

Circumcision and HIV prevention research: an ethical analysis

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A large, randomised controlled trial in 3274 men between the ages of 18 and 24 years showed that circumcision resulted in a significant 60% reduction in HIV infection.¹ If these results were to be confirmed by two continuing (unpublished) trials, there would be grounds to advocate circumcision as a public health intervention in high prevalence areas.

Several ethical issues arose in relation to this trial, such as the decision not to disclose participants' HIV status to them during the trial, the decision to pay participants, and early termination at the request of the trial's monitoring board.^{2–4} We address the ethical implications for future HIV prevention research, both for biological interventions, such as vaccine and microbicide trials, and for behavioural interventions, such as counselling. First, is there an ethical obligation to provide all male participants in future trials of HIV vaccines and other preventive methods with circumcision (as well as counselling and access to condoms)? Second, should future prevention trials select or stratify participants by circumcision status? Third, should the design of such trials be altered in light of the established effectiveness of circumcision—eg, by requiring circumcision for the control groups?

Ethical obligation to provide circumcision

The general view is that there is an obligation to provide participants in HIV preventive trials with access to proven, preventive measures, such as behavioural counselling and condoms. For instance, according to the UNAIDS guidance document on HIV vaccine research: “Reducing the risk of HIV infection throughout the trial among participants is an essential ethical component of HIV preventive vaccine trials. All trial participants should receive comprehensive counseling concerning methods of decreasing the risk of transmission of HIV. This should include the basic principles of safe sexual practice and safe use of injection equipment, as well as education concerning general health and treatment of sexually transmitted infections (STIs). Investigators should provide trial participants appropriate access to condoms, sterile injecting equipment (where legal) and treatment for other STIs.”⁵

This guideline distinguishes obligations for counselling from those related to condoms. Researchers must actively provide counselling, but need only provide appropriate access to condoms. Although the obligation to provide access to condoms is weaker than requiring provision of condoms to trial participants, investigators need to ensure that condoms are available at or near the trial site, and there should be no economic or other barriers to their acquisition by trial participants.

If circumcision proves an effective HIV prevention method, and mass circumcision programmes are adopted as a public health intervention, there could be an analogous obligation for researchers to ensure that people enrolled in HIV prevention research trials are provided with circumcision as part of the trial design. Alternatively, researchers could be obliged to ensure appropriate access to circumcision by removing financial and other barriers. Or, it might be sufficient for researchers to inform the participants about the importance of circumcision for HIV prevention.

The justification for provision of counselling and condoms in HIV vaccine and preventive trials should help to address this issue. The standard obligation seems to be to remove barriers to access to effective methods of prevention, but not necessarily to ensure that they are used. Consistent use of condoms is an effective method for prevention of sexual transmission of HIV,⁶ but investigators are required to promote this practice, rather than to force people to use condoms. Impeding access, or not doing enough to remove barriers to access, would be morally questionable. But individuals will ultimately decide for themselves whether or not to use condoms.

By contrast, counselling has an unknown effect on the transmission of HIV infections. Although some studies indicate that counselling reduces risk behaviour,⁷ others caution that this effect is not consistent, and may be only temporary.⁸ If the sole rationale for provision of a preventive method to trial participants was its proven effectiveness in the reduction of HIV transmission, there would be little justification for making counselling an ethical requirement in HIV preventive research. So why is there nevertheless a widely accepted ethical requirement to provide counselling? The obligation seems to derive not from the method's proven effectiveness, but from the principle of informed consent and the disclosure of relevant information as part of this process. Risk reduction counselling is part of the obligation to provide information about risk behaviour, rather than an attempt to implement a behavioural intervention with a known or quantifiable reduction in risk of HIV infection. As with condoms, it is left to the participants to decide whether to act on this information.

The ethical requirements to provide counselling and condoms as part of HIV preventive trials, therefore, are based on the general requirements (1) to provide relevant information to participants in clinical trials, (2) not to impede or place any barriers on access to known preventive methods, and (3) to actively promote the use

of known preventive methods. There seems to be no ethical obligation to ensure that participants make effective use of known protective methods, although one would probably want to attempt to ascertain the usage of preventive methods as part of the design of preventive trials. According to these general requirements, researchers would be obliged (1) to inform trial participants of the known effectiveness of circumcision in reducing HIV transmission, (2) not to impede or discourage participants in the trial from becoming circumcised, and (3) to actively promote circumcision as part of the counselling process.

Is there a stronger ethical obligation to actively provide circumcision as part of the trial design? Researchers might, for example, be expected to designate a place where participants in trials could be circumcised if they wished, and to pay for this procedure as part of the clinical trial costs, if it was not paid for by the public health care system or by a participant's regular health insurance. What possible justification could there be for an obligation not only to provide information, reduce access barriers, and promote circumcision, but also to ensure that trial participants are provided with the procedure?

First, an obligation to provide circumcision could be justified on the basis that participation in an HIV preventive trial might lead participants to feel less inhibited about engaging in risky sexual behaviour. In this case, the general obligation to keep risks in a trial to a minimum dictates that preventive measures to counterbalance this increased risk of infection should be provided. On the basis of this argument, any preventive measures, such as condom use, counselling, and circumcision could all be required with the aim of reducing the risk of infection caused by disinhibition. However, this is a weak justification, because currently, there is very little evidence for such disinhibition among participants in HIV prevention trials. (The randomised controlled circumcision trial did, however, report a higher degree of risk behaviour in the circumcision group.) Even so, providing information and counselling about circumcision and reducing any barriers to access might be sufficient to counter any potential disinhibition behaviour associated with participation in the trial.

Second, there is an argument of gratitude to trial participants, or justice as reciprocity. In this case, the obligation arises because trials of methods for HIV prevention contribute to social benefits, such as the development of improved methods of HIV prevention, participants should be rewarded by the provision of a preventive intervention.⁹ This justification would require researchers to evaluate the overall risks and benefits of taking part in the trial, and to show that fair compensation for participation would include one or more of these preventive interventions. But is the provision of preventive measures as part of the trial the most appropriate way to express gratitude?

Third, there is a moral justification for the provision of circumcision to trial participants, based on the fundamental ethical requirement for any person to do what they can to help others in need. The obligation to provide preventive measures as part of a trial would then depend on the proven effectiveness of the intervention, and the justification would be in terms of acceptable or reasonable costs in relation to the magnitude of benefits one could expect. If we assume that circumcision is as effective as it seems from this randomised controlled trial, and that it is an economical intervention, then there may be an obligation for researchers to promote it, and perhaps even to ensure access as part of the trial costs. However, in this case there could also be an even stronger moral obligation on responsible health authorities to ensure access to such interventions as part of the health care system. Consequently, this so-called Good Samaritan argument (ie, the requirement to prevent avoidable harm), would only oblige researchers to provide information, to remove any access barriers, and to actively encourage participants to access what should be available in the country's health care system. (The issue of researchers' obligations when cheap and effective interventions are not provided by a country's health care system is beyond the scope of this report.^{10,11})

Finally, if circumcision were to be proven sufficiently beneficial to be recommended as a standard intervention, would there be an associated obligation to provide it to research participants? In assessing the effectiveness of a new drug, researchers are required to provide the standard therapy to research participants, including the control group, on the basis that they should be provided with any interventions and drugs that they are otherwise entitled to. But if, for whatever reasons, circumcision does not become widely adopted within a population, then it cannot be classed as a standard intervention. In addition, the provision of circumcision to participants in an HIV prevention trial could reduce the relevance of the results for the wider population. Therefore, although research sponsors could be commended if they decided to provide circumcision to trial participants, there is no clear justification for making circumcision an ethical requirement for HIV prevention trials.

Circumcision as an eligibility criterion

Even if researchers do not have special ethical obligations to actively provide circumcision, should they stipulate circumcision as an eligibility criterion for men enrolled in trials for HIV vaccines or other preventive methods? The most appropriate policy option will depend on the prevailing circumcision practices in a particular society.

If a substantial proportion of the male population becomes circumcised, then an appropriate trial design for prevention measures, including vaccines, would be to test these additional measures on circumcised men, by making circumcision an inclusion criterion for male

trial participants. This trial design will produce results applicable to the specific population of circumcised men.

However, circumcision is controversial in some populations because of complex traditional, religious, and cultural beliefs. If a substantial proportion of the male population chooses not to become circumcised, despite the availability of—or removal of barriers to—circumcision, then circumcision should not be used as a criterion for inclusion or exclusion of trial participants. This type of HIV prevention trial, including a placebo control arm, would be better able to show whether any new preventive measures would be applicable to uncircumcised men in the population.

In populations in which circumcision is adopted haphazardly, investigators might have to stratify participants on the basis of circumcision status. This raises other challenges. Stratification would reduce the power of preventive trials, and would mean an increase in the number of participants in future trials of HIV vaccines and other preventive methods, which, in turn, would raise costs. With the limited funding for such research, additional cost might decrease the number of preventive methods that could be tested.

Circumcision in the control arm

An important question is, should circumcision be used as a comparator in future HIV prevention trials? The justification for provision of circumcision as a standard intervention could be interpreted to mean that the control group in an HIV vaccine or other preventive trial should be provided with circumcision instead of a placebo. According to the Declaration of Helsinki, any new intervention should be tested against existing effective interventions, and not against placebo.

If a trial of an HIV vaccine showed a 60% reduction in transmission, the general understanding is that there would be an obligation to test any new vaccine candidates against this first generation vaccine. Drug trials do not always include a placebo as a control. For instance, when the acellular pertussis vaccine trials were proposed, a placebo design was rejected in the USA, because of the existence of a proven, effective, though still unsatisfactory, whole-cell pertussis vaccination programme, although placebo-controlled trials have been done in Sweden.¹² Similarly, coronary artery bypass surgery for angina pectoris was tested against drug treatment, without any placebo group.¹³ Certainly, the identification of a vaccine with a 60% protective effect would justify its widespread use as a public health measure. However, such recommendations are not always followed. Historically, the target populations for such interventions—young adults—have a poor uptake of vaccines, and adult vaccination programmes, such as vaccination against hepatitis B for high risk groups, have not been very successful.¹⁴ Nevertheless, any new HIV vaccine candidate would probably be tested against a first-

generation vaccine with a proven 60% effectiveness, unless the existing vaccine was unacceptable for other reasons such as high cost or side-effects. Why? Any new vaccine would have to show a higher protective effect or reduced disadvantages to be socially valuable. Consequently, the appropriate trial design is a comparison between the existing vaccine and a new candidate vaccine. An additional ethical argument is that researchers could not deny the control group an existing vaccine that is known to be effective.

However, HIV vaccines differ from circumcision in relevant ways. The social and cultural reasons for not undergoing circumcision are likely to be different from the reasons for not being vaccinated, and each prevention strategy might be preferable to men within some segments of the population. Where there is a low uptake of circumcision for social or cultural reasons, there could still be value in recommending a vaccine with a lower protective effect than the 60% reduction in infection after circumcision. Low or haphazard adoption of circumcision within the trial population would add to both the scientific and ethical justifications for including a placebo group in any trial in that population, and it would not be difficult to recruit uncircumcised men to participate in the trial. In this case, the most relevant, scientifically and socially valuable question is to test whether the candidate vaccine is better than current practice—ie, no circumcision. However, this justification does not address the UNAIDS guidance document recommendation that currently accepted preventive strategies should be added to the interventions tested in the trial, and should be made available to both the control and intervention groups.

In conclusion, until an effective HIV vaccine candidate has been identified, future HIV vaccine candidates can still ethically be tested against a placebo, despite the proven 60% reduction of HIV infection in circumcised men. The design of such vaccine trials should be tailored to generate knowledge relevant to the population, including women and uncircumcised men.

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