Initial Treatment for HIV Infection — An Embarrassment of Riches

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Drugs that are used to treat patients with human immunodeficiency virus (HIV) infection are classified according to their target. The first ones to be developed were nucleoside reverse-transcriptase inhibitors (NRTIs), which lead to premature termination of the nascent DNA chain, and nonnucleoside reverse-transcriptase inhibitors (NNRTIs), which bind and inhibit reverse transcriptase. The viral protease inhibitors were next. NRTIs, NNRTIs, and protease inhibitors remain the staples of highly active antiretroviral therapy, but other targets, such as the CCR5 receptor, the fusion peptide, and viral integrase, have recently yielded promising molecules.

At this time, eradication of HIV is impossible. Rebound inevitably follows cessation of therapy, and therapy must therefore be lifelong. With more than 20 drugs to choose from, there is an embarrassment of riches. Possible combinations are almost endless, as are the possibilities of side effects, either beneficial or damaging drug interactions, and the development of viral resistance.

Early in the antiretroviral-therapy era, the combination of indinavir (a protease inhibitor) and zidovudine and lamivudine (both NRTIs) predominated as the reference treatment. In 1999, the NNRTI efavirenz, in combination with zidovudine and lamivudine, proved to be more effective in diminishing the plasma concentration of HIV type 1 (HIV-1) RNA (the “viral load”) than the reference treatment.1 Indinavir has since been largely replaced by atazanavir or lopinavir combined with a small dose of ritonavir to boost absorption and plasma levels.

Current guidelines recommend initiating antiretroviral therapy with two NRTIs in combination with either an NNRTI or a protease inhibitor.2 So the first question is, Which NRTIs and which protease inhibitor do we choose? And the second question is, Which is better, an NNRTI or a protease inhibitor? Phase 4 studies that compare treatment strategies are desirable, but they are difficult to do. In a rapidly moving field such as HIV therapy, what is the “reference treatment”? Trials have to be large and continue for a long time, and patients may vote with their feet and refuse to continue with a therapy that they judge, rightly or wrongly, to be inferior to the latest miracle drug. And large trials that continue for a long time are expensive. Drug companies have little to gain, and much to lose, from comparing one of their already marketed drugs with another that may be better. The National Institutes of Health, through the Clinical Trials Network, have very properly undertaken trials such as the Strategies for Management of Antiretroviral Therapy (SMART; ClinicalTrials.gov number, NCT00027352),3 which showed that intermittent treatment was inferior to continuous treatment for patients with HIV infection.

In this issue of the Journal, Riddler et al.4 report on the AIDS Clinical Trials Group Study A5142, which compared three drug combinations in the initial therapy of 753 patients with HIV infection: efavirenz plus two NRTIs (efavirenz group), lopinavir–ritonavir plus two NRTIs (lopinavir–ritonavir group), and lopinavir–ritonavir plus efavirenz (NNRTI-sparing group). As previously noted, the first two regimens were popular and widely prescribed. The third is theoretically attractive, since it avoids the use of NRTIs, which are suspected of contributing to side effects. An uncontrolled study of 86 patients showed that this combination would be effective, although it was not well tolerated: after 48 weeks, 24% of patients either discontinued the study regimen because of adverse events or were lost to follow-up.5 A study by Boyd et al. looked at efavirenz with ritonavir-boosted indinavir as an NNRTI-sparing option, with similar conclusions.6
The results of the study by Riddler et al. are difficult to put in a nutshell. We want regimens that win in all categories: suppression of HIV-1 RNA, an increase in the CD4 cell count, a lack of emergence of resistance, low toxicity, and simplicity. However, the study by Riddler et al. yields a split decision. When the regimens were ranked according to suppression of HIV-1 RNA, the efavirenz group had the best results, closely followed by the NRTI-sparing group and the lopinavir–ritonavir group, although the difference between the efavirenz group and the NRTI-sparing group was not significant. When the regimens were ranked according to the emergence of drug resistance, the winner was the lopinavir–ritonavir group, followed by the efavirenz group and the NRTI-sparing group, and again the difference between the lopinavir–ritonavir group and the efavirenz group was not significant. Finally, as measured by the proportion of patients who discontinued or changed their treatment, all three groups had similar rates of adverse events.

Patients who participate in clinical trials differ from the majority who do not participate — one reason why clinical practice often cannot reproduce published results. Efavirenz causes side effects involving the central nervous system, including sleep disturbances with vivid dreams, dizziness, and daytime drowsiness. Such symptoms are frequent and troublesome early on; they largely disappear after a few weeks of therapy. Nonetheless, in all studies we are aware of, a sizeable percentage of patients discontinued efavirenz because of these effects; the proportion was particularly high among patients who acquired HIV through illicit drug use, partly because efavirenz interferes with methadone. We are struck by the fact that Riddler et al. did not record much of this type of discontinuation in their study. This suggests that their patients were greatly motivated to continue their prescribed regimen, perhaps through their repeated and close contact with the investigators — a type of Hawthorne effect* that is difficult to duplicate in routine practice.

Another problem with the study relates to the NRTIs that were administered in the efavirenz group and the lopinavir–ritonavir group. All patients received lamivudine, but the second NRTI was zidovudine (which was assigned to 42% of patients), extended-release stavudine (24%), or tenofovir (34%). NRTIs differ in both side effects and efficacy. Since the study started, the formulation in the lopinavir–ritonavir capsule has been replaced by tablets that produce a more consistent plasma drug level and are perhaps associated with less diarrhea and nausea. Extended-release stavudine has never been marketed because of pancreatic toxicity. Tenofovir and emtricitabine (a drug that was not used in the study) have become the reference NRTI combination. In summary, these reservations cast doubt on the future applicability of the study’s findings — doubts that will not be easily resolved by further studies.

Nonetheless, on the basis of this study, it seems that efavirenz plus two NRTIs is hard to beat. In addition to the stated results, one has to consider the low pill burden, since brand-name formulations contain efavirenz, emtricitabine, and tenofovir for a one-pill daily regimen, and the fact that in most countries, efavirenz costs less than lopinavir–ritonavir. These data should challenge the 40% of clinicians who start antiretroviral treatment with a protease inhibitor and should reassure those who, in resource-limited settings, must use combinations of NRTIs and NNRTIs because they are cheaper.

Will new drugs dethrone efavirenz? Etravirine (an NNRTI), raltegravir (an integrase inhibitor), and maraviroc (a CCR5 inhibitor) are targeted to patients with drug-resistant virus. But because of their excellent pharmacokinetics and initially favorable side-effect profiles, these drugs have a potential for earlier use and in a few years may even be successfully combined.

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Multiple Biomarker Panels for Cardiovascular Risk Assessment
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Guidelines for the assessment of cardiovascular risk remain focused squarely on established risk factors.1 Although it is known that tools based on these risk factors, such as the Framingham Risk Score, have a number of limitations when applied in clinical practice — performing reasonably well for groups but not necessarily for individuals and underestimating long-term risk among younger persons2 — it has proved surprisingly difficult to improve on established risk factors for the prediction of cardiovascular disease. Of the many strategies that have been proposed to improve risk stratification, the measurement of plasma biomarkers is particularly attractive as compared with alternatives such as cardiovascular imaging.

Numerous biomarkers have been proposed to have mechanistically plausible links to clinical cardiovascular disease, with many reported to identify people at an increased risk for future cardiovascular events independently of the presence of established risk factors. Typically, however, the risk increment captured by elevated levels of these markers is modest, and little improvement is seen in traditional measures of discrimination such as the C statistic or the area under the receiver-operating-characteristic curve. Much of the recent debate over emerging biomarkers focuses on the questions of how much incremental value is provided and what the best metrics are to quantify improvements in screening performance.3,4

One strategy that has been proposed to improve on the limitations of individual biomarkers is to combine multiple biomarkers into an integrated score or algorithm. However, an evaluation of 3209 participants from the Framingham Heart Study failed to validate this approach.5 Although persons with high biomarker scores had an increased risk of death as compared with those with low scores, the increment in the C statistic over the model with traditional risk factors was small. Similarly, in the Cardiovascular Health Study, which included 5808 older Americans, the addition of six novel biomarkers did not improve discrimination beyond established risk factors among subjects with or without chronic kidney disease.6 Thus, despite decades of research and the introduction of numerous candidate biomarkers and putative risk factors, risk prediction for cardiovascular disease in the population appears to have progressed only marginally.

An article in this issue of the Journal suggests that measurable progress with the use of biomarkers could be possible. Zethelius et al.7 report data from an evaluation of multiple biomarkers in a community cohort of elderly men. Among 1135 men with a mean age of 71 years at study entry (661 of whom were free of cardiovascular