AIDS: patient power puts research on trial

Trials of zidovudine, a drug that may delay the onset of AIDS, are about to begin in Britain. But there is a problem. The patients themselves may stay away

Duncan Campbell

IT IS CLEAR that the drug zidovudine, formerly known as AZT, can prolong the lives of some people with AIDS. A different question, and one which thousands of HIV-positive people (and their doctors) would like to know the answer to, is whether this drug, given earlier in the course of the disease, can put off the development of AIDS.

To find out the answers to such questions, medical scientists normally carry out trials to compare the outcome in people treated with the drug being evaluated, against that of people given a placebo. This type of "placebo-controlled" trial aims to avoid any bias which might arise because the patient expects to get better as a result of taking the drug.

The organisers of the trial allocate patients to treatment with drug or placebo in a randomised way. In addition, because doctors might report their patients' condition differently according to their faith in the new drug, many trials are also "double blind". In other words, neither doctor nor patient knows who is taking drug and who is taking placebo.

According to many medical statisticians, such trials balance the potential benefits of a previously unevaluated treatment against the potential risks. Those in the treatment arm may benefit from the new drug, if it is effective, but they are also exposed to any unwelcome—and unknown—side effects it may have. Those taking the placebo derive no benefit from the drug, but will be protected from side effects.

Last July, the British Medical Research Council announced that it was setting up a randomised blind placebo-controlled trial, based in several centres, to evaluate the effectiveness and safety of zidovudine in HIV-infected people without symptoms. The trial is being run jointly by the MRC, its French equivalent, INSERM, and the manufacturers of zidovudine, Wellcome, who are supplying the drug free.

The trial took almost a year to set up, because of arguments about its design between Wellcome and the MRC's scientists. Now that they have come to agreement, they have found that prospective participants are challenging their research methods.

The physicians running the trial, doctors from the major London hospitals, and many potential participants met last month to discuss the study. The meeting was arranged jointly between the MRC's working party on the trial, the London-based AIDS charity, the Terrence Higgins Trust, and the British support group for people infected with HIV, Body Positive.

Ian Weller, the consultant at the Middlesex Hospital who chairs the MRC's working party, said the trial presented a unique situation. "With AIDS," he said, "sharing information with patients has been absolutely critical to compliance [with a trial] . . . It's inevitable in such a young population that they're going to be better informed."

Weller and Karen Gelmon, the doctor in charge of the trial, heard many criticisms of its design. These concerned two aspects: the use of placebo controls and the fact that the trial is to be double blind. There was also a call from HIV-positive people to be kept better informed of the results of research.

But these arguments were only the latest in the "long and troubled gestation" of the British trial of zidovudine, said Weller. Researchers initially planned the trial after the Third International Conference on AIDS, held in Washington in June 1987. Since then, the design of the trial has repeatedly been revised.

It was almost abandoned on two occasions. Only in the spring of this year did scientists from the MRC finally persuade Wellcome that they and not the pharmaceuticals company should have control of the trial. This has now been agreed. The MRC and INSERM now hope to recruit some 2000 people infected with HIV to the trial at 63 different centres, half of them in Britain and half in France.

Until the MRC took over control of the trial, the draft protocol agreement, a confidential document outlining the design of the trial, gave Wellcome a degree of control over publication that many researchers found unacceptable. Clause 4 of the protocol's "terms and conditions" required every participating doctor to agree to "obtain Wellcome's written consent before the publication of medical or scientific papers arising from [the trial]". The protocol specifically forbade doctors to object if Wellcome refused permission to publish "for the purpose of protecting an application for a patent".

Doctors also had to agree to keep the protocol itself confidential, and not to disclose it to patients or other researchers without Wellcome's specific permission. The MRC, by contrast, has made the protocol for its trial openly available.

Many of the problems raised at the consultative meeting held last month in London have dogged a similar trial of zidovudine which has been under way in San Francisco and other centres in the US since the end of 1987. Despite the aims of a blinded trial, many patients volunteering for the American trial have done so only in the hope of getting the drug. They are already convinced that taking zidovudine early will arrest the effects of HIV infection.

A far worse practice, according to Paul Volberding, AIDS chief at San Francisco General Hospital, is "drug sharing". Some groups of people participating in trials have admitted pooling their supplies to ensure that each person in the group gets at least some of a potentially therapeutic drug. The sharers did not aim to destroy the trial. They were desperate patients who felt coerced into joining trials in order to have any chance of getting a drug which might be effective against AIDS.

American researchers also believe that, once in a trial, many patients establish privately whether they are on the treatment or placebo arm. It is possible, in major cities in the US, to ask a laboratory to analyse the capsules to see if they contain drug or placebo. With zidovudine, it is particularly easy for patients or physicians to spot whether they are getting the real thing by looking at the results of the patients' ordinary blood counts.

Volberding said: "If the volume of your red cells doesn't go up, you're on the placebo." The red cell volume, called MCV in blood counts, will rise from around 90 to 100 after a few months on zidovudine, and usually goes on rising after that.

Karen Gelmon, the doctor in charge of the European trial, acknowledged that, as a result, maintaining a double-blind trial would be difficult if not impossible. According to the proposed design, physicians will be told neither their patient's MCV counts nor certain other results which may be significant indicators of the progress of HIV disease.

These indicators include, for example, the count of T4 helper cells (one of the cells which HIV attacks) and the measurement of the level of the viral core protein, p24, in the blood. Many HIV-positive gay men follow research on AIDS and HIV infection reported in *Nature*, *The Lancet* and the *British Medical Journal* (and *New Scientist*) at least as avidly as their doctors, and often more rapidly. They are now used to interpreting laboratory markers as the best available test of the state of their immune systems, whether they are clinically ill or well.

As a result, there are fears that some patients would find a trial blinded in this way unacceptable. In major cities in the US, many physicians and self-help groups now start patients without symptoms on experimental or prophylactic drugs if their T4 helper cell count drops below 200 or 400 (depending on where they set the limit), or if the viral antigen p24 appears in their blood.

Meurig Horton, AIDS programme officer at the Health Education Authority, argued at the consultative meeting that because of the significance of these markers in predicting the course of the disease, they should be used as the formal "end point" of the British trial of zidovudine. Under the MRC's present design, only those patients "progressing" to more serious, symptomatic disease (not necessarily AIDS) would be taken out of the trial and offered "open label" zidovudine (if they wanted it).

Most leading British specialists in AIDS

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Cut the red tape: people with AIDS and their supporters, outside the federal building in San Francisco earlier this year, call for faster evaluation of new drugs

believe, however, that the available evidence does not yet justify such widespread early use of experimental drugs. Gelmon and Weller argue that such a change to the design of the trial would be premature at this stage. An independent Data Safety and Ethical Committee with access to all the results will meet every four months to review all aspects of the trial. If new research confirms the reliability of the laboratory markers in analysing the progression of the disease, then, said Weller, the end points would be changed.

Another factor which makes trials difficult to run, and one unique to the epidemic of AIDS and HIV infection, is the immense range of literature produced by many American groups on alternative and experimental drugs and therapies. The American Foundation for AIDS Research (AmFAR) produces a biannual *Directory of Experimental Treatments for AIDS and ARC*, which gives a comprehensive review of all, known trials and protocols.

Project Inform, a pressure group based in San Francisco, produces a long listing of *Federally Approved Medications for Treatment of AIDS and AIDS Related Conditions*; the project's literature includes advice on how to import drugs not approved in the US from Mexico or other centres overseas. There are many regular newsletters in the US directed at people with AIDS and HIV infection which are medically extremely well informed.

In consequence, information about HIV travels extremely fast. Patients often begin experimenting with new drugs when—or even before—clinical trials start. So it has become essential that scientific trials of new drugs begin quickly, before their use becomes widespread in the community.

Small-scale tests using zidovudine to treat asymptomatic HIV-infected people in Amsterdam, Florida, and San Francisco have already shown promising results. Researchers in Amsterdam, led by Joep Lange, found that the side effects of zidovudine in healthy HIV-positive men were "mild, transient and infrequent". There was a "striking" reduction in the size of the patients' swollen lymph nodes. According to information presented to the international conference on AIDS held in Stockholm last June, only 2 out of 24 patients without symptoms needed blood transfusions, compared with 20 to 50 per cent of patients with AIDS.

The drug worked better, too. In almost all patients, use of zidovudine appeared to switch off or reduce activity by the human immunodeficiency virus rapidly and permanently. In contrast, patients who had decided that they did not want to take zidovudine had rising levels of the p24 viral antigen in their blood.

In San Francisco, doctors working at Positive Action Healthcare, a clinic specialising in treating HIV-positive people, have monitored a group of about 50 men infected with HIV but with no symptoms who have been taking zidovudine for six months. They found that the number of the men's T-helper cells rose by an average of 37 per cent, compared with an average 25 per cent fall in the previous six months during which they did not take zidovudine.

Alan Levin, the director of the clinic, is strongly opposed to "normal" trials involving placebos. He said: "It has become unethical to study the effectiveness of an HIV treatment by comparing treated patients to others who are forcibly denied treatment and allowed to progress to well-known life-threatening complications or death. Laboratory tests available to any physician make it abundantly clear when treatment is working or not".

For these and other reasons, the American trial of zidovudine in infected people without symptoms has faced tremendous difficulties. Since the trial began, 30 per cent of the 1900 participants have dropped out. Almost all of them were on the placebo arm—and, presumably, had found this out. Some of those who dropped out, researchers then discovered, had re-entered the trial under a different name at a different centre. It has become clear from the American experience that most people were motivated to enter the trial merely to get access to zidovudine, free of charge.

The new Anglo-French trial could face similar problems. Prospective participants at the consultative meeting privately acknowledged that they had failed to comply with the terms of previous trials in which they had taken part. Some had shared drugs; others had taken additional drugs, such as dextran sulphate or AL721, without telling their doctors; yet others had decided, without telling their doctors, to stop taking the drug because they feared side effects. Many of those consulted thought that a blind trial would place unhelpful stress on both patients and doctors. They wanted an unblinded trial.

There are many historical precedents for unblinded trials, in which patients can choose either to take the drug and risk its side effects, or to serve as controls. But the MRC's scientists say that running the trial unblinded would risk many kinds of statistical error. Even if the patients studied appeared to be evenly matched on important medical factors, other criteria might later turn out to be important. If the trial seemed to show a benefit for those taking the drug, the authorities might still not license it because of criticisms of its results.

Tony Pinching, a consultant at St Mary's Hospital in Paddington, said after the meeting: "If people are not willing to go into the trial when it's discussed properly with them, then we'll have to go back to the drawing board and design a better trial that is acceptable and will resolve the questions." He noted that it was "plausible up to a point to do an unblind trial". But, he said, many of the problems in the US should not occur in Britain because of differences in the delivery of health care and the system for approving drugs.

In the US, the authorities have not yet approved zidovudine for use in asymptomatic HIV infection. So, although it is already widely believed to be efficacious, many people who would like to take it cannot get it because insurance companies will not pay for and doctors will not prescribe such costly "experimental" treatments. The patients then join trials in a state of desperation.

In Britain, however, doctors are free to prescribe (and the NHS will pay for) any as-yet unapproved medicine which the practitioner feels is clinically and medically justifiable. Although most AIDS specialists like Pinching and Weller are extremely reluctant to prescribe zidovudine to asymptomatic HIV patients until the results of a trial are available, they and their colleagues may do so if a patient is keen to take it. Some clinics in Britain do now offer zidovudine to HIV-positive patients whose blood shows the markers that may predict progression to AIDS mentioned earlier. In these cases, the patient would usually have to sign a special consent form acknowledging that the use of zidovudine was experimental and potentially risky. Pinching says that in Britain, "HIV-positive people who wish to go on the drug can basically get hold of it."

The researchers remain ready to reconsider the design of the trial if participants do not like it. But at the moment, they hope that they will be able quickly to recruit enough people with suitably "philosophical attitudes" to comply with the restrictions of the present design. □

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