AIDS trials, civil liberties and the social control of therapy: Should we embrace new drugs with open arms?

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The unique challenges posed by AIDS (acquired immune deficiency syndrome) have ramifications far beyond the bounds of the disease itself. Nowhere is this felt more acutely than in the biomedical research and drug regulatory communities. AIDS activists compel researchers and government regulators to re-evaluate the conventional wisdom concerning tests of new therapies.[1] Anyone who thinks this problem is specific to AIDS should consider that changes could affect the way in which all new therapies are evaluated.

The demands have occasionally been extreme. The AIDS epidemic has provided some groups with an opportunity to call for an end to most government regulation of investigational therapies, which they believe should be used solely with the informed consent of the recipient (*New York Times*, Jan. 27, 1987: A21). Other AIDS groups have called for a ban on the use of placebos. The AIDS Coalition to Unleash Power (ACT UP) has called placebo trials "a medically sanctioned form of Russian roulette",[2] and *Le Manifeste de Montréal*, published by a coalition of AIDS groups at the Vth International Conference on AIDS, held June 4 to 9, 1989, in Montreal, stated that "placebo trials must be regarded as inherently unethical when they are the only means of access to particular treatments".[3]

Other, less extreme demands require thoughtful consideration by the medical research community. Most AIDS groups recognize the need for valid scientific study of new agents but are frustrated by logistic and bureaucratic delays. Many have questioned the randomized, controlled trial as being paternalistic, coercive and an infringement on fundamental civil rights. Civil liberties experts have presented powerful arguments in favour of enhanced rights to self-determination in the context of AIDS.[4] AIDS groups have suggested alternative trial configurations, such as the open-arm clinical trial, that they believe would provide earlier access to non-validated therapies and be more compassionate and ethical than traditional trials.

In this article we review the concept of open-arm clinical trials and present their advantages and disadvantages. We need to find a solution that optimizes individual freedoms at a minimum cost to scientific validity and public protection. As stated by Dixon,[4] whatever the solution it "should be as broad as possible to reflect the respect of Canadians for personal self-determination in that which affects us most personally and intimately, and as narrow as is necessary to leave materially undisturbed the public interests served by the social control of therapy".

A new reality

Many must wonder why these issues are prominent now, in the AIDS era. "What is special about AIDS", observes Dixon,[4] "is that persons with AIDS possess . . . the political power needed to confront

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the therapeutic system with a case for the rights of all catastrophically ill patients. . . . They have added their very powerful voice to what has traditionally been an either silent or politically disorganized constituency."

At the extreme some AIDS groups want to end regulation; they openly support the importation and distribution of nonvalidated therapies and have even fostered the sharing of investigational drugs in clinical trials.

Delaney[5] described the situation in which "AIDS study centers throughout the [United States] tell of widespread concurrent use of other treatments; frequent cheating, even bribery, to gain entry to studies; mixing of drugs by patients to share and dilute the risk of being on placebo; and rapid dropping out of patients who learn they are on placebo". Although this is likely the activity of a few, it can have devastating effects on therapeutic progress. We believe that most AIDS groups appreciate the importance of trials in advancing the goals of therapy; however, they want an equal say in the design and conduct of the research intended to help people with AIDS, and they have the organization and resources to raise challenging questions about that research.

Therefore, the AIDS research community faces a new reality. It has always had to contend with the scientific, bureaucratic and logistic barriers that inevitably impede biomedical research, but now there is a highly organized and politically astute patient population, however heterogeneous in its objectives. Unless the legitimate concerns of this community are addressed through dialogue and unless the right of a dying person to self-determination and the right of the state to public protection are reconciled, therapeutic progress could be seriously threatened. As Dr. Jere T. Goyan,[6] dean of pharmacology, University of California at San Francisco, stated, "We need to consider alternative study designs that offer the patient the maximum hope for cure and the opportunity for some control over his or her destiny. . . . What I am suggesting is the need for a reexamination of all the assumptions on which the scientific requirements of the present system are based."

Illustrative case

Consider an investigational antiviral agent, drug X, intended for use early in HIV (human immunodeficiency virus) infection to prevent or postpone deterioration and AIDS. A phase-III randomized clinical trial is proposed that pits drug X against the standard therapy, which at present would be placebo, although zidovudine (AZT) could soon become the standard therapy as a result of current placebo-controlled trials; the trial would then compare drug X with AZT.

In a conventional randomized controlled trial eligible consenting subjects are randomly allocated to receive either drug, and their outcomes are monitored. In such a trial with an open arm (Fig. 1) the eligible subject is offered either the open arm or the clinical trial. Subjects who choose the open arm would receive drug X in an unblinded fashion and would be monitored; those who choose the clinical trial would be randomly assigned to either the experimental or the control group. In this design the open arm is offered to the same people who are eligible for the controlled trial.

The open-arm concept is not new; it can be said to exist whenever the experimental intervention is already available outside of the trial. For example, in a randomized trial that compared mastectomy with lumpectomy for breast cancer, since both therapies were available in the community open arms already existed at the time of the trial.[7] However, in the present context open-arm trials are both novel and controversial; the investigational therapy is neither validated for the clinical condition nor available outside the context of the trial. Under such circumstances, in the conventional trial the only access to the nonvalidated therapy is through participation in

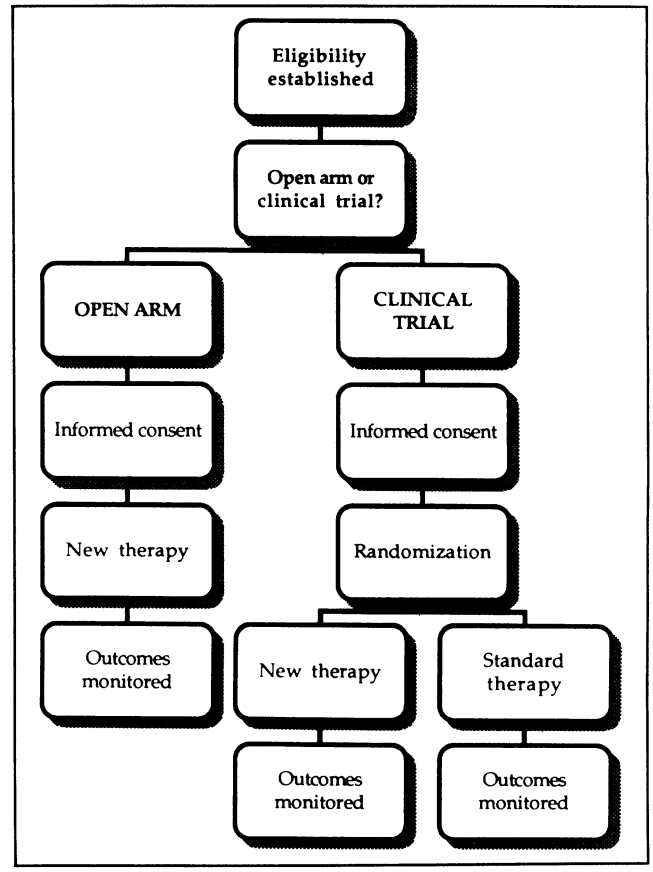

Fig. 1: Design of randomized controlled trial with open arm.

the randomized trial; in the open-arm trial direct access is provided for participants who choose the open arm.

Ethical requirements of a controlled clinical trial

Aside from informed consent a clinical trial has two main ethical requirements. The first is "equipoise" — a term used by Fried[8] and Freedman[9] to indicate a state of genuine uncertainty about the relative merits of the therapies under consideration. In other words, the trial must begin with an "honest null hypothesis".[9] If, for example, there were reasonable consensus that drug X was clearly superior to the standard therapy a state of equipoise would not exist and the trial would be unethical. The second requirement is that the trial must be designed and executed so that equipoise is either disturbed or established. Therefore, the trial must provide conclusive scientific evidence that drug X is superior or inferior to the standard therapy or that the therapies are equally effective. This implies that the trial must have both internal and external validity and that in the case of a negative result the power must be sufficient for the result to be considered conclusive. A trial that is unlikely to resolve the underlying scientific question is a disservice to the study subjects and to potential recipients.

The case for open-arm trials

The open-arm design has its greatest support among AIDS community groups and their advocates. At the Workshop on HIV Clinical Trials, in London, Ont., Nov. 17 to 18, 1988, a coalition of people with AIDS requested that all trials of experimental treatments include an open arm. They argued that open-arm trials are inherently more ethical and compassionate than randomized controlled trials since they offer patients more control over their medical treatment. The randomized format is thought to be coercive because subjects are forced into the trial as the only way to receive the experimental agent. Delaney[5] asserted, "Many patients and their advocates find it morally repugnant to deny potentially life-saving treatment to the masses to force a few into clinical studies."

A related advantage to the open-arm design is the commitment of the remaining participants, who enter the randomized trial. ACT UP[10] claimed that "if the people who enrol in a trial are truly desperate to get the drug at any cost, they will do whatever it takes to enter a protocol. . . . If, however, the drug is available outside the trial to those who absolutely need it, those people who enrol in a trial will more likely be those who can abide by the rigors of the trial." Delaney[5] stated that the volunteers who remained "would be more likely to act as pure research subjects, entering studies not solely out of a desperate effort to save their lives".

Since people who elect to enter the open arm would be followed up, they constitute a case series of subjects taking the new drug and thus provide some scientific information about side effects and toxicity and some circumstantial evidence of benefit. If the open arm contains subjects who were technically ineligible for the trial but for whom the drug might ultimately be prescribed, it can provide actual experience with the drug that would not otherwise be forthcoming from the trial.

Community groups and advocates have often cited the advantage that more people would have access to the new drug and its clinical benefit at an earlier stage in its evaluation. Without open access patient groups have created large "underground" networks to purchase and distribute putative therapies for HIV infection. As Delaney[5] noted, "While most of this is benevolent, there is every reason to expect that it will become less so over time as entrepreneurs learn to exploit it." Proponents argue that open arms would obviate the need for such networks and avoid the possibility of exploitation.

The case against open-arm trials

In general some useful information about side effects and toxicity would be provided by people who elect to enter the open arm. However, valid scientific evidence of efficacy and effectiveness would be unavailable because of the lack of an adequate control group. Historical or contemporaneous control groups from other populations might be constructed, but there are well-known methodologic problems with such an approach.[11]

The potential for an open arm to introduce bias is great. Subjects who enter and complete the controlled trial will differ from those who enter the open arm by virtue of volunteer and compliance biases.[12] Thus, the controlled trial could be carried out in a biased subset of the total potential recipients. The extent of the bias would depend on the relative proportions of eligible subjects who choose the open arm or the trial. If in the early stages of the trial 90% of all eligible subjects chose the open arm, the bias could be severe, and the trial might no longer be considered ethical. Conversely, if 90% of the eligible subjects chose the randomized trial the bias would be minimal. The extent of the bias could be assessed through a comparison of outcomes between the open-arm participants and those randomly allocated to receive the new therapy.

An open arm may cause recruitment and sample-size problems. There appears to be little incen-

tive for eligible subjects to enter the randomized controlled trial. Those who want the drug can choose the open arm, whereas those who do not want it need only avoid the trial altogether. Such an option was exercised by women who avoided a randomized trial of lumpectomy versus mastectomy[7,13] and simply sought out their desired therapy. As a result that study had severe recruitment problems and might have failed had the randomization not been modified.[14] If the presence of an open arm in an HIV trial were to create recruitment problems the randomized trial would fail to reach its recruitment target. In addition, subjects would always have the option to switch to the open arm to receive the drug. Thus, the presence of an open arm could increase the likelihood of withdrawal from the clinical trial and thus create analytic complications and exacerbate sample-size problems. The trial might end up with insufficient statistical power to detect important differences.

More likely the open arm would lead to recruitment problems that would force the investigators to lengthen the recruitment period and hence the study's duration. This would postpone the resolution of the scientific question. The participants in the ultimately inferior arm of the trial would experience longer exposure to the inferior treatment. Freedman[15] warned that "the failure to complete these trials will serve neither the patients themselves — who serve as guinea pigs for treatments of unproved efficacy, and pay for the privilege — nor future patients who are denied the advantage of prior validation of treatments".

Finally, we turn to the argument that open-arm trials are more compassionate since they allow earlier access to the experimental therapy. Most researchers do not accept that rigorous evaluation through clinical trials is coercive, unethical and lacking in compassion. Richman[16] stated that "on the contrary, properly designed clinical studies of experimental drugs will relieve the most suffering and do the most good, certainly in the long run, and almost certainly in the short run", and "the open distribution of unproved drugs is not compassionate and this approach in fact often delays access of needy patients and health care workers to the critical information that will prolong life and reduce suffering". For these reasons many believe that open-arm trials are unethical. There is a "catch-22" to the argument that open-arm trials allow more people access to the new drug earlier. This will be an advantage only if the drug turns out to be beneficial. For example, an open-arm trial of cyclosporine therapy for AIDS would have exposed many more subjects to a therapy now known to be harmful.[17] Of over 70 agents introduced for possible HIV therapy only 1 has reached the stage of demonstrated clinical effectiveness; many, including cyclosporine,[17] castanospermine[18] and dextran sulfate,[18] have been shown to be possibly harmful.

Rebuttal

Charges of paternalism greet the argument that people with HIV illness must be protected from the potential harmful effects of untested therapies. Advocates of patients with AIDS contend that it is equally possible for new therapies to do more good than harm and that people with serious illnesses should have the opportunity to make informed decisions whether to take the risk. The arguments concerning the possible adverse effects of open arms on recruitment into clinical trials is countered by several points. First, AIDS groups have recognized these concerns and have promised to work to ensure sufficient numbers of subjects. They want to test the viability of open-arm trials rather than argue the hypothetical possibilities of recruitment problems. Proponents indicate several attractions of clinical trials besides access to novel therapy; these include specialized medical care, intensive follow-up, possible beneficial cointerventions that may not otherwise be available and access to health care in countries without universal health insurance.

Alternative trial designs

We believe there are alternatives to open-arm trials that address the concerns of AIDS groups and meet the scientific demands for rigour. The most compassionate and ethical approach is rapid but valid evaluation of promising new therapies. Several techniques can be applied to improve the rapidity and increase the acceptability of randomized clinical trials of HIV therapies with minimal cost to scientific integrity.

The first alternative involves various techniques known collectively as sequential analysis[19] — analysis of the results of a trial on a continuing or frequent interim basis so that the trial can be ended as soon as a definitive result is available. Although blinded sequential analyses with tight, prespecified stopping rules entail some scientific drawbacks, including the tendency to produce biased estimates of the treatment effect, the advantages in the current climate of HIV clinical evaluation outweigh the drawbacks. These techniques can be advantageous only when the delay between the entry to the trial and the outcome is short relative to the period of recruitment.

There is no absolute reason why a randomized trial must distribute subjects equally to the experimental and control arms. The unbalanced design is an alternative in which two-thirds of the subjects, for

example, are allocated to the new therapy and one-third to the standard. This is simple to do, addresses some of the same issues as an open arm and only loses some statistical power relative to a balanced design. There is, however, no compromise to internal or external validity.

There is also no reason why all trials must use the same classic type I and type II error levels; these levels should be determined on the basis of the societal costs of making false-positive and false-negative errors and not simply convention. It seems ludicrous to maintain the same levels for trials of HIV therapy that one would use for a trial of acne lotion. Thus, we might agree to accept a greater chance than the usual 5% of falsely accepting a new drug for AIDS as being superior to standard therapy. This would reduce the number of subjects required and lead to earlier termination if the drug were clearly beneficial or harmful. A price would have to be paid in the form of an increased false-positive rate, but it is preferable to a state of therapeutic anarchy.

The question of access to nonvalidated therapies ultimately comes down to an assessment of two important rights: the individual right to self-determination and the right of the state to effect some form of control to protect the public and advance science. With regard to chronic illness Dixon[4] explored these rights through two of the avenues open to migraine sufferers: "one in which they have an absolutely unfettered right to scour the earth for novel therapies for their affliction, and in which they will have no practical chance of success; and another in which they relinquish a measure of their therapeutic autonomy to a social and scientific authority that will organize a search for a cure in terms of the scientific method". Under these conditions Dixon argued that the latter was the rational choice and judged "a very limited paternalism acceptable given the very substantial benefits gained through its narrow operation". However, the balance is said to shift in the presence of a life-threatening condition such as AIDS in which life expectancy is often exceeded by the reasonable expectancy of a therapeutic advance. Dixon claimed that under these conditions "a catastrophic illness induces a special set of circumstances which can make the personal freedom to seek therapy of paramount importance".

Another alternative to the open-arm trial is the "catastrophic threshold", which stems from the recognition of the enhanced rights mentioned in the previous paragraph. Under this proposal for the study of a new therapy a point in the natural history of HIV illness should be defined so that patients beyond this threshold would have access, under close supervision, to the new agent while it was being evaluated in clinical trials involving people who are at earlier stages of the disease. The threshold would be shifted as the therapies and our understanding of the natural history of AIDS change. The precise definition of the threshold would be reached through consensus among investigators, sponsors, regulators, community groups and other interested parties. In general the catastrophic threshold at a point in time is meant to identify seriously ill patients for whom clinical science has little to offer, primarily those for whom there is no standard therapy at that point and those who have failed to respond to the standard therapy of the day.

At present the threshold might be defined to include people with AIDS or severe immune dysfunction who have failed to respond or are intolerant to AZT or who have an AIDS manifestation for which there is no worthwhile therapy. Under this definition all people with AIDS would be considered catastrophically ill except those responding well to AZT. The provision of the catastrophic threshold would clearly have cost implications for government and drug sponsors alike.

The catastrophic threshold is similar in spirit to the Emergency Drug Release Programme, in which a physician may request an unapproved drug for a patient on compassionate grounds. However, the threshold would be based on clear criteria derived through consensus and would provide a mechanism for wider release of the drug to all those beyond the threshold; such people would be followed up in an uncontrolled, separate, "catastrophic open arm" of the trial.

In some ways the catastrophic threshold is similar to the "parallel track" proposal in the United States, in which a separate arm runs parallel to the clinical trial for people who would not otherwise enter the trial and who meet certain additional criteria.[10,20] However, the parallel track is proposed for situations other than those we have delineated; for example, it would be available to patients with a disease as severe as that of subjects in the controlled trial but for whom the trial is geographically inaccessible. We prefer the catastrophic threshold because geographic inaccessibility should not be a problem in Canada owing to the impending nation-wide network for HIV clinical trials. If it were to remain a problem the best solution would be not the open distribution of untested drugs in regions with less access but, rather, the expansion of the trials to include all regions.

In the United States the parallel track would also be open to people who are ineligible for the trial but for whom the new drug is not absolutely contraindicated. For example, patients who take other medications concomitantly or have certain prespecified conditions are customarily excluded from trials so that the evaluation of drug toxicity and side

effects is more pure. An alternative would be to relax the eligibility criteria to include virtually all patients for whom the new therapy is not absolutely contraindicated; if necessary the analysis could be stratified to screen out the statistical "noise" created by their inclusion. Moreover, additional data about actual drug effectiveness would be provided, and considerable resentment and confusion might be avoided. For example, with a parallel track a person in the controlled trial might know of someone at the same stage of HIV infection who has open access to the new drug because of apparent loopholes in the trial's eligibility criteria. The argument that the expanded eligibility criteria would enlarge the trial and increase its costs is not valid, because all of the participants in the parallel track would have received the drug and been followed anyway. We believe that the minimal compromise to scientific purity, if any, would be outweighed by the trial's greater applicability to affected people and the attendant improvement in trial acceptability and recruitment that might arise.

Conclusions

We recommend that HIV clinical trials be rapidly deployed and sequential analysis be used with strict stopping rules, when possible, to provide scientifically valid information in the shortest time. In addition, such techniques as unbalanced randomization and relaxation of conventional confidence levels should be considered. Eligibility criteria should be as relaxed as possible to include all patients for whom the new drug might eventually be used. A catastrophic threshold should be defined so that people whose clinical condition places them beyond the threshold may still receive the agent, in a closely monitored fashion, while it is being evaluated through clinical trials involving people whose HIV infection is at an earlier stage. We believe that this combination of strategies is superior to open-arm trials. The combined strategy will provide the validity required by science as well as the expediency, compassion and human rights demanded by affected people inside and outside of the trial.

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