

Perspectives

Strategies for Management of Antiretroviral Failure

Scott M. Hammer, MD

At the Atlanta course in February, Scott M. Hammer, MD, discussed antiretroviral failure, one of the most pressing current issues for clinicians. Dr Hammer reviewed current approaches to initial failure and salvage therapy, examining the data on specific treatment regimens and on treatment interruptions.

Antiretroviral failure can be associated with a variety of factors, including drug-resistant variants, subinhibitory drug levels, and host immune failure (Figure 1). Drug failure can be defined clinically as disease progression, immunologically as CD4+ cell count decline, or virologically as plasma HIV-1 RNA increase. With the drive to identify drug failure early, increases in viral load most commonly serve as the definition for drug failure and the trigger for decisions to modify therapy. Among the issues to be considered in managing antiretroviral failure is that of what threshold of increase in viral load should serve as a trigger for modifying treatment. This decision will depend on the philosophy of the physician and patient and is also affected by whether it is the first regimen failure or a case of multiple regimen failure. If a change in regimen is considered necessary, the primary question becomes that of how the regimen may be modified to preserve virologic, immunologic, and clinical benefit.

Treatment Changes in Early (First) Virologic Failure

A central question in initial virologic failure is whether all drugs or just selected drugs in the regimen should be changed. Data from the AIDS Clinical Trials Group (ACTG) 343 study indicate that the first resistance mutations to arise in a protease inhibitor/dual nucleoside reverse transcriptase inhibitor (nRTI) regimen that

Dr Hammer is Professor of Medicine at Columbia University College of Physicians and Surgeons and Chief of the Division of Infectious Diseases at Columbia Presbyterian Medical Center in New York City.

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includes lamivudine are those associated with lamivudine resistance. These results have been borne out with indinavir in the Trilege study, as well as in ACTG 347 with amprenavir and in other data with ritonavir in a lamivudine-containing combination. In 17 patients exhibiting viral rebound during induction-maintenance therapy with indinavir/zidovudine/lamivudine in ACTG 343 (mean weeks on therapy, 45; mean weeks of rebound, 25), none exhibited phenotypic resistance to indinavir (1 exhibited the protease inhibitor-associated M46L resistance mutation), whereas 14 (82%) had phenotypic resistance to lamivudine and the lamivudine-associated

M184V resistance mutation. Such findings indicate that it may not be necessary to change all drugs in a failing regimen and suggest approaches that can potentially preserve drugs for current use or future recycling. However, failure in such cases should still be interpreted as regimen failure and narrow substitutions should be viewed with caution; if part of the regimen is to be maintained, the goal of substituting new drugs must be to substantially bolster the regimen potency.

General options for alternative treatment in initial treatment failure are shown in Table 1. In the case of protease inhibitor-containing initial regimens, susceptibility to protease inhibitors may be retained in subsequent regimens. However, data from ACTG 343 and the Trilege study indicate that suboptimal indinavir blood levels contributed to initial virologic failure; protease inhibitor pharmacokinetics and thus potency can be improved by addition of low-dose ritonavir. With regard to other drugs in initial regimens, resistance to lamivudine or to nonnucleoside reverse transcriptase inhibitors (NNRTIs) is likely if they were components of an initial regimen that failed. In triple nRTI initial treatment, it has been found that although lamivudine resistance is associated with some degree of abacavir cross-resistance, the relatively small

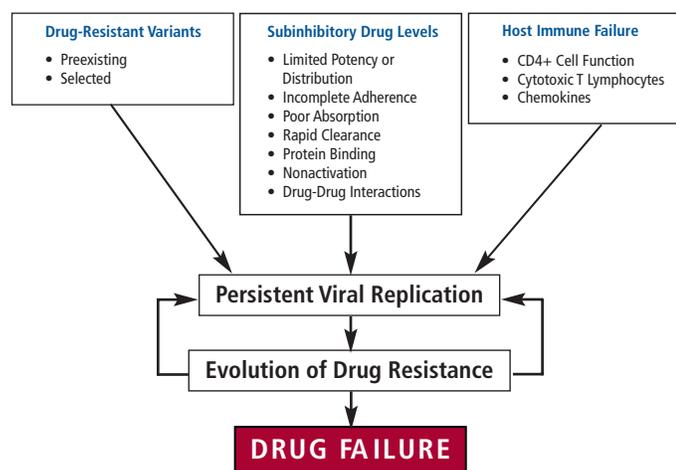


Figure 1. Factors contributing to antiretroviral failure. Adapted from Hirsch et al. *JAMA*. 1998.

Table 1. Options for Treatment Failure

| Initial Regimen | Alternative Regimen | Comments on Initial Regimen |
|------------------|---------------------|---|
| PI/2 nRTIs | 2 PIs/2 nRTIs/NNRTI | PI susceptibility may be retained; lamivudine resistance likely if in regimen |
| NNRTI/2 nRTIs | 1-2 PIs/2 nRTIs | NNRTI resistance likely; lamivudine resistance likely if in regimen |
| 3 nRTIs | 2 PIs/NNRTI/2 nRTIs | Abacavir may still be useful if in first regimen |
| 2 PIs/2 nRTIs | 2 PIs/NNRTI/2 nRTIs | PI susceptibility may be retained; lamivudine resistance likely if in regimen |
| PI/NNRTI/nRTI(s) | 2 PIs/2 nRTIs | NNRTI resistance likely; lamivudine resistance likely if in regimen |

PI indicates protease inhibitor.

decrease in abacavir susceptibility (2- to 3-fold) may permit the drug to retain some usefulness in a salvage regimen in the absence of concomitant zidovudine resistance.

Delayed Immunologic Deterioration in Protease Inhibitor Failure

Virologic failure on an initial protease inhibitor-based regimen may prompt more aggressive response in terms of altering treatment. However, a delayed CD4+ cell count decline in patients in whom protease inhibitor-based treatment is failing is frequently observed. This observation has raised the issue of how rapidly changes in regimen need to be made in treatment-experienced patients in whom therapeutic options may be limited. In a recent study by Deeks and colleagues of initiating protease inhibitor-containing therapy after a median of 24 months of nRTI exposure, 55% of the 482 patients exhibited virologic failure during the median follow up time of approximately 37 months. Median time to virologic failure was 14.7 months after beginning the protease inhibitor treatment. The rate of immunologic failure (return to CD4+ cell count at the time of starting protease inhibitor treatment) lagged behind the

rate of virologic failure. Among those patients with virologic failure, median time to return to baseline CD4+ cell count was 36.4 months. These data suggest that there may be a prolonged period during which CD4+ cell counts are relatively preserved following virologic failure on a protease inhibitor-based regimen. However, they also indicate that CD4+ cell decline is likely to occur, warranting caution in strategies that involve delay in making changes in a failing regimen. Moreover, protease inhibitor resistance and cross-resistance will become progressively more pronounced with continuing protease inhibitor use in the presence of viral replication.

Options in Multiple Failure

Options in multiple virologic failure include employing as many new drugs as possible in combination with continued or recycled drugs; use of multidrug rescue therapy involving 5 to 10 different drugs; strategic treatment interruptions (STIs); addition of hydroxyurea (with didanosine or didanosine/stavudine) to a multidrug regimen; and the use of investigational drugs.

In the CNA2007 study, abacavir, amprenavir, and efavirenz were employed in highly antiretroviral-experienced patients

in whom a protease inhibitor-based regimen failed. NNRTI-naive patients with plasma HIV RNA levels less than 40,000 copies/mL exhibited an initial decrease in viral load of 1.3 log with a 1-log decrease being maintained for 16 weeks. Viral load returned toward baseline levels within 16 weeks in all NNRTI-experienced patients and in NNRTI-naive patients with higher viral load levels. Approximately half of patients who were NNRTI-naive with a viral load of less than 40,000 copies/mL had suppression of HIV RNA levels to less than 400 copies/mL at 16 weeks, compared with 5% of those who were NNRTI-experienced and had an initial viral load of more than 40,000 copies/mL. These findings, which need confirmation in additional studies, suggest that success with such a regimen is more likely to occur in NNRTI-naive subjects, and if the switch to the regimen is made at relatively lower viral load levels. It should be noted, however, that efavirenz has been shown to lower amprenavir levels substantially; this effect may have influenced the results of the CNA2007 study. Preliminary data suggest that the addition of low-dose ritonavir may block this effect.

Data from ACTG 398 suggest that in patients in whom a protease inhibitor therapy is failing, dual protease inhibitor therapy and no prior exposure to NNRTIs are associated with improved response

The ACTG 398 study assessed whether a change to all new drugs or the addition of a second protease inhibitor to a new 4-drug class regimen improves virologic outcome in patients with virologic failure on a protease inhibitor-containing regimen. Patients with more than 16 weeks of protease inhibitor experience and plasma HIV RNA levels above 1000 copies/mL were given amprenavir, abacavir, efavirenz, and adefovir dipivoxil and randomized to one of 4 treatment arms consisting of placebo,

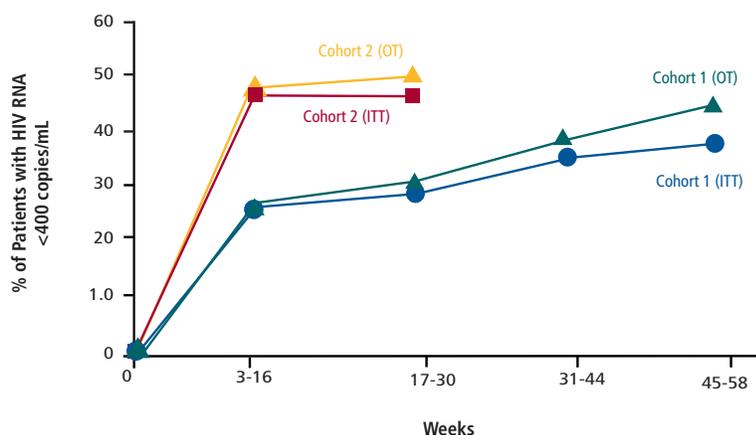


Figure 2. Proportion of patients with viral load less than 400 copies/mL in 2 cohorts receiving multidrug rescue therapy. ITT indicates intent-to-treat analysis; OT indicates on-treatment analysis. Courtesy of Julio S. G. Montaner, MD.

saquinavir (soft-gel capsule), indinavir, or nelfinavir. Patients with prior exposure to 1 protease inhibitor and those with prior exposure to 2 were randomized among 3 and 2 arms, respectively, to protease inhibitors with which they had no prior experience. Those having prior experience with 3 protease inhibitors were randomized among all 4 arms and thus may have received a protease inhibitor to which they had already been exposed. Patients were stratified according to prior NNRTI experience.

Comparison of the combined dual protease inhibitor arms and the single protease with respect to proportions of patients achieving viral load of less than 200 copies/mL at 24 weeks was significantly different in the dual versus single protease inhibitor arms (35% v 23% respectively; $P=0.002$). This level of suppression was achieved in 47% of dual protease inhibitor recipients and 33% of single protease inhibitor recipients who were NNRTI-naïve and in 19% and 8%, respectively, of those who were NNRTI-experienced. Overall, a viral load of less than 200 copies/mL was achieved in 43% of NNRTI-naïve patients and 16% of NNRTI-experienced patients (the difference was statistically significant with stratification for protease inhibitor experience and treatment arm). Among patients who stayed on treatment for 24 weeks, 65% of NNRTI-naïve patients achieved viral load of less than 200 copies/mL. Despite the fact that the proportions of patients achieving viral load levels of less than 200 copies/mL were somewhat disappointing in the ran-

domized treatment arms by intent-to-treat analysis, decreases in viral load averaged 1 log below baseline at 24 weeks; such decreases are likely to be associated with clinical benefit if sustained.

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Multidrug rescue therapy regimens usually consist of 5 to 10 drugs, including recycled drugs that are not specifically selected on the basis of *in vitro* resistance patterns. These regimens may include 2 or 3 protease inhibitors, 1 or 2 NNRTIs, 2 to 4 nRTIs, a nucleotide reverse transcriptase inhibitor (nRTI) if available, and hydroxyurea (plus didanosine with or without

stavudine). The rationale for use of such a regimen in salvage therapy is that viral quasi species exhibit differential resistance patterns that may be attacked by various components of the multidrug regimen. Montaner and colleagues have reported on the use of treatment regimens consisting of the nRTIs stavudine, didanosine, lamivudine, and abacavir, the NNRTI nevirapine with or without delavirdine, 2 protease inhibitors, and hydroxyurea. Substantial proportions of patients in 2 cohorts have achieved virologic response to viral load levels below 400 copies/mL on such regimens (Figure 2). Tolerance, adherence, cost, and toxicity are obvious problems with such demanding and complicated regimens.

Strategic treatment interruption as an approach to regaining virologic control has received considerable attention recently. The rationale for this approach is that removal of selective pressure will permit more sensitive, wild-type virus to gain predominance, and result in renewed activity of recycled drugs. In studies of this approach performed by Miller and colleagues in the Frankfurt HIV Cohort, patients with extensive treatment experience, including at least 1 year of protease inhibitor treatment, who were receiving regimens containing at least 2 protease inhibitors, underwent treatment interruptions for at least 2 months. Pre- and post-interruption data are available for 39 patients in the cohort. Interruption was associated with significant increases in the proportions of patients with HIV that exhibited increased susceptibility to each of the drugs used. Overall, a shift to a wild-type virus occurred in 26 of 39 patients previously exhibiting resistance to a median of 8 drugs. The remainder of the patients, in whom no shift occurred, also exhibited resistance to a median of 8 drugs. During interruption, median viral load increased by 0.71 log (from 5.07 to 5.87 log) and median CD4+ cell count decreased by 89/ μ L (from 155/ μ L to 49/ μ L). At 8 weeks after reinitiation of antiretroviral therapy, viral load had decreased by 2.8 log in those with a shift to wild-type virus and by 1.02 log in those with no shift. Viral load of less than 500 copies/mL was achieved within 24 weeks in 18 of 25 patients with a shift to wild-type virus and in 2 of 12 with no shift. Patients with a shift to wild-type virus had a significantly higher CD4+ cell count prior to treatment interruption than did those without a shift. These patients also had a significantly greater decrease in CD4+ count during

treatment interruption (122 v 29 cells/ μ L). Overall, only 22 of 42 patients had returns to their pre-interruption CD4+ cell count; median times to return to the baseline CD4+ cell count were 336 days among those with a shift to wild-type virus and 209 days among those with no shift to wild-type.

Deeks and colleagues reported an assessment of virologic and immunologic outcome of STI in patients with failure (viral load >500 copies/mL) of a protease inhibitor-based regimen for at least 1 year and current viral load greater than 2500 copies/mL. Patients had been on a stable treatment regimen for more than 16 weeks. In the 18 patients reported on thus far, average baseline CD4+ cell count was 245/ μ L and viral load was 4.6 log; patients had been on protease inhibitor therapy for an average of 36 months and with virologic failure for 31 months, exhibiting an average 56-fold decrease in protease inhibitor susceptibility. After 12 weeks off treatment, average CD4+ cell count had declined by 94 cells/ μ L and viral load had increased by 0.82 log, changes similar to those observed by Miller and colleagues, and isolates in 16 of 17 patients had reverted to protease inhibitor susceptibility. The mean time to phenotypic switch to wild-type virus in these patients was 8.5 weeks. The switch to wild-type virus appeared to be associated with an increased rate of viral load increase and CD4+ cell count decline, suggesting increased replicative fitness and pathogenicity of the wild-type virus.

Findings with STI to date suggest that reversion to drug-susceptible virus frequently does occur and that subsequent treatment is associated with decreases in viral load and increases in CD4+ cell count. However, the acute declines in CD4+ cell count during interruption may result in risk for opportunistic disease and return to baseline CD4+ cell counts may require prolonged periods of time or may fail to occur in some patients. An additional potential problem with such interruption is that archived viral subpopulations are not eliminated, and viral drug resistance is likely to reemerge in the absence of a maximally suppressive regimen. Finally, the longer-term effectiveness of this approach remains to be ascertained.

Conclusions

A number of general conclusions regarding management of antiretroviral failure

can be offered:

- All potential reasons for failure should be evaluated, including adherence, pharmacokinetics, and resistance.
- Increasingly difficult challenges are posed by progression from first failure to second failure to multiple failures.
- As the therapeutic options become more limited, so do the goals of therapy.
- The role of resistance testing in guiding therapy is increasing and such testing will become a routine part of clinical management.
- The current suboptimal success rates in salvage therapy are a function of drug class cross-resistance, overlapping toxicities, and limited therapeutic alternatives.
- The principles of successful salvage therapy are established. The key to success is the availability of new drugs active against viruses resistant to the current generation of drugs.

Suggested Reading

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Announcement

Resistance Testing Guidelines Updated *

The International AIDS Society—USA panel on the use of antiretroviral drug resistance testing in adult HIV-1 has issued updated recommendations. The report of the international panel of experts was published in the May 10, 2000 issue of the *Journal of the American Medical Association*. Available data correlating viral resistance and poor response to therapy, the genotype and phenotype assay methods to assess potential resistance, the current limitations of resistance testing, and the further research that is warranted, are reviewed. In this con-

text, specific clinical situations in which resistance testing is recommended or may be considered to aid in optimizing individual patient care are presented.

The report can be accessed from the *JAMA* Web site: <http://jama.ama-assn.org/>. Reprints will be included in the next issue of this publication.

*Hirsch MS, Conway B, D'Aquila RT, et al. *Antiretroviral drug resistance testing in adult HIV-1 infection: recommendations of an International AIDS Society—USA Panel*. *JAMA*. 2000;283:2417-2426.

Correction

The March 2000 issue of *Topics in HIV Medicine* contained an error on page 35, Table 4 (Trials in Antiretroviral-Experienced Patients). In the ACTG 364 study (Abstract 531), the correct proportion of patients with plasma viral loads below 50 copies/mL in the 1-2 new nRTIs/efavirenz group was 44% and in the 1-2 new nRTIs/nelfinavir group it was 22%.