Male circumcision is an efficacious, lasting and cost-effective strategy for combating HIV in high-prevalence AIDS epidemics

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In their recent article, "Male circumcision is *not* the 'vaccine' we have been waiting for!", Green *et al.* claim that the incorporation of male circumcision (MC) as an additional HIV prevention strategy is based on 'incomplete evidence, and is premature and ill-advised' [1]. The authors attempt to refute a prior article with a similar title published in the same journal, which urged immediate action to implement safe MC services based on the scientific evidence for HIV prevention and other aspects of reproductive health [2]. We respond as follows to the various claims in the paper by Green *et al.*, according to their main allegations:

"Recommending MC is both premature & ill-advised"

On the contrary, there is overwhelming scientific evidence of the efficacy of MC for HIV prevention. Given the urgent need to confront the AIDS epidemic devastating some parts of Africa, and following recent disappointing results of many other prevention strategies [3–5], several ethical analyses have concluded that it is unethical not to offer heterosexual men at risk of exposure to HIV infection access to safe, voluntary circumcision services [6–8,101].

"Early termination of the randomized controlled trials"

All three of the randomized, controlled trials (RCTs) were terminated early by their independent data monitoring committees because the high level of efficacy (approximately 60%) in each of the three trials meant it was no longer ethical to deny circumcision services to the men in the control arms [2,6–13,101]. As Green *et al.* have suggested, large treatment effects resulting in trial termination may overestimate the true treatment effect. There are, however, a number of reasons why early termination of these RCTs is unlikely to have biased the trial results [13]. First, all three trials had conservative predetermined stopping rules that were met in each case. Second, the consistency of the results and the indication of a somewhat stronger effect of the intervention over time in two of the trials argue that, if anything, the early stopping may have underestimated the effect. Third, the risk of overestimating the treatment effect decreases when the number of events is at least approximately 200, which was the total number of events in the RCTs [14]. Finally, the observed effect in each of the MC trials was not larger than expected, but was virtually identical to that seen in many previous observational studies [2,13,15–17].

"The durations of the experiments were short"

Green *et al.* cite the Kenyan trial data from the 18–24-month period during which HIV risk was similar in the intervention and control arms [1]. By contrast, in the Ugandan trial, the impact became stronger over time, with a rate ratio of 0.25 (95% confidence interval [CI]: 0.05–0.94) in the 12–24-month period [11], and a similarly stronger effect over time was observed in the South African study [9,13,18]. Such subgroup analyses should be interpreted cautiously, however, since the trials were not powered to look at impact in subintervals. Biologically, there is no reason why the protective effect of foreskin removal would decline over time, and ecological data from Africa and south/southeast Asia support this, with countries in which MC is universally practiced, often very early in life, consistently having much lower HIV prevalence than countries where MC is uncommon [2,13,19–22,102,103]. Similar patterns are also seen within countries; for example, circumcised men in the Eastern Cape of South Africa were found to have 60% lower HIV prevalence than uncircumcised men in the same region [23].

"No long-term follow-up has been or can be done"

On the contrary, the Kenyan and Ugandan cohorts are being actively followed and data will be available for up to 5 years of follow-up. The Kenyan trial has now reported results extending to three and a half years of follow-up and found that the 59% protective effect of MC has been sustained and apparently increased to approximately 65% [104]. A recently published study from Kenya found no increase in reported risky behavior among the men randomized to MC [24]. Additionally, MC services are now being provided

more broadly in all three of the study communities, with knowledge, perceptions, behaviors and HIV infection rates being carefully studied.

"A large number of participants were lost to follow-up"

Each trial achieved over 90% of their expected study visits, and there is no evidence that those with incomplete follow-up had a different risk profile. Furthermore, those men who missed their last visits also contributed person-years to the analyses during follow-up [9–11,13].

"Many infections appear to be from nonsexual sources"

This theory has been thoroughly repudiated by the WHO and virtually all reputable scientists [25,26]. HIV infections among men reporting no sexual activity or 100% condom use were most likely due to under-reporting of sexual behavior, given that the vast majority of adult HIV infection in sub-Saharan Africa results from sexual transmission [25,26]. For example, the unreliability of self-reported sexual behavior was revealed in the Ugandan MC trial, in which 561 men reported never having had sex, and yet 49 (8.7%) of these individuals were seropositive for herpes simplex virus type 2, an infection that is transmitted nearly exclusively through sexual activity [Gray R, Pers. Comm.].

"Conflicting results from observational studies"

On the contrary, a systematic review and meta-analysis of 27 observational studies found strong and consistent evidence that circumcised men were at significantly reduced risk of HIV, and in 15 studies that adjusted for potentially confounding factors, the association was even stronger [15]. This result is consistent with numerous other observational studies [13,16,17,21,102,103]. It is important to note that, since MC status is often associated with particular patterns of behavior, results from observational studies should be adjusted for potential confounding factors.

Recent Demographic and Health Survey (DHS) data from some countries do not show higher HIV prevalence in uncircumcised men [1,27]. Although this appears puzzling, it is important to remember the limitations of this type of data for assessing associations. These include misclassification of self-reported MC status [28], distinct features of uncircumcised men (such as inhabiting very remote regions) in countries where MC is almost universal, the situation that in countries where MC is not traditionally practiced most men get circumcised for medical reasons (typically recurrent STIs) and so are at higher risk of becoming or already having become HIV infected [29], and lack of adjustment for other confounding factors. For example, after adjusting the 2003 DHS data for sexual behavior in Kenya, an 11-fold higher HIV prevalence in uncircumcised men became apparent [102]. And in some parts of Africa, Lesotho for example, 'circumcision' refers to having been culturally initiated in the traditional coming-of-age rituals, even though in most cases little if any foreskin removal actually occurs [105]. Ultimately, findings from RCTs are the accepted 'gold standard' of scientific evidence in public health, and thus they are more convincing than apparently conflicting observations from some cross-sectional studies including the DHS (in which other proven HIV co-factors, such as condom use, are similarly often not associated with HIV prevalence, due to confounding variables [30]).

"MC status is irrelevant after accounting for the number of HIV-infected sex workers"

This argument has no scientific credibility. The Talbott paper cited by Green *et al.* contains no data on MC itself, and has been categorically dismissed by the WHO [31] and systematically rebutted by 27 international HIV researchers [103,106–110].

"Lack of risk calculation"

Calculation of the HIV incidence per sexual exposure would rely on study participants accurately reporting the number of times they have been exposed. The validity of such self-reports is questionable, and the notion that the participants had 'not given fully informed consent' because they were not informed (at the beginning of the study) about the per-incidence risk of exposure, which can only be ascertained *post facto*, is incongruous.

"Other unconsidered factors"

Green *et al.* claim that men in the trials were provided incentives to participate, and thus the results cannot be generalized to the real world. Providing compensation for transport and other expenses is standard practice in all RCTs and does not invalidate the results [6,111]. MC is a voluntary procedure, performed with informed consent on men who desire it; thus the trial results, obtained under such conditions, are applicable to consenting men in similar high HIV-prevalence settings. That some men in both study arms (though much more so in the control arms) still became infected despite the 'repeatedly reinforced' counseling

messages, provision of condoms and free healthcare highlights the critical need for effective HIV prevention strategies such as MC in addition to promotion of behavior change [2–5,13,21,102,103].

"MC could lead to increased HIV transmission"

The Rakai, Uganda trial of MC in HIV-positive men that Green *et al.* cite in fact did not find a significantly increased risk of HIV transmission to their female partners (relative risk: 1.59; 95% CI: 0.7–4.3) [32]. Risk was highest among the female partners of circumcised men in couples who resumed sex before wound healing (27.8%), but was similar between the female partners of circumcised men who did not resume sex before wound healing (9.5%) and the partners of uncircumcised men (8.8%) [32]. We certainly share the concern of Green *et al.* about possible expansion of unsafe circumcision practices, and hence we strongly advocate adequate provision of safe medical MC practices in order to meet the growing demand in high HIV-prevalence regions of Africa [2,4,13,21].

"Risk compensation"

Although there was no evidence of a 'false sense of security' or 'risk compensation,' which may occur with virtually any public health intervention [33,112] during any of the MC trials [9–11,13,24] or in a recent Kenyan study of a 'real-world' community clinic setting [34], it is essential to develop communication strategies to ensure that clear and consistent messages are disseminated and that MC is promoted within the context of broader HIV prevention strategies [2,4,13,33,34,112,113].

"Complication rates"

Non-life-threatening and treatable complications (mainly excess bleeding and wound infection) were reported by fewer than 4% of trial participants in South Africa and Kenya, and among the over 5000 men circumcised in the three RCTs, no serious or permanent complications were reported [9–11,13]. Studies of neonatal MC in the USA and Israel report complication rates below 0.5%, consistent with the American Academy of Pediatrics Circumcision Policy Statement [35–38]. Very few complications have, moreover, been reported in the Middle East, North and West Africa, where MC is almost universal [105].

"Cost of MC"

It is not possible to compare directly the cost of condoms to the cost of MC. MC is a reliable once-off, permanent procedure and, unlike condoms, requires no ongoing user-adherence. One circumcision procedure is estimated to cost US$30–60 in Africa, and neonatal MC usually costs only about a third of this [39,40]. Various modeling studies show MC to be not only cost-effective but also cost-saving, at between US$100 and US$900 per infection averted in medium-to-high HIV prevalence settings, depending on a number of factors including the population HIV incidence and time horizon considered [39–42]. Furthermore, models predict that more rapid scale-up of MC would result in even higher cost-effectiveness [39,40].

"Unethical medical practice"

Neonatal and young boy circumcision is common in most African cultures (both Muslim and predominately Christian) [19,105] and was never an imposition of the West. On the contrary, historically MC was practiced in nearly all of Africa, and in many parts of southern Africa, such as Botswana, it was largely the influence of European missionaries – who deemed traditional initiation rites as 'pagan' – which led to the gradual abandonment of such rituals that included MC [2,112,114]. Over a dozen studies among previously noncircumcizing groups in nine sub-Saharan Africa countries have found MC to be widely acceptable [43,44,112]. As mentioned previously, several recent ethical analyses have concluded that it is unethical to deny safe MC services in high HIV-prevalence settings [6,101], and guidelines have been developed by WHO/UNAIDS and other organizations for implementation of safe, voluntary MC services [45,101,112,113].

"More effective prevention strategies available"

No other intervention against sexually transmitted HIV has been confirmed to be efficacious in multiple RCTs. More than 25 years into the global epidemic, additional HIV prevention strategies, such as MC, are urgently needed [3–5,112]. Modeling studies as well as real-world ecological data indicate that scale-up of MC in many regions of southern and east Africa is very likely to prevent millions of new HIV infections in African women as well as men [2,4,13,19–22,39–42,46,102,103].

"Male circumcision & HIV in the USA & Europe"

The main modes of HIV transmission in the USA have been, historically, sex between men and injecting drug use. MC obviously has no impact

on the latter and, although it probably offers some protective effect in men engaging in insertive anal sex, it will not directly protect men who practice receptive anal sex, which is the main route of infection in men who have sex with men. It is therefore not surprising that HIV rates are generally higher in the USA than in most European countries, despite higher MC rates in the former [47]. That said, it is noteworthy that the proportion of heterosexual transmission due to female-to-male (as opposed to male-to-female) infection appears to be far higher in Europe than in the USA, consistent with the influence of MC [47,48].

"Other important confounding factors exist"

RTCs are designed to control for confounding factors. The issue of generalizability is addressed by the fact that the three trials were conducted in different regions of Africa, in different settings (urban, rural and peri-urban), and among different age groups, yet resulted in remarkably consistent findings [13].

Conclusion

In summary, the proven efficacy of MC and its high cost-effectiveness in the face of a persistent heterosexual HIV epidemic argues overwhelmingly for its immediate and rapid adoption, especially in high HIV-prevalence settings. The benefits of MC are clear: it is a once-off, effective procedure that is unusually culturally acceptable and sought after in many parts of Africa [2,13,43,44,112]. In addition, MC provides a rare and important opportunity to access a hard-to-reach population – sexually active men at high risk of HIV exposure – with a potentially life-saving intervention combined with behavior change messages, HIV testing and counseling services, condom provision, STI screening and treatment, and links to reproductive health and other gender-related matters [27,34,112,113].

As more and more people in sub-Saharan Africa become needlessly infected with HIV, the time has come for urgent and decisive leadership, not circular and unscientific arguments about an intervention whose efficacy has been proven beyond a reasonable doubt [49,50]. As with other previously 'controversial' topics, such as the link between cigarette smoking and lung cancer (or more recently between carbon emissions and climate change), it is time to move beyond debating the merits of this evidence in professional journals and other legitimate communication outlets and to start implementing effective programs for safe, voluntary MC and reproductive health in high HIV-prevalence regions.

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