Research ethics and HIV clinical trials

Abstract
Investigations into the medical, epidemiological and social aspects of HIV give rise to difficult questions in research ethics. The number and location of many people affected with HIV, combined with a lack of access to basic health care and stigma associated with the disease have caused significant controversies, particularly for international collaborations. This article briefly surveys some of the significant ethical issues arising from biomedical research into HIV and highlights the regulatory mechanisms in place which aim to balance complex and conflicting rights and interests in this difficult field of research.

Acknowledgements
The author thanks Richard Ashcroft, Linda McDonald and Anna Smajdor for valuable discussions when drafting this paper.

Introduction
As the HIV pandemic enters its third decade, with over 38 million people infected, the demand for a treatment or preventive vaccine is acute. The virus has now spread to every region of the world and rates of new infections are still rising dramatically in sub-Saharan Africa, Eastern Europe and Asia. Over 20 million people have died of AIDS since 1981[1].

The effectiveness of any putative treatment or preventive measure against HIV must, of course, be proven through research. To date, research in communities living with or at-risk of HIV infection has enabled much to be learned about preventing the spread of the virus and maximising quality of life for those already infected. Antiretroviral medications have provided a major breakthrough, although they remain available to only a fraction of those who require them.

Investigations into treatments for HIV raise a broad range of issues. Drawing on the broad themes of standards of care and appropriate community tailoring, this article reviews the significant moral problems arising from biomedical research into HIV and presents some suggestions for the conduct of ethical research.

Research Ethics and HIV

Biomedical research on HIV focuses on many different aspects of the virus, including potential vaccines[2], the use of microbicides to prevent infection[3], prevention of maternal-foetal transmission[4,5] and the preventive significance of male circumcision[6]. Undertaking this research is not, however, an easy task[7,8].
HIV research is subject to several ‘macro’ considerations. Grady, for example, highlights the issue of when to move to a large-scale efficacy trial, in light of the distinct scientific uncertainty associated with HIV but also the public health justification for a vaccine. She also cites the potential for social (as opposed to physiological) harm through research participation and the importance of not forgetting about behavioural interventions which can prevent HIV infection in the first place[9]. Schüklenk and Hogan discuss the issue of non-compliance by research participants and the balancing of paternalism with autonomy required to solve the problem[10]. Complexity is also introduced by the nature of HIV trials, often large in scale in international in coverage, highlighting disparities in wealth, power and infrastructure between researchers and participants.

From a ‘micro’ ethical perspective, if a research proposal is to be reviewed by a UK NHS Research Ethics Committee, several aspects of the study should be examined before approval is granted[11]. These include the scientific design of the study, recruitment of participants, obtaining informed consent, care and protection of participants, ensuring participants’ confidentiality and issues relevant to the participants’ community.

Several policy documents and guidelines guide researchers who work in the field of HIV clinical trials. These include comprehensive guidelines produced by UNAIDS[12], the Council for International Organisations of Medical Sciences[13] and The World Medical Association [14].

**Significant controversies in HIV research**

Between these ‘macro’ and ‘micro’ issues lies a complex and interwoven web of ethical conundrums, particularly affecting research in developing countries. These various problems can be grouped into two classes: (1) ensuring acceptable standards of care for research participants; and (2) tailoring research to meet the local needs of the community where it is being done[15].

**Ensuring acceptable standards of care for research participants**

Determining how participants in a research study should be treated is fundamental to the acceptability of any project. Two aspects of HIV research have caused particular problems: the use of placebo-controlled trials and continuance of care after a trial has ended.

In the late 1990’s, controversy arose over the use of placebos in research trials. In many of the countries where HIV research is done, health-care for people with the virus is virtually non-existent. Questions therefore arose as to whether it was acceptable for control participants to receive a placebo medication when an effective treatment already existed, but which was unavailable or unaffordable in the research region [8, 16].

On the one hand, using placebos may lead to an ethical double-standard in which trial participants in the developing world are exploited through not receiving the same level of care as those in the West. However, this disparity may be justified by recourse to the general disparities in the global allocation of health care, which is not something HIV research can overcome[15, 17].

In 2000, the World Medical Association (WMA) appeared to take the former view. When reformulating the *Declaration of Helsinki*, Article 29 was added, requiring that any new method
should be tested against the best available treatment, suggesting it was acceptable to undertake a placebo-controlled trial only when there was genuine uncertainty in the community about what constituted the preferred treatment[14]. But in the context of the developing world, what constitutes the best treatment?

In 2002, the WMA added a note of clarification to Article 29. This states a placebo-controlled trial may be ethically acceptable even if there is a proven therapy, if there are compelling and scientifically sound reasons why the use of a placebo is necessary to determine the safety or efficacy of a new therapeutic[14]. This recognises that were it not for the permissibility of placebo-controlled trials, prospective research participants in the developing world may be denied access to research. However, argument on this issue is far from resolved.

The conduct of HIV research in the developing world has also attracted criticism as to the standards of treatment provided to trial participants after a research project has ended[15, 18, 19]. While an intervention may be successful during a trial (to the great benefit of all who received it) resource constraints often prevent the intervention remaining available after the trial has ended, leaving participants with no continuance of care.

This outcome seems to breach the goal that all research projects must aim to improve the health of the population in which they are being carried out[20]. It may also undermine the process of informed consent, particularly given the vulnerability and desperation of many potential participants[19]. As an alternative, good-faith arrangements need to be established at the start of a research project, including provisions for ongoing clinical care after the project ends; albeit recognising the fact that this process is not always straightforward and will be subject to political intervention[8]. In the very least, however, it seems reasonable to claim that any successful trial should be used in advocacy for introducing the treatment widely; and researchers should not simply ‘abandon’ their study populations at the end of a project.

**Tailoring research to meet the local needs of the community**

Given that the majority of HIV infections occur in developing countries, it makes sense to undertake a research with these populations. However, it is important to avoid merely imparting Western research practices and principles to these groups. Instead, it is vital to tailor the research design to the specific needs of the target community.

The first point to consider is informed consent; and here it is important to account for the cultural context of a study population. Statements to participants which may seem straightforward in the West may have very different connotations in the developing world. For example, framing a diagnostic HIV test as a ‘benefit’ of research participation may mislead vulnerable groups. Further, for many potential research participants, access to a trial may be the only way to obtain any kind of health care, which could induce participation. Additionally, local understanding on the part of the research team is vital, to ensure consent mechanisms account for and respect local knowledge, beliefs and customs[8,18].

A related issue is the potential for research participants to conflate the research context with clinical care, or something else entirely. If certain benefits are only available to trial participants, they could enter the trial under the therapeutic misconception that they will receive individually tailored care[8, 18]. This issue is not confined to the developing world – some participants in London-based HIV research projects, for example, are asylum seekers. A
number of this group erroneously believe that participating in a research trial may help their application for asylum[21]. All trial participants should therefore be made explicitly aware that they are not receiving free health care or other non-research related benefits.

Further issues arise in the context of vaccine trials. The nature of these trials is such that healthy volunteers (often women) are required. There is a danger that, without appropriate and full explanation, trial participants or their partners may harbour a false sense of security about reduced susceptibility to HIV infection[18]. By misinterpreting the safety of the vaccine intervention or placebo being trialled, they could end up much worse-off (infected with HIV) than they would have been had they not participated.

Berkley highlights another potential problem with vaccine trials: how to care for those who become infected during the trial [22]. That is, should these participants be provided with the best possible standard of care, or merely the best care available in that community?

Conclusion

HIV research, particularly that undertaken in developing countries, raises a diverse and complex range of ethical problems. Many of these issues are ongoing, with no agreement yet reached between opposing parties. At the very least, it seems necessary that all researchers recognise and take into account the complex and interrelated challenges that can arise. This recognition should form part of a ‘situational analysis’ of every research project, to embrace all local needs and sensitivities.

While a global ethic may be unattainable, the strategies, partnerships, policies and political commitments that have emerged to date is laudable. It is also important that in future projects researchers, governments, HIV/AIDS organisations and (perhaps most importantly) participants actively collaborate on research design, implementation and follow-up. Efforts should focus on addressing these overlapping ethical issues and developing long-term solutions within a framework of global justice.

References

21. Personal communication, Linda McDonald.