Editorial Response: What Is Antiretroviral Failure?

Current strategies in antiretroviral therapy have resulted in dramatic reductions in the incidence of opportunistic infections and the overall morbidity associated with HIV disease in the United States. This is temporally associated with the widespread use of highly active antiretroviral therapy (HAART) that includes HIV-1 protease inhibitors (Pis) [1]. HAART has also been shown to dramatically reduce HIV-1 plasma viral load and sustain this suppression, in comparison with earlier monotherapy or dual therapy with nucleoside analogues (NAs) [2]. However, numerous issues have recently emerged that have dampened the enthusiasm for these therapeutic regimens.

HAART regimens in general are complicated and, as such, present adherence problems. Some regimens require that patients take 10–20 pills per day in divided doses. Individual medications within a regimen may also require a fixed schedule or strict ingestion criteria with regard to meals. Strict adherence to regimens may not be possible, secondary to psychosocial factors (previous or concurrent diseases, mental health or legal issues, homelessness, substance abuse, divorce, incarceration, or pregnancy) or ethnic-cultural issues (the patient’s perception of HIV disease state, risks/benefits of therapy, and their relationship with health providers).

Side effects after long-term PI use, such as lipodystrophy, dyslipidemias, and diabetes mellitus, have now been described [3]. Interactions with other medications, particularly those utilizing the hepatic cytochrome P450 system (3A4 isoenzyme) for their metabolism, have precluded the use of many classes of medications that can be used concurrently with PIs [4, 5]. Because of drug interactions, drug-absorption issues, toxicity history, and underlying drug-resistant variants, among other factors, patients previously treated with antiretroviral agents may not demonstrate a predicted response with a new regimen [6].

Clough et al. [7], in this issue of Clinical Infectious Diseases, provide some insight into what factors associated with PI-including regimens determine partial virological responses. Their retrospective study was performed with a cohort of ~100 subjects. The median duration of prior NA therapy was 2 years, and indinavir was the only PI used. Only a few subjects in this study received two new NAs in addition to indinavir. The investigators measured adherence rates by using patient and provider questionnaires and audits of prescription-refill records. Sociodemographic variables in their study that predicted an incomplete response (defined as a viral load of >400 copies/mL at ≥20 weeks after the start of therapy with indinavir and one new NA) included nonwhite race, low CD4 cell counts, concurrent prophylaxis for Pneumocystis carinii pneumonia, active substance abuse, medication nonadherence, missed clinic appointments, and high baseline viral loads.

Only 40% of the total cohort had a viral load of <400 copies/mL after 20 weeks of therapy. In 60% of subjects with baseline viral loads of <30,000 copies/mL the viral load became undetectable, compared with only 30% of those whose baseline viral loads were >300,000 copies/mL. This is not surprising since HAART in drug-naive subjects has generally resulted in maximal viral load reductions in the 2.5–3.0-log10/mL range [8]. The expected viral load reductions in antiretroviral-experienced patients, particularly zidovudine (ZDV)–experienced patients, are somewhat less [9].

Natural history studies have demonstrated that high viral load levels after seroconversion are predictive of more rapid disease progression [10]. Although this was confirmed in chronically infected subjects in the AIDS Clinical Trials Group Study 175 as well, a 1- or 2-log reduction in viral load following 8 weeks of therapy was associated with significant incremental reductions in the risk of opportunistic infections or death. This reduction in risk was found even in subjects with baseline viral loads of >106 copies/mL. Furthermore, these dramatic results were achieved in the pre-PI era with dual NA therapy and didanosine monotherapy [11].

Thus, although viral load suppression (<400 copies/mL, or now <50 copies/mL) is the desired goal, successful clinical outcomes can be achieved with more modest reductions in viral load. Further complicating this goal and strategy are recent reports of discordant virological and immunologic responses with HAART-experienced patients. Several patients have now been described who have had minimal virological responses, in the presence of profound and sustained increases in CD4 cell counts [12]. Whether this translates to long-term clinical non-progression remains to be determined.

It is interesting that in the study by Clough et al. [7], all seven ZDV-naive subjects had a complete response, vs. only 36% of those who were ZDV-experienced. Other previously used NAs were not predictive of this lack of response. This may be related in part to the presence of ZDV-resistant strains. Although genotyping was not performed in the current study, a mutation at codon 215 in the HIV-1 reverse transcriptase gene, known to confer ZDV resistance, has been associated with an increased risk of clinical progression and with the lack of or a partial virological response after the introduction of new NAs [13, 14].

Other mutations in the reverse transcriptase and protease

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genes are known to impart cross-resistance or class resistance to NAs and PIs [15]. Genotyping may have offered a partial explanation for the lack of virological response in this cohort. Other studies have shown that lack of or a partial virological response in previously NA-treated patients after the addition of indinavir to the treatment regimen was associated with resistance to indinavir [16]. Finally, although the study by Clough et al. [7] was performed 2 years ago in PI-naive subjects, new concerns about suboptimal virological responses to HAART now include the transmission of PI- and NA-resistant strains in drug-naive subjects [17].

The definition of a complete response in this study was a viral load of <400 copies/mL. Although the only assay currently approved by the U.S. Food and Drug Administration (HIV-1 Monitor; Roche Diagnostics, Somerville, NJ) has a lower copy limit of 400 copies/mL, recent results of clinical studies using newer, third-generation or ultrasensitive viral load assays have demonstrated that virological failure (a return to baseline viral load) is likely when a viral load nadir of <50 copies/mL has not been achieved [18]. The kinetics of virological reduction following initiation of HAART indicate that a first phase of decline (resulting in a reduction of ≥2 logs/mL) is achieved in 4–8 weeks. The second phase of decline (to <50 copies/mL) may not be achieved for up to 24 weeks [19]. This second phase may represent the effects of HAART in lymphoid tissue (large reservoirs of virus) or sanctuary sites (e.g., brain or testes) that require more prolonged drug exposure to reduce the number of HIV-infected cells within the population.

By sampling blood at 20 weeks, Clough et al. [7] may have missed the virological nadir in some subjects whose therapy had already failed virologically. Sampling later would have introduced further bias, as more subjects in whom complete suppression was not achieved earlier would have had treatment failure because of resistance. By using a 400-copy/mL viral load threshold, the investigators may also be overestimating the number of subjects who would have had a complete and durable virological response (i.e., <50 copies/mL). Whether a sustained virological response at <50 copies/mL is required over the long term to prevent clinical progression remains to be determined.

The study by Clough et al. [7] also demonstrates that adherence to HAART regimens was difficult and that providers and patients estimated adherence poorly. Patient and provider adherence assessments were concordant with pharmacy-refill records for 64% and 52% of patients, respectively. Provider and patient assessments of adherence were concordant in only 65% of the cases. These percentages are consistent with the findings of Bangsberg et al., who recently noted that patient questionnaires overestimated adherence when compared to direct, random pill counts [20].

These low levels of adherence may be related to the regimen that was prescribed to this cohort. Because indinavir dosing must be every 8 hours, adherence may be more difficult than with other currently prescribed PI-containing regimens. Other regimens containing nelfinavir or the combination of ritonavir and saquinavir have demonstrated equivalent virological efficacy with twice-daily dosing [21, 22]. Improved adherence was confirmed in earlier NA studies with twice-daily dosing [23].

Other variables affecting regimen adherence include number of pills, food requirements, gastric acid requirements, adverse effects, drug interactions, storage restrictions, and availability of liquid formulations. Emerging strategies to improve antiretroviral adherence now include potent non-PI (PI-sparing) regimens such as with triple NAs (e.g., ZDV/lamivudine [3TC]/abacavir, 2 pills twice daily) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) and NAs (nevirapine/didanosine/3TC, 8 pills once daily) [24, 25]. Furthermore, NNRTIs have been successfully substituted for PIs in patients with undetectable viral loads [26].

National consensus guidelines on antiretroviral therapy provide a conceptual framework for practitioners to use in the management of cases [27]. Clinical trials, from which most of these recommendations have been established, may introduce result bias in terms of patient motivation and adherence to regimens, in comparison with real situations in clinical practice. A broad range of complex issues defines treatment success in clinical practice. Practitioners must define realistic virological and immunologic goals based on adherence that incorporate the antiretroviral experience and psychosocial and ethnocultural makeup of patients [28]. Understanding these aspects will allow practitioners to design regimens that promote adherence and virological success for all patients.

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References


