DEBATE

Voluntary male medical circumcision

Matthew Kesinger, Peter S Millard

The thoughtful editorial by Professor Ncayiyana concerning the national circumcision programme in South Africa[1] rests on two central arguments: first, that the scientific evidence is insufficient to justify such 'serious energy, money and resources', particularly when circumcision programmes have the potential of diverting money from other more effective interventions; and second, that risk compensation (the potential increase in risky behaviour after circumcision) may nullify any benefits of circumcision.

The scientific evidence

There are few medical or public health interventions that are based upon evidence as strong and consistent as that for the effectiveness of male circumcision in preventing female-to-male transmission of HIV. Ncayiyana reviews the cumulative evidence from early observational studies, and from the three landmark randomised controlled trials in Africa. He notes that the studies were stopped early. However, they were not stopped early by investigators; individual studies were stopped by their independent Data and Safety Monitoring Board because the evidence was strong enough to deem unethical the withholding of circumcision from the control group. All men were then offered circumcision and, as Ncayiyana points out, an opportunity for direct long-term follow-up was lost. However, not all was lost. Observational research continues to strengthen the experimental findings. For example, a community-based survey of the Orange Farm community was recently presented, which showed an increase in circumcision coverage from 15.6% in 2007 to 49.4% in 2010, with a concomitant HIV seroprevalence of 20% among uncircumcised men and 6.2% among circumcised men, and no correlation between circumcision status and sexual behaviour.[2]

Risk compensation – does it exist?

Ncayiyana argues that circumcision may increase risk compensation and therefore increase HIV transmission. The Orange Farm trial did indeed find a slight increase in risky behaviour in the circumcised men, but, in spite of this, there was a still 60% reduction in HIV transmission.[3] On the other hand, the Uganda trial 'did not find evidence that men in the intervention group adopted higher sexual risk behaviours than those in the control group. This could have been due to the intensive health education provided during the trial to minimise risk compensation.'[4]

The Kenyan trial found that 'the differences (of risk behaviour) between the two groups are attributable to increases in safer sexual practices in the control group rather than to riskier behaviour patterns in the circumcision group, indicating that risk compensation did not occur during the 24 months of this study'.[5] In fact, condom use went up in both groups and unprotected sex went down in both. This is probably a function of intensive counselling. Further studies in the Kenyan cohort and community show that risk compensation is not a necessary consequence and that circumcision can be used as an opportunity to educate men about HIV prevention.[6-8]

Most importantly in relation to South Africa, Ncayiyana cites a survey by Bridges *et al.* claiming that this study links demand for circumcision with the idea that a circumcised man no longer needs to use a condom.[9] But the results of this study are: 'Johannesburg, South Africa, shows that demand for circumcision is largely determined by the perceived benefits of reduced HIV/STI transmission risk, better hygiene and better sex … [O]ur analysis shows that – in the aggregate – condom avoidance is not perceived as a benefit of circumcision. Our findings suggest that moral hazard concerns related to risk compensation via condom avoidance associated with male circumcision are exaggerated.'[9]

Cost and impact of circumcision

Finally, Ncayiyana compares the HIV epidemic in South Africa with Australia and the USA, stating that Australia does not recommend universal circumcision, and that it therefore is not right for South Africa. There are very different drivers for the HIV epidemic in South Africa versus Australia, and comparing them is unwise. In Australia, for example, 100 cases of heterosexually transmitted HIV are diagnosed annually.[10] On the other hand, in South Africa about 1 400 new HIV infections occur per day, almost all via heterosexual transmission.[11] And despite the relatively high rate of heterosexual transmission (31%) in the USA, the seroprevalence rate is 0.4% and the major route of transmission is men who have sex with men,[12] which is certainly not the case in South Africa.

The high heterosexual transmission rate in South Africa means that the number of men who must be circumcised to prevent one HIV infection is much lower than in the USA or Australia. UNAIDS and the World Health Organization (WHO), using South African data and heterosexual transmission models, estimate that one new HIV infection can be avoided for every 5 to 15 circumcisions.[13] And this estimate takes into account possible risk compensation across the entire population.

Large-scale circumcision will consume resources, energy and time, but, as Hillary Clinton said, 'we all must step up our use of combination prevention'.[14] Because the impact of circumcision is so much greater in South Africa, scaling up circumcision is much more cost-effective compared with other countries. The cost savings in HIV prevention in high-prevalence areas is estimated at between US$150 and nearly $900 per infection prevented over a 10-year time horizon.[13] If 1 000 adult males were circumcised in South Africa's Gauteng province alone, $2.4 million could potentially be saved in HIV treatments over 20 years.[15] The money saved on treatment could be reinvested in testing, treatment, and prevention of vertical transmission – other methods of prevention that Ncayiyana points out have a proven impact.

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The medical proof doesn't get much better than VMMC

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The editorial[1] on voluntary medical male circumcision (VMMC) has many scientific inaccuracies and ignores the latest literature. Previous 'scientific' challenges on the VMMC evidence have had rebuttals co-signed by many local prevention scientists.[2,3] Ncayiyana does not acknowledge that despite the long presence of the prevention 'abstain, be faithful and condomise' (ABCs), the impact on HIV prevention progress has been slow, resulting in hundreds of thousands of mostly young South Africans dying. Substantially lowering incidence will only be achieved with the introduction and scale-up of new technologies.

To argue that VMMC has not been 'field tested' is inaccurate. The editorial's opening sentence quotes the 'real world' evidence. In Orange Farm, where many men were circumcised, a study demonstrated a 76% decrease in new HIV infections among those circumcised. Uganda reported a similar post-trial result (73%).[4] This builds on the observational evidence quoted in the editorial. It is unclear why neonatal VMMC is 'proscribed' in South Africa, as the editorial and many anti-VMMC groups claim; it occurs for cultural, religious and health reasons, and there is no law barring it. To ask for long-term evidence of the efficacy for HIV prevention of VMMC in neonates will take over 20 years to measure. It is biologically implausible that it would not have the same effect as in adults, and not implementing it would mean we do not protect the next generation of young men from a life-threatening illness. No similar evidence is requested for interventions such as hepatitis B or human papillomavirus vaccines.

Independent safety boards terminated the three VMMC efficacy studies, and not the researchers. Not to offer a proven (around 60% protective) intervention to the control group on stopping the studies violates clinical research ethics. Ncayiyana selectively quoted a statement by the Australian Federation of AIDS Organisations that 'correct and consistent condom use, not circumcision, is the most effective means of reducing female-to-male transmission, and vice-versa'. But there is no published evidence comparing the two interventions. Additionally, the organisation's (2007) statement later states that the epidemiology of HIV transmission completely differs between Australia and Africa, and its website stated in 2011 'Circumcision significantly reduces the rate of HIV acquisition (50 - 70%) in men with HIV-positive female partners.'[5] The 'scathing critique' of the MMC data by Van Howe and Storms referred to by Ncayiyana makes very little sense. They claim that 'Conservatively for the three trials, 89 of the 205 infections (43.1%) were sexually transmitted.' How were the other infections acquired? The choices would seem to be injection drug use or contact with blood and blood products. The evidence for the predominantly heterosexual transmission of HIV in sub-Saharan Africa is overwhelming. Furthermore, if the infections were not sexually transmitted, how would the condom use data discrepancy argued in the editorial as a weakness of the three studies then prevent them? The discussion on the various differential rates regarding VMMC and observed HIV prevalence in different South African communities relies on circumcision self-reports, which are unreliable when assessing culturally performed circumcision, in which the amount of foreskin removed varies. These observational studies are rendered irrelevant by good randomised control trial and follow-up community evidence.

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We found no reference to the assertion that black Americans have the highest rates of circumcision among American men, rather the opposite.[6] The argument that VMMC does not protect women from HIV is peculiar. Reducing the pool of HIV among men, in a predominantly heterosexual epidemic, will mean fewer men with HIV, who will expose fewer women. It also appears to reduce circulating HPV, and therefore likely to reduce cervical cancer rates,[7] as demonstrated in other communities where MMC is the norm. The risk disinhibition data from properly conducted studies does not suggest any additional risk taking.[8,9]

South Africa has some of the world's top HIV prevention scientists, and almost all of the biomedical breakthroughs in the field have either occurred in South Africa or included South Africans, including VMMC. The call for VMMC implementation came from South Africans after the Orange Farm study results were announced, was considered by the Department of Health (DoH), and was discussed extensively by all 19 sectors within the South African National AIDS Council (SANAC). The VMMC consensus involved prominent South Africans beyond the health sector, including Deputy President Motlanthe, who chairs the SANAC. Only after careful consideration of the science and the social and cultural issues around VMMC did the DoH and the SANAC decide to include VMMC in the 2012 - 2016 National Strategic Plan. This intervention is regarded as a game changer in South Africa's HIV prevention efforts and all provinces are prioritising efforts to accelerate access. The DOH has committed large budgets to VMMC rollout, and contrary to the editorial, is not kowtowing to donor agency agendas for support. Funding for VMMC from donors was requested from the South African government and granted, much like other support to ART and vaccine rollout. This national decision aligns with international recommendations from the WHO and UNAIDS.

No one argues that any one HIV prevention intervention will work alone, or that VMMC is 100% protective. Drivers of the HIV epidemic are complex and there is no 'one size fits all' prevention. However, the ABCs have proved insufficient in South Africa or elsewhere, in terms of reversing the HIV epidemic or addressing the complex drivers of HIV transmission. We need additional interventions to make an impact, using the combination prevention approach now adopted internationally and locally. Modelling studies strongly suggest increasingly striking implications of scaling-up of VMMC in averting millions of infections and deaths and saving billions of rands in the long run. Further delay will be a major failure to capitalise on scientific evidence to save lives and improve the quality of life of our population. Circumcision has an evidence base for efficacy, especially for protecting men, rivalling the best proved interventions in medicine. Its implementation will be complex, challenging and costly, but it works, and is needed as part of our prevention toolbox.

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Voluntary male medical circumcision – Dan Ncayiyana responds

I thank the above authors, all acknowledged HIV/AIDS experts, for their robust responses. South Africa and the SA HIV/AIDS research community have indeed been at the forefront of the global effort to better understand and to contain the HIV/AIDS epidemic, and there is no gainsaying the motive of the VMMA proponents to control and ultimately to eradicate the disease. That said, the envisaged mass roll-out of a surgically invasive prophylactic intervention is without historical parallel, and it is only appropriate that the VMMC project is deliberated within the medical profession beyond the immediate circles of the panels and committees driving the initiative.

The significance of the evidence from the three African randomised controlled trials (RCTs) is not at issue. However, this evidence seems to have acquired considerable interpretation creep along the way, with inferences of 'lifelong protection', and of benefits of neonatal circumcision that are not self-evident from the RCTs. Clark *et al.* boldly assert in respect of sub-Saharan Africa that '*Mandating* [my emphasis] neonatal male circumcision is an effective therapy that has minimal risks, is cost efficient and will save human lives. Neonatal male circumcision is medically necessary and ethically imperative'.[1] There is no good evidence to back this up. Based on their interpretation of the Children's Act 38 of 2005, paediatric surgeon and ethicist Sidler and colleagues[2] hold the view that 'infant non-therapeutic circumcision in South Africa (is) illegal, making the discussion of forced infant circumcision moot'.

The debate is about what the evidence means and what its role should be in the greater HIV prevention strategy. UCT's Myers and Myers have cautioned that 'given the epidemiological uncertainties, and the cultural, ethical and logistical barriers, it seems neither justified nor practicable to roll out male circumcision as a mass anti-HIV/AIDS intervention'.[3] Pointing to the long history of circumcision as an intervention in search of a malady, they remind us that 'Superficially convincing justifications for this surgery have abounded since the mid-19th century'[4] to prevent masturbation, insanity, idiocy, epilepsy, TB, STIs, cervical cancer, and penile cancer. Certainly, circumcision should be readily accessible to individuals who, forearmed with full information on the potential benefits, the caveats and the unknowns, make a personal choice to be circumcised.

To argue that 'despite the long presence of the ABCs, HIV

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prevention has been slow' is not fair comment. It is counterintuitive to believe that VMMC will fare any better, or that men will be any more amenable to having their foreskin excised than they are to wearing a condom. On the contrary, VMMC is likely to meet with ever-increasing resistance, not least because of deeply rooted cultural attitudes,[5] much as this dimension has tended to be underplayed in the VMMC euphoria. More importantly, it is worth recalling that until fairly recently, the ABC message has struggled to be heard in the face of AIDS denialism, with the TAC fighting running battles with the political establishment, doctors in the public service getting punished for promoting orthodox HIV practices, and Dr Matthias Rath peddling miracle AIDS cures under the protection of top government officials. That the HIV incidence has shown signs of abatement at all is evidence of the staying power of the ABC strategy.

My concern about offshore funding (and much of the advocacy) driving VMMC is not off the wall. Venter was quoted in the *NEJM* [6] as expressing similar sentiments that 'Currently all of the funding is coming from Western nations … and this makes people suspicious.' This remains the case in most southern African countries beyond our borders. I remain sceptical that VMMC has been sufficiently field-tested to validate a mass VMMC campaign, or that the goal to circumcise millions of men in our region in 5 years is even achievable. Without detracting from the imperative to pursue a multi-pronged prevention strategy, I believe that the proven, simpler and more affordable approaches of the ABCs, VCT and ARTs should remain the primary prevention strategy in our region.

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