

# Topics in HIV Medicine®

A publication of the International AIDS Society–USA

## Perspectives

Making Sense of the HIV Immune Response 4

*Paul A. Goepfert, MD*

*Basics of HIV Infection • The Antibody Response • Cell-Mediated Immunity • Recent Findings in HIV Immunology • A Model of HIV Immunopathogenesis*

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Bone Disorders, Hypertension, and Mitochondrial Toxicity in HIV Disease 10

*Meg D. Newman, MD*

*Osteonecrosis Risk Factors, Diagnosis, and Treatment • Osteopenia and Osteoporosis • Managing Hypertension in HIV Patients • Lactic Acidosis During Antiretroviral Therapy*

---

HIV and Hepatitis B Virus: Options for Managing Coinfection 16

*Douglas T. Dieterich, MD*

*Characteristics of Hepatitis B in Coinfection • Options for Initial Treatment • Lamivudine Resistance • Symptomatic Hyperlactatemia and Activity of Tenofovir • New Drugs in Development*

---

Substance Abuse and HIV Infection 20

*Henry Francis, MD*

*Defining Substance Abusers • Medical and Psychiatric Comorbidities • HIV Infection Among Drug Users • Treating Substance Abuse Through a Global Approach • Drug Information Resources*

---

## Review

Use of Club Drugs by HIV-Seropositive and HIV-Seronegative Gay and Bisexual Men 25

*Frank Romanelli, PharmD, BCPS, Kelly M. Smith, PharmD, and Claire Pomeroy, MD*

*Prevalence of Club-Drug Use • Associated High-Risk Sexual Behaviors • Interactions With Antiretroviral Drugs and Immune Function • Clinical Effects of Common Club Drugs: MDMA, GHB, and Ketamine*

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We also are pleased to announce a new 8-member editorial board established to further improve the quality of the journal. For a list of members, please see page 3.

This first issue of the new year begins with a review of the HIV immune response and tools for its assessment. The other 4 articles in this issue examine complications and comorbidities in HIV infection: bone disorders, hypertension, and mitochondrial toxicity; hepatitis B virus infection; and substance abuse and addiction. In the final article, Romanelli and colleagues focus on use of “club” drugs such as methylenedioxymethamphetamine (MDMA), gamma hydroxybutyrate (GHB), and ketamine, reviewing their association with high-risk sexual behavior and their effects in HIV-infected individuals.

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## Announcements

Metabolic Complications Recommendations 9  
Correction 32  
Guidelines for Authors and Contributors 33  
Subscription Request 34  
Educational Programs of the International AIDS Society–USA 35

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## Perspective

# Making Sense of the HIV Immune Response

*A considerable amount of new information on HIV immunology has been generated over the past several years using novel techniques designed to assess HIV-specific immune responses. An understanding of the basic mechanisms involved in immune response and of these novel assessment techniques can aid the clinician in interpreting the literature in the area and considering the potential impact of new findings on clinical practice. Paul A. Goepfert, MD, provided an overview of HIV immunology at the Clinical Pathway of the Ryan White CARE Act 2002 All Grantee Conference held in Washington, DC, in August 2002.*

Important advances in techniques designed to examine the immune response have allowed investigators to study HIV-specific immune responses in ways that were impossible only a few years ago. As a result, there has been a tremendous increase in the understanding of HIV immunopathogenesis, and clinically relevant findings from this research are becoming much more common. A basic understanding of applied immunology facilitates interpretation of new findings and their implications for clinical practice.

There are 3 basic levels of human defense against infections: surface barriers, innate defenses, and adaptive (or acquired) responses. This discussion focuses on adaptive responses, since most of the recent notable studies concerning HIV immunopathogenesis have provided information on this aspect of response.

When a viral pathogen such as HIV infects a cell, the host responds with both B-cell (humoral) and T-cell (cell-mediated) immune mechanisms. A sub-

set of the T cells, known as CD4+ or helper T cells, can be viewed as the orchestrators of the adaptive immune responses. The CD4+ T cells recognize foreign antigens bound to host proteins

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Most of the recent notable studies of HIV immunopathogenesis have focused on adaptive responses to infection

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and aid B cells (eg, through production of various cytokines) in the production of antibodies. These antibodies have the potential to neutralize cell-free virus, thereby preventing subsequent viral infection of target cells in the body. They also participate in the lysis of infected cells by recruiting natural killer (NK) cells in a process termed antibody-dependent cell-mediated cytotoxicity. CD4+ T cells also aid in the stimulation and recruitment of another subset of T cells, the CD8+ T cells (eg, through production of cytokines). These CD8+ T cells, commonly referred to as cytotoxic T lymphocytes or CTLs, are able to target and lyse virally infected cells by recognizing foreign antigens bound by host proteins. Given that CD4+ T cells play a central role in the host response to pathogens and that infection of these cells by HIV leads to their destruction, it is easy to envision how HIV might destroy the immune system over time. Nevertheless, the exact details of this process are being elucidated in ongoing studies throughout the world.

## Antibody Response

Anti-HIV antibodies have been of particular interest, given the potential for this arm of the immune system to be exploited in the development of an effective HIV vaccine. As noted, antibodies are able to bind cell-free virus and potentially prevent established infection in the challenged host. Such prevention seems ideal in combating HIV, which establishes a lifelong presence after initial infection. The hypothesis that inducing antibody response to HIV might permit effective vaccination is supported by 2 findings: (1) that the ability to induce antibody response is correlated with the efficacy of all commercially licensed vaccines (eg, those for measles, mumps, and rubella); and (2) that anti-HIV antibodies are protective against HIV infection in passive transfer experiments in nonhuman primates (see below). Optimism for attempts to develop anti-HIV vaccines that induce antibody response, however, is tempered by the fact that most effective vaccines prevent disease rather than the establishment of infection. Another caveat is that the correlation of antibody response with vaccine efficacy does not demonstrate a causal relationship between antibody response and prevention of infection or disease.

Although the presence of HIV-specific antibodies can be routinely detected by their ability to bind to proteins, it is generally believed that those antibodies that neutralize HIV—that is, neutralizing antibodies—are needed for an effective vaccine. Thus, studies in this area have focused on measuring neutralizing antibody responses. The basic neutralizing antibody assay is performed by mixing an HIV isolate with antibodies (usually in the form of serum; Figure 1). The excess, unbound antibodies are then washed off and the viral isolate is incubated with peripheral blood mononuclear cells (PBMCs). After a period of time in culture (about 5 days), the amount of

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virus growth is calculated by measuring the amount of HIV p24 antigen. By comparing the amounts of viral growth with and without antibodies, the percent neutralization can be calculated.

In animal experiments, a particular strain of virus or components of the virus that induce neutralizing antibody responses can be used as a vaccine to stimulate antibody response in vivo. Numerous passive transfer experiments have shown that when the serum of an immunized animal (which includes the elicited antibodies) is transferred to another animal, the latter animal is protected against a viral challenge when that challenge consists of a viral isolate that is identical to that used in the vaccine. Unfortunately, these studies have shown that when the same animal is challenged with a strain of virus that is different from the vaccine strain, no protection against infection is conferred. Most anti-HIV vaccines evaluated to date in both human and nonhuman investigations have thus only been able to induce antibody that neutralizes viruses very similar to the vaccine strain.

The significance of this problem is evident when the tremendous genetic diversity of HIV is considered—both among the range of virus types known to infect humans throughout the world and as reflected in genetic variants within a particular infected individual. For example, among the clade-B HIV-1 subtype prevalent in infections in the United States, there is a 30% genetic divergence among viral variants that can be reflected in the viral components targeted by the antibodies. In other parts of the world, a number of other clades of virus exhibit even greater genetic heterogeneity. Also, antibodies produced in response to vaccination fail to neutralize primary HIV isolates—that is, virus isolated from an infected individual. Despite these obstacles, various groups are attempting to design vaccines with the ability to neutralize a broad range of primary HIV isolates.

### Cell-Mediated Immunity

Unlike antibody responses, which are generated in response to a foreign antigen alone, cell-mediated immune responses require that the T cells be presented with foreign antigen bound to

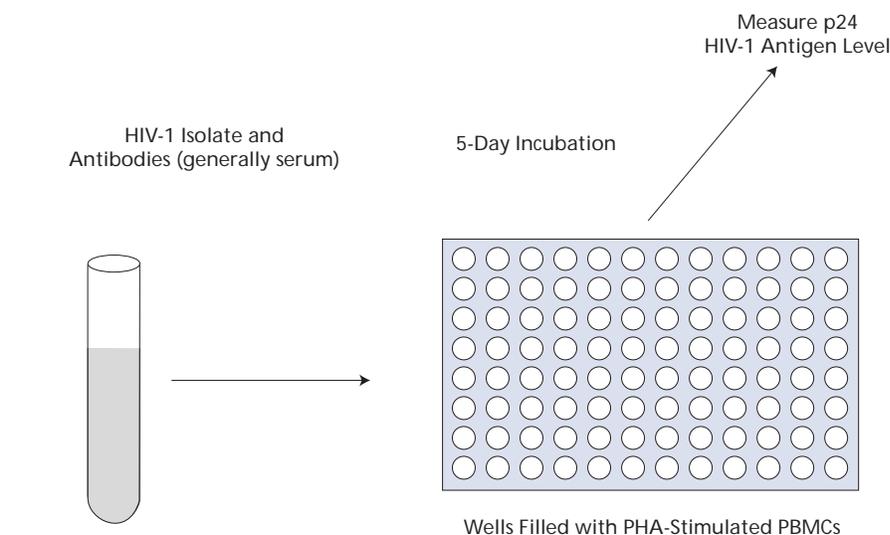


Figure 1. General schema for neutralizing antibody assay. The amount of virus growth is calculated by the amount of p24 antigen, and the percent neutralization, in turn, is calculated by comparing the amounts of virus growth with and without antibodies. PBMCs indicates peripheral blood mononuclear cells; PHA indicates phytohemagglutinin, a reagent used to stimulate T cells nonspecifically.

host proteins. These host proteins are known as the major histocompatibility complexes (MHCs), or human leukocyte antigens (HLAs). CD8+ T cells recognize foreign peptides of about 9 to 11 amino acids in length bound to MHC class I molecules, and CD4+ T cells recognize peptides of 11 to 20 amino acids in length bound to MHC class II molecules. MHC class I proteins are present on most human cell types, and they generally bind only those peptides that are synthesized within the cell itself. MHC class II proteins are found only on antigen-presenting cells, such as macrophages, dendritic cells, or lymphocytes. These cells are able to endocytose and process exogenous proteins into smaller peptides that are subsequently bound to class II molecules for presentation to and recognition by a CD4+ T cell. Therefore, as a general rule, CD8+ T cells respond to foreign antigens synthesized within a cell (ie, requiring infection of that cell), while CD4+ T cells respond to antigens encountered outside of the cell. Since viral infections feature both endogenous and exogenous antigens, both CD8+ and CD4+ T cell responses are elicited.

In the past, the measurement of cell-mediated immune responses has relied on the capacity of cells to proliferate and function in vitro. CD4+ T cells have been

measured by stimulating PBMCs with a desired protein (such as HIV p24) and leaving them in culture for several days (Figure 2). The cells are then placed in the presence of tritiated thymidine, and cellular proliferation is measured by the amount of incorporated thymidine. CD8+ T cell function is measured by mixing PBMCs with cells that have been infected with HIV or recombinant viruses that express HIV proteins (such as recombinant vaccinia viruses). The target cells are then radiolabeled with chromium. The amount of chromium released from the labeled cells is calculated and serves as a measure of the amount of cell lysis that occurs via activity of the CD8+ T cells.

In recent years, a more direct and easier method has been developed to measure both CD4+ and CD8+ T-cell responses. This assay relies on the detection of antigen-specific cytokine production by T cells. Both CD4+ and CD8+ T cells secrete interferon- $\gamma$  (IFN- $\gamma$ ) in response to antigen-specific stimulation. In addition, both of these types of T lymphocytes are stimulated with peptides of 15 to 20 amino acids in length. Peptides (15-20 amino acids in length overlapping by 10-11 amino acids) are therefore used to stimulate PBMCs. These peptides are generally pooled to represent the various HIV proteins (Gag,

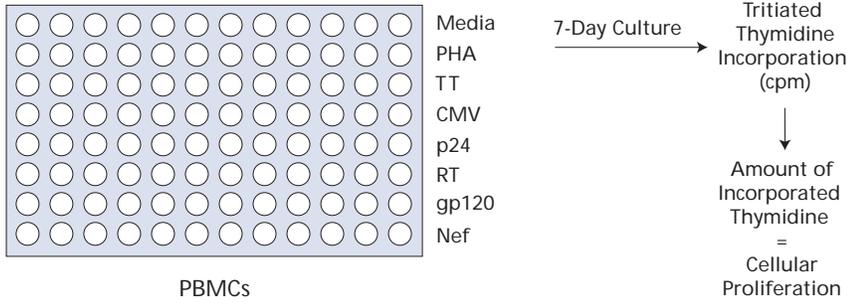


Figure 2. General schema for lymphoproliferative assay to measure CD4+ T cells. CMV indicates cytomegalovirus; PHA, phytohemagglutinin; PBMCs, peripheral blood mononuclear cells; RT, reverse transcriptase; TT, tetanus toxoid.

Pol, Env, etc), and positive responses can subsequently be determined down to the specific 15-to-20 amino acid peptide.

The detection of cytokine production is performed using a variety of methods: currently, the most common are the enzyme-linked immunospot (ELISPOT) assay and the intracellular cytokine staining (ICS) assay. The ELISPOT assay (Figure 3) detects the amount of IFN- $\gamma$  secretion per cell represented as spots on a plate. These spots are then counted manually or with an automated counter. This assay generally does not discriminate as to whether the responses are due to CD4+ or CD8+ T cells and relies on a separate test to deplete either or both of these T-cell types to determine the cellular phenotype of the response. The ICS assay uses anti-IFN- $\gamma$  antibodies conjugated to a fluorescence marker to detect intracellular production of this cytokine, and the staining of the IFN- $\gamma$  is analyzed using a flow cytometer. Since the CD4+ and CD8+ T cells can be separately stained using individual antibodies conjugated with different fluorescence markers, the cell type responsible for the secretion of IFN- $\gamma$  can be determined in the same test.

Another way to detect the presence of antigen-specific CD8+ T cells is by using a reagent known as a tetramer. The tetramer itself is synthesized by taking an MHC class I heavy chain and folding it with beta-2 microglobulin ( $\beta_2m$ ) in addition to the foreign peptide of interest. This complex is then bound to a streptavidin molecule through a biotinylation site engineered into the MHC class I/ $\beta_2m$ /peptide complex. The tetramer reagent derives its name from the fact

that it consists of 4 of these molecular complexes bound to the tetravalent streptavidin molecule, which is subsequently conjugated to a fluorescence marker. This tetramer can then be used to bind and identify a specific type of CD8+ T cell.

The tetramer will bind only CD8+ T cells that are restricted by both the MHC class I and the foreign peptide that was engineered into the tetramer. Therefore, although the tetramer reagent is extremely specific and will detect only 1 type of HIV-specific CD8+ T cell, it can be used to readily and easily detect the presence of these specific CD8+ T cells. The tetramer assay cannot detect the function of a cell. However, when it is combined with assays such as the ELISPOT or the ICS assay, which detect the production of cytokines, it is possi-

ble to detect both the presence and function of specific CD8+ T cells (Figure 4). Similar tetramer reagents are also being produced that have the capacity to detect specific CD4+ T cell responses, but these assays are not nearly as far along in development as the tetramer assays to detect CD8+ T cell responses.

## Recent Findings in HIV Immunology

A number of recent findings have contributed to our understanding of HIV immunology and posed additional questions. For example, Schmitz and colleagues (*Science*, 1999) were interested in determining which HIV-related immune responses controlled viral replication. The investigators used an anti-CD8+ antibody to deplete the CD8+ T cells of rhesus macaque monkeys chronically infected with simian immunodeficiency virus (SIV). Prior to the depletion of CD8+ T cells, SIV replication was well-controlled in all of the monkeys. However, after the depletion of the CD8+ T cells, control of viral replication was lost. In some of these monkeys, the CD8+ T cells actually regenerated and, when they did, control of viral replication was regained. This study and others like it clearly show that the SIV-specific CD8+ T cells play an important role in controlling viral replication. Since SIV infection is a good model for HIV pathogenesis, such findings suggest

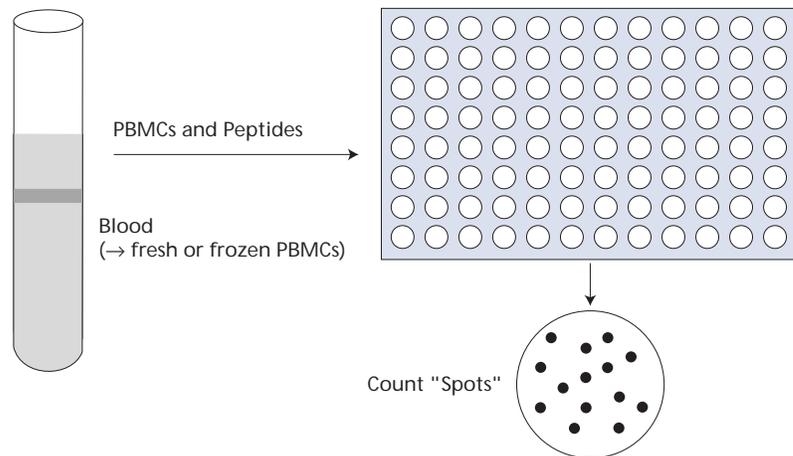


Figure 3. General schema for interferon- $\gamma$  enzyme-linked immunospot (ELISPOT) assay. PBMCs indicates peripheral blood mononuclear cells.

that CD8+ T cells play a similar role in controlling viral replication in HIV infection. Additional studies demonstrating a temporal relationship between HIV-specific CD8+ T cells and control of viral replication in humans support this suggestion.

Given the important role that CD8+ T cells play in controlling viral replication, many investigators have attempted to develop vaccines that elicit HIV-specific CD8+ T-cell responses. Several groups have used SIV vaccines as a model for HIV vaccine development. Amara and colleagues (*Science*, 2001) observed a high level of SIV Gag-specific T-cell responses when monkeys were immunized with a DNA vaccine that encodes SIV-specific proteins followed by a recombinant modified vaccinia Ankara (rMVA) virus that encodes the same SIV-specific proteins. These monkeys were then challenged with SIV at 27 weeks after their vaccine boost. Although all of the monkeys became infected, the monkeys that received the SIV-specific vaccines exhibited control of viral replication and preservation of CD4+ T-cell counts. Monkeys that did not receive vaccine had high levels of viral replication and a precipitous drop in their CD4+ T-cell counts after SIV challenge. These and similar findings have encouraged hope for the development of a vaccine that elicits CD8+ T-cell responses. Although these vaccines may not protect against infection, they may protect against disease progression by controlling viral replication. HIV-infected individuals with controlled viral replication may also be at lower risk of subsequently transmitting the virus.

Another important study that focused on the immune responses to HIV was performed by Rosenberg and colleagues (*Nature*, 2000). These investigators had observed that HIV-specific CD4+ T-cell responses as measured by a lymphoproliferative assay were of high magnitude in individuals who were HIV-infected but did not exhibit progressive disease over long-term follow-up (long-term nonprogressors, LTNPs). These lymphoproliferative responses were not generally detectable in patients with chronic progressive infections. The investigators theorized that one reason virus was controlled in the LTNPs was that HIV-specific CD4+ T-cell responses

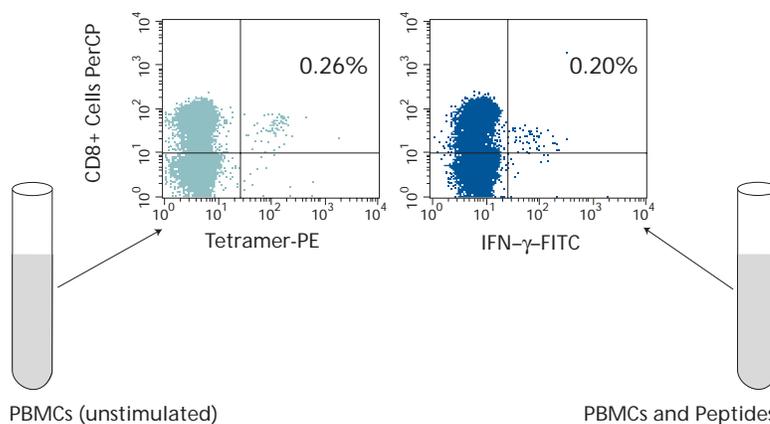


Figure 4. Tetramer assay showing that 0.26% of CD8+ T cells are specific for a peptide used in the assay (left) and stimulation of CD8+ T cells with the same peptide showing that most of these cells are functioning (right) as indicated by IFN-γ production. PerCP indicates peridinin chlorophyll markers; PE, phycoerythrin; FITC, fluorescein isothiocyanate (all types of fluorescence markers).

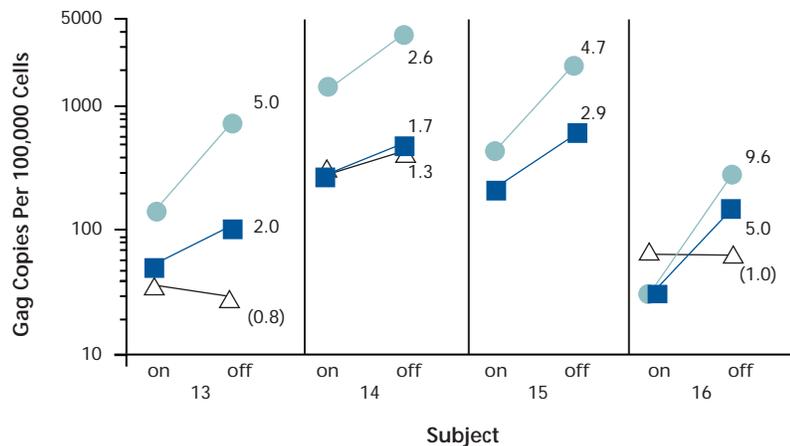
were preserved. They also believed that these CD4+ T-cell responses would be present in a person with acute viral infection but would diminish shortly thereafter.

The authors subsequently demonstrated that individuals identified with acute HIV infection who also began potent antiretroviral therapy had very high lymphoproliferative responses, the magnitude of which was comparable to that seen in LTNPs. When potent antiretroviral therapy was discontinued in these patients after at least 6 months of therapy, 3 of 8 patients exhibited control of viral replication (plasma HIV-1 RNA level <5000 copies/mL), and 4 of the 5 remaining patients exhibited control of viral replication after further rounds of starting and stopping antiretroviral therapy. It is important to note the limitations of this study, including the fact that it involved only a limited number of patients who were followed for short periods of time after treatment interruption. Much more work is needed in this area before firm conclusions can be made.

Another important limitation of the study by Rosenberg and colleagues is that the results have not been replicated in patients with chronic infection, as observed in numerous clinical trials. Additionally, there is no consistent evidence that immune responses are enhanced in chronically infected patients who undergo strategic treatment

interruptions (STIs). It is possible that STIs do not work in chronically infected individuals because these individuals have already lost their HIV-specific CD4+ T-cell responses. Rosenberg and colleagues hypothesized that HIV-specific CD4+ T cells may be preferentially infected and killed in early HIV infection. Therefore, although the absolute CD4+ T-cell counts may be relatively preserved after acute infection, the HIV-specific T cells are actually significantly depleted.

More recently, Douek and colleagues (*Nature*, 2002) reported findings consistent with the hypothesis proposed by the Rosenberg group. These investigators stimulated PBMCs with HIV-specific proteins or with proteins specific to cytomegalovirus (CMV), a well-controlled but chronic viral infection. They evaluated the secretion of IFN-γ and sorted the CD4+ T cells that secreted IFN-γ in response to the virus-specific antigens using a fluorescence-activated cell sorter. The sorted cells were then tested for the presence of HIV-specific DNA. These elegant studies showed that HIV-specific CD4+ T cells contain greater amounts of HIV-specific DNA and hence have a greater amount of HIV infection than do memory phenotype CD4+ T cells or CMV-specific CD4+ T cells. These differences were further enhanced when samples from patients who experienced a rapid viral rebound after undergoing an STI were evaluated (Figure 5). These studies therefore demonstrate that



**Figure 5.** Viral DNA in HIV-specific CD4+ T cells (green circles), memory (CD45RO+) CD4+ T cells (blue squares), and cytomegalovirus-specific CD4+ T cells (white triangles) of infected subjects on and off antiretroviral therapy, showing preferential infection of HIV-specific CD4+ T cells after stopping potent antiretroviral therapy. The magnitude of change in viral DNA is shown. Adapted with permission from Douek et al, *Nature*, 2002.

although STIs can be beneficial in patients with acute infection if viral replication is controlled, HIV-specific CD4+ T cells may be sacrificed very quickly in individuals who do not maintain control of viral replication following STI. The latter situation may be particularly relevant in chronically infected patients.

### Model of HIV Immunopathogenesis

In summary, a variety of data demonstrate that both CD4+ and CD8+ T cells are extremely important in controlling HIV infection. Preventive vaccines are now being designed to elicit HIV-specific CD8+ T cells in the hope of preventing disease progression. In a small number of individuals who began treatment shortly after acute HIV infection, HIV-specific CD4+ T-cell responses were preserved. In addition, these CD4+ T-cell responses seem to be important in controlling viral replication after subsequent discontinuation of antiretroviral therapy. However, it has also been found that when discontinuation of antiretroviral therapy leads to loss of virologic control, HIV-specific CD4+ T cells are preferentially infected and depleted when compared with the CD4+ T cells of other antigen specificities.

Based on this and other information, a model of HIV immunopathogenesis

based on virus-specific immunology can be hypothesized. In this model, an individual is infected with HIV, and CD8+ T cells with the specific help of CD4+ T cells are able to efficiently neutralize the virus infecting the CD4+ T cells. However, it is now quite clear that the virus rapidly mutates, with mutants that reduce recognition by CD8+ T cells being favored in the context of the selective pressure from CD8+ T cell activity. The mutated proteins or other HIV proteins can still subsequently serve as targets for CD8+ T cells. However, the CD8+ T cells are now acting without the presence of CD4+ T cells, because these HIV-specific CD4+ T cells have been lost as a direct consequence of infection. This presumably allows disease progression to occur; in the absence of antiretroviral therapy, CD4+ T cells are gradually depleted and CD8+ T-cell response is lost, with the infected individual ultimately developing clinical disease.

It must be noted that this model is not fixed, reflects the author's own hypothesis, and in fact is controversial in the field of HIV research. It undoubtedly will change and be reshaped with future experiments. In addition, all of the information gleaned from study in this area will enhance our understanding of HIV immunopathogenesis and lead to improved strategies in preventing and treating HIV disease.

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## IAS–USA Recommendations for Management of Metabolic Complications in HIV-1 Infection. Schambelan M, Benson CA, Carr A, et al. *JAIDS*. 2002.

Antiretroviral therapy has substantially reduced mortality for HIV-1-infected patients. However, an increasing number of adverse metabolic effects associated with such treatment are emerging. The mechanisms underlying these complications and their relationship to specific antiretroviral drugs remain unclear, and definitive data on managing metabolic effects are scarce. Nevertheless, the potential long-term risks and effects on quality of life are concerning to HIV clinicians and their patients.

In light of these concerns, the International AIDS Society–USA appointed a 12-member panel representing international expertise in HIV-1 patient care, antiretroviral therapy, and endocrine and metabolic disorders. The panel reviewed relevant data and developed recommendations for the clinical management of metabolic complications associated with antiretroviral therapy and HIV disease itself. Recommendations were developed by group consensus with emphasis on results of prospective, randomized, controlled trials in

HIV-1-infected patients where possible, although such data are scant at this time. The panel also considered expert opinion and data from ongoing trials, epidemiologic studies, laboratory-based investigations, and studies of similar complications in individuals without HIV-1 infection.

The IAS–USA panel concludes that controlled studies to determine the incidence, cause, risk factors, and most appropriate treatments for metabolic complications in HIV-1 infection are urgently needed. The recommendations are published in the November 1, 2002, issue of the *Journal of Acquired Immune Deficiency Syndromes*. The full text of the article is available online at [www.iasusa.org/pub/metcomp.html](http://www.iasusa.org/pub/metcomp.html) for a limited time or may be accessed on the *JAIDS* Web site ([www.jaids.com](http://www.jaids.com)) with a *JAIDS* subscription or pay-per-view fee.

The recommendations address diagnostic assessment, monitoring, and treatment for 5 areas.

### Glucose Intolerance and Diabetes Mellitus

- **Assessment and Monitoring:** Assess fasting glucose before initiation of or switch to a protease inhibitor (PI)-containing antiretroviral regimen, 3 to 6 months after starting or switching this therapy, and annually thereafter. In patients with risk factors for type 2 diabetes or those with severe body fat changes, 75 g of oral glucose may identify impaired glucose tolerance.
- **Treatment:** Encourage weight loss for overweight patients. For persistent fasting hyperglycemia, follow diabetes guidelines established for the general population. If drug therapy is indicated, preference should be given to insulin-sensitizing agents such as metformin (except for patients with renal disease or history of lactic acidemia) or thiazolidinediones (except for patients with preexisting liver disease). If possible, consider avoiding PIs in initial regimens for patients with preexisting glucose intolerance or diabetes.

### Lipid and Lipoprotein Metabolism Abnormalities

- **Assessment and Monitoring:** A fasting lipid panel (total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, and triglyceride levels) should be obtained before initiating or changing antiretroviral therapy, 3 to 6 months after therapy initiation or switch, and annually thereafter.
- **Treatment:** Follow National Cholesterol Education Program (NCEP) III guidelines for assessing cardiovascular risk and dietary and lifestyle alterations to lower cholesterol and triglyceride levels. If possible, avoid PIs in patients with preexisting cardiovascular risk, high lipid levels, or family history of hyperlipidemia. Follow NCEP III guidelines as a framework for use of lipid-lowering agents. If drug therapy is indicated, fibrates are recommended as initial therapy for hypertriglyceridemia, and pravastatin or atorvastatin preferred for patients with elevated cholesterol. If combination therapy is indicated, begin with a statin and add a fibrate if there is insufficient response after 3 to 4 months.

### Body Fat Distribution Abnormalities

- **Assessment and Monitoring:** No specific technique can currently be recommended for assessment and monitoring of body fat dis-

tribution changes, as no method has demonstrated sufficient sensitivity, specificity, or predictive value. Measurement of waist circumference, which can be done easily and inexpensively in a clinical setting, has been recommended in the NCEP III guidelines.

- **Treatment:** Based on the available evidence, no therapies for fat distribution abnormalities in the absence of other metabolic complications can be routinely recommended. The panel discussed existing data surrounding several potentially promising therapies that are now being tested in controlled clinical trials.

### Lactic Acidemia

- **Assessment and Monitoring:** Routine measurement of lactic acid levels is not recommended. Lactic acid levels should be monitored in patients receiving nucleoside reverse transcriptase inhibitors (NRTIs) who have symptoms consistent with lactic acidemia or who are pregnant. If alternative NRTIs are resumed after interrupting antiretroviral therapy for lactic acidemia, lactate levels should be monitored every 4 weeks for at least 3 months.
- **Treatment:** Discontinue antiretroviral therapy for all patients with confirmed lactate levels above 90 mg/dL (10 mmol/L) or for symptomatic patients with confirmed lactate levels above 45 mg/dL (5 mmol/L). No intervention apart from NRTI cessation is recommended. Restart combination therapy with nonnucleoside reverse transcriptase inhibitors and PIs after lactate levels normalize and symptoms resolve.

### Osteopenia, Osteoporosis, and Osteonecrosis

- **Assessment and Monitoring:** Routine screening for osteoporosis or osteonecrosis is not recommended. For patients with bone or joint pain, a radiographic examination of the involved bone and assessment of the contralateral joint are recommended.
- **Treatment:** Surgical resection of the bone is the only effective therapy for symptomatic osteonecrosis. If scanning demonstrates osteoporosis or if a pathologic fracture occurs in the setting of osteoporosis, consider bisphosphonate therapy.

## Perspective

# Bone Disorders, Hypertension, and Mitochondrial Toxicity in HIV Disease

*Osteonecrosis, osteopenia and osteoporosis, hypertension, and mitochondrial toxicity are among the medical conditions observed in patients with HIV disease. In some cases, these disorders have been associated with antiretroviral therapy or particular antiretroviral agents. In other cases, their etiology remains unclear. Meg D. Newman, MD, discussed data from studies of these conditions and current management approaches at the Clinical Pathway of the Ryan White CARE Act 2002 All Grantee Conference held in Washington, DC, in August 2002.*

## Case 1: Osteonecrosis

### Case Presentation

In 1996, a male patient who is currently 33 years old was in hospice care, with a CD4+ cell count of 1/μL, AIDS dementia complex, bilateral cytomegalovirus retinitis, Kaposi's sarcoma of the extremities, and recurrent bacterial infections. After several years of potent antiretroviral therapy, the patient's condition is much improved. In 2001, he presents with viral load below the assay detection limit and a CD4+ cell count of 480/μL. He is still blind in one eye, but is living independently and working part time. He describes new bilateral hip pain, worse in the right hip than in the left hip, and has no history of recent or remote trauma. Examination shows decreased internal rotation of the hips, with more significant findings for the right hip. Plain radiographs of both hips are unremarkable. Magnetic resonance imaging (MRI) with gadolinium shows bilateral osteonecrosis.

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### Discussion

Hip osteonecrosis in an HIV-infected patient was first reported in 1990, well before the advent of potent antiretroviral therapy. Subsequent reports of hip and multiple joint osteonecrosis were published in 1991 and 1993. Osteonecrosis may result from direct or indirect damage; sources of indirect damage include corticosteroid use, alcohol abuse, cigarette smoking, sickle cell anemia, coagulopathies, lupus, hyperlipidemia, and chronic pancreatitis. HIV infection may constitute a risk factor. Although protease inhibitor (PI) use has been broadly discussed as being associated with osteonecrosis, there is scant evidence of a direct causal effect.

The site of osteonecrosis is the subchondral bone located beneath the articular surface. The vascular supply to subchondral bone starts with arterioles and proceeds to sinusoids that turn at 180 degrees and exit as venules. Blood flow is slow and tortuous, making subchondral bone susceptible to microemboli, vasospasm, and increased intraosseous pressure that can occlude the bone. The femoral head is the most common site of osteonecrosis. In the case of corticosteroid use and chronic alcohol abuse, postulated mechanisms of injury consist of altered fat metabolism resulting in fatty liver or hyperlipidemia, with deposition of fat emboli. In addition, there may be increased intraosseous lipocytes in the marrow, resulting in increased intraosseous pressure with loss of small capillaries and subsequent ischemia. Individuals who smoke cigarettes are at 4-fold greater risk of osteonecrosis, which is probably associated with vasospasm. Ischemia leading to bone necrosis may be protracted or sudden. Death of osteocytes stimulates production of undifferentiated mesenchymal cells into the necrotic cancellous bone.

Some of these develop into osteoblasts, but bone resorption is ongoing and is ultimately more efficient. The result is that subchondral bone cannot adequately support the joint, and microfractures and collapse of the bone ensue.

A key point in the evaluation for osteonecrosis is never to rely on plain radiographs to rule out the disorder. In addition, early disease is difficult to detect on plain radiographs. MRI should be used instead, since it has a sensitivity of approximately 90% in detecting osteonecrosis. Bilateral hip imaging should be performed, since bilateral disease is present in approximately 40% of cases.

In a recently reported study by Miller and colleagues (*Ann Intern Med*, 2002), MRI revealed evidence of osteonecrosis in 15 (4.4%) of 339 asymptomatic HIV-infected patients and none of 118 HIV-uninfected patients. Six patients had bilateral disease. All lesions had typical features of osteonecrosis with diminished signal on T1-weighted images and bright signal on fat-suppressed T2-weighted images. Most patients had band- or ring-shaped lesions. Three of the 9 patients with unilateral disease had wedge-shaped lesions in the anteromedial aspect of the femoral head and 2 had small subchondral lesions in the anterior superior aspect of the femoral head. All patients with osteonecrosis had negative plain radiographs. On physical examination, 14 patients with osteonecrosis had abnormal findings, with 11 having abnormal range of motion; however, abnormalities were also found in patients without osteonecrosis in the same population. At the time of publication of these findings, 10 patients had reported some hip discomfort, but none had required surgery; since publication in July 2002, several have had surgery.

Among the 15 patients in the cohort with osteonecrosis, 93% were homosex-

ual men, 80% were white, 13% were black, and no one used injection drugs. Osteonecrosis was more common in the patients who used systemic corticosteroids, lipid-lowering agents, or testosterone, those who did bodybuilding exercises regularly, and those with detectable levels of anticardiolipin antibodies. It is unclear if the factor of bodybuilding is incidental or causal. Miller and colleagues postulated that bodybuilding could amplify intra-articular forces that initiate injury. It should be stressed that bodybuilding has not been associated with osteonecrosis in other studies and may simply be associated with this cohort only.

These investigators found no association between osteonecrosis and use or duration of use of PIs (most HIV-infected subjects in the study were receiving PIs) and stated that serum lipid levels were only marginally associated with risk of osteonecrosis. However, the significant association of use of lipid-lowering drugs with osteonecrosis suggests that patients with hyperlipidemia may be at increased risk even when lipid levels are currently controlled. Some PIs are associated with increases in lipid levels that often require lipid-lowering therapy. PI treatment thus may be an indirect causal factor in osteonecrosis.

Other studies have reported some association of osteonecrosis with risk factors in addition to PI use or HIV infection itself. Brown and Crane (*Clin Infect Dis*, 2001) found a 0.45% incidence of osteonecrosis, with 3 of the 6 patients with disease having such risk factors as smoking, hyperlipidemia, or steroid use. Scribner and colleagues (*J Acquir Immune Defic Syndr*, 2000) reported traditional risk factors in 22 of 25 patients with osteonecrosis, with increased risk being associated with increasing number of risk factors. All cases occurred in men; 28% had a history of alcohol abuse, 12% had used steroids, and 32% had hyperlipidemia.

Screening of asymptomatic patients for osteonecrosis currently is not recommended. However, any patient with persistent symptoms in the groin or hip should be assessed by MRI. Practitioners should be aware that patients who use short- or long-term steroids or lipid-lowering agents are at increased risk of osteonecrosis. Disease often is progres-

sive. Once symptoms of osteonecrosis develop, weight-bearing activity should be limited, and physical therapy should focus on improving range of motion. Surgical options include core decompression, vascular grafting, and total hip replacement. If osteonecrosis is diagnosed early in the course of the disease, treatment with core decompression is adequate; this is an outpatient procedure with low morbidity. In cases of severe or progressive disease, total hip replacement is usually necessary.

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**Case 2: Osteopenia and Osteoporosis**

**Case Presentation**

A 26-year-old HIV-infected man with a CD4+ cell count of 289/μL (nadir, 129/μL) read an article on the Internet about risk for osteoporosis. On the basis of this information, he wants a prescription for alendronate, a bone resorption inhibitor. He has never taken steroids and currently is a cigarette smoker. He is asymptomatic but believes that taking alendronate will prevent development of osteopenia and osteoporosis.

**Discussion**

The recently reported National Osteoporosis Risk Assessment Study (Siris et al, *JAMA*, 2001) in more than 200,000 postmenopausal women has provided some surprising findings regarding osteopenia and osteoporosis in the general population. The study showed that 40% of postmenopausal women had osteopenia and 7% had osteoporosis. Risk factors included smoking, glucocorticoid use, and Asian

or Hispanic heritage. Protective factors were greater body mass index, African-American heritage, estrogen use, and diuretic use. Eleven percent of the women had a baseline fracture of the rib, hip, wrist, or spine with minimal trauma by age 45 years. Such findings indicate that osteopenia and osteoporosis are much more common than previously believed, and may raise the suspicion that it is even more common in HIV-infected individuals.

In 1994, the osteoporosis working group of the World Health Organization published a definition for the diagnosis of osteoporosis in epidemiologic studies. They proposed that osteoporosis be defined as having a bone mineral density at the spine, hip, or wrist of 2.5 standard deviations or more below the mean for healthy young adult women, or as having a history of atraumatic fracture (Nelson et al, *Ann Intern Med*, 2002). Hence, osteoporosis is now defined as a bone mineral density test T score of less than -2.5 in women, with risk of fracture doubling with each standard deviation decrease in T score. The relationship between bone mineral density and fracture risk in men is undefined, and a T score of -2.5 in men actually represents a greater bone mineral density than in women. However, men with a maternal history of osteoporosis are at a 1.5-fold greater risk of disease than men without this background. Men develop hip fractures later in life and vertebral fractures earlier than women.

Data on osteopenia and osteoporosis in patients with HIV disease are confusing. A number of studies have been performed to elucidate the etiology of the disorder, with attention to the potential roles of potent antiretroviral therapy and PI treatment. Thus far, however, the role of such treatment remains unclear, and data in this regard are often conflicting. Many investigators have speculated that HIV infection in association with cytokine activation, direct infection of osteogenic cells, or hypogonadism may play a role in osteopenia and osteoporosis. Corticosteroid use, decreased physical activity, malnutrition, malabsorption, and smoking may play a role in disease in both HIV-infected and HIV-uninfected persons.

Lawal and colleagues (*AIDS*, 2001) studied 36 malnourished HIV-infected

men during the era prior to potent antiretroviral therapy, and 19 men and 3 women receiving potent therapy who had fat redistribution. On average, the patients receiving potent therapy were 15 kg heavier. No differences between the 2 groups were observed with regard to bone mineral content, bone calcium, or bone mineral density, but both groups had lower values for all 3 measures than did a group of HIV-uninfected patients.

In another study, Paton and colleagues (*Calcif Tissue Int*, 1997) found no difference in total bone mineral density or hip bone mineral density between 45 HIV-infected men treated in the pre-potent therapy era and a group of age-matched HIV-uninfected controls. HIV-infected patients had a 3% lower lumbar spine bone mineral density than control subjects, and 15 of the HIV-infected patients showed a 1.6% decline in total bone mineral density from baseline over 16 months of follow-up.

Carr and colleagues investigated whether osteopenia and osteoporosis might be associated with hyperlactatemia or mitochondrial disease (AIDS, 2001). They found that among 32 antiretroviral-naïve patients, 42 patients receiving nucleoside reverse transcriptase inhibitor (NRTI) therapy, and 147 receiving PI plus NRTI therapy, independent predictors of disease were higher pretreatment lactate levels (odds ratio, 2.39 per 1 mmol/L increase) and lower pretreatment body weight (marginally significant with an odds ratio of 1.06). They found no association between type or duration of PI treatment and bone changes or between lipodystrophy and bone changes. Overall, lower body weight was associated with lower total bone mineral density, and higher lactate levels were associated with lower bone mineral density of the spine. Claxton and colleagues (8th CROI, 2001), however, performed a similar study and found no association between lactate levels and bone mineral density. In another study, Tebas and colleagues (AIDS, 2000) found no association between visceral adiposity and osteopenia. However, Huang and colleagues (AIDS, 2001) did find an association between visceral adiposity and osteopenia.

More recently, Mondy and colleagues (9th CROI, 2002) reported a

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## The role of potent antiretroviral therapy in the etiology of osteopenia and osteoporosis remains unclear

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study in which 108 men and 17 women with a mean age of 41 years were assessed by dual-energy x-ray absorptiometry at baseline and at 48 and 72 weeks. Forty-six percent of the patients were found to have osteopenia or osteoporosis. Low bone mineral content was associated with a greater degree of weight loss and wasting, prior steroid use, past or current cigarette smoking, and longer duration of potent antiretroviral therapy. PI use was not significantly associated with low bone mineral density. Spine and hip bone mineral density increased by 3% and 2%, respectively, in the patient group over 72 weeks.

An additional suggestion that PI use may not be the primary culprit in osteopenia and osteoporosis came from a randomized study by Hoy and colleagues (2nd Int Conf Adverse Drug React Lipodystrophy HIV, 2000), in which discontinuation of PI treatment produced no change in bone mineral density over 48 weeks. Further, Amiel and colleagues (9th CROI, 2002) found that levels of osteocalcin, which is a marker for bone formation, were decreased in untreated patients and in treated patients not receiving a PI compared with patients receiving PI-containing therapy. Aukrust and colleagues (*J Clin Endocrinol Metab*, 1999) found that PI treatment was associated with increased osteocalcin. Previously, Wang and colleagues (8th CROI, 2001) had found that indinavir blocks in vitro and in vivo differentiation and function of osteoblasts. More recently, Wang and colleagues (9th CROI, 2002) found that administration of indinavir in mice for 5 weeks resulted in a 17% to 20% decrease in bone miner-

al density in lumbar vertebrae, tibia, and femur; a decrease in both cortical and trabecular bone mass; and a 25% decrease in bone volume, with the total number of osteoclasts and osteoblasts remaining unchanged.

These data provide little overall guidance for the HIV care practitioner in reducing risk of osteopenia and osteoporosis. Perhaps the guiding principle in this arena is to change what can be changed and accept what cannot be changed until the arrival of more definitive data. Thus, patients should be encouraged to stop smoking, to engage in weight-bearing exercise, and to practice good bone health by intake of the recommended 1.2 to 1.5 g of calcium and 400 to 800 units of vitamin D per day. A high threshold for withholding even short courses of systemic steroids should be maintained. Hypogonadism should be treated, since testosterone is important in suppressing osteoclast action, and wasting should be treated.

It is important to recognize that patients aged 45 years or older are at increased risk of osteopenia and osteoporosis, as are postmenopausal women. The most recent National Institutes of Health consensus statement on this subject indicates that bone mineral density screening should be performed in all patients receiving steroid treatment for 2 months or longer irrespective of age, as well as in all postmenopausal women. Screening is also recommended in other patients with conditions that put them at risk. Specific recommendations for screening in men currently are being formulated. In practice, screening in HIV-infected patients should be individualized, based on assessment of risk factors and the recognition that risk of osteopenia and osteoporosis increases with age and multiple risk factors. It is expected that clearer recommendations regarding screening for HIV-infected patients will be forthcoming in the relatively near future.

In the case described above, the patient did not receive alendronate after his initial presentation. The patient and his provider discussed his family history (he had no maternal or paternal risk factors), and his personal history revealed no risk factors other than smoking. (If it was determined that he had a number of risk factors, a dual-energy x-ray absorp-

tiometry scan would have been ordered.) The patient and his provider focused on increasing his intake of calcium and vitamin D and beginning an exercise program. The patient is now contemplating a smoking-cessation program.

### Case 3: Hypertension

#### Case Presentation

A 36-year-old woman without prior knowledge of her HIV infection status presented for the first time in May 1996 with a CD4+ cell count of 11/ $\mu$ L, *Pneumocystis carinii* pneumonia, alopecia, and herpes simplex virus infection. Her plasma HIV-1 RNA level was greater than 500,000 copies/mL. She was started on indinavir/stavudine/lamivudine. After 1 month, her viral load was below the assay detection limit and her CD4+ cell count was 25/ $\mu$ L; her condition continued to improve thereafter. In December 1997, she developed hypertension. The patient had gained 14 kg while on antiretroviral therapy; she had no family history of hypertension or evidence of any secondary causes of hypertension, and she was not using alcohol, injection drugs, or tobacco.

#### Discussion

Since body weight is a modifiable risk factor for hypertension, the patient should be encouraged to lose weight. Many practitioners would also substitute another PI for indinavir in this setting, on the basis of evidence demonstrating an association of indinavir treatment with hypertension. For example, a study by Cattelan and colleagues (AIDS, 2001) showed that 31 of 118 patients with no renal abnormalities who were receiving indinavir developed hypertension of stage 1 or greater (6 with stage 3, 5 with stage 2, 20 with stage 1), compared with none of 77 patients receiving other PIs (nelfinavir, saquinavir, or ritonavir) over a median 34 months of follow-up. The mean blood pressure in the indinavir group was 125/81 mm Hg at baseline and 136/91 mm Hg at the end of follow-up. The 31 patients who developed hypertension had a mean blood pressure of 153/100 mm Hg at the end of follow-up. In the

group not receiving indinavir, mean blood pressure was 126/82 mm Hg at baseline and 125/80 mm Hg at the end of follow-up. Among the patients who developed hypertension, 18 (58%) had a family history of hypertension. The hypertension was controlled with medication in 18 patients. Of 9 patients who stopped indinavir therapy, hypertension resolved in 4 and persisted in 5.

These data suggest that indinavir treatment is associated with hypertension, although the mechanism of this effect remains unclear. Patients on indinavir should be evaluated for hypertension at every visit, and discontinuation of the drug should be considered if hypertension develops. It may be appropriate to consider indinavir as a second-line PI in patients with hypertension or a family history of hypertension. With regard to potential mechanisms of the hypertensive effect, it may be that indi-

navir acts as a catalyst for latent hypertension in individuals with a genetic predisposition for the disorder. Additional studies are needed to assess the roles of obesity, alcohol use, non-steroidal anti-inflammatory drugs, tobacco, concomitant trimethoprim/sulfamethoxazole use, and prior use of antivirals in promoting hypertension in HIV-infected patients.

Untreated hypertension is responsible for serious end organ complications of the renal and cardiovascular system and thus needs to be screened for and treated in HIV-infected patients. Among the available antihypertensive agents, angiotensin-converting enzyme inhibitors are suited for those patients with renal disease or diabetes; however, African Americans with a low renin state may not respond to such treatment. Calcium channel blockers are suited for use in patients with a low renin state,

**Table 1. Drug-Drug Interactions Between Antiretroviral Agents and Antihypertensive or Antiarrhythmic Agents**

<b>Nucleoside Reverse Transcriptase Inhibitors</b>
<ul style="list-style-type: none"> <li>• Avoid using thiazide or loop diuretics with didanosine because of increased risk of pancreatitis. When the drugs are used together, the risk of pancreatitis is increased. If didanosine or a thiazide is used alone, each is associated with risk of pancreatitis. Used together, the risk is even greater.</li> </ul>
<b>Nonnucleoside Reverse Transcriptase Inhibitors</b>
<p><i>Cytochrome P450 interactions are key.</i></p> <ul style="list-style-type: none"> <li>• Efavirenz: Monitor clinical effects of all calcium channel blockers, including dihydropyridines (eg, nifedipine, nifedipine, nitrendipine).</li> <li>• Nevirapine: Theoretical risk for calcium channel blockers to vary in efficacy over time.</li> </ul>
<b>Protease Inhibitors</b>
<p><i>Cytochrome P450 interactions are key.</i></p> <ul style="list-style-type: none"> <li>• Amprenavir: Do not use with bepridil. May increase concentration of calcium channel blockers.</li> <li>• Indinavir: Significant interactions with calcium channel blockers and quinidine.</li> <li>• Lopinavir/ritonavir: Close monitoring is suggested with use of calcium channel blockers.</li> <li>• Nelfinavir: May result in high calcium channel-blocker levels. Amiodarone and quinidine should not be used with nelfinavir.</li> <li>• Ritonavir: Absolute contraindications include concurrent use with amiodarone, encainide, flecainide, propafenone, quinidine, and bepridil. Increases in area under the concentration-time curve (AUC) with multiple medications, including lidocaine, mexiletine, warfarin; metoprolol, pindolol, timolol; and all calcium channel blockers. Moderate decrease or increase in AUC with S-warfarin and losartan. Possible increase in AUC with doxazosin, prazosin, terazosin, digoxin, and tocainide.</li> </ul>

diabetes, or renal disease. Beta blockers are suited for use in younger patients with good cardiac conduction function. Their use requires attention to the potential for increased glucose, insulin, and triglyceride levels and decreased high-density lipoprotein cholesterol level. Caution should be exercised in using calcium channel blockers and beta blockers together because of the risk of cardiac conduction abnormalities. Both calcium channel blockers and beta blockers may be associated with sexual dysfunction. Diuretics can be used in first-line treatment or to augment other antihypertensive drugs. With diuretic use, patients should be monitored for electrolyte levels, hyperuricemia, and mild increases in cholesterol, glucose, and insulin levels.

There are a number of important interactions between antiretroviral agents and antihypertensive drugs that must be considered in deciding on antihypertensive treatment options. Most of these consist of nonnucleoside reverse transcriptase inhibitor (NNRTI) and PI interactions with antihypertensive agents mediated via the cytochrome P450 system (see Table 1). PIs, particularly ritonavir, also exhibit a number of important interactions with antiarrhythmic agents.

The patient discussed in this case stopped taking indinavir, but her hypertension did not resolve. Fortunately, it has been well controlled with labetalol. Three years after the events of this case, the patient became pregnant and delivered a healthy baby boy in 2002.

## Case 4: Mitochondrial Toxicity

### Case Presentation

A 52-year-old man was first diagnosed with HIV infection in April 1998. His plasma HIV-1 RNA level was 36,000 copies/mL and CD4+ cell count was 253/ $\mu$ L. The patient wished to begin antiretroviral therapy and was started on a regimen of indinavir/stavudine/lamivudine. At 16 weeks, the patient's plasma HIV-1 RNA level was less than 50 copies/mL and CD4+ cell count was 448/ $\mu$ L. At week 60, the patient complained of mild burning pain in the lower extremities and increased abdom-

inal girth. He also had intermittent nausea and fatigue, and experienced shortness of breath on exertion, but denied having chest pains. Laboratory results at this time showed plasma HIV-1 RNA level of less than 50 copies/mL; CD4+ cell count of 420/ $\mu$ L; normal white blood cell count and differential; packed cell volume, 41%; sodium, 142 mEq/L; potassium, 4.1 mEq/L; chloride, 100 mmol/L; bicarbonate, 20 mEq/L; normal serum creatinine; blood urea nitrogen, 21 mg/dL; glucose, 172 mg/dL; aspartate aminotransferase, 36 U/L; alanine aminotransferase, 30 U/L; alkaline phosphatase, 134 mU/mL; triglycerides, 487 mg/dL; cholesterol, 218 mg/dL; and total bilirubin, 2.2 mg/dL (1.7 indirect). Possible management choices for this patient include continuing the current antiretroviral regimen, with reevaluation in 2 weeks; changing the regimen; and stopping all antiretroviral therapy.

### Discussion

This patient's symptoms and laboratory results are consistent with lactic acidosis due to mitochondrial toxicity. Antiretroviral therapy should be stopped, since this is a life-threatening condition, with mortality ranging from 30% to 60%. The goal in managing mitochondrial toxicity is to diagnose it as early as possible. Early symptoms include fatigue, abdominal pain, weight loss, malaise, nausea, vomiting, and anorexia, with axonal neuropathy sometimes present. These symptoms worsen as toxicity progresses. The evolution of the disorder may be fulminant or insidious, and symptoms can develop after years of tolerating nRTI treatment. In any patient presenting with such symptoms, the bicarbonate level should be checked and anion gap calculated; the venous lactate level should be measured if the condition is suspected. The threshold of suspicion for this disorder should be very high in any patient presenting with these symptoms. It is noteworthy that women, particularly those with greater body mass index, have accounted for a disproportionate number of the cases of lactic acidosis reported thus far.

Treatment with stavudine appears to be associated with mitochondrial toxicity, and the use of stavudine and didano-

sine together appears to augment the risk (Boubaker et al, *Clin Infect Dis*, 2001; Coghlan et al, *Clin Infect Dis*, 2001). Zidovudine has also been associated with such toxicity. Potent therapy including nRTIs other than zidovudine and stavudine can usually be safely instituted once toxicity has resolved. Routine monitoring of lactate levels is not recommended in patients receiving potent therapy including nRTIs. There is considerable evidence that mild elevations of serum lactate levels are common in asymptomatic patients receiving nRTIs (estimated incidence, 15%-35%), with such elevations being chronic and compensated (John et al, *AIDS*, 2001). The mild hyperlactatemia in such patients has a poor predictive value for development of symptomatic lactic acidosis.

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## Perspective

# HIV and Hepatitis B Virus: Options for Managing Coinfection

*At the International AIDS Society–USA course in New York in October 2002, Douglas T. Dieterich, MD, presented the case history of a patient coinfecting with HIV and hepatitis B virus (HBV). HBV infection in patients with HIV is associated with worse prognosis for HBV disease than in patients without HIV and complicates management of both diseases. However, newer treatment options for chronic HBV infection increase the potential for successful management.*

## Case History: HIV/HBV Coinfection

### Case Presentation

A 44-year-old man with chronic HIV and hepatitis B virus (HBV) infections was referred for treatment in 1999. His prior liver biopsy showed chronic hepatitis with portal/periportal necroinflammatory activity, septal fibrosis, and architecture distortion, yielding a diagnosis of transition to cirrhosis (grade 3-4). The patient had been treated with interferon alfa 5 MU per day for 3 months prior to referral but had discontinued treatment owing to intolerable, disabling adverse effects. He was receiving an unusual antiretroviral regimen of abacavir/stavudine/nevirapine.

Initial laboratory results showed elevated liver enzymes with alanine aminotransferase (ALT) of 164 U/L and aspartate aminotransferase (AST) of 136 U/L, albumin of 3.8 g/dL, and platelet count of 69,000, with the higher ALT and lower albumin and platelet values all suggesting cirrhosis. INR was 1.5; HBV DNA level was 46 million copies/mL, a relatively low concentration; and the patient was HBV e-antigen-positive, indicating active viral replication, and e-antibody-negative. HIV infection was well con-

trolled on the current antiretroviral regimen, with plasma HIV-1 RNA level of 150 copies/mL and CD4+ cell count of 352/ $\mu$ L. The HBV-related diagnosis was chronic HBV infection with cirrhosis.

### Discussion: Characteristics of HBV Disease in HIV/HBV Coinfection

Worldwide, there are approximately 40 million individuals infected with HIV and approximately 400 million infected with HBV, including approximately 1 million and 1.25 million, respectively, in the United States. It is estimated that 10% of HIV-infected individuals are HBV surface antigen-positive (Rustgi et al, *Ann Intern Med*, 1984) and that HIV-infected individuals are 3 to 6 times more likely to develop chronic HBV infection than HIV-uninfected individuals (Bodsworth et al, *J Infect Dis*, 1991). Although HIV is an RNA virus and HBV is a DNA virus, both integrate into the host cell genome, with the primary targets being CD4+ cells and hepatic cells, respectively. Both also utilize reverse transcriptase in replication, are susceptible to nucleoside reverse transcriptase inhibitors (nRTIs) and nucleotide

reverse transcriptase inhibitors (nRTIs), and exhibit mutations that confer resistance to nRTIs.

The effect of HIV/HBV coinfection on liver-related mortality is demonstrated by recently reported data from the Multicenter AIDS Cohort Study (Thio et al, 9th CROI, 2002). As shown in Figure 1, follow-up of approximately 5000 patients over more than 14 years has shown that individuals with HIV/HBV coinfection have risk of liver mortality that is 14 times greater than that in individuals who are HIV-uninfected and HBV surface antigen-negative; the risk is also markedly greater than that in those who are HIV-infected/HBV surface antigen-negative or HIV-uninfected/HBV surface antigen-positive. HIV/HBV coinfection is also associated with much higher rates of cirrhosis than is HBV infection alone (Colin et al, *Hepatology*, 1999).

### Clinical Course: Initial Treatment

Treatments approved by the US Food and Drug Administration (FDA) for chronic HBV infection currently consist of interferon alfa 5 MU once daily or 10 MU 3 times weekly for at least 16 weeks,

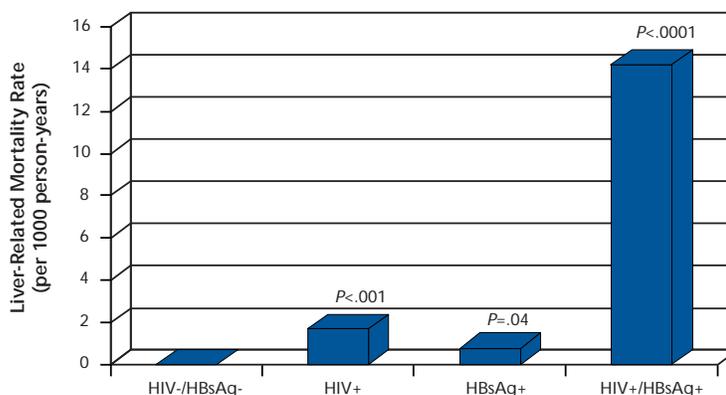


Figure 1. Liver-related mortality rates in Multicenter AIDS Cohort Study subjects who are HIV-uninfected and hepatitis B virus (HBV) surface antigen-negative (HIV-/HBsAg-), HIV-infected and HBsAg- (HIV+), HBV surface antigen-positive and HIV- (HBsAg+), and HIV+/HBsAg+. Adapted with permission from Thio et al, 9th CROI, 2002.

Dr Dieterich is Vice-Chair and Chief Medical Officer at the Mt Sinai School of Medicine in New York, NY.

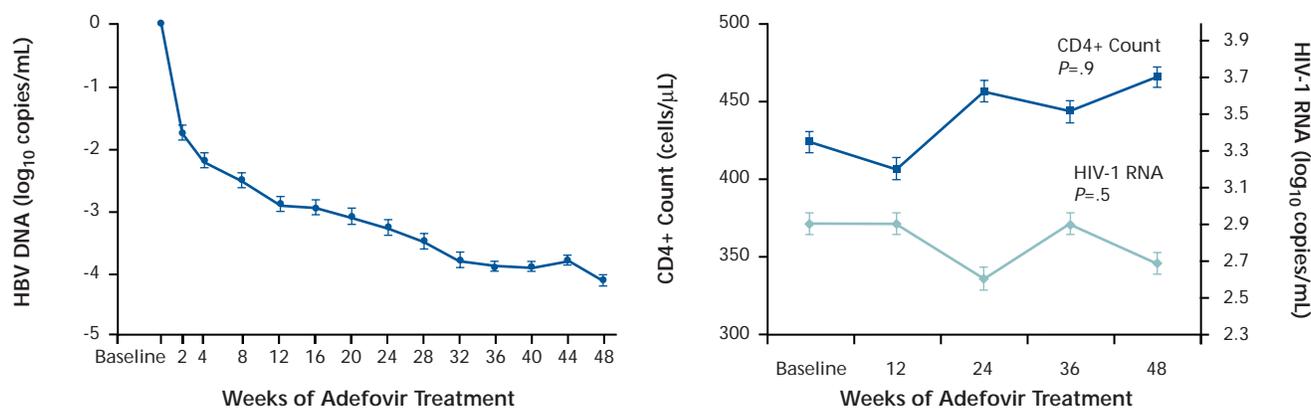


Figure 2. Left: Effect of adefovir treatment on hepatitis B virus (HBV) DNA level by study week in 31 HIV/HBV-coinfected patients with lamivudine-resistant HBV. Right: Effect of treatment on plasma HIV-1 RNA level and CD4+ cell count. Adapted with permission from Benhamou et al, *Lancet*, 2001.

lamivudine 100 mg once daily for at least 12 months, and, as of September 2002, adefovir 10 mg once daily. At the time of the patient's presentation in 1999, would any of the following constitute rational treatment for the patient?

- Addition of lamivudine 100 mg daily
- Initiation of pegylated interferon alfa 1.5 μg/kg weekly plus ribavirin 11.5 mg/kg
- Addition of lamivudine 150 mg twice daily plus famciclovir 500 mg twice daily
- Institution of no treatment due to high risk associated with borderline decompensated cirrhosis

**Discussion: Lamivudine Resistance**

Lamivudine at a suboptimal dose for treating HIV infection should not be used in this setting because of the risk of emergence of HIV resistance to the drug. Withholding of any HBV treatment is not recommended since the patient could benefit from treatment. Pegylated interferon alfa plus ribavirin is indicated for use in hepatitis C virus infection, and the pegylated interferon alfa part of this combination probably has good activity against HBV (as well as some activity against HIV), but the combination is not yet FDA-approved for use against HBV infection. The patient started lamivudine at the 150 mg twice-daily dose recommended for use in HIV infection and famciclovir 500 mg twice daily, a combination that has some synergistic activity in vitro and in vivo. The patient's ab-

cavir/stavudine/nevirapine regimen was continued.

In response to treatment, HBV viral load dropped below detection limits (<200 copies/mL by polymerase chain reaction) by December 1999 after approximately 3 months of therapy. By June 2000, however, HBV viral load had increased to 500 million copies/mL. HBV resistance to lamivudine is predictable and occurs with more rapidity in HIV/HBV-coinfected patients, appearing in almost half of this group after 2 years and in 90% after 4 years (Lai et al, *N Engl J Med*, 1998; Chang et al, *Antivir Ther*, 2000; Benhamou et al, *Hepatology*, 1999).

With regard to the patient's HIV infection status, in February 2000, his plasma HIV-1 RNA level increased to 56,000 copies/mL, with a CD4+ cell count of 320/μL. In March 2000, treatment was changed to didanosine/stavudine/lopinavir/ritonavir, and lamivudine/famciclovir for the HBV infection was continued. The patient's CD4+ cell count increased to 562/μL, and plasma HIV-1 RNA level was suppressed to less than 50 copies/mL for prolonged periods interspersed with blips up to 150 to 900 copies/mL.

Although not available for use in this patient at the time of the HBV relapse, adefovir is now an option in the case of HBV resistance to lamivudine. This drug was initially developed for use in HIV infection at much higher doses than that used for HBV infection and is associated with unacceptable risk for nephrotoxicity at these higher doses. At lower doses,

however, adefovir has been found to maintain activity against HBV resistant to lamivudine as a result of the presence of the M204I, M204V, L180M plus M204I, or L180M plus M204V mutations. In an open-label pilot study of adefovir in HIV/HBV-coinfected patients with lamivudine-resistant HBV reported by Benhamou and colleagues (*Lancet*, 2001), adefovir 10 mg per day produced a decrease in HBV DNA of 4 log<sub>10</sub> copies/mL over 48 weeks of treatment (Figure 2). No alteration in HIV-1 RNA level was observed, indicating that adefovir at this dosage has little likelihood of anti-HIV effects and thus is unlikely to confer resistance. A substantial but not statistically significant increase in CD4+ cell count was observed, likely associated with control of HBV replication rather than any anti-HIV effect. In this study, reversible grade 1 increases in serum creatinine levels were observed in 2 patients, with neither case considered related to adefovir treatment, and no serum phosphate abnormalities were observed.

**Clinical Course: Adverse Events**

In October 2000, the patient noted numbness and tingling in his feet while he was still receiving didanosine/stavudine/lopinavir/ritonavir for anti-HIV therapy and lamivudine/famciclovir for anti-HBV therapy. He was diagnosed with neuropathy, and his serum lactate level was 5.6 mmol/L. Adefovir had become available through a compassionate-use program. How should treatment be changed?

- Addition of adefovir 10 mg for HBV treatment and substitution of zalcitabine for stavudine in the antiretroviral regimen
- Substitution of adefovir for the lamivudine/famciclovir regimen
- Addition of tenofovir
- Discontinuation of all treatment

### Discussion: Symptomatic Hyperlactatemia and Activity of Tenofovir

In this case, the best choice was to discontinue all treatment since the patient had symptomatic hyperlactatemia. This option was further supported by the patient's liver disease status. The liver is a primary organ in lactate metabolism, and serum lactate levels serve as a measure of liver function. Data from 210 cases of paracetamol-induced acute liver failure reported by Bernal and colleagues (*Lancet*, 2002) indicate that arterial lactate level is an effective predictor of death from liver failure, with mean lactate levels being 8.5 mmol/L in those who died and 1.4 mmol/L in those who survived. The onset of symptomatic hyperlactatemia usually occurs when serum lactate levels are 3 mmol/L or higher; increases to greater than 5 mmol/L are often associated with acidosis, and mortality rates are extremely high in acidotic patients. Risk factors for symptomatic hyperlactatemia include female sex, obesity, and hepatitis C virus infection, HBV infection, or other liver disease.

Lactic acidosis and other metabolic abnormalities have been associated with mitochondrial toxicity due to nRTI use. Cihlar and Chen investigated the potential for causing mitochondrial toxicity via incorporation of active forms of nRTIs and the nRTI tenofovir by cellular polymerase  $\gamma$  enzymes (*Antiviral Chem Chemother*, 1997). Their results indicate that stavudine, didanosine, and zalcitabine exhibit relatively high incorporation and that tenofovir, lamivudine, and zidovudine exhibit low incorporation. In a recently reported study comparing tenofovir/lamivudine/efavirenz (n=299) and stavudine/lamivudine/efavirenz (n=301) over 48 weeks in patients with HIV disease, nRTI- and nRTI-associated toxicities occurred in 3% of patients receiving the former regi-

men and 11% receiving the latter. Peripheral neuritis/neuropathy occurred in 2% versus 7%, lipodystrophy in 1% versus 4%, lactic acidosis in 0% versus less than 1% (3 cases), and pancreatitis in 0% for both groups (Staszewski, 14th Int AIDS Conf, 2002).

Tenofovir is currently approved by the FDA for treatment of HIV infection only. The drug has been shown to be active against both lamivudine-susceptible and -resistant HBV, however, with no difference in 50% inhibitory concentration. Studies in HIV-infected patients indicate that tenofovir monotherapy results in a 0.6- $\log_{10}$  copies/mL decrease in plasma HIV-1 RNA level. In a large study of patients with HBV infection, half of whom had lamivudine-resistant virus, tenofovir 300 mg once daily produced a decrease in HBV DNA level of 4  $\log_{10}$  copies/mL from baseline over 48 weeks and a 5- $\log_{10}$  copies/mL decrease compared with placebo (Figure 3; Cooper et al, 14th Int AIDS Conf, 2002). In a small study of 12 HIV/HBV-coinfected patients with suppression of plasma HIV-1 RNA level but uncontrolled HBV replication, the addition of tenofovir 300 mg once daily to lamivudine 150 mg twice daily produced a nearly 4- $\log_{10}$  copies/mL decrease in HBV DNA level over 24 weeks, accompanied by a CD4+ cell increase of approximately 70/ $\mu$ L. As in the study of adefovir, the CD4+ cell increase appears to be due to control of HBV replication, since the patients' HIV-1 RNA levels were suppressed below detection limits throughout the study (Bochet et al, 9th CROI, 2002).

### Clinical Course: Resuming Treatment

All of the patient's medications were stopped for 3 months, during which time serum lactate level declined to 1.8 mmol/L. Treatment was restarted with tenofovir/abacavir/lopinavir/ritonavir. After 3 months on treatment, the patient was HBV e-antigen-negative and e-antibody-positive, with HBV DNA level reduced to less than 200 copies/mL. Plasma HIV-1 RNA level was less than 50 copies/mL and CD4+ cell count had increased to 676/ $\mu$ L.

### Future Treatment Options

Lamivudine and tenofovir offer the prospect of treating HIV and HBV infection with the same drug, and adefovir and tenofovir offer options in the setting of lamivudine-resistant HBV, although, as previously mentioned, tenofovir for treatment of HBV infection is not yet FDA-approved. Investigators are currently studying the use of combination therapy for HBV infection and data supporting its use should be available soon. Like HIV, HBV mutates frequently, and single-nRTI therapy for HBV infection has been shown to lead to drug resistance, making a strong argument for using at least 2 drugs active against HBV. There are few data on HBV resistance associated with nRTIs such as tenofovir and adefovir.

A number of new agents for treating HBV infection are also in development. Assessment of Ld-thymidine (LdT) and Ld-cytidine (LdC) in the woodchuck model of HBV, which precisely mimics

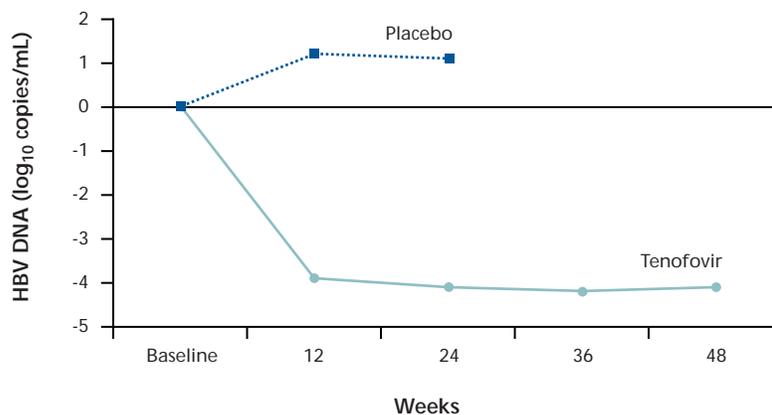


Figure 3. Change in hepatitis B virus (HBV) DNA level over 48 weeks of treatment with tenofovir or 24 weeks with placebo in 12 patients with HBV infection, half with lamivudine-resistant HBV. Adapted with permission from Cooper et al, 14th Int AIDS Conf, 2002.

the HBV carrier state in humans, has shown a pronounced effect of LdT 10 mg/kg in reducing HBV viral load and synergism of the LdT and LdC at doses of 1 mg/kg. LdT is being investigated in a phase 2B trial in 105 patients with chronic HBV infection. Week 12 safety and antiviral results were submitted to the FDA and supported initiation of phase 3 studies. Weeks 12 and 24 data will be available in the near future. The valine ester of LdT (val-LdT), which exhibits a prolonged half-life compared with the parent compound, is being developed as an anti-HIV drug and also exhibits anti-HBV activity. In an ongoing phase 1/2 trial examining doses of 50 mg to 400 mg in patients with HBV infection, val-LdT 200 mg and 400 mg both produced 2- $\log_{10}$  copies/mL decreases in serum HBV DNA level over 4 weeks.

Entecavir is an investigational guanine analogue that inhibits all 3 HBV polymerase functions (priming, negative strand formation, and positive strand synthesis). In phase 2 trials, reductions in serum HBV DNA of between 2  $\log_{10}$  and 3  $\log_{10}$  copies/mL were achieved with entecavir doses of 0.5 mg and 1.0 mg once daily (de Man et al, *Hepatology*, 2001). The ongoing entecavir phase 3 program is scheduled to enroll more than 2000 HBV-infected patients worldwide to receive treatment at 0.5 mg (nRTI-naive patients) or 1.0 mg (patients with virologic failure on lamivudine) for 48 to 96 weeks, with a 24-week post-treatment follow-up. The primary end points are liver histology findings and proportion of patients with HBV DNA below limits of detection.

Other new investigational agents with HBV activity include emtricitabine (FTC), diaminopurine dioxolane (DAPD), and clevudine (L-FMAU). Emtricitabine, which has activity against HIV, is not effective against lamivudine-resistant HBV but offers the potential advantage of once-daily dosing. DAPD is also active against HBV and HIV, including many drug-resistant strains of the latter. L-FMAU is a fluorinated uracil compound; unlike fialuridine, a fluorinated uracil compound that caused severe mitochondrial toxicity, L-FMAU does not undergo conversion to the D-isomer form and has not been associated with

mitochondrial toxicity. Use of L-FMAU in combination with either emtricitabine or DAPD results in prolonged decreases in HBV DNA of between 2  $\log_{10}$  and 3  $\log_{10}$  copies/mL after treatment as brief as 4 weeks. Such findings suggest the potential for use of short intensive courses of combination therapy that may permit patients to gain immunologic control in chronic infection.

## Conclusions

In conclusion, HBV infection results in higher rates of liver disease in HIV-coinfected patients than in individuals without HIV infection. Lamivudine resistance in HBV is becoming increasingly common. Adefovir and now tenofovir offer activity against lamivudine-resistant HBV, with the latter also offering anti-HIV activity in coinfecting patients. Drugs in development promise to expand the ability to treat HBV infection, as well as HIV infection in coinfecting patients. Management of HBV infection in HIV-infected patients is now more complex than when few treatment options were available but is also more likely to be successful thanks to the newer treatment options.

*Presented in October 2002. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Dieterich in November 2002.*

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## Perspective

# Substance Abuse and HIV Infection

*Substance abuse facilitates the spread of HIV infection and complicates its management. Successful treatment of HIV disease and other comorbidities in substance abusers requires treatment of substance abuse. At the Clinical Pathway of the Ryan White CARE Act 2002 All Grantee Conference held in Washington, DC, in August 2002, Henry Francis, MD, discussed characteristics of substance abuse in the United States and obstacles and approaches to successful treatment.*

### Who Are Substance Abusers?

Substance abuse can be defined as the repeated use of a substance even with the knowledge of its negative health consequences. Abused substances may be legal or illicit and thus include alcohol and nicotine as well as marijuana, cocaine, heroin, amphetamines, tranquilizers, hallucinogens, steroids, inhalants, and “club” drugs. Addiction plays a major role in substance abuse, and behavioral addictions, such as sex addiction, can also have important social, public health, and medical consequences.

The prevalence of drug use in the United States is shown in Table 1. The stigma attached to illicit drug abuse obscures the impact of abuse of legal substances on society. Nicotine is a highly addictive drug and cigarette smoking is associated with staggering health care costs. The total cost of crime, accidents, and destruction of property associated with illicit drug abuse in the United States is approximately \$50 billion over a 10-year period, which is one third less than costs for similar alcohol abuse-related damages over 2 years. The stigma attached to illicit drug abuse also prevents the recognition, or results from the failure to

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recognize, that underlying addiction is a chronic disease requiring treatment, rather than a social problem.

Illicit drug use according to age, sex, and ethnicity is shown in Table 2; alcohol use is shown in Table 3. Men tend to use illicit drugs more than women do. Incidence of drug addiction tends to be highest among African Americans, followed by Hispanic Americans and white Americans. White Americans, however, have greater rates of alcohol use and addiction. Although these demographic patterns of substance abuse and addiction are not completely understood, they at least partly reflect accessibility and social practices.

Important new drug abuse trends include the abuse of club drugs (see related article, page 25) and anabolic steroids among young people. Club drugs include methylenedioxymethamphetamine (MDMA, ecstasy), flunitrazepam (Rohypnol), gamma hydroxybutyrate (GHB), gamma butyrolactone (GBL), and ketamine. MDMA abuse increased from 5.8% to 8% among 12th-graders from 1998 to 1999. Methamphetamine addictions are replacing opiate addictions in several areas in the world and promise to become an even larger problem in the United States. Anabolic-androgenic steroid abuse increased from 2% to 2.7% among 10th-graders from 1998 to 1999. Because of increased pressure to perform in sports, abuse of steroids by young women rivals that of young men, and it is estimated that 175,000 high-school-aged women have used steroids at least once. Typical patterns of use include sharing needles for group injections with the aim of building muscle together, and these practices have been associated with substantial transmission of disease. Cessation of steroid use is associated with withdrawal symptoms.

The question “Who are substance abusers?” is thus not an easy one to answer. It may not be surprising that 53% of the general population in the United States have used illicit drugs at one time or another. However, some

aspects of the profile of the “average” injection drug user may be surprising: 60% are men, 45% are white, 43% have completed high school, and 53% are employed.

### Drug Abuse and Disease

Among injection drug users in this country, some 40% to 45% are HIV-infected, 30% have a positive test result with tuberculin skin testing, 80% to 90% are hepatitis C virus (HCV)-seropositive, 40% are hepatitis B virus (HBV)-seropositive, and 60% use alcohol. The frequency of other sexually transmitted diseases (STDs) ranges from 0% to 80%, and STDs are more common in women than in men. Such data are known only for injection drug users, who account for approximately 10% of the estimated 6 million active drug users in the United States. Levels of such comorbidity in noninjection drug users are likely somewhere between those observed in injection drug users and those in the general population. However, it is also believed that the drug-using population is larger than estimated and that significant comorbidity occurs in the unaccounted-for segments of this population.

Comorbidity is the rule in substance abuse—drug users typically use more

**Table 1. Prevalence of Drug Use in the United States**

Drug	Current User Estimate
Alcohol	109,029,000
Tobacco	66,476,000
Marijuana	12,122,000
Cocaine	1,676,000
Hallucinogens	1,264,000
Inhalants	539,000
Stimulants	1,018,000
Heroin	123,000

Adapted from the 2001 National Household Survey on Drug Abuse of the Substance Abuse and Mental Health Services Administration.

**Table 2. Estimated Illicit Drug Use (Percent of Population) By Age, Sex, and Ethnicity in the United States**

Age (yrs)	White	Hispanic	African American
12-17	10.3	9.9	9.9
18-25	13.6	11.1	17.1
26-34	7.1	5.4	9.4
>35	3.2	3.5	4.8
<b>Sex</b>			
Male	7.7	7.7	12.0
Female	-	-	5.2

Adapted from the 1998 National Household Survey on Drug Abuse of the Substance Abuse and Mental Health Services Administration.

than 1 drug and have more than 1 disease—and it complicates patient management. A third of addicts have overt psychiatric comorbidity; in others, psychiatric problems become evident during treatment, with psychosis emerging in response to drug treatment in some. Often, psychiatric illness must be managed before the patient can begin treatment for medical illness and substance abuse. Disease contracted as a result of risk behaviors also complicates management. These diseases can be split into 2 conceptual categories: those that pose a public health threat, such as HIV disease, hepatitis, other STDs, and tuberculosis; and those that do not, such as cellulitis, endocarditis, and meningitis. In this latter context alone, billions of dollars are spent treating complications of drug abuse that could be prevented with rigorous adoption of a focus on treatment and prevention of drug abuse. Additional management complications stem from problems with interactions between drugs used to treat substance dependence and those that treat medical and psychiatric illnesses. Further, many substance abusers appear to have increased tissue and organelle injury that can complicate drug treatment.

With regard to HIV infection in substance abusers, injection drug users have a high rate of HIV disease, as noted above. In addition, approximately 25% to 30% of noninjection drug users have HIV infection. Drug-sharing and sex networks frequently overlap. Transmission of HIV can occur through needle sharing and sex, and the use of some noninjection drugs, such as crack cocaine, is associated with frequent unsafe sex

practices and increased risk of transmission of HIV infection and other STDs. Transmission can also occur in the absence of needle sharing through reuse of the cotton wads that are used to filter injected heroin or cocaine solutions. Virus-containing blood from the reused syringe of one person is deposited in the cotton wad and then washed into the drug solution to be injected by another person when the solution is filtered through the reused cotton wad. Persons infected in this manner may believe that they are at no risk for HIV transmission and can subsequently infect others through unprotected sex, which they perceive as “safe” because they do not share needles.

As noted, the prevalence of other STDs among drug users is highly variable, with prevalence and incidence varying in part according to the substance of abuse. Notable associations include those of syphilis and crack cocaine use; trichomoniasis in injection drug-using women, which is associated

with vaginal inflammation that may facilitate HIV transmission; and a high rate of sexual transmission of HBV (30%-50%) in injection drug users. Approximately 60% of the 4 million cases of HCV infection are in injection drug users, with sexual transmission accounting for less than 20% of cases. HCV transmission among drug users can be blood-borne, as a result of sharing razors and the straws used to snort drugs, which can cut the nasal mucosa and draw blood. Infection occurs in 50% to 80% of injection drug users within the first 2 years of use. Coinfection with HBV and HCV dramatically accelerates HCV disease progression in the drug-using population, with progression to severe liver disease occurring in 2 or 3 years in some cases. HCV infection is emerging as a substantial problem in younger persons in association with abuse of injection drugs, including steroids.

Medical and psychiatric drug therapy can be complex in patients receiving methadone for opiate addictions. Table 4 shows the effects of antiretroviral drugs on serum methadone concentrations, with the interactions primarily reflecting pharmacokinetic interactions between methadone and the nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) mediated by cytochrome P450 metabolism. It should be noted that measurable changes in serum levels of methadone with coadministration of these agents are not always accompanied by clinically significant effects (eg, withdrawal symptoms). Clinical effects have been observed with nevirapine and efavirenz among the NNRTIs and with nelfinavir among the PIs. Interactions of

**Table 3. Estimated Alcohol Use (Percent of Population) By Age, Sex, and Ethnicity in the United States**

Age (yrs)	White	Hispanic	African American
12-17	20.9	18.9	13.1
18-25	65.0	50.8	50.3
26-34	65.2	53.1	54.8
>35	56.2	47.7	38.3
<b>Sex</b>			
Male	61.2	56.8	49.0
Female	49.2	33.6	32.3

Adapted from the 1998 National Household Survey on Drug Abuse of the Substance Abuse and Mental Health Services Administration.

methadone with other commonly used drugs are shown in Table 5.

In treating medical and psychiatric disease in substance abusers, both substance abuse and concomitant disease must be identified and treated. Substance abuse is a chronic disease requiring chronic treatment, beginning with identification of the disease, detoxification, and stabilization.

### Treating Substance Abuse

Treatment of substance abuse requires a global approach to the patient, necessitating access to and use of health systems focused on the mental, physical, and environmental aspects of disease. Thus, effective treatment must confront physical disease (mental and physical aspects), genetic disposition to addiction, family situation, and historical and social situation. It must also confront stigma and treatment bias. Resources required for effective treatment are shown in Figure 1.

It must be stressed that treatment with methadone, buprenorphine, or levomethadyl acetate does not cure addiction. First, these drugs are used to treat only opiate addiction. Second, the only proven effect of methadone is that it decreases the amount of craving by patients during treatment for addiction. Thus, the role of methadone and the other drugs is to provide a stabilizing influence so that interventions designed to alter the patient's thinking, behavior, and environment, or to prepare the patient for return to a negative environment, can be implemented over a period of time. Drug therapy alone for treatment of addiction has a very low success

**Table 4.** Effects of Antiretroviral Drugs on Serum Methadone Concentrations

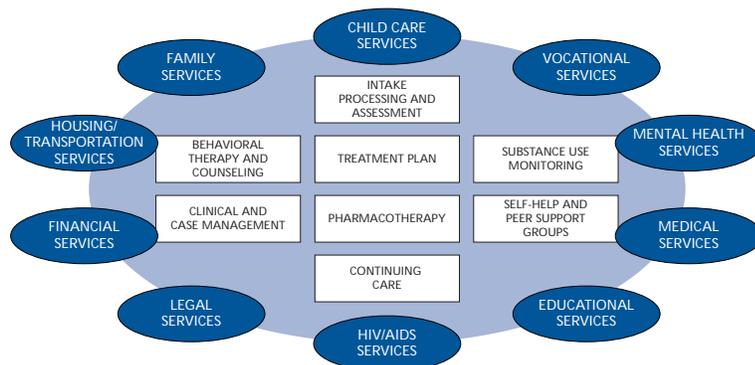
Drug	Effects
<b>Nucleoside Reverse Transcriptase Inhibitors</b>	
Zidovudine	No change
Didanosine	No change
Zalcitabine	Not studied
Stavudine	No change
Lamivudine	No change
Abacavir	Increase in methadone clearance
<b>Nonnucleoside Reverse Transcriptase Inhibitors</b>	
Nevirapine	Decrease in methadone levels by 46%, opiate withdrawal common, potential heroin use relapse
Delavirdine	Increase (modest) in methadone levels
Efavirenz	Decrease in methadone levels by 48%, opiate withdrawal common, potential heroin use relapse
<b>Protease Inhibitors</b>	
Indinavir	No change
Ritonavir	Decrease in methadone levels (study design limits clinical utility of data)
Nelfinavir	Decrease in total (but not free) methadone levels
Saquinavir	Decrease in R-methadone levels when administered with ritonavir
Amprenavir	No effect on R-methadone levels
Lopinavir/ritonavir	Decrease in methadone levels, opiate withdrawal

Adapted with permission from Gourevitch, *Mt Sinai J Med*, 2001.

rate: about 1 in 10 patients.

It is commonly believed that injection drug users have a low rate of adherence to drug treatment and other thera-

peutic regimens. This belief results in substantial treatment bias—treatment may be withheld from such patients, or patients may become discouraged by biased attitudes of health care practitioners. However, history of injection drug abuse is actually a poor predictor of treatment adherence, as are race, sex, age, socioeconomic status, level of education, and occupation. Factors that accurately predict patient adherence include patient health beliefs, ease of access to health care practitioners, familiarity of treatment setting, existence of a social support system for the patient, perceived support from clinical staff, and simplicity of medication regimens (Williams, *J Assoc Nurses AIDS Care*, 1997; Huang, *Int Conf on AIDS*, 1989; Samuels et al, *J Acquir Immune Defic Syndr*,



**Figure 1.** Components of a comprehensive substance abuse treatment program. Adapted from the National Institute on Drug Abuse, 1999.

**Table 5.** Effects of Other Commonly Used Drugs on Serum Methadone Concentrations

Drug	Effects
Rifampin	Decrease in methadone levels, severe opiate withdrawal
Rifabutin	No change, mild opiate withdrawal
Fluconazole	30% increase in methadone levels (unknown clinical significance)
Phenytoin	Decrease in methadone levels
Phenobarbital	Decrease in methadone levels
Carbamazepine	Decrease in methadone levels
Fluvoxamine	Increase in methadone levels by 20%-100%
Sertraline	Transient mild increase in methadone levels

Adapted with permission from Gourevitch, *Mt Sinai J Med*, 2001.

1990; Morse, *Soc Sci Med*, 1991). The patient's belief in the health system, which often must be encouraged and supported, is of enormous importance to adherence and treatment success in substance-abuse patients.

The goal of substance-abuse treatment is to return the patient to productive functioning. Treatment reduces drug abuse by 40% to 60%, reduces associated crime by 40% to 60%, and increases employment prospects by 40% (Craven et al, *J Acquir Immune Defic Syndr*; 1990; Morse et al, *Soc Sci Med*, 1991). Appropriate treatment for substance abuse is as successful as treatment of other chronic conditions such as diabetes, asthma, and hypertension.

### Conclusions

Perhaps the greatest impediment to the effective treatment of substance abuse is the view that the condition is a social problem rather than a disease. The response to behaviors resulting from addiction is more frequently incarceration than renewed or intensified efforts at stabilizing and treating the substance abuser. The costs associated with substance abuse are enormous, including costs associated with the high frequency of HIV disease and other diseases in the substance-abusing population. Prevention of substance abuse prevents associated complications and reduces costs to society. In this regard, it bears noting that children between the ages of 8 and 12 whose parents or caregivers warn them about the dangers of drugs and

other abused substances are half as likely to become addicted to or engage in significant abuse of drugs as those who do not receive such direct attention.

It is important that health care practitioners have access to information on current trends in abused substances and their effects on those who use them. Web site addresses where such information is available are listed in Table 6.

*Presented in August 2002. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Francis in December 2002. A Webcast of the original course lecture by Dr Francis is available online at [www.iasusa.org/webcast](http://www.iasusa.org/webcast).*

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

**Table 6.** Sources of Information on Substance Abuse, Its Treatment, and Abused Substances

<a href="http://www.nida.nih.gov">www.nida.nih.gov</a>	National Institute on Drug Abuse
<a href="http://www.whitehousedrugpolicy.gov">www.whitehousedrugpolicy.gov</a>	Office of National Drug Control Policy
<a href="http://www.dea.gov">www.dea.gov</a>	US Drug Enforcement Administration
<a href="http://www.bluelight.nu">www.bluelight.nu</a>	Descriptions of the experiences of adolescents taking various drugs; these descriptions can be helpful in identifying unusual clinical presentations associated with drug use
<a href="http://www.erowid.org">www.erowid.org</a>	Up-to-date list of drugs used by young people, information on biochemistry of these drugs and their clinical effects

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## Review

# Use of Club Drugs by HIV-Seropositive and HIV-Seronegative Gay and Bisexual Men

Frank Romanelli, PharmD, BCPS, Kelly M. Smith, PharmD, and Claire Pomeroy, MD

**Abstract.** Club drugs such as methylenedioxymethamphetamine (MDMA, ecstasy), gamma hydroxybutyrate (GHB), and ketamine are among the fastest-growing drugs of abuse in the United States. Reports have shown that some gay and bisexual men are likely to engage in club-drug use in a myriad of venues. This is concerning given that the use of club drugs has been linked to high-risk sexual behaviors. Further, the use of club drugs by HIV-seropositive individuals may have detrimental outcomes on disease progression by either influencing adherence, resulting in drug-drug interactions with antiretrovirals, or potentially compounding immune suppression. Clinicians caring for HIV-seropositive and -seronegative individuals should be aware of the clinical effects and management guidelines associated with these chemicals. This article reviews the available literature with regard to the use of club drugs by HIV-seropositive and -seronegative gay and bisexual men. Although club-drug use may be associated with many risk behaviors for HIV infection, this review focuses on risk behavior among gay and bisexual men since this is the group for which the most data have been reported. The clinical effects and management guidelines associated with these agents are described, and the potential detrimental effects of these substances on HIV disease are discussed.

## Introduction

Recent reports of increasing incidences of both HIV and AIDS within the United States emphasize the need to improve preventive efforts and better identify concomitant behaviors that contribute to the spread of HIV and AIDS among persons at risk.<sup>1</sup> Many public health researchers are examining the social factors that contribute to the spread of HIV, including behaviors that increase the chances that individuals will choose to engage in high-risk practices such as unprotected sex.<sup>2</sup> One underrecognized concern is the use of club drugs among gay and bisexual men and the contribution that drug use may make in encouraging high-risk sexual practices. Although abuse of club drugs and the potential adverse consequences of such abuse are associated with many risk behaviors, this review focuses on risk behaviors of gay and bisexual men, since this is the population for which the most data have been published.

Club drugs are substances used in a recreational fashion to enhance social experience. Because these drugs produce social

disinhibition, they have been used to heighten sexual experiences. In addition, club drugs have been used to facilitate date rape because they produce retrograde amnesia.<sup>3</sup> The use of club drugs first gained popularity in Europe and later in the Americas with the advent of raves, all-night parties with a prolonged style of dance to fast-paced, repetitive music often accompanied by laser light displays. Methylenedioxymethamphetamine (MDMA, ecstasy), gamma hydroxybutyrate (GHB), and ketamine are the chemical substances most commonly referred to as "club drugs."<sup>4</sup> Each of these chemicals may be consumed to heighten the user's rave or party experience by increasing the energy to dance for prolonged periods of time or by decreasing social inhibitions.

The incidence of club-drug use among the general population continues to increase at an exponential rate.<sup>5,6</sup> The National Drug Intelligence Center equates the expanding production, availability, and use of MDMA to that of cocaine and heroin.<sup>5</sup> Use of MDMA is now estimated to be the fastest-growing drug-abuse problem in the United States. In 2000, 1.3 million high-school seniors had consumed MDMA, and approximately 450,000 admitted to being current users.<sup>6</sup> MDMA has become the most common stimulant used in bars and clubs in many areas of the country, a figure that has increased as traffickers target such venues. Although not as well quantified, anecdotal reports indicate distressing increases in the use of GHB and ketamine as well.<sup>5,6</sup> Some highly publicized deaths have been associated with the use of club drugs, and it should be emphasized that these drugs may contribute to HIV infection and many more deaths by encouraging high-risk behaviors. To further define this problem, we reviewed the available literature regarding use of club drugs by gay and bisexual men.

## Epidemiology

No controlled trials have compared the prevalence of club-drug use among gay and bisexual men to that of the general population or among other individuals at higher risk of HIV transmission. Several studies have, however, examined prevalence particularly among gay and bisexual men alone. Mansergh and colleagues conducted a cross-sectional survey study of 295 gay and bisexual men in the San Francisco Bay Area who had attended a circuit party in the previous year.<sup>7</sup> Circuit parties most often encompass 2- or 3-day-long weekend events attended primarily

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by gay and bisexual men from across the country. The typical circuit party weekend involves a series of social gatherings that culminate with one main dance event. Anecdotally, circuit parties are associated with a high incidence of drug use and sexual behavior, leading many to hypothesize an increased incidence of high-risk sex. In this study, all respondents reported use of club drugs during circuit party weekends. Specifically, 75% of respondents reported having used MDMA; 58%, ketamine; and 25%, GHB. Two-thirds of the men reported having some form of oral or anal sex, 49% reported having anal sex, and 28% reported having unprotected anal sex during the 3-day period. An association was found between the use of club drugs and the incidence of high-risk sexual behavior. These researchers concluded that use of club drugs might encourage high-risk behaviors and that targeted preventive efforts are needed for gay and bisexual men who attend circuit parties.

Klitzman and colleagues conducted a pilot study to examine the correlation between MDMA abuse and high-risk sexual behaviors among 169 gay and bisexual men through the use of an anonymous questionnaire distributed at 3 New York City dance clubs.<sup>8</sup> One-third of all respondents reported MDMA use at least monthly, and there was a strong and statistically significant correlation between MDMA use and history of recent repeated unprotected anal intercourse. This association remained equally strong following control for age, ethnicity, and all other forms of drug abuse, including ethanol.

Waldo and colleagues examined correlates of drug use and risky sexual behavior in a group of young gay and bisexual men (aged 15-17 years) and their older counterparts (aged 18-22 years).<sup>9</sup> An interviewer-administered cross-sectional survey was administered to 719 gay and bisexual men. Blood specimens were collected and tested for HIV and evidence of other known sexually transmitted diseases. HIV seroprevalence was lower among those aged 15 to 17 (2%) than among those aged 18 to 22 (6.8%). Men aged 15 to 17 used MDMA less frequently than those aged 18 to 22. In both age groups use of MDMA was associated with unprotected anal intercourse.

Suspecting that club-drug use among gay and bisexual men would mirror or exceed national trends and recognizing that club-drug use might predispose to high-risk sexual practices, Colfax and colleagues conducted a cross-sectional survey study in San Francisco to examine the prevalence of club-drug use and high-risk sex practices during circuit party weekends.<sup>10</sup> They found that 80% of circuit party attendees had used MDMA; 66%, ketamine; and 29%, GHB. Drug use was statistically more common during circuit party weekends than during non-circuit party weekends ( $P < .001$ ). Also concerning was that the incidence of unprotected anal sex with partners of unknown HIV serostatus or opposite serostatus was reported by 21% of HIV-seropositive and 9% of HIV-seronegative respondents. The authors concluded that, at least during circuit party weekends, the use of club drugs is strongly associated with the incidence of behaviors that place individuals at risk for HIV transmission.

Mattison and colleagues also examined the use of club drugs within circuit party settings.<sup>11</sup> A brief questionnaire involving demographics, drugs used, sexual activity, and reasons for attendance at circuit parties was provided to a nonrandom sample of party attendees at 3 separate venues in 1998 and 1999. A total of 1169 usable questionnaires were obtained.

Club-drug use during the previous 12 months was high, with greater than 50% of all respondents reporting having used MDMA or ketamine. Frequent use of MDMA and ketamine was associated with high-risk sexual practices such as unprotected anal sex. Interestingly, the most common reasons for attending a circuit party were "to be uninhibited and wild" and "to have sex." These responses are consistent with the high incidence of unprotected sex observed in the cohort. Although several limitations, such as lack of randomization, characterize this trial, researchers concluded that intensive preventive and interventional efforts are needed among gay and bisexual men who use club drugs and attend circuit parties.

Authors from each of these trials expressed concern about the degree to which club drugs influence a user's decision to have unprotected anal sex. This is not surprising given the disinhibiting effect of most club drugs. Although most of these studies had several limitations, they do reveal important and unrecognized factors that may contribute to high-risk sexual behaviors among gay and bisexual men in the United States. These trials demonstrate the need for HIV clinicians to be familiar with the clinical effects and issues surrounding the use of club drugs.

### Club Drugs in HIV-Seropositive Individuals

Concerns have been raised regarding the dangers of club-drug use among HIV-seropositive individuals on antiretroviral medications. The abuse of any drug or chemical substance inherently results in obstacles to adherence. Serious drug interactions may also result from concurrent use of club drugs and antiretroviral medications. Clinicians should also be cognizant of the fact that most club drugs are rarely sold in their pure form and are often adulterated with other chemicals such as dextromethorphan, aspirin, lysergic acid, or pseudoephedrine.<sup>12</sup>

Harrington and colleagues reported the case of a 29-year-old man with AIDS on a regimen consisting of twice-daily doses of saquinavir 400 mg and ritonavir 400 mg who ingested approximately a half teaspoonful (2.5 mL) of GHB. Within 20 minutes he became unresponsive with clonic contractions of the left side of his body.<sup>13</sup> Emergency medical personnel found the patient responsive only to painful stimuli and with a heart rate of 40 beats per minute. The patient eventually required intubation and over a 3-hour period was stabilized and extubated. Upon questioning, the patient admitted to ingesting 2 MDMA tablets 29 hours prior to admission, a half teaspoonful of GHB 6 hours prior to admission, and an additional half teaspoonful of GHB just prior to his loss of consciousness. The patient reported ingesting GHB in order to counteract the stimulant effects of MDMA. Interestingly, the patient reported that prior to taking protease inhibitors (PIs), he often used similar quantities of GHB as a sleep aid without any adverse effects. The patient maintained that his last dose of MDMA was 29 hours prior, yet its effects persisted and prompted him to ingest GHB.

Many amphetamines, including MDMA, are metabolized via the cytochrome P450 (CYP450) system. More specifically, MDMA is metabolized by the CYP2D6 isoform. The majority of commercially available PIs, including ritonavir, will inhibit this isoenzyme and others (eg, CYP2C9, CYP2C19). It is likely that in this case ritonavir inhibited the metabolism of the MDMA,

resulting in prolonged and persistent effects of the substance. Clearance of GHB is mediated partially by systemic oxidation and partially by first-pass metabolism via the CYP450 system. Inhibition of the CYP450 system by ritonavir might explain this patient's exaggerated response to the agent. This case report illustrates the potential adverse effects that may be seen when club drugs such as MDMA and GHB are coadministered with antiretrovirals, particularly PIs with CYP450 inhibitive properties.

Henry and colleagues described a fatal interaction involving MDMA and ritonavir in a 32-year-old white man with AIDS.<sup>14</sup> The patient had been taking zidovudine and lamivudine for a number of years, and ritonavir was added to his regimen 1 month prior to admission. The patient reported commonly using MDMA without any untoward adverse effects. On the night of admission, the patient visited a club and reported ingesting 2.5 MDMA tablets (estimated MDMA dose of 180 mg, calculated from the MDMA content of a remaining tablet found in the patient's supply). While at the club, the patient became tachycardic with a pulse rate of up to 200 beats per minute. He experienced tonic-clonic convulsions, vomited, and later experienced cardiorespiratory arrest. Attempts at resuscitation were unsuccessful. In autopsy, the only illicit drug detected was MDMA at a serum level of 4.56 mg/L. Previously reported toxic ingestions of 42 and 18 MDMA tablets led to serum levels of 7.72 mg/L and 4.05 mg/L, respectively. Similar to the case reported by Harrington and colleagues, it was hypothesized that ritonavir acted as an inhibitor of the CYP450 system and in this case may have resulted in lethal MDMA serum levels. In evaluating potential interactions between club drugs and antiretrovirals, clinicians should be careful to review metabolic pathways and properties of the agents in question.

Some reports are now finding correlations between club drugs and transient immune suppression. This is particularly concerning given the number of HIV-seropositive patients who may be using these agents. Pacifici and colleagues conducted a placebo-controlled crossover study in which 17 healthy adult men were administered 2 repeated doses of 100 mg of MDMA at 4- and 24-hour intervals.<sup>15</sup> The researchers found that MDMA produced a time-dependent decrease in the CD4+/CD8+ cell ratio due to a decrease in CD4+ cells. They also noted a reduction in functional responsiveness of lymphocytes to mitogenic stimulation and a simultaneous increase in natural killer cell activity. Significant residual effects were noted up to 48 hours following exposure to MDMA. The researchers hypothesized that the immunosuppressive effects of MDMA are related to inductions in cortisol secretion. While US research in this area is hampered by MDMA's status as a controlled substance, this trial suggests significant implications for future research.

Pacifici and colleagues also examined the immune effects of administration of MDMA with and without ethanol in 6 healthy adult men.<sup>16</sup> Single oral doses of MDMA (100 mg), ethanol (0.8 g/kg), a combination of MDMA and ethanol, and placebo were administered, with a washout interval of 1 week between each. Acute MDMA administration produced time-dependent immune dysfunction in association with serum concentrations of the drug, as well as increased serum cortisol levels. Similar to the previously mentioned trial, a reduction in CD4+ cell counts and simultaneous increases in natural killer cell activity were

noted. The largest reductions in CD4+ cells were seen in individuals who received MDMA combined with ethanol, indicating some synergism between the 2 agents. Immune function appeared to trend toward baseline 24 hours after MDMA administration.

Both of these pilot studies of the effects of club drugs on immune status have limitations. The reported CD4+ cell count variations appear short-lived and transient and may simply reflect normal diurnal fluctuations. Sample sizes are also small and have yet to show any clinical significance. Recognizing the limitations of the research, larger well-controlled trials must be designed to truly elucidate drug effects from confounding factors. As previously mentioned, research in this area is limited by MDMA's controlled-substance status within the United States.

## Clinical Effects and Management of Club-Drug Ingestions

As common as club-drug use is among gay and bisexual men, regardless of HIV serostatus, little information is available in the literature regarding antiretroviral medications and club-drug interactions. Also, many health care professionals, including pharmacists, are unfamiliar with the clinical effects and management strategies for toxic ingestions of these substances. Clinicians caring for HIV-seropositive patients should be particularly familiar with the clinical effects of these agents. Patients should be questioned regarding their consumption of these substances, and clinicians should be prepared to counsel and advise patients regarding their use. In many instances it may be advisable to involve psychiatric and substance abuse counselors, as the issues surrounding drug abuse of any kind are often complex and multifactorial. The 3 major club drugs—MDMA, GHB, and ketamine—are reviewed below.

### Methylenedioxymethamphetamine

MDMA was initially developed in 1914 as an appetite suppressant.<sup>17</sup> The drug was never marketed, but some efficacy was demonstrated in the 1970s as a means to enhance communication in behavioral therapy sessions.<sup>18</sup> In the 1980s, MDMA became popular among young adults attending raves and all-night clubs, and its increasing abuse and evidence of adverse health effects contributed to the drug being classified as a schedule I controlled substance in 1985.<sup>19</sup> In 2001, however, the US Food and Drug Administration (FDA) approved a clinical trial examining MDMA's effects on posttraumatic stress disorder. This was the first FDA-approved clinical trial involving MDMA since the drug became a controlled substance.<sup>20</sup>

MDMA is commonly manufactured in clandestine laboratories throughout Europe and the United States. A great deal of the product is imported from Amsterdam. In addition to ecstasy, various street names for MDMA exist, including X, ADAM, XTC, and hug drug.<sup>19</sup> Tablets, which typically contain from 50 mg to 150 mg of active drug, are usually imprinted with a popular icon such as the Nike swoosh or Motorola symbol. Users sometimes refer to MDMA by these imprints (eg, "a smurf pill"). MDMA is typically purchased in the setting where it will be used, most commonly at raves. Prices range from \$20 to \$40 per tablet, and it is not uncommon for tablets to be adulterated

with other chemicals, including aspirin, dextromethorphan, and pseudoephedrine.<sup>21</sup>

MDMA is structurally similar to the stimulant methamphetamine and to the hallucinogen mescaline, lending to its effects as both a stimulant and hallucinogen.<sup>21</sup> MDMA affects neurotransmitters, including serotonin, dopamine, and norepinephrine.<sup>22</sup> Release of these neurotransmitters by presynaptic neurons is often increased and their metabolism by monoamine oxidases inhibited, resulting in excessive synaptic concentrations.<sup>22</sup>

The clinical effects of MDMA typically begin within 30 to 60 minutes of ingestion, with a duration of action lasting approximately 6 to 8 hours.<sup>23</sup> The term “ecstasy” comes from many of the effects produced by the drug, which include euphoria, feelings of closeness, altered visual and sensory perception, increased libido, and increased energy.<sup>24</sup> Diminished hunger and thirst are also common effects. MDMA use is usually accompanied by characteristic paraphernalia, including pacifiers or candy suckers, which are used to avoid bruxism, a common effect associated with the drug. Glowsticks and brightly colored necklaces and bracelets may be displayed to heighten visual hallucinations. Vicks VapoRub is also commonly used to enhance the effects of MDMA.<sup>25</sup> VapoRub may be directly inhaled, rubbed above the upper lip, or applied to the inside of a surgical or painter’s mask. The distinctive odor and sensations produced by the product are often amplified and exaggerated by MDMA use. Because MDMA alone or in combination with physical activity can quickly result in elevated body temperature, consumption of large quantities of water or other fluids is a common practice. Users must be cautious as excessive consumption of water may result in hyponatremia. MDMA may also promote excessive dancing, a phenomenon commonly known as marathon dancing. Marathon dancing may contribute to dehydration and hyperthermia.<sup>26</sup> In an effort to combat dehydration, many raves supply beverages known as “power drinks” or “smart drinks” that are fortified with amino acids and vitamins.

Serious adverse effects have been reported following the ingestion of as little as 1 MDMA tablet.<sup>27</sup> Tachycardia and hypertension are the result of sympathomimetic stimulation, and the psychedelic effects of the drug are a result of serotonergic stimulation.<sup>27</sup> More severe complications of ingestion, including seizures, cerebral edema, and serotonin syndrome, have been reported.<sup>28</sup> Confusion, depression, insomnia, anxiety, and paranoia have been reported to occur for weeks following ingestion.

Chronic use of MDMA has been correlated with cognitive impairment in both humans and animals. Cognitive impairment is believed to be related to changes in the structural components of serotonergic neurons.<sup>29</sup> Positron emission tomography brain scans of MDMA users have revealed significant reductions in the number of serotonin transporters; the magnitude of transporter loss was associated with extent of use of MDMA.<sup>29</sup>

Diagnosis of MDMA intoxication is based primarily upon history and examination. The most common findings on presentation include agitation, anxiety, tachycardia, and hypertension.<sup>27</sup> Clinicians should be particularly suspicious of patients presenting with MDMA-associated paraphernalia (eg, brightly colored bracelets and other jewelry, pacifiers, and bottled water).

No antidote exists for MDMA ingestion, but management should involve monitoring for serious adverse effects including arrhythmias, hyperthermia, and rhabdomyolysis. Gastric decontamination with activated charcoal may be helpful within 60 minutes of MDMA ingestion; unfortunately, few patients will present within this time frame. Supportive care should be provided. Agitation and anxiety may be controlled with benzodiazepines, and hypertension with labetalol, phentolamine, or nitroprusside. Pure beta-adrenergic blocking agents may worsen hypertension by causing unopposed alpha-stimulation and should be avoided.<sup>21</sup> Hyperthermia can be managed with rapid external cooling using tepid water. Neuromuscular blockade to induce paralysis is the most effective method for core body temperature reduction, but requires intubation. Treatment of serotonin syndrome with dantrolene or cyproheptadine may be effective, but aggressive supportive care with rapid cooling remains the mainstay of therapy.<sup>28</sup> Rhabdomyolysis is managed by alkalizing the urine with the administration of intravenous sodium bicarbonate. In severe cases of renal failure, hemodialysis may be indicated.

Detection of MDMA remains a conundrum for clinicians. MDMA may be detected in samples by immunologic assay for related chemicals such as amphetamine and methamphetamine.<sup>30</sup> In order to detect the presence of MDMA alone, larger concentrations of the drug must be present in the serum, and testing procedures for MDMA alone are only 50% as sensitive as those for amphetamine and methamphetamine.<sup>23</sup> Traditional toxicology screens that employ thin-layer chromatography can detect MDMA metabolites in the urine. Gas chromatography/mass spectrometry may be used to confirm positive immunoassay tests.

Numerous HIV-specific issues surrounding acute and chronic ingestion of MDMA exist. As noted, clinicians should be cognizant that MDMA tablets often contain contaminants. The clinical effects of these contaminants as well as their potential for interacting with antiretrovirals should be considered. Fluid status changes associated with excessive hydration from copious water ingestion or dehydration from excessive dancing can complicate the adverse effects associated with specific antiretrovirals. Fluid status changes can intensify the effects of antiretroviral-induced diarrhea, and dehydration may precipitate indinavir-associated nephrolithiasis.<sup>31</sup> Patients with underlying wasting syndrome might be more prone to the appetite-suppressing effects of MDMA and should be carefully monitored for reductions in weight. “Power drinks,” which are often consumed with MDMA, may contain amino acids and other vitamin supplements that may lead to compound toxicity. Patients on amprenavir should particularly avoid supplements containing vitamin E.<sup>32</sup> Lastly, many HIV-seropositive patients with depression may be managed with selective serotonin reuptake inhibitors (SSRIs). These patients should be aware that concomitant use of SSRIs with MDMA might result in the serotonin syndrome.

### **Gamma Hydroxybutyrate**

GHB is a naturally occurring fatty-acid derivative of the central nervous system (CNS) neurotransmitter gamma aminobutyric acid (GABA).<sup>33</sup> In the United States, GHB was originally intro-

duced as an anesthetic agent, but a lack of analgesic effects coupled with reports of seizure-like activity destined the drug for failure.<sup>34</sup> Since that time, placebo-controlled trials have examined the role of the GHB analogue oxybate sodium for the management of narcolepsy-associated cataplexy. Recently, the FDA approved oxybate sodium, a GHB analogue, for the treatment of cataplexy. The drug is a schedule III controlled substance that will be available only through a stringent FDA closed-distribution system.<sup>35</sup> Street and slang names for GHB include liquid ecstasy, G, Georgia home boy, gib, liquid X, salty water, and soap.<sup>3</sup>

Originally introduced as a dietary supplement in 1990, GHB was touted by many trainers and body builders as a means to increase muscle mass, metabolize fat, and stimulate libido.<sup>36</sup> As the agent's popularity increased, users became familiar with its ability to produce a euphoric state. In late 1990, the FDA banned all over-the-counter sales of GHB.<sup>37</sup> By this time GHB had already entered the club-drug scene and many had become aware of its potential use as a "date-rape" drug. In early 2000, GHB was designated a schedule I controlled substance in the United States, but it is often imported from European sources or manufactured in clandestine laboratories. Many Internet sites advertise "recipes" for the home production of GHB and GHB manufacturing kits. GHB is most commonly available as an oral solution (ie, "Liquid X," "Liquid E"). In settings of abuse, the chemical is commonly available in small vials or mixed with bottled water. A common dose of GHB is 1 capful of the liquid, which typically sells for \$5 to \$10.

Since the reclassification of GHB to schedule I, chemical precursors of GHB have become popular sources of the drug. Gamma butyrolactone (GBL) and 1,4-butanediol (1,4-BD) are both chemical precursors of GHB that produce similar effects. GBL is widely used in the chemical industry and is available from chemical supply companies and health stores.<sup>38</sup> Following ingestion, GBL is rapidly converted to GHB by endogenous lactonase enzymes.<sup>23</sup> GBL is more rapidly absorbed and produces a longer duration of action than GHB.<sup>39</sup> In 1999, the FDA issued a warning alerting the public of the dangers of GBL and asked manufacturers for a voluntary recall of the product.<sup>40</sup> 1,4-BD is also available in health stores and the FDA has warned of its abuse potential. Following ingestion, 1,4-BD is metabolized by alcohol dehydrogenase to gamma hydroxybutyraldehyde, which is in turn metabolized to GHB by aldehyde dehydrogenase.<sup>23</sup> Because ethanol preferentially binds alcohol dehydrogenase, prolonged toxicity may occur when 1,4-BD is ingested concurrently with ethanol.<sup>41</sup>

GHB is thought to mediate various processes including sleep cycles, temperature, cerebral glucose metabolism, and memory.<sup>42</sup> GHB, a metabolite of GABA, is normally found within the CNS in concentrations that are 1/1000 that of GABA.<sup>43</sup> GHB is also believed to influence endogenous dopamine levels, possibly increasing concentrations through interactions with GABA receptors.<sup>42</sup> GHB is commonly abused by bodybuilders who believe in the agent's purported ability to increase muscle mass. The agent is thought to prolong slow-wave sleep, which is the period when the greatest concentration of growth hormone is released.<sup>45</sup> Although use of GHB has been associated with some short-term increases in growth hormone, these findings have not been demonstrated in large, well-controlled clinical trials.

GHB's lipophilic properties facilitate its ability to rapidly cross the blood-brain barrier.<sup>46</sup> The drug is primarily metabolized by the lungs and expired as carbon dioxide.<sup>47</sup> Additionally, 2% to 5% of the drug is eliminated renally. Peak plasma concentrations occur within 20 to 60 minutes of ingestion, and the half-life of the agent is 20 minutes.

Clinical effects following GHB ingestion usually develop within 15 to 30 minutes.<sup>3</sup> These effects are amplified with coingestions of alcohol or other CNS depressants.<sup>21,41</sup> Dose-related CNS depression is the most common manifestation of ingestion.<sup>43,46</sup> With increasing doses, CNS depression progresses from amnesia and hypotonia to drowsiness, dizziness, and euphoria. GHB is often ingested to counteract the stimulant properties associated with other club drugs such as MDMA. Tonic-clonic seizures have been reported in a number of cases and electroencephalogram changes have been seen in animal models. Garrison and colleagues reported a case series of 78 patients who had ingested GHB; 9% of the users developed some form of seizure-like activity.<sup>48</sup> However, in another case series involving 88 patients with GHB ingestion, no patients had reported any seizure activity.<sup>49</sup> These reports are difficult to interpret because random muscular contractions caused by GHB are often misinterpreted as seizures.

Respiratory depression is also a common manifestation of GHB ingestion. Most patients will maintain airway patency, although some may require intubation with mechanical ventilation.<sup>49</sup> Cardiovascular effects include bradycardia and hypotension. Bradycardia has been reported in as many as 36% of users and is correlated with level of consciousness. Gastrointestinal effects include vomiting and hypersalivation.<sup>50</sup> Vomiting is more common when GHB is coingested with ethanol. Hypothermia (ie, a core body temperature of less than 35°C) has been reported commonly in as many as 31% of patients.<sup>49</sup>

GHB has been associated with cases of sexual assault or "date rape."<sup>3</sup> The drug is easily administered because of its liquid dosage form. GHB's powerful intoxicating properties will cause victims to lose consciousness as well as the ability to resist or recall a sexual assault.<sup>51</sup> These effects make assault cases involving GHB difficult to prosecute because attackers may claim that the incident was consensual.

No antidote exists for GHB ingestion.<sup>51</sup> Generally, most ingestions are self-limiting and patients can be managed with supportive care. Most patients recover within 7 hours of ingestion without the need for intubation,<sup>49,51</sup> although severe ingestions may require intubation. Since GHB is a sedative amnestic, rapid-sequence intubation may be accomplished with paralytics alone.<sup>43</sup> Aggressive suction will be needed as patients may have large amounts of oral secretions. Clinicians should be cognizant of cases involving 1,4-BD and ethanol coingestion, since these patients may present with prolonged or recalcitrant toxicity requiring more aggressive management.

GHB is not detected by routine urine or serum toxicology screening.<sup>52</sup> Diagnosis is most often made based upon history and presentation.<sup>3,43</sup> Gas chromatography and mass spectroscopy are the most precise methods for the detection of GHB; however, these testing methods will not differentiate GHB from its precursors, GBL and 1,4-BD. Serum levels greater than 50 mg/mL are associated with a loss of consciousness, and levels greater than 260 mg/mL with unresponsive coma.<sup>53</sup> GHB is

rapidly metabolized and therefore any delay in testing will lower the likelihood of detection. Generally, delays beyond 12 hours after ingestion will lead to undetectable results.<sup>3</sup>

There are several issues around GHB use specific to HIV-infected patients. Because of GHB's powerful sedative effects, it may be used by HIV-seropositive patients with insomnia in attempts to promote or enhance sleep. GHB should be used with caution by HIV-seropositive patients with predisposing seizure disorders or with opportunistic infections that may lower seizure threshold (ie, toxoplasmosis, cryptococcal meningitis). Use of GHB in these situations may precipitate seizure-like activity. Lastly, GHB use may cause severe nausea, vomiting, and gastrointestinal-tract irritation that may complicate antiretroviral therapy and affect adherence. GHB detoxification may precipitate a withdrawal phenomenon, which may necessitate hospitalization for symptomatic management and to ensure antiretroviral adherence.

## Ketamine

Ketamine, a derivative of phencyclidine hydrochloride (PCP), was introduced in the 1960s as a dissociative anesthetic.<sup>54</sup> The advent of safer, more effective anesthetic products has greatly diminished the clinical use of ketamine. Ketamine may still be used in some pediatric critical-care settings and is commonly used in veterinary medicine for animal sedation. Street and slang names for ketamine include special K, K, kit-kat, super acid, super K, and jet.<sup>12</sup>

Prescription ketamine is available as an injection formulation and is classified as a controlled substance in most states. Federally, the substance is classified as a schedule III drug product. Ketamine is difficult to manufacture and therefore the most common mode of acquisition is through diversion of the prescription product. Theft of ketamine from veterinary clinics and animal hospitals is common. Ketamine is believed to have entered the club-drug scene in the 1980s. Originally, the drug is thought to have been a common adulterant in MDMA tablets.<sup>55</sup> As users became familiar with ketamine's effects, its use as a sole agent emerged. Street cost of ketamine is estimated to be approximately \$80 per gram. Users may inject, ingest, or snort the product. However, ingestion is less common because the product undergoes extensive first-pass metabolism.

Ketamine's structural resemblance to PCP lends to its ability to interact with the N-methyl-D-aspartate channel, inhibiting it noncompetitively and also preventing glutamate activation.<sup>56</sup> Ketamine also indirectly interacts with a number of cellular receptors including the muscarinic, nicotinic, cholinergic, and opioid receptors. Inhibition of neuronal reuptake of norepinephrine, dopamine, and serotonin has also been demonstrated.<sup>54</sup>

In social settings, ketamine is most commonly snorted, and its effects are abrupt in onset and last only 30 to 45 minutes.<sup>55</sup> Lower doses of the drug result in analgesic effects, and higher doses will produce amnesic effects.<sup>3</sup> Patients often describe a dissociative feeling of "floating over one's body."<sup>57</sup> These out-of-body experiences are often referred to by users as "trips to K-land" or "K-holes."<sup>57</sup> Visual hallucinations and a lack of coordination are also common and not surprising given the drug's similarities to PCP.<sup>3,57</sup> Cardiovascular toxicity has been reported

in the form of reflex sympathetic activation, hypertension, tachycardia, and arrhythmias.<sup>54</sup> Because ketamine is an amnesic agent, respiratory depression and apnea are also commonly encountered manifestations of ingestion. Interestingly, many ketamine users report that the drug's effects are dependent upon the setting in which it is used. Noisy or rowdy settings may be correlated with negative effects and therefore certain users prefer not to use the drug in rave or club settings.<sup>58</sup>

The tasteless, odorless, and colorless characteristics of ketamine have made it an increasingly common date-rape drug.<sup>3</sup> The chemical can be easily and surreptitiously added to most beverages, and increasing numbers of facilitated sexual assault cases involving ketamine have been reported.<sup>56</sup> Loss of consciousness accompanied by anterograde amnesia and vivid hallucinations are common. Thus, the victim is rendered uncom- bative and potentially unreliable as a witness.

Similar to PCP ingestion, supportive care remains the cornerstone of management for ketamine ingestion.<sup>3</sup> Attention should be paid to respiratory and cardiac function. The vivid hallucinations associated with ketamine may be minimized by placing the patient in a tranquil environment with minimal external stimuli. Clinicians should be aware that coingestion of ethanol or other club drugs will only compound toxic effects. Death from ketamine ingestion is rare.<sup>59</sup> Serum levels of both ketamine and its active metabolite norketamine can be obtained, but testing is not generally available to most clinicians.<sup>60</sup> Of note, many immunoassays to detect PCP will cross-react with ketamine.<sup>61</sup>

Few HIV-specific issues relating to ketamine exist. Adherence to antiretroviral regimens is the primary concern, and the hallucinogenic effects of the drug may affect drug-taking behavior. Cardiovascular effects of the drug may be deleterious among patients with underlying heart disease or lipid abnormalities. As a substrate of the CYP450 system (specifically 3A4), ketamine may interact with certain antiretrovirals, particularly the PIs.

## Conclusion

Club drugs are popular substances of abuse among gay and bisexual men, particularly at circuit parties and other social gatherings. Commonly used to decrease social inhibitions, these agents also appear to promote high-risk sexual behaviors and have been associated with increased HIV transmission rates. Additionally, club drugs may produce significant and potentially lethal drug interactions with antiretroviral medications. Therefore, clinicians caring for HIV-seropositive individuals as well as officials designing preventive public health programs should be familiar with the clinical effects and management guidelines for these substances of abuse. Additionally, clinicians should be aware that use of club drugs or any other mind-altering substance by any individual might lead to high-risk sexual behavior contributing to HIV transmission.

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## Correction

An error was made in "Antiretroviral Treatment for Adult HIV Infection in 2002: Updated Recommendations of the International AIDS Society–USA Panel," which was reprinted in the September/October 2002 issue from *JAMA* (2002;288:222-235). In the second paragraph on page 266, the third sentence should have read, "Ritonavir inhibits enzymes of the cytochrome P450 system; it may act early on absorption and first-pass metabolism,

increasing peak plasma concentrations with a coadministered PI (eg, with *lopinavir or saquinavir*); or it may inhibit subsequent metabolism and extend the half-life of the second PI with an increase in trough level of drug (eg, with *indinavir or amprenavir*)." In the original version the examples in parentheses, indicated above with italic type, were incorrectly reversed.

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<sup>1</sup>International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2001. Available at <http://www.icmje.org>. Accessed November 5, 2002.



## Educational Programs of the International AIDS Society–USA

Established in 1992, the International AIDS Society–USA is a not-for-profit physician education organization. The mission of the International AIDS Society–USA is to improve the treatment, care, and quality of life of persons with HIV and AIDS through balanced, relevant, innovative, and state-of-the-art education and information for physicians who are actively involved in HIV and AIDS care. The organization's educational activities are particularly intended to bridge clinical research and patient care.

### IAS–USA Change of Address

The International AIDS Society–USA has moved. Please note the new address, phone number, and fax number:

International AIDS Society–USA  
425 California Street, Suite 1450  
San Francisco, CA 94104-2120

Phone: (415) 544-9400  
Fax: (415) 544-9401

### Cases on the Web – [www.iasusa.org/cow](http://www.iasusa.org/cow)

*Cases on the Web* is an ongoing series of case-based, advanced online CME activities produced by the International AIDS Society–USA. Editor in Chief, Michael S. Saag, MD; Co-Editor, Meg D. Newman, MD.

#### CURRENT PRESENTATIONS

**Liver Dysfunction Associated With Antiretroviral Therapy**  
Andrew Carr, MD

**Current Issues in HIV/Hepatitis Coinfection**  
Lorna M. Dove, MD

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

**Initiation of Antiretroviral Therapy**  
Constance A. Benson, MD

### Eleventh Annual Winter/Spring CME Course Series

*Improving the Management of HIV Disease®: Advanced CME Courses in HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management*

These courses will review timely and clinically relevant issues in the management of HIV disease, including updates from the 2002 Conference on Retroviruses and Opportunistic Infections. Topics will include new insights in HIV disease pathogenesis, strategies for antiretroviral management, metabolic complications, hepatitis coinfection, and the worldwide HIV epidemic. For course updates and registration information, please visit our Web site at [www.iasusa.org](http://www.iasusa.org).

**Los Angeles, California**  
Saturday, March 8, 2003  
Los Angeles Marriott Downtown  
Chairs: Ronald T. Mitsuyasu, MD, and Paul A. Volberding, MD

**Atlanta, Georgia**  
Thursday, March 20, 2003  
Westin Peachtree Plaza  
Chairs: Michael S. Saag, MD, and Jeffrey L. Lennox, MD

**New York, New York**  
Friday, March 28, 2003  
Hilton New York  
Chairs: Gerald H. Friedland, MD, and Paul A. Volberding, MD

**Chicago, Illinois**  
Thursday, April 24, 2003  
Hyatt Regency McCormick Place  
Chairs: John P. Phair, MD, and Harold A. Kessler, MD

**San Francisco, California**  
Tuesday, May 6, 2003  
Hotel Nikko San Francisco  
Chairs: Paul A. Volberding, MD, and Stephen E. Follansbee, MD

**Washington, DC**  
Tuesday, May 20, 2003  
Marriott at Metro Center  
Chairs: Henry Masur, MD, and Michael S. Saag, MD

**For information about any of these programs, please contact the International AIDS Society–USA.  
Phone: (415) 544-9400 • Fax: (415) 544-9401 • E-mail: [info@iasusa.org](mailto:info@iasusa.org) • Web Site: [www.iasusa.org](http://www.iasusa.org)**

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