Volume 10 Issue 5 November/December 2002

Topics in HIV Medicine™

A publication of the International AIDS Society–USA

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About This Issue

This issue contains 5 *Perspectives* articles based on the International AIDS Society–USA continuing medical education courses held in Denver, Washington, DC, and San Francisco in May and June 2002, and at the *Clinical Pathway* of the Ryan White CARE Act 2002 All Grantee Conference held in Washington, DC, in August 2002. Donna E. Sweet, MD, discussed issues related to the ongoing question of when to initiate antiretroviral therapy in HIV-infected individuals and factors in selecting initial drug regimens. Scott M. Hammer, MD, presented cases to illustrate issues in HIV resistance that are encountered in clinical practice, and he discussed appropriate management responses. Judith S. Currier, MD, discussed issues in the management of HIV-infected women, focusing primarily on those related to pregnancy. Henry Masur, MD, reviewed the decline in opportunistic infection rates since the advent of potent antiretroviral therapy, along with evidence that indicates that these declines have diminished and perhaps reversed in some populations. Finally, Andrew F. Angelino, MD, discussed issues and approaches to diagnosis and treatment of depression in HIV-infected patients.

The Drug Resistance Mutations Group of the International AIDS Society–USA reviews new data on HIV-1 drug resistance with the goal of maintaining a current list of mutations in HIV-1 associated with resistance to antiretroviral drugs. This list, presented in the IAS–USA Drug Resistance Mutations Figures in this issue, has been revised and updated since it was last published in the May/June 2002 issue of this journal.

Unrestricted educational grants supported this issue of *Topics in HIV Medicine* and the 2002 *HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management* program. Additional support was received for the Denver course, *Current Challenges in HIV Disease: A Case-Based, Advanced Course in Clinical HIV Management,* and for the *Clinical Pathway,* the fifth annual HIV clinical conference for Ryan White CARE Act grantees. We gratefully acknowledge:

Major Grant Support

These 3 companies have continuously supported this program at the major grant support level since its inception 10 years ago.

Bristol-Myers Squibb Co.

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Substantial Grant Support

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Generous Grant Support

Gilead Sciences, Inc.

Merck US Human Health

ViroLogic, Inc.

Additional Support

HIV/AIDS Bureau of the Health Resources and Services Administration of the US Department of Health and Human Services (subcontract to grant #6 H4A HA 00058)

Colorado and Mountain Plains AIDS Education and Training Centers

Topics in HIV Medicine™

Topics in HIV Medicine (formerly *Improving the Management of HIV Disease*) is published by the International AIDS Society–USA. This publication is intended to be a resource for physicians and other health care practitioners who are actively involved in HIV and AIDS care.

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All authors and contributors provide disclosures of financial interests, and this information is available at the end of each article.

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Subscription Information
Topics in HIV Medicine is published 4 to 6 times a year. To obtain a complimentary subscription or notify the International AIDS Society–USA of a change in address, please contact the International AIDS Society–USA at the address listed below or use the Subscription Request/Address Change form at the back of this issue.

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Fax: (415) 561-6740

Web site: http://www.iasusa.org
E-mail: topics@iasusa.org

On the Web
Current and previous issues of *Topics in HIV Medicine* are available online at www.iasusa.org.

Printed in USA • October 2002
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Perspective

Initial Antiretroviral Therapy: When and With What to Begin

At the International AIDS Society–USA course in Denver in May 2002, Donna E. Sweet, MD, discussed issues related to the ongoing question of when to initiate antiretroviral therapy in HIV-infected individuals and factors in selecting an initial drug regimen. Current treatment guidelines offer some consensus on the question of timing. Selection of the initial therapy focuses on the choice between regimens based on nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, or protease inhibitors.

The optimal time to initiate antiretroviral therapy in asymptomatic HIV-infected patients with CD4+ cell counts above 200/µL is not known. The rationale for starting therapy early includes the potential for improved virologic suppression, preservation of immune function, and reduction in sexual and perinatal HIV transmission. The rationale for later initiation of therapy includes the potential avoidance of drug resistance and adverse effects and difficulty in adherence to complex drug regimens, as well as reduced cumulative cost of treatment. Commonly considered risks and benefits associated with the approaches of early versus later initiation are shown in Table 1.

Guidelines for Initiating Treatment

Current guidelines for antiretroviral therapy reflect a movement away from early initiation of treatment (ie, at high CD4+ cell counts and detectable viral load), largely based on recognition that because of latent infection, viral eradication is not likely; that risk of near-term disease progression is low, even in relatively advanced infection; and that restoration of immunologic function can occur at lower CD4+ cell counts than previously believed. In combination with considerations regarding difficulty of adherence to antiretroviral therapy, cumulative toxicities of potent regimens, and avoidance of drug resistance to preserve future treatment options, these factors argue strongly for some delay in initiation of treatment.

Current US Department of Health and Human Services (DHHS) guidelines and International AIDS Society–USA (IAS–USA) recommendations, for example, suggest that treatment be initiated in any patient with symptomatic disease and in those with asymptomatic disease if CD4+ cell count is less than 200/µL, irrespective of plasma HIV-1 RNA level. For asymptomatic patients with CD4+ cell counts above 200/µL, the recently published IAS–USA report (Yeni et al, JAMA, 2002) recommends that the decision to begin therapy be individualized based on CD4+ count and rate of decline, plasma HIV-1 RNA level, patient interest in and potential to adhere to therapy, and risk of toxicity and drug interactions. Initiation of therapy should be considered in patients with a high plasma HIV-1 RNA level (eg, >50,000 copies/mL) or a rapidly declining CD4+ cell count. Similarly, the DHHS guidelines (available at www.hivatis.org) state that for asymptomatic patients with CD4+ cell counts of 200 to 350/µL and any plasma HIV-1 RNA level, treatment should be offered, with the proviso that controversy exists over the pros and cons of treatment in this population. For asymptomatic patients with CD4+ cell counts greater than 350/µL and plasma HIV-1 RNA above a threshold level (30,000 copies/mL on branched-DNA assay and 55,000 copies/mL on reverse transcriptase polymerase chain reaction assay), the DHHS guidelines indicate that clinical experts differ in their recommendations but many would offer treatment, whereas for those with plasma HIV-1 RNA levels below this threshold, many experts would defer treatment and

Table **1.** Risks and Benefits of Early Versus Delayed Initiation of Antiretroviral Therapy

Benefits	Risks
Early Therapy	
• Control of viral replication may be easier to achieve and maintain	• Drug-related reduction in quality of life
• Possible delay or prevention of immune system compromise	• Greater cumulative drug-related adverse events
• Lower risk of resistance with optimal viral suppression	• Earlier emergence of drug resistance if viral suppression is suboptimal
• Possible decreased risk of HIV transmission	• Limitation of future antiretroviral treatment options
Delayed Therapy	
• Avoid negative effects on quality of life	• Possible risk of irreversible immune system depletion
• Avoid drug-related adverse events	• Possible greater difficulty in suppressing viral replication
• Delay emergence of drug resistance	• Possible increased risk of HIV transmission
• Preserve maximum number of future drug options when HIV disease risk is highest	

Adapted from US Department of Health and Human Services, 2002.

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observe the patient course. This change in thinking to a more delayed approach to initiation of therapy has occurred as the problems of adherence to complex regimens (Mannerheimer et al, 13th Int AIDS Conf, 2000), potential long-term consequences of metabolic complications (Schambelan et al, *J Acquir Immune Defic Syndr*, in press), adverse impact of antiretroviral therapy on quality of life (Gill et al, *J Acquir Immune Defic Syndr*, 2002), and emergence of HIV resistance to antiretrovirals (Richman et al, 41st ICAAC, 2001) have all become more obvious.

Such recommendations are supported by a variety of data. For example, an analysis of time to death or an AIDS-defining event among 12,040 antiretroviral-naive patients beginning a 3-drug regimen at 12 centers in Europe, Canada, and the United States showed that a CD4+ cell count of 200/µL or greater at the time of starting treatment was associated with a higher probability of survival and that an HIV-1 RNA level of 5 $\log_{10}$ copies/mL or above was associated with a lower probability of survival (Egger et al, 41st ICAAC, 2001). In a retrospective review of data from 1162 patients at the Johns Hopkins University, Sterling and colleagues found that viral load at initiation of potent antiretroviral therapy was not predictive of progression to a new opportunistic infection or death (8th CROI, 2001). A CD4+ cell count of less than 200/µL was associated with a highly significant hazard ratio of 4.3 for progression compared with an initial cell count of 351 to 500/µL (referent range). A CD4+ cell count of 201 to 350/µL at initiation of therapy was associated with a statistically nonsignificant hazard ratio of 1.6 compared with the referent range.

Other studies have also shown poorer virologic response when treatment is initiated at lower CD4+ cell counts. For example, in a study reported by Levy and colleagues (8th CROI, 2001), 1266 treatment-naive patients were randomized to efavirenz or indinavir plus lamivudine/zidovudine, or efavirenz plus indinavir. The proportion of patients with plasma HIV-1 RNA levels less than 50 copies/mL at 96 weeks was markedly lower among those with CD4+ cell counts of less than 200/µL at the start of treatment than among those with higher cell counts. The Centers for Disease Control and Prevention (CDC) Adult and Adolescent Spectrum of HIV Disease Project, a record review of 5110 patients beginning 2- or 3-drug regimens in 1994 or later, showed that the hazard ratios for death at 2 years among patients with CD4+ cell counts of less than 200/µL (but not among those with counts of 200-499/µL) at the start of treatment were significantly greater than the risk for patients with counts above 500/µL (Kaplan et al, 8th CROI, 2001).

Cohort data indicate a lack of benefit of initiating therapy at CD4+ cell counts above 350/µL. In a study by Hogg and colleagues (JAMA, 2001) of 1219 patients, those who began therapy with CD4+ cell counts below 200/µL were more likely to progress to AIDS or death than those initiating with counts of at least 200/µL. Rates of disease progression or death were uniformly low in those initiating at counts of at least 200/µL. The results suggest that antiretroviral therapy may safely be initiated at CD4+ cell counts substantially lower than 500/µL, but should begin before counts drop below 200/µL. Phillips and colleagues (JAMA, 2001) found that among 3226 patients, virologic suppression could be achieved even in those with a low CD4+ count and high plasma HIV-1 RNA level prior to starting therapy. Lower CD4+ counts and higher plasma HIV-1 RNA levels at baseline were not associated with poorer virologic outcomes.

Is There an Advantage to Starting Therapy at Higher CD4+ Cell Counts?

Clinical Outcome

Not all clinicians are comfortable with delaying initiation of treatment until lower CD4+ cell counts have been reached, and there is evidence to support beginning treatment earlier. In a retrospective analysis by Chaisson and colleagues (JAMA, 2000), virologic response was assessed in 553 patients who began a triple-drug regimen after July 1996 and received at least 6 months of therapy. The patients were stratified according to initial CD4+ cell count and viral load. Virologic response was defined as plasma HIV-1 RNA level of less than 400 copies/mL within 6 months of treatment initiation and no measurement above 1000 copies/mL after initial response. The mean follow-up time was 824 days. Compared with patients with baseline CD4+ cell counts less than 200/µL, odds ratios for initial response were 0.98 (95% confidence interval [CI], 0.61-1.57) among patients with initial cell counts of 200 to 350/µL and 1.8 (95% CI, 1.10-2.96) among those with initial cell counts greater than 350/µL; respective odds ratios for durable response were 1.4 (95% CI, 0.82-2.42) and 1.9 (95% CI, 1.14-3.08). Compared with patients with baseline plasma HIV-1 RNA levels greater than 100,000 copies/mL, odds ratios for initial response were 2.5 (95% CI, 1.59-4.04) among those with baseline levels of 25,000 copies/mL or less and 1.8 (95% CI, 1.10-2.90) among those with levels of 25,000 to 100,000 copies/mL; respective odds ratios for durable response were 2.5 (95% CI, 1.45-4.35) and 1.7 (95% CI, 0.94-3.11). It was thus concluded that baseline CD4+ cell counts greater than 350/µL and plasma HIV-1 RNA levels of 25,000 copies/mL or less were associated with better initial and more durable virologic response.

> Cohort data suggest therapy may safely be initiated at CD4+ cell counts <500/µL, but should begin before counts drop to <200/µL

In a case-control prospective substudy in the Swiss HIV Cohort, Opravil and colleagues (AIDS, 2002) assessed progression to CDC category B or C disease or death in 363 antiretroviral-naive asymptomatic patients initiating therapy at CD4+ cell counts greater than 350/µL and 363 control patients not initiating therapy. At baseline, CD4+ cell counts were 487 and 498/µL and plasma

HIV-1 RNA levels were 4.2 $\log_{10}$ and 4.1 $\log_{10}$ copies/mL, respectively. Follow-up was 2.1 years among cases and 1.3 years among controls. Among cases, 29% remained on their initial antiretroviral regimen, 29% were on no regimen after follow-up, and 45% interrupted treatment at least once. Reasons for stopping at least 1 drug were virologic failure in 3.3% of cases and intolerance in 17.9%. During follow-up, CDC category B or C disease occurred in 4.7% of cases versus 17.1% of controls, and death occurred in 1.1% versus 3.3%, respectively. These findings indicate that early initiation of treatment in asymptomatic patients significantly delays disease progression and death.

Prevention of Transmission

Available data indicate that both male-to-female and female-to-male sexual transmission of HIV is related to plasma viral load. Other data indicate that viral load in genital secretions is reduced in patients on antiretroviral therapy, and modeling studies suggest that reductions in viral load would decrease the number of new infections (Blower et al, *Science*, 2000). Whether antiretroviral therapy-induced reductions in viral load actually do decrease transmission will need to be determined in a clinical trial. Further, the benefits of this effect may be tempered by increased transmission of drug-resistant virus from patients with inadequate viral suppression on treatment.

Cost-Effectiveness

Available evidence suggests that earlier initiation of antiretroviral therapy is associated with cost-savings compared with later initiation, and that antiretroviral therapy, irrespective of when it is started, compares well with other accepted therapeutic modalities in terms of cost per life-year gained. Using data from the Johns Hopkins cohort, Kauf and colleagues (1st IAS Conf HIV Pathog Treat, 2001) found that initiation of antiretroviral therapy at CD4+ cell counts greater than 500/µL was more cost-effective than initiation at 350 to 500/µL or at less than 350/µL, with a cost-effectiveness ratio of $17,879 per life-year gained. This ratio compares favorably with those for other accepted medical interventions, such as lovastatin to prevent coronary disease, screening mamography for women aged 40 to 79 years, and coronary artery bypass surgery for men aged 50 years. The investigators concluded that early initiation of treatment has the potential to reduce overall cost of treatment while improving patient outcomes. Table 2 shows this cost-effectiveness ratio and other estimates for antiretroviral therapy by CD4+ cell count at initiation.

> The question of whether antiretroviral therapy-induced reductions in viral load decrease transmission needs to be addressed in a clinical trial

Initial Regimens

Selection of Regimen

Recommendations for initial treatment included in current antiretroviral therapy guidelines may appear complicated. In considering initial treatment options, a simplified approach may be to view the decision as a choice of either 2 nucleoside reverse transcriptase inhibitors (nRTIs) plus a nonnucleoside reverse transcriptase inhibitor (NNRTI), 2 nRTIs plus a protease inhibitor (PI), or a triple-nRTI combination. The PI-containing regimens may include PIs that are pharmacokinetically boosted with low-dose ritonavir (ie, saquinavir, indinavir, lopinavir [which is coformulated with low-dose ritonavir], or amprenavir) or an unboosted PI. The boosted PI regimens may provide enhanced drug levels and may allow easier dosing schedules. A triple-nRTI initial regimen is well-tolerated and may be particularly useful in younger patients who may be prone to suboptimal adherence.

Selection of specific drugs for the initial regimen may be difficult given the many potential combinations, and may rely in part on clinical judgment regarding which regimen is likely to be better accepted or tolerated by the individual patient. Nevertheless, there are some comparative data on virologic response and duration of response that may influence decisions in this regard. In the trial by Levy and colleagues (8th CROI, 2001) noted above, approximately 80% of patients (n=422) receiving efavirenz/zidovudine/lamivudine maintained plasma HIV-1 RNA levels of less than 50 copies/mL at 96 weeks, compared with approximately 66% on indinavir/zidovudine/lamivudine (n=415) and 60% on efavirenz/indinavir (n=429).

Ruane and colleagues (1st IAS Conf HIV Pathog Treat, 2001) conducted a randomized, double-blind trial studying

Table **2.** Cost-Effectiveness Ratios for Antiretroviral Therapy From Selected Studies According to CD4+ Cell Count at Initiation

Intervention	ICER (US dollars/ life-year gained)
Antiretroviral therapy initiated when CD4+ count ≥500 cells/µL*	13,000
Antiretroviral therapy initiated when CD4+ count ≥500 cells/µL**	17,300
Antiretroviral therapy initiated when CD4+ count >500 cells/µL†	17,879
Antiretroviral therapy initiated when CD4+ count <200 cells/µL‡	20,000

ICER indicates incremental cost-effectiveness ratio. *Freedberg et al, *N Engl J Med,* 2001. **Schackman et al, *Am J Pub Health,* 2001. †Kauf et al, 1st IAS Conf HIV Pathog Treat, 2001. ‡Moore and Bartlett, *Pharmacoeconomics,* 1996.

lopinavir/ritonavir plus stavudine/lamivudine versus nelfinavir plus stavudine/lamivudine in 653 treatment-naive patients with a mean baseline plasma HIV-1 RNA level of 4.9 $\log_{10}$ copies/mL and CD4+ cell count of 259/µL. At week 60, in an intent-to-treat analysis, 63% of patients in the lopinavir/ritonavir arm achieved plasma HIV-1 RNA levels of less than 50 copies/mL compared with 51% in the nelfinavir arm (P=.001). The mean increases in CD4+ cell count were not significantly different: 246 and 224/µL, respectively. The most common adverse effects were triglyceride and other lipid level elevations.

In a trial comparing abacavir plus fixed-dose lamivudine/zidovudine with indinavir plus fixed-dose lamivudine/zidovudine, 66% of patients in the abacavir arm achieved plasma HIV-1 RNA levels of less than 400 copies/mL versus 50% of patients in the indinavir arm (P=.002) at 48 weeks on intent-to-treat analysis (Vibhagool et al, 1st IAS Conf HIV Pathog Treat, 2001).

Recent data indicate that tenofovir, the nucleotide reverse transcriptase inhibitor (n*t*RTI) recently approved by the US Food and Drug Administration, is an effective component of initial therapy. In a randomized, double-blind, placebo-controlled study (Staszewski et al, 14th Int AIDS Conf, 2002), 600 antiretroviral-naive patients received either tenofovir/lamivudine/efavirenz once daily or stavudine/lamivudine/efavirenz twice daily. Mean baseline plasma HIV-1 RNA level was 4.9 $\log_{10}$ copies/mL and mean baseline CD4+ cell count was 279/µL. In an intent-to-treat analysis at 48 weeks, plasma HIV-1 RNA level was suppressed to less than 400 copies/mL in 87% of patients in both treatment arms. Plasma HIV-1 RNA level was less than 50 copies/mL in 82% of patients in the tenofovir arm and 81% of patients in the stavudine arm.

It remains unclear whether triple-drug regimens provide adequate antiretroviral effect in patients with advanced disease, with many studies suggesting that such combinations are less effective in patients with CD4+ cell counts below 200/µL than in those with less-advanced disease. In the AIDS Clinical Trials Group 388 study, a randomized, open-label trial (Fischl et al, 9th CROI, 2002), 517 predominantly treatment-naive patients with CD4+ cell counts less than 200/µL or plasma HIV-1 RNA levels greater than 80,000 copies/mL received indinavir plus fixed-dose lamivudine/zidovudine, indinavir/nelfinavir plus fixed-dose lamivudine/zidovudine, or indinavir/efavirenz plus fixed-dose lamivudine/zidovudine. During a median follow-up of 108 weeks, the efavirenz 4-drug regimen performed better than the 3-drug regimen, and both the 3-drug regimen and the efavirenz 4-drug regimen performed better than the nelfinavir 4-drug regimen. Serious adverse effects were similar in the 3 groups but occurred earlier with the nelfinavir regimen. In another study, the 4-drug combination of abacavir and efavirenz plus fixed-dose lamivudine/zidovudine produced plasma HIV-1 RNA levels of less than 50 copies/mL at 48 weeks in 68% of patients on intent-to-treat analysis (Parenti et al, 39th IDSA, 2001).

It remains unclear whether triple-drug regimens provide adequate antiretroviral effect in patients with advanced disease

Selection of nRTI Backbone

Dual nRTI backbones (or nRTI/n*t*RTI backbones) are a common feature of antiretroviral regimens. Selection of the agents to be used may depend on antiretroviral effect, tolerance, and resistance patterns. In a study reported by Domula and colleagues (9th CROI, 2002), 108 patients received initial treatment with efavirenz plus one of 3 nRTI backbones: fixed-dose lamivudine/zidovudine (n=38), stavudine/lamivudine (n=35), or stavudine/didanosine (n=35). Initial mean CD4+ cell counts were 286, 166 (significantly lower than other groups), and 235/µL, respectively. After 48 weeks, plasma HIV-1 RNA level was less than 50 copies/mL in 79% of patients overall. CD4+ cell counts increased by 180/µL in the lamivudine/zidovudine backbone group, 245/µL in the stavudine/lamivudine backbone group, and 281/µL in the didanosine/stavudine backbone group. The latter regimen has been associated with considerable toxicity. In this study, the efavirenz/stavudine/lamivudine arm had the lowest drop-out rate.

With regard to potential for resistance, stavudine can select for the classical zidovudine resistance mutations, and such mutations have been detected in zidovudine-naive patients. A study with stavudine-experienced, zidovudine-naive viremic patients showed that nRTI resistance mutations (specifically D67N and L210W) were present in 41% of 29 patients receiving stavudine/didanosine versus 33% of 106 patients receiving stavudine/lamivudine for a longer duration; multi-nRTI resistance mutations (Q151M, T69N, and 69SS insertion complex) were found in 20.6% versus 5.6%, respectively. These findings suggest that the stavudine/lamivudine combination may be less likely to select for nRTI-resistant mutants than the stavudine/didanosine combination (Ross et al, 9th CROI, 2002).

Advantages and Disadvantages of Initial Regimens

Table 3 summarizes potential advantages and disadvantages of initial treatment with triple-nRTI, NNRTI-based, and PI-based combinations. Advantages of each include sparing treatment with other drug classes for later use. Clinical endpoint data are lacking for the triple-nRTI and NNRTI-based approaches.

Dosing requirements for many of the drugs used in all of the potential regimens have improved markedly over the past several years. For example, among nRTIs, didanosine can now be given at 400 mg once daily (pill or suspension), zidovudine at 300 mg twice daily, fixed-dose lamivudine/zidovudine as one 150-mg/300-mg pill twice daily, and fixed-dose lamivudine/zidovudine/abacavir as one 150-mg/300-mg/300-mg pill twice daily. Among NNRTIs, nevirapine can be given at 400 mg once daily, with the dose of efavirenz remaining at 600 mg

once daily. Among PIs, the boosted combinations of ritonavir/saquinavir are given at 400 mg/400 mg twice daily, ritonavir/indinavir at 400 mg/400 mg or 200 mg/800 mg twice daily, and ritonavir/amprenavir at 200 mg/600 mg twice daily. Nelfinavir alone can now be given at 1250 mg twice daily.

Presented in May 2002. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Sweet in September 2002.

Financial Disclosure: Dr Sweet has no affiliations with commercial organizations that may have interests related to the content of this article.

Suggested Reading

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Table **3.** Advantages and Disadvantages of Triple-nRTI, NNRTI-Based, and PI-Based Initial Therapy

Advantages	Disadvantages
Triple-nRTI	
• Easier to use and adhere to • Avoids PI and NNRTI adverse effects* • Limited cross-resistance within the class • Drug interactions are manageable • Preserves PIs and NNRTIs for later use	• Clinical endpoints are unknown • Long-term virologic efficacy may be suboptimal with high baseline viral load
NNRTI-Based	
• Avoids PI-related adverse effects* • Generally easier to use and adhere to • Fewer drug-drug interactions • Preserves PIs for later use	• Clinical endpoints are unknown • Resistance to NNRTIs requires single or few mutations • Emergence of cross-resistance for entire NNRTI class
PI-Based	
• Documented clinical, virologic, and immunologic efficacy • Benefit despite viral breakthrough • Resistance requires multiple mutations • Targets HIV at 2 steps of viral replication • Preserves NNRTIs for later use	• May be difficult to use and adhere to • May be associated with long-term adverse effects (lipodystrophy, insulin resistance and hyperlipidemia)* • Mild to severe inhibition of cytochrome P450 system • Emergence of cross-resistance with other PIs

NNRTI indicates nonnucleoside reverse transcriptase inhibitor; nRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor. *Some adverse effects attributed to PI-based therapy, such as metabolic abnormalities, have not been proven to be strictly associated with the use of PI-containing regimens. Metabolic abnormalities have also been described, albeit uncommonly, in patients on nRTIs alone and in patients on no antiretroviral therapy. Adapted from US Department of Health and Human Services, 2002.

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Perspective

HIV Drug Resistance: Implications for Management

Selection of antiretroviral treatment based on drug resistance profile is a crucial element in maintaining optimal response to therapy in individual patients. Interpretation of results from resistance testing continues to increase in complexity with increasing numbers of resistance mutations and resistance mutational interactions identified, increasing numbers of drugs used, and increasing prevalence of resistance in patients with recent infection and those taking antiretroviral therapy. At the International AIDS Society–USA course in San Francisco in June 2002, Scott M. Hammer, MD, presented cases to illustrate issues related to HIV resistance that are encountered in clinical practice, and he discussed management responses for these situations.

Underlying Concepts in HIV Resistance

Genetic variants of HIV are continuously produced in the absence of drug pressure as a result of high viral turnover and the inherent error rate of the HIV-1 reverse transcriptase enzyme. Mutations at each codon site are produced daily, and the viability of resultant mutant virus depends on replication competence and the presence of selective pressure exerted by antiretroviral drugs or the immune system. In the absence of drug pressure, double mutations in the same viral genome can occur, although simultaneous occurrence of 3 or more mutations in the same genome is a rare event. Further, numerous natural polymorphisms exist. Thus, mutations that confer resistance to antiretroviral drugs can be present before a patient begins drug treatment and can evolve rapidly with drug use. High-level resistance emerges with a single mutation in the presence of certain drugs, and use of these drugs confers the greatest risk for emergence of resistance if they are not used in maximally suppressive regimens. These include lamivudine (eg, M184V mutation) and nonnucleoside reverse transcriptase inhibitors (NNRTIs), including efavirenz (eg, K103N mutation) and nevirapine (eg, Y181C mutation). Resistance to agents that require multiple mutations evolves more slowly. Use of partially suppressive antiretroviral regimens inevitably leads to development of resistance. Thus, a goal of treatment is to set a high genetic barrier to resistance through the use of potent combination regimens.

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Mutations that confer cross-resistance to other drugs in the same class are of particular importance

The number of identified antiretroviral drug resistance mutations (including those identified for investigational agents) increased from 42 in 1994 to 144 in 1997 and 236 in 2000. Please see page 21 for the current list of resistance mutations as maintained by the International AIDS Society–USA Drug Resistance Mutations Group, showing mutations in the reverse transcriptase and protease genes associated with antiretroviral resistance. Of particular importance among the identified mutations are those that confer cross-resistance to other drugs in the same class. Thus, among nucleoside reverse transcriptase inhibitors (nRTIs), the codon 151-associated complex of mutations and the codon 69 insertion complex confer cross-resistance. In addition, the classic zidovudine-associated resistance mutations at codons 41, 67, 70, 210, 215, and 219, which are now called NAMs (nRTI-associated mutations), confer cross-resistance to nRTIs except lamivudine. Among NNRTIs, there is considerable clustering of resistance mutations in 2 sections of reverse transcriptase, and mutations at codons 103 and 188 confer class cross-resistance. Protease inhibitor (PI) resistance mutations are classified as major and minor. Major mutations are those that tend to be selected first by the drug and cause a decrease in phenotypic susceptibility by themselves (usually occurring in the enzyme active site). Minor mutations are those that tend to appear subsequently and to cause changes in phenotypic sensitivity in the presence of major mutations rather than by themselves. Frequently, these mutations are compensatory, permitting the virus to replicate more efficiently in the presence of major resistance mutations. Mutations at codons 46, 82, 84, and 90 confer cross-PI resistance. It is a striking finding regarding PI resistance mutations that approximately one quarter to one third of the amino acids in protease can be altered with the enzyme remaining functional.

The following clinical cases illustrate some of the complexities in the emergence of HIV resistance and resistance testing.

Case 1: Acute HIV Infection

Case Presentation and Decision Point 1

A 20-year-old woman presents with complaints of fever, malaise, headache, mild neck stiffness, sore throat, lymphadenopathy, and rash 2 weeks after returning from a vacation during which she had unprotected sex with a new male partner. Differential diagnosis is broad and may include nonspecific viral syndrome, mononucleosis associated with cytomegalovirus (CMV) and Epstein-Barr virus, acute toxoplasmosis, and acute HIV infection. Physical examination shows temperature of 101°F, maculopapular rash on the torso, oral ulcers, mild neck stiffness, and cervical

lymphadenopathy. The initial laboratory evaluation shows hemoglobin of 13.5 g/dL; somewhat low white blood cell (WBC) count at $3.1 \times 10^3/\mu L$ with 56% polymorphonuclear cells, 35% lymphocytes, and 9% atypical lymphocytes; and minimally elevated aspartate aminotransferase of 47 U/L and alanine aminotransferase of 50 U/L. Cerebrospinal fluid (CSF) tap shows WBC of 30/µL with 99% lymphocytes, mildly elevated protein at 50 mg/dL, and normal glucose level. Should subsequent laboratory evaluation consist of Monospot, CMV IgG and IgM, *Toxoplasma* IgG and IgM, hepatitis serologies, HIV antibody, plasma HIV-1 RNA level, CSF HIV-1 RNA level, or all of these?

Discussion

It is reasonable to consider performing all of these laboratory assessments, except for the CSF HIV-1 RNA assay, since diagnostic efforts should be focused on the practical and standard assays to start. Although suspicion may be high for acute HIV infection, the mononucleosis-like symptoms call for wider evaluation, and hepatitis serology is indicated even if HIV infection is suspected because simultaneous coinfection may have occurred. Both the HIV antibody test and plasma HIV-1 RNA assay should be performed, since the antibody test may be negative if the patient has acute infection.

Decision Point 2

Laboratory results indicate negative Monospot and serologies for CMV, toxoplasmosis, and hepatitis A, B, and C virus infections. The HIV antibody test is negative, but plasma HIV-1 RNA assay indicates a viral load of 15,000,000 copies/mL. The patient has a CD4+ cell count of 450/µL. Should treatment be started—for example, with a regimen including 2 nRTIs in combination with efavirenz, abacavir, or lopinavir/ritonavir—or should the patient be referred to a clinical trial? Should a resistance test be performed, and should treatment be delayed until results of the resistance test are available?

Discussion

Reasonable options to consider to begin therapy include any of the regimens listed or, preferably, referral to a clinical trial. Deferring therapy in the case of acute infection is not recommended, since there is the potential for the intervention to maintain or restore HIV-specific immunity during primary infection. Although therapy or enrollment in a clinical trial should not be deferred until results of resistance testing are available, resistance testing should be performed. As shown in Table 1, a 9-city study of prevalence of antiretroviral drug resistance in 377 cases of recent HIV infection demonstrated a significant increase in prevalence of resistance to any drug in all drug classes and to multiple classes, with 12.4% of cases from 1999 to 2000 having resistance to 1 or more drugs and 6.2% having resistance to 2 or more drug classes (Little et al, *N Engl J Med*, 2002).

Decision Point 3

The patient refused enrollment in a clinical trial and started a regimen of lopinavir/ritonavir/zidovudine/lamivudine, for which she reported 100% adherence. Her plasma HIV-1 RNA level was 15,000 copies/mL after 2 weeks and 1500 copies/mL after 4 weeks. Results of the genotypic test became available at this point and showed the presence of a single T215D zidovudine resistance mutation. Should the regimen be changed by substituting stavudine for zidovudine or stavudine/didanosine for lamivudine/zidovudine, or by adding abacavir or tenofovir; or should the current regimen be continued?

Discussion

The best course in this instance is likely to continue the patient on the current regimen. The T215D mutation is not associated with high-level zidovudine resistance and has not been associated with treatment failure unless further mutational evolution occurs. This mutant appears to be a revertant from previously harbored virus with a T215F/Y mutation. The finding suggests that virus in this patient has reverted to the T215D mutant after infection with the T215F/Y form or that the revertant had emerged in the individual from whom she acquired HIV infection.

Decision Point 4

The patient's plasma HIV-1 RNA level increases to 5000 copies/mL at 8 weeks and to 10,000 copies/mL at 12 weeks. Genotypic analysis from week 4 shows K70R, T215Y, and M184V resistance mutations. Based on this information, should the same regimen be continued, should treatment be changed by substituting stavudine for zidovudine or by switching treatment to lopinavir/ritonavir/efavirenz/abacavir/tenofovir, or should the patient undergo a structured treatment interruption?

Table **1.** Change in Prevalance of Drug Resistance at Baseline in Clinical Isolates in a 9-City Study

High-Level* Drug Resistance By Phenotypic Assay	Patients With Drug-Resistant Virus 1995-1998	1999-2000	*P* Value
Any 1 or more antiretroviral drug	3.4%	12.4%	.002
Nucleoside reverse transcriptase inhibitor	2.3%	6.2%	.07
Nonnucleoside reverse transcriptase inhibitor	1.9%	7.1%	.03
Protease inhibitor	0.4%	8.0%	<.001
≥ 2 drug classes (multidrug resistance)	1.1%	6.2%	.01

*High-level resistance was defined as >10-fold decrease in susceptibility. Adapted with permission from Little et al, *N Engl J Med,* 2002.

Discussion

The K70R and T215Y mutations are classic zidovudine-associated resistance mutations, and the M184V mutation is a classic lamivudine-associated resistance mutation. No PI resistance mutations were detected at this visit. The current regimen should be changed to a regimen that will result in optimal viral suppression, and the likelihood of cross-resistance for zidovudine and stavudine argues against substitution of the latter for the former. The addition of efavirenz, abacavir, and tenofovir to lopinavir/ritonavir is reasonable, since (1) there are no NNRTI resistance mutations; (2) abacavir can still be effective in the presence of the M184V mutation and relatively few zidovudine-associated mutations; and (3) tenofovir can be expected to remain active in the context of the observed mutations.

Outcome

The patient was switched to the lopinavir/ritonavir/efavirenz/abacavir/tenofovir regimen. Plasma HIV-1 RNA level was below the assay detection limit (<50 copies/mL) at weeks 16, 20, and 24.

Case 2: Asymptomatic Established Infection

Case Presentation and Decision Point 1

A 35-year-old man with HIV infection has been observed for 8 years and has had a slowly declining CD4+ cell count. At the current visit, the CD4+ cell count is 275/µL, plasma HIV-1 RNA level is 50,000 copies/mL, and the patient wishes to begin treatment. Should treatment be started with a PI-based regimen such as indinavir/ritonavir, lopinavir/ritonavir, or nelfinavir plus 2 nRTIs; an NNRTI-based regimen such as efavirenz plus 2 nRTIs; or a triple nRTI regimen such as abacavir/zidovudine/lamivudine?

Discussion

The NNRTI-based and triple-nRTI regimens are reasonable choices for beginning treatment. At this level of CD4+ cell count and plasma HIV-1 RNA, these regimens should be successful, assuming good drug adherence. In Dr Hammer's opinion, this permits patients and clinicians to defer use of a PI-based regimen and avoid the potential metabolic toxicities.

Decision Point 2

Treatment is initiated with an efavirenz-based regimen. There are a number of possible nRTI "backbone" options for this patient; zidovudine/lamivudine is chosen. The patient reports full adherence to the new regimen. At 12 weeks, the patient's plasma HIV-1 RNA level is less than 50 copies/mL and CD4+ cell count has increased to 350/µL. However, at 24 weeks, plasma HIV-1 RNA is 500 copies/mL and a repeat test indicates a level of 1000 copies/mL. A sample is sent for genotypic analysis. Are the results most likely to show wild-type virus, the lamivudine-associated M184V mutation, the K103N efavirenz-associated mutation, both M184V and K103N, or zidovudine-associated mutations (eg, M41L, K70R, T215Y)?

> Although initiation of therapy in acute infection should not be deferred until results of resistance testing are available, resistance testing should be performed

Discussion

Breakthrough resistance in this situation is most likely to be caused by mutations to drugs to which high-level resistance occurs with a single-step mutation—in other words, those with a low genetic barrier to resistance. Thus, in this case, resistance is likely due to the efavirenz-associated mutation or the lamivudine-associated mutation. One or both mutations are observed in patients receiving both drugs, with no apparent preferred order of appearance and with both mutations sometimes emerging nearly simultaneously.

Decision Point 3

Genotypic assay results indicate the presence of the efavirenz-associated K103N mutation. Given that the patient's plasma HIV-1 RNA level is 1000 copies/mL, which of the following constitute reasonable approaches to management: continuing the same regimen, efavirenz/lamivudine/zidovudine, until plasma HIV-1 RNA level rises above 10,000 copies/mL; substituting nevirapine, abacavir, or lopinavir for efavirenz; switching the entire regimen to lopinavir/ritonavir/stavudine/didanosine; substituting lopinavir/ritonavir for efavirenz and substituting abacavir for zidovudine; or adding tenofovir?

Discussion

Changing the regimen by substituting lopinavir/ritonavir or abacavir for efavirenz makes the most sense in this case. Substitution of nevirapine is not an option given the NNRTI class cross-resistance conferred by the K103N mutation. Substitution of nRTIs may be considered unnecessary since no NAMs were detected. However, it is possible that minority populations of nRTI-resistant mutants (eg, M184V mutants) were not detected by the genotypic test; thus the switch from efavirenz to abacavir, resulting in an nRTI-only regimen, may be riskier than the switch to lopinavir/ritonavir. Although waiting to make a change in regimen until a plasma HIV-1 RNA level of 10,000 copies/mL may be reasonable in some settings, it is predictable in this case that additional resistance mutations will appear with inadequate suppression, and it is highly likely that the M184V resistance mutation will emerge. The accumulating data concerning the efficacy of tenofovir in treatment-experienced and treatment-naive patients makes use of this drug in this situation an alternative option. There is, however, a dearth of published experience with use of tenofovir in the specific situation described here.

Outcome

The patient's regimen was changed by substituting lopinavir/ritonavir for efavirenz. Plasma HIV-1 RNA level decreased to less than 50 copies/mL and remained at this level.

Case 3: The Treatment-Experienced Patient

Case Presentation and Decision Point 1

A 45-year-old man makes his first visit to the office. He has a 15-year history of HIV infection and prior exposure to stavudine, didanosine, zidovudine, lamivudine, nevirapine, nelfinavir, and indinavir. His regimen for the past year has been indinavir/ritonavir/stavudine/abacavir. His CD4+ cell count is 300/µL (nadir count of 100/µL) and plasma HIV-1 RNA level is 12,000 copies/mL. Phenotypic assay results show the following changes in susceptibility: 70-fold to zidovudine, greater than 100-fold to lamivudine, 5-fold to didanosine and stavudine, 10-fold to abacavir, 5-fold to efavirenz, 10-fold to lopinavir, 12-fold to amprenavir, and 6-fold to tenofovir. Is this patient best managed by continuing the current regimen, recommending a structured treatment interruption, instituting a mega-combination regimen of zidovudine/lamivudine/didanosine/abacavir/efavirenz/nevirapine/lopinavir/ritonavir/amprenavir/hydroxyurea, instituting a regimen of abacavir/tenofovir/efavirenz/lopinavir/ritonavir/amprenavir, or seeking out a clinical trial or expanded access program for new agents?

Discussion

The patient's susceptibility profile shows multiple drug resistance with high-level zidovudine and NNRTI resistance. In a patient with moderately depressed CD4+ cell count and moderately elevated viral load, maintaining the current regimen and seeking out investigational options are reasonable choices. Use of the abacavir/tenofovir/efavirenz/lopinavir/ritonavir/amprenavir regimen is also a reasonable option. If the latter regimen is chosen, one would be most reliant on the ritonavir-enhanced dual-PI component and potentially the efavirenz, if higher-level NNRTI resistance is not harbored in a reservoir. The abacavir and tenofovir may provide minimal to no activity, given the fold-changes in resistance, but subpopulations that may retain susceptibility to one or both of these agents may not be detected with the standard method of resistance testing. Further, even minimal additional antiretroviral activity may help protect the "core" of the new regimen. The mega-combination option is a viable one, but issues of tolerance and adherence are substantial with this approach.

This case represents a common scenario in clinical practice. There is a high prevalence of drug resistance in patients receiving potent antiretroviral therapy. The HIV Cost and Services Utilization Study (Richman et al, 41st ICAAC, 2001) found that 63% (132,442) of HIV-1-infected Americans who had survived the first 2 years of the potent antiretroviral therapy era had plasma HIV-1 RNA levels greater than 500 copies/mL and that 78% had resistance to at least 1 drug and 51% had resistance to multiple drug classes. Robust treatment options are lacking for many of these patients. The option of watching and waiting for new treatment options is supported by data indicating a prolonged time to return of CD4+ cell count to baseline levels after virologic failure on potent antiretroviral therapy. A study by Deeks and colleagues (AIDS, 2002) indicated that the time to such immunologic failure after virologic failure was 36.4 months. This delay of immunologic failure appears to be associated with reduced replicative fitness or capacity of HIV with PI-associated resistance mutations, resulting in reduced cytopathic effect on CD4+ cells.

Decision Point 2

How might management differ, given the same options as above, if the patient discussed in case 3 had a CD4+ cell count of 100/µL instead of 300/µL and plasma HIV-1 RNA level of 100,000 copies/mL instead of 12,000 copies/mL at the current presentation?

Discussion

Use of the abacavir/tenofovir/efavirenz/lopinavir/ritonavir/amprenavir regimen is a reasonable option in this scenario. A change of 8-fold or greater in susceptibility to abacavir indicates that the drug will have little effectiveness. Similarly, the 6-fold change in susceptibility to tenofovir suggests that this drug will have little effectiveness, since a greater than 4-fold change is associated with loss of the likelihood of any response. On the other hand, changes in susceptibility to efavirenz such as the 5-fold decrease seen in this case are common among wild-type isolates, representing naturally occurring polymorphisms, and might not of themselves indicate loss of effectiveness of the drug. The combination of lopinavir/ritonavir and amprenavir may be expected to further boost the effects of the PIs in this case. Thus, use of this regimen is essentially based on the hope that a dual enhanced PI/efavirenz-based regimen will be effective in the patient and the possibility that abacavir and tenofovir will add some additional activity.

> In multi-regimen failure, the option of watching and waiting for new treatments is supported by data indicating a prolonged delay of immunologic failure after virologic failure

At this point, structured treatment interruptions should not be attempted outside the setting of a clinical trial. As shown in studies by Deeks and colleagues (*N Engl J Med*, 2001), interruption of treatment in patients harboring virus resistant to multiple drugs generally results in reversion of virus to wild-type susceptibilities at periods ranging from 2 to 12 weeks after stopping treatment. However, this switch in phenotypic susceptibility is accompanied by inflections in the slopes of plasma HIV-1

RNA level increases (eg, rapid increases of 0.8-1 $\log_{10}$ HIV-1 RNA copies/mL) and CD4+ cell decreases (eg, rapid decreases of 100/µL). These decreases may place patients at risk for opportunistic diseases. Any potential application of this approach to resensitize virus awaits additional examination in clinical studies.

Additional Considerations in Management

Common questions and issues in the management of HIV drug resistance are summarized below.

In evaluating a patient with virologic failure on the first regimen, which tests from among genotype, phenotype, and virtual phenotype should be ordered?

Many practitioners would order a genotypic test, since such testing allows detection of mutations that may be emerging prior to any marked change in phenotypic susceptibility. The virtual phenotype test is essentially a genotypic test with an interpretation system that is linked to a large relational database of genotypes and phenotypes.

Of the currently available types of tests, which should be ordered in the case of a patient with a history of numerous regimen failures?

Given the likelihood of numerous resistance mutations to multiple drugs in such a patient, and the likelihood of complex resistance interactions, phenotyping to determine which drugs might still be active may be of greater assistance in making decisions about managing treatment than genotyping.

Is stavudine active against zidovudine-resistant virus?

Zidovudine resistance mutations confer cross-resistance to stavudine, even though phenotyping may not demonstrate this resistance unless a low cutoff is set.

Does hypersusceptibility to NNRTIs improve response to efavirenz?

Hypersusceptibility to NNRTIs in the presence of multiple nRTI mutations has been observed in a number of studies. Patients with virus that is hypersusceptible to efavirenz exhibit a better virologic response to treatment with the drug.

Which mutations are associated with tenofovir resistance?

Tenofovir resistance has been shown to be mediated by the K65R and T69S insertion mutations, and multiple nRTI mutations, especially M41L and L210W (Miller et al, 9th CROI, 2002) and T215Y/F. As noted above, a change in susceptibility of more than 4-fold is associated with a probable loss of any response to the drug.

In addition to the observation that NAMs confer considerable cross-class resistance in HIV, there have been a number of other recent findings regarding nRTI resistance. One is that the mechanism of zidovudine resistance has been demonstrated to be that of pyrophosphorolysis (Arion et al, *Biochemistry*, 1998; Arion et al, *J Biol Chem*, 2000). Another is that stavudine and stavudine/didanosine select for zidovudine resistance mutations and the Q151M complex (Coakley et al, AIDS, 2000); thus, care is required in interpreting resistance testing results for stavudine and didanosine.

In which clinical scenarios should resistance testing routinely be performed?

Resistance testing is clearly warranted in the following settings: primary (acute) infection, simultaneously with initiation of treatment; first-regimen failure; multiple-regimen failure; and pregnancy. With regard to primary infection, treatment should not be delayed until resistance results are known. In cases of established infection (up to 2 years) in drug-naive patients, baseline resistance testing is reasonable to perform, given the prevalence of drug resistance in patients with recent infection (Little et al, *N Engl J Med*, 2002). In cases of longer established (>2 years) HIV infection, whether resistance testing is performed as part of baseline evaluation in antiretroviral-naive patients depends on prevalence of drug resistance in the patient's locale and on clinician index of suspicion of likelihood of drug resistance.

Presented in June 2002. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Hammer in September 2002.

Financial Disclosure: Dr Hammer has served as site investigator for or consultant to Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Roche-Trimeris, Shionogi, Shire BioChem, Tibotec-Virco, and Triangle.

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Perspective

HIV Infection in Women: Selected Issues in Pregnancy

At the International AIDS Society–USA course in Denver in May 2002, Judith S. Currier, MD, discussed issues in the management of HIV-infected women, focusing primarily on those related to pregnancy. She used 2 case presentations to illustrate questions concerning sex differences in viral load and CD4+ cell counts, appropriate antiretroviral therapy for pregnant women, prevention of mother-to-child transmission, and adverse events in pregnancy.

Case 1: Viral Load in HIV-Infected Women and Antiretroviral Treatment in Pregnancy

Case Presentation

A 36-year-old woman recently tested seropositive for HIV infection and is interested in beginning antiretroviral therapy. She believes that she was infected 3 years previously. Her current CD4+ cell count is 270/µL and her plasma HIV-1 RNA level is 9000 copies/mL; 6 months ago, her levels were 320/µL and 5000 copies/mL, respectively. The patient lives with her boyfriend and works as a physical therapist. She has no history of injection drug use, does not smoke tobacco, and only occasionally consumes alcohol. She has no significant past medical history; her current physical exam and laboratory evaluation, including PAP smear, are unremarkable; and she has no signs or symptoms of HIV infection. The patient is receiving no medication other than oral contraceptives (ethinyl estradiol/norethindrone). Should antiretroviral therapy be initiated in this patient? If so, with what type of regimen—for example, nevirapine plus 2 nucleoside reverse transcriptase inhibitors (nRTIs), 3 nRTIs, a protease inhibitor (PI)-based regimen, or efavirenz plus 2 nRTIs?

Dr Currier is Associate Professor of Medicine at the University of California Los Angeles and Associate Director of the UCLA CARE Center.

Discussion

For some clinicians, this patient's CD4+ cell count alone would provide sufficient rationale for beginning treatment. The relatively low viral load might be a point in favor of delaying treatment in an asymptomatic patient. In this regard, however, it is important to consider that several studies have shown that viral load in women is lower than that in men in early disease (Figure 1), both among patients infected through injection drug use and among those infected through sex. Data from these studies consistently suggest a 0.3- to 0.5-$\log_{10}$ difference in viral load by sex. These data also indicate that CD4+ cell counts are somewhat elevated in women, similar to findings in HIV-uninfected populations. Although some studies have shown no difference in viral load between men and women, these have tended to be studies in small numbers of patients or in patients with advanced HIV infection. Thus, if the decision about whether to initiate therapy involves consideration of viral load, it is reasonable to interpret viral load in this patient as being equivalent to a somewhat higher viral load in a male patient.

With regard to a potential initial regimen, one primary consideration is the patient's current use of oral contraceptives. Avoidance of drugs that would interact with the oral contraceptive via the cytochrome P450 system is recommended if oral contraceptive use is to be maintained. Also, women taking amprenavir should be instructed not to use estrogen-based hormonal contraceptives containing ethinyl estradiol/norethindrone, because these drugs have been found to decrease the concentration of amprenavir. Thus, the triple-nRTI regimen and the efavirenz/double-nRTI regimen are likely candi-

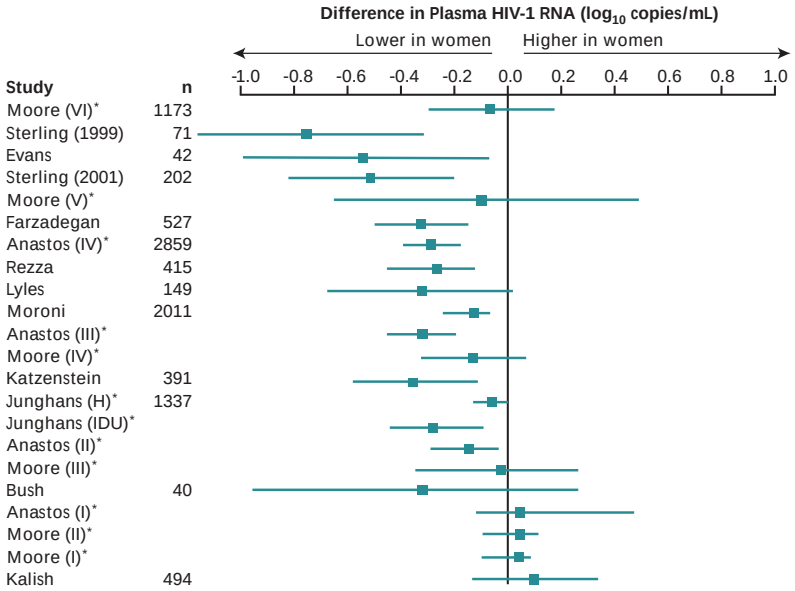

Figure **1.** Estimated differences in mean $\log_{10}$ plasma HIV-1 RNA levels between men and women. Studies are listed in ascending order of median CD4+ cell count, and multiple strata are indicated in parentheses for studies by Moore (I-VI) and Anastos (I-IV). Two groups of subjects are shown for Junghans: heterosexual transmission (H) and injection drug use (IDU). Adapted with permission from Gandhi et al, *Clin Infect Dis,* 2002. *Number represents total in study and not total in strata.

dates for use in this patient. If efavirenz is chosen, a second form of birth control is recommended given the teratogenic potential of this agent and the lack of sufficient data on the impact of efavirenz on contraceptive efficacy.

Clinical Course, Continued

How would selection of treatment differ if the patient stated that she was planning to become pregnant or if it were found that she was already pregnant? For example, should the initial regimen be zidovudine/lamivudine, or zidovudine/lamivudine combined with nevirapine, a PI, or efavirenz? Would it be prudent to delay therapy until the end of the first trimester of pregnancy?

Discussion

Among these treatment options, the dual nRTI combination of zidovudine/lamivudine alone should be avoided because it produces suboptimal viral suppression and is thus likely to result in drug resistance. As noted above, efavirenz should be avoided in women who are planning pregnancy or who are pregnant because of its potential teratogenic effects. In a patient who is planning pregnancy, initiation of treatment might be recommended to provide viral suppression and to evaluate response to the regimen selected. In a woman who is already pregnant, delay of treatment after the first trimester is a reasonable option, as is initiation of treatment with a safe and effective regimen.

Goals of treatment during pregnancy are to achieve optimal viral suppression in the mother, prevent transmission to the child, and maximize the safety of both. Some reassurance regarding safety of antiretroviral treatment for the developing fetus has been provided by data from the Antiretroviral Pregnancy Registry (Garcia et al, 41st ICAAC, 2001). The prevalence rates of birth defects were 2.4% (20/819; 95% confidence interval [CI], 1.5-3.8) among infants with exposure to any antiretroviral drug during the first trimester, 2.2% (26/1207; 95% CI, 1.4-3.2) among infants with exposure during the second/third trimesters, and 2.3% (46/2026; 95% CI, 1.7-3.0) among all exposed infants. These figures compare well with the overall prevalence rates of birth defects of 3.1/100 and 2.2/100 for the first day of life reported by the Centers for Disease Control and Prevention (CDC) in HIV-unaffected pregnancies.

The mode of delivery has been an issue in prevention of transmission. A meta-analysis and a randomized trial have demonstrated the efficacy of elective cesarean delivery in preventing vertical transmission of HIV from mothers receiving zidovudine alone or no antiretroviral treatment. However, whether there is additional benefit from this mode of delivery in mothers receiving potent antiretroviral therapy remains undefined. The Pediatric AIDS Clinical Trials Group study 367 assessed outcomes of 2087 pregnancies in HIV-infected women at 67 centers between 1998 and 2000 (Shapiro et al, 9th CROI, 2001). Transmission rates were 4.3% in 1998, 4.1% in 1999, and 1.6% in 2000. The use of combination antiretroviral therapy increased from 74% in 1998 to 78% in 1999 and 86% in 2000. Elective cesarean delivery was used in 12%, 29%, and 29% of deliveries during these 3 years. Overall, transmission rates were lower with more intensive antiretroviral therapy and did not vary by mode of delivery.

> PACTG study 367 found that mother-to-child transmission rates did not vary by mode of delivery

Case 2: Pregnancy and Adverse Effects of Treatment

Case Presentation

Dr Currier next presented the case of a 35-year-old HIV-infected woman at 38 weeks of gestation who presented to the emergency department with nausea, vomiting, and abdominal pain for 48 hours. She had a nontoxic appearance, with blood pressure of 120/70 mm Hg, heart rate of 90 bpm, no fever or diarrhea, and no vaginal discharge. She reported mild right upper quadrant pain. Laboratory evaluation showed normal complete blood count, platelet count, and coagulation. Alanine aminotransferase (ALT) was 138 U/L, aspartate aminotransferase (AST) was 200 U/L, and amylase and lipase levels were normal. Electrolytes were sodium, 132 mEq/L; potassium, 4.5 mEq/L; chloride, 96 mmol/L; and bicarbonate, 18 mEq/L. The urinalysis was unremarkable. The transaminitis and metabolic acidosis suggested the potential for lactic acidosis. Further work-up showed that the patient had normal to mild fatty changes to the liver on ultrasound testing, negative hepatitis serology, pH of 7.43 mm Hg, P_{CO_2} of 24 mm Hg, P_{O_2} of 108 mm Hg, and negative toxicology screen; her venous lactate level, however, was 13.8 mmol/L.

The patient had been diagnosed with HIV infection 3 years earlier, 2 months after a severe (possible seroconversion-associated) viral illness. Her initial CD4+ cell count was 320/µL and her plasma HIV-1 RNA level was 750,000 copies/mL. She was started on a regimen of fixed-dose lamivudine/zidovudine plus ritonavir/saquinavir, and developed zidovudine-related nausea that did not improve over time. At 6 and 9 months after starting treatment, plasma HIV-1 RNA level was less than 50 copies/mL, and CD4+ cell count had increased to 627/µL at 9 months. Her treatment was changed to didanosine/stavudine/nevirapine and she remained on this regimen throughout the pregnancy because she tolerated it well and her plasma HIV-1 RNA level remained less than 50 copies/mL. No problems occurred during the pregnancy until the time of her presentation.

After hydration, the patient had a lactate level of 15 mmol/L. Should the patient stop antiretroviral therapy and have a cesarean delivery with or without zidovudine coverage during delivery? Should therapy be stopped and delivery held off? Or should the patient be given riboflavin and L-carnitine and undergo delivery while continuing antiretroviral treatment?

Discussion

Lactic acidosis is a rare but potentially fatal complication associated with nRTI treatment. Symptoms include nausea and vomiting, abdominal pain, weight loss, malaise, and dyspnea or tachypnea. Laboratory findings include increased anion gap and increased lactic acid and lactate/pyruvate levels. Hepatic steatosis, consistent with the finding of the mild fatty change to the liver observed in this patient, can occur during pregnancy in association with lactic acidosis, and the condition may be indistinguishable from steatosis associated with nRTI use. Acute fatty liver of pregnancy develops in approximately 1 in 7000 to 13,000 pregnancies. It occurs during the third trimester and is accompanied by symptoms of abdominal pain, nausea, vomiting, and rapid onset of hepatic failure with coagulopathy and encephalopathy. Histology shows a predominantly microvesicular steatosis with mitochondrial disruption on electron microscopy and no necrosis. Management is focused on early diagnosis and prompt delivery. There are limited data on risk of recurrence, although recurrence has been observed with subsequent pregnancy.

In this case, antiretroviral therapy was stopped and the baby was delivered by cesarean section under zidovudine coverage, with the mother also receiving riboflavin and L-carnitine. The baby was in good condition. The mother, however, developed coma and hepatic and renal failure requiring intubation and intensive care unit support for 10 days. Lactate levels improved very slowly to 9.5 mmol/L at 7 days and 5.0 mmol/L at 14 days postpartum. Liver and muscle biopsies showed no mitochondrial abnormalities and a predominantly microvesicular hepatic steatosis, although macrovesicular changes were also detected. It could not be determined whether the patient had fatty liver of pregnancy or hepatic steatosis associated with nRTI use.

Shortly after this patient was seen, details of the deaths of 3 women receiving didanosine and stavudine during pregnancy were released in a "Dear Health Care Provider" letter issued by the manufacturer (Food and Drug Administration, 2001). All 3 women had received didanosine/stavudine throughout their pregnancy. One woman also had received the investigational agent atazanavir, and one, whose fetus expired in utero, also had received nelfinavir. The third woman, whose death was reported in postmarketing surveillance and whose infant expired during cesarean delivery, also had received nevirapine. These deaths resulted in the addition of a warning to the prescribing information that didanosine/stavudine should be used with caution during pregnancy and only if potential benefits outweigh risks.

More recently, at the 9th Conference on Retroviruses and Opportunistic Infections (Marcus et al, 2002), information was reported on 6 additional women who had received didanosine/stavudine for more than 12 weeks in the manufacturer's studies since 1997. Among the 6 women, there were 3 uncomplicated term deliveries, 1 late therapeutic abortion, and 2 pregnancies that were ongoing in women who had switched regimens after the initial report of deaths. An earlier study found that short-term use of the combination in the third trimester in a mother-to-child transmission prevention study resulted in no complications among 77 women treated. Thus, length of exposure may be an important determinant of risk of complications with this combination.

Clinical Course, Continued

The patient gradually improved. Off antiretroviral therapy, her plasma HIV-1 RNA level was less than 200 copies/mL and CD4+ cell count was 326/µL at day 14. Three weeks later, plasma HIV-1 RNA level increased to 151,000 copies/mL and the patient complained of night sweats and mild swollen glands. At this time, the patient's ALT was 22 U/L, AST was 38 U/L, and lactate level was 0.5 mmol/L. Should the patient be restarted on antiretroviral treatment using a nonnucleoside reverse transcriptase inhibitor (NNRTI) and PI, a regimen of abacavir/lamivudine/NNRTI, or some other regimen, or should she continue to be observed off treatment?

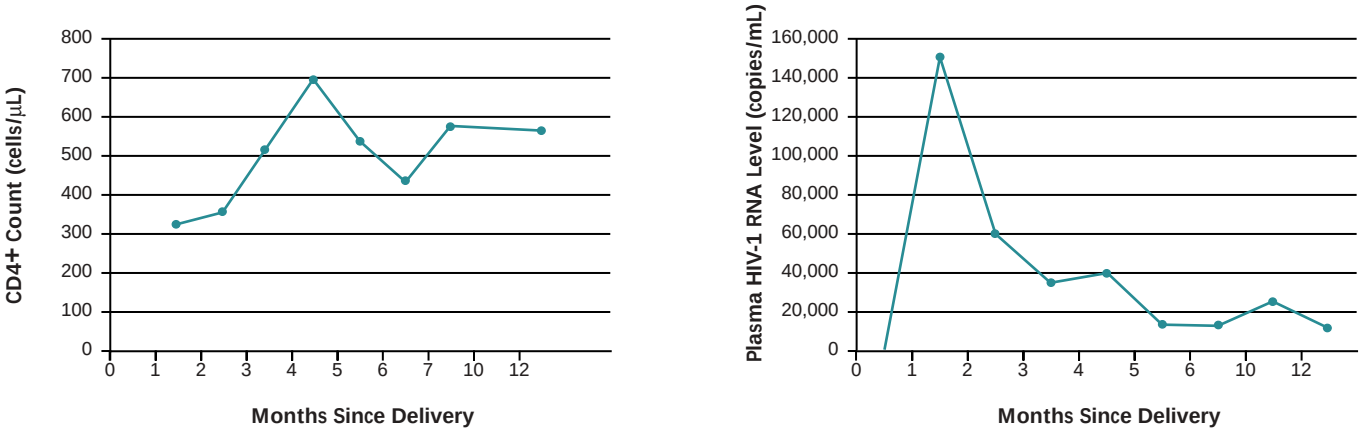

Figure **2.** CD4+ cell count (left) and plasma HIV-1 RNA level (right) by months after delivery and cessation of antiretroviral therapy for patient in Case 2.

Discussion

In this case, the best course would appear to be observing the patient off treatment, both because of the need for recovery from the near fatal episode of lactic acidosis and because of the potential for resolution of what seemed to be recurrence of antiretroviral syndrome after cessation of therapy. After 6 months of observation off therapy, the patient's CD4+ cell count had increased to 576/µL and plasma HIV-1 RNA level had decreased to 14,374 copies/mL (Figure 2). With continued follow-up for more than 1 year, the patient's CD4+ cell count leveled off at approximately 550/µL and plasma HIV-1 RNA level remained below 20,000 copies/mL. The patient remains off antiretroviral therapy with close follow-up and the baby is doing very well.

There are limited data on rechallenge of patients with nRTIs after episodes of symptomatic lactic acidosis. In one report by Lonergan and colleagues (8th CROI, 2001) involving 17 patients, 9 who had been receiving stavudine/lamivudine at presentation were rechallenged with either abacavir/lamivudine (n=7) or zidovudine/lamivudine (n=2), 4 who had been receiving stavudine/didanosine were given either abacavir/zidovudine/lamivudine (n=2) or abacavir/didanosine (n=1), 3 who had been receiving stavudine/didanosine/lamivudine were given abacavir/zidovudine/lamivudine (n=2) or abacavir/didanosine/lamivudine (n=1), and 1 who had been receiving stavudine 80 mg/abacavir was given stavudine 40 mg/abacavir. Patients had received their former nRTI regimens for a median of 12 months (range, 3.5-24 months) and received their rechallenge regimens for a median of 10 months (range, 6-17 months). During the rechallenge period, compared with the former nRTI-treatment period, the number of patients with gastrointestinal symptoms decreased from 16 to 0, median lactate level decreased from 4.4 mmol/L (range, 3.3-19 mmol/L) to 1.5 mmol/L (range, 1.0-1.9 mmol/L), and median ALT level decreased from 135 U/L (range, 26-288 U/L) to 22 U/L (range, 10-159 U/L). The number of patients with plasma HIV-1 RNA level less than 400 copies/mL was 12 on the former regimen and 14 during rechallenge.

In cases such as the one discussed here, risk of complications during future pregnancy remains unknown. A prudent course if the patient desires to become pregnant again is first to ensure that an antiretroviral regimen can be tolerated and provide maximal suppression for a defined period (eg, 6 months). If this goal is achieved, pregnancy can be considered with very close follow-up if the patient is aware that recurrent fatty liver is possible and that its risk cannot be quantified.

Conclusion

Important factors in managing antiretroviral therapy in women include consideration of the patient's childbearing goals or plans before initiation of treatment, use of therapy that maximizes benefit to the mother during pregnancy while reducing risk to the fetus, and heightened awareness of the potential for lactic acidosis. Although routine monitoring of lactate levels is not recommended in asymptomatic patients, levels should be monitored in patients with unexplained weight loss, nausea, or abdominal pain, and possibly during pregnancy.

Presented in March 2002. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Currier in August 2002.

Financial Disclosure: Dr Currier has served as a consultant and scientific advisor to Abbott, Agouron, Bristol-Myers Squibb, GlaxoSmithKline, and Serono. She has also received grant support from Abbott, Agouron, Bristol-Myers Squibb, and Merck.

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Drug Resistance Mutations in HIV-1

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The International AIDS Society–USA (IAS–USA) Drug Resistance Mutations Group reviews new data on HIV drug resistance with the goal of maintaining a current list of mutations associated with clinical resistance to HIV. This list, presented as the IAS–USA Mutations Figures, has been revised based on data from the 11th International HIV Drug Resistance Workshop in Seville, Spain, in July 2002, and other recent conferences. The figures have been updated since they were last published in the May/June 2002 issue of this journal.

New Drugs Added to the Mutations Figures

The most notable change in this update is the addition of the HIV entry inhibitor class. The first agent added to the figure is enfuvirtide, a fusion inhibitor that is not approved by the US Food and Drug Administration (FDA) but is available through an expanded access protocol. Resistance mutations in the gp41 envelope gene have been identified primarily at positions 36 to 45 of the first heptad repeat (HR1) region. The mutations listed on the figure—G36D/S, I37V, V38A/M, Q39R, N42T, and N43D—are from preliminary data[1-3]; further research is needed to evaluate the clinical relevance of these and other mutations.

Atazanavir, also only available through an expanded access protocol, has been added to the protease inhibitor (PI) category. The mutations included for atazanavir (V32I, M46I, I50L, I54L, A71V, V82A, I84V, N88S, and L90M) are based on recent data from studies using the drug as the initial PI, and as a subsequent PI in combination with saquinavir.[4]

Other Revisions

In light of the expanding information offered in the notes accompanying the figures, the name "Footnotes" has been changed to "User Notes."

The E44D and V118I mutations are now included as nRTI-associated mutations (NAMs). The NAMs (M41L, E44D, D67N, K70R, V118I, L210W, T215Y/F, and K219Q/E) are associated with cross-resistance to nucleoside reverse transcriptase inhibitors (nRTIs) and are represented in the figures by vertical pink lines (see user note 2). In this revision, the NAMs lines have been extended to lamivudine in recognition of data that indicate that the E44D and V118I mutations confer resistance to lamivudine only in the presence of multiple other NAMs.[5]

The IAS–USA Mutations Figures are available on a pocket-sized folding card. To order copies, please contact the IAS–USA at (415) 561-6720 (phone) or resistance@iasusa.org.

In the user notes, the discussion of revertant mutations in codon 215 has been updated. New data indicate that an expanded list of substitutions at 215 confer increased risk of virologic failure of zidovudine and stavudine in antiretroviral-naive adults starting therapy with these drugs.[6-8] The T215Y mutant may emerge quickly from these mutations in the presence of zidovudine or stavudine.

The IAS–USA Drug Resistance Mutations Group welcomes comments on the mutations figures and user notes. Please send your evidence-based comments, including relevant reference citations, to the IAS–USA at resistance@iasusa.org or by fax at (415) 561-6740. Please include your name and institution.

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

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

Multi-nRTI Resistance: 151 Complex	A	V	F	F	Q
	62	**75**	**77**	**116**	**151**
	V	I	L	Y	M

Multi-nRTI Resistance: 69 Insertion Complex[1]	M	A	D	▼	K	L	T	K
	41	**62**	**67**	**69**	**70**	**210**	**215**	**219**
	L	V	N	insert	R	W	Y/F	Q/E

Multi-nRTI Resistance: NAMs[2]	M	E	D	K	V	L	T	K
	41	**44**	**67**	**70**	**118**	**210**	**215**	**219**
	L	D	N	R	I	W	Y/F	Q/E

Zidovudine[3,4]	M	E	D	K	V	L	T	K
	41	**44**	**67**	**70**	**118**	**210**	**215**	**219**
	L	D	N	R	I	W	Y/F	Q/E

Stavudine[3-5]	M	E	D	K	V	L	T	K
	41	**44**	**67**	**70**	**118**	**210**	**215**	**219**
	L	D	N	R	I	W	Y/F	Q/E

Didanosine[6,7]	K	L
	65	**74**
	R	V

Zalcitabine	K	T	L	M
	65	**69**	**74**	**184**
	R	D	V	V

Abacavir[8]	K	L	Y	M
	65	**74**	**115**	**184**
	R	V	F	V

Lamivudine[9]	E	V	M
	44	**118**	**184**
	D	I	V/I

Tenofovir[3,10]	K
	65
	R

Nonnucleoside Reverse Transcriptase Inhibitors

Multi-NNRTI Resistance[11]	K	Y
	103	**188**
	N	L

Multi-NNRTI Resistance: Accumulation of Mutations[12]	L	V	Y	G	M
	100	**106**	**181**	**190**	**230**
	I	A	C/I	S/A	L

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

Delavirdine[13]	K	Y	Y	P
	103	**181**	**188**	**236**
	N	C	L	L

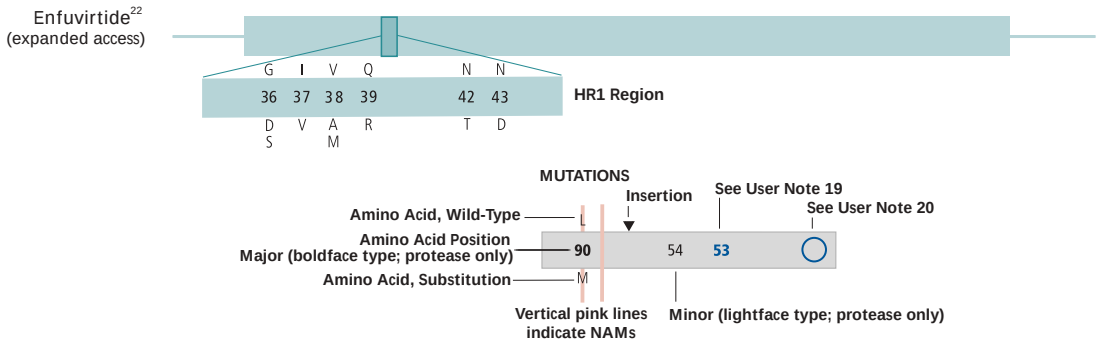
Efavirenz[13-15]	L	K	V	Y	Y	G	P
	100	**103**	**108**	**181**	**188**	**190**	**225**
	I	N	I	C/I	L	S/A	H

MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS

Protease Inhibitors[16]

Multi-PI Resistance: Accumulation of Mutations[17]	L								M				I					V	I	L
	10								**46**				54					**82**	**84**	**90**
	F I R V								I L				V M L					A F T S	V	M
Indinavir[18]	L	K	L		V		M	M					I		A	G	V	V	I	L
	10	20	24		32		36	**46**					54		71	73	77	**82**	**84**	90
	I R V	M R	I		I		I	I L					V		V T	S A	I	A F T	V	M
Ritonavir	L	K			V	L	M	M					I		A		V	V	I	L
	10	20			32	33	36	46					54		71		77	**82**	**84**	90
	F I R V	M R			I	F	I	I L					V L		V T		I	A F T S	V	M
Saquinavir	L									G			I		A	G	V	V	I	L
	10									**48**			54		71	73	77	82	84	**90**
	I R V									V			V L		V T	S	I	A	V	M
Nelfinavir	L			D			M	M							A		V	V	I	N	L
	10			**30**			36	46							71		77	82	84	88	**90**
	F I			N			I	I L							V T		I	A F T S	V	D S	M
Amprenavir	L				V			M	I		I		I			G			I		L
	10				32			46	47		**50**		54			73			**84**		90
	F I R V				I			I L	V		V		L V M			S			V		M
Lopinavir/ Ritonavir[19,20]	L	K	L		V	L		M	I		I	F	I	L	A	G		V	I		L
	10	**20**	**24**		**32**	**33**		**46**	**47**		**50**	**53**	**54**	63	**71**	**73**		**82**	**84**		**90**
	F I R V	M R	I		I	F		I L	V		V	L	V L	P	V T	S		A F T S	V		M
Atazanavir[21] (expanded access)					V			M			I		I		A			V	I	N	L
					32			46			**50**		54		71			82	84	88	90
					I			I			L		L		V			A	V	S	M

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



For each amino acid residue, the letter above the bar indicates the amino acid associated with wild-type virus and the letter(s) below indicate the substitution(s) that confer viral resistance. The number shows the position of the mutation in the protein. Mutations selected by protease inhibitors in Gag cleavage sites are not listed because their contribution to resistance is not yet fully defined. HR1 indicates first heptad repeat; NAMs indicates nRTI-associated mutations; nRTI indicates nucleoside reverse transcriptase inhibitor; NNRTI indicates nonnucleoside reverse transcriptase inhibitor; PI indicates protease inhibitor. The figures were last published in *Topics in HIV Medicine* in June 2002.

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.

User Notes

The IAS–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, presented as the IAS–USA mutations figures, includes mutations that may contribute to a reduced virologic response to a drug. These mutations have been identified by one or more of the following criteria: (1) in vitro passage experiments; (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. Drugs that have been approved by the US Food and Drug Administration (FDA) or are available through expanded access protocols are included. Additional information on the mutations is provided, where necessary, in these user notes.

1. The 69 insertion complex, consisting of a mutation at codon 69 (typically T69S) and followed by an insertion of 2 or more amino acids (S-S, S-A, S-G, or others), is associated with resistance to all FDA-approved nRTIs. The 69 insertion complex is often accompanied by mutations at other sites. Some other amino acid changes from the wild-type T in codon 69 without the insertion may also be associated with broad nRTI resistance.

2. The nRTI-associated mutations (NAMs), including M41L, E44D, D67N, K70R, V118I, L210W, T215Y/F, and K219Q/E, are associated with cross-resistance to nRTIs and are represented by vertical pink lines. Zidovudine and stavudine select for these mutations, and as such, the positions and mutations are indicated on the bars along with the pink lines. For other nRTIs, the NAMS are not commonly selected by those drugs, but the presence of the NAMs confers cross-resistance to the drugs. This is represented by pink lines only at the positions.

The E44D and V118I mutations are listed as NAMs. In a recent study, the E44D and V118I mutations were more common in virus from patients treated with zidovudine and lamivudine, and were associated with higher-level resistance to zidovudine (Kuritzkes et al, *Antimicrob Agents Chemother,* in press). When present together with other NAMs, the E44D and V118I mutations confer resistance to lamivudine. Analysis from the AIDS Clinical Trials Group (ACTG) study 136 has shown that the V118I mutation is commonly selected by a zidovudine/didanosine regimen (Shafer et al, *J Infect Dis,* 1995). Findings from ACTG study 241 have shown that the E44D mutation is commonly selected by zidovudine/didanosine (Hanna et al, *J Infect Dis,* 2002) and that the E44D mutation is associated with a significantly worse response to treatment with zidovudine and didanosine, with or without nevirapine (Precious et al, *AIDS,* 2000). 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).

3. The M184V mutation may enhance susceptibility to zidovudine, stavudine, or tenofovir. This effect may be overcome by an accumulation of NAMs or other mutations. The clinical significance of this effect is not known.

4. Recent data on revertant mutations in codon 215 indicate that the T215D/C/S/E/N/A/V substitutions confer increased risk of virologic failure of zidovudine and stavudine in antiretroviral-naive adults starting therapy with these drugs (Riva et al, *Antivir Ther,* 2002). In vitro studies and preliminary clinical studies suggest that the T215Y mutant may emerge quickly from these mutations in the presence of zidovudine or stavudine (Garcia-Lerma et al, *Proc Natl Acad Sci U S A,* 2001; Lanier et al, *Antivir Ther,* 2002; Riva et al, *Antivir Ther,* 2002).

5. Mutations at codon 75 (V75T/M/S/A) have been observed in vitro and may confer a low-level change in susceptibility to stavudine (Lacey et al, *Antimicrob Agents Chemother,* 1994).

6. The K65R mutation or the L74V mutation, alone or in combination with the NAMs and/or T69D/N can lead to didanosine resistance.

7. Based on preliminary, yet-unpublished data, the M184V mutation does not appear to have a negative impact on in vivo responses to didanosine, even though the mutation reduces susceptibility in vitro. (Winters et al, *Antivir Ther,* 2002; Eron et al, *Antivir Ther,* 2002; Pozniak et al, *Antivir Ther,* 2002).

8. When present with NAMs, the M184V mutation contributes to reduced susceptibility to abacavir and is associated with impaired response in vivo. However, when present alone, the M184V mutation does not appear to be associated with a reduced virologic response to abacavir in vivo (Harrigan et al, *J Infect Dis,* 2000).

9. The E44D and V118I mutations were reported to confer low-level resistance to lamivudine when accompanied by several other nRTI-associated mutations (M41L, D67N, L210W, T215Y/F, K219Q/E) in the absence of a concurrent M184V mutation (Hertogs et al, *Antimicrob Agents Chemother,* 2000). Data presented but not yet published (D'Arminio-Monforte et al, 8th CROI, 2001), reported no association over the short term between E44D or V118I and virologic response to a lamivudine-containing combination regimen. (See also user note 2.)

10. The accumulation of NAMs (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E [note: data here do not include E44D and V118I]) increases resistance to tenofovir. Mutations M41L and L210W contribute more than others. Therefore, the number and type of NAMs will determine the degree of reduced response. T69D/N/S may also contribute to a reduced response to tenofovir (Miller et al, *Antivir Ther,* 2002; Lu et al, *Antivir Ther,* 2002; Masquelier et al, *Antivir Ther,* 2002).

11. The K103N or Y188L mutation alone can substantially reduce the clinical utility of all currently approved NNRTIs.

12. Accumulation of 2 or more of these mutations substantially reduces the clinical utility of all of the currently approved NNRTIs.

13. The prevalence of the Y318F mutation in clinical isolates along with mutations K103N, Y181C, or P236L was approximately 5%, 2%, and 15%, respectively (Kemp et al, *Antivir Ther,* 2001). In vitro this mutation confers resistance to nevirapine, delavirdine, and efavirenz.

14. The Y181C/I mutation is not selected by efavirenz, but its presence contributes to low-level cross-resistance to the drug. Clinical impact of this mutation may be overcome with a fully active antiretroviral combination regimen, although no clinical trial data yet address this question.

15. V108I and P225H each contribute to efavirenz resistance when present in combination with other NNRTI-associated mutations. Although V108I or P225H alone does not confer measurable resistance in laboratory strains of HIV-1, their presence in a clinical isolate may indicate prior selection for efavirenz-resistant variants.

16. Resistance mutations in the protease gene are classified as either "major" or "minor" (if known).

> Major: In general, major mutations are either (1) selected first in the presence of the drug; or (2) shown at the biochemical or virologic level to lead to an alteration in drug binding or an inhibition of viral activity or viral replication. By themselves, major mutations have an effect on phenotype. In general, these mutations tend to be the major contact residues for drug binding.
>
> Minor: In general, minor mutations appear 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 virus carrying major mutations.

17. Accumulation of 4 or more of these mutations is likely to cause multi-PI resistance (Palmer et al, AIDS, 1999; Shafer et al, *Ann Intern Med*, 1998).

18. For indinavir, the mutations listed as major may not be the first mutations selected, but they are present in most clinical isolates in combination with other mutations.

19. Major and minor mutations have not been designated for lopinavir/ritonavir-associated resistance since currently there are no clear data defining degrees of influence with this drug combination. The accumulation of 6 or more of these mutations is associated with a diminished response to lopinavir/ritonavir. The product information states that accumulation of 7 or 8 mutations confers resistance to the drug. However, recent data suggest as few as 4 mutations can be associated with such high-level resistance (Prado et al, AIDS, 2002). Further clinical experience and research are needed to better define the mutations that affect the clinical effectiveness of lopinavir/ritonavir. It is reasonable to consider phenotyping to assess this in individual cases.

20. Protease mutation L63P is common in viruses that have never been exposed to PIs (Kozal et al, *Nat Med*, 1996) and may be more prevalent in viruses from patients in whom a PI-containing regimen has failed. However, by itself, L63P does not cause any appreciable increase in the IC_{50} for any PI. L63P is listed for lopinavir/ritonavir (and not any other PI) because studies have shown that this mutation, when present with multiple other mutations, is associated with clinical failure.

21. Atazanavir is currently available through an expanded access protocol and is not approved by the US FDA. When administered to patients as the initial PI, atazanavir selects for the mutations I50L and A71V (Colonno et al, *Antivir Ther*, 2002). When used as a subsequent PI in combination with saquinavir, atazanavir selects for I54L and I84V (Colonno et al, *Antivir Ther*, 2002). In vitro, atazanavir selects for V32I, M46I, I84V, and N88S (Gong et al, *Antimicrob Agents Chemother*, 2000). Although other major mutations, such as V82A and L90M, have not been selected for by atazanavir either in vitro or in vivo, these mutations have been shown to confer cross-resistance to atazanavir, particularly when present in combination with each other or with other known PI resistance mutations (Colonno et al, *Antivir Ther*, 2000).

22. Enfuvirtide is currently available through an expanded access protocol and is not approved by the US FDA. To date, resistance mutations in the gp41 envelope gene have been identified primarily at positions 36 to 45 of the first heptad repeat (HR1) region. These mutations have been identified in viruses from patients treated with the drug and have been shown to confer resistance or reduced susceptibility (Wei et al, *Antimicrob Agents Chemother*, 2002; Sista et al, *Antivir Ther*, 2002; Mink et al, *Antivir Ther*, 2002). It is important to note that wild-type viruses in this region show a 500-fold range in susceptibility, and mutations in other regions in the envelope may affect susceptibility to enfuvirtide. Further research is needed to evaluate the clinical relevance of these mutations.

Financial Disclosure: The authors disclose the following affiliations with commercial supporters that may have interests related to the content of this article.

Dr Brun-Vézinet has received grant support from bioMérieux, Bristol-Myers Squibb, GlaxoSmithKline, PE Biosystems, and Visible Genetics and has served as a consultant to GlaxoSmithKline and Visible Genetics.

Dr Clotet has received grant support from Bristol-Myers Squibb, Gilead, Roche, and Visible Genetics.

Dr Conway has received research support from Boehringer Ingelheim and research funding from Abbott, Agouron, Bristol-Myers Squibb, Schering, and Triangle.

Dr D'Aquila has served as a speaker or on a speakers bureau for Agouron, Bristol-Myers Squibb, Gilead, ViroLogic, and Visible Genetics and as a consultant to Bristol-Myers Squibb and GlaxoSmithKline.

Dr Demeter has served on the speakers bureau and scientific advisory committee for GlaxoSmithKline and has received research support from Applied Biosystems and Bristol-Myers Squibb/DuPont Merck.

Dr Grant has served as a consultant to Visible Genetics. He has received honoraria from Agouron, GlaxoSmithKline, and ViroLogic and research support from Virco, ViroLogic, and Visible Genetics.

Dr Johnson has served as a consultant to GlaxoSmithKline and Bristol-Myers Squibb and as a speaker or on a speakers bureau for Abbott, Boehringer Ingelheim/Roxane, Bristol-Myers Squibb, Chiron, GlaxoSmithKline, Merck, Roche, Vertex, and ViroLogic. She has received grant support from Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, and Visible Genetics.

Dr Kuritzkes has served as a consultant to Abbott, Bristol-Myers Squibb, Chiron, Gilead, GlaxoSmithKline, Ortho Biotech, Roche, Shire, Serono, Triangle, Trimeris, ViroLogic, and Visible Genetics. He has received honoraria from Abbott, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Roche, and ViroLogic and grant support from Abbott, Bristol-Myers Squibb, GlaxoSmithKline, Roche, Tanox, Triangle, Trimeris, and Visible Genetics.

Dr Loveday has served as a consultant to GlaxoSmithKline and Visible Genetics and as a scientific advisor to Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Roche, and Visible Genetics. He has received grant support from Abbott, GlaxoSmithKline, Roche, and Visible Genetics.

Dr Richman has served as a consultant to Abbott, Achillion, Bristol-Myers Squibb, Chiron, Gilead, GlaxoSmithKline, Merck, Novirio, Pfizer, Roche, Tibotec-Virco, Triangle, and ViroLogic.

Dr Schapiro has served as a scientific advisor to Roche and Visible Genetics and on the speakers bureau for Abbott, Bristol-Myers Squibb, and Roche. He has received other financial support from GlaxoSmithKline and Virology Education.

Dr Shafer has served on the speakers bureau for Bristol-Myers Squibb, GlaxoSmithKline, and Merck and has received grant support from Abbott, Agouron, Applied Biosystems, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Merck, Roche, and Visible Genetics.

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Perspective

The Changing Nature of the Prevention and Management of Opportunistic Infections

As related by Henry Masur, MD, at the International AIDS Society–USA CME course in Washington, DC, in May 2002, opportunistic infection rates have declined since the advent of potent antiretroviral therapy. However, there is evidence to indicate that these declines have stalled and perhaps reversed in some populations in association with long-term antiretroviral failure and inadequate access to care.

The use of chemoprophylaxis for opportunistic infections and the advent and widespread use of potent antiretroviral therapy were associated with a marked decline in rates of most opportunistic infections in HIV-infected individuals from the early 1990s through 1997. However, a recent report from the Adult/Adolescent Spectrum of Disease Project indicates that additional reductions in rates for many opportunistic infections were not observed between 1997 and 1999 (McNaghten et al, 39th IDSA, 2001). One explanation for these observations is that more patients are experiencing immunologic decline in association with long-term virologic failure of antiretroviral therapy. An optimal virologic response (ie, viral suppression to below limits of assay detection) is not achieved in many patients with initial or subsequent treatment. Continued virologic failure places such patients at increased risk of disease progression. For example, a 2000 review of 20 potent therapy arms in antiretroviral treatment studies (Bartlett et al, AIDS, 2001) indicated that, on intent-to-treat analysis in the majority of the study arms, 50% or less of patients achieved plasma HIV-1 RNA levels less than 50 copies/mL at 48 weeks. An increased incidence of opportunistic infections during virologic failure is not currently supported in the published literature, however.

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A second explanation for the absence of continued decline in opportunistic infection rates is the continued spread and progression of HIV disease in patient groups that are not receiving adequate medical care. In some sites in Washington, DC, for example, many patients are now presenting with opportunistic infections as the initial manifestation of HIV disease. Adult/Adolescent Spectrum of HIV Disease Project data on 2365 patients developing *Pneumocystis carinii* pneumonia (PCP) from 1996 through 1999 indicate that 45% were not in care at the time they developed PCP, compared with 41% of 3863 patients who developed PCP from 1993 through 1996. The proportion of patients developing PCP who were in care and met the criteria for PCP prophylaxis but received no prophylaxis was 6% in the period from 1993 to 1996, and increased to 14% in 1996 to 1999. A large proportion of patients developing PCP were in care and met criteria for and received PCP prophylaxis, but developed PCP because of nonadherence or resistance to prophylactic regimens. A smaller proportion of patients continue to develop PCP at CD4+ cell counts higher than the level established as the criterion for institution of primary PCP prophylaxis, which is 200/µL or less.

Opportunistic Infection Risk and Prophylaxis

CD4+ cell count still appears to be a reliable predictor of risk for opportunistic infections in the potent antiretroviral therapy era. In terms of heightening diagnostic vigilance for opportunistic infections, however, it has long been recognized that risk extends to patients with CD4+ cell counts above the levels established as threshold levels for initiation of prophylactic therapy. For example, data from the Multicenter AIDS Cohort study (Phair et al, *N Engl J Med*, 1990) prior to the advent of potent therapy showed that among patients developing PCP within 6 months of a medical visit, one quarter had a CD4+ cell count greater than 200/µL. Thus clinicians should keep in mind that the "thresholds" published for opportunistic infections are general guidelines, not absolute boundaries of susceptibility. Both prior to the era of potent antiretroviral therapy and currently, opportunistic infections will occasionally occur at unusually high CD4+ cell counts.

There are data to indicate that the CD4+ cell count nadir reached prior to restoration of CD4+ counts to greater than 200 cells/µL is not predictive of increased risk for opportunistic infections. As shown in a study by Miller and colleagues (*Ann Intern Med*, 1999), opportunistic infection incidence rates and 95% confidence intervals in patients with CD4+ count nadirs of less than 200, 150, 100, or 50 cells/µL did not differ substantially (incidence rates of 3.7-8.1 per 100 patient-years) when cell counts increased to greater than 200/µL on potent therapy. However, the incidence rate was dramatically elevated to 72.9 per 100 patient-years in patients with persistently low CD4+ cell counts (Figure 1).

> Many patients are now presenting with opportunistic infections as the initial manifestation of HIV disease

These and other data indicating that CD4+ cell count increases on potent antiretroviral therapy are associated with reduced risk for opportunistic infec-

tions have led to recommendations for discontinuation of prophylaxis based on CD4+ cell count and adequate control of plasma HIV-1 RNA level. Currently, there are specific CD4+ cell count-based guidelines for discontinuation of primary prophylaxis for PCP, toxoplasmosis, and *Mycobacterium avium* complex (MAC) infection and secondary prophylaxis for these infections and for cytomegalovirus (CMV) disease and cryptococcosis (USPHS/IDSA, 2001). Data are currently insufficient to recommend discontinuation of secondary prophylaxis for histoplasmosis or coccidioidomycosis based on CD4+ cell count. However, many practitioners with considerable experience with these latter types of infections are of the opinion that discontinuation of prophylaxis is safe with sufficient CD4+ cell count increase on potent antiretroviral therapy.

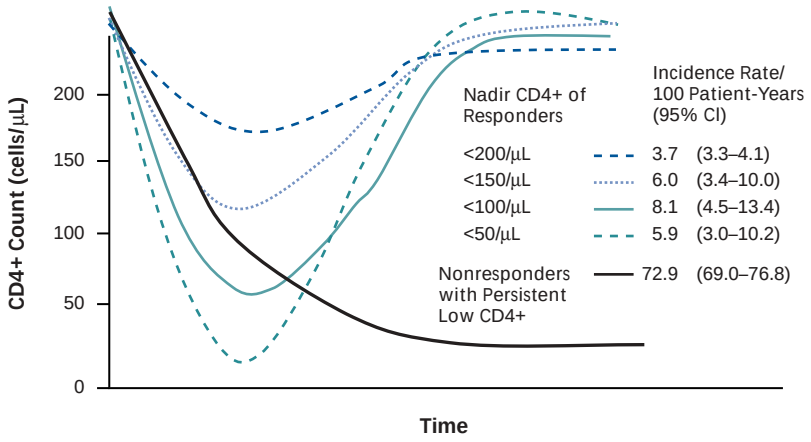

Figure **1.** Effect of pretreatment nadir CD4+ cell count on incidence of opportunistic infections in patients whose CD4+ cell count increased to greater than 200/µL on potent antiretroviral therapy (responders) and incidence in patients with persistently low cell count (nonresponders). Adapted with permission from Miller et al, *Ann Intern Med,* 1999.

HIV-Associated Pulmonary Disease

Pulmonary disease remains one of the most common infectious complications encountered in patients with HIV disease. PCP, tuberculosis, and pneumococcal and *Haemophilus* infections remain common among pulmonary infections, as does infection due to atypical and viral pathogens. Less common causes of disease include histoplasmosis and coccidioidomycosis, toxoplasmosis, and Kaposi's sarcoma. Among the relatively less common pulmonary complications, cases of disease caused by *Aspergillus*, *Staphylococcus*, and lymphoma are increasing in frequency. Pathogens that may cause pulmonary disease in other immunosuppressed populations and that cause other types of disease in HIV-infected patients, but that remain rare causes of pulmonary disease in the latter, include CMV, MAC, herpes simplex virus, and *Rhodococcus*.

Changes in the spectrum of HIV-related pulmonary disease have been observed during the potent antiretroviral therapy era. Data from 204 patients seen at a Georgetown consult service from 1993 to 1995 indicate that pulmonary manifestations were due to PCP in 74 patients (36%), other bacterial infection in 59 (29%), CMV in 14 (7%), and lymphoma in 7 (3%). By comparison, data from 51 patients seen in the same consult service from 1997 to 2000 indicate that manifestations were due to PCP in 9 (18%), other bacterial infection in 24 (47%), CMV in 2 (4%), and lymphoma in 8 (16%; Wolff and O'Donnell, *Chest*, 2001). However, the types of opportunistic infections observed may depend on the patient populations studied. As noted, experience at some centers indicates that many HIV-infected individuals without adequate connections to health care are now presenting with opportunistic infections as initial manifestations of HIV disease, and the frequency with which PCP is encountered is greater among such individuals.

Current Status of PCP Diagnosis and Management

PCP should be considered in any HIV-infected individual with pulmonary disease. Although suspicion should be heightened in patients with lower CD4+ cell counts, it should be remembered that PCP occurs at counts greater than 200/µL in a sizable proportion of patients. PCP has a variety of radiologic presentations. Although symmetrical diffuse interstitial infiltrates are most common, the presentation can include asymmetrical infiltrates, nodules, lobar disease, and cavitation. Specific diagnosis can be made in a very high percentage of cases using bronchoalveolar lavage and immunofluorescence staining. In practiced hands, diagnosis can be made in a high percentage of cases using induced sputum and immunofluorescence. There is considerable interest in polymerase chain reaction (PCR)-based diagnostic techniques for PCP. One recent study showed that PCR analysis of simple oral washes was associated with 91% sensitivity, 94% specificity, 76% positive predictive value, and 98% negative predictive value (Fischer et al, *J Infect Dis*, 2001). Quantitative PCR techniques for PCP diagnosis currently are being developed, and may be commercially available in the relatively near future.

Trimethoprim/sulfamethoxazole (TMP-SMX) remains the drug therapy of choice for PCP, with adjunctive corticosteroids being used in patients with severe disease. Pentamidine is also an effective therapy, but is associated with adverse effects. Other treatment options, including atovaquone and clindamycin-primaquine, have not provided sufficient efficacy to be considered as first-line treatment. There is some evidence that *P carinii* can become resistant to TMP-SMX, which may explain some proportion of the disease incidence in patients receiving TMP-SMX prophylaxis. Since attempts to culture *P carinii* have met with failure, conventional resistance testing of the organism has not been performed. However, within the past several years,

the target enzyme of TMP-SMX, dihydropteroate synthase (DHPS), has been sequenced, and it has been found that mutations in the enzyme are associated with sulfa drug resistance in pneumococci and other organisms. A study performed by Danish investigators indicates that mortality due to PCP is greater in patients exhibiting the DHPS mutations (Helweg-Larsen et al, *Lancet*, 1999). Mutations appear to be more common in patients with prior exposure to sulfa drugs, and have been found in stored samples from patients treated in the 1990s and 1980s. There is thus some concern that *P carinii* resistance to TMP-SMX, although not a problem currently, could become a problem in the future.

Immune Reconstitution Syndromes

Immune reconstitution syndromes in patients initiating potent antiretroviral therapy have been described in the settings of PCP and a variety of other pathogens, including CMV, MAC, tuberculosis, herpes simplex virus, varicella-zoster virus, hepatitis C virus, and oral human papilloma virus. There are not yet good guidelines for distinguishing between reactivation syndromes and acute infections. The potential for immune reconstitution syndromes in patients initiating potent antiretroviral therapy should be taken into account in those cases in which HIV-infected patients not receiving antiretroviral treatment present with an acute opportunistic infection. Delay of antiretroviral treatment until the acute infection has completely resolved should be considered in these cases. Randomized clinical trials of immediate versus deferred antiretroviral therapy in acutely ill patients are needed.

In an illustrative case (Wislez et al, *Am J Respir Crit Care Med*, 2001), a patient presenting with PCP and a PO_2 of 59 was started on TMP-SMX and showed normal PO_2 and considerably improved radiologic findings on day 15. After initiation of potent antiretroviral therapy, the patient returned on day 26 in respiratory failure; PO_2 was 69 and an infiltrate was observed on x-ray. Biopsy showed the presence of very few *P carinii* organisms and an intense inflammatory response, indicating that the respiratory syndrome was due to provocation of the immune response to PCP despite relative absence of the organisms.

Similar cases have been described in both patients with prior opportunistic infections and those in whom presence of an opportunistic pathogen was previously unrecognized. For example, it appears that nearly every patient with a history of CMV retinitis in whom potent antiretroviral therapy is initiated will develop some degree of retinal inflammation due to immune reactivation syndrome, with deterioration of vision occurring in some. Other cases have described reactivation syndromes involving, for example, cryptococcal pulmonary infection and MAC infection of mediastinal lymph nodes in patients with no history of acute opportunistic infection. In some cases, resolution of the syndrome occurs without specific treatment and with continuation of potent antiretroviral therapy.

Conclusion

Opportunistic infections are still occurring in HIV-infected individuals. In some settings, many of the patients with opportunistic infections are patients who are not receiving adequate medical care for HIV disease, including an increasing number who present with opportunistic infections as the initial manifestation of HIV disease. The recent leveling off, and perhaps increase, of opportunistic infection rates is also likely attributable in part to immunologic decline in the large number of patients maintained on virologically failing antiretroviral regimens for prolonged periods. Renewed attention to guidelines for prophylaxis and treatment for opportunistic infections is warranted. Additional work is needed in providing information on distinguishing between acute opportunistic infections and immune reactivation syndromes and defining optimal management of the latter. For the future, it is hoped that better antiretroviral regimens and the addition of immunotherapy to antiretroviral treatment will permit more patients to achieve viral control adequate to prevent immunologic deterioration. For example, novel approaches to raising CD4+ cell counts such as interleukin-2 have considerable promise. It is also hoped that advances can be made in identifying and providing quality treatment to the large number of HIV-infected individuals who currently are at increased risk of disease progression because of lack of medical care.

Presented in May 2002. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Masur in July 2002.

Financial Disclosure: Dr Masur has no affiliations with commercial organizations that may have interests related to the content of this article.

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Perspective

Depression and Adjustment Disorder in Patients With HIV Disease

Depressive symptoms are common in patients with HIV disease, reflecting in part the contribution of preexisting depressive illness to risk behaviors for acquisition of HIV infection. Depression complicates management of HIV disease by increasing the likelihood of nonadherence to antiretroviral treatment regimens. HIV-infected patients with depressive symptoms may also be more likely to engage in behaviors that put others at risk of infection. These issues and approaches to diagnosis and treatment of depression in HIV-infected patients were discussed by Andrew F. Angelino, MD, at the Clinical Pathway *of the Ryan White CARE Act 2002 All Grantee Conference held in Washington, DC, in August 2002.*

Depressive symptoms are common in HIV-infected patients. In a 1991 survey of patients presenting to the Johns Hopkins HIV clinic for their first medical visit, the AIDS Psychiatry Service found that 54% of patients had Axis I (non-substance abuse) psychiatric disorders, including 20% with major depression and 18% with depressive symptoms associated with adjustment disorder (Lyketsos et al, *Int J Psychiatry Med*, 1994). The epidemic nature of HIV disease in the arena of psychiatric practice is indicated by these and other findings in this survey. In particular, 74% of HIV-infected patients had a substance use disorder, 18% had cognitive impairment, and 27% had a personality disorder.

Practitioners in HIV clinics have long anticipated the need for counseling services at the time of diagnosis and for ongoing mental health support as the disease progressed. At the beginning of the HIV epidemic, when the prognosis of the disease was especially grim and most patients died within 18 months of their diagnosis, there was a high degree of practitioner burnout since little more than palliative care could be offered. Although the advent of potent antiretroviral therapy has allowed patients a substantial increase in life expectancy, depressive symptoms are still extremely common. Depressive symptoms may lead patients toward higher-risk behavior, such as injection drug use (McDermott et al, *Hosp Community Psychiatry*, 1994), and may contribute to nonadherence to medical therapies (Singh et al, AIDS *Care*, 1996). In effect, depression may lead patients to become HIV-infected, concentrating a high proportion of depressed patients in the HIV clinic, and may then lead those patients to be nonadherent to antiretroviral therapy or therapy for opportunistic infections, resulting in a sicker population of patients at the clinic. Sicker patients are more demoralized by their sickness, which may worsen depression. A vicious cycle is thus perpetuated (Figure 1). Depressed HIV-infected patients may also be more likely to engage in behaviors that put others at risk of HIV infection. Important goals of treating depression in the HIV-infected patient thus include removing barriers to HIV disease treatment adherence and reducing the risk of transmission of infection, in addition to improving other aspects of function and quality of life for the individual patient.

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Diagnosis of Depression: Differentiating Depression and Adjustment Disorder

Despite the knowledge that depression may lead to HIV infection and that HIV infection may worsen depression, depression remains underdiagnosed and undertreated in medical clinics. Lack of correct diagnosis is explained in part by the fact that providers find it difficult to distinguish major depression from depressive symptoms associated with adjustment disorder or demoralization. Undertreatment is explained in part by the inadequate availability of specialty referral (eg, psychiatrists, psychologists) and by the refractory nature of depressive syndromes.

The differential diagnosis of depression includes major depression, adjust-

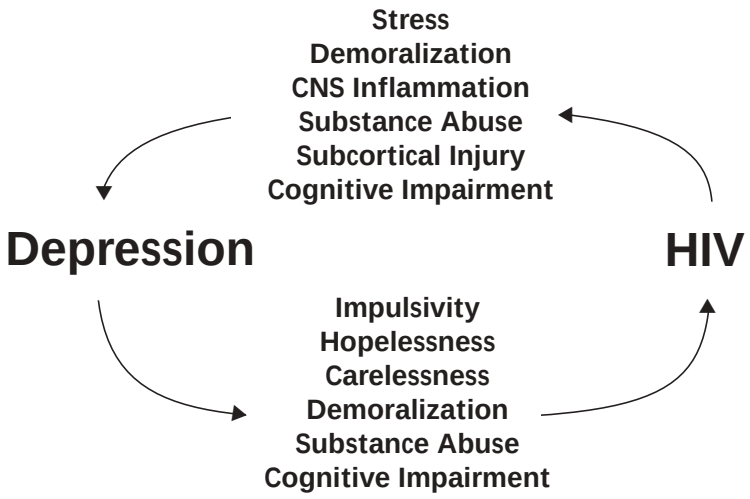

Figure **1.** Interrelationship of depressive symptoms and HIV infection. CNS indicates central nervous system.

ment disorder or demoralization, dementia, delirium, substance use disorders, and a number of medical mimics, including, but not limited to, hypothyroidism, anemia, drug side effects, malnutrition, and hypotestosteronemia. When other potential causes of depressive symptoms can be ruled out, symptoms of depression due to major depressive disorder and those due to adjustment disorder need to be distinguished. The distinction is much more than one of degree—it concerns pathology and etiology. Major depression can be conceptualized as a disease of the brain, affecting those neural systems that control mood. Demoralization or adjustment disorders are disorders that arise from a patient's meaningful reaction to particular life circumstances or events. The symptoms of major depression and demoralization may appear similar, but in fact there are often subtle differences.

The distinction between major depression and adjustment disorder is more than one of degree and concerns pathology and etiology

Major depression is a syndrome that centers around low mood and anhedonia (Table 1). Anhedonia is the inability to feel pleasure from normally pleasurable experiences. Pleasure can be conceived of as falling into categories of "yeah!" or "ahhhh...." The "yeah!" is the type experienced more as a jolt (eg, when one bowls a strike or hits the jackpot); it is probably a dopaminergic frontal lobe response. The "ahhhh..." is a feeling of calm, relaxation, or satiety (eg, that associated with the experience of a good meal or a good book); it is probably related to endogenous opioid activity. Both types of pleasure typically are missing in major depression. Thus, depressed patients will sometimes report that they have a decreased amount of excitement or joy from a usually happy circumstance and sometimes will complain that they feel no amount of satiety or comfort after an experience that normally makes them feel at ease. As much as patients with major depression feel sad, they also describe an empty feeling and often feel as if they have the inability to experience good feelings or happiness.

In contrast, patients with demoralization may be able to experience pleasure normally when they are distracted from thoughts of the demoralizing circumstance or event. When they are reminded of the demoralizing circumstance or event, however, they often feel sadness welling up and overcoming them.

Patients with major depression often have a diminished vital sense. They describe this phenomenon as feeling fatigued and having a heavy pressure in their chests, and they often have somatic complaints of aches, pains, and, occasionally, gastrointestinal disturbances. When asked, patients who are depressed frequently will say that they feel sick. In contrast, patients who are demoralized generally feel healthy but can identify external circumstances or events to which their response includes a feeling of physical upset. For example, a patient having a conflict with a spouse may feel upset and have physical symptoms of such distress when at home with the spouse.

Evaluation of patients with depressive symptoms is complicated by the fact that somatic complaints frequently require medical investigation to ensure that they are not related to opportunistic disease. Furthermore, for patients with major depression as well as those with adjustment disorder, anxiety and sadness resulting from hearing bad news, such as being told of a lower-than-expected CD4+ cell count, may worsen feelings of fatigue and somatic symptoms, thus alarming the patient and provider and potentially leading to more investigation for causes, and more anxiety, and so on. A careful balance must be maintained between investigation of symptoms for medical etiology and reassurance that the symptoms are stress-related and no further investigation is warranted.

Table **1.** Phenomenology of Major Depression

- Diminished mood and hedonic responsiveness
- Decreased vital sense
- Decreased self-attitude
- Neurovegetative symptoms
  - Early morning awakening
  - Appetite change
  - Diminished libido
  - Cognitive impairment ("pseudodementia")

Many patients with major depression also suffer a diminished self-attitude and believe that they are worthless and that life is hopeless for them. This often leads to despair and thoughts of suicide. In HIV disease patients, suicidal thoughts may be active or can take the form of a passive death wish; patients may act out the death wish, for example, by stopping antiretroviral therapy to allow the disease to progress and end their life. In contrast, very few patients with demoralization suffer from global self-attitude changes. On occasion, however, the demoralized patient may complain of feelings of failure or guilt; this is particularly prominent in patients who have lost a loved one, who may express these feelings in such statements as "I wish I had not argued with him so much," or "I should have told her I loved her more often." However, many patients with adjustment disorder can recognize this so-called "survivor guilt" and use it as an impetus to avoid taking things for granted.

Patients with major depression also suffer from neurovegetative symptoms. Patients complain of decreased sleep, especially waking early in the morning with the inability to fall back to sleep. Further, they have diminished appetite with weight loss. Occasionally, they will say that food does not taste good, exhibiting a lack of hedonic response to the taste of the food they have chosen. They may eat sweets or high-fat foods in an attempt to stimulate pleasure or produce a feeling of satiety, and may eat enough of these foods to gain weight.

Patients with major depression may also exhibit decreased libido, and may express lack of interest in sexual activity, or, similar to eating sweets, may engage in reckless or uninhibited sex in an

attempt to recapture lost excitement. In addition, depressed patients will report slowed thinking and decreased concentration and memory. Although this has been termed "pseudodementia" of depression, the term is misleading; the dementia exhibited is a real but reversible decline in cognitive function associated with slowed brain activity. Patients with demoralization may report some of these neurovegetative symptoms; however, the effect in major depression is often much more striking.

To further differentiate between major depression and demoralization, one may inquire about family history, past experiences, and precipitating events and circumstances. Major depression often runs in families. A clear history of other family members with major depression who responded to antidepressant medication is a clue that the patient giving the history also may have major depression. Care should be taken in interpreting patient-provided histories, however. Many people suffer demoralization in their lifetime that may be mistakenly identified as depression; also, a family history of depression that went unrecognized or untreated by professionals may be misleading. Major depression is often a recurring illness and patients often describe more than one episode in their lifetime of similar feelings of sadness with the lack of ability to have enjoyment and a diminished self-attitude. Patients with demoralization or adjustment disorder may or may not have recurring episodes. By definition, demoralization and adjustment disorder have a precipitating event or circumstance 100% of the time. In contrast, patients suffering from an episode of major depression will be able to point to a precipitating event or circumstance only about 50% of the time.

Confidence in the diagnosis of major depression can be built by finding a strong family history of depression in which a family member has responded to treatment, a lack of precipitating event, and a recurrence of similar symptoms several times throughout the patient's lifetime. Once the clinician reaches a diagnosis of demoralization or major depression, an appropriate course of treatment should begin.

Table 2. Some Commonly Prescribed Antidepressants*

- Tricyclic Agents
  - Imipramine (Tofranil)
  - Desipramine (Norpramin)
  - Amitriptyline (Elavil, Endep)
  - Nortriptyline (Aventyl, Pamelor)
  - Protriptyline (Vivactil)
  - Doxepin (Sinequan)
  - Trazodone (Desyrel)
- Bupropion (Wellbutrin)
- Selective Serotonin Reuptake Inhibitors
  - Fluoxetine (Prozac)
  - Sertraline (Zoloft)
  - Paroxetine (Paxil)
  - Fluvoxamine (Luvox)
  - Citalopram (Celexa)
- Selective Norepinephrine Reuptake Inhibitors
  - Venlafaxine (Effexor)
  - Nefazodone (Serzone)
- Noradrenergic and Specific Serotonergic Antidepressant
  - Mirtazapine (Remeron)

*The US proprietary name(s) for each drug is listed in parentheses following the generic name.

Antidepressant Treatment of Major Depression

In most cases, the treatment for depression is antidepressant medication. There are many available medications that have demonstrated efficacy in the treatment of major depression (Table 2). A number of these specifically have been shown to be efficacious in the treatment of major depression affecting patients with HIV disease (Elliott et al, *Semin Clin Neuropsychiatry*, 1998). To date, no single antidepressant medication has been shown to be more efficacious than any other medication for major depression in patients with or without HIV disease. It should be noted that *efficacy* is a property of the medication, that is, it is the ability of the medication to successfully treat the illness for which it is prescribed. This does not mean, however, that a given medication will be *effective* for a particular patient. One reason that a medication may not be effective is that it simply does not correct the underlying metabolic disturbance in the brain of the patient with major depression.

Table 3. Side Effects of Selected Antidepressants

- Tricyclic Agents
  - Sedation
  - Weight gain
  - Constipation
  - Urinary retention
  - Dry mouth
  - Blurred vision
  - Orthostasis
- Selective Serotonin (5-HT) Reuptake Inhibitors
  - Nausea—5-$HT_{2A,2C,3}$ inhibition
  - Sexual dysfunction—5-HT_2 inhibition
  - Anxiety (fluoxetine > sertraline = citalopram > paroxetine)
  - Insomnia (fluoxetine > sertraline)
  - Sedation (paroxetine > citalopram)
- Bupropion
  - Anxiety
  - Insomnia
  - Nausea
- Selective Norepinephrine Reuptake Inhibitors
  - Activation (venlafaxine)
  - Hypertension (venlafaxine)
  - Sedation (nefazodone)
  - Anxiety (nefazodone)
  - Nausea (nefazodone)
- Noradrenergic and Specific Serotonergic Antidepressants
  - Sedation (mirtazapine)
  - Weight gain (mirtazapine)

Although the mechanism of action in antidepressant medicines is known, the specific neurochemical disturbance in a given patient with major depression has yet to be demonstrable in a clinically relevant way. If a particular drug that corrects a certain neurochemical disturbance is prescribed, but the patient's neurochemical disturbance is not corrected by the drug's action, that medication will not be effective.

In a large proportion of patients, antidepressant medications fail because of nonadherence to the medications prescribed. Any medication that has a potential positive effect also has a potential for side effects. Antidepressant side effects are listed in Table 3. A good rule of thumb to increase adherence to antidepressant medicines is to prescribe antidepressants with side effect profiles that either treat patient symptoms or do not worsen patient symptoms. An example of this would be prescribing a medication that is sedating for a patient who

has trouble sleeping, or prescribing a medication that slows gastrointestinal motility for a patient who has diarrhea. In general, prescribing a drug that may cause diarrhea to a patient who already suffers from diarrhea will result in the patient's nonadherence to the medication.

Once patients initiate treatment with antidepressant medications, their progress should be monitored for the alleviation of symptoms and the development of new side effects. It is generally thought to be a good idea to begin with low doses of antidepressant medications and titrate slowly to full doses, using therapeutic serum drug level monitoring for those drugs for which such levels have been established. While it is good practice to start low and go slow, it is likewise important to persist in increasing doses to full doses or therapeutic serum levels and to add additional agents if necessary until a response is achieved. Augmenting agents include lithium, triiodothyronine, and antipsychotic drugs. Although lithium has pronounced toxicity, it is the best studied augmenting agent and has well-defined therapeutic serum levels. If response is not observed at therapeutic serum levels after a few weeks, it is not likely to occur, and the drug can be discontinued.

Another augmenting strategy is to combine antidepressants with different mechanisms of action. For example, a selective serotonin reuptake inhibitor can be combined with a serotonin-norepinephrine reuptake inhibitor, or either or both can be combined with bupropion, which has a predominantly dopaminergic effect. Although none of these approaches can assure a response in every patient with major depression, the Johns Hopkins AIDS Psychiatry Service has found that partial or full response can be achieved in approximately 85% of patients overall and in greater than 90% of patients who adhere to therapy (Figure 2; Treisman et al, *HIV, AIDS and the Brain*, 1994).

There are no data to support the use of antidepressant medications as a key element of treatment for adjustment disorders. There is opportunity for research into the role of neurochemical changes in patients suffering reactive sadness from life circumstances, however, and thus into the role of antidepressants as adjunctive treatments.

Psychotherapy for Adjustment Disorders and Major Depression

Patients with mild adjustment disorders centering around bad news (eg, the worsening of HIV disease status) and patients with major depression benefit from supportive psychotherapy. Supportive psychotherapy includes education regarding the psychiatric illness and the practice of therapeutic optimism, which encourages and sustains the belief that therapeutic response can occur with continued treatment. Regular meetings with a provider to discuss feelings and to urge patients to keep going in treatment are often of great benefit. Support groups and informal counseling sessions can be added as needed. A patient with a more severe adjustment disorder should be referred to a professional counselor for any of the various forms of psychotherapy appropriate to his or her condition.

A general principle in many cases for psychotherapy is to identify those elements of the patient's condition or circumstances that may be under the patient's control to change. With encouragement from the therapist for the patient to practice those changes, the sense of empowerment or mastery that ensues often alleviates the patient's demoralized state. Cognitive-behavioral therapy is one form of psychotherapy that focuses on altering feelings by first changing thoughts and actions. Many patients state that they will be able to make important life changes when they are free from their bad feelings; in cognitive-behavioral therapy, the patient is encouraged to learn that first one must *do* better and then one will *feel* better. The many other forms and goals of psychotherapy that can be employed are beyond the scope of this discussion.

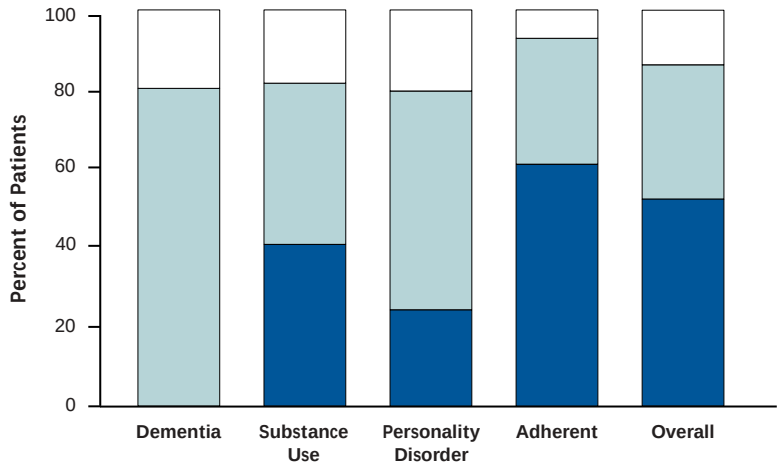

Figure **2.** Full (in blue), partial (green), or no (white) response to antidepressant therapy in HIV-infected patients with major depression according to complicating factors (dementia, substance use disorder, personality disorder), and in those adherent to antidepressant treatment, and overall. Adapted from Treisman et al, *HIV, AIDS and the Brain,* 1994.

Addressing Substance Use Disorders

Substance abuse and depressive symptoms are connected in a number of ways. Major depression increases the likelihood of substance use and abuse; many individuals resort to alcohol or drug use in the attempt to replace the lost "yeah!" and "ahhhh..." pleasures. Depressive symptoms can be caused by substance intoxication or withdrawal (substance-induced mood disorder). Patients may also experience adjustment disorder or demoralization as a result of losses experienced through substance use (eg, partners, savings, jobs, homes). Patients with substance-induced mood disorder usually are free from depressive symptoms after the first several weeks of abstinence, whereas

substance-using patients with major depression frequently have episodes of depression during their abstinence.

In the experience of the Johns Hopkins AIDS Psychiatry Service, it is virtually impossible to effectively treat depression in a patient with ongoing substance abuse. Thus, the first step in treating depressive symptoms in all patients with substance use disorders is to stop the substance use. A general behavioral approach that can be used in this setting is to: (1) stop the behavior; (2) identify comorbidities and sustaining factors for the behavior and eliminate them; (3) repeat steps 1 and 2 as necessary; and (4) identify initiating factors and address them (if necessary). Sustaining factors for behaviors can be conceptualized as mutable stimuli and immutable stimuli; the former are those that can be changed or avoided, and the latter are those that cannot be avoided and the responses to which must be directly extinguished. Part of the therapy for patients in this arena is determining which stimuli for substance use are avoidable or changeable and which are inevitable. Patients may be assisted in making a list of "triggers" and examining each item on the list with an eye toward change or avoidance. For example, a man with alcoholism who reports he buys liquor only at a liquor store can be instructed to avoid the street on which the liquor store is located. One immutable stimulus for the substance-abusing HIV-infected patient might be the patient's feelings regarding HIV infection, such as the above-mentioned demoralization. Since the feelings may be present continually or recurrently because the infection is not yet curable, the patient's response to these feelings should be directly addressed in counseling or psychotherapy, with a prescription of new, non-substance use behaviors to replace those behaviors that maintained the addiction.

Conclusion

In summary, major depression and adjustment disorder or demoralization are 2 major forms of psychiatric disturbance associated with depressive symptoms. Patients with depressive symptoms may be at increased risk for transmission of HIV infection due to increased likelihood of engaging in high-risk behaviors; similarly, HIV-infected patients with depressive symptoms may be at increased risk of transmitting HIV to others through risk behaviors. In addition, patients with depressive symptoms who have HIV infection may have increased risk for nonadherence to medical therapies and worsening of illness. Major depression and demoralization can often be differentiated on the basis of symptoms, family history, pattern of recurrence of illness, and the presence or absence of precipitating circumstances or events. Both major depression and demoralization are treatable conditions, and their identification and treatment lead to improved function and quality of life and may result in reduced risk of transmission of HIV to uninfected individuals.

Presented in August 2002. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Angelino in September 2002. A Webcast of Dr Angelino's original course lecture is available online at www.iasusa.org/webcast.

Financial Disclosure: Dr Angelino has served on speakers bureaus for Agouron, AstraZeneca, Eli Lilly, GlaxoSmithKline, Ortho Biotech, Pfizer, Schering, and Wyeth-Ayerst.

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ACKNOWLEDGMENTS

We acknowledge our audience, funders, faculty members, consultants, and other contributors for their contributions to IAS–USA programs in 2002. Their support makes our programs possible.

HIV/AIDS Practitioners

We thank our audience—the participants in our continuing medical education (CME) courses and our readers—for actively participating in our programs and providing feedback on how we can improve the quality and relevance of our activities.

Funders

For support of the 2002 volume of *Topics in HIV Medicine* and the 2002 winter/spring course series *Improving the Management of HIV Disease: HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management*, we gratefully acknowledge:

Major Grant Support
Bristol-Myers Squibb Company
GlaxoSmithKline
Roche Laboratories

Substantial Grant Support
Abbott Laboratories
Agouron Pharmaceuticals, Inc.
Boehringer Ingelheim Pharmaceuticals, Inc.
Schering Laboratories

Generous Grant Support
Gilead Sciences, Inc.
Merck US Human Health
ViroLogic, Inc.

For support of 2002 *Cases on the Web* and the 2002 course series *Current Challenges in HIV Disease: A Case-Based, Advanced Course in Clinical HIV Management*, we gratefully acknowledge:

Major Grant Support
GlaxoSmithKline

Substantial Grant Support
Abbott Laboratories
Agouron Pharmaceuticals, Inc.
Schering Laboratories

Generous Grant Support
Gilead Sciences, Inc.
Ortho Biotech Products, L.P.

For support of the San Diego course, we also thank the ***HIV/AIDS* Bureau of the Health Resources and Services Administration** of the US Department of Health and Human Services, in conjunction with the **Pacific AIDS Education and Training Centers.** For support of the Denver course, we thank the **Colorado and Mountain Plains AIDS Education and Training Centers.**

For support of the *Clinical Pathway*, the fifth annual HIV clinical conference for Ryan White CARE Act grantees, held in August 2002, we thank the **HIV/AIDS Bureau of the Health Resources and Services Administration** of the US Department of Health and Human Services (subcontract to grant #6 H4A HA 00058).

Donors

Donations from the following organizations and individuals are directed to a fund established to distribute *Topics in HIV Medicine* to practitioners in resource-limited settings.

We gratefully acknowledge donations from the following organizations:
NPB Research Co., Ltd., Japan; the Reed Lowenstein and Melanie Hanan Philanthropic Fund, San Francisco; Wherehouse Music, Geary Boulevard, San Francisco; Delta Sigma Theta, Delta Phi Chapter, Muncie, Indiana

We are also grateful to the following individual donors:
A. Aldrich, J. A. Andrilli, M. Bachmann, S. D. Back, J. Bernett, R. M. Buckley, A. F. Burnside, O. Calubiran, M. Day, B. Ellis, A. I. Gelman, M. E. A. Guroy, M. Halpern, B. Hamilton, T. A. Hemmingsen, M. M. Hicks, A. Higgins, H. E. Hill, F. M. Homeyer, S. W. Hosea, A. Iezza, P. F. Jurgensen, C. LaBoy, S. Lau, R. E. MacKay, L. M. Mihm, O. D. Mitkin, L. A. Phillips, M. Policar, B. Postic, M. C. Reyelt, A. Schachter, J. E. Schwendinger, L. Tan, N. Thiessen, M. Tribolati, C. R. Vane, E. K. Ventocilla, A. A. Vernon, D. Williams, J. R. Williams, A. Yougandhar, A. H. Zalski

We also acknowledge those who contributed subsequent to this issue going to press.

Gifts in Kind

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IAS–USA courses this year included the 10th annual winter/spring series, *Improving the Management of HIV Disease: HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management;* the 8th annual fall series, *Current Challenges in HIV Disease: A Case-Based, Advanced Course in Clinical HIV Management;* and the *Clinical Pathway,* the 5th annual HIV clinical conference for Ryan White CARE Act Title III and IV providers.

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Antiretroviral Therapy Panel

The Antiretroviral Therapy Panel published its first set of recommendations in 1996. Subsequent updates have been published in 1997, 1998, 2000, and most recently in July 2002 in the *Journal of the American Medical Association*.

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Resistance Testing Panel

The Resistance Testing Panel published recommendations in 1998 and 2000. Its updated recommendations were submitted for publication in spring 2002.

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Drug Resistance Mutations Group

The Drug Resistance Mutations Group was convened in 2000 to maintain an ongoing, up-to-date database of HIV drug resistance mutations reflecting current research in the field. Each year, the group issues several updates to its list of mutations, the most recent of which appears in this issue of *Topics in HIV Medicine* and at www.iasusa.org.

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Metabolic Complications Panel

The Metabolic Complications Panel was convened in 2000, and its recommendations will be published in 2002.

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Liver Dysfunction Associated With Antiretroviral Therapy
Andrew Carr, MD

Current Issues in HIV/Hepatitis Coinfection
Lorna Dove, MD

Initiation of Antiretroviral Therapy
Constance A. Benson, MD

HIV Therapy in "Triple-Diagnosed" Patients: HIV Infection, Drug Use, and Mental Illness
Gerald H. Friedland, MD

UPCOMING TOPICS

Management of Antiretroviral Failure
- Role of drug resistance
- Late-stage failure issues
- Pros and cons of 5+ drug combinations

Therapeutic Drug Monitoring
- Current data from clinical trials
- Use in clinical practice

Interpretation of Resistance Tests
- Multidrug resistance mutations
- Tenofovir and NAMs
- Phenotyping and new data on drug cutoffs

Initiation of Therapy
- What drugs to start with
- New treatment options

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