

Perspective

Current Concepts in Antiretroviral Therapy Failure

Currently, the goal for the first and second, and possibly the third, antiretroviral regimen is the suppression of HIV replication to plasma levels below assay detection (ie, < 50 HIV-1 RNA copies/mL). In patients with advanced treatment failure and resistance to numerous drugs, the goal of therapy has been to reduce viral load as much as possible and to maintain immunologic and clinical integrity. With the recent availability of new drugs and new classes of drugs, complete suppression of viral replication may be possible even in late salvage. When designing a regimen for a patient for whom antiretroviral therapy has failed, the regimen should contain at least 3 active drugs, and regimens are best selected with assistance from genotypic and phenotypic drug resistance testing. The selection should also be guided by knowledge of potential pharmacokinetic interactions among drugs. This article summarizes a presentation on antiretroviral failure by Carlos del Rio, MD, at the 8th annual clinical meeting for Ryan White CARE Act clinicians in New Orleans in June 2005, sponsored by the International AIDS Society–USA and includes more recent data presented at the 13th Conference on Retroviruses and Opportunistic Infections (CROI) in 2006.

With current treatment options, the goal for the first, second, and third regimens of antiretroviral therapy is suppression of HIV replication to plasma levels below 50 HIV-1 RNA copies/mL (Hammer et al, *JAMA*, 2006). Such a level of suppression minimizes the risk of the emergence of viral resistance. In patients with advanced treatment failure and multi-drug resistance, the goal of therapy has been to reduce viral load as much as possible and to maintain immunologic and clinical integrity.

However, with the recent approval of new agents such as darunavir (formerly TMC-114) and the development of new classes of drugs such as the integrase inhibitors, it may be possible to achieve complete suppression of viral replication even in advanced failure.

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Virologic Failure Rates in Initial Treatment

Data on 4143 patients from 5 observational cohorts in Europe and North America who were started on initial 3-drug regimens between 1996 and 2002 indicate that the annual rate of virologic failure (plasma HIV-1 RNA level > 500 copies/mL within 6 to 12 months of starting antiretroviral therapy) declined from 40% to 25% during that period (Lampe et al, CROI, 2005). Risk of virologic failure was lower among patients who were older, who had lower baseline viral load, and who had an absence of an AIDS diagnosis, and among men who reported having sex with men as a risk factor. It is important to note, however, that in many US clinics there are increasing numbers of patients who have acquired HIV through injection drug use or who are first diagnosed with AIDS and high viral loads and thus virologic failure of the initial regimen in such populations is likely to also be higher. In addition, because of transmission of drug-resistant virus, a “naive patient” may in fact be infected with a virus that is already resistant at baseline, which increases the likeli-

hood of virologic failure. Because of recent data suggesting that up to 16% of treatment-naive patients have evidence of antiretroviral resistance, guidelines recommend genotypic resistance testing prior to initiation of antiretroviral therapy (<http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>).

What is Treatment Failure and Why Does It Occur?

Several studies suggest that the median time to failure of the initial antiretroviral therapy regimen is approximately 1.6 years. Lack of adherence—whether due to toxicity, poor tolerability, or inconvenient dosing frequency or food interactions—is a major cause of virologic failure. Pharmacologic and pharmacogenetic factors in failure can include: drug interactions resulting in inadequate or excessive drug exposure or competition for nucleoside pools (eg, between tenofovir and didanosine); genetic factors, such as mutations in the cytochrome P4502B6 isoenzyme that prolong the half-life of efavirenz, and mitochondrial haplotypes that can affect nucleoside analogue reverse transcriptase inhibitor (nRTI) toxicity; and inadequate or excessive dosing for body weight or renal or hepatic function.

Another factor may be the use of combinations that are not sufficiently potent or that are antagonistic (eg, the triple nRTI regimen tenofovir/abacavir/lamivudine, Gallant et al, *J Infect Dis*, 2005). Virologic failure may also occur due to low-level mutant populations of circulating virus or mutant virus archived in reservoirs in the body. Clonal analysis may demonstrate mutations not identified by population genotyping or phenotyping.

Antiretroviral therapy can fail for a variety of reasons. Some patients fail to respond to antiretroviral therapy

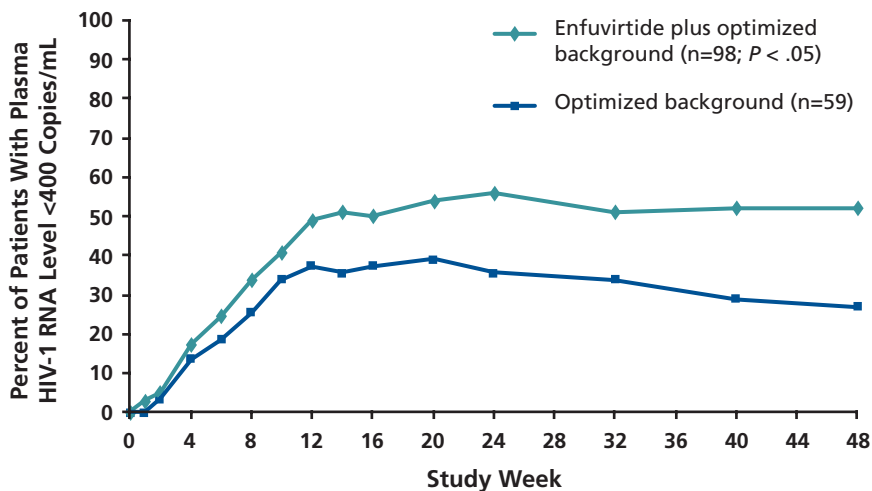


Figure 1. Effect on virologic response (plasma HIV-1 RNA <400 copies/mL) of addition of enfuvirtide in patients receiving active lopinavir/ritonavir and 2 or more other active agents over time in the TORO 1 study. Data are from intent-to-treat analysis (switching or discontinuation equals failure). Adapted from data presented by Miralles and Demasi, IDSA, 2004.

due to drug toxicity or intolerance. In these cases, changing the regimen to one that the patient can tolerate is imperative. Immunologic failure occurs when the CD4+ cell count declines despite treatment.

Virologic failure occurs when the plasma HIV-1 RNA level is not suppressed to or maintained at less than 50 copies/mL on antiretroviral therapy. In those cases the emergence of drug resistance mutations to the prescribed regimen is possible and thus genotypic or phenotypic testing (or both) should be performed prior to selecting the next regimen.

It is important that viral rebound be distinguished from transient low-magnitude increases or “blips” in viral load observed in patients in whom viral replication is otherwise fully suppressed. Available data indicate that there is no association between blips and virologic failure or new drug resistance mutations, and that most blips are due to normal statistical variation (Havlir et al, *JAMA*, 2001; Nettles et al, *JAMA*, 2005). These transient increases can occur during intercurrent illness and after vaccinations. HIV superinfection may also result in blips.

When To Change Regimens

Initial antiretroviral therapy regimens

should be changed after evaluating adherence and pharmacologic or other reasons for virologic failure and confirming the increase in viral load. Failure due to incomplete virologic suppression or virologic rebound requires a change to a potent regimen of active drugs guided by resistance testing when feasible. Resistance testing is recommended in cases in which a plasma HIV-1 RNA level greater than 500 to 1000 copies/mL is observed, and testing should be performed while the patient is still receiving the current regimen (Hirsch et al, *Clin Infect Dis*, 2003). Treatment failure due to toxicity, intolerability, or inconvenience in the setting of virologic suppression allows for the substitution of a single drug, and is the only time that single-drug substitution should be performed.

A change in regimen should be made as soon as virologic failure is confirmed for nonnucleoside analogue reverse transcriptase inhibitor (NNRTI)-based regimens even if resistance testing is not available, due to the low genetic barrier to resistance among currently available NNRTIs. For failing protease inhibitor (PI)-based regimens, changes should also be made early if the regimen includes a PI with a low genetic and pharmacologic barrier to resistance (eg, nelfinavir). Changes do not necessarily have to be made as

rapidly—eg, in the absence of guidance from resistance testing—for failing PI-based regimens that include PIs with a higher barrier to resistance (eg, ritonavir-boosted PIs).

Choosing the Next Regimen

As discussed above, the goal of a second regimen should continue to be to achieve virologic suppression to less than 50 copies/mL of plasma HIV-1 RNA. When available, resistance testing should guide the choice of drugs in the new regimen; when resistance testing is not available, knowledge of common resistance patterns likely to result from the first regimen should be taken into account. A general principle for management of antiretroviral therapy failure at any time during treatment is that a regimen should contain at least 3 active drugs; the number of active drugs in a regimen is correlated with better virologic response even in heavily pretreated patients.

A variety of data from studies of salvage therapy show that better response is associated with a lower viral load at the time of treatment switch, the use of a regimen that includes a drug class the patient has not received before and the use of a ritonavir-boosted PI. It is becoming increasingly evident that the sequence of PIs used can affect the activity of these drugs. It is important to note that not just any 3 drugs new to the individual patient will form an appropriate strategy in the absence of knowing the resistance patterns of the new drugs, since they may have cross-resistance with a drug to which the patient’s virus has already developed resistance. In addition, it is important to know about potential drug-drug interactions when selecting drugs for use in a regimen.

Boosted PIs in salvage therapy. The use of ritonavir-boosted PIs in salvage therapy is supported by several recent studies. In the MaxCmin1 trial, virologic response was observed in approximately 75% of patients receiving ritonavir-boosted saquinavir and those

receiving ritonavir-boosted indinavir, but on intent-to-treat analysis in which switching equals failure, the response rates were approximately 70% with the former regimen and 50% with the latter (Dragsted et al, *J Infect Dis*, 2003). In MaxCmin2, lopinavir/ritonavir was associated with a virologic response rate of 65% at 48 weeks on intent-to-treat analysis, compared with 57% for ritonavir-boosted saquinavir ($P = .0006$; Youle et al, 2nd IAS Conf, 2003).

Another recent study compared lopinavir/ritonavir with unboosted atazanavir plus 2 genotype-selected nRTIs in patients with virologic failure on their current PI-based regimen. After 24 weeks, the lopinavir/ritonavir regimen produced a $2.11\text{-log}_{10}\text{-copies/mL}$ reduction in HIV-1 RNA compared with a $1.67\text{-log}_{10}\text{-copies/mL}$ reduction with atazanavir ($P = .0032$; Nieto-Cisneros et al, IAS Conf, 2003). A subsequent study compared atazanavir/ritonavir, lopinavir/ritonavir, and saquinavir-boosted atazanavir along with tenofovir and another nRTI in patients with at least 2 prior antiretroviral therapy regimens and prior treatment with at least 1 PI (DeJesus et al, CROI, 2004). Mean $\log_{10}\text{-copies/mL}$ reductions in HIV-1 RNA levels were 1.93 with atazanavir/ritonavir, 1.87 with lopinavir/ritonavir, and 1.55 with atazanavir/saquinavir, and mean increases in CD4+ cells/ μL were 110, 121, and 72, respectively. This study concluded that atazanavir/ritonavir and lopinavir/ritonavir have similar efficacy in patients with this defined level of prior experience. It is important to note that tenofovir reduces atazanavir levels and that atazanavir should always be boosted with ritonavir if it is being administered in a regimen that includes tenofovir.

Another trial compared ritonavir-boosted fosamprenavir on a once-daily schedule (1400 mg fosamprenavir/200 mg ritonavir), ritonavir-boosted fosamprenavir on a twice-daily schedule (700 mg/100 mg), and lopinavir/ritonavir plus 2 genotype-selected nRTIs on a twice-daily schedule in PI-experienced patients. The 2 twice-daily regimens appeared to be

equivalent (although the study was not large enough to demonstrate statistical equivalence), and virologic response, defined as reduction in plasma HIV-1 RNA level to less than 50 copies/mL, occurred in 46% of the ritonavir-boosted fosamprenavir group and 50% of the lopinavir/ritonavir group at 48 weeks. In a study that evaluated ritonavir-boosted fosamprenavir 700 mg/100 mg plus lopinavir/ritonavir 400 mg/100 mg twice daily and ritonavir-boosted fosamprenavir 1400 mg/100 mg plus lopinavir/ritonavir 533 mg/133 mg twice daily (Wire et al, CROI, 2004), the concentrations of fosamprenavir and lopinavir were substantially reduced ($>50\%$) with both strategies. Increasing the dose did not compensate for the antagonistic interaction, and the higher doses were poorly tolerated. The antagonistic interaction between ritonavir-boosted fosamprenavir and lopinavir makes the combination unlikely to be useful.

Enfuvirtide. The HIV entry inhibitor enfuvirtide can be a highly valuable drug in salvage regimens but unfortunately it is too often reserved for use when no other options are left. As initially shown in the TORO 1 study, the addition of enfuvirtide to optimized background therapy in highly antiretroviral therapy-experienced patients (3 classes, average of 12 drugs) resulted in an improvement in plasma HIV-1 RNA level-decrease from $0.76\text{-log}_{10}\text{-copies/mL}$ to $1.70\text{-log}_{10}\text{-copies/mL}$ ($P < .0001$) (Lalezari et al, *N Engl J Med*, 2003). The benefit of enfuvirtide in achieving virologic response was evident even among those patients in whom lopinavir/ritonavir was active and who also received 2 or more other active drugs (Figure 1; Miralles and DeMasi, IDSA, 2004).

Other important data coming out of the TORO studies involved predictors of virologic response (plasma HIV-1 RNA level <400 copies/mL) at 24 weeks. Significant predictors of response were a baseline CD4+ cell count greater than $100/\mu\text{L}$ (odds ratio [OR], 2.4; $P < .001$), a baseline plasma HIV-1 RNA level less than 100,000 copies/mL (OR, 1.8; $P < .0022$), the

prior use of 10 or fewer antiretroviral drugs (OR, 1.8; $P = .0058$), and the presence of 2 or more active drugs in the regimen (OR, 2.8; $P < .0001$) (Montaner et al, 2nd IAS Conf, 2003).

Darunavir. The recent approval by the FDA of darunavir (previously known as TMC-114), increases the possible treatment options for patients with triple-class experience in whom therapy is failing. Pooled data from the POWER 1 and 2 studies (de Meyer et al, CROI, 2006) as well as additional data from POWER 3 (Molina et al, BHIVA, 2006), demonstrate that virologic response to darunavir diminishes in patients with 10 or more PI resistance mutations and that the presence of V32I, L33F, I47V, I54L, and L89V at baseline predicts diminished virologic response to darunavir (de Meyer et al, CROI, 2006). See also, Johnson et al in this issue). With the availability of darunavir in clinical practice and until additional agents are approved, a major challenge will be the availability of additional active antiretrovirals to pair it with.

Therapeutic drug monitoring. The VIRADAPT study (Durant et al, *AIDS*, 2000) initially showed the value of therapeutic drug monitoring of PI treatment, with decreases in viral load being greater in patients in whom optimal PI concentrations were maintained than in those who had suboptimal concentrations and a regimen selected via genotyping. The greatest decreases occurred in patients with optimized PI levels and genotypic test results. Some retrospective studies have shown a correlation of virologic response with inhibitory quotient (IQ)—that is, the drug concentration, expressed as area-under-the-concentration curve or trough level, divided by the drug sensitivity, expressed as the 50% inhibitory concentration or fold change in drug susceptibility. In general, PI treatment is most amenable to therapeutic drug monitoring, since PI levels are most amenable to manipulation through dose increases or ritonavir boosting. However, it should be noted that wide intra-indi-

vidual variation in levels of drug can make monitoring problematic. In a recent study in 10 patients with plasma HIV-1 RNA levels of less than 50 copies/mL, pharmacokinetic variance (intra-individual coefficient of variability) was a median of 43% for PIs and 26% for NNRTIs, and there was no correlation of the changes in drug levels with suppression of viral load. Viral load blips occurring in these patients were not associated with the lower drug concentrations observed within each patient (Nettles et al, *JAMA*, 2005). In conclusion, we do not currently know the value of therapeutic drug monitoring (TDM) in clinical care but the AIDS Clinical Trials Group (ACTG) study 5146 is comparing TDM with standard of care for PIs as salvage therapy, and results are expected to be available in 2006.

Integrase inhibitors. The recent advances in the development of these agents by both Merck and Gilead suggest that these new drugs will be of significant benefit to the treatment-experienced patients in whom therapy is failing. In the phase II study with the Merck integrase inhibitor (MK-0518), triple class-experienced patients were studied comparing 3 doses of MK-0518 (200 mg, 400 mg, or 600 mg orally twice daily) with placebo with an optimized background regimen. At week 16, all 3 doses of MK-0518 were significantly better than placebo in achieving complete suppression of viral replication (between 56% and 72%, compared with 19% for placebo, achieved an HIV-1 RNA level below 50 HIV-1 RNA copies/mL; [Grinsztejn et al, CROI, 2006]) and this drug is about to enter phase III studies.

Continuing antiretroviral therapy with detectable viral load. There appears to be a clinical benefit to continuing even a failing antiretroviral regimen in heavily pretreated patients with multi-drug resistant virus who thus have little or no prospect of achieving suppression of viral replication if the regimen is changed. For example, a recent analysis of a large French database showed that among

patients with CD4+ cell counts less than 200/ μ L, the annual rates of developing AIDS-defining events were: 24% in patients stopping or interrupting therapy, 14% ($P < .001$) in those continuing antiretroviral therapy with detectable virus, and 6% ($P < .001$) in those with undetectable viral load. Among patients with CD4+ cell counts between 50/ μ L and 100/ μ L the rates were 20%, 15% ($P = .07$), and 8% ($P < .001$). Finally, among patients with CD4+ cell counts less than 50/ μ L, the rates were 58%, 44% ($P < .001$), and 27% ($P < .001$) respectively (Kousignian et al, CROI, 2005).

Using resources to construct an active regimen. Despite the benefit to continuing a regimen even if there is a detectable viral load, an optimized regimen should be used if one can be identified. In the Master-IMPROVE study, patients in whom at least 2 prior regimens had failed and who had CD4+ cell counts of less than 200/ μ L and plasma HIV-1 RNA levels of 1000 to 20,000 copies/mL for at least 6 months either stayed on their current regimen or were switched to a boosted PI and optimized nRTI regimen (Nasta et al, CROI, 2005). Patients had a mean of 6 years of antiretroviral therapy exposure and an average of 3 prior failed regimens. Patients receiving the optimized regimen had a 1.5 \log_{10} copies/mL-decrease in viral load compared with a 0.2 \log_{10} copies/mL-decrease in those maintaining their current regimen, with CD4+ cell counts increasing by 60/ μ L in the former group and decreasing by 10/ μ L in the latter group. Resistance data are not yet available from this study. Nevertheless, these results underscore the fact that if an optimized regimen can be constructed, it is expected to provide a better response than that of remaining on a current failing regimen even if the failing regimen remains partially suppressive.

Treatment Interruptions

Despite the past enthusiasm over the potential use of treatment interrup-

tions as a strategy in heavily pretreated patients (eg, to permit reemergence of drug-susceptible virus as a dominant strain), treatment interruption should not be considered a viable option in patients with advanced immune suppression at the time of virologic failure. For more information, refer to “Structured Treatment Interruptions—New Findings,” by Dr Constance A. Benson, in this issue.

The Future

In the foreseeable future, there will be additional drug options including drugs with new viral and cellular targets. These new drugs should facilitate the task of constructing active regimens and provide more alternatives in extending effective treatment.

Summary

The current approach to managing antiretroviral therapy failure can be summarized as follows:

- Review goals of therapy
- Review antiretroviral history
- Assess adherence, tolerability, and pharmacokinetics
- Perform resistance testing while the patient is still on the suspect or failing regimen
- Identify potentially effective drugs or classes
- If a PI is going to be used, utilize pharmacokinetic enhancement with ritonavir
- Consider novel strategies (eg, therapeutic drug monitoring)
- Consider use of newer agents through clinical trials expanded access programs.

Presented by Carlos del Rio, MD, in June 2005. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr del Rio in July 2006.

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