Less than the Sum of Its Parts: Failure of a Tenofovir-Abacavir-Lamivudine Triple-Nucleoside Regimen

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(See the article by Gallant et al., on pages 1921–30.)

Current guidelines for the treatment of HIV-1 infection recommend the initiation of antiretroviral therapy with a combination of a nonnucleoside reverse-transcriptase inhibitor (NNRTI) or a ritonavir-boosted protease inhibitor (PI) in combination with 2 nucleoside reverse-transcriptase inhibitors (NRTI) [1]. These potent, convenient, and generally well-tolerated first-line regimens achieve durable suppression of plasma HIV-1 RNA levels in most patients. Nevertheless, these regimens are not ideal for all patients. Triple-NRTI regimens have seemed like attractive alternatives, because they lack the toxicities and metabolic interactions of NNRTIs or PIs. Unfortunately, the activity of such regimens has often proved disappointing. In this issue of the Journal of Infectious Diseases, Gallant et al. report the results of a trial of a novel triple-nucleoside combination of tenofovir disoproxil fumarate (DF), abacavir, and lamivudine [2]. Because each of these drugs individually possesses substantial anti-HIV-1 activity, the combination should, in theory, be quite potent.

In their study, Gallant et al. randomized 340 treatment-naive subjects to receive once-daily tenofovir DF/abacavir/lamivudine or efavirenz/abacavir/lamivudine. Baseline characteristics (median plasma HIV-1 RNA level of 4.7 log_{10} copies/mL and median CD4+ cell count of 251 cells/mm^3) were similar to those of subjects from most contemporary studies of treatment-naive subjects. Reports by participating protocol investigators of high rates of virologic failure in study participants, together with similarly high failure rates noted in smaller pilot studies of the same regimen, prompted the sponsor (GlaxoSmithKline) to conduct an unplanned interim analysis of data from the 194 patients for whom at least 8-week follow-up data were available as of 7 July 2003. Results of this interim analysis revealed a virologic failure rate of 49% in the tenofovir DF arm versus 5% in the efavirenz arm ($P < .001$). The signature tenofovir DF resistance mutation (K65R) was found in samples from more than one-half of subjects tested at the time of virologic failure.

Several other studies of the same regimen have shown similar conclusions. Reports of uncontrolled experiences with tenofovir DF/abacavir/lamivudine in 2 practice settings found high rates of failure and frequent emergence of the K65R mutation [3, 4]. Likewise, the Tonus trial (an open-label pilot study of tenofovir DF/abacavir/lamivudine) was halted when virologic failure was observed in 12 of 36 subjects after only 12 weeks of follow-up [5]. Other triple-nucleoside regimens have also performed less well than NNRTI- or PI-containing regimens, but they have not shown such high rates of rapid virological failure [6, 7].

What accounts for the poor performance of these regimens? In vitro studies have failed to demonstrate any antagonism between 2- and 3-drug combinations of tenofovir DF, abacavir, and lamivudine when wild-type and drug-resistant viruses are used [8, 9]. Similarly, pharmacokinetic studies have shown no effect of any one of these drugs on plasma levels of the others [10, 11], nor do tenofovir DF or abacavir appear to reduce intracellular levels of carbovir triphosphate (the active moiety of abacavir) or phosphonothymoxypropyl adenine (PMPA) diphosphate (the active form of tenofovir), respectively, in peripheral blood mononuclear cells (PBMCs) from treated subjects [10].

Gallant et al. suggest that a low genetic barrier to resistance could account for their results. As they note, 2 point mutations—K65R and M184V—together confer resistance to all drugs in the regimen. In fact, the K65R mutation alone might...
be sufficient to confer resistance to tenofovir DF, abacavir, and lamivudine. However, K65R was detected in HIV-1 sequences from only 54% of subjects in whom genotyping was performed at the time of virologic failure. Clonal analysis of samples from these subjects suggests that the K65R and M184V mutations arose initially on separate viral genomes, followed by the selection of viruses carrying both mutations [12]. Nevertheless, if resistance is invoked as the principal explanation for the failure of tenofovir DF/abacavir/lamivudine, it is difficult to explain why one-half of the failures occurred in subjects without K65R, particularly given that M184V sensitizes HIV-1 to tenofovir DF and has only a modest effect on susceptibility to abacavir.

Two other mechanisms deserve consideration as potential explanations. One hypothesis is that the tenofovir DF–mediated inhibition of the enzyme purine nucleoside phosphorylase (PNP) leads to an accumulation of naturally occurring dNTPs, which thereby favors incorporation by HIV-1 reverse transcriptase of the natural purine dNTPs over the purine analogue NRTIs [13]. Both PMPA mono- and diphosphate inhibit PNP activity in vitro, but no effect of tenofovir DF or abacavir on purine dNTP pools in PBMCs was observed [14]. A second hypothesis is that nucleosides and nucleotide analogues are not uniformly distributed or activated in different CD4+ cell populations. For example, phosphorylation of zidovudine to zidovudine triphosphate occurs best in activated lymphocytes, whereas didanosine is readily metabolized to its active form in both resting and activated cells [15]. Such physiological compartmentalization could result in the activity of only 1 or 2 NRTIs, rather than all 3 NRTIs, in some cells. This hypothesis could explain the pattern of drug resistance observed in Gallant et al.’s study—if tenofovir DF or abacavir are active only in some cells but not in others, then resistance to lamivudine could be sufficient to undermine the activity of the entire regimen.

The results of Gallant et al.’s study highlight the need for formal clinical trials to evaluate novel antiretroviral regimens before they are adopted into routine clinical practice, even when all components of the regimen are approved drugs. These results also underscore the importance of carefully monitoring such trials. It may not be possible to remove all risk from clinical trials, but vigilance on the part of investigators and prompt action on the part of sponsors, as in the study discussed here, can help to minimize the exposure of subjects to regimens that turn out to be inferior.

References


