THE TREATMENT-EXPERIENCED PATIENT: A CASE-BASED APPROACH*

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ABSTRACT

Patients with extensive prior treatment experience and treatment-resistant HIV are common in clinical practice and present difficult challenges. In patients with limited exposure to antiretroviral drugs, the goal of therapy is complete virologic suppression. For a patient who has had extensive prior treatment, complete virologic response may not be possible and a more realistic goal may be to preserve immune function and prevent clinical progression. Assessment of the patient’s viral genotype may identify patterns of HIV mutations that predict resistance to particular antiretroviral medications, and also can help identify the treatment strategies that are most likely to be effective. In patients who have a large number of resistance-associated mutations, phenotype resistance testing may be easier to interpret, and thus more helpful in identifying potentially effective antiretroviral agents. Therapeutic approaches that have been evaluated in patients with poor treatment response include the continuation of lamivudine therapy, the combination of 3 protease inhibitors (PI; ie, “double-boosted” PI therapy), the use of new PIs (eg, tipranavir), and the use of newly developed drug classes (eg, HIV entry inhibitors). Several new antiretroviral agents are currently in clinical development.

One of the most difficult challenges in the treatment of HIV infection is the assessment and management of highly treatment-experienced patients. According to guidelines developed by the US Department of Health and Human Services, the first step in the process of deciding on HIV treatment is to review the goals of therapy. For a patient with limited prior treatment, the goal of therapy is maximal virologic suppression. For a patient with extensive prior treatment, it may not be possible to achieve complete virologic suppression, and a more realistic goal in some patients with few or no treatment options is to preserve immune function and, if possible, to avoid clinical progression.

CASE STUDY: THE TREATMENT-EXPERIENCED PATIENT

The patient, WS, is a 44-year-old man with AIDS who has been referred because he has “exhausted all options.” He was found to have HIV infection in 1993 when he first presented with thoracic zoster. His CD4 cell count at that time was 188 cells per mm³. He received a series of antiretroviral therapies (ART) over the next years, beginning with zidovudine monotherapy and stavudine monotherapy. When dual nucleoside reverse transcriptase inhibitors (NRTI) were the treatment of choice, he received zidovudine plus didanosine and was subsequently switched to zidovudine and lamivudine. Then he received 3-drug regimens of zidovudine, lamivudine, plus indinavir, and stavudine, lamivudine, and efavirenz. He says that he also received other regimens that he cannot recall. The patient had difficulty with adherence to some of his prior regimens, but he has recently improved. He was recently hospitalized for bacterial pneumonia and was found to have Kaposi’s sarcoma lesions on his left lower extremity. His current multidrug regimen is stavudine, lamivudine, abacavir, lopinavir, and ritonavir. His HIV viral load level is currently 61 000 copies per mL.

*Based on a presentation given by Dr Gulick at a satellite symposium held in conjunction with the 43rd Annual Infectious Disease Society of America Meeting in San Francisco, California, on October 6, 2005.
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and his CD4 cell count is 2 cells per mm³. He says that he wants to do “everything he can to treat this.”

The patient described here already shows signs that he has significant immunosuppression and is experiencing clinical events. The next step in developing a treatment plan is the careful review of the patient’s ART history to assess adherence, tolerability, and the potential for pharmacokinetic interactions with other medications that the patient has taken. Resistance testing should be performed while the patient is taking the failing ART, and novel strategies should be considered, such as the use of ritonavir-boosted protease inhibitor (PI) therapy. Therapeutic drug monitoring also may be considered, although this is not a standard approach. The goal of these procedures is to identify drugs or drug classes to which the patient is most likely to respond, which may include investigational agents.

WS’s HIV genotype was assessed. The patient has several resistance-associated mutations. The M184V mutation indicates resistance to lamivudine and emtricitabine. He has 5 of 6 thymidine analog-associated mutations, at reverse transcriptase positions 41, 67, 210, 215, and 219. A substitution at position 74 also suggests resistance to didanosine. It is likely that he will be highly cross-resistant to all available NRTIs. He has 2 important substitutions that affect susceptibility to nonnucleoside reverse transcriptase inhibitor (NNRTI) agents at positions 181 and 190. This is not a surprising finding considering his history of efavirenz use. On the basis of this patient’s genotype, there is little hope of achieving potent virologic activity from NRTI or NNRTI drugs. For the PIs, the patient’s HIV genotype exhibits 8 major substitutions. However, the absence of substitutions at positions 84 and 90 suggests that he has at least some degree of susceptibility to 1 or more PIs.

In a patient with a complex genotype, such as this one, the phenotype may be more easily interpreted and thus more helpful in suggesting potential therapeutic options. For NRTIs, the fold changes in the concentration of the agent required to produce a 50% reduction in viral replication (inhibitory concentration 50%) were: zidovudine (0.9), lamivudine (>56), didanosine (2.3), stavudine (2.1), abacavir (2.0), and tenofovir (1.1). One surprising finding is that although the patient has experienced significant zidovudine exposure in the past, the fold change in sensitivity to this agent is only 0.9. This may be related to interactions among resistance mutations. In particular, the M184V mutation may restore at least partial susceptibility to zidovudine and tenofovir. This suggests that zidovudine or tenofovir may be potential agents for the next regimen if lamivudine or emtricitabine is continued. For didanosine and stavudine, these values are above the known clinical cut-offs for the phenotype, indicating significantly reduced susceptibility to both drugs. Surprisingly, there is some retained susceptibility to abacavir. Therefore, the phenotype suggests NNRTIs that may provide at least partial virologic activity. For the NNRTIs, the fold changes for all agents were greater than 146, indicating complete phenotypic resistance to this class. For PIs, the fold changes were: indinavir (92), ritonavir (120), nelfinavir (>70), saquinavir (6), amprenavir/ fosamprenavir (13), and lopinavir (99). It should be noted that these values were obtained for each of the PIs without pharmacokinetic boosting by ritonavir.

Should lamivudine be continued in the patient’s next regimen? Although he is highly resistant, there may be virologic benefits as a result of mutational interactions and/or decreased viral replication capacity. A recent report at the 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment held in July 2005 in Rio de Janeiro, Brazil, examined the value of continuing lamivudine in patients who had the M184V mutation at baseline. In this prospective clinical trial, 58 patients on lamivudine-containing regimens with viral load levels greater than 1000 copies per mL and CD4 cell counts greater than 500 cells per mm³ who were requesting a treatment interruption were randomized to stop all therapy or to stop all therapy except lamivudine. For patients who stopped all therapy, viral load rapidly increased after treatment was discontinued. The rebound in viral load level was significantly lower in patients who continued to receive lamivudine, as was the rate of decline of CD4 cells. Patients who continued to receive treatment also were less likely to lose M184V resistance mutations over the 48-week follow-up period. When the investigators examined the replication capacity of HIV for both patient groups, HIV in the treatment interruption group exhibited a 10-fold increase in replication capacity compared to baseline, whereas in the group that continued lamivudine, replication capacity was increased only by a factor of 2. Thus, continuing lamivudine clearly has some benefit even in treatment-experienced patients.

Another possible option is the use of 3 PIs together, an approach that has been referred to as “double-boosted” PI treatment. Although this option has recently received increasing attention, there are poten-
tial reasons to be concerned. The use of 3 PIs has not been shown to improve virologic outcomes to an extent greater than 2 PIs, and there are concerns about the potential for pharmacokinetic interactions. The use of 3 PIs was examined in the AIDS Clinical Trials Group 5143 clinical trial, in which treatment-experienced patients were randomized to 1 of the 3 options: a lopinavir-ritonavir regimen \( (n = 9) \), a fosamprenavir-ritonavir regimen \( (n = 8) \), or the 3 PIs together \( (n = 17) \). Pharmacokinetic analysis revealed that levels of amprenavir (the active metabolite of the prodrug fosamprenavir) and lopinavir were reduced by more than 50% with the 3-drug combination than with the 2-drug combinations, suggesting the potential for reduced clinical effectiveness when the 3 PIs are combined (Figure 1). A summary of pharmacokinetic interactions among 3-drug PI combinations in the clinical literature (David Back, Personal communication) found that 3-drug PI combinations produce highly variable and unpredictable pharmacokinetic interactions. In many cases, 3-drug regimens reduce the plasma concentrations of at least one PI. Although there are some combinations that are not known to result in pharmacokinetic interactions (eg, lopinavir-ritonavir combined with indinavir or saquinavir), there are no clinical data that demonstrate the comparative effectiveness of these regimens.

A new PI, tipranavir, recently was approved for the treatment of heavily treatment-experienced patients or those patients with resistance to multiple PIs. The efficacy of tipranavir was examined in the Randomized Evaluation of Strategic Intervention in Multi-Drug Resistant Patients with Tipranavir (RESIST) 1 clinical trial, which enrolled patients who had been treated with ART for at least 3 months with 2 prior PI regimens. The patients had at least one PI resistance mutation but fewer than 2 mutations at protease positions 33, 82, 84, or 90. All of the patients had ongoing viremia with a median viral load level of 67,000 copies per mL and the median CD4 cell count at baseline was 123 cells per mm\(^3\). The patients had a median of 15 prior PI mutations, with 12-fold to 77-fold resistance to currently available PIs. Treating physicians optimized background therapy based on resistance test results and treatment history, and the patients were randomized to receive ritonavir with tipranavir or with the patient’s individually selected comparator PI. After 24 weeks, patients in the tipranavir group exhibited a mean reduction in viral load of approximately 0.9 log copies per mL, compared to a reduction of approximately 0.3 log copies per mL for patients who received comparator PIs.

Perhaps the best studies to characterize management strategies for treatment-experienced patients are the T-20 (enfuvirtide) versus Optimized Regimen Only (TORO) studies, which examined the efficacy and safety of the HIV fusion inhibitor enfuvirtide for the treatment of drug-resistant HIV with a background ART optimized with resistance testing. The TORO 1 study enrolled 491 patients who were previously treated with at least 3 HIV drug classes. The patients had received a median total of 12 prior antiretroviral drugs; the mean baseline viral load was 158,000 copies per mL, and the mean baseline CD4 cell count was approximately 80 cells per mm\(^3\). The patients underwent resistance testing and optimization of background ART and were randomized 2 to 1 to receive the fusion inhibitor, enfuvirtide, or not. Patients who received optimized background therapy alone demonstrated a reduction in HIV viral load level of 0.8 log copies per mL, a finding that demonstrates the importance of a thorough treatment history and the use of resistance testing to optimize management in treatment-experienced patients. However, the

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**Figure 1.** Effect of Lopinavir/Ritonavir on Steady-State Mean Amprenavir Concentration (±2SD)* in HIV-Infected Subjects

- **Fosamprenavir + lopinavir/ritonavir (arm C; \( n = 15 \))**
- **Fosamprenavir/ritonavir (arm B; \( n = 8 \))**

*Administered as fosamprenavir.

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*Vol. 6 (3B) ■ March 2006*
patients who also received enfuvirtide demonstrated a significantly better 1.7-log reduction in HIV viral load ($P < .001$ compared to optimized background alone). Protocol-defined virologic failure (ie, defined as a failure to reduce viral load by at least 0.5 log copies/mL after 6 weeks or a failure to reduce viral load by at least 1.0 log copies/mL after 14 weeks) was more common among the control patients than among patients who received enfuvirtide (Figure 2). Thus, agents with novel mechanisms of action should provide significant antiretroviral activity, even in patients who have developed significant resistance to the 3 traditional classes of HIV drugs.

Despite the effectiveness of enfuvirtide, many clinicians and patients are hesitant to use it because of the requirement for twice-daily injections. A newly developed needle-free injector system (ie, Biojector 2000) is approved by the US Food and Drug Administration (FDA) to deliver subcutaneous or intramuscular injections of up to 1 mL. The injection system contains a disposable needle-free syringe and carbon dioxide cartridges that power the mechanism. The incorporation of the use of the Biojector into the labeling of enfuvirtide is under review by the FDA. The use of the Biojector device to administer enfuvirtide therapy was reported at the 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment in an observational study of 32 patients who were using enfuvirtide administered by needle injections and changed to the Biojector. The occurrence of injection site reactions with the needle-free injector was reduced by 50% compared to conventional needle injections, and the device was rated by patients as “easier to use.”

The effectiveness of enfuvirtide in treatment-experienced patients was examined in a subset of patients from the RESIST clinical trial who had not previously been treated with enfuvirtide. After optimization of background therapy, the patients were treated with tipranavir and enfuvirtide or comparator PIs boosted with ritonavir and enfuvirtide. A virologic response (ie, decrease in HIV RNA >1 log copies/mL) was noted for 70% of patients who received tipranavir and enfuvirtide, compared to 29% of patients receiving comparator PIs boosted with ritonavir plus enfuvirtide. A reduction in viral load to less than 400 copies per mL was noted for 54% of patients with tipranavir and 21.3% with comparator PIs. This study demonstrates that it is possible to attain significant reductions in viral load levels even in treatment-experienced patients.

Similar results were obtained with an investigational PI, darunavir, in a study that was presented at the 12th Conference on Retroviruses and Opportunistic Infections in 2005. Darunavir is a potent investigational PI with activity against PI-resistant HIV. In this study, patients who had previously been treated with 3 HIV drug classes, who had at least 1 primary PI mutation, and who exhibited evidence of ongoing viremia were randomized to the best available PI or to darunavir, boosted with ritonavir, at 1 of 4 doses. In a planned interim analysis at 24 weeks, the highest dosage of darunavir (ie, darunavir 600 mg with ritonavir 100 mg twice daily) was superior to the best available PI therapy combined with optimized antiretroviral drugs. Viral load decreased by 1.8 log copies per mL with darunavir versus 0.3 log copies per mL with conventional PI treatment. Reduction of viral load to fewer than 50 copies per mL was noted overall in 47% of patients with darunavir and 9% with the comparator PIs. In the small subset of patients who first used enfuvirtide as part of their background ART, viral load reduction to fewer than 50 copies per mL

![Figure 2. Time to Protocol-Defined Virologic Failure, as of Week 24](image-url)
was noted for 67% of patients with darunavir and 16% of patients with comparator PIs.

Several new agents are being developed for patients with HIV infection. These include new investigational agents in the traditional HIV drug classes (ie, NRTIs, NNRTIs, and PIs), in addition to the development of new drug classes with novel mechanisms of action. It is expected that these agents will retain full antiretroviral activity even in treatment-experienced patients. HIV entry inhibitors include agents that prevent CD4 attachment and chemokine receptor inhibitors that target CCR5 and CXCR4 receptors. Other new classes include HIV integrase inhibitors and maturation/gag processing inhibitors. Of these, the agents in the most advanced stages of clinical development are the CCR5 inhibitors. In clinical trials of these agents, patients are screened with a tropism assay that measures HIV that is R5-tropic (ie, HIV that uses the CCR5 receptor to enter cells), rather than patients with HIV that is tropic for the X4 receptor or those having a mixed viral population with R5 and X4 tropism. In initial clinical studies, the CCR5 inhibitors aplaviroc, maraviroc, and vicriviroc have produced reductions of HIV viral load of approximately 1.5 log copies per mL.11-13 All 3 of these agents have entered phase II/III studies in treatment-naive and treatment-experienced patients, although studies of aplaviroc recently were suspended as a result of several cases of severe hepatotoxicity and studies of vicriviroc in treatment-naive individuals were suspended because of suboptimal antiretroviral activity (compared to efavirenz). The first integrase inhibitor shown to demonstrate activity against drug-resistant viruses in clinical studies was L870,810. This agent was evaluated in a pilot study that demonstrated reduction of HIV viral load of 1.7 to 1.8 log copies per mL over 10 days14 but it was associated with hepatotoxicity in animal studies. Another integrase inhibitor, MK-0518, is being evaluated in phase I and II clinical trials. Finally, maturation inhibitors work late in the life cycle of HIV to inhibit gag processing. An investigational agent, PA-457, has been evaluated at 4 dose levels.15 Over a 10-day treatment period, PA-457 at the highest dose tested produced a decrease in HIV viral load of approximately 1 log copies per mL.

**Structured Treatment Interruptions**

Should a patient be allowed to suspend ART temporarily before beginning a new treatment regimen? There has been some suggestion that a structured treatment interruption (STI; “drug holiday”) during salvage therapy may promote reversion to wild-type virus and that this may have benefits in terms of choosing the next regimen.9 The effects of STI during salvage therapy were examined by Lawrence et al in a study of 270 patients with treatment failure who were randomized to a 16-week treatment interruption or to an immediate change to another regimen.16 Although the viral load levels did not significantly differ between the 2 groups, the patients who did not suspend therapy exhibited significantly higher mean CD4 cell counts and fewer clinical events (Figure 3).16

![Figure 3. Kaplan-Meier Estimates of the Cumulative Incidence of Progression of Disease or Death](image-url)
However, a smaller study conducted in France found that temporarily suspending treatment before instituting a new regimen significantly improved viral suppression and CD4 cell counts. In this study, patients who had failed to respond adequately to previous ART underwent an 8-week STI before beginning a multidrug regimen. Virologic response (ie, reduction in viral load level of at ≥1 log copies/mL) after 12 weeks of salvage therapy was noted for 62% of patients who had an STI versus 26% of patients who received drug therapy alone immediately (P = .007). Patients in the STI group also had lower mean viral loads and higher CD4 cell counts. Current treatment guidelines suggest that STIs should not be done routinely in treatment-experienced patients because of the risk of clinical events, but because of this French study and other ongoing studies, this question is not completely resolved.

After discussing the risks and benefits of STI, the patient declined to stop his current regimen before starting his new regimen. Reviewing his treatment history and resistance testing results, we chose a regimen of zidovudine/lamivudine/abacavir plus tenofovir plus saquinavir/ritonavir plus enfuvirtide. He was found eligible to enroll in a clinical trial of an investigational PI (versus best-available PI) together with an optimized background ART, enrolled, and was randomized to receive the investigational PI (with ritonavir boosting). On his new regimen of zidovudine/lamivudine/abacavir plus tenofovir plus investigational PI/ritonavir plus enfuvirtide, he achieved rapid virologic suppression, eventually to an HIV RNA level of fewer than 50 copies per mL, which he has now sustained for over a year. At the same time, his CD4 cell count has increased steadily to 183 cells per mm3. He continues to tolerate the regimen, although concerns about “injection fatigue” prompted us to obtain the needle-free device (Biojector) for delivery of enfuvirtide. He has experienced no further signs or symptoms of HIV disease.

CONCLUSIONS

The approach to the treatment-experienced patient includes reviewing treatment goals and the patient's history of HIV treatment, assessing past treatment adherence, and considering the tolerability, toxicity, and pharmacokinetic drug interactions with previous and proposed therapies. Drug resistance testing, obtained while the patient is taking his or her failing regimen, can suggest possible therapeutic options to reduce viral replication and preserve immune response. Ideally, the next regimen will have 2 fully active agents or, if that is not possible, other additional agents that can provide partial virologic activity. Newer agents—from traditional classes or with novel mechanisms of action—may provide significant virologic activity in patients with resistance to currently available antiretroviral drugs; they are available by prescription through expanded access programs or through clinical trials and should be pursued. STIs in treatment-experienced patients are not recommended at present. Recent developments in the assessment and treatment of treatment-experienced patients offer new hope for effectively controlling HIV disease in this challenging patient population.

REFERENCES

5. Hicks C. RESIST-1: a phase 3, randomized, controlled, open-label, multicenter trial comparing tipranavir/ritonavir (TPV/r) to an optimized comparator protease inhibitor/r (CPI/r) regimen in antiretroviral (ARV)-experienced patients: 24-week data. Presented at: 44th ICAAC; October 30-November 2, 2004; Washington, DC. Abstract H-1137a.


