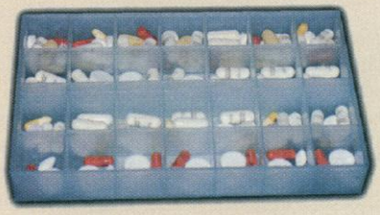
LETTERS

A "best strategy"

Researchers debate what is the best way for "clinical trialists" to develop and test "effective therapies" against HIV (below, 1 week's supply of pills for a patient). And, in disagreement with earlier letters, a reader states that Nobel winners deserve to keep "every single cent" of their $1-million prize.



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Antiretroviral Drug Trials

While Joep M. A. Lange's Policy Forum (25 Apr., p. 548) raises many of the problems faced by clinical trialists in developing effective therapies for human immunodeficiency virus (HIV) infection, he offers no solutions. Indeed, we have concerns that some of his views are misleading and may jeopardize future developments. For example, Lange criticizes the Quattro trial as an example of a trial that includes "suboptimal" therapies. We vigorously reject this suggestion.

Quattro, which was designed in 1993 and started in 1995, may be more topical in 1997 than we could have imagined. It is comparing, over 64 weeks, four reverse transcriptase (RT) inhibitors—Zidovudine (AZT), Lamivudine (3TC), Loviride (LVR), and zalcitabine (ddC), either together or sequentially (each for 8 weeks), with a two-drug regimen of AZT plus 3TC. Quattro seeks to answer two questions: first, whether a combination of four RT inhibitors is more effective (in terms of suppression of viral load) or more toxic than two RT inhibitors, and second, whether concurrent therapy is better than sequential treatment. As far as we are aware, no other trial has explored the use of four drugs in this way.

Although Lange considers that the two-drug regimen (AZT plus 3TC) is suboptimal, it is widely used in Europe as a first-line regimen for initiating therapy. The limited evidence about the sequential use of drugs, including the two studies to which Lange refers, we find unconvincing. One was an uncontrolled study of only 10 patients carried out by his own group (*1*). The other was a randomized trial of 41 patients receiving AZT plus didanosine (ddI) given either concurrently or alternating. It showed a significant difference in changes in CD4 count over a year (which supports concurrent therapy), but suggested that the CD4 trajectories were converging (*2*).

Quattro and relevant data from other trials and clinical studies have been under close review by the Coordinating Committee and by the independent Data and Safety Monitoring Committee (DSMC), which last reviewed the data in March 1997 and recommended continuation of the trial. The DSMC was aware of Lange's criticisms of the trial at the time. Quattro is not a double-blind trial; participants are free to change treatment at any time. Their options for further therapy include all of the protease inhibitors, ddI, and stavudine (d4T). In fact, many of the participants have chosen to continue their allocated treatment beyond 64 weeks (the planned end of the trial), at least until the results are available later this year.

Lange's main hypothesis is that the goal of antiretroviral therapy is the avoidance of viral resistance and that therefore regimens of less than three drugs are suboptimal. But the relationship between resistance and clinical outcome has not yet been clearly defined. For example, in the Delta trial, where the regimens of AZT plus ddI or ddC resulted in clinical benefits in terms of survival and disease progression compared with AZT monotherapy, it was assumed that this result was due to the delayed emergence of resistance in the combination regimens. However, the 215 and 41 mutations associated with AZT resistance and phenotypic resistance emerged more rapidly in the combination groups, although the viral load (plasma RNA) remained lower (*3*). Further, experiences with AZT and 3TC show that clinical benefits may be seen from adding 3TC in individuals already treated with AZT, possibly because AZT-resistant viruses have renewed susceptibility or because the virus with mutations in response to both AZT and 3TC is less "fit."

In the long term, complex regimens of multiple drugs may yet prove disappointing (because of poor compliance resulting from major and minor toxicities, but also because the development of multidrug resistance

may occur much more rapidly than therapeutic optimists expect). It is, unfortunately, quite possible that all of the current regimens are, to use Lange's phrase, "suboptimal" and the best strategy at present for asymptomatic individuals may be to take none of the existing cocktails, but to wait for improved treatments. We prefer to seek robust evidence about which therapies are truly "suboptimal."

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Lange and Jon Cohen (News & Comment, 25 Apr., p. 520) excellently summarize the current dilemmas in anti-HIV drug development. Despite the recent successes of combination drug therapy in HIV-infected patients, there is still much room for improvement, as not everyone experiences "miraculous" effects; in addition, the problems of toxicity, compliance, drug resistance, and costs become very relevant if long-term administration of these drugs is necessary to maintain these benefits. However, as explained by Lange and by Cohen, the current availability of these effective combinations also impedes progress: because of the logistics, costs and time-consuming aspects of human clinical trials, it is becoming increasingly complicated to prove the efficacy of novel antiviral drugs or the superiority of new drug combinations against the existing "gold" standard of combination therapy because it is unethical to treat "control" groups with anything less than the currently best available treatment. How can we avoid these dilemmas that threaten to break our stride in finding better treatments for HIV infection?

One answer is to use appropriate animal models. While murine models are appropriate for initial screening, further testing can be done in nonhuman primate models, where HIV infection best resembles that in humans. Recently, macaque models for anti-HIV drug testing have improved substantially. By using different study designs (including manipulating variables such as initiation of drug treatment relative to virus inoculation, the duration of treatment, the age of the animals, and the virulence and drug susceptibility of the virus inoculum), investigators have demonstrated that macaque models can address specific questions relevant to the treatment of human HIV infection (*1*).

Some pharmaceutical companies, unfortunately, are reluctant to test their experimental compounds in animals, even after these drugs have been approved by the Food and Drug Administration. We think that testing promising new treatment strategies in animal models will actually accelerate progress and save not only time and money, but also many human lives.

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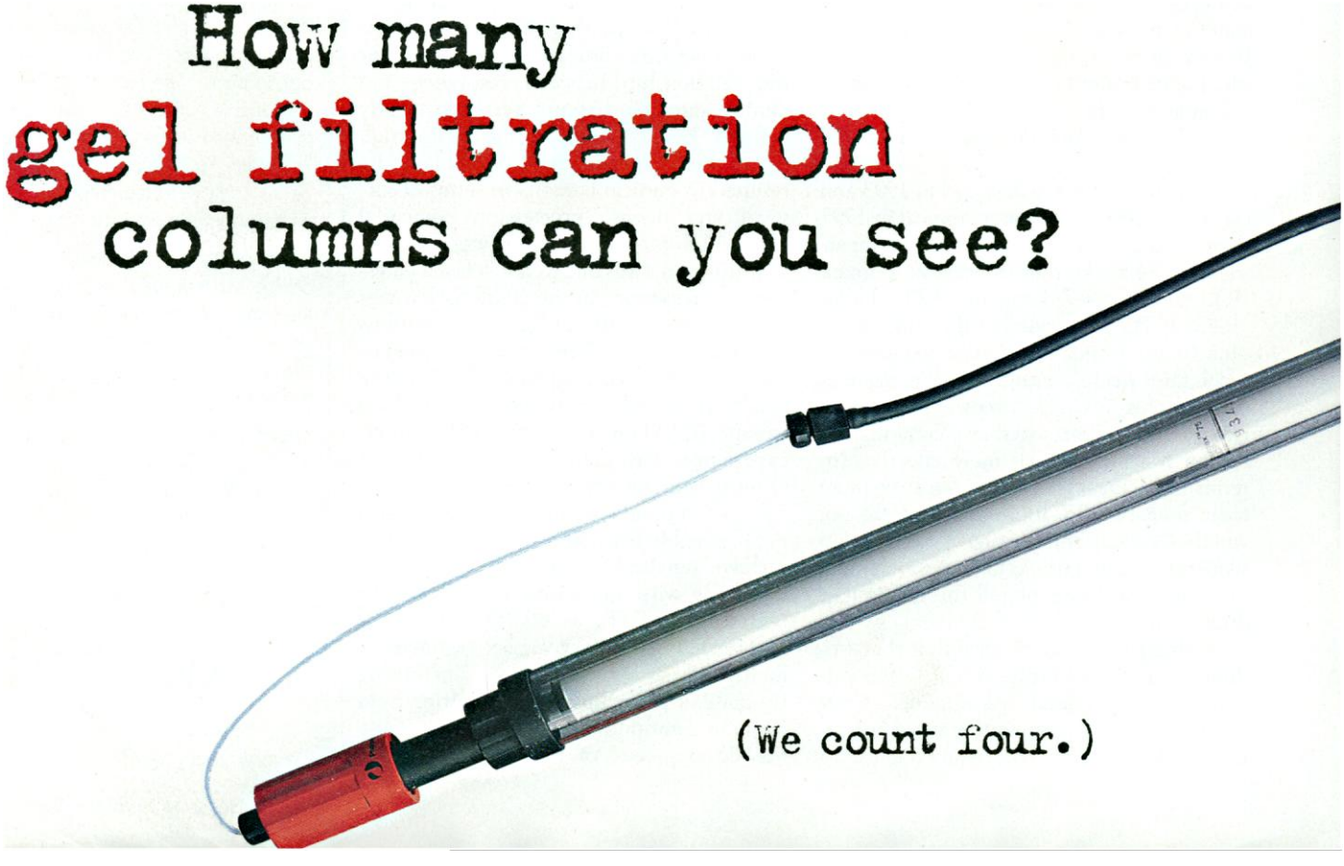

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Response: I thank Van Rompay and Marthas for their valuable comments regarding the potential utility of animal models for antiretroviral drug testing. I fully agree that these can help provide a solid scientific basis to guide human clinical trials. It is, however, implicit in the last sentence that animal models do not obviate the need for testing in humans. For one thing, there may be important differences in drug metabolism between species.

Moreover, I did not intend to seem pessimistic about the possibility of proving the efficacy of novel antiretroviral drugs in humans in a situation where there are only "maximally suppressive" regimens to compare. In fact, I allowed for a very short period of monotherapy testing to establish antiretroviral activity and listed parameters that may still distinguish between drug regimens and components thereof, including the durability of the antiviral effect, the vulnerability of the antiviral effect, the antiviral effect in sanctuaries for the virus, the level of immune reconstitution, and short- and long-term toxicity.

It is not clear to me why Breckenridge, Kitchen, and Darbyshire say that I offer "no solutions." It does appear, however, that their self-proclaimed "vigorous" rejection of my use of the Quattro study as an example of a trial that includes suboptimal therapies is backed by rather feeble arguments. The statement that "no other trial has explored the use of four drugs in this way" is not a recommendation. To my knowledge, there has also not been a trial on jumping off the Empire State Building as a treatment for HIV infection. The authors' apparent disregard for solid virological data generated in relatively small studies (*1*) ignores the biology of the disease and its relevance for HIV therapeutics. Progress in our understanding of HIV infection, its treatment, and the failure thereof has mainly come from intense virological investigations conducted in relatively few subjects (*2*), not from MRC-sponsored megatrials like Concorde (*3*). Concorde, a huge trial that established that the efficacy of AZT monotherapy is of limited duration, did not provide any explanation for this result because no virological investigations to speak of were done in the context of this trial. The authors profess to seek "robust evidence" about therapies, but the MRC's track record in this area reminds one of the tenth law of *The House of God*: "If you don't take a temperature, you can't find a fever" (*4*, p. 420).

Although Breckenridge *et al.* state that AZT plus 3TC is widely used in Europe as a first-line regimen for initiating therapy, this would be considered gravely irresponsible by the HIV physicians in my country and by many other leading HIV physicians for the reasons outlined in my Policy Forum and a recent Editorial (*5*). In our experience, in most patients who initiate treatment with such a combination, viral resistance to 3TC will have developed within 20 weeks (*6*). The fact that the Quattro DSMC has not recommended stopping the trial may have to do with the fact that the simultaneous quadruple therapy arm in this trial is far from optimal itself. Loviride is a nonnucleoside reverse transcriptase inhibitor of questionable potency (*7*), 3TC confers a degree of cross resistance to ddC (*8*), and 3TC and ddC may in fact be antagonistic because both drugs are cytidine analogs.

Contrary to what Breckenridge *et al.* state, I do not believe that the goal of antiretroviral therapy is the avoidance of viral resistance. The goal should be to restore or maintain the health of our patients, or both, and the only way to do that in the long run is to make sure that antiretroviral drug effect is maintained over time and that future therapeutic options are being kept open. In face of the clear superiority of various triple therapy regimens over combinations of two drugs (9), the statement that "the relationship between resistance and clinical outcome has not yet been clearly defined" does not seem supported. The Delta trial results only lend support to the hypothesis that suboptimal suppression of viral replication, as is attained with the double nucleoside combinations used, will lead to development of resistance. What the authors do not mention in their discussion of the Delta virology results is that the ddI and ddC in the combination arms still exerted their suppressive effect after the development of AZT resistance, something that had already been established in another trial (*10*). À propos, Breckenridge *et al.* should be grateful that there is such a thing as a Delta virology study for them to cite, because initially the MRC did not see a great need for it.

Although 3TC may still be of benefit in those with AZT-resistant virus (*11*), and 3TC-resistant virus may be less fit than wild-type virus, it should be evident that it is even better to maintain 3TC sensitivity (*12*). One eye is better than no eye, but two eyes are even better. Plus, again, 3TC resistance may compromise future options (*8*).

The concerns of Breckenridge *et al.* that my "misleading" views "may jeopardize future developments" seem hollow to me. Unfortunately, we don't have to wait for the future to observe the results of the MRC's condoning of suboptimal therapies.

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What Nobelists Deserve

I am appalled by the "communist" attitudes expressed in all three published letters on the issue of Nobelists' taxes (2 May, p. 661). These letters give the impression that the Nobel prize money is more like illicit gambling proceeds, better to be confiscated for the benefit of the "institutions" or the "national debt," certainly to be taxed. Having known a Nobel laureate personally, I can testify that in winning the prize, what counted most was his insight gained through thinking about an important scientific issue for a long time before everyone else, and a lot of hard work to bring an original idea to fruition, not necessarily a deeper dip into the common pool of research funds. Indeed, major breakthroughs in science often generate huge economic returns for humanity that make the $1-million prize paltry by comparison. Giant contributions to science deserve every single cent of the Nobel Prize—that's my bottom line. The only concesssion I am willing to make is that, because people tend to receive the prize after they are well established, when they need the money least, if they donate part of their prize to charitable causes (and they often do), then it is to be appreciated, not demanded.

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An "Excellent Exercise"

The article "Fermilab group tries plain English" by James Glanz (Research News, 11 Apr., p. 199) describes an excellent idea. It would be great if every major research university and organization produced a World