are considerably more likely to be circumcised than are blacks or Hispanics (81% vs 65% or 54%).⁵⁶

We, therefore, find it astonishing that such a bold claim can be made using sources that state the opposite to support it.

Risk compensation

The article confidently predicts that *Risk compensation will accompany the circumcision solution in Africa*. Here the article ignores the fact that this issue has been studied extensively, and research generally indicates little or no risk compensation.⁵⁷ It then goes on to make various unsubstantiated assumptions, including one that condoms are 98% effective, to calculate that the impact of a fifteen-fold increase in the rate of circumcision could be accompanied by a relative 41% increase in the use of condoms. The fifteen-fold figure is repeated at the end of the next section of the article following further questionable statistics (discussed below).

Leap of faith

The assertion that *Interventions and medications that demonstrate efficacy in a research setting are often failures in a clinical setting. Circumcision will provide another example of this* is incorrect, having no evidence to support it. Van Howe once predicted that it was unlikely that a trial would find a protective effect of circumcision against HIV.⁵⁸

The article's claim that *the association between circumcision status and HIV infection was present primarily in studies of high-risk men* misrepresents the literature. The association is in fact seen in most settings and, as the 2003 Cochrane review put it, *The results from existing observational studies show a strong epidemiological association between male circumcision and prevention of HIV, especially among high-risk groups*.⁵⁹ Most recently, the Cochrane Committee conducted a very exten-

sive analysis of the trial data, leading them to state *inclusion of male circumcision into current HIV prevention guidelines is warranted and no further trials are required*.⁶⁰

The next claim is that *observational studies of general populations have for the most part failed to show an association between circumcision status and HIV infection*. Nothing could be further from the truth. Of the three sources cited, one is a single 16-year old observational study⁶¹ which did not fully adjust for potentially confounding factors such as greater number of sexual partners and higher circumcision rate amongst men in the upper strata of Tanzanian society. The second contradicts the article's claim, since that study reports *an intact foreskin was associated with an increased risk of HIV infection: combined odds ratio 1.43 (1.32 to 1.54) with a fixed effect model and 1.67 (1.25 to 2.24) with a random effect model*.⁶ The third source cited is a meta-analysis by Van Howe, which was the subject of severe criticism^{6,7} for its inappropriate methodology leading to an erroneous conclusion. A recent textbook on meta-analyses discusses in detail this particular meta-analysis as an illustrative example of how Simpson's paradox can lead to incorrect results.⁶² Similarly, a review of methods and techniques in meta-analysis noted that *Although this [Simpson's] paradox is usually illustrated with hypothetical examples, in one meta-analysis [Van Howe's] that used simple data pooling to test the protective effect of circumcision against AIDS infection in sub-Saharan African men, conclusions were reached that were diametrically opposed to those of a subsequent meta-analysis in which appropriate techniques were used*.⁶³

It is noteworthy that every correctly-performed meta-analysis of observational studies of MC and HIV has reported a protective effect. For example, like the Cochrane Committee,⁵⁹ Weiss *et al.* reported that *male circumcision is associated with a significantly reduced risk of HIV infection among men in sub-Saharan Africa, particularly those at high risk of HIV*.⁴⁰ A later as-treated meta-analysis of the 15 observational studies that adjusted for potential confounders found a protective effect of 65%, this being identical to the 65% figure obtained from a meta-analysis of the initial findings of the three randomized controlled trials.³⁷ Another meta-analysis, of 13 studies, 85% of which were from sub-Saharan Africa, reported a 53% protective effect for general populations and 69% for high-risk populations.⁶⁴ If MC status was ascertained by self-report the protective effect was 45%, but if by direct genital examination in the clinic it was 65%.⁶⁴ These particular authors pointed out that the current data on MC satisfy 6 of the 9 criteria of causality as outlined by Sir A.B. Hill,

namely strength of association, consistency, temporality, coherence, biological plausibility, and experiment.⁶⁵

The article then asserts that *there is no scientific reason to believe that the RCT results would necessarily apply to the general population*. While we agree that circumcision might not affect monogamous partnerships, how can the article explain UNAIDS data showing a strong inverse correlation between circumcision rate in general populations and HIV prevalence?⁴⁶ So the claim that *increasing condom use from 48% up to 51.8% would result in the same gains as increasing the circumcision rate from 5% up to 75%* should be seriously questioned.

Attractive, less invasive, less expensive, more effective alternatives

In this section, the article starts out by citing Gisslequist *et al.* saying that *most infections can be attributed to non-sexual transmission*. The arguments by those authors have, however, been shown to be fallacious.⁶⁶ While anti-retroviral therapy has prolonged the lives of those infected with HIV, the cost is enormous, making it unaffordable and unsustainable in developing countries.⁶⁷ Moreover, prevention of infection is preferable to compliance with a strict regimen of daily medication.

Even though the *test-and-treat* model the article proposes is based on a study in Africa, its cost makes it beyond the reach of generalized populations in Africa. In countries such as the USA, *poor engagement in care for HIV-infected individuals will substantially limit the effectiveness of test-and-treat strategies*.⁶⁸ What's more, *The belief that having an undetectable viral load leads to lower infectiousness was associated with [a] greater number of partners, including nonpositive partners, and less condom use*,⁶⁹ so that *programs aimed at testing and treating people living with HIV/AIDS for prevention require attention to adherence and sexual behavior*.⁶⁹

It is then claimed that *many HIV experts consider primary prevention extremely wasteful and ineffective*. So why then is so much effort going into developing a prophylactic vaccine against HIV? And why are governments spending billions vaccinating school girls against the two types of HPV that cause 70% of cervical cancers, when only a tiny proportion of those girls, a proportion which is impossible to identify individually in advance, will go on to get cervical cancer later in life?^{70,71}

The article then criticizes modeling by the WHO and others that has demonstrated the enormous savings in lives and costs from increasing MC in high prevalence settings.⁷² In so doing, they allude to the possibility that the findings over the 1.5-2 years of the trials

will not hold up over the longer term. In fact by 4.5-5 years effectiveness has now been shown to have *increased*.^{73,74} Even in low prevalence settings such as the USA, infant circumcision has been shown to be cost-saving for HIV prevention.⁷⁵ Furthermore, the suggestion that condoms will be cheaper has to assume that funding for the extremely low 2.5 cents cost per condom will persist in poverty-stricken HIV-ravaged countries. On average, condom use is at best inconsistent even in developed countries where people *can* afford them.⁷⁶⁻⁸⁰ In the trials, condoms were provided free and participants received regular counseling, but their use was low.^{13,81} In Africa the association between condom use and HIV is, moreover, complex.^{16,82,83} The article cites one of Van Howe's publications that concluded that circumcision removes the most sensitive part of the penis,⁸⁴ failing to point out that a reanalysis of the data from that study disproved its conclusions.² The article also chose not to refer to the bulk of the literature,³⁹ including RCT data that means show either no difference⁸⁵ or improvement⁸⁶ in sensitivity in circumcised men.

Near the end of the article we see more unsubstantiated claims such as *with the push for circumcision, public health workers in Africa are finding that resources that previously paid for condoms are now being redirected to circumcision. With every circumcision performed, 3000 condoms will not be available and that a health care provider is prevented from caring for someone in need of medical care* and so on. Such fear-mongering is unhelpful and seems based more on ideological opposition to circumcision per se than on any sober and objective analysis of the existing scientific evidence.

Conclusions

Our critique of Van Howe and Storms' article has highlighted some of the more audacious claims therein. Other claims not addressed here are even more transparently incorrect, being based on assumptions or idealistic, but unsubstantiated, optimism devoid of evidential support. In consideration of all these factors, we find that publication of this paper is quite unhelpful to international objectives aimed at stemming the epidemic of HIV, at least as far as heterosexual transmission is concerned, and especially in high prevalence settings such as sub-Saharan Africa. The level of protection deemed acceptable for vaccines against influenza^{87,88} justifies claims that infant MC can be regarded as a *surgical vaccine*.^{39,89,90} But we emphasize that it should be seen as part of a comprehensive package that

includes promoting changes in behavior, the use of condoms, and other important prevention approaches. Just as both airbags (which are always in place) and seatbelts (which need to be applied each time) are needed, *both* circumcision and changes in behavior should be promoted to help alleviate the spread of HIV worldwide.⁹¹

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