Current Problems and the Future of Antiretroviral Drug Trials

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Advances in our knowledge regarding the pathogenesis of human immunodeficiency virus (HIV) infection (*1*) and increasing options for the treatment and monitoring of this infection (*2*) dictate new approaches to the conduct of clinical trials of antiretroviral therapies (*3*).

To maintain antiretroviral drug activity, the minimal goal of therapy should be to suppress HIV replication as much as possible for as long as possible (*4*). Allowing for residual HIV replication will invariably lead to outgrowth of drug-resistant virus (*5*) and therapy failure. Given the existence of a fair amount of cross-resistance to anti-HIV drugs of similar classes (*6*), development of resistance to one particular agent can sometimes severely compromise alternative therapeutic options (Fig. 1). With a maximally suppressive triple drug regimen (Fig. 1, regimen 1), consisting of simultaneous treatment with drugs A, B, and C, one can safely switch to one or more alternative drugs in case of intolerance, patient preference, and so on, because the virus is still fully sensitive to these agents. With a suboptimal sequential regimen of treatment with drugs A, B, and C (Fig. 1, regimen 2), the moment resistance to any one drug has developed, cross-resistance will mean that certain alternatives have also ceased to be of benefit. Treating with regimen 2 is like going down a one-way street to disaster with no side alleys to allow escape. Moreover, preventing drug resistance goes beyond the interest of the individual; increasing circulation of drug-resistant HIV strains will compromise future therapeutic options at a population level (*7*).

Despite the relatively simple principles of antiretroviral therapy and the existence of tools to monitor that therapy, suboptimal therapies are still being used. This may be because of economic considerations, the need to treat patients who have already undergone multiple therapies, patient intolerance of the drugs, poor compliance, or physician ineptitude, to name a few common reasons. This is a severe problem that deserves far more attention and regulation than it actually gets. In the present paper, however, we are primarily concerned with clinical trials. It is self-evident that in clinical trials, the least we can do for patients who are willing to help advance knowledge is to try to treat them according to the highest current standard. As Robert Schooley said a few months ago, "There is no need to keep showing the superiority of better viral load reductions" (*8*).

Yet even today, suboptimal regimens are still being evaluated for many reasons. The list discussed below is by no means comprehensive, but I do think that the factors on it merit attention.

Accidental use of suboptimal therapies. Promising in vitro effects may be followed by disappointing in vivo effects. An example is the recombinant soluble CD4 (sCD4) story. Only after this "magic bullet" failed to live up to its promise in clinical trials were the proper in vitro experiments done, with primary rather than highly adapted laboratory strains of HIV (*9*). Other examples are the demise of a promising HIV-1 *tat* inhibitor (*10*) and of some HIV-1 protease inhibitors (*11*) in early clinical trials. Antagonism between drugs may have been responsible for the poor performance of the zidovudine-stavudine combination in non–antiretroviral-naïve patients in the AIDS Clinical Trial Group (ACTG) 290 trial (*12*).

The risk of such accidents may be minimized by doing the appropriate groundwork. It is easy to say all of this with hindsight, though; mistakes will continue to be made even with the most cautious approach. If we knew all the answers already, there would be no further need to do clinical trials.

Regulatory requirements may dictate the use of suboptimal therapies. The requirement for monotherapy data, the requirement that treatment show superiority over a long-abandoned standard of care, and the rewarding of short-term pursuit of clinical end points all heavily contribute to the use of suboptimal therapies (often in patients with advanced infection). An example is the Abbott 247 trial, in which 1090 heavily pretreated patients with peripheral blood $CD4^+$ cell counts of <100 per cubic millimeter were randomized to receive either the protease inhibitor ritonavir or a placebo in addition to their current nucleoside analog reverse transcriptase (RT) inhibitor regimen. Ritonavir led to a 43% reduction in mortality after a median follow-up of just over 6 months (*13*). For practical reasons and from a regulatory perspective, this is the most efficient trial design, but it is also the best way to select for resistance to the invaluable protease inhibitor (*3*). In fact, this is reflected in the viral load curves of the patients from the Abbott 247 trial, which resemble the curves shown in Fig. 1, regimen 2 (*13*). I believe that it would have been in the best interest of the patients if, instead of ritonavir being added to the drugs they were already taking, the patients had been switched to non–cross-resistant nucleoside analog RT inhibitors simultaneously with the beginning of ritonavir treatment. For tuberculosis, adding a single new drug to a failing or inadequate regimen is the best way to select for drug resistance and to shorten the duration of the effect (*14*). As indicated above, the situation is the same for HIV (*3*).

It is clear that only a very short period

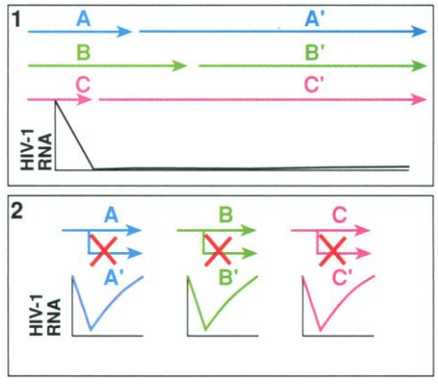

Fig. 1. Simultaneous treatment with antiretroviral drugs A, B, and C (regimen 1) versus sequential treatment with drugs A, B, and C (regimen 2). The graphs show viremia as HIV-1 RNA levels plotted against time. In regimen 1, with total suppression of viremia, drug A may be replaced by an alternative drug A′ that will be similarly effective. The same is true for drugs B and C, which may be replaced by drugs B′ and C′, respectively. In regimen 2, sequential monotherapy will lead to suboptimal suppression of viremia, and resistance to the consecutive drugs will develop rapidly. When drug A is no longer effective, drug A′ is no longer a valid alternative because of the development of cross-resistance. Drugs B′ and C′ will also not be effective once resistance develops to drugs B and C, respectively.

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of monotherapy testing should be allowed. Given the viral dynamics of HIV infection, with very high viral turnover rates, a drug's ability to interfere with viral replication in acutely infected cells (responsible for 99% of the plasma viremia) should become apparent within a few days (*1*). In addition, safety testing does not require prolonged monotherapy because, in clinical practice, drugs will be used almost exclusively in combination. Studying antiviral effects in potential sanctuaries for the virus, such as certain long-lived cell populations or the central nervous system, may be part of follow-up studies, in which drugs may (must, from a patient perspective) be used in combination.

Rapid conditional approval (possible in the United States but not in the European Community) should facilitate the adequate use of antiretroviral drugs. The obvious financial gain that industry would get from early approval could be balanced by a requirement for rigorous postmarketing testing, financed by the pharmaceutical industry and executed by independent organizations, such as the ACTG.

Ignoring the biology of the disease may result in the use of suboptimal therapies. Sometimes, scientific progress and evolving insights into HIV pathogenesis are not reckoned with sufficiently in clinical trial designs. It is not hard to find an example. In 1995, the British Medical Research Council–sponsored Quattro trial began and will complete its full course in 1997. It is a three-arm clinical trial comparing simultaneous quadruple therapy; sequential monotherapy with the same four drugs, each given in 8-week periods; and simultaneous therapy with two of the four drugs. One of the drugs in all three regimens is 3TC (lamivudine), a highly effective but also very vulnerable anti-HIV drug, which selects for high-level viral resistance within a few weeks if any replication is permitted to continue (*5*, *15*). The data on development of 3TC resistance were widely available when the Quattro trial started (*15*). Another drug in the quadruple and in the sequential regimens is a non-nucleoside RT inhibitor, a class of drugs that exhibits characteristics of rapid resistance development that are similar to those of 3TC (*16*). Moreover, sequential treatment strategies with nucleoside analog and non-nucleoside RT inhibitors had already been shown to be less than optimal (*17*) when the Quattro trial began. In light of all the available data on viral dynamics (*1*), the prognostic value of viral load (*2*), resistance development (*4*–*6*, *15*), and the superiority of various triple-therapy regimens over less suppressive regimens (*18*), I am amazed at the design and continuation of such a trial.

The pursuit of short-term economic interests by pharmaceutical companies may dictate the use of suboptimal therapies. This is typically exemplified by the exclusive or near-exclusive use of "incestuous" drug combinations in combination therapy trials of drugs produced by particular companies. Product A from company A would best be combined with product B from company B, but it is only made available to an investigator if he or she combines it with product C, again from company A or at least not from company B. Investigators around the world are experiencing this type of restriction. Necessary trials are delayed or cannot be done because of it. There is also a tendency to rapidly and widely publicize positive data and to delay or refrain from publication of studies with a negative outcome (*19*).

All of this is wrong and disgraceful and is not in the long-term interests of the pharmaceutical companies themselves. If antiretroviral agents are going to be used properly so that HIV infection can be turned into a chronic disease, there is room and need for many drugs on the market. Burning up therapeutic options prematurely is not only very cynical but in the end is self-defeating. By that time, however, the marketing manager will have moved on to another division or another company. It can only be hoped that people in the industry who take a long-range view will stand up and will prevail. Extension of the patent lives of drugs could make it easier. There should also be legislation, analogous to anti-trust laws, against exclusive use of incestuous drug combinations in clinical trials. Lack of publicity regarding negative data could be partially circumvented if there were a regulatory requirement to publish all-relevant data (positive and negative) within a certain time frame after completion of a trial. Here the cooperation of medical journals is essential.

Where Do We Go from Here?

Contrary to a rather common notion, our ability to do proper clinical trials does not cease to exist when there are only "maximally suppressive" regimens to compare. Parameters that may distinguish such regimens or components thereof include the durability of the antiviral effect; the vulnerability of the antiviral effect (or conversely, its "robustness") (*5*); the antiviral effect in sanctuaries for the virus (such as the central nervous system and long-lived cell populations) (*20*); the availability of subsequent options in case a regimen fails; short- and long-term toxicity; ease of intake and compliance; quality-of-life measures; cost efficiency; the level of immune reconstitution; and, last but not least, clinical end points, including survival.

Now that (near) total suppression of HIV replication appears feasible, there is renewed interest in the study of the immune system during therapy (*21*), generating questions such as the following: Is complete immune reconstitution possible? If so, at what disease stages? Can immune-based therapies contribute to clinical outcome? (*22*) May prophylaxis against certain opportunistic infections be stopped once the $CD4^+$ cell count has risen above a threshold?

With prolonged patient survival, new HIV-related disease manifestations may appear. Besides long-term efficacy and toxicity monitoring, this is another good reason for rigorous and prolonged postmarketing follow-up.

The challenge for us now is to identify maximally suppressive therapeutic strategies that will confer the greatest and longest immunological and clinical benefits at the lowest toxicity and cost and will thus benefit the greatest number of HIV-infected people possible. If chronic suppressive therapy is the best we can attain, long-term safety and compliance become essential issues, and the aim of therapy will be to suppress viral replication for as long as possible, using as few drugs as possible. It then becomes important to establish whether "maintenance therapy" with a few drugs is possible after "induction therapy" with a more aggressive regimen. If curative therapy is possible, an all-out approach would be warranted. In such a case, acute toxicity and discomfort comparable to that seen in patients during chemotherapy for cancer would be acceptable (*23*). But it may be artificial to present chronic suppressive and curative therapy as two wholly different scenarios; one may eventually lead to the other.

Desirable characteristics of future antiretroviral drug studies include a long follow-up period; flexibility with regard to drug regimens; comprehensive sampling (that is, not only sampling from blood but also from other tissues, such as lymphatic tissues or tissue sanctuaries such as the central nervous system and genital secretions); a strong pharmacology component; and a strong science component. Without a good scientific base, it is often better not to do the trial at all. Future trials will thus require the involvement of a rather large multidisciplinary team. These trials will not be large and simple but long, complex, and expensive. A cohort study–like approach will allow for maximum utilization of resources and patients.

In my view, now that adequate monitoring tools are available (*2*), "strategic trials" to answer questions such as when to start,

when to change, and when to stop are obsolete. Except for long-term nonprogressors, who are exceedingly rare (*24*), from a medical perspective there is no good reason not to start antiretroviral therapy as soon as the HIV-infected patient is mentally ready for it (*23*). Therapy may be changed if there is virological or immunological failure, for reasons of tolerance, or because new developments hold greater promise. Therapy may be stopped when it has ceased to be effective and there are no alternatives, and when the patient is ready for it. Or it may be stopped in the course of viral eradication protocols. There is no element of magic to it.

Simple principles do not necessarily make simple practice. Even when there were only three nucleosides available, care by HIV specialists could be shown to improve outcome significantly as compared with care by nonspecialists (*25*). To quote D. D. Richman: "The complexity of drug regimens, with each drug having distinct activities, toxicities, pharmacological profiles and patterns of drug resistance, calls for the administration of HIV chemotherapy by specialists analogous to the practice of oncology" (*5*).

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19. For instance, the comparison between zalcitabine (ddC) and zidovudine (ZDV) in antiretroviral-naïve patients (ACTG 114), showing inferiority of ddC to ZDV, to my knowledge still has not been published many years after completion of the trial. I am not sure, however, whether the blame for such delayed reporting always lies with the pharmaceutical company concerned. It may also lie with the investigators or medical journals concerned, who may not be very eager to publish "nonsexy" study results.
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