

## *An ethical dilemma*

### Availability of antiretroviral therapy after clinical trials with HIV infected patients are ended

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*Professor Cleaton-Jones describes the dilemma faced by South African ethics committees asked to approve clinical trials of treatments for HIV infection. We asked a member of a patient advocacy group, clinical trial coordinators, an ethicist, and a representative of a drug company to give their views*

Guidelines on good clinical practice for drug trials clearly state that ethics committees must ensure that the safety, integrity, and human rights of the subjects participating in a particular trial are protected.<sup>1</sup> Fundamental concepts are informed consent and risk or benefit to participants in a trial. For many clinical trials, ethical clearance is straightforward but those involving people infected with HIV generally are not.

Here, we are dealing with a condition that is presently incurable with variable progression, drug treatment is expensive, and emotions run high. These matters are common to all countries, but those of us living in Africa have an added burden—Third World conditions and an estimated 13 million people infected with HIV, usually from heterosexual sex.<sup>2</sup> In South Africa the most recent published results for the fifth unlinked anonymous national HIV survey show that HIV infection in women attending antenatal clinics has risen from a national average of 1.35% in 1991 to 7.57% in 1994.<sup>3</sup> In some parts of the country the rate is as high as 14.35% and is increasing.<sup>3</sup> Because of a shortage of resources, antiretroviral drugs for treating HIV are not provided by South African public health services: these are available only in the private sector at great expense.

Given this high prevalence of HIV it is understandable that multinational drug companies are attracted to carrying out trials in our country, with its combination of a large infected population and proved medical expertise. Ethics committees are currently receiving trial protocols for combinations of drugs from such companies. All protocols provide for the free supply of trial drugs for a specified period, usually two to three years, for patients satisfying the inclusion criteria. The trials are well designed and comprehensive, but there is no guarantee that the drug treatment will be continued beyond the end of the trial. Therein lies the problem. South African ethics committees use guidelines on ethics for medical research provided by the South African Medical Research Council.<sup>4</sup> Comprehensive as these are, they do not solve the following dilemma.

What is the responsibility of a trial sponsor to a trial subject who responds to treatment that will not be available after the end of the trial? With most diseases this is not a problem since alternative treatments are available. However, when no other treatment is available to trialists what should be done? If a patient infected with HIV responds to the test drugs, may one ethically withhold the drugs at the end of the trial, thereby depriving the person of benefit? My committee's opinion up to the present has been that it is not ethical to do so and that such trial subjects must continue to receive the antiretroviral treatment after the trial ends until they cease to benefit or are enrolled into another trial. Naturally, most companies have not received this opinion with joy. Their argument is that informed consent, which clearly states the length of a trial, takes care of the problem. In theory this is correct, but South Africa has large numbers of people insufficiently educated to understand the implications of what they are consenting to.

In early trials, when monotherapy was the rule, many companies complied with our requirement, but combination therapy has altered company policy. Companies often must purchase another manufacturer's drug to use in conjunction with their own. As a compromise, companies are generally prepared to provide their trial drug until it is no longer under development or is commercially available or they will provide zidovudine alone. Since combination therapy is the current optimal treatment,<sup>5,6</sup> can ethics committees allow patients to revert back to a less effective treatment? Furthermore, even if a drug becomes commercially available, is it ethical to halt treatment knowing that neither the health service nor trial subject can afford it?

Investigators fall into two clear camps. Some will not undertake trials unless there is an arrangement for their patients to receive drugs long term or to be enrolled in subsequent trials. Others know that their patients would normally receive no treatment at all, so

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two to three years of treatment is of some benefit at least and may buy time for future breakthroughs.

A further complication is the variation in policy of ethics committees. Our committee, established in 1966, is the oldest and most experienced in South Africa and is known to be conservative. Protocols not accepted by us, we know, have been readily approved in the private sector or at other institutions. To be fair to all concerned we have sought personal opinions from research coordinators in HIV trial groups in Canada and Australia. In Canada continuation of drug treatment beyond the trial is expected, but this is simpler because a drug company can continue to supply its own drug to be added to the antiretroviral treatment available from the public health services. In Australia it is accepted that drug companies are unlikely to provide long term treatment, and colleagues there believe that monotherapy, with at least a double nucleoside, after completion of a trial is acceptable when no other treatment is available.

Realistically, the level of illness required for inclusion into trials is such that many subjects may not survive past the trial period. Surely, agreement can be made on a response to the trial drugs so that only

those responding may continue treatment; those not responding may be taken out of the trial to free resources for the responders beyond the trial.

This has been debated at length in our committee with investigators, trial sponsors, and potential subjects. The most strident voices of all are those of patients infected with HIV, who feel that the decision to participate in a trial is theirs alone, not that of an ethics committee acting in a paternalistic manner. But ethics committees have to ensure that patients are not exploited and that benefit outweighs risk.

- 1 CPMP Working Party on Efficacy of Medicinal Products. *Good clinical practice for trials on medicinal products in the European Community*. Brussels: Commission of the European Communities, 1990. (9148/90-EN.)
- 2 Quinn TC. Global burden of the HIV pandemic. *Lancet* 1996;348:99-106.
- 3 Fifth national HIV survey in women attending antenatal clinics of the public health services in South Africa October/November 1994. *Epidemiol Comments* 1995;22:90-100.
- 4 *Guidelines on ethics for medical research*. Revised edition. Tygerberg: South African Medical Research Council, 1993.
- 5 Volberding PA. Improving the outcomes of care for patients with human immunodeficiency virus infection. *N Engl J Med* 1996;334:729-31.
- 6 Schooley RT, Ramirez-Ronda C, Lange JMA, Cooper DA, Lavelle J, Lefkowitz L, et al. Virologic and immunologic benefits of initial combination therapy with zidovudine and zalcitabine or didanosine compared with zidovudine. *J Infect Dis* 1996;173:1354-66.

## Strident, but essential: the voices of people with AIDS

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In the developed world the voices of advocacy groups for people infected with HIV have long been strident. This stridency arose from the behaviour of drug companies, which, together with physicians, were controlling access to, and knowledge about, antiretroviral treatments. Many such groups have a good understanding of the required protocols for drug trials and the available treatments which may prolong lives.

In South Africa the community of people infected with HIV has yet to raise its strident voice. Its stand is largely tentative, unarticulated, and mostly ignored. As a member of NAPWA—the National Association of People Living With HIV/AIDS—I am part of the growing community of HIV infected people working to change this. I attended a meeting of the ethics committee chaired by Professor Cleaton-Jones at which a proposed trial protocol was being evaluated. It was the first time that a member of an advocacy group had been present. It is, as Cleaton-Jones said in his article, our “safety, integrity, and human rights” which are being decided on, and we must have a voice and be heard in the debates about which trials will be supported and undertaken and which will not.

Yet, I found it difficult—because of the diversity of views and of our ignorance about the debate about treatment—to confidently articulate the views of my community on trials of drugs for treating HIV. There is a tension between investigators and clients with regard to these trials. To researchers the trials are often seen as experiments and we are research subjects, whereas to people like myself the trials are something far more important: they are seen as treatment rather than research—and are often the only way in which we in

South Africa have any access to treatment—as well as being a source of hope that the new drug combination will prove to be the “magic bullet.” This tension is particularly acute because the quality of medical care is highly variable and there is little recognition from the government or the drug companies of the need to make effective treatments available at a price that most people could afford. The final tension is, as Cleaton-Jones points out, what happens to the research subjects once the trial is over.

Although there is a strong feeling that it is unethical to allow people to enter trials when the treatment will cease after a specified time, many people feel that access to limited and potentially beneficial treatment is better than no treatment at all. There is always the hope that a way will be found for beneficial treatments to continue. Both these views are debated in the community of HIV infected people. This is essential so that when members of our community are asked to give “informed consent” they have been well prepared, given Cleaton Jones’s recognition of the inability of many researchers to explain the protocols clearly and effectively to those “insufficiently educated to understand the implications of what they are consenting to.”

These tensions need to be resolved. Our voice must be heard, not in a patronising and glib way, but in a manner which indicates a real commitment to seeing our concerns as genuine worries rather than irritating stridency. Of course, the widely divergent community of HIV infected people at present allows for investigators to exploit our differences and lack of detailed knowledge to engage some sectors but not others. Cleaton-Jones’s article highlights the need for NAPWA to develop a