When More Is Less

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(See the article by Demeter et al. on pages 552–8)

Landmark studies on the dynamics of HIV-1 infection, conducted nearly a decade ago, provided the theoretical framework on which the modern approach to combination antiretroviral therapy is based [1]. It is now accepted dogma that the high turnover rate of the virus, coupled with a high mutation rate—a consequence of the low fidelity of reverse transcriptase—leads to the accumulation of mutations in the viral quasispecies over time. According to this model, individual drug-resistance mutations are represented many times in the quasispecies; double-mutants are less common, and specific triple mutants are relatively rare [2]. Antiretroviral regimens consisting of several drugs with nonoverlapping resistance patterns erect a genetic barrier to resistance, because multiple mutations—which are unlikely to be preexisting in any single viral genome—are needed to reduce activity of the regimen.

Because the level of plasma HIV-1 RNA at steady state is a function of the replication rate and because the replication rate is a determinant of the mutation rate, it is reasonable to assume that patients with high plasma HIV-1 RNA levels are more likely to harbor preexisting drug-resistant variants than are patients with lower virus loads. Likewise, patients with advanced HIV-1 disease may be at greater risk for the development of drug-resistant virus. In such patients, the genetic barrier of triple combination therapy might not suffice to prevent emergence of resistance and ensure durable suppression of virus replication. Indeed, for certain 3-drug combination regimens, high virus load and low CD4 cell count are associated with a greater risk of treatment failure [3].

Against this background, AIDS Clinical Trials Group protocol 388 (ACTG 388) was designed to test the hypothesis that 4-drug regimens would be more efficacious than a standard 3-drug regimen in subjects with advanced HIV-1 disease (defined as a plasma HIV-1 RNA level of \( \geq 80,000 \) copies/mL and/or a CD4 cell count \( \leq 200 \) cells/mm\(^3\)) and a limited history of prior antiretroviral treatment [4]. Patients received a 3-drug regimen of zidovudine, lamivudine, and indinavir (the indinavir arm) or a 4-drug regimen of zidovudine and lamivudine plus efavirenz and indinavir (the efavirenz-indinavir arm) or nelfinavir and indinavir (the nelfinavir-indinavir arm). The efficacy of the efavirenz-indinavir regimen was superior to that of the standard indinavir regimen, but efficacy of the nelfinavir-indinavir regimen was significantly worse. Greater toxicity and lower adherence rates in the nelfinavir-indinavir arm appeared to explain this result.

Additional light is shed on the results of ACTG 388 by the analysis by Demeter et al. [5] of genotypic and phenotypic drug resistance in this trial in the current issue of Clinical Infectious Diseases. Demeter et al. [5] found that phenotypically susceptible virus was present at the time of virologic failure in 55% of patients in the nelfinavir-indinavir arm, compared with 22% in the triple-drug control arm \( (P = .006) \). Particularly striking was the markedly higher prevalence of lamivudine resistance at the time of virologic failure in the triple-therapy arm (78%), compared with that in the nelfinavir-indinavir arm (43%; \( P = .003 \)) and the efavirenz-indinavir arm \( (P = .002) \).

Although the regimens used in ACTG 388 no longer are considered to be standards of care, these results nevertheless provide important insights into the relationship between drug resistance and treatment failure. First, this study offers additional evidence that not all treatment failure is associated with development of drug resistance. Second, these data again illustrate the principle that the rate at which resistance emerges depends on the relative advantage conferred to the virus by particular mutations [2]. Therefore, resistance to lamivudine and/or efavirenz (cases in which a single point mutation confers high-level resistance) was observed most often, whereas resistance to the thymidine analogues and protease inhibitors...
occurred infrequently. In this respect, results of the current study reinforce the importance of a genetic barrier to resistance. Similar results were noted in ACTG protocol 364, a study in which patients were randomized to receive efavirenz, nelfinavir, or both after failure of nucleoside reverse-transcriptase inhibitors (NRTIs) [6, 7].

At the same time, the results of ACTG 388 illustrate the overriding importance of tolerability, adherence, and pharmacokinetics in determining long-term success of an antiretroviral regimen. As noted by Demeter et al. [5], the finding that lamivudine resistance was detected in fewer than one-half of subjects with virologic failure in the nelfinavir-efavirenz arm likely reflects decreased drug exposure due to the poor tolerability of that regimen. Similarly, the finding that phenotypic resistance to lamivudine or efavirenz was detected in fewer than one-half of subjects with virologic failure in the indinavir-efavirenz arm suggests that many of the failures in this arm, which was more effective overall, were also due to nonadherence. These results demonstrate that potential gains in potency of multidrug regimens may be offset by greater complexity, decreased tolerability, and lower adherence as more drugs are added.

Results of the article by Demeter et al. [5] also illustrate the complex relationship between treatment adherence and development of HIV-1 drug resistance. Resistance is least likely to emerge in patients with high levels of adherence to potent regimens (because virus replication is suppressed) and in those with very low levels of adherence (because of minimal drug exposure) [8]. The risk of resistance is greatest in those with intermediate levels of adherence and in those with high levels of adherence to suboptimal regimens. In these cases, ongoing virus replication in the setting of significant drug exposure leads to selection of drug-resistant virus.

If the resistance data are extrapolated to the study population as a whole, then the overall risk of developing phenotypic resistance was 24% in the indinavir arm, 21% in the nelfinavir-efavirenz arm, and 17% in the efavirenz-efavirenz arm. Thus, the higher rates of resistance at the time of virologic failure in the indinavir and efavirenz-efavirenz arms, compared with that in the nelfinavir-efavirenz arm, are offset by lower rates of virologic failure in those arms. The relative costs associated with the risk of virologic failure and the emergence of drug resistance in each of these treatment arms could be compared by considering the number of future drug options remaining after failure of each regimen, an approach that quantifies the effect of any given therapeutic strategy on drug resistance [7].

Although the results of ACTG 388 seem to favor use of the efavirenz-efavirenz regimen in treatment-naïve patients with advanced disease, the study did not examine the efficacy of a 3-drug regimen of zidovudine, lamivudine, and efavirenz in this population. In ACTG 384, a 4-drug regimen of zidovudine, lamivudine, efavirenz, and nelfinavir was no more effective than a 3-drug regimen of zidovudine, lamivudine, and efavirenz, even in patients with high baseline plasma HIV-1 RNA levels [9]. A randomized trial to determine the benefits of adding abacavir as a fourth drug to a zidovudine-lamivudine-efavirenz regimen is currently underway in the Adult ACTG (ACTG A5095) [10]. Pending results of that trial, it is best to adhere to the current HIV-1 treatment guidelines of the US Department of Health and Human Services (revised 23 March 2004), which recommend triple-drug regimens comprising 2 NRTIs and efavirenz or lopinavir/ritonavir for initial treatment of HIV-1 infection (http://www.aidsinfo.nih.gov). As ACTG 388 shows, when it comes to combination antiretroviral therapy, more is sometimes less.

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References