ABOUT THIS ISSUE...

This issue contains 4 updates for HIV clinicians: a summary of recent clinically relevant developments in HIV pathogenesis and antiretroviral therapy and 3 discussions of specific challenges for clinical management. The presentations summarized in these articles were given at the International AIDS Society–USA recent Fall 1999 CME course series, Current Challenges in HIV: A Case-Based, Advanced Course in Clinical HIV Management and at the 1999 Winter/Spring program, HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management.

Dr John A. Bartlett’s review of new data, presented at the New York course in October, covers HIV pathogenesis, resistance, treatment strategies, and new antiretroviral drugs. A summary of talks given by Dr David M. Simpson in Atlanta and Los Angeles in February examines current knowledge of HIV-associated dementia and neurocognitive impairment. At the New York course, Dr Susan Cu-Uvin outlined considerations for antiretroviral therapy during pregnancy, and at the Los Angeles course in November, Dr Francesca J. Torriani presented 2 cases that illustrate current issues of HIV/hepatitis C virus coinfection.

The March 2000 issue of Improving the Management of HIV Disease will mark the eighth year of publication and the introduction of a new name and expanded content. The new name, Reviews in HIV Medicine™, will better reflect the current review and update format of the presentation summary articles as well as describe new features such as brief research updates and original review articles of selected key issues. The goal of the publication remains to serve as a resource for physicians and other health care providers actively involved in HIV and AIDS care, presenting recent advances in HIV as interpreted by experts in the field. We invite our readers’ ongoing feedback on how we can best achieve this goal.

Unrestricted educational grants supported this issue of Improving the Management of HIV Disease and the 1999 HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management program.

We gratefully acknowledge:

Major, continuous grant support since 1992 from

Bristol-Myers Squibb Company
Glaxo Wellcome Inc.
Roche Laboratories

Substantial grant support from
Abbott Laboratories
DuPont Pharmaceuticals Company
Merck US Human Health

Generous grant support from
Agouron Pharmaceuticals, Inc.
Gilead Sciences
Pharmacia & Upjohn Company
Rxane Laboratories/Boehringer Ingelheim Inc.

Of note, presentations summarized in 3 of the articles in this issue were originally given at the Fall 1999 course series, Current Challenges in HIV Disease: A Case-Based, Advanced Course in Clinical HIV Management. The Fall series was supported by all of the above companies as well as by generous grant support from Schering Laboratories.
IMPROVING THE MANAGEMENT OF HIV DISEASE

A publication of the
International AIDS Society–USA

VOLUME 7 ISSUE 6 DECEMBER 1999

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RECENT ADVANCES IN HIV PATHOGENESIS AND ANTIRETROVIRAL THERAPY

At the New York course in October, John A. Bartlett, MD, discussed recent findings in 4 specific areas of interest: HIV-1 infection pathogenesis; antiretroviral resistance; comparative effects of initial antiretroviral regimens; treatment intensification strategies; strategies to enhance drug exposure; and newer investigational antiretroviral drugs.

PATHOGENESIS

Recent observations related to HIV-1 disease pathogenesis that may warrant the attention of clinicians include those regarding plasma HIV RNA "blips" during antiretroviral therapy, viral resistance characteristics, and the HIV-specific immune response during antiretroviral treatment.

HIV RNA Blips

Many clinicians have observed transient increases in plasma HIV RNA to detectable levels in patients with viral load that has previously been maintained below the limits of detection of previous assays (eg, detection limits of 400 to 500 plasma HIV RNA copies/mL) or current sensitive assays (limits of 40 to 50 copies/mL), and that subsequently returns to levels below limits of detection. Recent findings suggest that such intermittent viremia may be associated with replenishment of the HIV cellular reservoir. In a study in 32 patients who had exhibited controlled viral replication on protease inhibitor-based therapy for up to 3 years, measurement of levels of replication-competent HIV in the cellular reservoir (by quantitative microcultures of CD8+ cell-depleted cultures) showed that the half-life of such virus was 49 weeks. Intermittent viremia was detected (by sensitive assay) in 24 of the 32 patients. When viral decay rate was assessed according to whether patients had exhibited intermittent viremia, the decay rate was 59 weeks among those with intermittent viremia and 26 weeks in those with no intermittent viremia. Additional study is required to determine the potential clinical significance of this phenomenon.

Resistance in Early Treatment

Until recently, it had generally been assumed that virologic failure of triple antiretroviral therapy due to resistance emergence was associated with resistance to all drugs in the regimen. However, newer findings suggest that early failure of potent therapy may be the result of resistance to a single component. Studies of 2 different populations by Havlir and colleagues and Holder and colleagues analyzed genotypic changes in patients with virologic failure on zidovudine/lamivudine/indinavir therapy. Results indicated that indinavir-associated resistance was relatively uncommon and that most patients had the lamivudine-associated M184V resistance mutation without accompanying zidovudine or indinavir resistance mutations. Similarly, a study of patients in whom therapy with amprenavir/zidovudine/lamivudine was failing has shown that viral rebound occurred in the absence of resistance mutations, a low frequency of amprenavir mutations, and the association of rebound with the M184V mutation.

Resistance and Treatment Interruption in Treatment-Experienced Patients

Miller and colleagues recently performed a retrospective observational study of the effects of treatment interruption in a group of 39 heavily pretreated patients who exhibited phenotypic resistance to a median of 8 antiretroviral drugs. With treatment interruption, the viral population reverted to predominantly wild-type virus in 26 patients, with the resistant phenotype remaining prevalent in 13. The baseline plasma viral load levels were 4.98 log HIV RNA in those with wild-type virus and 5.46 log in those with phenotypically resistant virus; after drug discontinuation, viral load increased by 0.98 log in the group with wild-type virus and by 0.34 log in the group with resistant virus. Baseline CD4+ cell counts were approximately 180 µL in the wild-type virus group and 60 µL in the resistant phenotype group; after discontinuation of treatment, CD4+ cell counts decreased by 122 µL in the former and 29 µL in the latter. Subsequent initiation of salvage therapy resulted in a 2.60-log decrease in viral load in the patients with wild-type virus, compared with a 1.02-log decrease in those with resistant virus, with 18 of 25 of the former group and 2 of 11 of the latter group having plasma HIV RNA levels below 500 copies/mL at week 24 of treatment.

These findings indicate that reversion to wild-type virus may be common on treatment interruption and that such reversion is associated with a greater increase in viral load and greater decline in CD4+ cell count but a better response to subsequent treatment. On the assumption that high-level resistance was present in all patients, the relative stability of viral load and CD4+ cell count in those with resistant virus is consistent with reduced replicative fitness of the viral population. Although no conclusions about therapeutic implications of such findings can be made on the basis of this experience in a small group of patients, the observations indicate that randomized, controlled studies of controlled treatment interruption in heavily pretreated patients are warranted.

HIV-1-Specific Immune Response

Recent data from several small populations of patients have indicated that HIV-specific CD8+ cytolytic T-lymphocyte (CTL) activity is retained at high levels in individuals who have long-term nonprogression of HIV infection in the absence of an-
tiretroviral therapy. Another study suggests that this CTL activity is dramatically diminished in those patients in whom antiretroviral treatment is successful in suppressing viral replication. The implication is that reduced antigenic stimulation resulting from suppression of viral replication is responsible for the decrease in CTL activity.

These studies have created interest in the potential for strategic treatment interruption in order to spur the HIV-specific immune response. A number of investigators have now reported improved control of plasma HIV RNA level in patients off treatment after a series of treatment interruptions. Figure 1 depicts the course of plasma viral load and HIV-specific CTL response to viral antigens during and after treatment interruptions in 1 of 6 patients studied by Ortiz and colleagues. The patients initiated antiretroviral therapy during acute HIV infection and then became intermittently adherent. As shown, HIV-specific immune responses increased coincident with treatment interruption, and the increase in viral load following the last interruption was followed by spontaneous control of viremia in association with increased HIV-specific response. Of note, these observations were made only in patients beginning treatment during acute infection, and therefore cannot be extrapolated to patients with established HIV infection.

**ANTIRETROVIRAL MANAGEMENT**

**Initial Therapy**

Options currently available for initial antiretroviral treatment include 2 nucleoside reverse transcriptase inhibitors (nRTIs) plus a protease inhibitor, 2 nRTIs plus a nonnucleoside reverse transcriptase inhibitor (NNRTI), and triple nRTI therapy. Thus far, relatively few trials have assessed the comparative benefits of these initial approaches. One non-blinded trial comparing the triple therapy regimens of efavirenz/zidovudine/lamivudine and indinavir/zidovudine/lamivudine with the double combination of efavirenz/indinavir has indicated that efavirenz-containing triple therapy resulted in reduction of viral load to below sensitive assay detection limits in a significantly greater proportion of patients than did indinavir-containing triple therapy over 48 weeks of treatment. Another trial comparing abacavir/zidovudine/lamivudine with indinavir/zidovudine/lamivudine resulted in reduction of viral load to below sensitive assay detection limits in 40% of patients in the abacavir arm and 46% of patients in the indinavir arm on intent-to-treat analysis at 48 weeks. However, in patients with baseline plasma HIV RNA levels above 100,000 copies/mL, the indinavir arm had HIV RNA declines to below the sensitive assay limit (45% vs 31%).

In addition to potency, durability of antiretroviral effect should be a crucial consideration in selection of initial therapy. A number of ongoing trials currently are evaluating comparative long-term effects of initial regimens. In the Atlantic trial, 298 patients were randomized to receive initial therapy with indinavir, nevirapine, or lamivudine each in combination with stavudine/didanosine and followed over the course of long-term treatment. Patients began treatment with a relatively low median plasma HIV RNA level of 4.2 log.
raising the possibility that results may not generally apply to typical populations of patients beginning antiretroviral therapy. Intent-to-treat analysis at 48 weeks showed that plasma HIV RNA levels below 50 copies/mL were achieved in 57% of the indinavir group, 51% of the nevirapine group, and 49% of the lamivudine group at this time point. The ongoing AIDS Clinical Trials Group (ACTG) 384 study and the CLASS trial, which is scheduled to start in early 2000, have also been designed to assess the long-term effects of the strategic sequencing of therapy.

Treatment Intensification

Intent-to-treat analyses of trials of initial potent antiretroviral therapy indicate that approximately 50% to 60% of patients achieve plasma HIV RNA levels below 50 copies/mL by 24 weeks on available triple-drug regimens. Strategies to prevent early failure of therapy include use of more aggressive initial regimens—ie, 4- or 5-drug combinations—and early intensification of initial treatment by addition of a single drug. Potential drawbacks of use of more aggressive initial regimens include the challenge to the patient’s ability to maintain adherence, potential increases in adverse effects, increased cost, potential for development of additional antiretroviral resistance, and limitation of future therapeutic options for patients failing on the more aggressive regimens. An additional drawback is the potentially unnecessary use of such regimens in the many patients who would otherwise achieve viral suppression on triple therapy.

A challenge of early intensification is that of identifying patients with increased likelihood of early treatment failure. A recent analysis of patients in ACTG studies 343 and 320 indicated that plasma viral load early after initiation of treatment may provide a basis for predicting which patients will not exhibit suppression of viral load to below assay detection limits. Patients with plasma HIV RNA levels greater than 500 copies/mL at week 8 were at substantially increased risk of having levels above 50 copies/mL at week 24 than those patients with lower viral load at week 8. An ACTG protocol has been designed to assess early intensification with abacavir in abacavir-naive patients receiving any 3- to 5-drug protease inhibitor- or NNRTI-based therapy in whom plasma viral load at 8 weeks is above 500 and below 10,000 HIV RNA copies/mL. Patients are to be randomized to addition of abacavir or placebo by week 12, with the primary end point being proportion of patients with plasma HIV RNA level below 50 copies/mL by week 24.

Recent data indicate that plasma viral load levels early after initiation of antiretroviral treatment may be predictive of subsequent failure to achieve viral load below detection limits

Another potential approach to treatment intensification is that of addition of a drug or drugs when virologic failure occurs following initial successful suppression. ACTG 5061 will study patients with CD4+ cell counts above 100/µL who have exhibited increases in plasma HIV RNA levels of 500 to 10,000 copies/mL after at least 24 weeks of initial treatment with a potent protease inhibitor-based regimen. Patients will be assessed for viral resistance patterns. Those with virus demonstrating sensitivity to 2 of their original 3 drugs, including the protease inhibitor, and demonstrating sensitivity to abacavir, amprenavir, or didanosine, may enter. The subjects will discontinue the drug from the original regimen to which their virus is resistant, and substitute abacavir, amprenavir, or didanosine/hydroxyzene. They will be followed for 24 weeks, with the primary outcome measure being proportion of patients with plasma HIV RNA level below 50 copies/mL at week 24.

Drug Exposure

A number of recent studies have illustrated the importance of maximizing drug exposure in enhancing antiretroviral effect. In ACTG 359, patients with virologic failure on an indinavir-based regimen were randomized to receive combinations including ritonavir/saquinavir or nelfinavir/saquinavir plus delavirdine or adefovir or both. Delavirdine increased blood levels of all protease inhibitors; patients who received delavirdine had the best virologic outcomes. Of note, development of the investigational drug adefovir in the United States was stopped by the company in December 1999. The expanded access program for this drug has been discontinued. Those patients currently receiving adefovir on expanded access will continue to be provided with the drug as long as they are receiving benefit from it.

Lopinavir (ABT-378) is an investigational protease inhibitor that exhibits a marked increase in plasma levels when coadministered with ritonavir. Study of the lopinavir/ritonavir combination as a replacement for a protease inhibitor in patients in whom the first protease inhibitor-containing regimen is failing showed that 94% of patients had a decrease in plasma HIV RNA level greater than 0.5 log within 14 days. Levels declined to below 400 copies/mL in 24 of 70 patients. The addition of nevirapine plus a new nRTI at 2 weeks resulted in plasma HIV RNA levels below 400 copies/mL in 84% of patients at 24 weeks on as-treated analysis. In the M97-720 study assessing optimal dosage of lopinavir/ritonavir, one group of treatment-naive patients (group 1) was randomized to lopinavir/ritonavir 200/100 mg twice a day or 400/100 mg twice a day alone for 3 weeks followed by addition of the combination of stavudine/lamivudine to both regimens. Another group of treatment-naive patients (group 2) was randomized to lopinavir/ritonavir 400/100 mg twice a day or 400/200 mg twice a day, plus the stavudine/lamivudine
combination. The regimens were well tolerated, with only 1 of 32 patients in group 1 and 3 of 69 in group 2 discontinuing treatment and none discontinuing treatment due to adverse effects (1 due to nonadherence). At 24 weeks, plasma HIV RNA levels were below 400 copies/mL in 93% of patients in group 1 and in 94% of patients in group 2. Lopinavir is currently available in the United States on a limited expanded access program.

NEW INVESTIGATIONAL ANTIRETROVIRALS

In addition to lopinavir and lopinavir/ritonavir, a number of other new investigational antiretroviral drugs are currently in early clinical testing or development. Pentafuside (T-20), the first drug in the fusion inhibitor class to be developed, has been found to have activity in extensively pretreated patients. As a peptide, the drug must be administered parenterally, with twice-daily subcutaneous administration appearing to be the most convenient dosing method thus far. In the recent T-20-205 study, conducted by Lalezari and colleagues, safety of and response to twice-daily subcutaneous injection was assessed in 71 heavily treatment-experienced patients rolled over from prior short-term pentafuside studies. Patients were receiving a median of 4 antiretroviral drugs while on study and previously had received a median of 11 antiretroviral drugs. All patients were protease inhibitor-experienced and 93% had prior experience with nRTIs, NNRTIs, and protease inhibitors; 36% were off all antiretroviral treatment during study screening. At baseline, patients had a median plasma HIV RNA level of 4.9 log and median CD4+ cell count of 70/µL. As shown in Figure 2, viral load decreased by more than 1.5 log after 4 weeks of pentafuside treatment and remained at more than 1 log below baseline levels at week 16 in the total population. A similar effect was observed in analysis confined to those patients with triple antiretroviral class exposure and resistance. An ongoing study is assessing the effect of pentafuside-containing combination therapy in patients failing initial protease inhibitor-based treatment.

T-1249 is a newer investigational fusion inhibitor that has been designed to bind to a region of the HIV envelope gp41 region different from that to which pentafuside binds. T-1249 is active in vitro against pentafuside-resistant viral isolates. It is currently in Phase I study.

Investigational nRTIs include emtricitabine (FTC) and DAPD. Emtricitabine is a lamivudine-like drug that can be administered once daily; since the principal resistance mutation associated with emtricitabine is the M184V mutation characteristic of lamivudine resistance, the drug is not likely to have utility in patients with lamivudine experience. A short-term comparison of emtricitabine and lamivudine has suggested that the former may have greater antiretroviral activity. DAPD has activity in vitro against zidovudine- and lamivudine-resistant virus, and currently is being assessed in Phase I studies. Trials on the investigational nRTI lodenosine were recently stopped by the manufacturer.

Investigational NNRTIs include emivirine (MKC-442), AG-1549, and GW-420867. Emivirine has modest single-drug antiretroviral activity and has demonstrated good activity when administered in combination with 2 nRTIs. The drug, which can be given twice daily, cannot be coadministered with protease inhibitors due to significant drug interactions. Both AG-1549 and GW-420867 exhibit activity in vitro against isolates with the efavirenz K103N resistance mutation; trials to determine activity of these drugs in vivo are in progress.
CONCLUSIONS


Clinical trials evaluating sequencing strategies and new antiretroviral drugs will be crucial in developing an improved standard of care.

**Dr Bartlett is Associate Professor of Medicine at Duke University Medical Center in Durham, North Carolina.**

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**SUGGESTED READING**


Selected Neurologic Manifestations of HIV Infection: Dementia and Peripheral Neuropathy

David M. Simpson, MD, discussed neurologic manifestations of HIV infection at the Los Angeles and Atlanta courses in February.

Neurologic complications of HIV disease are common and frequently devastating in effect. Primary neurologic disorders are those directly related to HIV or cofactors of infection, and remain poorly understood. Primary disorders include HIV-associated dementia in adults and progressive encephalopathy in children, HIV-associated (vacular) myelopathy, and distal peripheral neuropathies. The cumulative prevalence of peripheral neuropathy is over 30%, that of dementia approximately 15% to 20%, and that of myelopathy approximately 5% to 10%. Recent experience suggests that the frequency of dementia has declined and that of neuropathy is increasing. The rates of incidence of secondary opportunistic neurologic conditions, including central nervous system (CNS) toxoplasmosis, primary CNS lymphoma, cryptococcosis, and cytomegalovirus disease, all at approximately 5% in older surveys, have also declined.

HIV Dementia

Evidence for a primary pathogenetic effect of HIV infection in dementia includes (1) the presence of the virus in the CNS, with entry during acute infection demonstrated in cerebrospinal fluid (CSF) and pathology studies; (2) infection of microglial cells (resident inflammatory cells of monocyte-macrophage lineage in the brain); (3) correlation of neurocognitive deficits with CSF HIV viral load; and (4) effectiveness of antiretroviral treatment in reducing or preventing dementia (with most data in this regard for zidovudine).

Factors suggesting that HIV is not the direct cause of dementia include (1) the absence of evidence of infection of neurons and glial cells (the primary functional cells in the brain); (2) the relatively modest degree of antiretroviral efficacy in ameliorating dementia; and (3) the absence of a correlation of clinical dementia with CNS viral load as demonstrated in immunohistochemical studies. With regard to the latter factor, however, a number of studies have shown that viral RNA levels in the CSF are correlated with degree of dementia. The likely mechanisms by which HIV causes damage to the CNS include the effects of direct infection as well as the elaboration of a number of toxic substances. Cytokines produced in response to infection, including tumor necrosis factor-α and interleukin-1β, are toxic to both neurons and astrocytes, with the effects probably mediated by disruption of calcium and N-methyl-D-aspartate (NMDA) channels. In addition, HIV sheds gp120, which is directly toxic to neurons in cell culture.

Although the pathophysiology of CNS damage remains imperfectly understood, what is known has suggested a number of potential strategies for treating dementia. These include the proven benefits of antiretroviral therapy and the theoretical benefits of cytokine blockers, calcium channel blockers, glutamate/NMDA channel antagonists like memantine, and antioxidants. A consideration in the use of antiretrovirals is the ability of drugs to cross the blood-brain barrier. In the brain, which may be crucial to reduction of virus in the CSF and to prevention of resistance mutation patterns different from those in the blood. The degree of protein binding is an important determinant of availability of drug for CSF penetration. As a class, nucleoside reverse transcriptase inhibitors (NRTIs) exhibit less protein binding (eg, zidovudine, 36%; stavudine, 0%; zalcitabine, 3%; lamivudine, 35%; abacavir, 50%) than do nonnucleoside reverse transcriptase inhibitors (NNRTIs) (nevirapine, 60%; delavirdine, 98%; efavirenz, 99%) or protease inhibitors (indinavir, 60%; ritonavir, 98%; saquinavir, 98%; amprenavir, 90%).

Investigation of the treatment strategies mentioned above has included a placebo-controlled study demonstrating the efficacy of high-dose zidovudine in the treatment of HIV dementia. A preliminary study of nimodipine showed trends toward benefit and a placebo-controlled study of abacavir did not demonstrate superiority over background antiretroviral treatment. In addition, an ongoing AIDS Clinical Trials Group (ACTG) 301 study is examining the effects of the NMDA antagonist memantine in the treatment of HIV dementia. A trial of selegeline, a monoamine oxidase-type B (MAO-B) antagonist, is under development.
Figure 1. World Health Organization (WHO) analgesic ladder: management of pain in AIDS. Adapted from World Health Organization. Cancer Pain Relief. 1986.

DISTAL SYMMETRIC POLYNEUROPATHY

Distal symmetric polyneuropathy (DSP) is the most common of the major neuro muscular syndromes in HIV disease. Others include mononeuropathy multiplex (limited in early HIV disease and progressive in late disease); progressive polyradiculopathy (late onset); inflammatory demyelinating polyneuropathy (early onset more frequent than late); and myopathy (all stages of HIV disease).

More than one third of patients with advanced HIV disease have clinically or electrophysiologically detectable DSP. Although DSP is less common in the earlier stages of HIV, almost all patients with AIDS have evidence of axonal nerve degeneration at autopsy. Thus it is not surprising that as patients are living longer, often with advanced HIV disease, the frequency of peripheral neuropathy is increasing.

Distal symmetric polyneuropathy is clinically characterized by symmetric sensory complaints and primarily numbness and/or burning pain in the feet. Symptomatic muscle weakness is unusual until advanced DSP is present. The clinical diagnosis of DSP can be made on the basis of depressed or absent reflexes at the ankle relative to the knee, elevated threshold to vibration in the feet, and reduced threshold to pinprick and cold in a stocking-glove distribution. Joint position sensation usually is relatively preserved.

Numerous factors may confound the diagnosis of HIV-related DSP, including the presence of diabetes, alcohol dependency, vitamin B_{12} deficiency, and particularly the use of neurotoxic drugs including dideoxynucleoside antiretrovirals (eg, didanosine, zalcitabine, stavudine), as well as such drugs as vincristine and isoniazid. In a cohort study performed by Dr Simpson and colleagues, nearly half of HIV-infected patients with DSP had additional potential causes of neuropathy, primarily consisting of diabetes, the use of didanosine or dapsone, and alcohol use.

With regard to the potential for antiretroviral drugs to cause DSP, although the databases from which statistical conclusions have been drawn are frequently marred by poor prospective criteria for neuropathy, it is generally acknowledged that didanosine, stavudine, and zalcitabine have a clear neurotoxic effect. Evidence also suggests that hydroxyurea may exacerbate didanosine and stavudine toxicity. Data on didanosine indicate that the incidence of DSP is dose-related, with the frequency varying among studies; it has been observed that patients with DSP on didanosine can tolerate didanosine rechallenge at lower doses. Data from the didanosine treatment Investigational New Drug (IND) experience indicate that neuropathy is more common among patients with a prior history of neuropathy. Distal symmetric polyneuropathy is the major dose-limiting toxicity of zalcitabine, with the frequency clearly dose-related. Stavudine-associated peripheral neuropathy also is dose-related.

Given the range of frequencies of neuropathy in various databases, Dr Simpson and colleagues performed a sub study of ACTG 175 to determine incidence of peripheral neuropathy in the study population. ACTG 175 involved nearly 2500 patients with CD4+ cell counts of 200 to 500/μL who received zidovudine or didanosine alone or zidovudine combined with didanosine or zalcitabine. The substudy data demonstrated that study sites were often inaccurate in diagnosis of distal symmetric neuropathy and causal attribution to the study drug. Peripheral neuropathy was diagnosed by the site investigators in 9% of the population. The incidence of DSP as diagnosed on review by the substudy investigators was highest in the zidovu-
dine/zalcitabine arm (6%). Significant predictors of DSP were older age and poorer Karnofsky scores. Approximately 40% of patients were able to continue the originally assigned study drugs with and sometimes without dose reduction.

As with other neurologic complications in HIV disease, the cause of primary HIV-associated DSP is poorly understood. Wallerian degeneration of variable severity is universal, with a characteristic “dying back” of the peripheral axons. All nerve fiber types are affected. There is a moderate macrophage infiltration in the peripheral nerve although primary HIV infection of the nerve is not demonstrable. Preliminary evidence suggests that affected nerves express cytokines such as tumor necrosis factor and interleukin-1, which may contribute to neuropathogene-

sis, as in CNS disease. A novel skin/epi-
dermal nerve punch biopsy technique has emerged as a quantitative measure of DSP. Normal cutaneous innervation is characterized by a plexus of small branching nerves extending to the surface of the skin; neuropathy is characterized by dissolu-
tion of these epidermal fibers.

Management of DSP

Management of DSP begins with identifi-
cation and correction of metabolic or nutritional causes of neuropathy. Poten-
tially neurotoxic drugs currently or previously used should be identified. Dose-reduction or discontinuation of an antiretroviral drug associated with neu-
ropathy should be considered. However, considera-
tion must also be given to the vi-
roleptic benefit derived from use of the drug; in some cases, a cost-benefit analy-
sis may indicate that continued viroleptic control is favored at the cost of continued neuropathy, with treatment for the latter being attempted.

As with diabetic and alcoholic neu-
ropathies, drugs that can be employed in the attempt to provide pain relief include analogies, tricyclic antidepressants, anti-
convulsants, or topical drugs. The World Health Organization (WHO) analgesic ladder for pain management is shown in Figure 1. Breitbart and colleagues re-
ported a study in AIDS patients with a variety of pain syndromes and showed

that 85% were receiving inadequate anal-
gesic medication according to this standard. A study in cancer patients indi-
cated inadequate analgesia in 42%.

Physician and health care system barriers to use of analgesia and patient reluctance to provide accurate reports of pain should be confronted in order to achieve ade-
quate pain management.

A number of different drugs and ap-
proaches to treatment of neuropathy have been or currently are being assessed. A controlled study of peptide T showed no beneficial effect of the drug on pain or secondary measures of neuropathy including clinical and electrophysiological parameters. A trial comparing acupuncture with sham acupuncture showed no symptomatic benefit of the technique using meridian acupuncture points. In ACTG 242, patients with painful neu-
ropathy received amitriptyline, the lido-
caïne oral derivative mexiletine, or placebo. As shown in Figure 2, after 10 weeks of treatment, while there were trends favoring the amitriptyline arm, no significant differences in improvement in pain scores were observed among treatment groups. The fairly dramatic placebo effect observed is common in pain studies and highlights the need for critical consider-
ation of anecdotal reports of pain

improvement attributed to drugs or tech-
niques in uncontrolled settings.

More promising results have been achieved in studies of a 5% topical lido-
caine available in patch or gel form (Lidoderm). The drug is absorbed mini-
mally from the skin; dermal analgesia occurs within 1 hour and is maintained for 6 to 12 hours. It has demonstrated effec-
tiveness in placebo-controlled trials in postherpetic neuralgia and is now FDA-
approved for this indication. In an open-
label study by Dr Simpson and col-
leagues, 30 patients with painful HIV

neuropathy received the 5% lidocaine gel and were assessed for pain response using patient and examiner-administered ques-
tionnaires and a pain relief rating scale. Seventy-four percent of patients reported moderate to complete relief of pain (mod-
erate relief, 33%; much, 37%; complete, 4%). Fifteen percent reported slight relief and 11% reported no relief. Overall, a signi-
ificant decline in pain (P=0.01) and

significant global pain relief (P=0.001) were found, with adverse effects, primar-
ily dry skin, being minimal. On the basis of these findings, a placebo-controlled trial has been performed and is under analysis.

Dr Simpson and colleagues also re-
cently performed a small placebo-control-
ed trial of the novel anticonvulsant lam-
otriline in patients with painful HIV-
associated neuropathy. Lamotriline blocks voltage-sensitive sodium channels and inhibits glutamate/aspartate release. It is not significantly protein-bound and has no effect on the cytochrome P450 system. Lamotriline has shown promise in small studies in neuropathy and has proven effec-
tive in trigeminal neuralgia in placebo-
controlled studies. In the trial by Dr Simpson and colleagues, lamotriline treatment was associated with a significant reduction in pain score compared with placebo. This benefit was observed only in the patients not receiving neu-
rotoxic antiretroviral drugs. Rash was the most common adverse effect, occurring in 5 of 20 lamotriline recipients; the rash can be minimized by initiating treatment at a low dose of 25 mg a day with gradual escalation to 300 mg a day over approxi-
mately 6 weeks. An attempt to replicate these results is underway in a large multi-
center trial of lamotriline in the treatment
of painful HIV neuropathy.

The effects of recombinant human nerve growth factor in HIV-associated neuropathy were recently assessed by McArthur and colleagues in ACTG 291. Nerve growth factor is neurotrophic for small nerve fibers and is produced in the developing or damaged peripheral nervous system. Recombinant nerve growth factor has been found to have a positive therapeutic effect in Phase II trials of diabetic neuropathy and has been found to prevent neuropathy in animal models of chemotherapy-induced neuropathy (eg, vincristine, cisplatinum).

In ACTG 291, 270 patients stratified by didanosine, zalcitabine, or stavudine use were randomized to twice-daily subcutaneous injections of recombinant nerve growth factor (0.1 μg/kg or 0.3 μg/kg) or placebo for an 18-week treatment period, followed by a 4-week washout and 48 weeks of open-label treatment. The primary adverse effect over 18 weeks was local ache, pain, or discomfort, occurring in 15% of placebo recipients and 25% and 48% of low-dose and high-dose nerve growth factor recipients, respectively. In the active treatment groups, the local hyperalgesia, which occurred in a quarter-sized area around the injection site, resulted in unblinding of approximately one third of the patients. With regard to effectiveness, patients in both nerve growth factor groups had sign-
ificant reductions in average pain intensity ratings compared with placebo recipients at 18 weeks and after the washout period. Overall, pain intensity score and global pain assessment data favored the higher nerve growth factor dose. Both nerve growth factor groups also experienced a significant improvement in pinprick sensation compared with the placebo group. However, no significant effect of treatment was observed on quantitative sensory testing or clinical examination. Epidermal/skin biopsies showed no differences in nerve density among treatment groups. However, the lack of evidence of nerve regeneration in these secondary measures should be interpreted with caution, since the placebo-controlled study period may not have been of sufficient duration to demonstrate nerve regrowth. Data from a 48-week open-label follow-up of these patients are under analysis.

CONCLUSIONS

Factors in selecting an antiretroviral management plan include general clinical status, immunologic function, virologic status including viral load and resistance, and interaction of antiretroviral drugs. Neurologic disease status and the potential for neurologic disease should also be considered in formulating a management plan, including the potential effects of neurotoxic antiretroviral drugs. As the pathophysiology of HIV-associated neurologic complications is elucidated, measurement of CSF HIV RNA levels and the ability of antiretroviral drugs to cross the blood-brain barrier may assume increased importance in selection of antiretroviral therapy. Investigation continues to identify pathogenesis-based treatments for such complications as HIV-associated dementia and peripheral neuropathy and to optimize symptomatic treatment of painful neuropathy.

Dr Simpson is Associate Professor of Neurology, Director of the Neuromuscular Division and Clinical Neurophysiology Laboratories, and Director of the Neuro-AIDS Research Center at Mount Sinai Medical Center in New York City.
SUGGESTED READING


ANTIRETROVIRAL TREATMENT DURING PREGNANCY

Factors to be considered in antiretroviral management of pregnant HIV-1 infected women were discussed by Susan Cu-Uvin, MD, at the New York course in October.

Prior to the use of antiretroviral treatment to prevent perinatal transmission of HIV-1, an estimated 1000 to 2000 children were born with HIV infection in the United States each year. In 1994 the Pediatric AIDS Clinical Trials Group (PACTG) 076 demonstrated that use of zidovudine from gestational age of 14 weeks, during labor and delivery (intravenous), and for the first 6 weeks postpartum in infants reduced vertical transmission from 22.6% with placebo to 7.6% with zidovudine. This finding led to the 1994 US Public Health Service (USPHS) recommendations for antepartum, intrapartum, and postpartum use of zidovudine. Between 1992 and 1998, there was a 67% decrease in the number of annual cases of perinatally acquired AIDS (Figure 1), with this decrease occurring in association with increasing use of zidovudine. More recently, as is discussed below, updates on these and other guidelines focus on aggressive antiretroviral management for HIV-infected pregnant women.

Maternal plasma viral load level is an important determinant of risk of vertical transmission


FACTORS IN VERTICAL TRANSMISSION

Approximately 30% of cases of mother-to-child transmission appears to occur in utero, with the remainder occurring during labor and delivery with exposure of the infant to birth canal secretions and blood and through breastfeeding. Although transmission via breastfeeding is unusual in the United States and other developed countries due to advice against breastfeeding and the availability of alternative nutrition, it remains common in developing areas.

Two recent studies have demonstrated that plasma viral load is an important determinant of risk of transmission. In the Women and Infants Transmission Study (WITS), transmission was observed in none of 57 cases in which the mother’s plasma HIV RNA level was below 1000 copies/mL, compared with a 16.6% (32/193) transmission rate for viral load of 1000 to 10,000 copies/mL; 21.3% (39/183) for levels of 10,001 to 50,000 copies/mL; 30.9% (17/54) for levels of 50,001 to 100,000 copies/mL; and 40.6% (26/64) for levels above 100,000 copies/mL. In the PACTG 185 study, maternal plasma HIV RNA level was the sole independent predictor of transmission; significant increases in odds ratios for transmission of 2.4 (P=0.02) and 3.4 (P=0.001) were observed for every 1-log increase in plasma viral load at baseline and at delivery, respectively.

The role of viral load in the genital tract has yet to be fully elucidated. It is unclear what risk may be posed by high levels of virus in the genital tract in the setting of plasma virus suppression. It is also unclear whether there may be different concentrations of virus in colostrum and mature milk, and whether the duration of breastfeeding or presence of inflammation may modify the risk of transmission via this route. Other factors associated with transmission include: advanced disease stage; nutrient deficiency, particularly vitamin A deficiency (eg, in sub-Saharan Africa); prematurity of deliv-
TABLE 1. PRECLINICAL AND CLINICAL DATA ON THE USE OF ANTIRETROVIRALS IN PREGNANCY

<table>
<thead>
<tr>
<th>nRTIs</th>
<th>FDA Category</th>
<th>Placental Passage (Newborn:Mother Drug Ratio)</th>
<th>Carcinogenicity</th>
<th>Teratogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>C</td>
<td>0.85 (humans)</td>
<td>Vaginal tumors (rodents)</td>
<td>None (rats, rabbits, mice)</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>C</td>
<td>0.3–0.5 (monkeys)</td>
<td>Thymic lymphomas (rodents)</td>
<td>Hydrocephalus (rats)</td>
</tr>
<tr>
<td>Didanosine</td>
<td>B</td>
<td>0.5 (humans)</td>
<td>Negative</td>
<td>None (rats, mice, rabbits)</td>
</tr>
<tr>
<td>Stavudine</td>
<td>C</td>
<td>0.75 (monkeys)</td>
<td>Not completed</td>
<td>None</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>C</td>
<td>1.0 (humans)</td>
<td>Negative</td>
<td>None</td>
</tr>
<tr>
<td>Abacavir</td>
<td>C</td>
<td>Rats</td>
<td>Not completed</td>
<td>Still birth, lower body weight (rats)</td>
</tr>
</tbody>
</table>

**NNRTIs**

<table>
<thead>
<tr>
<th>NNRTIs</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Delavirdine</td>
<td>C</td>
<td>Unknown</td>
<td>Not completed</td>
<td>Abortion (rabbits)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>C</td>
<td>1.0 (humans)</td>
<td>Not completed</td>
<td>None (rats, rabbits)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>C</td>
<td>1.0 (rats, rabbits, primates)</td>
<td>Not completed</td>
<td>Anencephaly, anophthalmia, cleft lip (monkeys)</td>
</tr>
</tbody>
</table>

**Protease Inhibitors**

<table>
<thead>
<tr>
<th>Protease Inhibitors</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Indinavir</td>
<td>C</td>
<td>Substantial (rats), low (rabbits)</td>
<td>Not completed</td>
<td>None (rats, rabbits)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>B</td>
<td>Midterm fetus, 1.15; late-term fetus, 0.15–0.64 (rats)</td>
<td>Not completed</td>
<td>None (rats, rabbits)</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>B</td>
<td>Minimal (rats, rabbits)</td>
<td>Not completed</td>
<td>None (rats, rabbits)</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>B</td>
<td>Unknown</td>
<td>Not completed</td>
<td>None (rats, rabbits)</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>C</td>
<td>Unknown</td>
<td>Not completed</td>
<td>Abortion, skeletal abnormalities (rabbits)</td>
</tr>
</tbody>
</table>

NNRTI indicates nonnucleoside reverse transcriptase inhibitor; nRTI indicates nucleoside reverse transcriptase inhibitor. FDA Category B indicates that no tests in pregnant women have been performed and that animal testing shows absence of adverse effects. Category C indicates that the drug should be used only if benefits outweigh risks in the context of absence of studies in pregnant women and the finding of adverse effects in animal studies. Adapted from Centers for Disease Control and Prevention, MMWR Morb Mortal Wkly Rep. 1998;47(RR-2):1-30.

ery; duration of membrane rupture; mode of delivery; invasive procedures; and chorioamnionitis.

**EFFECT OF PREGNANCY ON HIV INFECTION**

There have been concerns that pregnancy may accelerate progression of HIV disease in association with decreases in immunoglobulins, complement levels, and cell-mediated immune measures. However, available data indicate that pregnancy has little effect on progression among patients with early or asymptomatic infection. Fewer data are available on the effects of pregnancy on disease progression in patients with advanced disease. In a study by Chu and colleagues among HIV-infected women between 15 to 44 years of age in the United States, there was a high rate of pregnancy (17%) with the exception of apparently reduced fertility in patients with severe advanced immunosuppression (3%). A recent study by Dr Cu-Uvin and colleagues indicated that there were no differences in estradiol or progesterone levels during the menstrual cycle between HIV-infected women and uninfected women, suggesting that ovulation remains unimpaired in infected women.

**CURRENT RECOMMENDATIONS FOR ANTIRETROVIRAL TREATMENT**

In 1998, the USPHS issued new recommendations for the use of antiretroviral drugs in pregnant HIV-infected women. The general principles of these recommendations are: (1) decisions regarding the use of antiretroviral drugs during pregnancy should be made by the woman after discussion with the health care provider about the known and unknown benefits and risks of treatment; (2) assessments should be made of HIV disease status, CD4+ cell count, plasma viral load, prior or current antiretroviral therapy, gestational age, and supportive care; and (3) therapy should be the same as in nonpregnant women, with consideration of the potential impact of therapy on the fetus and infant. The use of antiretroviral drugs during pregnancy requires consideration of several important issues, most of which have not been adequately investigated. These issues include the potential need to modify dosing during pregnancy.
due to physiologic changes, the potential for short- and long-term effects on the fetus and infant, the effectiveness of the regimen in reducing risk of perinatal transmission, and the need for antiretroviral treatment for the health of the pregnant woman.

Data indicating the importance of plasma viral load to risk of transmission suggest that potent antiretroviral therapy may play a major role in further reducing risk of mother-to-child transmission. Use of combination therapy in pregnant women has become commonplace, with some reports of no HIV transmission with the use of combination therapy. However, it remains the case that relatively little is known about the effects of many antiretroviral drugs on development of the fetus and infant.

Table 1 summarizes current preclinical and clinical data relevant to the use of antiretroviral drugs in pregnancy by antiretroviral class. All available antiretrovirals are either FDA Category B, indicating that no tests in pregnant women have been performed and that animal testing has shown the absence of adverse effects, or Category C, indicating that the drug should be used only if benefits outweigh risks in the context of the absence of studies in pregnant women and the finding of adverse effects in animal studies. Placental passage for the majority of the drugs has been confirmed in human or animal studies. Carcinogenic effects in animals have been found for zidovudine and zalcitabine in rodents, with testing being negative for didanosine and lamivudine and not yet completed for the other available antiretroviral drugs. No animal teratogenicity has been reported for nucleoside reverse transcriptase inhibitors (nRTIs). Among nonnucleoside reverse transcriptase inhibitors (NNRTIs), delavirdine has been associated with abortion in rabbits. Efavirenz has been associated with serious effects in primate (monkey) studies; it remains unclear whether this effect is attributable only to efavirenz, since primate studies with other antiretroviral drugs are lacking. Teratogenic effects have not been observed with protease inhibitors in animal studies, with the exception of abortion and skeletal abnormalities associated with amprenavir in rabbits.

With regard to actual use of antiretroviral therapy in pregnancy, US databases on zidovudine use indicate the general absence of adverse effects. The PACTG 076 study in 477 women and 419 infants indicated that zidovudine treatment was associated with mild toxicity in the fetus and infant, consisting of mild transient anemia, with no adverse effects on growth parameters and no prematurity or congenital anomalies observed. In the combined databases from PACTG 076/219 and the WITS study including 727 children with zidovudine exposure, no tumors of any kind were observed over a mean follow-up of 38.3 months (1100 person-years). Follow-up of the PACTG 076/219 population for 5.6 years showed no adverse effects on weight, height, head circumference, or cognitive/developmental function, and no deaths or malignancies.

Data from France have included the disturbing occurrence of biopsy-proven mitochondrial dysfunction in 8 of 5000 children exposed to antiretroviral treatment (zidovudine or zidovudine/lamivudine) in utero, with 2 deaths occurring in children exposed to zidovudine/lamivudine. However, the combined experience of the WITS study, the PACTG, the Perinatal AIDS Collaborative Transmission Study (PACTS), and the Pediatric Surveys of Disease indicate no proven cases of mitochondrial dysfunction in 23,758 children with zidovudine exposure.

With regard to combination therapy, a Swiss study in 37 pregnant women receiving antiretroviral therapy, including 16 receiving a protease inhibitor, indicated that effects in women consisted of anemia in 15; elevated transaminases in 4; nausea/vomiting in 4; glucose intolerance in 2; nephrolithiasis in 2; diarrhea in 2; hypertension in 1; and insulin-requiring diabetes in 1. Adverse effects in 30 infants included a high rate of prematurity, with premature births occurring in 10 cases. Other adverse effects consisted of anemia in 8; cutaneous angioma in 2; cryptorchidism in 2; transient hepatitis in 1; intracerebral hemorrhage in 1; and extrahepatic biliary atresia in 1.

Dr. Cu-Uvin and colleagues recently performed a review of the effects of protease inhibitor-containing combination therapy during pregnancy in 89 women at 6 sites in the mainland United States and Puerto Rico; the data indicate no excess of prematurity. In these women, protease inhibitor use consisted of nelfinavir in 36, saquinavir in 33, indinavir in 23, and ritonavir in 5; concomitant use of nRTIs consisted of zidovudine/lamivudine in 65%, zidovudine/didanosine in 18%, and other combinations in 17%. Protease inhibitor treatment was initiated prior to conception in 18 women; at weeks 2.5 to 14 in 12; weeks 15 to 28 in 44; and weeks 29 to 37 in 14. Birth parameters in infants were normal (excluding a neonate who died at 22 weeks with a weight of 430 g); mean birth weight (n=86, including 3 sets
of twins) was 2934 g; mean height (n=78) was 48.6 cm; mean head circumference (n=71) was 33.4 cm; and mean Apgar scores (n=77) were 7.4/8.5 at 1 and 5 minutes. Adverse events in the infants consisted of anemia in 10 (none requiring transfusion); hyperbilirubinemia in 5; diarrhea in 3; neutropenia in 2; and phymosis in 2. The prematurity rate was 19.1%, comparable to prior reports of rates for HIV-infected women not receiving a protease inhibitor-containing therapy. Multiple regression analysis showed no differences in prematurity rate according to gestational age of initial protease inhibitor exposure, with only the use of cocaine and premature membrane rupture significantly associated with prematurity.

These data provide little guidance regarding when to initiate therapy or what type of therapy to initiate in pregnant HIV-infected women, particularly those in the first trimester of pregnancy. It should, nevertheless, be emphasized that pregnancy should not be viewed as a contraindication to antiretroviral treatment, and that standards of care applicable to nonpregnant HIV-infected patients should also be applied to pregnant patients. Based on assessment of disease status, some women not yet receiving antiretroviral therapy may consider delaying the initiation of therapy until after 10 to 12 weeks of gestation. For those already receiving antiretroviral therapy, if treatment is to be discontinued during the first trimester or for some other reason during pregnancy, all drugs should be stopped simultaneously to avoid the emergence of drug resistance.

**Short-Course Therapy**

Short-course antiretroviral therapy would appear to have a relatively minor role in the United States compared with that in developing countries; nevertheless, it may apply to cases within the 5% to 20% of women in the United States with no prenatal care as well as to those in whom HIV infection is identified late in pregnancy. A number of recent studies have demonstrated that short-course antiretroviral therapy is effective in preventing vertical transmission. In the Bangkok Perinatal Zidovudine Study, a regimen of zidovudine 300 mg twice daily from gestational age of 36 weeks and 300 mg every 3 hours during labor in nonbreastfeeding women resulted in an approximately 50% reduction in transmission rate from 18.6% with placebo to 9.2% with zidovudine. Use of this regimen in a breastfeeding population in the Ivory Coast resulted in a 37% reduction in transmission. In another study in the Ivory Coast/Burkina Faso in a breastfeeding population, the same regimen plus 1 week of postpartum zidovudine resulted in a 38% reduction in transmission.

In a study in a breastfeeding population in Uganda, a single dose of nevirapine 200 mg during labor plus an oral dose of 2 mg/kg in the infant within 72 hours of delivery were compared with a single dose of zidovudine 600 mg during labor plus 300 mg every 3 hours during labor and 4 mg/kg twice daily for 1 week in the infant. At postpartum day 3, transmission rates were 8.2% in the nevirapine group and 10.4% in the zidovudine group (P=0.354). Significant reductions in the nevirapine group, however, were observed at 6 to 8 weeks and 14 to 16 weeks. Transmission rates at these times were 11.9% (nevirapine) vs 21.3% (zidovudine) (P=0.0027) at 6 to 8 weeks and 13.1% (nevirapine) vs 25.1% (zidovudine) (P=0.0006) at 14 to 16 weeks.

The PETRA trial in South Africa, Tanzania, and Uganda, is a placebo-controlled comparison of the combination of zidovudine/lamivudine given (1) prepartum, intrapartum, and postpartum; (2) intrapartum and postpartum; and (3) intrapartum alone. Preliminary results indicate that compared with transmission in the placebo group, rates were reduced by 53% with the prepartum/intrapartum/postpartum regimen and by 38% with the intrapartum/postpartum regimen, with the intrapartum alone regimen exhibiting no preventive efficacy.

**Cesarean Section Delivery**

Delivery by elective cesarean section is associated with lower rates of transmission than with other modes of delivery, independent of zidovudine treatment during pregnancy and birth. The European Mode of Delivery Collaboration study showed a reduction in transmission rates from 10.2% with vaginal delivery to 3.5% with cesarean section (odds ratio, 0.4), consisting of a transmission rate of 2.4% in mothers having elective cesarean section (odds ratio, 0.3) and a transmission rate of 8.8% in those undergoing emergency cesarean section (odds ratio, 1.0). In a meta-analysis of 15 studies involving 8533 mother-child pairs, the International Perinatal HIV Group showed that the rate of transmission in elective cesarean section was 8.2% compared with 16.8% in vaginal delivery (adjusted odds ratio, 0.42) and 16.2% in nonelective cesarean section (adjusted odds ratio, 0.45). Transmission rates fell further with antiretroviral treatment; the study found a 2% transmission rate for elective cesarean section with monotherapy vs a 7.3% transmission rate for other modes of delivery plus monotherapy.

Data such as these have prompted the American College of Obstetrics and Gynecology to recommend elective cesarean section at 38 weeks along with zidovudine treatment for HIV-infected pregnant women. However, these recommendations are based on data predating the combination therapy era, and contain the caveat that transmission rates might be reduced so substantially by combination antiretroviral therapy that no additional benefit of elective cesarean section would be observed. As noted, current experience with combination therapy indicates that transmission rates may be reduced to 2% to 3%. Because the efficacy of cesarean section in women receiving combination therapy or in those with low viral load is unknown, it may be premature to implement widespread elective cesarean section in women receiving combination therapy. It must also be considered that in the context of what may be small or negligible additional benefit in prevention of transmission by elective cesarean section, the risks of postpartum morbidity and costs of operative delivery assume greater relative importance.

Dr Cu-Uvin is Assistant Professor of Obstetrics and Gynecology at Brown University School of Medicine in Providence, Rhode Island.
**Suggested Reading**


MANAGEMENT OF HIV/HEPATITIS C COINFECTION: TWO CASES

At the Los Angeles course in November, Francesca J. Torriani, MD, discussed 2 cases of hepatitis C in HIV-1-infected patients and provided information on general characteristics of coinfection that impact management decisions.

HIV-1/hepatitis C virus (HCV) coinfection is frequent because of common routes of transmission, although the parenteral route is predominant in HCV infection and the sexual route is predominant in HIV infection. Risk factors associated with HCV transmission include multiple sexual partners and low socioeconomic status. A retrospective analysis in Europe indicated that 50% to 60% of HCV-seropositive patients were HIV-seropositive, and that 56% of HIV-seropositive patients were HCV-seropositive. Estimated 1999 prevalence rates for the United States are approximately 4 million for HCV infection and approximately 1 million for HIV infection.

Several studies suggest that HCV/HIV coinfection is associated with increased morbidity and mortality. In a cross-sectional study of 547 patients in Spain with HIV infection, all of whom were injection drug users, 116 had HCV coinfection. About 15% of the subjects with HIV infection progressed to cirrhosis over a median duration of HCV infection of 6.9 years. Approximately 2.6% of those without HIV infection progressed to cirrhosis over a median duration of 23.2 years. Data from other studies indicate that cirrhosis is more frequent in patients who are coinfected than in those with HIV infection alone (33% vs 11%), and that mortality is higher in coinfected patients than in those with HIV infection alone (11% vs 6.8%). In addition, coinfection is associated with an increase in the rate of maternal-fetal HCV infection from 7% to more than 25%. A recently reported study in a hemophilia cohort indicated that coinfection was associated with a relative risk of progressive liver disease of 7.4 compared with HCV infection alone, and that progression to AIDS and death after liver failure was markedly higher in the coinfected patients.

Dr Torriani presented 2 patient cases that illustrate current clinical issues in the field.

CASE 1

Presentation

A man with HIV disease presented in March 1999 with a history of herpes zoster in 5/98 and Pneumocystis carinii pneumonia and HCV infection with elevated transaminases in 12/98. The patient denied use of injection drugs or ethanol, had felt better since beginning potent antiretroviral therapy, and was committed to treatment. On examination, the patient was HCV antibody-positive, had alanine aminotransferase (ALT) levels of 100 to 200 U/L, and normal prothrombin time/partial thromboplastin time (PT/PTT) and albumin. He was taking lamivudine/stavudine/nevirapine and had a CD4+ cell count of 300/μL, increased from a pretreatment level of less than 80/μL, and a plasma HIV RNA level below 400 copies/mL.

Diagnosis

Available tests for HCV include the recombinant immunoblot assay (RIBA), qualitative plasma HCV RNA, quantitative plasma HCV RNA, and HCV branch DNA assay. Although a quantitative HCV RNA test could be performed in this scenario, plasma HCV RNA level before treatment has not been demonstrated to be
predictive of outcome. It may be of greater importance initially to determine if the patient has replicating HCV by using a qualitative assay. In this case, a qualitative assay and branch DNA assay were performed. The patient had a positive polymerase chain reaction (PCR) for HCV and a branch DNA assay showed HCV RNA levels below 20 Meq/mL, indicating the presence of active replication but low viral load.

Additional tests to consider in this scenario include a liver panel, hepatic function panel, hepatic ultrasound, and other hepatitis virus serologies. Hepatic ultrasound would be useful at this point only in detecting hepatomegaly, but would be of use subsequently in guiding biopsy. All of these tests were performed for this patient. Hepatic synthesis tests were normal, other hepatitis virus serologies were negative, and the patient had a slightly enlarged liver on ultrasound (20 cm) with a normal size spleen.

**Management**

The patient’s course on antiretroviral therapy is shown in Figure 1. Due to elevated ALT, nevirapine was replaced in the initial regimen with abacavir. When ALT continued to increase, all therapy was stopped, with a subsequent decrease in ALT. The patient resumed treatment with lamivudine/stavudine/nelfiavir, with a subsequent increase in ALT. The ALT again normalized with treatment interruption, and the same antiretroviral regimen was reinstituted. The patient continued to show response to antiretroviral treatment and was unwilling to discontinue therapy even in the face of the asymptomatic increases in transaminases.

At this point, potential clinical approaches include stopping all antiretroviral treatment and beginning HCV treatment, continuing antiretroviral treatment and beginning HCV treatment, or continuing antiretroviral treatment and performing a liver biopsy to help determine whether treatment for HCV is indicated. Dr Torriani’s group elected to continue antiretroviral treatment and perform a liver biopsy. The patient had an asymptomatic rise in transaminases without associated liver dysfunction. The differential diagnosis was direct toxicity of antiretroviral treatment, or more probably, an increased immune reactivity to HCV.

**Discussion**

Since HCV infection is often asymptomatic until complications arise, and laboratory abnormalities are nonspecific, practitioners should have a low threshold for screening patients at risk. Second or third generation enzyme-linked immunosorbent assays (ELISAs) are sensitive, but the occurrence of false-negative results should prompt confirmation of the presence of replicating virus in plasma using an HCV RNA PCR. Once the diagnosis of chronic HCV has been established, staging and grading of hepatic disease should be performed. Transaminases and functional tests will be useful but not specific. To date, hepatic biopsy is the only valid prognostic tool available to determine if the HCV disease should be treated. Ultrasound is generally useful in guiding the biopsy. Management of coinfection with HIV and HCV requires knowledge of both infections, as well as of interactions of and toxicities due to HIV and HCV treatments.

**Presentation**

A 34-year-old HIV-infected man with a history of injection drug and ethanol use presented with persistent asymptomatic ALT elevations in the 160 to 282 U/L range, negative serologies for hepatitis B virus, and normal PT/PTT and albumin levels. On 2 occasions more than 2 years apart, the patient tested negative for HCV antibody. However, HCV RNA testing indicated a plasma level of greater than 1x10^6 copies/mL.

**Diagnosis**

A liver biopsy was performed in this patient. In the hands of an experienced practitioner, a liver biopsy poses a small risk of complications and provides results that can guide treatment decisions. The biopsy revealed fibrous expansion of portal areas, grade two-thirds portal inflammation, piecemeal necrosis, and activity in more than two thirds of lobules, yielding a Knodell score of 11. These

**Figure 2. Clinical course in case 2 patient.** ALK PHOSPH indicates alkaline phosphatase; ALT indicates alanine aminotransferase. 3TC indicates lamivudine; d4T, stavudine; ADV, adefovir; ABC, abacavir; EFV, efavirenz; NFV, nelfinavir. Courtesy of Dr Torriani.
TABLE 1. RESPONSE RATES IN STUDIES OF INTERFERON THERAPY IN HCV/HIV COINFECTION

<table>
<thead>
<tr>
<th></th>
<th>Response Rate at End of Treatment</th>
<th>Sustained Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyer et al, 1992</td>
<td>4/12</td>
<td>1/12</td>
</tr>
<tr>
<td>Orlando et al, 1993</td>
<td>5/12</td>
<td>1/12</td>
</tr>
<tr>
<td>Soriano et al, 1996</td>
<td>26/80</td>
<td>18/80</td>
</tr>
<tr>
<td>Mauss et al, 1998</td>
<td>8/17</td>
<td>5/17</td>
</tr>
<tr>
<td>TOTAL</td>
<td>54/150 (36%)</td>
<td>32/150 (21%)</td>
</tr>
</tbody>
</table>

Courtesy of S. Mauss, MD.

findings indicated that the patient was in need of treatment but was also less likely to respond to it.

Management

The patient’s course on antiretroviral therapy is shown in Figure 2. Initial treatment in June 1998 with lamivudine/stavudine/abacavir/efavirenz/nelfinavir resulted in rash attributed to nelfinavir, prompting discontinuation of the drug. (Note that rash is also a potential serious adverse effect of abacavir in cases of abacavir hypersensitivity; rechallenge should not be attempted due to association with life threatening toxicity and death.) The patient then developed elevated liver function tests while taking the 3-drug combination. Antiretroviral therapy was stopped despite decreased CD4+ cell count and a plasma HIV RNA level that had increased to nearly 1 x 10⁶ copies/mL. In June 1999 therapy was resumed with lamivudine/abacavir/nelfinavir/stavudine, but quickly stopped due to jaundice.

In this scenario, management options include electing to not resume antiretroviral treatment and starting HCV treatment, continuing antiretroviral therapy and starting HCV treatment, or electing to not resume antiretroviral treatment and waiting for a decrease in transaminases. Generally, in cases such as this one, Dr. Torriani has stopped antiretroviral therapy and waited for decreases in transaminase levels, or has attempted to continue antiretroviral therapy while initiating treatment for HCV infection. In this particular case, because all antiretroviral regimens were associated with elevations of transaminases and total bilirubin, it was decided to not resume antiretroviral therapy and to treat the HCV infection with interferon for 2 months. Potent antiretroviral therapy was then reintroduced with lamivudine/abacavir/nelfinavir/stavudine. The patient improved clinically, with control of HCV infection indicated by decreases in ALT and bilirubin levels.

This case highlights the need to use caution when selecting drug therapy for HIV/HCV coinfection. Protease inhibitors, particularly ritonavir and indinavir, have been associated with hepatotoxic effects. Nucleoside reverse transcriptase inhibitors have been associated with mitochondrial toxicity. The potential for interaction of ribavirin and zidovudine toxicities, particularly anemia, may be cause for concern. In addition, ribavirin reduces the level of the active form of zidovudine and there is evidence of a similar effect on stavudine, raising the possibility of decreased antiretroviral efficacy when these drugs are used together. Other hepatotoxic drugs that are used in coinfect patients include hydroxyurea and isoniazid and rifampin in those with tuberculosis.

Discussion

Much is to be learned about HCV treatment in coinfection. Interferon treatment in HIV-infected patients remains controversial. Initially, there were concerns that interferon might be less effective in HIV-infected patients and that higher dosages might be required for treatment. A number of small studies over the past several years suggest that responses to interferon monotherapy in coinfect patients are similar to those in non-HIV-infected patients, with pooled data indicating an end-of-treatment response rate of 36% and a sustained response rate of 21% (Table 1).

Available data indicate that responses to interferon monotherapy in coinfect patients are similar to those in patients without HIV infection.

Randomized studies of chronic HCV infection in HIV-negative patients have demonstrated that the combination of interferon and ribavirin for 24 or 48 weeks is associated with a 2- to 3-fold increase at end of treatment and sustained virologic and biochemical responses. Up to 43% of patients achieved a sustained virologic response regardless of genotype, plasma HCV RNA level, or presence of cirrhosis. There have been no completed
randomized studies of interferon/ribavirin combination therapy in HCV/HIV coinfection. Future studies will address the issues of efficacy, tolerability, and potential interactions between the reverse transcriptase inhibitors and ribavirin.

With regard to patient identification and selection for treatment, the most important initial steps are (1) identification of patients at risk for coinfection; (2) awareness that HCV serology may yield false-negative results; (3) confirmation of the presence of active replication by HCV RNA assay; (4) staging and grading of both HCV and HIV disease; (5) ruling out of other viral hepatitis; and (6) ruling out of contraindications to interferon or ribavirin treatment.

With regard to potential outcomes of HCV treatment, patients with a low risk/benefit ratio are those with higher CD4+ cell counts (ie, >200/µL), no alcohol abuse, and low to moderate hepatic inflammation or fibrosis; those with a high risk/benefit ratio include patients with uncontrolled or advanced HIV infection and those with liver failure. It is hoped that the next generation of coinfection studies will help to answer questions regarding which patients to treat and when to treat. For example, it remains unclear whether antiretroviral-naive patients should receive treatment for HIV or HCV infection first, or receive treatment for both simultaneously. In the case of antiretroviral-experienced patients, optimal strategies for controlling HIV, containing with antiretroviral failure, and addressing hepatotoxicity remain undefined.

PEGylated interferon may improve tolerance and antiviral effect by avoiding high peak and low trough drug concentrations

It is also hoped that more potent and less toxic treatments for HCV infection can be developed. One potential advance in this regard is the development of interferon to which a polyethylene glycol (PEG) moiety has been added to prolong half-life. Once-weekly PEGylated interferon achieves sustained elevated drug levels, avoiding the high peak levels and low trough levels characteristic of daily standard interferon that may result in toxicity and decreased antiviral effect.

Treatment with PEGylated interferon is to be evaluated in the Pegasys HIV/HCV Coinfection Trial, the first multinational, large-scale, randomized trial in patients with coinfection. In this trial, a projected total of 740 patients will be randomized to once-weekly PEGylated interferon, PEGylated interferon/ribavirin, or thrice-weekly standard interferon alfa 2a/ribavirin. Patients will be tested for response after 12 months of treatment and for sustained response 6 months after discontinuation of treatment. Eligible patients will be those with HCV RNA above 1000 copies/mL, ALT above the limit of normal on 2 occasions, and compensated liver disease; CD4+ counts of above 200 cells/µL or of 100 to 200 cells/µL; and plasma HIV RNA below 5000 copies/mL, with HCV disease proven by biopsy within the past year. Stable antiretroviral therapy for at least 6 weeks is requested prior to enrollment; if no antiretroviral treatment is in place, patients will be requested not to start antiretrovirals for the initial 6 weeks of the study. Intensive monitoring of CD4+ cell count, plasma HIV RNA, and plasma HCV RNA will be performed. Pharmacokinetic studies for the possible interaction between nRTIs and ribavirin as well as intensive viral dynamics studies will be performed at selected sites. The trial is expected to set new standards for treatment of coinfected patients.

Dr Torriani is Assistant Adjunct Professor of Medicine, Division of Infectious Diseases, at the University of California San Diego.

SUGGESTED READING


(Continued)
SUGGESTED READING (CONTINUED)


ANNOUNCING THE SECOND ANNUAL COURSE

THE SCIENCE AND TREATMENT OF HIV

March 25–March 29, 2000
Snowmass Village, Colorado

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The International AIDS Society–USA designates this educational activity for a maximum of 16 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

THE SCIENCE AND TREATMENT OF HIV

AN ADVANCED CME COURSE FOR CLINICIANS

March 25 - 29, 2000
Snowmass Village, Colorado

SECOND ANNUAL COURSE

Snowmass Village is 200 miles west of Denver and 10 miles from Aspen, Colorado. The area features world-class skiing, with a choice of 4 outstanding slopes—Snowmass, Aspen Mountain, Buttermilk, and Aspen Highlands. Other exciting activities in Aspen and Snowmass include snowshoeing, dogsledding, ice skating, hot air balloon rides, cross-country skiing, sleighrides, and shopping. All meeting activities will take place at the Silvertree Hotel.

THIS COURSE WILL COVER

- The basic biology and pathogenesis of HIV infection; host and viral perspectives
- Strategies for effective long-term use of antiretroviral treatments, including
  - New drugs and combinations
  - New monitoring tools (including resistance testing)
  - Complications of HIV disease and its treatments
- Viral resistance issues

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Registration brochures are now available.

To receive more information on CME credits, agenda, and registration, please contact:

International AIDS Society–USA
Presidio of San Francisco
1001 B O'Reilly Ave., PO Box 22916
San Francisco, CA 94129-0916

Symposium Voice Mail: (415) 561-6725
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Fax: (415) 561-6740
E-mail: cme@iasusa.org
Web site: www.iasusa.org

IMPROVING THE MANAGEMENT OF HIV DISEASE
REGISTRATION
Registration is open to physicians and active health care providers only.
To preregister for this conference, please complete the attached registration form and send it with payment to the address/fax number listed on the form. If you are using a credit card for payment, you may register by either fax or mail; registrations that include checks or money orders must be mailed. Incomplete applications will not be processed and will be returned for completion. You will receive a letter confirming your registration along with more detailed information on the agenda and location of the course.

Registrations received on or before:
February 17, 2000 .............................................. $425
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February 17, 2000 .............................................. $525

On-site registration will be allowed, space permitting. Please call the IAS–USA for information on registration transfer, cancellation, and refund policies.
The course fee includes attendance at the course, a course syllabus, daily continental breakfast, afternoon snacks, and opening night reception for the course attendees.

Representatives and employees of commercial companies (pharmaceutical, diagnostic, medical product, advertising, insurance, investment, or communications firms) must contact the International AIDS Society–USA regarding registration.

ACCOMMODATIONS
LODGING AND AIR TRAVEL
Accommodations are available at the Silvertree Hotel and Wildwood Lodge. The Silvertree Hotel is a ski-in/ski-out resort, while Wildwood Lodge is only 50 yards from the ski lifts. The International AIDS Society–USA has reserved a block of single and double rooms for this course.

The Silvertree Hotel, deluxe single or double .................. $180 per night
The Wildwood Lodge, superior single or double .......... $105 per night

Other types of accommodations, including condominiums, can be reserved through the hotel reservation department on a space-available basis.

 Lodging, air travel, and ground transportation reservations can be made by calling 800-766-9627 (800-SNOWMASS) or 970-923-2010. Please request a reservation with the "International AIDS Society–USA Meeting."

COURSE REGISTRATION
The Science and Treatment of HIV
An Advanced CME Course for Clinicians
Saturday, March 25–Wednesday, March 29, 2000, Snowmass Village, Colorado

PLEASE TYPE OR PRINT CLEARLY. Full payment must accompany this form and all information must be provided. For additional registrants, please photocopy this form.

Name: __________________________________________
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Currently, for how many HIV-infected patients are you providing care? __________________________
What proportion of your patients are HIV infected? _________% _________
Do you work for a commercial company? (If yes, you must call the IAS–USA prior to registering).
☐ YES ☐ NO

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VOLUME 7, DECEMBER 1999
Cases on the Web

An ongoing series of case-based, advanced online CME activities from the International AIDS Society-USA on HIV InSite

CASE TOPICS

Resistance Testing in Antiretroviral Management
by Michael S. Saag, MD
Guest Editor: Daniel R. Kuritzkes, MD

Still Available to January 31, 2000
Clinical Management Issues in Antiretroviral-Experienced Patients
by Paul A. Volberding, MD
University of California San Francisco

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ACKNOWLEDGMENTS

The International AIDS Society–USA gratefully acknowledges our funders, faculty members, contributors, and other individuals for their significant contributions to IAS–USA programs in 1999 and their continued support of our mission: to improve the treatment, care, and quality of life of persons with HIV and AIDS through balanced, relevant, innovative, and state-of-the art physician education.

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The International AIDS Society–USA CME course programs are made possible through unrestricted educational grant support from commercial companies committed to supporting CME in the field of HIV and AIDS. In the interest of objective, balanced, and scientifically rigorous programs, the International AIDS Society–USA seeks funding from companies with competing products; these companies have no input or control over program content or selection of faculty. We are grateful for the support of the following companies:

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We appreciate the ongoing donation of QuarkXPress software from the Gill Foundation, and the gift of software from Adobe Systems Incorporated.

PROFESSIONAL SERVICES

Our thanks to Larry Duling of Golden Street Printing, Mohammed Ismail of BPS Reprographic Services, and Dorian Tran of QQ Printing for printing; Christine Hunter of Hunter Direct Marketing and Ron Norlin of American Business Communications for mailing services; and Craig High, Diana Voigts, Mary Birchler, Diana DeFrancesco, Brigitte Niquette, and Kurt Bigenho for art design and production.

Additional thanks to Steven Akers for transcription services; Trish Nichol of TMB Enterprises for course evaluation expertise; Múfrida Bell and David Sweet for copy editing and proofreading work; Matthew Stenger, Greg Szekeres, and Leslie Hanna for medical writing; Steve Conrad for ARS work; and Jane Garrison, Karen Gilbert, and Mel Watson for their ongoing assistance.

We appreciate Rachel Moreaux and Lori Lee for their computer expertise, and Nicolé Mandel for her work on Cases on the Web.

Finally, we are grateful for our full-time and part-time staff: Marisha Beall, Amanda Beacom, Misako Hill, Damien Miller, Gina Rodriguez, Renée Skeels, Edna Stoehr, Demia Sunda, Michelle Tayag, Geoff Volarza, Phillip Watson, James Williams, and Michael Chiu.
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Hyatt Regency Chicago
Early Registration Fee: $25.00

San Francisco, CA
The Ritz-Carlton San Francisco
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Friday, February 11, 2000
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Saturday, February 26, 2000
Chairs: Ronald T. Mitsuyasu, MD, and Paul A. Volberding, MD

Wednesday, March 8, 2000
Chairs: Martin S. Hirsch, MD, and Robert T. Schooley, MD

Wednesday, March 22, 2000
Chairs: Gerald H. Friedland, MD, and Paul A. Volberding, MD

Wednesday, April 19, 2000
Chairs: John P. Phair, MD, and Harold A. Kessler, MD

Tuesday, April 25, 2000
Chairs: Paul A. Volberding, MD, and Stephen E. Follansbee, MD

May 2000
Exact dates and locations to be announced.

For information about any of the courses, please contact the International AIDS Society–USA

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