UAB SCHOOL OF MEDICINE
Division of Continuing Medical Education

iMEDOPTIONS

NEW STRATEGIES: OPTIMIZING ANTIRETROVIRAL THERAPY FOR TREATMENT-EXPERIENCED PATIENTS

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Disclosure

Dr. Hardy has disclosed that he has received grant/research support from Boehringer Ingelheim and has served as a consultant for Boehringer Ingelheim, ViroLogic, GlaxoSmithKline and Bristol-Myers Squibb.

In this activity he discusses the investigational antiretroviral agents fosamprenavir and tipranavir, and off-label dosing regimens of atazanavir/ritonavir.

Target Audience

This activity is intended for physicians, pharmacists, and other healthcare community members providing frontline clinical care for persons with HIV/AIDS.

Goal

The goal of this activity is to enable participants to devise effective strategies for the management of treatment-experienced HIV-infected patients.

Learning Objectives

Upon completion of this activity, participants should be able to:

- Discuss the importance of establishing a therapeutic partnership with patients to maximize the likelihood of good adherence
- Review the outcomes of studies of treatment interruptions before initiation of a salvage regimen
- Describe the role of resistance testing in guiding the selection of effective regimens for treatment-experienced patients

Credit Hours Available

- Physicians: Up to 0.75 category 1 credits toward the AMA Physician's Recognition Award

Each physician should claim only those hours of credits he/she actually spent in the activity.

Instructions for Credit

Participation in this self-study activity should be completed in approximately 0.75 hours. To successfully complete this activity and receive credit, participants must follow these steps during the period from September 14, 2003 through September 13, 2004:

1. Register online at http://clinicaloptions.com/hiv/
2. Read the target audience, learning objectives, and faculty disclosures. Study the educational activity online or printed out.
3. Study the educational activity online or printed out.
4. Submit answers to the post-test questions and evaluation questions online.

After submitting the evaluation, you may access your online certificate by clicking the "My CME" tab. Records of all CME activity on the site can be found there.

Accreditation

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The University of Alabama School of Medicine designates this continuing medical education activity for a maximum of 0.75 category 1 credits towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the activity.

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INTRODUCTION

The number of HIV-infected patients who are treatment-experienced is steadily increasing, due both to the life-prolonging effects of potent, combination antiretroviral therapy and the imperfect status of our current therapeutic agents and strategies. Partially suppressive, complex regimens with substantial side effects have challenged even the most adherent patient, frequently resulting in resistant virus and treatment failure. It is estimated that nearly 50% of HIV-infected patients in the United States are currently receiving their second or later antiretroviral regimen, and 25% have received at least 3 regimens.[1] Mega-HAART regimens commonly used to treat patients at the "salvage" end of the treatment-experienced spectrum have been reported to result in fairly good rates of short-term viral suppression but at the high cost of frequent adverse effects. The long-term benefit and durability of these kinds of regimens is questionable.[2]

Strategies for antiretroviral therapy have progressively evolved from a "nothing works so anything goes" mentality to a true science based on emerging, well-founded principles that guide clinicians in making rational and thoughtful treatment decisions. Likewise, steady and ongoing improvements have been achieved in antiretroviral regimens, and the options available for today's newly diagnosed patient are more potent, better tolerated, less complex (ie, fewer daily dosing occasions, fewer dietary restrictions) and easier to take (ie, smaller pill count and size) than those available just a few years ago. However, HIV researchers and clinicians face an ongoing challenge to translate these advances into strategies for treatment-experienced patients whose therapeutic options have been diminished by their prior treatment history.

PERTINENT FACTORS TO BE CONSIDERED

Although many factors influence the success of antiretroviral therapy, they can be grouped into two intertwined but distinct general categories: those that are patient-related, and those that are treatment-related, including both virologic and immunologic factors. Although there is obvious overlap between these areas, an attempt to distinguish them will be made.

PATIENT-RELATED FACTORS

Building a Therapeutic Alliance With Our Patients

Too often, we healthcare providers, in our eagerness to help our patients live healthier, happier lives, lose sight of the fact that while we are overwhelmingly convinced of the beneficence of antiretroviral therapy, our patients—the persons taking the pills days-in and days-out—may still harbor doubts as to the risk:benefit ratio of therapy. Those of us who cared for HIV-infected patients during the 1980s and early 1990s still remember those dark days of death and dying. We may ask ourselves: How could any patient not be overjoyed that these miraculous medications are available to save them from a horrible AIDS death? However, many of our current

patients may have little or no memory of those dark days and reasonably question these "wonder drugs."

For this reason, it can be helpful to delve into a patient's personal belief system regarding antiretroviral therapy and the importance of their physical, and psychological participation in their treatment. After all, they are the ones who will have to swallow the potentially burdensome drug regimens, and face the prospects of enduring daily toxicities such as diarrhea, nausea, skin complaints, occasional kidney stones, and the stigmatizing disfigurement of lipodystrophy. It is easy to see how patients, who have never experienced a day of HIV-related illness, may fail to see the forest for the trees, when their undetectable viral load and rising $CD4^+$ cell count come at the price of a wasted face and limbs that mark them out as being HIV-positive as surely as did Kaposi's sarcoma lesions in the past.

The process by which patients become "treatment-experienced" is without doubt multifactorial. Constant challenges to patients' beliefs that antiretroviral therapy is a beneficent force in their lives too often encourages nonadherence. When an ember of doubt about the merits of therapy enters into a patient's mind, and is then fanned by admonishments of drug toxicity, a friend's successful response to a holistic approach, or scientific reports that treatment interruptions may hold some benefit, a blaze of "benign" nonadherence may follow. This may take the form of omitting a specific agent that is associated with troublesome side effects, or titrating the dose to a more tolerable one. The concept of life-long therapy, which physicians propose in a very matter-of-fact way, may cause waves of overwhelming angst to those destined to take it. We, the thoroughly convinced prescribers who sometimes revel in how we "got a patient to undetectable" with an artfully designed regimen, need to remind ourselves who is actually doing the work to suppress the virus.

Before a patient embarks on a new regimen, exploring with him or her the possible reasons why the previous regimen(s) failed can be a very therapeutic exercise, just as artful and necessary to overall virologic success as interpretation of a genotype assay. Posing simple, direct questions in a nonjudgmental manner (eg, "How often do you miss doses of your medications?" as opposed to "You don't miss doses, do you?") can elicit a refreshingly honest dialogue between patient and provider which may reveal the truth behind the causes of treatment failure and influence the selection of the next regimen. Providers sometimes forget the impact of their presence on a patient's response to questions about how well they are keeping up their end of the "therapeutic bargain." Both patients and providers alike strive to achieve "perfection"—undetectable viral load—with antiretroviral therapy and when this is not reached, something or someone is to blame. Since adherence is often considered to be the patient's job, responsibility for a continuously detectable viral load may be perceived to fall on the shoulders of the "bad patient." Something for providers to consider.

Adherence

Optimal adherence to antiretroviral therapy is often difficult for many patients to achieve. A commonly cited study found that 95% adherence to a HAART regimen was required to achieve optimal rates of virologic suppression: approximately 80% of patients who achieved this level of adherence had undetectable viral load.[3] The relevance of this study to current therapeutic strategies has been questioned, because it was conducted in the early HAART era when protease inhibitor (PI)-based regimens had more complex requirements. Nevertheless, it still makes a valid point about the high degree of adherence required for successful suppression of a highly mutable biologic agent such as HIV-1. On average, 95% adherence means that a patient taking a twice-daily regimen can miss or delay 3 doses per month and no more. This may be more difficult than it sounds when one considers requirements such as the need to refill prescriptions every 30 days, to have medications available when working and traveling, to have consistent insurance coverage, in addition to purposeful avoidance of predictable side effects like nausea, diarrhea, or insomnia at inopportune times.

Other recent data have demonstrated that the relationship between adherence to a highly effective antiretroviral regimen and the probability of developing resistance is a bell-shaped curve distribution (Figure 1).[4,5] Thus, both low (<70%) and high (≥95%) rates of adherence are associated with relatively low probability of resistance: 10% or less for the PI nelfinavir and 20% or less for the nucleoside reverse transcriptase inhibitor (NRTI), lamivudine. In contrast, adherence rates between 70% and 90% are associated with the highest probability of developing resistance, because it is in this range that drug exposures are inadequate to achieve virologic suppression but sufficiently high as to provide selective pressure. Thus, patients with very bad or very good levels of adherence face a lower risk of developing resistance than those who are moderately good but not great adherers.

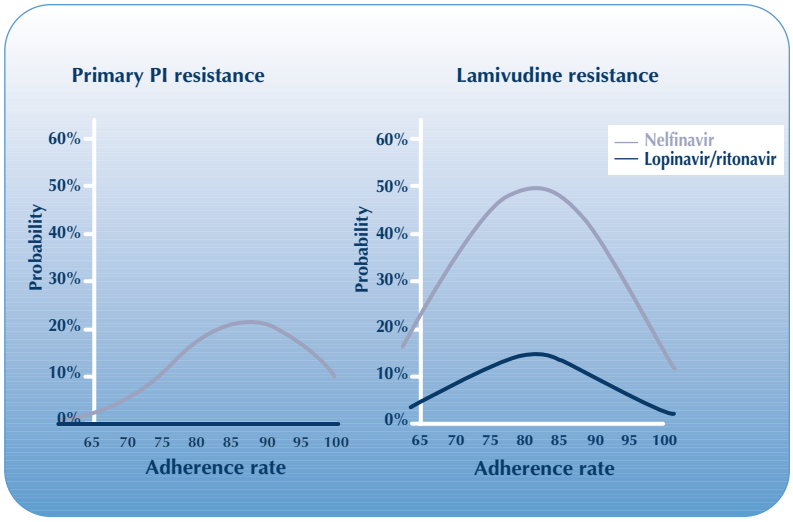

FIGURE 1. Relationship between suboptimal adherence and risk of resistance among patients receiving a nelfinavir- or lopinavir/ritonavir-based regimen in study 863[5]

This observation alone clearly demonstrates the importance of taking adherence into consideration when constructing a new regimen for a treatment-experienced patient. If a patient could not maintain adherence to a high-pill-count, multiple-dosing regimen with significant gastrointestinal or central nervous system side effects, there is a strong likelihood that history will repeat itself if he or she is switched to a similar regimen. Creating regimens to which patients have little chance of adhering increases the opportunity for treatment failure and further development of resistance.

This knowledge offers providers a perfect opportunity to re-establish a therapeutic alliance with their patients. A frank discussion of the patient's current position on the treatment spectrum (ie, how close to a salvage or "last-chance" regimen) can help the patient better understand the importance of his or her commitment to making the new regimen work. Reiterating the precise manner in which a patient should take the new regimen and having the patient repeat it back to the provider can help to establish whether the patient understands these requirements. Asking the patient to write down the new regimen with dosing instructions at the conclusion of the appointment can also confirm that he or she does not leave with important basic questions unanswered or misunderstood. Ten to 20 minutes of time invested on this occasion can help to provide a sound foundation for the new regimen.

TREATMENT-RELATED FACTORS

Structured Treatment Interruptions (STIs)

The concept of using structured treatment interruption (STI) as a strategy to improve virologic response to a subsequent antiretroviral regimen in treatment-experienced patients with highly resistant HIV-1 was initially demonstrated by Miller and colleagues[6] and Deeks and associates[7] in small pilot studies. This approach was based on the observation that when antiretroviral therapy is discontinued for a period of time (2-12 weeks, in general), the drug-resistant HIV-1 that comprises the predominant circulating quasispecies is replaced by a predominantly wild-type viral population, because drug-resistant virus is generally less fit than, and is outcompeted by, wild-type virus. When the majority of virus has reverted to the more susceptible wild-type, then a regimen of multiple (often recycled) antiretroviral agents is used to decrease viral load. Thus, this approach hinges not so much on using new agents as on genetic manipulation of the virus to try temporarily to

increase its susceptibility to recycled agents. The study by Miller and colleagues showed that factors associated with a positive response to treatment re-initiation included higher CD4+ cell count at the start of STI, a shift to wild-type virus during STI, and the number of new drugs in the regimen. Lack of response to treatment was associated with higher HIV-1 RNA levels at the start of STI and fewer active drugs in the new regimen. The authors did not evaluate the consequences of treatment interruption in terms of clinical progression of HIV-1 disease due to the nonrandomized nature of this pilot study. An important shortcoming of these pilot studies was the lack of a concurrent control group of patients treated with similar recycled regimens without a preceding STI.

Recently, two well-controlled trials randomized highly treatment-experienced patients to begin a new regimen selected on the basis of resistance testing, either with or without a preceding STI.

These two studies, CPCRA 064[8] and GigHAART[9] have important differences, as detailed in Table 1, and reached entirely different conclusions about the value of STI in this setting.

The GigHAART study showed a clear benefit to STI, in that patients who discontinued therapy for 8 weeks prior to the initiation of a salvage regimen had superior virologic responses after 48-56 weeks of treatment than those who did not undergo an STI. Compared with CPCRA 064, patients in this study were generally more immunologically suppressed (median CD4+ cell count, 26 vs 180 cells/mm^3), more viremic (median HIV-1 RNA level, 5.3 vs 5.0 $\log_{10}$ copies/mL), and received more intensive salvage regimens (8-9 vs 3-4 agents) A preliminary univariate subanalysis demonstrated that full or partial genotypic reversion to wild-type virus was associated with greater viral load suppression, but it appeared also to be associated with higher baseline CD4+ cell count and lower baseline HIV-1

CHARACTERISTIC	CPCRA 064	GIGHAART
N	270	68
Baseline CD4+ cell count (cells/mm^3)	Mean = 180	Median = 26
Baseline HIV-1 RNA level ($\log_{10}$ copies/mL)	Mean = 5.0	Median = 5.3
Duration of STI	16 weeks	8 weeks
Salvage regimen	3-4 drugs	6-9 drugs
Difference in virologic response between STI vs no-STI arms	Mean -0.76 vs -0.66 $\log_{10}$ copies/mL reduction at month 12	Mean -0.79 vs -0.37 $\log_{10}$ copies/mL reduction by week 48-56 50% vs 24% had >1.0 $\log_{10}$ copies/mL reduction at week 24 (ITT)
Difference in immunologic response between STI vs no-STI arms	Mean -54 vs +37 cells/mm^3 at month 4 Mean +7 vs +42 cells/mm^3 increase at month 12	Mean +51 vs +7 cells/mm^3 at week 24 Mean +69 vs +7 cells/mm^3 increase by week 48-56
Clinical progression in the STI vs no-STI arms	8 deaths in each arm 17 vs 5 disease progression events	2 deaths in each arm by week 48-56

TABLE 1. Comparison of CPCRA 064 and GigHAART studies [9,9]

RNA level. It remains to be seen whether reversion to wild-type continues to an independent predictor of good response in a multivariate analysis.

In contrast, CPCRA 064 demonstrated that a 16-week treatment interruption was associated with no benefit and perhaps even with harm due to clinical disease progression during the period off-therapy. Compared with GigHAART, patients in this study had higher $CD4^+$ cell counts, lower HIV-1 RNA levels and received less intensive salvage regimens. Analyses of patients with $CD4^+$ cell counts above or below 100 cells/mm^3 at baseline and those with different baseline genotypic susceptibility scores (GSS; susceptibility to 0, 1 or ≥2 agents) did not identify any subpopulation that derived benefit from the STI.

Thus, there remains controversy as to whether STI is an effective strategy to improve the response to antiretroviral therapy. Because each trial enrolled a distinctive patient population, studied different durations of STI, and used different kinds of salvage regimens, it is difficult to compare the two studies. It may only be appropriate to glean from these studies that the strategy of STI in the setting of drug-resistant virus is beneficial only in patients similar to, and treated in a like manner as, those in the GigHAART trial and not those in CPCRA 064.

Use of Resistance Testing

Previous controversies regarding whether and when to use resistance testing, and the relative merits of genotyping vs phenotyping, are increasingly becoming resolved. Three expert panels—the US Department of Health and Human Services,[10] the International AIDS Society-USA,[11] and the EuroGuidelines group[12]—have recently issued recommendations on the use of resistance testing, and all agree that it is recommended for any patient in whom antiretroviral therapy has failed (Table 2). Randomized clinical trials have shown benefits for both genotypic and phenotypic drug resistance testing (reviewed by Hirsch and colleagues[10]). Analyses also suggest that resistance testing is cost-effective: Models based on the results of published resistance testing trials show that the cost-effectiveness of resistance testing was intermediate between that of *Pneumocystis carinii* pneumonia prophylaxis and *Mycobacterium avium* complex prophylaxis.[13] In the absence of data from comparative trials, there is insufficient evidence to favor one resistance testing approach over the other. On balance, it appears that genotyping may be preferred after failure of a first or second regimen, when mutation patterns are expected to be relatively simple. By contrast, phenotyping appears

Setting	DHHS[10]	IAS-USA[11]	EuroGuidelines[12]
Primary infection	Recommend	Recommend *	Recommend
Before PEP (testing of source patient)	—	—	Recommend
Before initiating therapy in chronic infection	Consider	Recommend **	—
Before changing therapy in treatment failure	Recommend	Recommend	Recommend
Before initiating therapy in pregnancy	Consider	Recommend ***	Recommend ***
Before treating pediatric patients	—	—	Recommend ****

TABLE 2. Current Guidelines for Resistance Testing

* In primary infection, and in patients believed to have been infected within the previous 12 months
** If patient is believed to have been infected within the previous 2 years (and possible longer)
*** Only if mother is viremic
**** Only if mother was viremic and on treatment at time of birth

most advantageous in highly treatment-experienced patients carrying virus with numerous PI-resistance mutations.

As reviewed by Dr Walmsley, the TORO 1 and 2 trials demonstrated an unequivocal benefit of enfuvirtide (T-20) in highly treatment-experienced patients. In addition to the benefit derived from using an entirely new class of agent that is not affected by pre-existing drug resistance, the regimen that was coadministered with enfuvirtide played a crucial role in successful therapy. An optimized background (OB) regimen was individually selected for each patient based on the results of genotypic/phenotypic resistance testing performed during screening for the study, and consisted almost entirely of recycled agents used in previous failed regimens. The clinical value of the baseline resistance testing is reflected in the remarkable degree of virologic suppression (-0.5 to -0.6 $\log_{10}$ copies/mL) achieved by patients in the control arms of the studies who received the OB regimen alone. It is doubtful that this degree of durable viral suppression would have been seen in this highly treatment-experienced patient population without the assistance of baseline resistance testing to construct the OB regimen. Likewise, the suppressive, durable, antiviral efficacy of enfuvirtide was due to both the intrinsic activity of this novel agent and the contribution of the OB regimen selected on the basis of the screening phenotype. Thus, an analysis of the predictors of virologic success at a median of 24 weeks of follow-up in the TORO studies revealed that the use of at least 2 active drugs, based on phenotypic resistance testing at baseline, was significantly associated with viral suppression.[14] In other words, the phenotypic susceptibility score was positively correlated with HIV-1 suppression (Table 3; Figures 2 and 3).

Use of New Agents in Treatment-Experienced Patients

As previously demonstrated in several clinical trials of antiretroviral therapy in highly treatment-experienced patients, the use of a larger number of active agents in a new treatment regimen correlates with a greater antiviral

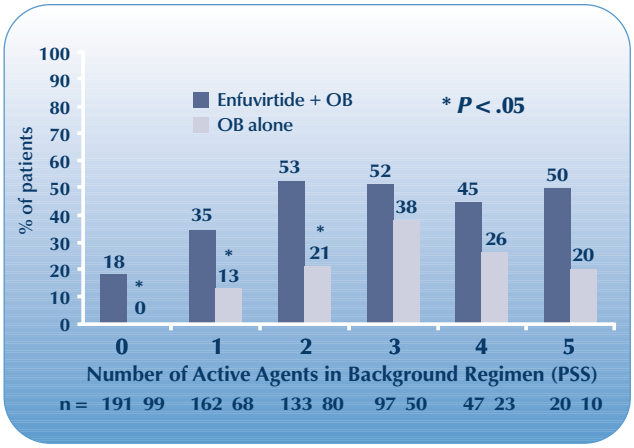

FIGURE 2. Relationship betwen number of active agents in OB regimen and proportion of patients achieving HIV-1 RNA ,400 copies/mL in TORO 1 and 2 studies

response.[6,14] Thus, the availability of new agents is particularly important in constructing a regimen for treatment-experienced patients, especially those with extensive resistance to currently available agents.

As reviewed by Dr Walmsley, agents that hold particular promise for such patients include:

- Enfuvirtide
- Ritonavir-boosted atazanavir
- Ritonavir-boosted tipranavir and perhaps
- Ritonavir-boosted fosamprenavir

The potent, durable antiviral activity of enfuvirtide has been clearly demonstrated by the 48-week data from the TORO 1 and 2 studies.

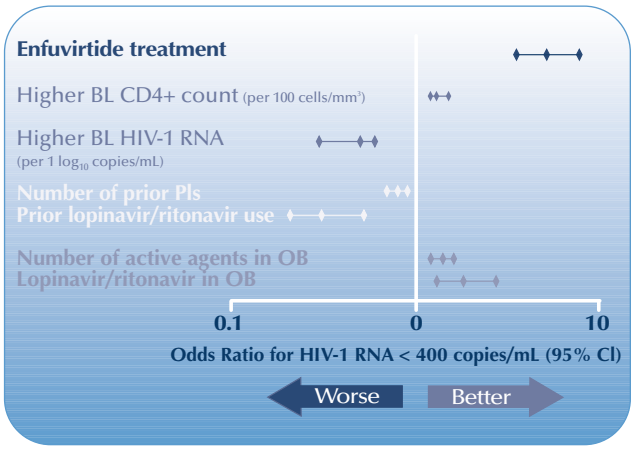

FIGURE 3. Factors associated with HIV-1 RNA <400 copies/mL at week 24 of TORO 1 and 2 studies (multiple logistic regression)

These data confirm that this first entry inhibitor unequivocally provides benefit for the patient population most in need of new antiretroviral agents. Although enfuvirtide demonstrated antiviral activity even in patients whose OB regimen included no active agents, the best results were seen when enfuvirtide was combined with additional active agents.[14] Thus, use of enfuvirtide should ideally not be deferred until patients have no other therapeutic options, but should be considered at a time when additional active agents can be coadministered. The observation that the incidence and severity of adverse events, especially injection-site reactions, remained stable during 48 weeks of follow-up provide reassurance about its long-term safety and tolerability. It is anticipated that expanding clinical experience with enfuvirtide, as well as results from ongoing clinical trials, will further define the optimal use of this new agent.

The promising but short-term (24-week) data demonstrating similar antiviral activity of atazanavir/ritonavir compared with lopinavir/ritonavir may offer a new option to PI-experienced patients, although further studies are needed to define its precise role.[15] Although this study enrolled less treatment-experienced patients than those in the TORO studies, it is reassuring that atazanavir/ritonavir appeared to have similar activity to lopinavir/ritonavir in patients who had received 1 or 2 previous PIs, without adversely affecting patients' lipid profile.

Fosamprenavir is expected to be approved by the Food and Drug Administration in the Fall of 2003. Its potential role in the management of treatment-experienced patients remains to be clarified by longer-term data from studies comparing fosamprenavir/ritonavir with lopinavir/ritonavir in treatment-experienced patients.[16]

Ritonavir-boosted tipranavir is currently being studied in Phase III trials (RESIST I and II) in triple-class-experienced patients (similar to those enrolled in TORO 1 and 2) in North and South America, Europe, and Australia. Eligible patients must have at least 1 but not more than 2 so-called protease inhibitor resistance-associated mutations (PRAMs; mutations at codons 33, 82, 84 or 90). The trials together will enroll over 1300 patients globally and are expected to be completed in 2005. The Phase II trial of tipranavir/ritonavir demonstrated a median reduction in HIV-1 RNA of approximately 1.0 $\log_{10}$ copies/mL after 2 weeks of monotherapy.[17] Further data from the RESIST trials are highly anticipated as this new nonpeptidometic PI may hold significant promise for treatment-experienced patients.

CONCLUSIONS

The growing number of treatment-experienced HIV-infected patients in countries with access to antiretroviral agents highlights the need not only for new antiretroviral agents but also for new

Factors Associated with Therapeutic Success at Week 24 in TORO 1 and 2 Studies

- Use of enfuvirtide
- No prior use of lopinavir/ritonavir
- Higher baseline $CD4^+$ cell count
  - Odds ratio (OR) = 3.0 (95% CI, 2.1, 4.2) for >100 vs <100 cells/mm^3 among enfuvirtide recipients
- Number of active drugs in the OB regimen (≥2 active drugs; P <.0001)
  - OR = 2.6 (95% CI, 1.8, 3.7) for >2 vs <2 active drugs among enfuvirtide recipients
- Exposure to 10 or fewer prior antiretroviral drugs (P <.0058)
  - OR = 1.8 (95% CI, 1.2, 2.7) for <10 vs >10 prior drugs among enfuvirtide recipients

TABLE 3. Factors Associated with Therapeutic Success at Week 24 in TORO 1 and 2 Studies

strategies to maximize their use.

Before starting a new regimen in a treatment-experienced patient, clear, frank discussion between healthcare providers and treatment-experienced patients is essential to identify and resolve basic issues which may stand in the way of a productive therapeutic alliance. Establishing such an alliance can help to achieve the high degree of adherence required for HAART to be successful. Attention to these issues can be as important as ordering and interpreting a genotype prior to starting a new regimen.

Data from the GigHAART study suggest that a planned treatment interruption may be beneficial in a small and specific population of highly treatment-experienced patients. However, the majority of less-advanced treatment-experienced patients do not appear to derive sustained benefit from this strategy, even though early pilot studies and shortterm results looked promising. Health care providers should consider this strategy with great caution, given the negative outcomes of CPCRA 064.

Baseline resistance testing, especially phenotyping, provides essential information for constructing a potent and durable regimen in highly treatment-experienced patients—optimally with, but also even without, the availability of a new agent. Although not trials of resistance testing per se, the design of the TORO 1 and 2 trials provide evidence of the benefits of resistance testing in advanced treatment-experienced patients. Other studies with similar designs, such as the RESIST trials of tipranavir/ritonavir, may provide further insights.

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