Ethical Issues related to the Orange Farm Study

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Author: Prof Keymanthri Moodley
Position: -
Institution: Bioethics Unit-Tygerberg Division, Faculty of Health Sciences and Centre for Applied Ethics University of Stellenbosch South Africa
E-mail: KM@sun.ac.za
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The role of circumcision in protecting against the acquisition of HIV infection has been documented in a number of observational studies [1-7]. However, the quality of these studies is questionable [8], and many have been inconclusive. Hence a causal relationship between circumcision and HIV prevention has not been established to date on the basis of existing data. The first experimental study designed to establish a firm causal relationship between circumcision and HIV prevention was conducted in a semi-urban area near Johannesburg, South Africa, from July 2002 to February 2004 [9]. The authors randomized 3274 heterosexual men, 1617 of whom were medically circumcised at the beginning of the trial. The control group comprised 1657 men who were uncircumcised. Three follow-up visits were scheduled at 3, 12, and 21 months. The men were tested for HIV at the start of the trial and at all follow-up visits, but both participants and investigators were blinded to the results at the trial site. Participants were, however, offered the opportunity of establishing their HIV status on a voluntary basis. After the 12-month clinic visit, an interim data analysis indicated that 20 of the HIV-negative men in the intervention group had seroconverted while 49 men in the control group had become HIV positive. This corresponded with a relative risk reduction of 0.40. Hence, circumcision reduced the risk of acquiring HIV infection by 60%.

Circumcision of healthy individuals (neonates, children or adults) where healthy normal erectile tissue is surgically removed is itself ethically debatable [10-14]. The arguments for and against circumcision are set within the framework of collective cultural rights as opposed to individual rights. Circumcision has been rationalized within the Western individualistic tradition on medical grounds and in other contexts on religious or cultural grounds. Subjecting neonates and children to circumcision is viewed as a violation of the rights of children especially where measures to prevent pain are not used. In this regard, the harm principle is frequently invoked. Where adults are concerned, arguments revolve around protection of individual autonomy versus protection of cultural identity. In this trial, the procedure was conducted on adult males with assumed fully informed and voluntary consent under hygienic and standardized conditions [9]. Based on this assumption, the wider ethical debate on circumcision in general falls beyond the scope of this paper and will not be discussed further in relation to this study.

The ethical issues that will be discussed in this paper revolve around the inclusion of HIV-positive men in the trial and the associated non-disclosure of HIV status to trial participants by investigators. The blinding of investigators to the HIV status of trial participants also raises a number of ethical concerns. The role of the Research Ethics Committees (RECs) that approved this study will be explored. Finally, the controversy related to publication of this article will be examined.

As a point of departure, however, there are two important considerations that form a backdrop to any discussion on the ethics of this trial. Firstly, sub-Saharan Africa faces an unparalleled loss of life and human suffering as a result of the HIV/AIDS epidemic in this region, and scientists, researchers, clinicians, REC members and sponsors are equally committed to alleviating this suffering as a matter of urgency. Secondly, the medical profession is under increasing pressure to practice evidence-based medicine (EBM) based on randomized controlled trials as opposed to observational research [15]. Given these considerations, it is with great caution that one examines the ethical issues of this particular trial.

The crux of the ethical debate in this study centres around the inclusion of HIV-positive participants in the study coupled with non-disclosure of HIV status to participants and blinding of investigators to the HIV status of participants. Upon termination of the study, it emerged that 146 HIV-positive participants had been randomized on commencement of the study. A further 69 men had seroconverted during the course of the study (20 in the circumcision group and 49 in the control group). The investigators were hence blinded to the HIV-positive status of 215 participants over an 18-month period [9]. In defence of the investigators, all participants were offered voluntary counseling and testing (VCT) at the study centre or at a VCT clinic located 200m from the trial site. This was, however, not indicated in the patient information leaflet of the study. The information may have been communicated verbally to participants.

The investigators argued that the decision regarding non-disclosure of HIV status to participants or themselves was based on the premise that they did not want to make HIV testing compulsory. They also did not want to discriminate against men who may not have wanted to know their HIV status. Ultimately, HIV-positive participants were not excluded during screening to protect them from stigmatisation. A counterargument would hold that participants could have been protected from stigmatisation if there had been a list of exclusion criteria and if it were made clear to trial participants that men could be excluded from the trial for a number of different reasons as is the case in most other clinical trials. The investigators further justified inclusion of HIV-positive participants in the study, based on their belief that circumcision would confer benefit on HIV-positive participants in terms of protection against other sexually transmitted diseases (STDs) like syphilis. Furthermore, it was felt that HIV-positive participants could benefit from preventive counseling that was part of the design of the circumcision study. A counter argument would hold that protection from other STDs could have been achieved by counseling, condoms and hygiene education. This could have been made available outside the confines of the trial.

If we assume that most or all participants did voluntarily consult the clinics and accessed care, surveillance, counseling and treatment when indicated, the arguments for including HIV-positive participants in the trial may appear to be satisfactory. On the other hand, if most participants did not access these alternative VCT centres, they would have remained undiagnosed and untreated for 18 months. In addition their partners would have unknowingly been exposed.

If this had been the case, we may argue that investigators failed the test of beneficence [8] in respect of HIV-positive participants.

A number of arguments could be raised against inclusion of HIV-positive participants in this trial. Firstly, a precedent has already been set by other HIV prevention studies in SA, namely, HIV vaccine trials and microbicide trials -- where only HIV-negative participants are enrolled and HIV-positive participants are excluded without concern about stigmatization. If we are to draw an analogy between HIV vaccine and microbicide trials and this circumcision trial we

need to establish whether they are all comparable. Clearly all three types of trial need to enroll HIV-negative participants. Even though this circumcision trial enrolled HIV-positive participants the results reflect the findings amongst HIV-negative participants only. While HIV vaccines and microbicides would offer no benefit to HIV-positive participants, there is a weak argument that circumcision offers protection against other STDs. Finally, all three types of prevention trials result in a proportion of participants seroconverting.

In SA, treatment of HIV seroconvertors in the course of HIV vaccine and microbicide trials has raised considerable debate [16]. The ethical dilemmas inherent in the provision of care to these participants centre around the moral responsibility of sponsors and investigators to provide care to such volunteers. This moral responsibility is two-fold. Firstly there is the responsibility to patients who are screened out of the vaccine trial as a result of their being HIV positive and secondly, there is the responsibility of sponsors to participants who seroconvert during the trial.

According to guideline 23 of the draft revision of the 1993 CIOMS document [17]:

"When necessary for the conduct of the research, sponsors should provide facilities and personnel to make health care services available to the population from which research subjects are recruited."
Commentary on guideline 23 states that "although sponsors are not obliged to provide health-care facilities or personnel beyond that which is necessary for the conduct of the research, to do so is morally praiseworthy".

By extrapolation, it would seem plausible to assume that the sponsor has no responsibility to those HIV-positive volunteers identified during the screening process. However, the commentary continues to add that volunteers who are "rejected as research subjects because they do not meet health criteria for admission to the investigation" -- as would be the case with HIV-positive volunteers who are screened out of trials -- sponsors and investigators should refer such subjects to health care services. The commentary also indicates that sponsors and investigators should refer those "subjects or prospective subjects who are found to have diseases unrelated to the research". Hence it is imperative to ensure that a robust referral system is in place in the community before research commences.

Falling short of stating a moral obligation on sponsors to provide care for HIV-positive volunteers, Guidance point 16 of the UNAIDS document [18] indicates that "Sponsors need to ensure care and treatment for participants who become HIV-infected during the course of the trial". While there is no consensus on the standard of care that should be offered, a comprehensive care package is referred to and Guideline 16 suggests the provision of the best proven standard of care as an ideal but the provision of the highest attainable standard of care in the host country as a minimum.

Hence the options relating to responsibility for treatment and care of HIV seroconvertors on prevention trials may range from no obligation as this is only regarded as morally praiseworthy to a definite obligation based on the possibility of risk behaviour increasing on prevention trials. While this was not demonstrated in the phase 3 HIV vaccine trials, in this circumcision trial increased sexual activity was noted in the circumcised group [9,19].

In South Africa, research and care are integrally linked and often conducted at the same sites due to resource constraints. As such, it is impossible to conduct research without making provision for care whether this is care for illnesses related to the research study itself or other morbidity. It is therefore problematic that researchers on this trial were blinded to the HIV

status of their patients for 18 months. This implies that patients were undiagnosed for 18 months, did not receive treatment or prophylaxis for opportunistic infections and CD4 surveillance was omitted. When antiretroviral treatment became available at HIV clinics in SA in 2004, while the study was still in progress, these trial participants were not able to access such treatment either because they remained undiagnosed or because lack of CD4 surveillance did not allow investigators to refer patients when indicated.

When scientific journals are faced with an ethically challenging study, they have three options: decline publication of the study, ask authors for clarification and review the decision to publish or publish the study with an editorial and invite commentary. The ethical complexity of the Orange Farm study became apparent when the Lancet declined publication [19]. The Wall Street Journal indicated that the Lancet had rejected the study for reasons "unrelated to the data and scientific content" of the paper [19]. According to the principal investigator and primary author of the paper, this was largely due to the inclusion of HIV-positive participants in the trial with the associated implications for lack of treatment (personal communication). On the other hand, PLoS Medicine, after a thorough peer review process, decided to publish this article. One of the reasons for publication was related to the fact that two RECs (one South African and one French) had approved the ethics of the study [20]. This is a powerful statement and highlights the crucial role played by RECs in the clinical trial approval process. RECs are charged with the responsibility of human participant protection. This requires a thorough review of both the science and the ethics of a proposed research project. The protocol for this circumcision study was approved by the South African REC (the REC of the University of Witwatersrand) in February 2002. In the same year, the protocol for the first phase 1 HIV Vaccine Trial was submitted to the same REC and approval was granted. By September of 2002, it emerged that the sponsors of the HIV vaccine trial were not going to provide treatment for HIV seroconvertors on the trial. REC approval was subsequently withdrawn indicating the importance that the REC had attributed to participants who seroconvert on trials. When resolution was reached on provision of care to HIV seroconvertors, the REC again approved the studies. Given the emphasis placed on the care of HIV seroconvertors in the HIV vaccine trials, it is difficult to understand why the Wits REC seemed to be less concerned about the care of HIV seroconvertors on the circumcision trial during the planned 21-month duration of the trial. The chair of the South African REC that approved the study has indicated four important reasons [21] for the approval. Central amongst these reasons is the view that the trial held much potential for a scientific breakthrough in stemming the HIV pandemic. While this is indeed an important consideration for any REC, it is also reasonable to expect a degree of consistency at the REC level in treating all HIV prevention trials on an equal footing from an ethical perspective. Stigmatization is an important consideration where HIV/AIDs is concerned in South Africa. However, stigmatization may occur in any HIV prevention trial in which HIV-positive people are excluded. Regarding the French REC, an important question that needs to be considered is whether this study would have been approved if it were to be conducted in France? Finally, should scientific journals look beyond ethics committee approval when faced with an ethically complex study and consult with a panel of experts -- including bioethicists -- on the topic?

In conclusion, The Orange Farm study is scientifically and statistically robust but ethically concerning. The trial was approved by 2 RECs and published by PLoS Medicine, most likely based on its scientific strength as well as the importance and urgency of finding interventions to ameliorate the HIV pandemic. Perhaps the same scientific results would have been achieved with fewer ethical concerns if the investigators had simply included only HIV-negative participants as is the case with microbicide and HIV vaccine trials. Was this simply a case of the investigators trying too hard to be ethically correct in their attempts to prevent

stigmatisation? Was this simply a case of unintended harm as a result of the investigators intentions to do good? Should the investigators have been punished by refusal of publication by the Lancet? Have the RECs involved escaped too lightly? Clearly, this landmark trial has raised many ethical questions and has emphasized the importance of conducting research that is both scientifically and ethically robust.

Note: This paper is based on a presentation that I made at a symposium hosted by Dr Daniel Sidler on HIV and Circumcision at the Faculty of Health Sciences, University of Stellenbosch, South Africa on 24 November 2005.

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Competing interests declared: I have no conflict of interest to declare. I work as a clinical investigator - on vaccine trials (not circumcision or HIV vaccines), am a family physician and bioethicist, a GCP Trainer and am Vice-Chair of the Committee for Pharmaceutical Trials, University of Stellenbosch.