

## The trials of tenofovir trials

There is no better example of the problems of doing a trial in a developing-world country than for the drug tenofovir. This reverse-transcriptase inhibitor is effective in combination therapy for HIV infection. Six randomised trials against placebo were planned to test the drug for preventing HIV infection. The US Centers for Disease Control and Prevention (CDC) planned trials in Botswana and Thailand, and Family Health International (FHI), also in the USA, planned trials in Ghana, Cameroon, Nigeria, and Malawi.

Mid-March, FHI decided to cancel its trial in Nigerian prostitutes after local researchers failed to reach “the necessary scientific standards”. In February, Cameroon authorities stopped the tenofovir trial in prostitutes. Act Up-Paris, which is perhaps one of the most vigorous HIV/AIDS lobby groups, accused the trialists of acting unethically by not supplying treatment after the study, and by choosing to do their trial in women at high risk in a part of the world where a study is cheap. The study is expected to restart soon. The Thai trial in intravenous drug users was approved in early March, but an AIDS lobby group castigated the trialists for not providing treatment after the study and for not supplying free clean syringes and needles.

Such accusations are not wholly fair. The Thai Government will not allow clean injecting equipment to be distributed, and anyway, the CDC is not allowed by the US Government, which opposes such distribution, to do so. Trials in developing countries are cheaper than those in the western world and, in a prevention study, finding participants at high risk of HIV infection does mean a smaller sample is needed and that the study is over sooner. However, tenofovir’s manufacturer will supply at cost if approved for HIV prevention in the developing world.

Last week, the UK’s Wellcome Trust released ethical guidelines for clinical trials in developing-world countries. That release was timed to go with a discussion paper by the Nuffield Institute for Bioethics, also in the UK. Access to care after a study is a crucial difference between trials in the western world and in a developing country, where there may be no or limited access. The Wellcome Trust guidelines include a “reasonable expectation” that there will be such access and “encourage” grant applicants to think about this point, while pointing out that “in some cases it may be difficult to estimate . . . how financially or

logistically feasible it would be for a successful intervention to become available to patients within the host country”.

But guaranteeing treatment after a study, especially costly drugs for a chronic disease, is probably unfeasible, the Nuffield discussion paper says. It goes on to suggest negotiations about aftercare early in the planning phase. And, it continues, who is to decide on whether a treatment is effective and what about the delay between making that decision and regulatory approval for the drug being given?

The tension lies in the imperative about aftercare in the Declaration of Helsinki and the suggestions in other ethical guidelines. The 2000 Declaration of Helsinki states that: “At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified in the study”. The World Medical Association, who issue the Declaration, affirmed this position in May last year, after strongly felt representations had been made to the Association. Other guidelines, for instance those from UNAIDS in 2000, talk about the highest locally available level of care being needed for participants in HIV vaccine trials. UNAIDS is planning consultations to reach a consensus about ethics in prevention trials.

CDC and FHI investigators did meet local community groups and potential participants before starting their trials. In a comment on HIV vaccine trials in today’s *Lancet*, Naihua Duan highlights the importance of consumer research before a study. “HIV vaccine and vaccine trials, as public-health products that require consumer uptake and participation, also need to be grounded in consumer research to be successful in the public-health marketplace”, Duan writes.

In another comment in today’s *Lancet*, Peter Lurie and Dirceu Greco lambast the US Food and Drug Administration for trying to subvert the Declaration of Helsinki. But a debate in the *Journal of Medical Ethics* last year shows that there is no consensus about “standard of care”. Clearly, this dilemma needs sorting out, which will need to start with funders. The Bill & Melinda Gates Foundation funded the FHI trials with US\$6.6 million. Such funders need to think about also paying for and providing treatment after a trial ends. ■ [The Lancet](#)

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See [Comment](#) page 1119

See [Comment](#) page 1117

See *J Med Ethics* 2004; 30: 190–93, 194–97