Racist exploitation or exploitation of racism?

Discussions of the placebo-controlled clinical trials for HIV have focussed on methodological questions, ignoring the fact that treatments are available but unaffordable

Ronald Bayer

On September 18, 1997, an editorial denouncing the conduct of clinical trials in Africa, Asia and the Caribbean, designed to determine the efficacy of interventions to reduce maternal-foetal transmission of HIV appeared in the *New England Journal of Medicine*. (1) The attack signalled an escalation in a simmering battle over the conditions under which trials involving alternatives to the standard of care in Western nations for interrupting vertical transmission of HIV could occur. That encounter was, in turn, embedded in the far broader debate on the conditions under which research in poor, Third World nations, burdened by extraordinary rates of HIV infection, should take place.

In December 1993, the Data Safety and Monitoring Board of the US National Institute of Allergies and Infectious Diseases interrupted clinical trial 076 because preliminary data revealed a statistically significant and dramatic difference in vertical HIV transmission rates in those receiving AZT and those who had been given a placebo(2) (8.3% compared to 25.5%). The 076 regimen, involving giving AZT to the pregnant woman during the last two trimesters, an intravenous bolus of AZT during delivery, and AZT to the newborn for six weeks, soon became the standard of care.

Ironically, the costs of prophylactic treatment — $800 for the AZT alone (3)— put it out of reach of poor nations where the vast proportion of the estimated 580,000 newly-infected infants are born each year. Trials to determine radically cheaper alternatives to the 076 regimen were therefore of some urgency. In calling for such studies, the World Health Organisation noted that placebo-controlled trials "offer[ed] the best option for obtaining rapid and scientifically valid results". (4)

Fifteen of the 16 trials in developing countries — nine funded by the CDC or the NIH, five by other governments including Denmark, France, and South Africa, one by UNAIDS — involved the use of placebos.

No trial which denies access to the 076 regimen or an intervention thought to hold out the promise of being at least as effective as the prevailing standard of care would satisfy the requirements of ethical review in an industrial nation. Is it ethical to conduct such a trial in a poor country where the 076 regimen is financially out of reach as a potential therapy? (It is certainly affordable for the limited number of research subjects.) No, wrote Marcia Angell in the *New England Journal of Medicine*.

Citing the Declaration of Helsinki she noted that control groups had to be provided with the "best" current therapy, not that available locally. She compared the research studies to the infamous Tuskegee syphilis study in which poor, African-American men were studied for decades to learn the consequences of untreated venereal disease, even after effective, inexpensive therapy became available. Finally, she suggested that clinical trials had become big business, and as in any big business it was necessary to get the work done efficiently.

Angell's argument suggests that only a randomisation that included 076 as the control and an experimental arm that one had some reason to believe would be as good, if not better, would be acceptable.

Angell's editorial accompanied a Sounding Board pi[illegible] authored [illegible] Peter Lurie and Sid Wolfe, both physicians at the Health Research Group, part of Ralph Nader's Public Citizen organization.(5) That piece in turn had its origins in an open letter to the US department of health and human services. The letter writers cited the guidelines of the Council of the International Organisation of Medical Societies:

"An external sponsoring agency should submit the research protocol to ethical and scientific review according to the standards of the country of the sponsoring agency, and *the ethical standards applied should be no less exacting than they would be in the case of research carried out in the sponsoring country*" (emphasis supplied in letter).

Given the thrust of the CIOMS principles as well as those of the World Health Organization enunciated in the Declaration of Helsinki and the Nuremberg Code, it was remarkable, the letter's authors noted, that the studies had passed ethical review. They saw this as a sign of institutional failure, even corruption. Researchers in developing countries were from higher social classes than those who would be research subjects and were thus unlikely to safeguard the subjects' interests.

A second, different, charge was that while the new strategies might still be unaffordable in the nations being used for testing, the new knowledge could provide cheaper options for the industrialised nations.

Surprisingly, the letter goes on to make clear that the only acceptable research would raise the very questions of affordability.

"We are, therefore, not opposed to research that modifies the regimen provided in Protocol 076 in order to [illegible]tify a simpler, less expensive,

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similarly effective or more cost-effective intervention.... For example, one study arm could receive AZT and the other the experimental prophylactic regimen."

In their letter to the *NEJM*, rather than focusing on the ethics of a placebo-controlled trial in the post-076 era, Lurie and Wolfe asserted that the evidence of 076 called for equivalency trials. In so doing, their moral outrage was muted in the service of methodological critique. An equivalency trial, they pointed out, is conducted when one is interested in determining whether the second regimen is about as effective as the proven regimen, but less toxic or expensive. The knowledge of the 076 trial made it clear that shorter regimens would be more effective than placebos. "These findings seriously disturb the equipoise (uncertainty over the likely study result) necessary to justify a placebo-controlled trial on ethical grounds... "(5)

More critically, they believed that there was good reason to be optimistic that "researchers are quite capable of designing a shorter antiretroviral regimen that is approximately as effective as the ACTG 076 regimen."(5) -- a statement that has not gone unchallenged. Jeffrey Laurence of the Laboratory for AIDS Virus Research at the New York Hospital-Cornell University Medical College, noted, for example, that the less costly interventions are "certain to be less effective than the standard regimen."(6)

By way of summary then, those who have opposed the current trials have done so for a number of not always compatible reasons. Some argue that in the aftermath of clinical trial 076 research subjects in randomised trials must have access to the standard of care that prevails in the West, that the use of such AZT is affordable for the limited numbers enrolled in trials and that the duty to provide an AZT-based control arm stems from the special duty that is due research subjects regardless of local prevailing medical practice. Some are simply offended by the use of placebos in the aftermath of clinical trial 076 and urge comparisons of new interventions against historical controls—the local experience with untreated populations. Finally, there are those who, like Lurie and Wolfe, assert that since the time is ripe for equivalency trials, placebos are methodologically unwarranted.

In a reply in the *NEJM*, the CDC's David Satcher and the NIH's Harold Varmus located the criticised trials in the context of the profound poverty of many nations where vertical transmission is so critical an issue. They made clear that placebo-controlled trials were dictated by the urgency of the situation. Nevertheless, they rejected as "too simple" the argument that since most women in the countries when trials were conducted received no care, placebos represented no additional risk above standard practice, or that such trials could produce faster results with fewer subjects. Foregoing this justification reflected the effort to neutralise the charge that economic concerns had provided warrant for research designs involving a misuse of poor subjects.

They thus lost the opportunity to discuss whether conditions in many Third World Countries justified trials that would not require "very large numbers of women in order to see a statistically significant improvement," (6) or the question of how to balance the claims of research subjects and their offspring against those who would continue to suffer the risk of vertical transmission in trials of extended duration.

So they too, sought a methodological rationale. Only placebo-controlled trials would give "definitive" answers about which interventions worked, so governments could make "sound judgments about the appropriateness and financial feasibility of providing the intervention."(3). On methodological grounds, they argued that testing two or more interventions of unknown benefit against each other would not give infor th individual efficacies as well as on other questions such as toxicity or cost. In short, placebos were crucial to policy makers who had to make costly decisions about scarce public health resources.

To bolster thir argument, Satcher and Varmus underscored the extent to which consultation with host country scientists, physicians and others had produced agreement on research design.

It would not take much to imagine how Lurie and Wolfe would characterise such support. Nevertheless, the consent and collaboration of local groups here creates a picture far more complex than is suggested by the image of Western scientific imperialism imposing its will on hapless neo-colonial societies.

The controversy described above is not an instance of the ongoing clash between those believing in a single Western-dominated ethical standard for all research and those who believe that ethical standards should reflect local values. This was about the application of agreed-upon principles in radically different social conditions. The controversy is also striking because individuals known for their commitment to protecting research subjects' rights are confronting each other across a bitter divide.

This should signal that the issues involved are complex, not easily reduced to posturing and sloganeering. It is, therefore, especially troubling that Tuskegee has been invoked to denounce the trials. Tuskegee was both cruel and deceptive. There was not even the pretense of informed consent; the poor African-American men in that study were willfully deprived of socially affordable therapy. In the trials under attack, the women have given their informed consent—however problematical that may be (6); the studies have been examined by local review committees and an ethics committee of UNAIDS. Perhaps most important, everyone acknowledges that the 076 regimen is not socially

affordable in most nations, given the price of AZT and the infrastructure requirements for its administration.

The tragedy of the disputed trials is that they bear a profound moral taint. It is not, however, the taint of a malevolent research design. It is the taint of a world economic order within which effective prophylaxis for the interruption of HIV transmission from mother to foetus is available but unaffordable. That is true as well for a host of treatments for AIDS and other diseases. In a just world that would not be the case, and the very research under attack would be unnecessary. It is the social context of maldistribution of wealth and resources that requires these studies and that at the same time renders them so troubling.

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The state of drug research?

A research group working on behalf of some of the world's biggest pharmaceutical companies admitted to falsifying clinical data in trials of several drugs seeking US approval.

American Pharmaceutical Research Inc., its president and two employees pleaded guilty to conspiracy in connection with clinical trials it conducted for Bayer AG, Glaxo, Pfizer Inc., Rhone-Poulenc Rore, SmithKline Beecham plc and others.

Company spokespersons available for comment said they were not "seriously concerned that the fraudulent data had affected the outcomes of any FDA decisions."

The plea agreement, submitted in Los Angeles federal court, said data were falsified in experimental drugs for a range of ailments from asthma to heart diseases, as well as a birth control treatment.

Don McLearn, a spokesperson for the FDA which later approved some of those drugs, said it would probably now have to go back and re-evaluate trial data excluding American Pharmaceutical's contributions. But it was unlikely to lead to the recall of drugs now on the market. "We always require two controlled multi-centre trials and each one can involve as many as 10 different study centers, and maybe 100 investigators. So when you have one bad apple it's not the be-all and end-all. Our system doesn't depend on a single investigation. We have a fairly successful set of checks and balances."

The investigation of American Pharmaceutical Research showed the company often enrolled patients who did not meet the required profile for test subjects, or lied about the number of people who participated in trials. On one instance, it said it had tested a drug on 25 subjects, when in fact only a single patient had been involved. In other cases, when it could not find enough patients to qualify for the study, it used urine or blood samples taken from its own employees to qualify others.

US firm admits falsifying drug trials. *Express Pharma Pulse*, October 9, 1997

Irish research project abandoned after adverse publicity

A doctor was forced to abandon plans for a bone-metabolism study involving patients at St Ita's psychiatric hospital near Dublin, Ireland, following a campaign by the Irish Council for People with Disabilities.

After relatives of the patients received letters asking for consent for the study that would involve 50 patients receiving vitamin D injections and calcium supplements, with the other 50 acting as controls, media reports highlighted the Council statement that very few residents were able to give informed consent. "Many have no parents or guardians to advocate on their behalf. Most, if not all, would find a regime of frequent injections terrifying and distressing." The statement also said that the idea of imposing such a regimen on residents with disabilities was "ludicrous and barbaric".

The Eastern Health Board responded that the Council had misunderstood and misrepresented the situation, but that, in view of the anxiety which "uninformed reports of the study" may have caused the families, the doctor who has given "many years of excellent service to clients in the hospital has withdrawn her request for consent from the families" and will not be asking the hospital authorities to consider any proposal for such a study. The Council has written to the government demanding a full investigation of the "outrage".

Karen Birchard, *Th* *Te* 199