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JAMA. 2006;296:827-843

The International AIDS Society–USA

About This Issue

This issue features 2 *Perspectives* articles based on recent presentations at CME activities and conferences, as well as a review article, a special contribution, a reprint, and an insert. Carlos del Rio, MD has updated his discussion of antiretroviral therapy failure—first presented at the 2005 Ryan White CARE Act clinical meeting in New Orleans. Constance A. Benson, MD, offers new findings from studies on structured treatment interruptions drawn from her presentation at the International AIDS Society–USA (IAS–USA) CME course in San Francisco in April 2006. This issue also includes a review of studies of treatment for depression in HIV-infected individuals authored by Bunmi O. Olatunji, PhD, Matthew J. Mimiaga, MPH, Conall O'Cleirigh, PhD, and Steven A. Safren, PhD.

In a special contribution, the IAS–USA Drug Resistance Mutations Group has updated the current list of HIV-1 mutations associated with resistance to antiretroviral drugs. This issue also includes a reprint of "Treatment for Adult HIV Infection: 2006 Recommendations of the International AIDS Society–USA Panel," which was published in *The Journal of the American Medical Association* in August 2006. Finally, this issue is packaged with the new *Selected Oral Manifestations of HIV Disease* card based on a presentation by David A. Reznik, DDS (Reznik D, *Top HIV Med*. 2006;13:143-148).

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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 likelihood 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

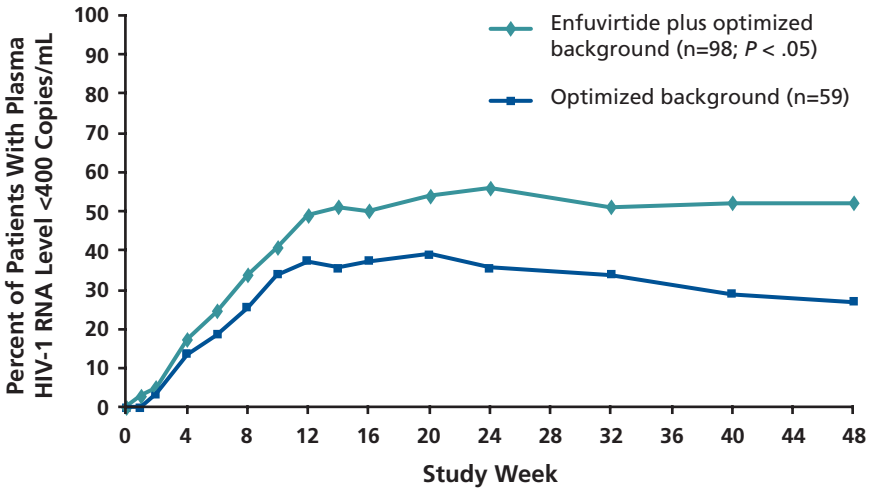

Figure **1**. Effect on virologic response (plasma HIV-1 RNA <400 copies/mL) of addition of enfuvirtide in patients receiving active lopinavir/ritonavir and 2 or more other active agents over time in the TORO 1 study. Data are from intent-to-treat analysis (switching or discontinuation equals failure). 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-$\log_{10}$-copies/mL reduction in HIV-1 RNA compared with a 1.67-$\log_{10}$-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 $\log_{10}$-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-$\log_{10}$-copies/mL to 1.70-$\log_{10}$-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/μL (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/μL, 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/μL and 100/μL the rates were 20%, 15% ($P = .07$), and 8% ($P < .001$). Finally, among patients with CD4+ cell counts less than 50/μL, 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/μL 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/μL in the former group and decreasing by 10/μL 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 interruptions 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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Suggested Reading

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Perspective

Structured Treatment Interruptions—New Findings

A number of recent studies have examined structured treatment interruption (STI) of antiretroviral therapy using CD4+ cell count-guided or time-based strategies in patients with chronic HIV infection and stable suppression of HIV RNA. On balance, data from these studies indicate that STI is associated with worse immunologic, virologic, and clinical outcomes than continuous antiretroviral therapy. However, the potential may still exist for use of short-term STI to manage drug toxicities in patients in this setting or to assess immunologic and virologic outcomes of novel interventions in carefully controlled clinical trials. This article summarizes a presentation on STI made by Constance A. Benson, MD, at the International AIDS Society–USA course in San Francisco in April 2006.

Structured treatment interruption (STI) of antiretroviral therapy has been evaluated in a number of settings. The rationale proposed to support the strategy is based on the following several hypotheses. (1) Investigators have proposed that in acute and chronic HIV infection, a rebound in virus replication after full suppression with antiretroviral therapy may act as a "therapeutic auto-immunization" that may boost host cellular immune responses. (2) In the setting of full suppression of viral replication with antiretroviral therapy in chronic infection, STI has been proposed as a strategy to conserve drug use and cost and to minimize drug toxicities. (3) In the setting of virologic failure in chronic infection, where the virus is resistant to multiple antiretroviral drugs and drug classes, STI has been proposed as a strategy to allow infecting virus to revert to wild-type virus with the theory that this will improve subsequent virologic response to treatment.

Most of the studies completed to date evaluating the use of STI in chronic HIV infection have not demonstrated significant or sustained benefits of the strategy. For example, findings in the Swiss-Spanish Intermittent Therapy Trial, reported in 2003, did not support the hypothesis for "therapeutic auto-immunization;" improved host cellular responses could not be achieved in most patients with chronic HIV infection, although a small number of patients appeared to have a short-term response (Fagard et al, *Arch Intern Med*, 2003). In the trial, 133 patients on antiretroviral therapy with plasma HIV RNA levels below 50 copies/mL and CD4+ cell counts greater than 300/µL underwent 4 cycles of 2 weeks off/8 weeks on antiretroviral therapy. Antiretroviral therapy was then stopped at week 40 and resumed if HIV RNA levels exceeded 5000 copies/mL at week 52. Only 17% of patients were responders—ie, had HIV RNA levels of less than 5000 copies/mL—at week 52, with the percentage dropping to 8% at week 96. When treatment was restarted, HIV RNA did not return to the baseline level of less than 50 copies/mL in 19% of patients; 1 patient developed resistance and had to switch antiretroviral therapy. Overall, the median CD4+ cell count decreased from 792/µL to 615/µL during the first 12 weeks off antiretroviral therapy, but stabilized thereafter. No clinical events occurred in the population.

Results in the setting of salvage therapy have also been disappointing. In 4 randomized clinical trials in patients with virologic failure and virus resistant to multiple antiretroviral drugs and drug classes (total n = 41–270 across 4 studies; treated with a mean of 3.6–7 antiretroviral drugs) and plasma HIV RNA level ranging from 4.3 to 5 $\log_{10}$ copies/mL at

Table **1**. Outcomes in the Staccato Trial

	CD4+ Cell Count-guided Structured Treatment Interruption	Continuous Antiretroviral Therapy	*P* Value
Time on antiretroviral therapy	37.5%	99%	--
AIDS events	0	0	NS
Deaths	1	1	NS
HIV RNA level <50 copies/mL	90.3%	91.8%	NS
CD4+ cell count >350/µL at end of randomized follow-up	60.5%	96.2%	.002
CD4+ cell count >350/µL after antiretroviral therapy resumed or continued	85.9%	96.9%	.01

NS indicates not significant. Adapted from data presented at the 13th CROI, 2006 (Ananworanich et al, CROI, 2006) and in Ananworanich et al, *Lancet*, 2006.

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baseline, rates of achievement of target HIV RNA level of less than 400 copies/mL in STI groups versus non-STI groups after STIs that ranged from 8 to 16 weeks, were 19% versus 11%, 45% versus 46% (target <50 copies/mL), 32% versus 12%, and 19% versus 33%, respectively (Benson et al, *J Infect Dis*, 2006; Katlama et al, *AIDS*, 2004; Lawrence et al, *N Engl J Med*, 2003; Ruiz et al, *J Infect Dis*, 2003). Only the French national agency for AIDS research (Agence Nationale de Recherche sur le SIDA, ANRS) 097 study demonstrated a statistically significant improvement in virologic response at 32 weeks of follow-up (Katlama el al, *AIDS*, 2004).

Overall, 3 of the 4 studies showed that STI is accompanied by an increase in viral load and a decline in CD4+ cell count, with curves for both after resumption of treatment being virtually superimposable with those in patients in whom treatment was not interrupted. The general conclusion to be made from these data is that STI is not beneficial as a strategy to improve treatment outcome for patients with highly drug-resistant virus and few treatment options.

The use of STI as a strategy to reduce overall drug costs, time on antiretroviral therapy, and to reduce toxicities associated with therapy has been the focus of more recent studies. With these objectives, data from 5 trials of CD4+ cell count-guided or time-based STI in chronic HIV infection, presented at the 13th Conference on Retroviruses and Opportunistic Infections (CROI) in 2006 in Denver, Colorado, are discussed below.

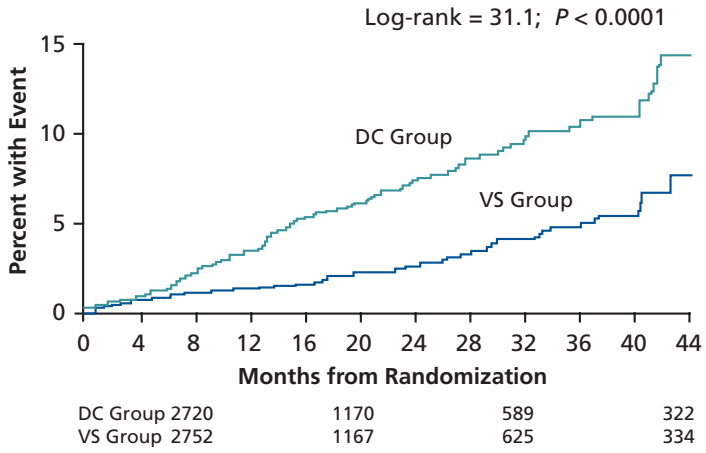

Figure **1**. Percentage of drug conservation group (structured treatment interruption) and viral suppression group (continuous antiretroviral therapy) with disease progression or death in the Smart trial. DC indicates drug conservation; VS, viral suppression. Adapted from preliminary data as presented at the 13th CROI, 2006 (El-Sadr et al, CROI, 2006).

Staccato Trial

In the Staccato trial, conducted in Southeast Asia, the Netherlands, and Australia, antiretroviral therapy-naive patients were treated with antiretroviral therapy until their plasma HIV RNA level was below 50 copies/mL and CD4+ cell count was greater than 350/μL for 6 months; the median time on antiretroviral therapy was 15 months (Ananworanich et al, CROI, 2006; Ananworanich et al, *Lancet*, 2006). Patients were randomized to receive continuous antiretroviral therapy (n=146) or STI guided by CD4+ cell count (n=284), with antiretroviral therapy being stopped for CD4+ counts greater than 350/μL and resumed for counts less than 350/μL. At 96 weeks, continuous antiretroviral therapy was resumed in all patients. Another arm in the trial that assessed STI in a 1 week on/1 week off strategy was discontinued early due to excess virologic failure. The primary endpoints were progression to AIDS or death and proportions of patients with CD4+ cell counts greater than 350/μL at the end of the randomized follow-up period and after resuming continuous antiretroviral therapy. Patients in the STI group spent 37.5% of the study duration on antiretroviral therapy; those receiving continuous antiretroviral therapy spent 99% of the duration on antiretroviral therapy.

There were no differences between groups with regard to the endpoints of AIDS events or deaths and no difference in the proportions of patients with HIV RNA below 50 copies/mL (Table 1). Significantly more patients in the continuous antiretroviral therapy group had CD4+ cell counts greater than 350/μL at the end of randomized follow-up and after continuous therapy was resumed. Among STI patients, CD4+ cell count declined rapidly in the first 8 weeks and more gradually thereafter; 5.8% of STI patients exhibited an acute retroviral syndrome. STI

Table **2**. Events Per 100 Patient-years in the Trivacan Trial

	CD4+ Cell Count-guided Structured Treatment Interruption	Continuous Antiretroviral Therapy	Relative Risk
Serious event	15.2	6.7	0.44
Death	1.2	0.6	0.48
Invasive bacterial infection	6.7	0.6	0.08
Tuberculosis	3.6	2.3	0.65
Viral resistance	11%	5%	--

Adapted from preliminary data as presented at the 13th CROI, 2006 (Danel et al, CROI, 2006).

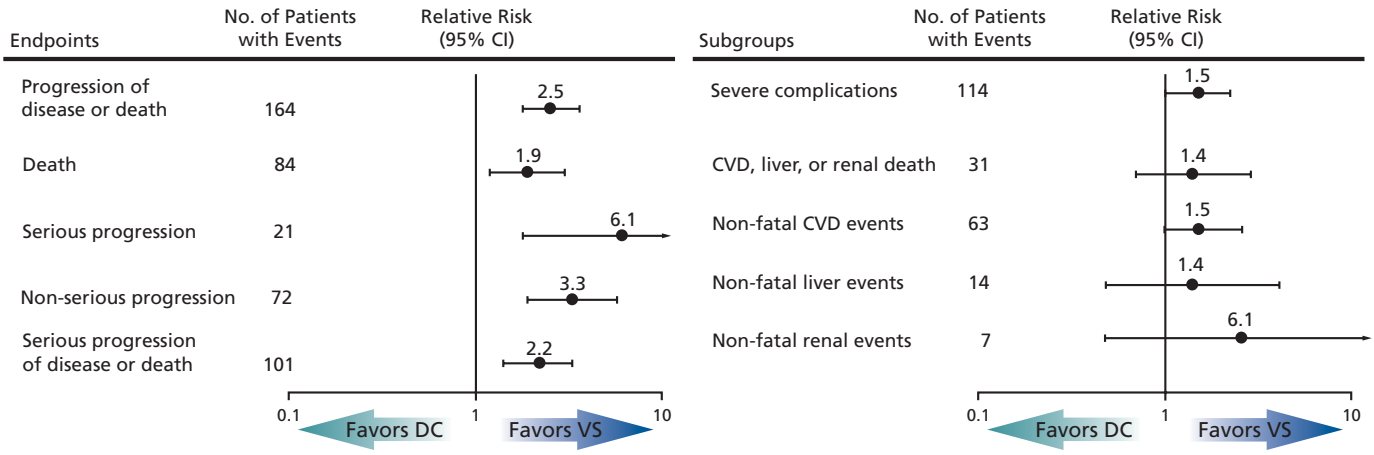

Figure **2**. Relative risks for primary (left) and severe complications (right) endpoints for drug conservation (DC) group versus viral suppression (VS) group in the Strategies for Management of Antiretroviral Therapy (Smart) trial. CI indicates confidence interval; CVD, cardiovascular disease. Adapted from preliminary data as presented at the 13th CROI, 2006 (El-Sadr et al, CROI, 2006).

patients had greater frequencies of candidiasis and decreased platelets, whereas patients on continuous antiretroviral therapy had more diarrhea and neuropathy. No differences in low-density lipoprotein cholesterol or triglyceride levels were observed between the groups. Reverse transcriptase inhibitor (RTI) and protease inhibitor (PI) resistance mutations were found in 5.6% and 2.4%, respectively, of STI patients. Overall, there was a 62% savings in the cost of antiretroviral therapy in the STI group.

Trivacan Trial

In the Trivacan trial, antiretroviral therapy-naive patients with CD4+ cell counts of 150/µL to 350/µL received antiretroviral therapy until their CD4+ cell count was greater than 350/µL and plasma HIV RNA level was below 300 copies/mL for 6 months (Danel et al, CROI, 2006). Patients were randomized to continuous antiretroviral therapy (n = 110), CD4+ cell count-guided STI in which antiretroviral therapy was stopped at 350/µL and resumed at 250/µL (n = 216), or STI consisting of 4 months on/2 months off antiretroviral therapy (n = 325). The primary endpoints were death or serious morbidity and percentage of patients with CD4+ cell count greater than 350/µL after 24 months.

The trial is ongoing for the time-based STI strategy arm, from which data will be available in the near future; however, the CD4+ cell count-based STI arm was stopped early due to an excess of serious morbidity. As noted in Table 2, the CD4+ cell count-guided group was at increased risk (although the increase did not reach statistical significance for individual categories) for each of the serious events, death, invasive bacterial infection, and tuberculosis, compared with the continuous antiretroviral therapy group and had a higher rate of antiretroviral drug resistance. The STI arm had a smaller CD4+ cell count increase and a lower plateau in CD4+ cell count than the continuous treatment arm. Overall, the serious morbidity rate was 2.6-fold greater ($P = .003$) in the STI arm, and this group had significantly more days in hospital and numbers of outpatient clinic visits ($P < .001$).

Table **3**. Baseline Characteristics in the Strategies for Management of Antiretroviral Therapy (Smart) Trial

	Drug Conservation Group (Structured Treatment Interruption)	Viral Suppression Group (Continuous Antiretroviral Therapy)
Median CD4+ cell count	596/µL	599/µL
Median nadir CD4+ cell count	250/µL	252/µL
HIV RNA level ≤ 400 copies/mL	71.0%	70.8%
Prior clinical AIDS	24.7%	23.4%
Antiretroviral therapy-naive	4.5%	4.8%
Years of prior antiretroviral therapy	6	6

Adapted from preliminary data as presented at the 13th CROI, 2006 (El-Sadr et al, CROI, 2006).

Smart Trial

In the Strategies for Management of Antiretroviral Therapy (Smart) trial, patients with CD4+ cell counts greater than 350/µL were randomized to antiretroviral therapy to suppress viral load as low as possible (viral suppression) or to the drug conservation strategy of deferring antiretroviral therapy until the CD4+ cell count was below 250/µL and then using episodic antiretroviral therapy to increase the count to greater than 350/µL (El-Sadr et al, CROI, 2006). The trial was planned to enroll 3000 patients in each arm, with an expected 910 primary

endpoint events at an average of 8 years of follow-up. The primary endpoint was clinical disease progression or death, with secondary endpoints being death alone, serious progression events, and serious complications (including cardiovascular, hepatic, and renal events). The trial was stopped after an interim analysis in January 2006, at which time the occurrence of 164 primary endpoints and an average of 14 months of follow-up showed a significantly increased risk of disease progression or death in the drug conservation group. Baseline characteristics of the study groups are listed in Table 3. There were 117 endpoint events in the drug conservation group, a rate of 3.7 per 100 person-years of observation, and 47 in the viral suppression group, a rate of 1.5 per 100 person-years, yielding a relative risk of 2.5 (95% confidence interval [CI], 1.8-3.6) for disease progression or death in the former ($P < .0001$). As can be seen in Figure 1, the separation between the 2 groups with regard to incidence of the primary endpoint began at about 3 to 4 months.

Relative risks for primary and secondary endpoints are shown in Figure 2; risk for each component of the primary endpoint, including death and serious progression, was significantly increased in the drug conservation group, and there was a borderline significant increase in risk for severe complications. After 36 months of follow-up, approximately 90% of the VS group remained on antiretroviral therapy; the proportion of patients in the drug conservation group receiving antiretroviral therapy at each month of follow-up steadily increased, with approximately 60% receiving antiretroviral therapy at 36 months. The drug conservation versus viral suppression groups spent 32% versus 7% of follow-up time with CD4+ cell counts below 350/µL, 7% versus 2% below 250/µL, and 3% versus 1% below 200/µL.

Based on preliminary data presented, the risk for disease progression or death was higher in the drug conservation group for all baseline CD4+ cell count strata (although the difference was not statistically significant in the lowest stratum), with these data suggesting that risk associated with the drug conservation strategy was independent of initial CD4+ cell count. Stratification by baseline viral load showed that risk of the primary endpoint was significantly elevated in drug conservation patients versus viral suppression patients with better suppression of viral load at baseline.

Table **4**. Outcomes in the Window Trial

	Structured Treatment Interruption	Continuous Antiretroviral Therapy	*P* Value
Time on antiretroviral therapy	52%	100%	--
CD4+ cell count <300/µL at 96 weeks	3.6%	1.5%	STI non-inferior
CD4+ cell count >450/µL at 96 weeks	75%	92%	.0001
HIV RNA level <400 copies/mL after 8 weeks back on antiretroviral therapy	81%	90%	.02
AIDS events	0	0	NS
Other*	9	2	NS
Change in CD4+ cell count	-155/µL	-8/µL	<.001

*No differences in lipodystrophy or dyslipidemia. NS indicates not significant. Adapted from preliminary data presented at the 13th CROI, 2006 (Marchou et al, CROI, 2006).

Window Trial

In the Window trial, patients with CD4+ cell counts greater than 450/µL and plasma HIV RNA levels of 200 copies/mL or less for at least 6 months were randomized to continuous antiretroviral therapy (n = 203) or STI (n = 200) consisting of 8 weeks on/8 weeks off antiretroviral therapy (Marchou et al, CROI, 2006). Patients with a CD4+ cell count nadir of less than 100/µL, those with abacavir or nevirapine in their antiretroviral therapy regimen, and those with hepatitis B virus infection were excluded from the trial. The primary endpoint was CD4+ cell count of less than 300/µL at 96 weeks. Overall, 362 patients (90%) completed 96 weeks of study. Results are listed in Table 4. The STI strategy was statistically noninferior to continuous antiretroviral therapy, with 3.6% of the STI group versus 1.5% of the antiretroviral therapy group meeting the primary endpoint. However, significantly smaller proportions of STI patients had CD4+ cell counts greater than 450/µL at 96 weeks and HIV RNA levels below 400 copies/mL after 8 weeks back on antiretroviral therapy following the 96-week follow-up period, and the decline in CD4+ cell count was statistically significantly greater in the STI group. Patterns of drug resistance in the 2 groups were similar.

ISS/Part Trial

In the ISS/Part trial, patients with viral suppression for a median of 24 months on their first antiretroviral therapy regimen were randomized to continuous antiretroviral therapy (n = 137) or sequential STI (n = 136) consisting of interruptions of 1, 1, 2, 2, and 3 months with each interruption followed by 3 months on antiretroviral therapy (Palmisano et al, CROI, 2006). The primary endpoint was proportion of patients with a CD4+ cell count greater than 500/µL at 24 months, and secondary endpoints included genotypic evidence of resistance and proportions of patients with an HIV RNA

Table **5**. Outcomes in the ISS/Part Trial

	Structured Treatment Interruption	Continuous Antiretroviral Therapy	*P* value
CD4+ cell count >500/µL	69.1%	86.5%	.0075
Virologic failure	26%	24%	NS
HIV RNA level <400 copies/mL	90%	91%	
HIV RNA level <50 copies/mL	60%	86.5%	
Change in CD4+ cell count	-26/µL	-8/µL	

NS indicates not significant. Adapted from preliminary data presented at the 13th CROI, 2006 (Palmisano et al, CROI, 2006).

level of less than 50 copies/mL and less than 400 copies/mL at 24 months.

As noted in Table 5, significantly greater proportions of patients in the continuous antiretroviral therapy group had CD4+ cell counts greater than 500/µL and HIV RNA levels less than 50 copies/mL at 24 months. There were 14 serious adverse events in each group. The cumulative risk of antiretroviral therapy resistance in the STI group was 30% at 24 months, significantly higher than that in the continuous antiretroviral therapy group.

Conclusion

Available data do not suggest that harm results from brief analytic treatment interruptions to assess virologic and immunologic responses to therapeutic immunization or other immunologic interventions in patients who retain CD4+ counts above the threshold of 250 to 350 cells/µL during the treatment interruption. Such treatment interruptions should occur only in patients who are being closely monitored in the clinical trial setting. However, the preponderance of data indicate that STI is not appropriate in the setting of chronic HIV infection in patients who are otherwise candidates for antiretroviral therapy—eg, in those with CD4+ cell counts of 350/µL or lower.

Short-term interruptions may be feasible to manage drug toxicities, but it is unclear precisely what duration of interruption constitutes a safe interruption, although as noted, the risk of progression or death in STI patients in the Smart Trial began to exceed that in the non-STI group at around 4 months, which could be interpreted to suggest that a "safe" interruption would be of shorter duration in a similar population. STI in chronically infected patients with multidrug-resistant HIV appears to offer no clinical or virologic benefit and should not be done. In this setting, however, there are limited data indicating a virologic benefit for interrupting an individual drug in a class for which there has been an accumulation of resistance mutations.

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Suggested Reading

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Top HIV Med. 2006;14(3):107-111

Review

A Review of Treatment Studies of Depression in HIV

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Depression is a prevalent and interfering, yet potentially treatable illness commonly comorbid with HIV/AIDS. In HIV, symptoms and diagnoses of depression have been associated with poor adherence to antiretroviral medication regimens and to accelerated disease progression. This article is a review of the existing literature on the treatment of depression in the context of HIV, including: (1) psychosocial and behavioral health interventions that directly target Diagnostic and Statistical Manual of Mental Disorders *(DSM) unipolar depressive disorders, (2) psychosocial interventions that indirectly target depressive symptoms, and (3) psychopharmacologic treatment studies for DSM-IV unipolar depressive disorders. Psychosocial and psychopharmacologic treatments of depression appear to be effective for individuals with HIV. However, additional methodologically rigorous trials are needed for definitive inferences regarding treatment efficacy. Because of the high frequency of depression comorbid with HIV, and the association of depression with important self-care behaviors in this population, identification of efficacious treatments for depression has the potential to improve both overall quality of life and, potentially, health outcomes.*

Introduction

Depression is a highly prevalent and interfering illness, with lifetime prevalence between 4.9% and 17.9% and a 1-year point prevalence of 10%.[1,2] Symptoms of depression include persistent sadness, loss of interest, decreased appetite, low concentration, sleep problems, guilt/worthlessness feelings, decreased energy, psychomotor retardation, and suicidal ideation. In addition to significant distress, symptoms of depression can also cause other health-related functional and quality of life impairments.

Depression, for example, is associated with poor adherence to medical regimens.[3] Meta-analytic data also show that depressed patients are 3 times greater than nondepressed patients to be nonadherent to medical treatment recommendations,[4] which is largely consistent with the literature reporting that depression in those with HIV is related to diminished health status and health-related quality of life.[5,6]

Studies on the course of HIV suggest that anywhere from 20 to 37% of infected individuals may also have diagnosable depression,[7,8] rates that appear to be higher than the general population estimates (see also Dew et al, 1997[9]; Rabkin, 1996[10]). In a more recent study of 129 people living with HIV/AIDS, approximately one-third scored 14 or higher (≥ mild to moderate depression) on the Beck Depression Inventory (BDI)[11] and 27% met criteria for a current mood disorder.[12] Williams and colleagues[6] found that depression was widespread (54.2%) in a sample of individuals living with HIV even after controlling for demographic characteristics. Furthermore, a recent meta-analysis of data from 10 studies examining the prevalence of depression among HIV-infected individuals revealed a 2-fold increase in rates of depression compared with HIV-uninfected individuals.[13] The current estimates may represent an underestimation as there is evidence that depression may be under diagnosed in the context of HIV medical care.[14]

Various factors may contribute to heightened depression in HIV-infected individuals including the effects of HIV on the brain, stigma, occupational disability, isolation, body image changes, bereavement, and debilitation.[15] The elevated rates of depression among those living with HIV may also be partially attributable to stressors (ie, constant reminder of illness, daily stress, and interference) that accompany maintaining a strict HIV treatment regimen.

Thus, recognizing and treating depression is important because of its association with poor self-care and worse health outcomes in those with HIV.[16,17] Although earlier studies in HIV failed to find an effect for depression and HIV symptoms,[17,18] a subsequent meta-analysis found that depressive symptoms were directly related to symptoms of HIV infection.[19] Additionally, studies conducted over longer time intervals have found significant relationships between depressive symptoms and HIV disease progression (ie, Burack et al, 1993[20]).

Depression has been shown to be associated with declines in CD4+ cell counts over time.[20,21] Depression also predicts accelerated decline of CD4+

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cell numbers and significant increases in HIV viral load over 2 years when controlling for the effects of antiretroviral medication.[22] Finally, there is evidence from various cohorts that depression predicts worse survival rates in individuals with HIV.[23] These health-related findings offer some insight into studies that have also shown that depressed individuals with HIV use significantly more health care and related services (ie, Williams et al, 2005[6]).

The negative impact of depression on the course of HIV may manifest in maladaptive self-care behaviors. Indeed, depression has been shown to be associated with sexual risk taking,[24,25] substance abuse,[26] and poor treatment adherence.[16,27,28] Importantly, poor adherence is associated with poor medical outcome as measured by viral load or CD4+ cell count.[16,27,29-31] Poor adherence can also result in the development of viral mutations, which can lead to drug resistance.[29,32-37]

Individuals with HIV present with different types of stressors and various medical complications that could potentially account for the high rates of depression. Development and implementation of treatments that specifically target depression have the potential to improve overall quality of life and health outcomes in those with HIV.

For example, relief from depression could potentially increase medication adherence (see Fulk et al, 2004[38], Safren et al, 2004[39]), which would in turn affect illness severity and progression. The impact of depression on the course of HIV has initiated the application of specific psychosocial and pharmacologic treatments targeting individuals with HIV and comorbid depression.

This article reviews studies that have directly and indirectly examined the effects of specific psychosocial and psychopharmacologic interventions for the treatment of depression in HIV. Based on this qualitative review of the literature, recommendations for empirically informed treatment of depression in individuals with HIV are offered.

Psychosocial Interventions For Depression in HIV

A search of the literature was conducted using MEDLINE and PsychINFO by pairing the words, "depression" and "HIV" with various combinations of the following words: "treatment," "intervention," and "psychosocial." We located additional studies by screening the bibliographies of articles retrieved in the search. As outlined in Table 1, the literature search revealed 4 studies with psychosocial interventions that specifically targeted depression and had an indicator of depressed mood as an entry criterion, and 6 studies that did not have depression as an entry criterion, but reported on depression outcomes as part of a structured intervention. These 2 general types of studies are described separately.

Psychosocial Interventions Directly Targeting Depression

Kelly and colleagues[40] randomly assigned 68 men with HIV infection who scored over 23 on the Center for Epidemiologic Studies Depression Scale (CES-D)[41] to 1 of 3 conditions: 8 sessions of cognitive-behavioral group therapy (CBT), 8 sessions of social support group therapy (SSG), or a comparison control condition. The CES-D is a widely used 20-item self-report scale that is used to screen for depression and assess the level of one's depressive symptoms. A score of 16 is indicative of clinically significant depressive symptoms, although it does not constitute a clinical diagnosis of depression.

The CBT group intervention consisted primarily of skills training with regard to cognitive restructuring, progressive muscle relaxation, imaginal and cue-controlled relaxation, safe sex practice, and problem solving. The SSG group intervention was primarily based on teaching coping skills. Standardized assessment of depression was conducted with the CES-D and the depression subscale of the Symptom Checklist-90 (SCL-90-D).[42] Participants that completed the CBT and SSG group intervention showed significantly lower scores on the depression subscale of the SCL-90 than the control comparison group. There was also a trend for participants that completed the SSG to report less depression on the CES-D than the comparison group. Analyses of clinical significance of changes in depression at post-intervention and 3-month follow-up revealed that 59% of the CBT and 71% of the SSG participants were judged improved at post-intervention and 52% of the CBT and 50% of the SSG participants were judged improved at 3-month follow-up. The SSG also tended to reduce frequency of unprotected receptive anal intercourse, but the CBT group resulted in less frequent illicit drug use.

Markowitz and colleagues[43] randomly assigned 32 HIV-seropositive patients scoring at least 15 on the Hamilton Depression Rating Scale (HAM-D)[44], and with a clinical impression of a DSM-III-R mood disorder (major depression, dysthymia, or depression not otherwise specified) to interpersonal psychotherapy or supportive psychotherapy. Interpersonal therapy in this randomized clinical trial helped patients relate changes in mood to their environment and social roles. Supportive psychotherapy was a nonspecific client-centered intervention with an added psychoeducation component.

Last-observation-carried-forward analysis indicated that at midtreatment, interpersonal psychotherapy participants' scores on the HAM-D and the BDI were significantly lower than participants in the supportive psychotherapy condition. These significant differences were also observed at the end of treatment. Completer analysis also revealed differential improvement that favored interpersonal psychotherapy over supportive psychotherapy. Specifically, participants given interpersonal psychotherapy improved by a mean of almost 10 points on the HAM-D and nearly 17 points on the BDI by midtreatment. Participants undergoing supportive psychotherapy improved only 6 points in the HAM-D and 5 points on the BDI at midtreatment. Significant increases were observed in physical functioning for those in the interpersonal psy-

chotherapy condition, but no such improvements were observed for those in the supportive psychotherapy condition.

Another study by Markowitz and colleagues[45] involved randomly assigning 101 HIV-infected individuals scoring 15 or higher on the HAM-D and with a clinical judgment of significant depressive symptoms to interpersonal psychotherapy, CBT, supportive psychotherapy, or supportive psychotherapy with imipramine. Interpersonal psychotherapy included procedures to help patients relate changes in mood to events in their environment, CBT strategies consisted primarily of cognitive restructuring, and supportive psychotherapy consisted primarily of client-centered skills and psychoeducation.

Results revealed that participants in the interpersonal psychotherapy and supportive psychotherapy plus imipramine condition showed significantly greater decreases in depression on the HAM-D and BDI than both the CBT and supportive psychotherapy without imipramine groups. Participants in the interpersonal psychotherapy condition also performed significantly better than those in the supportive psychotherapy condition on the BDI. Among therapy completers, interpersonal psychotherapy was associated with significantly greater decreases in depression than both CBT and supportive psychotherapy. Furthermore, changes in physical functioning were significantly associated with changes in mood across conditions. CD4+ cell count did not change significantly by group or over time.

Lee and colleagues[46] evaluated the efficacy of a combination of a modified CBT group therapy and antidepressant medication for HIV patients diagnosed with major depressive disorder or dysthymia. The treatment consisted of 20 weekly (sample mean, 15 sessions completed), 2-hour sessions, which was done to permit more intensive work on dysfunctional core beliefs and relapse prevention. Outcome measures showed substantial reductions in symptoms of depression as assessed by the HAM-D (mean HAM-D scores declined from 26 at time of intake to 9 posttherapy; an improvement of more than 50% in HAM-D scores for each patient was observed at 6-month follow-up). Similar findings were observed on the BDI. Specifically, posttherapy, participants showed a mean decline of 24 at baseline assessment to 15. Improvement of more than 50% on BDI scores for each patient was also found at 6-month follow-up. Furthermore, significant improvements were also observed in general functioning as assessed by the Global Assessment Scale (scores increased from 57 at baseline assessment to 72 posttherapy, and then to 80 at 6-month follow-up).

Psychosocial Interventions Indirectly Targeting Depression

Treatment outcome studies that did not require depression as an inclusion criterion have also been conducted with patients with HIV. For example, Mulder and colleagues[47] randomized 39 asymptomatic HIV-seropositive patients to either a group CBT, experiential therapy, or a waiting list control condition. The CBT intervention included training in cognitive restructuring, behavior change strategies, assertiveness skills, and stress management (including relaxation training). In the beginning of the CBT program, an individually tailored behavioral activation plan was implemented that included increasing physical exercise or practicing relaxation exercises on a daily basis.

The experiential group psychotherapy intervention focused on enhancing the participants' personal awareness of their inner experiential process including incongruence between emotional, cognitive, and behavioral schemata. Therapists for this condition adopted a nondirective role and content themes emerged that included mastering of crises, importance of a social network, sexuality, bereavement, disease-related anxiety, and finding a purpose in life. CBT and experiential group psychotherapy both produced significant reductions in depression, as assessed by the BDI, compared with the waiting list control condition, although there were no statistically significant differences between the CBT and experiential group psychotherapy condition.

Lutgendorf and colleagues[48] examined the efficacy of a 10-week group cognitive-behavioral stress management (CBSM) intervention on dysphoric mood in 39 HIV-seropositive, symptomatic gay men. Men were randomized to either the CBSM or a modified waiting list control condition. The stress management modules included didactic components explaining physiological effects of stress, stress-immune relationships, cognitive-behavioral theory, identification of cognitive distortions, rational thought replacement, coping and assertiveness skill training, anger management, and identification of social supports. The relaxation component included training in a range of relaxation techniques from which participants were encouraged to select the method that worked best for them.

Depressive symptoms were assessed using the BDI. Pre- and post-intervention blood draws were conducted to obtain measures of herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2) antibody titers, and measures of CD4+ (t-lymphocytes) and CD8+ (cytotoxic) cell counts. The intervention was associated with statistically significant decreases in depression. The intervention was also associated with greater immune control of latent HSV-2 virus, although no effect was observed for HSV-1 antibody titers, or CD4+ or CD8+ cell counts. Interestingly, lower levels of dysphoria were associated with lower HSV-2 antibody titers (indicating better immune control).

Antoni and colleagues[49] also evaluated the efficacy of CBSM relative to a waiting list control condition in symptomatic HIV-infected gay men. Results indicate that CBSM was associated with significant reductions in self-reported depressed affect, as assessed by the profile of mood states (POMS; McNair, Lorr, & Droppleman, 1981[50]) depression subscale for subjects in the intervention (n = 40) matched on questionnaire data to subjects in the control condition (n = 19). A subset of these

Table **1**. Psychosocial Treatments for Depressive Disorders and Symptoms in Patients with HIV

Reference and Study Design	Depression Entry Criteria	HIV Disease Stage	Enrolled/ Completed	Treatment Modality/ Duration/Type	Depression Measures	Significant Results and Health/Immune Outcomes
Kelly et al 1993[40] Randomized group CBT/SP, comparative trial	CES-D >16	HIV+ M= 24.1 months	77/44 experimental 38/27 control (men)	CBT, SP (8 sessions/group)	CES-D SCL-90-R	Results: Completers CES-D Change: CBT+SP = –8.0; Comp = –4.0 (P <.07) SCL-90-R (Dep) Change: CBT + SP = 0.8 (P < .05) Outcome: None
Markowitz et al 1995[43] Randomized IP/SP comparative trial	HAM-D ≥15 Clinical judgment of significant depressive symptoms	HIV+ > 6 months	IP: 19/14 SP: 17/16	IP/16 sessions (50 minutes)/ individual SP/8-16 sessions (30-50 minutes)/ individual	HAM-D BDI	Results: Completers HAM-D Change: IP = 10, SP = 6 BDI Change: IP = 17, SP = 5 Outcome: None
Markowitz et al 1998[45] Randomized IP/CBT/SP/SWI comparative trial	HAM-D ≥15 Clinical judgment of significant depressive symptoms	HIV+ > 6 months	101/69	IP, CBT, SP 8-16 sessions/ individual	HAM-D BDI	Results: Completers IP > CBT and SP CBT = SP IP=SWI Outcome: None
Mulder et al 1994[47] Randomized CBT/ET/WLC comparative trial	None	Asympto-matic HIV	11/8 12/7 15/12	CBT/15 sessions (2.5 hours)/ group ET/15 sessions (2.5 hours)/ group, WLC/4-month wait	BDI POMS-TMD	Results: Completers BDI Change: CBT+ET = –4.0, WLC = –0.2 (P <.01) POMS-TMD Change: CBT+ET= –6.0, WLC = 6.0 (P < .04) No significant difference between CBT and ET groups on mood outcomes. Outcome: None
Lutgendorf et al 1997[48] Randomized CBSM/WLC	None	HIV+ No AIDS diagno-sis, symp-tomatic	52/39 MSM	CBSM/10 sessions (135 minutes)/group	BDI POMS-DEP	Results: POMS-DEP Pre-Post Change: CBSM = –3.76 POMS-DEP Pre-Post Change: Control = +1.89 BDI Pre-Post Change: CBSM = –3.38 BDI Pre-Post Change: Control = +1.05 Outcome: Intervention-related reduction in HSV-2 antibody titers

(continued on page 116)

BDI indicates Beck depression inventory; CBSM, cognitive-behavioral stress management; CBT, cognitive-behavioral therapy; CES-D, Center for Epidemiologic Studies depression scale; ET, experiential group psychotherapy; HAM-D, Hamilton depression rating scale; HSV, herpes simplex virus; IP, interpersonal psychotherapy; M, mean; MDD, major depressive disorder; MSM, men who have sex with men; n/a, not available; POMS-DEP, profile of mood states depression subscale; POMS-TMD, profile of mood states total mood disturbance; SCL-90, symptom checklist-90; SLC-90-R (Dep), SCL-90 revised, depression scale; SP, supportive psychotherapy; SWI, imipramine and SP; WLC, wait-list control.

Table **1**. Psychosocial Treatments for Depressive Disorders and Symptoms in Patients with HIV (continued)

Reference and Study Design	Depression Entry Criteria	HIV Disease Stage	Enrolled/ Completed	Treatment Modality/ Duration/Type	Depression Measures	Significant Results and Health/Immune Outcomes
Lee et al 1999[46] Nonrandomized	DSM diagnosis of MDD or dysthymia	AIDS (category C) and HIV symptom (category B)	15/13	CBT w/ medication/ 20 sessions (2 hours)/group	HAM-D BDI	Results: HAM-D Pre-Post Change: –17 BDI Pre-Post Change: –9 Outcome: None
Antoni et al 2000[49] Randomized CBSM/WLC	None	HIV+ No AIDS diagnosis 200-700 CD4+ cells/μL or HIV symptom	59/n/a MSM	CBSM/10 sessions (135 minutes)/ group	POMS-DEP	Results: POMS-DEP Pre-Post Change: CBSM = –4.03 POMS-DEP Pre-Post Change: Control = +0.58 Outcome: Intervention-related reduction in urinary cortisol
Cruess et al 2000[51] Randomized CBSM/WLC	None	HIV+ No AIDS diagnosis 200-700 CD4+ cells/μL or HIV symptom	CBSM 42/37 WLC 23/20	CBSM/10 sessions (2.5 hours)/ group	POMS-TMD POMS-DEP	Results: POMS-TMD Pre-Post Change: CBSM = –11.2 POMS-TMD Pre-Post Change: Control = +3.78 POMS-DEP Pre-Post Change: CBSM = –2.32 POMS-DEP Pre-Post Change: Control = +0.84 Outcome: Intervention-related increases in testosterone CBSM: Significant pre-post decrease in HIV-related symptoms
Cruess et al 2002[52] Randomized CBSM/no treatment control trial	None	HIV symptomatic (category B only) or 200-700 CD4+ cells/μL	125/100 MSM	CBSM/10 sessions (2.5 hours)/group	BDI POMS-DEP POMS-TMD	Results: Completers BDI Change: CBSM = –3.31, Control = –1.1 (P <.10) Outcome: None
Blanch et al 2002[53] Open trial of group CBT	None	HIV infection for at least 3 months	49/39	CBT/16 weeks/ 1 session (2 hours)/week	BDI	Results: 74% had improved BDI scores Outcome: None

BDI indicates Beck depression inventory; CBSM, cognitive-behavioral stress management; CBT, cognitive-behavioral therapy; CES-D, Center for Epidemiologic Studies depression scale; ET, experiential group psychotherapy; HAM-D, Hamilton depression rating scale; HSV, herpes simplex virus; IP, interpersonal psychotherapy; M, mean; MDD, major depressive disorder; MSM, men who have sex with men; n/a, not available; POMS-DEP, profile of mood states depression subscale; POMS-TMD, profile of mood states total mood disturbance; SCL-90, symptom checklist-90; SLC-90-R (Dep), SCL-90 revised, depression scale; SP, supportive psychotherapy; SWI, imipramine and SP; WLC, wait-list control.

participants (34 CBSM, 13 wait-list controls) provided 24-hour urinary samples pre- and post-intervention, which yielded a measure of urinary free cortisol output. Those assigned to the CBSM intervention had significantly less cortisol output at the completion of the study compared with controls. In addition, greater decreases in depressed mood were related to greater decreases in urinary cortisol over the intervention period.

Cruess and colleagues[51] examined the efficacy of CBSM for psychological distress in 65 HIV-seropositive men. Participants were randomized to either a CBSM intervention or a wait-list control condition. Significant reductions were observed in depression, as assessed by the POMS depression subscale, for those in the CBSM condition. However, those randomized to the wait-list control condition showed no significant changes in depression. Furthermore, participants in the CBSM condition showed significant increases in testosterone whereas control participants showed significant decreases. Further, changes in depression were inversely related to changes in testosterone and post-intervention mean testosterone levels for the CBSM group were approaching that of healthy men of similar age.

Cruess and colleagues[52] also examined the efficacy of a 10-week CBSM intervention with 125 HIV-infected gay men. Participants were randomized to either the group CBSM intervention or a no treatment control condition. They report results for 100 participants who completed the intervention. The CBSM intervention was associated with significant reductions in depressive symptoms as measured by the BDI and the depression subscale of the POMS. However, little change on the BDI and the depression subscale of the POMS was observed in the no treatment control condition. Furthermore, increases in cognitive coping strategies (acceptance) and self-efficacy, and decreases in dysfunctional attitudes significantly predicted greater reductions in depressive symptoms.

Blanch and colleagues[53] evaluated the efficacy of a CBT group intervention for 39 patients having HIV infection for at least 3 months. The intervention program lasted for 16 weeks with 1 weekly session for 2 hours. The group intervention consisted of psychoeducation, problem solving, relaxation training, cognitive modification, and a behavioral activation component. Results revealed significant reductions in depression as assessed by the BDI. At 3 months of follow–up, 74% of the patients showed an improvement on the BDI scores. Of all patient characteristics at baseline, only transmission of the HIV infection by sexual intercourse and transmission by intravenous drug use predicted change in depression.

Summary: Psychosocial Treatment Studies of Depression in HIV

A review of the literature suggests that psychosocial interventions derived from a wide variety of theoretical orientations are effective in treating depression among individuals infected with HIV. Significant reductions were found in depression outcome studies in which psychosocial interventions either directly or indirectly targeted depression. Specifically, psychological interventions for depression in individuals with HIV appear to be significantly better than no treatment. However, less definitive inferences can be made regarding the relative efficacy of various psychosocial interventions for depression in HIV-infected individuals.

Although some studies seem to indicate that social support interventions have incremental (ie, better than other credible treatments) efficacy for the treatment of depression in HIV-infected individuals (ie, Kelly et al, 1993[40]), other studies offer evidence for the incremental efficacy of interpersonal psychotherapy (ie, Markowitz et al, 1995[43]). Very few studies have compared CBT-based treatments with other interventions in the treatment of depression in HIV-infected individuals. The limited available evidence does seem to suggest that CBT is equally as effective as other treatments (ie, Mulder et al, 1994[47]).

Psychopharmacologic Interventions: Depression in HIV

As outlined in Table 2, the literature search on pharmacologic interventions for depression in patients with HIV infection revealed 3 studies using selective serotonin reuptake inhibitors (SSRIs),[15,54,55] 2 studies examined the relative effects of SSRIs and tricyclic antidepressants (TCAs),[56,57] and 2 studies examined the effects of psychostimulants.[58,59]

Selective Serotonin Reuptake Inhibitors (SSRIs)

Zisook and colleagues[15] randomized 47 HIV-seropositive patients meeting diagnostic criteria for major depressive disorder and had a current depressed episode of at least 4 weeks duration and were at category A or B for HIV disease stage to receive either fluoxetine or a placebo. Patients were initially instructed to take 1 capsule (fluoxetine 20 mg or placebo) increasing to 2 and 3 capsules by the 4th and 5th weeks respectively. All patients attended a minimum of 7 weeks of supportive and psychoeducational group therapy.

No significant differences were found between patients receiving fluoxetine or a placebo on the clinical global impressions improvement scale (CGI-I). However, patients receiving fluoxetine demonstrated significant reductions in depression as assessed by the BDI and the HAM-D compared with those in the placebo condition. Furthermore, there were significantly more responders in the treatment group (64%) than in the placebo group (23%). Most prominent side effects reported by patients in the fluoxetine condition included nausea (48%), headaches (32%), dry mouth (32%), and diarrhea (24%). Patients in the placebo group were more likely to endorse effects of headaches (36%), nausea (23%), loss of appetite (18%), and insomnia (18%).

Rabkin and colleagues[54] randomized 120 HIV-seropositive patients meeting diagnostic criteria for major depressive or dysthymic disorder with no recent HIV-related opportunistic

Table **2**. Psychopharmacologic Treatment for Depression in Patients with HIV

Reference	Design	Depression Entry Criteria	HIV Disease Stage	Enrolled/ Completed	Antidepressant/ Dosage/Duration	Depression Measures	Significant Results
Selective serotonin reuptake inhibitors (SSRIs)							
Targ et al 1994[55]	Randomized, blind, placebo (with group psychotherapy control) trial	MDD or adjustment disorder with 24 item HAM-D >16	Asymptomatic HIV+ taking zidovudine	20/18 (MSM)	Fluoxetine/20 mg/ 12 weeks	HAM-D POMS POMS-DEP	No significant group differences
Zisook et al 1998[15]	Randomized, double-blind, placebo (with group psychotherapy control) trial	MDD (DSM-III-R) with current episode of 4 weeks duration	HIV disease category A or B	47/37 (men)	Fluoxetine/20-60 mg/6.4 weeks	HAM-D BDI-13 CGI-I	HAM-D mean change: fluoxetine, 12.1; placebo, 6.6 (P <.05). HAM-D ≥ 50% decrease: fluoxetine, 64%; placebo, 23% (P <.01). BDI mean change: fluoxetine, 5.9; placebo, 1.2 (P <.05)
Rabkin et al 1999[54]	Randomized, double blind, placebo-controlled trial	MDD or dysthymic disorder (DSM-IV)	HIV+ with no current opportunistic infection	120/87 (> 90% men)	Fluoxetine/20-40 mg/8 weeks/18-week follow-up	HAM-D CGI SCL-90-D BHS	CGI responders: fluoxetine, 74% (n=42); placebo 47%, (n=14). HAM-D mean change: fluoxetine, 13.1; placebo, 10.4
SSRIs and tricyclic antidepressants (TCAs)							
Elliott et al 1998[57]	Randomized, placebo-controlled, comparative trial	MDD (DSM-III-R) and 21-item HAM-D ≥18	HIV+	25/11 (> 90% male) 25/10 25/13	Paroxetine/33.9 mg/12 weeks Imipramine/162.5 mg/12 weeks Placebo/12 weeks	HAM-D CGI	HAM-D full responders: paroxetine, 55% (n=6); imipramine, 80% (n=8); placebo, 23% (n=3) CGI Responders: paroxetine, 46% (n=5); imipramine, 90%
Schwartz et al 1999[56]	Randomized, placebo-controlled, comparative trial	MDD (DSM-III-R) and 17-item HAM-D ≥14	HIV+ with no current opportunistic infection	8/8 (women) 6/4 (women)	Fluoxetine/20-40 mg/6 weeks Desipramine/75-100 mg/6 weeks	HAM-D CGI	HAM-D mean change: fluoxetine, 9.0; desipramine, 7.17 CGI responders: fluoxetine, 75% (n=6); desipramine, 50% (n=3)
Psychostimulants							
Fernandez et al 1995[58]	Randomized, double-blind comparative trial	MDD (DSM-III-R), and 24-item HAM-D ≥15	HIV+	12/9 8/6 (MSM)	Desipramine/150 mg/6 weeks Methylphenidate/30 mg/6 weeks	HAM-D MMPI-D BSI-D POM-D	No significant differences in pre-post change scores at 6 weeks between the groups. Significant one-tailed (P < .05) experiment-wise pre-post changes on all measures of depressed mood
Wagner et al 2000[59]	Randomized, double-blind, placebo controlled trial	MDD (DSM-IV) and debilitating fatigue	HIV+	23/22 (men)	Dextroamphetamine (dextro) 10-40 mg/2 weeks	HAM-D BSI-D BHS VAS	Responders: dextro, 73%; placebo, 25% (P < .05) *HAM-D mean change: dextro, 7.6; placebo, 5. *BSI-D mean change: dextro, 1.02; placebo, 1.05 *VAS mean change: dextro, −2.1; placebo, 0.9 (* not significant)

BDI indicates Beck depression inventory; BHS, Beck hopelessness scale; BSI-D, brief symptom inventory depression scale; CGI, clinical global impression; CGI-I, CGI-Improvement; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; HAM-D, Hamilton depression rating scale; MDD, major depressive disorder; MMPI-D, Minnesota multiphasic personality inventory depression scale; MSM, men who have sex with men; POMS, profile of mood states; POMS-DEP, profile of mood states depression subscale; POMS-TMD, profile of mood states total mood disturbance; SCL-90, symptom checklist-90; SCL-90-D, SCL-90 depression scale; VAS, visual analogue scale.

infection to 8 weeks of fluoxetine or a placebo. Fluoxetine dosage was fixed at 20 mg for the first 4 weeks and increased by 20 mg/day as indicated by the absence of clinical improvement and significant side effects. Patients were followed up for 18 weeks to assess the impact of treatment on immune markers. In an intent-to-treat analysis, 57% of fluoxetine patients and 41% of placebo patients were identified as responders on the HAM-D, but this difference was not statistically significant. Among patients who completed the study, however, significantly more patients responded to fluoxetine (74%) than to placebo (47%). However, fluoxetine treatment was not significantly related to CD4+ cell change over time. Six patients, all taking fluoxetine, discontinued treatment because of side effects (sleepiness, diarrhea, insomnia, upset stomach, overstimulation, rash) and 50% of patients taking placebo and 50% taking fluoxetine reported at least 1 treatment-related side effect during the trial.

Targ and colleagues[55] randomly assigned 20 participants with HIV infection scoring a 16 or higher on the HAM-D and who also met DSM-IV diagnostic criteria for either major depressive disorder or adjustment disorder with depressed mood to either structured weekly group therapy, focused on active skills in behavioral coping, in addition to fluoxetine (20 mg/day) or identical group therapy with placebo. Participants were enrolled for 12 weeks, and met with a study physician weekly to have questions answered relating to medication adherence and side effects. Among those who completed the study, patients in the fluoxetine treatment plus therapy group as well as the placebo plus therapy group reported significant reductions in depression. However, there was no statistical difference between the 2 treatment conditions.

Comparison of Tricyclic Antidepressants (TCAs) and SSRIs

Elliott and colleagues[57] randomly assigned 75 HIV-seropositive patients with major depressive disorder to receive paroxetine (an SSRI), imipramine (a TCA), or a placebo in a 12-week trial. Paroxetine treatment was initiated at 10 mg/day and subsequently increased to 20 mg/day and then 40 mg/day, in the first and second weeks, respectively. Imipramine treatment was initiated at 50 mg/day and subsequently increased to 100 mg/day and then 200 mg/day, in the first and second weeks, respectively. After the second week, neither the imipramine nor the paroxetine treatment groups had increased doses; decreased doses were only in relation to medical illness or serious drug complications. Forty-five percent (n = 34) of the study participants completed the entire 12-week trial. Intent-to-treat analysis revealed that both active drugs yielded significant reductions in depression, as assessed by the HAM-D, compared with placebo at week 6, week 8, and at week 12.

For participants who completed the treatment, both active drugs produced significant reductions in depression at week 8. However, only imipramine was superior to placebo at week 12. Intent-to-treat analysis showed significantly higher full response rates for paroxetine (38.9%) and imipramine (68.8%) than for placebo (13.6%) after 12 weeks. Common side effects reported in the paroxetine group included dry mouth (52%), nausea (24%), and headache (24%). Dry mouth (56%), heat palpitations (36%), and nausea (32%) were commonly reported in the imipramine group. Patients in the placebo condition were more likely to report concerns of anxiety (60%), nausea (36%), and dry mouth (28%). Treatment drop-out due to side effects was significantly greater among those in the imipramine treatment group compared to both other groups.

Schwartz and colleagues[56] examined the efficacy of 20 to 40 mg/day of fluoxetine (an SSRI) compared with 75 to 100 mg/day of desipramine (a TCA) in a group of 14 HIV-infected women with major depression. Because of insufficient power to detect statistical differences between groups, results were presented with descriptive statistics only. At baseline, participants receiving fluoxetine reported reductions in depressive symptoms, as assessed by the HAM-D, from baseline (20.88) to 6-week post assessment (11.88). Similar reductions in depression were observed for participants receiving desipramine from baseline (22.00) to 6-week post assessment (14.83). Sixty-three percent of patients receiving fluoxetine met criteria for a partial to full response and 50% of patients receiving desipramine met criteria for a partial to full response. Common side effects reported by patients in the fluoxetine group include dry mouth (25%), headache (25%), and nausea (25%). Those in the TCA group generally reported concerns of dry mouth (50%), headache (50%), and insomnia (50%).

Psychostimulants

Fernandez and colleagues[58] randomized 20 HIV-seropositive participants with depression to receive either desipramine or methylphenidate (a psychomotor stimulant) for a 6-week observational study. Subjects randomized to either the desipramine or methylphenidate treatment group had a mean daily drug dose of 150 mg or 30 mg, respectively. Significant reductions in depression as assessed by the HAM-D and the POMS depression subscale were observed for both medications at week 6 of treatment over baseline for both groups. However, there were no significant differences in pre-post change scores at 6 weeks between the groups. Treatment responder analysis revealed that 40% of all patients receiving desipramine showed greater than 50% reduction in HAM-D scores. Forty-three percent of all methylphenidate-treated patients demonstrated a greater than 50% reduction in HAM-D scores. Significant side effects were reported by 22% (ie, dry mouth) of the desipramine-treated patients versus 16% (ie, restlessness) of the methylphenidate-treated patients.

Wagner and colleagues[59] randomly assigned 23 HIV-seropositive men with depression to dextroamphetamine or placebo for a 2-week trial. Seventy-three percent assigned to dextroamphetamine responded to treatment

with significant reductions in mood and increases in energy level, compared with 25% improvement observed in participants assigned to placebo. Among completers in the dextroamphetamine group, significant improvement in depressive symptoms as measured by both the clinician-rated HAM-D and self-reported BSI depression subscale were found at week 2. The most common treatment-related side effects (reported by 22% of the sample) were overstimulation, insomnia, and loss of appetite or weight, or both, with each reported at some point during the treatment.

Summary: Pharmacologic Treatment Studies of Depression in HIV

A review of the literature suggests that a wide range of pharmacologic agents appear to be effective in the treatment of depression in HIV-infected individuals. Such agents included SSRIs, TCAs, and psychostimulants. Overall, the various pharmacologic agents appear to be better than placebo. However, there is no definitive evidence in the literature suggesting that any one pharmacologic agent is more efficacious than another in the treatment of depression in HIV-infected individuals. In fact, there is some evidence to suggest that some of the observed effects of active drug treatment may be partially attributable to high response to placebo.[57] Although active drug treatments generally demonstrate a statistically significant advantage over placebo, these differences tend to be relatively modest. These modest effects for active drug treatment could be a reflection of both dose and duration of treatment. Arguably the doses used in many of the pharmacologic trials are low (ie, with TCAs, paroxetine). Furthermore, the duration of treatment in many of the trials is approximately 6 weeks, which may be short for an efficacy assessment.

An important consideration in evaluating the effectiveness of pharmacologic treatment of depression in HIV-infected individuals is treatment drop-out. High attrition rates were very common, with estimates of drop-out rates at approximately 27%.[54] Although various reasons for treatment drop-out may be considered, side effects attributable to active drug treatment were not uncommon. For example, Rabkin and colleagues[54] found that 50% of patients taking fluoxetine reported at least 1 treatment-emergent side effect during the trial. The most frequent side effects reported were gastrointestinal symptoms including upset stomach and diarrhea (26%), nervousness (18%), sleepiness and appetite and weight loss (13% each), dry mouth (11%), and sexual dysfunction (10%). Thus, it appears that pharmacologic treatment of depression in HIV-infected individuals is more effective than placebo for patients who are able to tolerate it. However, a substantial portion of patients experience intolerable side effects, and this group may require consideration of alternative effective treatment.

Treatment Of Depression in HIV: A Methodological Critique

Defining Depression

Although there is evidence from clinical trials that psychosocial and pharmacologic treatments are effective for the treatment of depression in HIV-infected individuals, additional methodologic issues must be addressed in future clinical trials before more definitive inferences regarding efficacy can be made. One such issue is the marked variability in the operational definition of depression in HIV treatment studies.

For example, all participants evaluated by Markowitz and colleagues[45] were judged to have clinically significant depressive symptoms. However, only 53% met DSM-III-R criteria for a current mood disorder. Meaningful comparisons of treatment studies should be based on the notion that the condition being treated is reliably similar. However, there is some inconsistency in the classification of depression between and within psychosocial and pharmacologic HIV outcome studies. Depression is often identified in such studies as a disorder, a symptom, a syndrome, or a complaint. The consideration of "depression" as either the self-report of depression, major depression, or dysthymia could have implications for the generalizability of the treatment outcome findings.

For example, HIV patients with major depression may clinically differ from those who are more chronically depressed (ie, dysthymia). HIV patients with major depression or dysthymia may also clinically differ from those with just symptoms of depression as a result of a life stressor. Although the broad definition of depression does highlight the importance of defining outcome in the broadest possible fashion in terms of addressing the external validity of the findings obtained, the differences in the entry criteria for depression may limit comparisons between and within psychosocial and pharmacological treatment modalities.

This qualitative review of treatment studies of HIV seems to suggest that pharmacologic trials are generally more stringent in their definition of depression than psychosocial treatment studies. Pharmacologic trials typically infer the presence of depression in HIV-infected individuals based on structured diagnostic interview (major depression). However, the presence of depression in psychosocial treatment studies is often inferred based on cut of scores on self-report measures (depressive symptoms).

Thus, HIV patients in pharmacologic trials may present with more severe depression than those recruited in psychosocial treatment studies. The cut of scores used to infer depression in psychosocial treatment studies not only limits meaningful comparisons with pharmacologic trials, it also allows for limited comparison with other psychosocial treatment studies as different measures of depression (ie, BDI, CGI, POMS, HAM-D, CES-D, SCL-90) are often used. The use of different measures of depression in HIV-infected individuals makes comparisons across studies difficult as some measures emphasize the physical symptoms of depression and others focus exclusively on the affective aspects of depression.

Depending on the assessment

modality, depression may also be confounded with symptoms of HIV, as there is considerable overlap between the physical symptoms of depression and symptoms of HIV progression. The overlap between symptoms of depression and HIV becomes more important given that both psychosocial and pharmacologic treatment studies recruit patients across the whole range of disease stages. Importantly, patients at the later stages of HIV disease will appear more depressed because of the overlay of HIV-related disturbances of appetite, sleep, libido, weight, and energy, on symptom measures of depression and presumably will create difficulties assessing treatment impact (particularly on studies using the BDI for example). The overlap between symptoms of depression and HIV is an important issue for assessment and treatment outcome that has not been adequately addressed in the literature. The selection of the appropriate measures to diagnose and assess change in depression in HIV-infected individuals will surely need to account for these assessment considerations in future treatment trials.

Determining Treatment Efficacy

The evidence that psychosocial and pharmacologic treatments are efficacious for the treatment of depression in HIV must be considered in the context of the limitations of the clinical studies. Studies on the efficacy of psychosocial treatments for depression in HIV were largely consistent with the use of control conditions to rule out nonspecific treatment factors (ie, treatment credibility, expectation for improvement, experimental demand). These studies were also largely consistent in the direct comparison of validated techniques (ie, CBT vs SSG). However, the internal consistency of the clinical trials must be considered.

For example, the outcome of treatment studies utilizing different medication doses and duration of treatments across different treatment conditions[43,53] must be interpreted with caution. In addition to consistency in the delivery of treatment for depression in HIV, the presence of clearly defined target symptoms, reliable and valid measures, blind evaluators, appropriate assessor training, manualized treatment procedures, unbiased assignment to treatment conditions, and ratings of treatment adherence should be a prerequisite before inferences can be made regarding the efficacy of psychosocial and pharmacologic treatments of depression in HIV treatment outcome studies.

Future demonstrations of efficacy may well be aided by the consideration of dismantling designs to help identify the functional significance of specific aspects of multifaceted psychosocial treatment procedures. Similar methodologic considerations may be applied to pharmacologic treatment outcome studies in which random assignment may be used to assess the relative effects of a given pharmacologic treatment (eg, SSRI), no treatment (eg, wait-list), nonspecific factors (placebo), and credible pharmacologic alternatives (eg, TCA). Such design considerations in treatment outcome studies examining the efficacy of psychosocial and pharmacologic interventions for depression in patients with HIV would be consistent with a cost-effective agenda in which treatment delivery consists of only necessary and sufficient empirically based interventions.

Discussion

As the HIV epidemic grows, with 40,000 new infections per year[60], and with individuals living indefinitely on highly active antiretroviral therapy, so will the number of individuals with comorbid depression. However, established guidelines for treating depression in HIV are lacking. With the advent of studies identifying the consequences of depression in HIV infected individuals; the identification of effective treatments for depression should be a focus of further research. This qualitative review of the literature does suggest that a wide range of psychosocial and psychopharmacologic interventions are effective in the treatment of depression for individuals with HIV. However, continued research is needed to identify which treatments for depression are better for which patients with HIV under which set of circumstances. By matching specific treatments for depression to specific patients with HIV treatment, gains may be maximized.

Significant improvement in symptoms of depression was found in treatment outcome studies directly and indirectly targeting depression in HIV. Furthermore, it appears that CBT, interpersonal psychotherapy, and supportive therapy can be helpful in the treatment of depression in individuals with HIV. Identification of the treatment component that is common across these diverse psychosocial interventions that may account for the equivalent reductions in depression may be informed by consideration of predictors of treatment outcome.

For example, Cruess and colleagues[52] found that increases in coping strategies significantly predicted greater reductions in depression in HIV-infected individuals. Importantly, the coping technique examined emphasized acceptance, suggesting that perhaps coming to terms with HIV illness may have important implications for facilitating positive gains during treatment for depression. It is also possible that different psychosocial interventions utilize different techniques (ie, problem solving; psychoeducation) that may help maximize adaptive coping to illness. Maximizing adaptive coping in individuals with HIV and depression appears to be a useful strategy, given the multiple stressors that are involved in living with and maintaining a medication treatment regimen.[61,62]

This review of the treatment outcome literature suggests that pharmacotherapy is also effective for the treatment of depression in patients infected with HIV. Pharmacologic agents such as SSRIs, TCAs, and psychostimulants appear to be generally better than placebo. However, patients with HIV treated with placebo also often demonstrated substantial improvement in depressive symptoms.[15] Thus, it is unclear the percentage of variance in the efficacy of pharmacotherapy for depression in HIV that may be

accounted for by the "placebo effect," In fact, a recent meta-analysis of double-blinded, randomized controlled trials (7 studies that included 494 subjects) examining the efficacy of antidepressant treatment among HIV-seropositive depressed individuals found that the pooled effect size from the random effects model was 0.57.[63] However, placebo response explained nearly 62% of the variance in effect sizes across the studies.

It is also unclear in the treatment outcome literature if one pharmacologic agent has any incremental efficacy (over and above a placebo and the next best drug treatment) over another drug treatment. Furthermore, the determination of the utility of pharmacotherapy for depression in HIV should be partially dependent on how many patients can tolerate the treatment in its entirety. Indeed, adverse side effects are common in pharmacologic treatment trials for depression in HIV.[54] Furthermore, patients with HIV and comorbid depression often suffer from multiple physical complications and often receive many toxic medications. Thus, receiving more medication that potentially produces additional adverse effects may not be optimal.

Although both psychosocial and pharmacologic interventions seem to be effective for the treatment of depression in HIV, there is very little research suggesting if patients with HIV may receive more benefit from psychosocial or pharmacologic treatments. This is largely due to a paucity of rigorous treatment outcome studies directly comparing a psychosocial intervention with a pharmacologic intervention for depression in HIV. This qualitative review seems to suggest that psychosocial interventions are largely equivalent to pharmacologic interventions for the treatment of depression in HIV. However, the absence of a difference between psychosocial and pharmacologic interventions may be a result of the loose diagnostic criteria for depression in psychosocial treatment studies.

There is some evidence in the general depression treatment literature suggesting that the selection of psychosocial interventions over pharmacologic interventions may maximize treatment gains after treatment discontinuation. For example, Hollon and colleagues[64] found that depressed patients withdrawn from cognitive therapy were significantly less likely to relapse during continuation than patients withdrawn from medications (30.8% vs 76.2), and no more likely to relapse than patients who kept taking continuation medication (30.8% vs 47.2%). Consideration of potential treatment complications seems to suggest that psychosocial treatments may also offer an advantage as pharmacologic treatment of depression will likely be complicated by HIV illness, adverse drug effects, drug interactions, and potential for abuse. These considerations would support a model in which validated psychosocial interventions, when available, are considered first line treatments for depression in individuals with HIV.

Treatment of depression could result in substantial improvement in quality of life for patients with HIV. However, further research is greatly needed to determine if treating depression increases self-care behaviors such as adherence and if treating depression results in improvements in HIV-specific markers of disease severity or progression such as viral load or CD4+ count. Cook and colleagues[65] report a recent study examining the effects of treated and untreated depressive symptoms on the likelihood of utilization of antiretroviral therapy among a cohort of HIV-infected women who screened positive for probable depression. Regression analysis was used to estimate the impact of psychosocial mental health treatment on the probability of antiretroviral utilization, controlling for clinical indicators (CD4+ count, viral load), demographic features (race or ethnicity, income), and behavioral factors (recent crack, cocaine, or heroin use). Results showed that use of antidepressants plus psychosocial treatment, or psychosocial treatment alone significantly increased the probability of antiretroviral utilization, compared with receiving no depression treatment. Use of antidepressants alone did not differ significantly from receiving no depression treatment. These findings suggest that efforts to enhance access to psychopharmacologic and psychosocial treatments (or psychosocial treatment alone) may increase use of the most effective HIV therapies.

Ideally, an effective treatment of depression in HIV should also translate to changes in illness progression and increases in self-care behaviors. Preliminary work has begun to develop and evaluate treatments that specifically target HIV medication adherence and depression that has shown promising results in a case series[39] and is being tested by our group in 2 randomized controlled trials. Additionally, some studies have shown that effective psychosocial treatment of depression in HIV translates into improvements in immune outcomes of central importance for people managing HIV disease.

For example, Lutgendorf and colleagues[48] found that psychosocial treatment of depression in symptomatic HIV-seropositive gay men was associated with greater immune control of latent HSV-2 virus and lower levels of dysphoria were associated with lower HSV-2 antibody titers. Studies have also shown that psychosocial treatment of depression in symptomatic HIV-infected gay men is related to greater decreases in urinary cortisol and significant increases in testosterone.[49,51] These studies suggest that psychosocial treatment for depression may have important implications for HIV-specific markers of disease severity. However, much less is known of the effects of pharmacologic treatment for depression on similar HIV markers.

The current literature does support the utility of both psychosocial and pharmacologic strategies for the treatment of depression in HIV-infected individuals. However, there are several methodologic limitations of psychosocial and pharmacologic treatment outcome studies including high levels of attrition, variable stages of infection, variability in treatment duration, and more studies that target gay men than other risk groups such as injection drug

users, that limit strong inferences regarding treatment efficacy.[66] Indeed, the vast majority of the depression outcome studies are undertaken predominantly with HIV-infected men. Future treatment studies will need to focus on women, particularly given that minority women are now at substantial risk for HIV. The presence of systematic differences in depression entry criteria and outcome assessment based on these entry criteria is also an important limitation of current psychosocial and pharmacologic HIV treatment outcome studies. Indeed, differences in the operational definition of depression limits meaningful comparisons across treatment modalities and greatly impacts conclusions about the generalizability of the interventions. Future research addressing these and other methodological limitations may facilitate the development of more effective treatments of depression in HIV-infected individuals.

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Update of the Drug Resistance Mutations in HIV-1: Fall 2006

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The International AIDS Society–USA (IAS–USA) Drug Resistance Mutations Group is marking 6 years as an independent volunteer panel of experts focused on identifying key HIV-1 drug resistance mutations. The goal of the effort is to quickly deliver accurate and unbiased information on these mutations to HIV clinical practitioners.

This version of the IAS–USA Drug Resistance Mutations Figures replaces the version published in this journal in October/November 2005.[1] The IAS–USA Drug Resistance Mutations Figures are designed for use in identifying mutations associated with viral resistance to antiretroviral drugs and in making therapeutic decisions. Care should be taken when using this list of mutations for surveillance or epidemiologic studies of transmission of drug-resistant virus. A number of amino acid substitutions, particularly minor mutations, represent polymorphisms that in isolation may not reflect prior drug selective pressure or reduced drug susceptibility.

In the context of making clinical decisions regarding antiretroviral therapy, evaluating the results of HIV genotypic testing includes: (1) assessing whether the pattern or absence of a pattern in the mutations is consistent with the patient's antiretroviral history; (2) recognizing that in the absence of drug (selection pressure), resistant strains may be present at levels below the limit of detection of the test (analyzing stored samples, collected under selection pressure, could be useful in this setting); and (3) recognizing that virologic failure of the first regimen typically involves HIV-1 isolates with resistance to only 1 or 2 of the drugs in the regimen (in this setting, resistance most commonly develops to lamivudine or the nonnucleoside reverse transcriptase inhibitors [NNRTIs]).[2-6] The absence of detectable drug resistance following treatment failure may result from the presence of drug-resistant minority viral populations, patient medication nonadherence, laboratory error, drug-drug interactions leading to subtherapeutic drug levels, and possibly compartmental issues, indicating that drugs may not reach optimal levels in specific cellular or tissue reservoirs.

Revisions to the Figures for the August/September 2006 Update

Nucleoside (or Nucleotide) Reverse Transcriptase Inhibitors

Among the changes in the August/September 2006 version of the figures and user notes, user note 1 has updates about NNRTI hypersusceptibility. On the nucleoside (or nucleotide) reverse transcriptase inhibitor (nRTI) bars, the K70E mutation has been added to tenofovir. User note 4 discusses mutations outside of the reverse transcriptase gene region depicted on the figure bars. These mutations may prove to be important for HIV drug resistance. Also on the nRTI bars, the E44D and V118I mutations have been removed from stavudine and zidovudine because the significance of E44D or V118I when each occurs in isolation is unknown (see user note 5).

Nonnucleoside Reverse Transcriptase Inhibitors

The multi-NNRTI resistance bars have been removed because the presence of 2 or more of the NNRTI mutations depicted on these bars may lead to poorer long-term virologic response (see user note 12).

Protease Inhibitors

In the protease inhibitor (PI) category, the ritonavir bar has been removed because ritonavir is now used only for pharmacologic purposes, not as monotherapy, as discussed in user note 15. The "/ritonavir" designation has been added to atazanavir, fosamprenavir, darunavir, indinavir, and saquinavir to indicate boosting with low-dose ritonavir. User note 16 provides an update on how HIV-1 Gag cleavage site changes can cause PI resistance in vitro.

Based on new data (see user note 17), the following minor mutations have been added to atazanavir with or without ritonavir: L10C, K20T/V, E34Q, F53L/Y, I54A, I64L/M/V, V82F/I, and I93M. A darunavir/ritonavir bar has been added for the fully approved drug formerly known as TMC-114 (see user note 18). The darunavir/ritonavir major mutations on the bar are I50V, I54M, L76V, and I84V and the minor mutations are V11I, V32I, L33F, I47V, I54L, G73S, and L89V. Minor mutations added to saquinavir/ritonavir are: L24I, I62V, and V82F/T/S.

Comments?

The IAS–USA Drug Resistance Mutations Group welcomes comments on the mutations figures and user notes.

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MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (nRTIs)[1]

Multi-nRTI Resistance: 69 Insertion Complex[2] (affects all nRTIs currently approved by the US FDA)

M	A	▼	K	L	T	K
41	**62**	**69**	**70**	**210**	**215**	**219**
L	V	Insert	R	W	Y F	Q E

Multi-nRTI Resistance: 151 Complex[3] (affects all nRTIs currently approved by the US FDA except tenofovir)

A	V	F	F	Q
62	**75**	**77**	**116**	**151**
V	I	L	Y	M

Multi-nRTI Resistance: Thymidine Analogue-associated Mutations[4,5] (TAMs; affect all nRTIs currently approved by the US FDA)

M	D	K	L	T	K
41	**67**	**70**	**210**	**215**	**219**
L	N	R	W	Y F	Q E

	K	L	Y	M
Abacavir[6]	**65**	**74**	**115**	**184**
	R	V	F	V

	K	L
Didanosine[7,8]	**65**	**74**
	R	V

	K	M
Emtricitabine	**65**	**184**
	R	V I

	K	M
Lamivudine	**65**	**184**
	R	V I

	M	D	K	L	T	K
Stavudine[4,5,9,10]	**41**	**67**	**70**	**210**	**215**	**219**
	L	N	R	W	Y F	Q E

	K	K
Tenofovir[11]	**65**	**70**
	R	E

	M	D	K	L	T	K
Zidovudine[4,5,9,10]	**41**	**67**	**70**	**210**	**215**	**219**
	L	N	R	W	Y F	Q E

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)[1,12]

	K	V	Y	Y	P
Delavirdine	**103**	**106**	**181**	**188**	**236**
	N	M	C	L	L

	L	K	V	V	Y	Y	G	P
Efavirenz	**100**	**103**	**106**	**108**	**181**	**188**	**190**	**225**
	I	N	M	I	C I	L	S A	H

	L	K	V	V	Y	Y	G
Nevirapine	**100**	**103**	**106**	**108**	**181**	**188**	**190**
	I	N	A M	I	C I	C L H	A

Date of Revision: August 2006

MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS[13,14,15,16]

Atazanavir +/-ritonavir[17]

Wild-type	L	G	K	L	V	L	E	M	M	G	I	F	I	D	I	I	A	G	V	I	I	N	L	I
Position	10	16	20	24	32	33	34	36	46	48	**50**	53	54	60	62	64	71	73	82	**84**	85	**88**	90	93
Substitutions	I F V C	E	R M I T V	I	I	I F V	Q	I L V	I L	V	L	L Y	L V M T A	E	V	L M V	V I T L	C S T A	A T F I	V	V	S	M	L M

Fosamprenavir/ ritonavir

Wild-type	L	V	M	I	I	I	G	V	I	L
Position	10	32	46	47	**50**	54	73	82	**84**	90
Substitutions	F I R V	I	I L	V	V	L V M	S	A F S T	V	M

Darunavir/ ritonavir[18]

Wild-type	V	V	L	I	I	I	G	L	I	L
Position	11	32	33	47	**50**	**54**	73	**76**	**84**	89
Substitutions	I	I	F	V	V	M L	S	V	V	V

Indinavir/ ritonavir

Wild-type	L	K	L	V	M	M	I	A	G	V	V	I	L
Position	10	20	24	32	36	**46**	54	71	73	77	**82**	**84**	90
Substitutions	I R V	M R	I	I	I	I L	V	V T	S A	I	A F T	V	M

Lopinavir/ ritonavir[19]

Wild-type	L	K	L	V	L	M	I	I	F	I	L	A	G	V	I	L
Position	10	20	24	**32**	33	46	**47**	50	53	54	63	71	73	**82**	84	90
Substitutions	F I R V	M R	I	I	F	I L	V A	V	L	V L A M T S	P	V T	S	A F T S	V	M

Nelfinavir[20]

Wild-type	L	D	M	M	A	V	V	I	N	L
Position	10	**30**	36	46	71	77	82	84	88	**90**
Substitutions	F I	N	I	I L	V T	I	A F T S	V	D S	M

Saquinavir/ ritonavir

Wild-type	L	L	G	I	I	A	G	V	V	I	L
Position	10	24	**48**	54	62	71	73	77	82	84	**90**
Substitutions	I R V	I	V	V L	V	V T	S	I	A F T S	V	M

Tipranavir/ ritonavir[21]

Wild-type	L	I	K	L	E	M	K	M	I	I	Q	H	T	V	N	I	L
Position	10	13	20	**33**	35	36	43	46	47	54	58	69	74	**82**	83	**84**	90
Substitutions	V	V	M R	F	G	I	T	L	V	A M V	E	K	P	L T	D	V	M

MUTATIONS IN THE GP41 ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

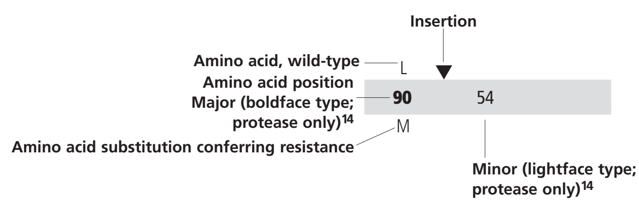
Enfuvirtide[22]

First heptad repeat (HR1) region

Wild-type	G	I	V	Q	Q	N	N
Position	36	37	38	39	40	42	43
Substitutions	D S	V	A M E	R	H	T	D

Amino acid abbreviations: A, alanine; C, cysteine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.

MUTATIONS



The International AIDS Society–USA Drug Resistance Mutations Group reviews new data on HIV drug resistance in order to maintain a current list of mutations associated with clinical resistance to HIV. This list includes mutations that may contribute to a reduced virologic response to a drug.

The mutations listed have been identified by 1 or more of the following criteria: (1) in vitro passage experiments or validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) genetic sequencing of viruses from patients in whom the drug is failing; (4) correlation studies between genotype at baseline and virologic response in patients exposed to the drug. In addition, the group only reviews data that have been published or have been presented at a scientific conference. Drugs that have been approved by the US Food and Drug Administration (FDA) are included (listed in alphabetical order by drug class). User notes provide additional information as necessary. Although the Drug Resistance Mutations Group works to maintain a complete and current list of these mutations, it cannot be assumed that the list presented here is exhaustive. Readers are encouraged to consult the literature and experts in the field for clarification or more information about specific mutations and their clinical impact.

User Notes

1. Numerous nucleoside (or nucleotide) reverse transcriptase inhibitor (nRTI) mutations, such as the M41L, L210W, and T215Y mutations, may lead to viral hypersusceptibility to the nonnucleoside reverse transcriptase inhibitors (NNRTIs) in nRTI-treated individuals. The presence of these mutations may improve subsequent virologic response to NNRTI-containing regimens in NNRTI treatment-naive individuals (Shulman et al, *AIDS*, 2004; Demeter et al, 11th CROI, 2004; Haubrich et al, *AIDS*, 2002; Tozzi, *J Infect Dis*, 2004; Katzenstein et al, *AIDS*, 2003). NNRTI hypersusceptibility can be conferred by 2 distinct phenotypes: increased enzyme susceptibility to NNRTI (eg, V118I/T215Y) or decreased virion associated levels of reverse transcriptase (eg, H208Y/T215Y and V118I/H208Y/T215Y). The viruses that contained less reverse transcriptase replicated less efficiently than those with wild-type levels of reverse transcriptase. (Clark et al, *Antivir Ther*, 2006). The clinical relevance of all these mutations has not been assessed.

2. The 69 insertion complex consists of a substitution at codon 69 (typically T69S) and an insertion of 2 or more amino acids (S-S, S-A, S-G, or others). The 69 insertion complex is associated with resistance to all nRTIs currently approved by the US FDA when present with 1 or more thymidine analogue-associated mutations (TAMs) at codons 41, 210, or 215 (Miller et al, *J Infect Dis*, 2004). Some other amino acid changes from the wild-type T at codon 69 without the insertion may also be associated with broad nRTI resistance.

3. Tenofovir retains activity against the Q151M complex of mutations (Miller et al, *J Infect Dis*, 2004).

4. Multi-nRTI resistance mutations, also known as nucleoside analogue-associated mutations (NAMs), are associated with resistance to numerous nRTIs. The M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E are known as TAMs. TAMs are a subset of NAMs that are selected by the thymidine analogues zidovudine and stavudine and are associated with cross-resistance to all nRTIs currently approved by the US FDA (Larder et al, *Science*, 1989; Kellam et al, *Proc Natl Acad Sci USA*, 1992; Calvez et al, *Antivir Ther,* 2002; Kuritzkes et al, *J Acquir Immune Defic Syndr*, 2004). Mutations at the C-terminal reverse transcriptase domains (amino acids 293–560) outside of regions depicted on the figure bars may prove to be important for HIV drug resistance. Mutations in the connection (A371V) and RNase H (Q509L) domains of reverse transcriptase are co-selected on the same genome as TAMs and increase significantly zidovudine resistance when combined with TAMs. They also increase, although to a much lesser extent, cross-resistance to lamivudine, abacavir, and tenofovir but not to stavudine or didanosine (Brehm et al. *Antiviral Ther,* 2006). In zidovudine-exerienced patients, it has been shown by drug susceptibility testing that, in the C-terminal domain, the mutations G335C, N348I, and A360I exhibited 30-, 35-, and 30-fold increases in zidovudine resistance, respectively. (Nikolenko et al, *Antiviral Ther,* 2006.) Three mutations (N348I, T369I, and E399D) in the reverse transcriptase C-terminus are associated with the increased resistance to zidovudine and to NNRTIs. Mutations at this level could modulate NNRTI resistance by affecting dimerization of p66/p51 heterodimers (Gupta et al. *Antivir Ther,* 2006). The clinical relevance of these mutations has not been assessed.

5. The E44D and the V118I mutations increase the level of resistance to zidovudine and stavudine in the setting of TAMs, and correspondingly increase cross-resistance to the other nRTIs. The significance of E44D or V118I when each occurs in isolation is unknown (Romano et al, *J Infect Dis*, 2002; Walter et al, *Antimicrob Agents Chemother*, 2002; Girouard et al, *Antivir Ther*, 2002).

6. The M184V mutation alone does not appear to be associated with a reduced virologic response to abacavir in vivo (Harrigan et al, *J Infect Dis*, 2000; Lanier et al, *Antivir Ther*, 2004). When present with 2 or 3 TAMs, M184V contributes to reduced susceptibility to abacavir and is associated with impaired virologic response in vivo (Lanier et al, *Antivir Ther*, 2004). The M184V plus 4 or more TAMs resulted in no virologic response to abacavir in vivo (Lanier et al, *Antivir Ther*, 2004).

7. The K65R mutation may be selected by didanosine and is associated in vitro with decreased susceptibility to the drug (Winters et al, *Antimicrob Agents Chemother*, 1997). The impact of the K65R mutation in vivo is unclear.

8. The presence of 3 of the following—M41L, D67N, L210W, T215Y/F, and K219Q/E—has been associated with resistance to didanosine (Marcelin et al, *Antimicrob Agents Chemother*, 2005). The K70R and M184V mutations are not associated with a decreased virologic response to didanosine in vivo (Molina et al, *J Infect Dis*, 2005).

9. The presence of the M184V mutation appears to delay or prevent emergence of TAMs (Kuritzkes et al, *AIDS,* 1996). This effect may be overcome by an accumulation of TAMs or other mutations. The clinical significance of this effect of M184V is not known.

10. The T215A/C/D/E/G/H/I/L/N/S/V substitutions are revertant mutations at codon 215, conferring increased risk of virologic failure of zidovudine or stavudine in antiretroviral-naive patients (Riva et al, *Antivir Ther*, 2002; Chappey et al, *Antivir Ther*, 2003; Violin et al, *AIDS*, 2004). In vitro studies and preliminary clinical studies suggest that the T215Y

mutant may emerge quickly from one of these mutations in the presence of zidovudine or stavudine (Garcia-Lerma et al, *J Virol*, 2004; Lanier et al, *Antivir Ther*, 2002; Riva et al, *Antivir Ther*, 2002).

11. The K65R mutation is associated with a reduced virologic response to tenofovir in vivo (Miller et al, *J Infect Dis*, 2004). A reduced response occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W (Miller et al, *J Infect Dis*, 2004). Slightly increased treatment responses to tenofovir in vivo were observed if M184V was present (Miller et al, *J Infect Dis*, 2004).

12. The long-term virologic response to sequential NNRTI use is poor, particularly when 2 or more mutations are present (Antinori et al, *AIDS Res Hum Retroviruses*, 2002; Lecossier et al, *J Acquir Immune Defic Syndr*, 2005). The K103N or Y188L mutation alone prevents the clinical utility of all NNRTIs currently approved by the US FDA (Antinori et al, *AIDS Res Human Retroviruses*, 2002). The V106M mutation is more common in HIV-1 subtype C than in subtype B, and confers cross-resistance to all currently approved NNRTIs (Brenner et al, *AIDS*, 2003; Cane et al, *J Clin Micro*, 2001).

13. The same mutations usually emerge whether or not PIs are boosted with low-dose ritonavir, although the relative frequency of mutations may differ. Data on the selection of mutations in antiretroviral-naive patients in whom a boosted PI is failing are very limited. Numerous mutations are often necessary to significantly impact virologic response to a boosted PI. Although numbers vary for the different drugs, 3 or more mutations are often required.

14. Resistance mutations in the protease gene are classified as either "major" or "minor," if data are available.

Major mutations in the protease gene are defined in general either as those selected first in the presence of the drug; or those shown at the biochemical or virologic level to lead to an alteration in drug binding or an inhibition of viral activity or viral replication. Major mutations have an effect on drug susceptibility phenotype. In general, these mutations tend to be the primary contact residues for drug binding.

Minor mutations generally emerge later than major mutations, and by themselves do not have a significant effect on phenotype. In some cases, their effect may be to improve replicative fitness of the virus containing major mutations. However, some minor mutations are present as common polymorphic changes in HIV-1 nonsubtype B clades, such as K20I/R and M36I in protease.

15. Ritonavir is not listed separately as it is currently used at therapeutic doses as a pharmacologic booster of other PIs. At higher doses tested previously in humans, ritonavir administered as monotherapy produces mutations similar to those produced by indinavir (Molla, *Nature Med,* 1996).

16. HIV-1 Gag cleavage site changes can cause PI resistance in vitro. It has been observed that mutations in the N-terminal part of *gag* (MA: E40K; L75R; K113E and CA: M200I; A224A/V), outside the cleavage site, contribute directly to PI resistance by enhancing the overall Gag processing by wild-type protease. (Nijhuis et al. *Antivir Ther,* 2006). The clinical relevance of these mutations has not been assessed.

17. In most patients in whom an atazanavir/ritonavir-containing regimen was failing virologically, accumulations of the following 13 mutations were found (L10F/I/V, G16E, L33F/I/V, M46I/L, I54L/V/M/T, D60E, I62V, A71I/T/L, V82A/T, I84V, I85V, L90M, and I93L). Seven mutations were retained in an atazanavir score (L10F/I/V, G16E, L33F/I/V, M46I/L, D60E, I84V, I85V); the presence of 3 or more of these mutations predicts a reduced virologic response at 3 months, particularly when L90M was present (Vora, et al, *Antivir Ther,* 2005). A different report (Bertoli et al, *Antivir Ther*, 2006) found that the presence of 0, 1, 2, or greater than or equal to 3 of the following mutations were associated with 92%, 93%, 75%, and 0% virologic response to atazanavir/ritonavir: L10C/I/V, V32I, E34Q, M46I/L, F53L, I54A/M/V, V82A/F/I/T, I84V; presence of I15E/G/L/V, H69K/M/N/Q/R/T/Y, and I72M/T/V improved the chances of response. For unboosted atazanavir, the presence of 0, 1, 2, or greater than or equal to 3 of the following mutations was associated with 83%, 67%, 6%, and 0% response rates: G16E, V32I, K20I/M/R/T/V, L33F/I/V, F53L/Y, I64L/M/V, A71I/T/V, I85V, I93L/M.

18. Darunavir (formerly TMC-114), boosted with ritonavir, was approved by the US FDA in June 2006. Resistance data are therefore still preliminary and limited. HIV RNA response to boosted darunavir correlated with baseline susceptibility and the presence of multiple specific PI mutations. Reductions in response were associated with increasing numbers of the mutations indicated in the bar. Some of these mutations appear to have a greater effect on susceptibility than others (eg, I50V versus V11I). Further study and analysis in other populations are required to refine and validate these findings.

19. In PI-experienced patients, the accumulation of 6 or more of the mutations indicated on the bar is associated with a reduced virologic response to lopinavir/ritonavir (Masquelier et al, *Antimicrob Agents Chemother*, 2002; Kempf et al, *J Virol*, 2001). The product information states that accumulation of 7 or 8 mutations confers resistance to the drug. In contrast, in those in whom lopinavir/ritonavir is their first PI used, resistance to this drug at the time of virologic rebound is rare. However, there is emerging evidence that specific mutations, most notably I47A (and possibly I47V) and V32I are associated with high-level resistance (Mo et al, *J Virol*, 2005; Friend et al, *AIDS* 2004; Kagan et al, *Protein Sci*, 2005).

20. In some nonsubtype-B HIV-1, D30N is selected less frequently than other PI mutations (Gonzalez et al, *Antivir Ther*, 2004).

21. Accumulation of more than 2 mutations at positions 33, 82, 84, and 90 correlate with reduced virologic response to tipranavir/ritonavir, although an independent role for L90M was not found. Detailed analyses of data from phase II and III trials in PI-experienced patients identified mutations associated with reduced susceptibility or virologic response. These include: L10V, I13V, K20M/R, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V. Accumulation of these mutations is associated with reduced response. Subsequent genotype-phenotype and genotype-virologic response analyses determined some mutations have a greater effect than others (eg, I84V versus I54M). Refinement and clinical validation of these findings are pending (Schapiro et al, CROI, 2005; Kohlbrenner et al, DART, 2004; Mayers et al, *Antivir Ther*, 2004; Hall et al, *Antivir Ther*, 2003; McCallister et al, *Antivir Ther*, 2003; Parkin et al, CROI, 2006; Bacheler et al, European HIV Drug Resistance Workshop, 2006).

22. Although resistance to enfuvirtide is associated primarily with mutations in the

first heptad repeat (HR1) region of the gp41 envelope gene, wild-type viruses in the depicted HR1 region vary 500-fold in susceptibility. Such pretreatment susceptibility differences were not associated with differences in clinical responses (Labrosse et al, *J Virol*, 2003). Furthermore, mutations or polymorphisms in other regions in the envelope (eg, the HR2 region or those yet to be identified) as well as coreceptor usage and density may affect susceptibility to enfuvirtide (Reeves et al, *Proc Natl Acad Sci USA*, 2002; Reeves et al, *J Virol*, 2004; Xu et al, *Antimicrob Agents Chemother*, 2005). Thus, testing to detect only the depicted HR1 mutations may not be adequate for clinical management of suspected failure (Reeves et al, *J Virol*, 2004; Menzo et al, *Antimicrob Agents Chemother*, 2004; Poveda et al, *J Med Virol*, 2004; Sista et al, *AIDS*, 2004; Su, *Antivir Ther*, 2004).

(continued from page 125)

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Chairs: Laura W. Cheever, MD, ScM, Michael S. Saag, MD, and Donna E. Sweet, MD
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October 17, 2006
New York Marriott Marquis
Chairs: Douglas T. Dieterich, MD, and Roy M. Gulick, MD

New York, NY
March 14, 2007
New York Marriott Marquis
Chairs: Gerald H. Friedland, MD, and Paul A. Volberding, MD

Los Angeles, CA
March 28, 2007
Renaissance Hollywood Hotel
Chairs: Ronald T. Mitsuyasu, MD, and Constance A. Benson, MD

Atlanta, GA
April 27, 2007
Westin Peachtree Plaza
Chairs: Michael S. Saag, MD, and Jeffrey L. Lennox, MD

Chicago, IL
May 7, 2007
Marriott Downtown Chicago
Chairs: John P. Phair, MD, and Harold A. Kessler, MD

Washington, DC
May 23, 2007
JW Marriott on Pennsylvania
Chairs: Henry Masur, MD, and Michael S. Saag, MD

San Francisco, CA
May 31, 2007
Grand Hyatt San Francisco
Chairs: Robert T. Schooley, MD, and Stephen E. Follansbee, MD

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