# Strategies for Treatment and Management of Antiretroviral Failures

*At the New York course, Scott M. Hammer, MD, discussed strategies for maintaining antiretroviral responses achieved with potent induction antiretroviral therapy as well as strategies for managing suboptimal response or antiretroviral failure.*

The current standard of antiretroviral therapy in the clinical setting is to begin treatment with a potent regimen to suppress plasma viral load below limits of detection of sensitive assays and to maintain as potent a regimen as possible with routine monitoring of clinical status, plasma HIV-1 RNA, and CD4+ cell count. Treatment with a protease inhibitor and 2 nucleoside reverse transcriptase inhibitors (nRTIs) has proven effective in initial therapy and is commonly used; however, there are a number of other options for the initial regimen treatment, including a nonnucleoside reverse transcriptase inhibitor (NNRTI) plus 2 nRTIs, 2 protease inhibitors plus 1 or 2 nRTIs, a protease inhibitor/NNRTI/nRTI(s) combination, and a triple-nRTI combination. Despite the large number of drugs currently available and the ability to combine them effectively in initial treatment, cross-resistance among drugs in particular classes—and decreased effectiveness even in the absence of genotypic evidence of cross-resistance—results in numerous difficulties in managing patients in whom there is a suboptimal response to the initial therapy, a subsequent treatment failure, or prior extensive exposure to available drug classes. A number of strategies have begun to be formulated to optimize management in this regard.

## INDUCTION–MAINTENANCE STRATEGIES

After profound suppression of viral burden has been achieved with therapy, the rationale for use of a maintenance regimen is that a simplified regimen might maintain suppression in the context of a reduced infected cell reservoir. However, this approach has proven unsatisfactory

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with maintenance regimens evaluated to date in clinical trials (Table 1). In ACTG 343, patients receiving zidovudine/lamivudine/indinavir who had plasma HIV-1 RNA levels below 200 copies/mL at 24 weeks were randomized to continued treatment with the triple regimen, zidovudine/lamivudine, or indinavir alone. In the Trilege study, patients receiving the same triple combination who had plasma HIV-1 RNA levels below 500 copies/mL at 12 weeks were randomized to continued triple-drug treatment, zidovudine/lamivudine, or zidovudine/indinavir. In the ADAM trial, patients receiving stavudine/lamivudine/nelfinavir/saquinavir with viral load below 50 copies/mL at 26 weeks were randomized to continuation of the 4-drug regimen, stavudine/nelfinavir, or nelfinavir/saquinavir. In each of these trials, failure rates were markedly higher in patients receiving the simplified maintenance regimens. These disappointing findings, however, do not indicate the lack of viability of such an approach; they more likely suggest the need for more prolonged or potent induction treatment and/or more potent maintenance regimens.

## "SWITCHING" THERAPY

Change from a potent induction regimen to another potent regimen may be advantageous to avoid or ameliorate toxic effects, despite continued suppression of viral load with the induction regimen. In the case of protease inhibitor toxicity, for example, an NNRTI/dual nRTI or triple nRTI regimen could be substituted for a protease inhibitor/dual nRTI regimen. Although the

**Table 1. Summary of Results of Induction–Maintenance Trials**

| Study | Induction Therapy | Maintenance Therapy | Failure Rate (%) |
|---|---|---|---|
| ACTG 343 (Havlir et al. *N Engl J Med*, 1998) | Zidovudine/lamivudine/indinavir | Zidovudine/lamivudine/indinavir | 4 |
| | | Zidovudine/lamivudine | 23 |
| | | Indinavir | 23 |
| Trilege (Pialoux et al. *N Engl J Med*, 1998) | Zidovudine/lamivudine/indinavir | Zidovudine/lamivudine/indinavir | 9 |
| | | Zidovudine/lamivudine | 31 |
| | | Zidovudine/indinavir | 22 |
| ADAM (Reijers et al. *Lancet*, 1998) | Stavudine/lamivudine/nelfinavir/ saquinavir | Stavudine/lamivudine/nelfinavir/saquinavir | 9 |
| | | Stavudine/nelfinavir | 57 |
| | | Nelfinavir/saquinavir | 71 |

number of drugs in the regimen may be unchanged, a potential benefit of switching may be simplification of the dosing regimen or reduction in total pill burden. A preliminary report by Ruiz and colleagues of the Spanish Lipodystrophy Study Group has indicated favorable early outcomes using this strategy in patients with lipodystrophy who were taking protease inhibitor-containing regimens. The target population was 100 patients who had received stavudine/lamivudine/protease inhibitor for at least 9 months, had plasma HIV-1 RNA levels below 400 copies/mL for at least 6 months, and who had protease inhibitor-associated lipodystrophy. The patients were randomized to continue treatment with their protease inhibitor-containing regimen or to predominantly change to stavudine/didanosine/nevirapine for 1 year; didanosine was substituted for lamivudine in the nevirapine-containing arm in order to avoid lamivudine resistance in case virologic failure occurred in the nevirapine group. In 29 patients in whom 12-week data were available, duration of prior protease inhibitor therapy was nearly 2 years, with viral suppression for 14 to 17 months and CD4+ cell counts greater than 500/µL. The 12-week data indicated that patients who switched to the nevirapine-containing regimen had significant decreases in cholesterol and triglyceride levels and significant improvement in subjective quality of life and physician and patient qualitative estimates of lipodystrophy. The CD4+ cell counts remained stable and plasma HIV-1 RNA levels generally remained below 50 copies/mL in both patient groups. A trend towards improvement in objective measures of lipodystrophy was observed in patients receiving the nevirapine-containing regimen, although changes did not achieve statistical significance. These data are preliminary, although they do suggest the ability to maintain virologic benefit and improve metabolic aspects of lipodystrophy over at least the short term by switching drug regimens. Additional data with longer follow-up time are needed.

## INTENSIFICATION

Intensification of treatment can consist of adding a drug to a regimen if initial response is good but not optimal, or adding a drug to an already successful regimen to promote durability of response. The latter approach currently is being investigated in ACTG 372. In this study, patients from ACTG 320 who received zidovudine/lamivudine/indinavir and in whom plasma HIV-1 RNA levels were maintained below 500 copies/mL were randomized to addition of abacavir or placebo to determine if the addition of the active drug could prolong the time to virologic failure. The former approach has been considered in cases in which the effect of a regimen in reducing viral load appears to be reaching a plateau, resulting in persistently detectable plasma HIV-1 RNA levels (Figure 1). In such cases, the addition of a drug at, for example, 12 to 16 weeks may achieve and maintain the desired additional reduction in viral load. There is some evidence from clinical trials that this approach may be of benefit. For example, in the initial ritonavir/saquinavir trial sponsored by Abbott Laboratories, the addition of stavudine/lamivudine or other nRTIs in patients in whom the initial therapy failed to achieve HIV-1 RNA levels below 200 copies/mL by week 12 resulted in maintained suppression for 60 weeks in the majority of cases. Similarly, in the Glaxo Wellcome 3003 trial, the addition of abacavir in patients receiving dual nRTI therapy resulted in durable responses through 48 weeks.

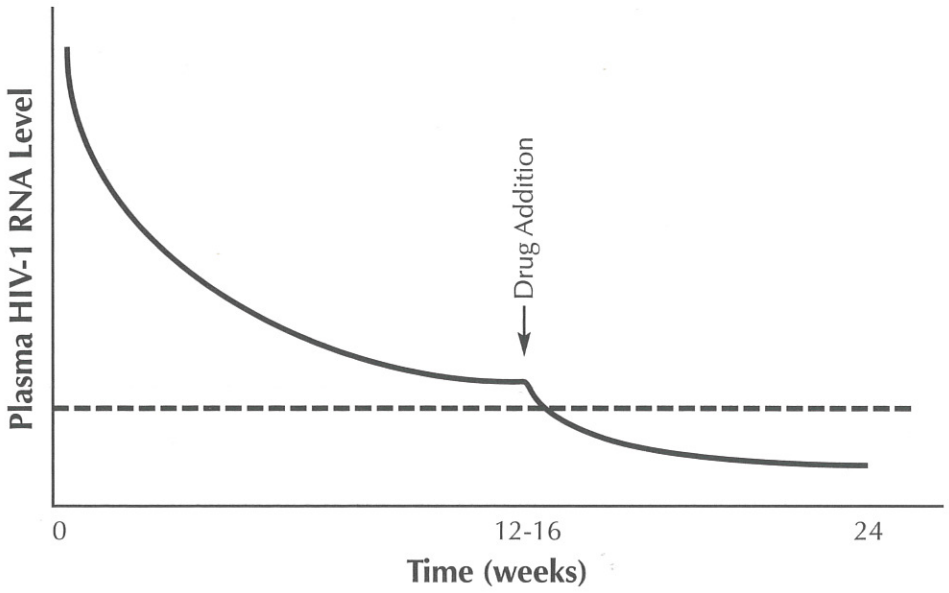


***Figure 1.*** *Example of good but suboptimal virologic response to induction therapy, in which slope of plasma HIV-1 RNA decrease indicates plateauing of effect before assay limit of detectability (dotted line) is achieved. The rationale in regimen intensification in such cases is to achieve a viral load below the level of detection with the objective of preventing the emergence of drug resistance and producing a durable response.*

Issues to be addressed with regard to treatment intensification include timing of intervention and whether frequency of plasma HIV-1 RNA monitoring should be increased during initial treatment to allow earliest appropriate intervention. In addition, there is a fine line between intensification and incremental therapy in the setting of early virologic failure. The latter is to be avoided as further drug resistance may be promoted. With regard to which class(es) of drug to use in intensification, those with a low genetic barrier to resistance (eg, an NNRTI or lamivudine) would be less ideal. Those requiring multiple mutations for resistance (eg, abacavir) may be more appropriate.

## MANAGEMENT OF ANTIRETROVIRAL FAILURE

Although antiretroviral failure can be defined clinically and immunologically, the most sensitive marker for failure currently available is a confirmed change in plasma HIV-1 RNA level. The differentiation of suboptimal response to induction treatment from early viral rebound due to regimen failure is a consideration in deciding whether to switch treatments based on virologic findings. The former might motivate regimen intensification, whereas the latter motivates early treatment of virologic

breakthrough. As part of routine clinical practice, other potential causes for decreased virologic effect—including poor drug absorption, lack of adherence, intercurrent illness, and immunization—should be investigated prior to intervention. An additional consideration in treatment change is the viral load threshold for intervention—ie, should any confirmed viral load using the most sensitive assays available trigger a change in treatment or should a higher threshold be used as a more practical approach. Many clinicians would accept any confirmed detectable virus as a trigger for changing therapy in the first occurrence of virologic failure. However, with fewer treatment options after subsequent failures, acceptance of a higher threshold might be required. This practice may be easier to rationalize given, for example, the fact that the CD4+ cell count often remains elevated for prolonged periods after protease inhibitor failure. In short, with currently available treatment options, it remains an issue whether rigorous pursuit of the standard of maintaining plasma HIV RNA levels below limits of detection after initial drug failure will result in the most durable responses in the long term or result in the earlier narrowing or exhaustion of subsequent treatment options.

*A recently recognized issue in switching regimens based on early virologic failure of protease inhibitor-, lamivudine-containing regimens is whether all drugs in the regimen need to be changed*

A major issue in switching regimens based on virologic failure is whether all drugs in the regimen need to be changed. Although current practice generally reflects the belief that total replacement of a failing regimen is warranted to avoid incremental therapy, recent data indicate that earliest failures in protease inhibitor/zidovudine/lamivudine regimens are associated with the codon 184 lamivudine-associated resistance mutation and an absence of protease inhibitor-associated mutations. In a group of 17 patients from ACTG 343 with viral rebound during indinavir/zidovudine/lamivudine therapy (means of 45 weeks on therapy and 25 weeks of viral rebound, and mean plasma HIV-1 RNA level of 27,819 copies/mL during rebound), indinavir and lamivudine phenotypic resistance was found in isolates from 0 and 14 patients, respectively, with the M46L protease mutation being found in 1 case and the lamivudine-associated M184V mutation being found in 14. Similar findings have been reported in the Trilege study and in the ACTG 347 study of amprenavir-containing triple therapy. At present, however, it is unclear how to integrate such information into clinical practice. Although resistance testing is likely to ultimately prove useful in guiding selective changes in combination regimens, current phenotypic and genotypic tests are subject to limitations, including the failure to detect minority resistance populations. Currently, then, changing only 1 component of a failing regimen would warrant particularly close monitoring for virologic response. Overall, it would appear to be prudent to change most if not all components of a failing regimen to avoid the potential consequences of incremental therapy until it is clearer how to integrate information on component failure into clinical practice.

A number of largely nonrandomized studies of salvage therapy after protease inhibitor failure have been reported over the past year. In a representative study (Glaxo Wellcome, CNA 2007), highly antiretroviral-experienced patients (including many patients with multiple protease inhibitor experience and multiple nRTI and/or NNRTI experience) in whom a protease inhibitor-containing regimen failed, were given the combination of abacavir/amprenavir/efavirenz. Those patients with baseline viral load levels 40,000 copies/mL or below who were NNRTI-naive had a good initial response with maintenance of a 1-log reduction in viral load at 16 weeks. Initial responses were poorer in NNRTI-experienced patients, particularly in those with higher baseline viral loads. Only 5% of NNRTI-experienced patients with baseline viral loads greater than 40,000 copies/mL had viral loads below 400 copies/mL at week 16, compared with approximately 50% of NNRTI-naive patients with baseline viral loads below 40,000 copies/mL. Similar findings have been observed in other studies. Response rates at 16 to 24 weeks have ranged from 5% to 70%, with better rates of response noted when a change in treatment was initiated at lower rather than higher viral loads.

There are considerable uncertainties about what regimen to use after failure of a protease inhibitor-containing regimen. The current knowledge of potential therapeutic options in the cases of prior protease inhibitor exposure can be summarized as follows: With regard to alternative protease inhibitors, (1) the response to indinavir or nelfinavir following saquinavir is blunted, indicating that the common saquinavir-associated L90M resistance mutation confers some degree of cross-resistance to other protease inhibitors; (2) the response to ritonavir/saquinavir in cases of failure on other protease inhibitors is no better than 50% to 70%; (3) based on preliminary clinical data, nelfinavir failure is associated with variable response to other protease inhibitors. Although the signature D30N nelfinavir-associated resistance mutation alone does not appear to confer cross-resistance to other protease inhibitors, the

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addition of other mutations to the codon 30 mutation does result in cross-resistance; (4) the amprenavir-associated I50V resistance mutation does not by itself cause protease inhibitor cross-resistance, but other mutations that do, commonly occur in the setting of amprenavir-failure; and (5) it is unclear what role amprenavir may have in salvage treatment.

With regard to NNRTIs, although replacement of a protease inhibitor-containing regimen with a NNRTI/dual nRTI regimen has been commonly advocated and employed, prior nRTI exposure compromises the effectiveness of such regimens. This is of particular importance for NNRTIs, since these drugs are subject to one-step, high-level resistance, and the potency of the overall combination is crucial to preventing rapid emergence of NNRTI resistance.

With regard to nRTIs, the potential compromise of response due to prior nRTI exposure must be considered a factor rendered more complicated by the fact that this decreased effectiveness is not always explained by known mutations conferring cross-resistance. Abacavir, which has been found to be a potent component of initial therapy, may have some promise for use in cases of first virologic failure, particularly since it retains reasonable activity against lamivudine-resistant virus. However, since the presence of multiple nRTI resistance mutations is associated with abacavir resistance, the use of abacavir in subsequent failures in highly nRTI-experienced patients is less efficacious.

Although the acyclic nucleotide reverse transcriptase inhibitor (n*t*RTI), adefovir dipivoxil, has only modest intrinsic activity, it may have a role in subsequent therapy, particularly since it has shown activity against lamivudine-resistant virus.

Hydroxyurea is currently being used as an adjunct in alternative antiretroviral regimens, with the majority of experience with the drug in combination with didanosine or didanosine/stavudine. These combinations have been associated with good virologic response usually accompanied by lack of change or a decrease in CD4+ cell count. There are some data to indicate that delayed introduction of hydroxyurea with the alternative regimen may improve the CD4+ cell response but this requires further study. An advantage of hydroxyurea is its apparent ability to preserve didanosine activity against didanosine-resistant mutants. Its utility with other nRTIs or nucleotide reverse transcriptase inhibitors (n*t*RTIs) remains to be fully defined.

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Based on these considerations, treatment after the initial regimen(s) fail remains largely an empiric choice involving as many new drugs as possible (eg, dual protease inhibitors plus nRTIs with or without an NNRTI). Data from controlled clinical trials are urgently needed to identify successful regimens and to define the potential role of resistance testing in guiding treatment changes. It is also clear that new drugs are needed to devise regimens that are active against multidrug-resistant virus.

## STRATEGIC MANAGEMENT

Dr. Hammer proposed a general strategy for antiretroviral management reflecting the above considerations. (1) Initiate therapy with a potent combination to drive plasma HIV-1 RNA level below the limit of detection, using the most sensitive available assays as part of routine clinical care. (2) Monitor plasma HIV-1 RNA level at 4, 16, and 24 weeks at the minimum, with more frequent early monitoring potentially being useful. In the case of an excellent response, treatment should be continued. In the case of good but suboptimal response, intensification or a change of regimen should be considered. It is important to note that with use of sensitive viral load assays, which have detection limits of 20 to 50 HIV-1 RNA copies/mL, the time to achieve viral loads below the levels of detection may be greater than 16 weeks (and may be as long as 32 weeks, although a delay of this amount of time may suggest possible adherence problems); thus, with use of such assays, monitoring the trajectory of decline in viral load is important. (3) Virologic monitoring should continue on a routine basis once plasma HIV-1 RNA level has been reduced to levels below detection; although 3-month intervals have been widely used, many clinicians now monitor more frequently (eg, every 2 months) to detect failure more promptly. (4) If plasma HIV-1 RNA becomes detectable, all potential reasons for drug failure should be evaluated, including nonadherence, poor drug absorption, intercurrent illness, and vaccination. If drug failure is evident or considered likely, changing the regimen at a lower plasma HIV-1 RNA level is more likely to be successful than delaying intervention until viral load is higher—although practical concerns may dictate otherwise. (5) The same principles apply in the case of failure of a second regimen; however, given the cumulative limitation of options, compromise is frequently necessary. (6) The current role of resistance testing in clinical decision-making is unclear, although it is likely to prove useful in the future. Thus, the importance of provider expertise in antiretroviral therapy decision-making will continue to increase.

*Scott M. Hammer, MD, is Chief of the Division of Infectious Diseases at Columbia-Presbyterian Medical Center and Professor of Medicine at Columbia University College of Physicians and Surgeons, New York, New York.*

## Suggested Reading


Ait-Khaled M, Rakik A, Thomas D, et al. HIV-1 baseline genotype/phenotype and virological response following salvage therapy with Ziagen (abacavir), Amprenavir, and Sustiva (efavirenz). Presented at: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 133.

Carpenter CCJ, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1998. Updated recommendations of the International AIDS Society–USA panel. *JAMA*. 1998;280:78–86.

Deeks SG, Grant RM, Beatty GW, et al. Activity of a ritonavir plus saquinavir-containing regimen in patients with virologic evidence of indinavir or ritonavir failure. *AIDS*. 1998;12:F97–F102.

Hammer S, Squires K, DeGruttola V, et al. Randomized trial of abacavir and nelfinavir in combination with efavirenz and adefovir dipivoxil as salvage therapy in patients with virologic failure receiving indinavir. Presented at: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 490.

Havlir DV, Marschner IC, Hirsch MS, et al. Maintenance antiretroviral therapies in HIV infected patients with undetectable plasma HIV RNA after triple-drug therapy (ACTG 343). *N Engl J Med*. 1998;339:1261–1268.

Kempf DJ, Rode RA, Xu Y, et al. The duration of viral suppression during protease inhibitor therapy for HIV-1 infection is predicted by plasma HIV-1 RNA at the nadir. *AIDS*. 1998;12:F9–F14.

Pialoux G, Raffi F, Brun-Vezinet F, et al. A randomized trial of three maintenance regimens given after three months of induction therapy with zidovudine, lamivudine, and indinavir in previously untreated HIV-1 infected patients (Trilege). *N Engl J Med*. 1998;339:1269–1276.

Reijers MH, Weverling GJ, Jurriaans S, et al. Maintenance therapy after quadruple induction therapy in HIV-1 infected individuals: Amsterdam duration of antiretroviral medication (ADAM) study. *Lancet*. 1998;352:185–190.

Rozenbaum W, Delphin N, Katlama C, et al. Treatment intensification with Ziagen in HIV infected patients with previous 3TC/ZDV antiretroviral treatment-CNAB3009. Presented at: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 377.

Ruiz L, Bonjoch A, Paredes R, et al. A multicenter, randomized, open-label, comparative trial of the clinical benefit of switching the protease inhibitor by nevirapine in HAART-experienced patients suffering lipodystrophy. Presented at: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract LB 14.

Tebas P, Patick AK, Kane E, et al. 60-week virologic responses to a ritonavir/saquinavir containing regimen in patients who had previously failed nelfinavir. Presented at: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 392.

Vernazza P, Katlama C, Clotet B, et al. Intensification of stable background antiretroviral therapy with Ziagen. Presented at: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 378.


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