

# THE HOPKINS HIV REPORT

A bimonthly newsletter for health care providers

## New CDC STD Treatment Guidelines

By Emily J. Erbelding, M.D., M.P.H.

In May, the Centers for Disease Control and Prevention (CDC) released a new version of their guidelines for the diagnosis and management of STDs [MMWR 51; RR06, 2002]. The previous version was released in 1998. These guidelines are reviewed and updated by expert consensus panels every 4-5 years, and they represent the standards for the clinical management of STDs in the U.S. This article will highlight and explain some important new changes in the CDC treatment guidelines that may have particular relevance to clinicians treating HIV-infected patients.

### Rescreening for Chlamydia

Chlamydia is a prevalent infection among adolescents and young adults and is the most common bacterial STD in the U.S. The sequelae of untreated chlamydia infection include pelvic inflammatory disease as well as tubal infertility and ectopic pregnancy related to tubal scarring. As such, it poses a particular health burden on women. Untreated chlamydial infection also biologically enhances HIV transmission. Asymptomatic chlamydia infections are common, both for men and for women, making aggressive screening programs among populations at risk the major public health strategy for reducing the adverse health outcomes associated with chlamydia infection. Recent reports describe a very high rate of reinfection among young persons treated for chlamydia [Burstein, et al. JAMA 1998;280: 521; Rietmeijer, et al. STD 2002; 9:65]. This reinfection rate is unlikely to be

*continued on page 2*

### Inside This Issue

Acute Neuromyopathy Syndrome . . . . .	5
Peripheral Neuropathy and HIV . . . . .	6
Substance Abuse and HIV . . . . .	8

## WHO Draft Guidelines for Antiretroviral Therapy in Resource Limited Settings

By Lisa A. Spacek, M.D., Ph.D.

On April 22, 2002, the World Health Organization (WHO) approved draft treatment guidelines for HIV-infected people in resource limited settings and recommended that 12 antiretroviral drugs be added to the Essential Medicines List. The primary purpose of the guidelines is to serve as a framework for health care policy leaders in developing nations as they begin to implement HIV treatment programs. The intent is to expand access to highly active antiretroviral therapy (HAART) to at least three million people with HIV/AIDS in Africa by 2005. This is a decisive step in advancing HIV care as a complement to established efforts in HIV prevention. However, the task of expanding access to HAART by more than a ten-fold increase is daunting, especially in settings where basic healthcare infrastructure is lacking.

The WHO guidelines were published in the wake of the launch of The Global Fund to Fight AIDS, Tuberculosis and Malaria, a public-private partnership led by United Nations Secretary General Kofi Annan. The Global Fund awarded \$378 million USD to 40 programs in 31 countries. An additional \$238 million USD will be awarded in the second round of funding, for a total of \$616 million USD. Of the \$378 million USD awarded in the first round, approximately 60% or \$227 million USD will fund HIV/AIDS projects, and an additional 15% or \$57 million USD will fund projects that address HIV/AIDS plus one or both of the other diseases (TB and/or malaria). The combined efforts of international entities such as WHO, UNAIDS, and the Global Fund along with local public health officials and health care providers will be necessary to face the formidable challenge of providing HIV treatment to the millions of people with HIV/AIDS.

The numbers of people infected with HIV in developing nations continues to increase daily. WHO estimates that 36 million adults and children in the developing world are living with HIV infection. Death rates due to HIV-related

illness in developing nations are equally catastrophic. In sub-Saharan Africa in 2001, 2.3 million people died from AIDS [UNAIDS, Dec. 2001]. This is in stark contrast to the peak death toll of 51,117 recorded in 1995 in the United States, which decreased to 15,245 in 2000 [CDC, HIV/AIDS Surveillance Report 2002;13]. The reasons for this disparity are multifactorial, but include limited access to care, including antiretroviral therapy and treatment for opportunistic infections, lack of technical and human resources, and insufficient funding to support either prevention or treatment. The objectives of the WHO draft guidelines address the following topics:

1. When to initiate HAART
2. Which HAART regimens to start
3. When to change therapy
4. Which alternative regimens to change to
5. How to monitor patients in resource limited settings

Additional topics include treatment of patients with concomitant medical conditions such as pregnancy, tuberculosis, and hepatitis. The draft guidelines are meant to standardize and simplify antiretroviral treatment without compromising the quality and outcomes of therapy.

### When to Initiate HAART

In resource-limited settings, the WHO recommends initiation of therapy based on clinical staging and CD4 lymphocyte count or total lymphocyte count. WHO Stage I includes those HIV-infected individuals who are asymptomatic or manifest persistent generalized lymphadenopathy; Stage II includes those with weight loss ( $\leq 10\%$  of body weight), minor mucocutaneous manifestations, herpes zoster, and recurrent upper respiratory tract infections; Stage III includes those with weight loss ( $>10\%$  body weight), unexplained chronic diarrhea, unexplained

*continued on page 3*



## New CDC STD Treatment Guidelines

*continued from page 1*

due to antibiotic failure, but rather is related to reinfection from contact with untreated sex partners or to new infection due to repeated exposure within a high prevalence sexual network. In this version of the treatment guidelines, the CDC recommends re-screening at 4-6 months following treatment of chlamydia in women.

### Fluoroquinolone Resistance Among *Neisseria gonorrhoeae* Isolates

There were over 350,000 cases of gonorrhea reported in the U.S. in 2000, the last year for which complete surveillance data have been released, making this the second most common reported infectious disease. Gonorrhea rates are highest among adolescents and young adults, particularly among racial and ethnic minorities living in poverty. Untreated gonorrhea causes reproductive sequelae similar to that of chlamydia, and it also biologically facilitates the transmission of HIV. Evolving antibiotic resistance represents a major obstacle to successful worldwide control of gonorrhea. Ciprofloxacin has been used to treat gonorrhea since 1993, with only sporadic reports of resistance in the U.S. through the 1990s. However, in 2000, ciprofloxacin resistance among *N. gonorrhoeae* isolates was reported to be endemic in Hawaii. Resistance was known to be endemic in Southeast Asia and countries of the Pacific Rim since the mid-1990s and appeared to be marching eastward. With this version of the STD Treatment Guidelines, the CDC warns that fluoroquinolone resistance has become so common on the west coast of the continental U.S. that ciprofloxacin, ofloxacin, and levofloxacin should no longer be used as first line therapy to treat gonorrhea infections. Cefixime and ceftriaxone are recommended as first-line antibiotics in Hawaii and California. Health care providers throughout the U.S. are encouraged to remain vigilant for the possibility of treatment failure when fluoroquinolones are used to treat gonorrhea, and to report identified cases of fluoroquinolone resistant gonorrhea to the CDC.

### Ongoing STD Prevention Needs of HIV-infected Persons

Current national HIV prevention strategies emphasize the need to provide more aggressive STD prevention services to

those already infected with HIV in the settings where they receive clinical services. This version of the CDC STD Treatment Guidelines makes a strong statement about the need for HIV clinical providers to regularly discuss sexual risk behaviors during clinic visits, provide risk reduction counseling to those whose behavior may continue to expose others to HIV, and screen for new, curable sexually transmitted infections (syphilis, gonorrhea, chlamydia) on an annual basis. A newly identified sexually transmitted infection in a person known to be HIV-infected signals the need for more intensive or more specialized counseling. More extensive guidelines for STD screening and counseling for use in the HIV treatment setting have been developed jointly by the CDC/IDSA and should be released shortly.

### Emphasis on STD Prevention Services for Men Who Have Sex With Men (MSM)

Rising rates of rectal gonorrhea and outbreaks of syphilis among men who have sex with men have been reported from many U.S. cities and indicate an urgent need for all health care providers to enhance STD screening, treatment, and prevention services in this population. Specific practice standards for MSM appear for the first time in the 2002 edition of the CDC STD Treatment Guidelines. Healthcare providers are urged to routinely discuss sexual risk behavior with all male patients, including specifically assessing the gender of partners. For MSM who are sexually active, the CDC guidelines recommend annual screening for HIV, syphilis, gonorrhea (oral, urethral and rectal sites) and for chlamydia (urethral and rectal sites). Though urine-based screening of asymptomatic men for gonorrhea and chlamydia through nucleic acid amplification tests is convenient and widely accepted, these tests have not yet been commercially licensed for specimens collected from oral or rectal sites. Detecting infection in these sites may require culture (and chlamydia culture may not be widely available). Hepatitis A and B vaccination for non-immune MSM patients is also recommended.

### Using Type-specific HSV-2 Serologic Tests

The majority of persons with recurrent outbreaks of genital herpes are infected with HSV-2. Antiviral therapy, either used

episodically to treat outbreaks, or used chronically for suppression, can either shorten the course of symptoms or prevent outbreaks. It is estimated that 50 million Americans are infected with HSV-2, and the vast majority of these are individuals who are either asymptomatic or who have not had symptoms that led a health care provider to diagnose genital herpes. These infected individuals still shed HSV-2 at nearly the same rates as those who have had symptomatic outbreaks and have been diagnosed with genital herpes. Viral detection methods (viral culture or tests based upon HSV antigen detection) are insensitive for the diagnosis, particularly if obtained from patients with atypical or healing herpes lesions. Type-specific herpes serologic tests based upon detection of antibodies to the glycoprotein G2 have been licensed in the U.S. since 1999, and when applied to a population with a relatively high risk for HSV-2 may be very useful in identifying cases. False positive tests can occur, and they are not useful tests for population-based screening. Because current tests on the market are IgG based, the current tests may be insensitive for detecting HSV infection in those who have new infection and have not yet seroconverted at the time of clinical evaluation. Serologic testing may be particularly useful in diagnosing infection in a person with lesions that are atypical but suggestive of herpes and in counseling the partner of a person with known genital herpes. Some experts recommend consideration of HSV-2 type specific testing for all persons presenting for HIV care [*STD* 2001;28:460].

### Summary

Providing effective clinical services for STDs in the clinical setting relieves symptomatic illness, prevents adverse sequelae of STDs, and prevents STD transmission in the wider community. Aggressive STD screening, appropriate clinical management, and effective risk reduction counseling in those already diagnosed with HIV infection and in those at high risk for HIV is a critical component of the national HIV prevention agenda. Copies of the Sexually Transmitted Disease Treatment Guidelines—2002 can be obtained from <http://www.cdc.gov/std>. ▲



## WHO Draft Guidelines for ART in Resource Limited Settings

*continued from page 1*

prolonged fever, thrush, oral hairy leukoplakia, pulmonary tuberculosis, severe bacterial infections, and those bed-ridden for less than 50% of the day during the past month; and Stage IV includes those with clinical syndromes consistent with AIDS and/or who have been bedridden for greater than 50% of the day during the past month. The guidelines, shown in Table 1, p. 4, recommend starting HAART in all patients with WHO Stage IV disease irrespective of CD4 lymphocyte count and in those with WHO Stage I, II, or III disease who have CD4 lymphocyte counts below 200 cells/mm<sup>3</sup> in areas where CD4 lymphocyte count is available. If CD4 lymphocyte count is unavailable, HAART is recommended in those with WHO Stage II or III disease with total lymphocyte counts below the range of 1,000 to 1,200 cells/mm<sup>3</sup>. Assessment of HIV viral load is

not considered essential for determining the need for therapy.

### Which HAART Regimens to Start

Recommendations for first-line HAART regimens include AZT/3TC accompanied by abacavir, efavirenz, nevirapine, nelfinavir or ritonavir-boosted indinavir, lopinavir or saquinavir. The combination of AZT/3TC/ABC is considered the most “user-friendly” regimen, as pill burden is minimal. This combination can be used during tuberculosis treatment without concern for drug interactions. The disadvantages include potency, cost, and the potential for serious or even fatal hypersensitivity reactions that could escape detection in resource-poor settings. In regions with a significant prevalence of infection with HIV-2 and HIV-1 Group O virus the recommendation is to avoid the use of

NNRTI-containing regimens except in patients with documented HIV-1 infection, given the inherent resistance of HIV-2 and Group O HIV-1 to these drugs.

### When to Change Therapy

Determination of the need to change therapy is based primarily on treatment failure and toxicity. Without routine assessment of HIV viral load, providers in resource limited settings will have to rely on clinical failure of therapy defined as “clinical disease progression with development of an opportunistic infection or malignancy when the drugs have been given a sufficient time to induce a protective degree of immune restoration.” Likewise, with limited laboratory monitoring to detect early signs

*continued on page 4*

# THE HOPKINS HIV REPORT

## EDITORIAL BOARD

**John G. Bartlett, M.D.**

*Professor of Medicine;  
Director, Division of Infectious Diseases;  
Director, The Johns Hopkins University AIDS Service*

**Richard E. Chaisson, M.D.**

*Professor of Medicine,  
Epidemiology, and International Health*

**Emily J. Erbelding, M.D., M.P.H.**

*Assistant Professor of Medicine and Pediatrics*

**Joel E. Gallant, M.D., M.P.H.**

*Associate Director,  
The Johns Hopkins University AIDS Service*

**Kelly A. Gebo, M.D., M.P.H.**

*Assistant Professor of Medicine and Epidemiology*

**Gregory M. Lucas, M.D.**

*Assistant Professor of Medicine*

## CONTRIBUTING EDITORS

**Jean R. Anderson, M.D.**

*Associate Professor of Obstetrics, Gynecology, and Medicine*

**Joseph Cofrancesco, Jr., M.D., M.P.H.**

*Assistant Professor of Medicine*

**James P. Dunn, M.D.**

*Assistant Professor of Ophthalmology*

**Charles W. Flexner, M.D.**

*Associate Professor of Medicine, Pharmacology and Molecular Science, and International Health; Associate Director of Graduate Training Program in Clinical Investigation*

**Rajesh T. Gandhi, M.D.**

*Instructor in Medicine, Partners AIDS Research Center  
Massachusetts General Hospital Boston, MA*

**Douglas A. Jabs, M.D.**

*Professor of Ophthalmology and Medicine*

**Brooks Jackson, M.D.**

*Professor of Pathology; Deputy Director for Clinical Affairs,  
Department of Pathology*

**Ciro R. Martins, M.D.**

*Assistant Professor of Dermatology*

**Justin C. McArthur, M.B., B.S., M.P.H.**

*Professor of Neurology and Epidemiology*

**Richard D. Moore, M.D.**

*Professor of Medicine and Epidemiology*

**Thomas C. Quinn, M.D.**

*Professor of Medicine, International Health,  
Molecular Microbiology and Immunology*

**Robert Siliciano, M.D., Ph.D.**

*Professor of Medicine,  
Molecular Biology and Genetics*

**Timothy R. Sterling, M.D.**

*Assistant Professor of Medicine*

**Glenn J. Treisman, M.D., Ph.D.**

*Associate Professor of Psychiatry and Medicine*

## NEWSLETTER STAFF

**Mary Beth Hansen, M.A.**

*Managing Editor*

**Lisa Darrach, B.A.**

*Design and Production*

**Sharon M. McAvinue**

*Business Development*

## SUPPORT

*The Hopkins HIV Report is published six times per year by The Johns Hopkins University AIDS Service, Division of Infectious Diseases. Publication of this newsletter is underwritten by a generous grant from GlaxoSmithKline; we gratefully acknowledge their support.*

©2002 The Johns Hopkins University AIDS Service, Division of Infectious Diseases. Permission to use and reproduce portions of this newsletter is hereby granted, provided that author and publication are fully credited and both the copyright and permission notice appear. All other rights reserved.

Visit The Johns Hopkins AIDS Service Website:  
<http://www.hopkins-aids.edu>

Canada Post Publications Sales Agreement  
# 40683044



## WHO Draft Guidelines for ART in Resource Limited Settings

continued from page 3

**Table 1. WHO Recommendations for Initiating Antiretroviral Therapy in Adults & Adolescents With Documented HIV Infection**

<b>If CD4 testing is available</b>
<ul style="list-style-type: none"> <li>• WHO Stage IV disease irrespective of CD4 cell count</li> <li>• WHO Stage I, II, III with CD4 cell counts &lt;200 cells/mm<sup>3</sup></li> </ul>
<b>If CD4 testing is unavailable</b>
<ul style="list-style-type: none"> <li>• WHO Stage IV disease irrespective of total lymphocyte count</li> <li>• WHO Stage II or III disease with a total lymphocyte count &lt;1000-1200 cells/mm<sup>3</sup></li> </ul>

of renal, hepatic or hematologic dysfunction, toxicity will manifest as clinical syndromes of renal failure, hepatitis, or anemia. Most concerning is the potential for morbidity and mortality related to advanced stages of drug toxicity that could have been detected earlier if greater resources were available.

### What to Change To

The recommendations for second-line regimens to be used in the event of treatment failure reflect the recognition that without viral load and drug resistance monitoring, virologic failure will have been present for an extended period prior to clinical treatment failure. Therefore, the development of drug resistance patterns based on early viral genetic mutations may differ from virologic resistance developed over prolonged antiretroviral exposure. In general, second-line regimens intended to follow AZT/3TC-containing regimens include d4T/ddI in addition to either NNRTIs, ritonavir-boosted PIs, or a combination. Further support for the initial use of AZT/3TC/ABC is due to the ability to spare both NNRTIs and PIs. This allows for a more potent salvage regimen in light of the high likelihood of extensive nucleoside resistance developing prior to clinically apparent treatment failure. If available, tenofovir could be used in salvage regimens because of its antiretroviral activity in some patients with nucleoside resistance.

### How to Monitor

In addition to the assessment of immunologic function as indicated by symptoms, clinical signs and lymphocyte

count, laboratory testing for the safe and effective use of HAART is divided into four categories: absolute minimum tests, basic tests, desirable tests, and optional tests (Table 2, below). Absolute minimum testing includes an HIV antibody test and hemoglobin or hematocrit level. Basic testing adds white blood cell count and differential, liver enzymes, serum creatinine and/or blood urea nitrogen, serum glucose, and pregnancy tests for women. Desirable tests include bilirubin, amylase, lipid levels and CD4 lymphocyte count. Testing for HIV viral load was deemed optional.

Given that HIV viral load testing is unlikely to be available in resource-limited settings, routine evaluation of HIV resistance is also unlikely to be available. Because it is necessary to monitor HIV resistance and document trends in antiretroviral drug susceptibility, the WHO, in collaboration with the International AIDS Society, is instituting a Global HIV Drug Resistance Surveillance Network. The goals of this effort will be to establish institutional networks by which to monitor drug resistance and disseminate region-specific strategies to address drug resistance patterns.

### Conclusions

The WHO guidelines are based on rigorous evaluation of data collected almost exclusively in developed countries. Of concern is whether guidelines created for HIV-infected populations of developed nations are adaptable to HIV-infected populations worldwide. Specifics regarding the presence of different HIV subtypes, endemic infections such as tuberculosis, genetic determinants, and other health measures such as nutritional status may introduce factors that alter response to treatment.

Developing nations that have successfully implemented HAART include Brazil, Thailand, Senegal, and Uganda. Studies are needed to examine responses to HAART and whether changes to the guidelines would better serve populations in different regions around the world. For example, initiation of HAART earlier in the course of HIV disease may have an impact on disease outcomes due to endemic mycobacterial infections such as tuberculosis. With initiation of HAART on a population-wide scale, continuous

surveillance of drug-resistant HIV will be needed to update treatment guidelines. A recent study conducted in Gabon demonstrated resistance to antiretroviral therapy [*J Acquir Immune Defic Syndr* 2002;29:165-168]. Of great concern is that antiviral drug resistance due to suboptimal therapies could limit the potency of available treatments.

Multiple studies conducted in developed nations have proven the tremendous benefit of HAART with its resulting dramatic decline in both morbidity and mortality. In developed or developing nations, HAART provides the only hope of survival for those with HIV infection who are able to adhere to daily lifelong therapy. Moreover, the availability of HAART can further enhance prevention activities by offering incentives to seek HIV testing, preventing mother-to-child transmission, and decreasing the risk of sexual transmission. The development of these WHO draft guidelines is a significant and definitive step toward expanding access to life-saving therapy to people living with HIV/AIDS worldwide. The WHO draft guidelines of April 22, 2002 are available online at: [http://www.who.int/HIV\\_AIDS/HIV\\_AIDS\\_Care/ARV\\_Draft\\_April\\_2002.pdf](http://www.who.int/HIV_AIDS/HIV_AIDS_Care/ARV_Draft_April_2002.pdf).

*Lisa A. Spacek, M.D., Ph.D. is a Fellow in the Division of Infectious Diseases of the Johns Hopkins University, School of Medicine. ▲*

**Table 2. WHO Guidelines for Laboratory Monitoring of Antiretroviral Use**

<b>Absolute minimum tests</b>
<ul style="list-style-type: none"> <li>• HIV antibody test</li> <li>• Hemoglobin or hematocrit</li> </ul>
<b>Basic tests</b>
<ul style="list-style-type: none"> <li>• White blood cell count and differential</li> <li>• Alanine or aspartate aminotransferase</li> <li>• Creatinine and/or blood urea nitrogen</li> <li>• Serum glucose</li> <li>• Pregnancy test for women</li> </ul>
<b>Desirable test</b>
<ul style="list-style-type: none"> <li>• Bilirubin</li> <li>• Amylase</li> <li>• Serum lipids</li> <li>• CD4 cell count</li> </ul>
<b>Optional tests</b>
<ul style="list-style-type: none"> <li>• HIV viral load</li> </ul>



## Acute Neuromyopathy Syndrome

By Justin McArthur, MBBS, M.P.H.

In the last three years a new form of HIV associated neurological disease has been described, often occurring in association with lactic acidosis in patients with prolonged use of stavudine (d4T, *Zerit*). While the clinical and pathological features are still being defined, the severity of this syndrome and its apparent high mortality rate warrant a discussion of what we know now.

The FDA adverse events reporting system identified 25 cases of this syndrome, with a fatal outcome in seven. Twenty-two of the 25 reported were on d4T, making this agent the leading, but not the only, culprit [Marcus K, 9th CROI 2002, Abstract LB14]. The neurological features include ascending paresis, areflexia, and development of cranial neuropathies. These features overlap with those of Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy), and some patients develop severe neuropathic limb pains and myopathic weakness. The differential diagnosis includes transverse myelitis, the neuromuscular weakness accompanying West Nile encephalitis, and botulism. Serum CPK and lactate are usually elevated, and EMG/nerve conduction studies show a mixed pattern with both axonal neuropathy and myopathy.

The ACTG Neurology group is attempting to collect prospective information on this new syndrome from ACTG trials and clinical cases. A proposed case definition is included below, and clinical details can be sent to this author at [jm@jhmi.edu](mailto:jm@jhmi.edu). The full extent of the syndrome is unclear, and the pathophysiological mechanisms are currently unknown. Therapy is confined to discontinuation of the offending agent. Since the dideoxynucleoside analogues are known to inhibit mitochondrial DNA polymerase [Kakuda T, *Clin Ther* 2000; 22:685-708; Chen C-H, Vazquez-Padua M, Y-C C, *Molecular Pharmacology* 1991; 39:625-628]), the enzyme that maintains DNA, their prolonged action might lead to energy failure. Recently techniques to assay mitochondrial DNA levels have been developed, and several studies have now shown that levels are suppressed either in PBMCs or subcutaneous fat after prolonged exposure to dideoxynucleosides (ddx) [Cote, *N Engl J Med* 2002; Shikuma C,

2001; Cherry C, 2002 in press.] In collaboration with colleagues at the Alfred Hospital in Melbourne, we have used the simple technique of punch skin biopsies to quantify mitochondrial DNA in subcutaneous fat. Levels of mtDNA were significantly lower in individuals who were using ddx agents. Prospective evaluation of

subjects at both institutions is underway through clinical questionnaires and physiological testing and measurement of the density of unmyelinated nerve fibers in the epidermis to examine whether the measurement of mtDNA in this way can predict sensory neuropathy associated with antiretroviral toxicity. ▲

### Proposed Case Definition for Acute Neuromyopathy and Lactic Acidosis Syndrome

[Prepared by Justin McArthur MBBS, M.P.H., David Simpson M.D., and the ACTG Neuropathy Working Group]

1. New onset of limb weakness, with or without sensory involvement
  - Either acute [1-2 weeks] or sub-acute [>2 weeks]
  - Affecting either lower or both lower and upper extremities
2. Absence of potentially confounding illnesses excluded by comprehensive neuromedical evaluation (e.g. myasthenia gravis, myelopathy, hypokalemia, stroke)

#### Notes:

1. Documented hyperlactatemia is not required for this case definition, but all available serum lactates should be recorded. See notes below.
2. Grading system:
  - Mild: New muscle weakness appreciable, but not significantly limiting everyday functioning.
  - Moderate: New muscle weakness significantly limiting everyday functioning, e.g. walking, climbing stairs, carrying groceries.
  - Severe: New muscle weakness severely limiting everyday functioning, e.g. unable to walk more than few steps, unable to dress or bathe.
3. Diagnostic categorization:
  - “Possible” acute neuromyopathy: Confounding conditions present, or comprehensive neuromedical evaluation NOT completed.
  - “Probable:” Comprehensive neuromedical evaluation completed and no exclusionary conditions identified.
  - “Definite:” Meets criteria for probable, and serum lactate is 2x upper limit of normal before or with the onset of weakness.
4. Record use of current antiretrovirals and all antiretrovirals within the past 12 months.



# Peripheral Neuropathy and HIV

By Michael J. Polydefkis, M.D.

Peripheral nerve damage is one of the most common neurological complications of HIV infection and its treatment. Of these, the distal sensory neuropathies, which occur in the advanced stages of HIV disease, are the most common, affecting approximately 30% of AIDS patients. It is important, however, to recognize that other forms of peripheral nerve disease occur in HIV infection. Many are caused by other infectious agents and are therefore potentially treatable. This article will briefly review less common forms of peripheral nerve injury in HIV and will then focus on the HIV associated sensory neuropathies.

## Peripheral Neuropathies other than HIV Associated Sensory Neuropathies

In the early phase of HIV disease, patients may develop acute or chronic inflammatory demyelinating neuropathy (AIDP, CIDP). AIDP, also known as Guillain Barré syndrome (GBS), can be the initial manifestation of HIV infection and is indistinguishable clinically and electrophysiologically from that seen in uninfected patients. One feature of HIV-associated AIDP is a mononuclear CSF pleocytosis accompanying elevated CSP. This contrasts with non-HIV GBS in which there are typically no cells in spinal fluid. The precise epidemiologic figures of AIDP in HIV disease are unknown, though there is some evidence that the pleocytosis from HIV infection is directly related to the neuropathy. The mainstay of treatment is plasmapheresis and IV immune globulin, and the prognosis does not appear to be different from non-HIV associated AIDP.

CIDP (Chronic inflammatory demyelinating polyneuropathy) may also be the presenting illness for HIV disease and generally occurs with CD4 counts between 200-500 cells/mm<sup>3</sup>. This condition can be thought of as a chronic form of GBS. Patients typically have absent or reduced reflexes as well as patchy numbness and weakness. CSF examination often shows a mild mononuclear pleocytosis in addition to an elevated protein. Treatment centers on immunomodulation and is potentially problematic in the setting of HIV disease given the pre-existing immunosuppression. Corticosteroids, plasmapheresis, IVIG and cyclosporin have all been used successfully. No clear guidelines for anti-retroviral therapy exist, though it seems prudent to avoid potentially neurotoxic agents.

Mononeuropathies such as Bell's palsy have been suggested to occur at higher rates in HIV-infected people, though precise figures are unknown. Mononeuropathy multiplex (MM) can occur early in HIV disease as a result of immune dysfunction or vasculitis. Clinically, these patients have asymmetric, patchy sensory or motor deficits. In vasculitis, pain generally precedes motor or sensory deficits. Nerve biopsy is necessary to confirm the diagnosis. Electrodiagnostic testing is helpful in confirming asymmetric abnormalities, excluding multiple entrapment neuropathies as well as in identifying an appropriate site for biopsy. Therapy is determined by etiology, with vasculitis requiring immunosuppression.

An often painful, distal sensorimotor neuropathy associated with CD8 hyperlymphocytosis and a Sjögren's-like syndrome can occur during symptomatic HIV infection and potentially could be confused with HIV-associated sensory neuropathy. This disorder has been termed diffuse infiltrative lymphocytosis syndrome (DILS). Only patients with CD8 hyperlymphocytosis and MHC class HLA DR5 or DR6 alleles appear to be at risk, and the mean CD4 cell count in DILS patients is 260 cells/mm<sup>3</sup>, with one third having AIDS. Clinically, DILS develops as a subacute, often painful neuropathy commonly accompanied by parotid enlargement and sicca syndrome. Many patients have systemic involvement, such as lymphadenopathy, splenomegaly or interstitial pneumonia. Electrodiagnostic testing generally reveals a length-dependent axonal process, though evidence of demyelination is present in 15% of cases. CSF analysis is notable for a nonspecific mononuclear pleocytosis and striking xanthochromia. Pathology reveals a non-destructive angiocentric T cell infiltrate in the epi- and endoneurium. Treatment is centered on HIV suppression, with HAART resulting in complete recovery in two-thirds of patients.

A progressive polyradiculopathy (PP) can develop in patients with advanced HIV disease and CD4 cell counts of 50 cells/mm<sup>3</sup> or less. Patients usually present with subacute low back and radicular pain over a period of days. Weakness progresses to flaccid paralysis with sensory loss and frequently urinary difficulties. The upper extremities are rarely involved. The most common cause is CMV, with approximately 10% of cases occurring while on CMV maintenance therapy and 38% having evidence of CMV infection elsewhere, usually retinitis. Other causes include lymphomatous meningitis, syphilitic radiculopathy, herpes simplex or herpes zoster myeloradiculopathy, toxoplasmosis, and mycobacterial infection. CSF analysis is essential in distinguishing among these possibilities. A predominant polymorphonuclear pleocytosis, commonly above 200 cells/mm<sup>3</sup>, with a low CSF glucose is typical of CMV infection. CSF cytology, VDRL and viral PCR studies are also useful, while imaging studies are important in ruling out mass lesions. Early recognition and treatment of CMV polyradiculopathy can prevent an otherwise devastating outcome.

A mononeuropathy multiplex occurring in the setting of advanced HIV disease is almost

### EDITORIAL POLICY & DISCLAIMER

Organizations providing financial support do not participate in the editorial process or otherwise influence editorial decisions. The information presented in *The Hopkins HIV Report* represents the standards of care of the Johns Hopkins University AIDS Service. Every effort is made to ensure the timeliness and accuracy of information presented in this newsletter, but standards of care change rapidly; therefore, the authors, editors, and publisher will not in any way be held liable for the timeliness of information or for errors, omissions, or inaccuracies in this publication. Readers should review carefully the product information contained in manufacturers' package inserts for any drug mentioned in this publication; mention of products does not constitute endorsement.

### THE HOPKINS HIV REPORT IS FREE

Are you reading a copy of the *Hopkins HIV Report* that belongs to someone else? Request your own using one of two easy methods (why not? It's free.):

- The easiest: Go to <http://hopkins-aids.edu>, click on "Publications" (at the top of the screen), look for the *HHR* link, then click on "Subscribe online," fill out the form, and submit.

- The other method: Send your name and complete mailing address to:

*The Hopkins HIV Report*, Distribution  
P.O. Box 651266  
Potomac Falls, VA 20165-1266

Change of address? Please let us know by sending a postcard with both your old (very important) and your new address to:

*The Hopkins HIV Report*, Change of Address  
P.O. Box 651266  
Potomac Falls, VA 20165-1266

Problems: If you have requested the newsletter and are not receiving it (the *HHR* is published every other month—Jan., Mar., May, June, Sept., Nov.), send a postcard to the address listed above or an e-mail to: [hivreport@PMR-printing.com](mailto:hivreport@PMR-printing.com)

All other correspondence should be sent to:

Mary Beth Hansen, M.A.  
Managing Editor, *HHR*  
JHU ID @ Lighthouse Point  
2700 Lighthouse Point, STE 220  
Baltimore, Maryland 21224



## Peripheral Neuropathy and HIV

always due to CMV infection. As with CMV polyradiculopathy, evidence of CMV infection elsewhere is common, particularly in the retina. CSF analysis in CMV mononeuropathy multiplex differs from CMV PP in that a polymorphonuclear pleocytosis is often not present, though CMV PCR is usually positive. Most patients improve after treatment with foscarnet or ganciclovir.

### The HIV Associated Sensory Neuropathies

The most common peripheral nerve complication in HIV infection is a length-dependent, axonal sensory neuropathy that is dominated by neuropathic pain. The HIV associated sensory neuropathies (HIV-SN) include both distal sensory polyneuropathy (DSP) due to IV infection, and antiretroviral drug toxic neuropathy (ATN) caused by the dideoxynucleosides (ddC, d4T, and ddI). These two forms of HIV-SN are phenotypically identical and affect approximately 30% of AIDS patients. They are characterized by painful dysesthesias in the feet and legs, described as “painful numbness,” “aching,” or “burning.” HIV-SN is a major source of morbidity among AIDS patients. Symptoms are generally worse at night and can be aggravated by innocuous stimuli, such as bed sheets or wearing shoes. Abnormalities on examination are generally limited to sensory nerve fibers and include reduced or absent ankle reflexes and increased vibratory and pin thresholds. Affected patients can often test normally on routine nerve conduction testing. This reflects the prominent small caliber sensory nerve involvement in HIV-SN and the fact that these nerves are “invisible” to nerve conduction/EMG testing. Skin biopsy and visualization of epidermal nerve fibers is a useful diagnostic tool in such instances.

DSP is associated with advanced HIV disease, with lower CD4 count and higher viral load being risk factors. An association between viral set point and the subsequent development of HIV-SN has been suggested. Autopsy studies have demonstrated pathological abnormalities in the peripheral nerves of virtually all patients dying from AIDS, and sub-clinical abnormalities in peripheral nerve function are common on detailed testing. This suggests a gradual progression of nerve damage in HIV disease with much of it being silent, before development of DSP. HIV itself appears to play an indirect role in the development of DSP in that macrophage activation and

aberrant proinflammatory cytokines are thought to mediate the neurotoxicity.

While the incidence of most neurological complications of HIV has fallen dramatically over the past decade, HIV-SN has become more prevalent, coinciding with the use of dideoxynucleoside drugs. ATN has subsequently emerged as a common cause of HIV-SN.

The only distinguishing characteristic of ATN is the temporal association with use of dideoxynucleoside NRTIs; otherwise the two conditions are virtually indistinguishable. The onset of ATN ranges from one week to 6 months, depending on the NRTI and the dose administered. Symptoms may continue to worsen after discontinuation of the offending agent, followed by improvement in most but not all patients over a period of weeks to months. Pathophysiologically, ATN differs from DSP and has been linked to mitochondrial dysfunction. Importantly, patients with pre-existing DSP appear to be at increased risk of developing ATN. Dideoxynucleoside NRTIs may trigger neuropathic symptoms in patients with pre-existing, silent neuronal damage due to HIV infection.

Treatment of HIV-SN is largely symptomatic. In the case of ATN, the suspected offending agent should be discontinued or the dose reduced, if possible. Several agents that have been effective in other painful neuropathies have not shown efficacy in HIV-SN, including amitriptyline, mexiletine, topical capsaicin and acupuncture. Both 5% lidocaine and gabapentin have been

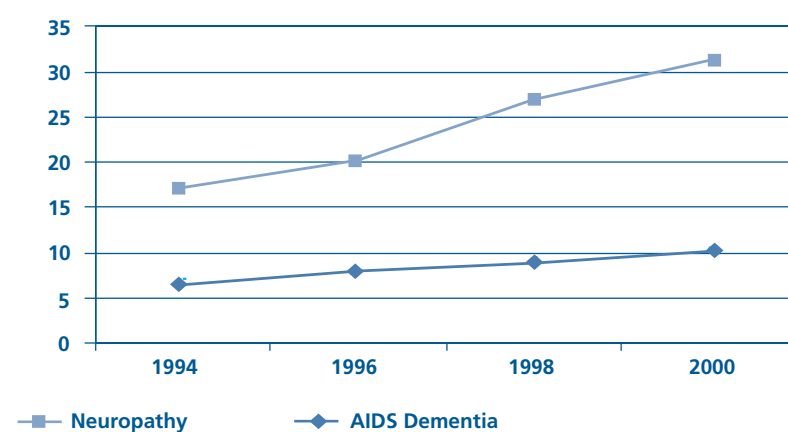
used successfully in open-label trials, but controlled data is lacking. Anecdotal evidence suggests that topiramate may also be beneficial. Currently, the only therapies shown to be effective in randomized, placebo-controlled clinical trials are lamotrigine and recombinant human nerve growth factor, of which the latter is not commercially available. The beneficial effect of lamotrigine appears to be most pronounced in ATN patients, and the risk of rash is minimal if the dose is slowly titrated upwards. Both lamotrigine and topiramate have the added advantage of not affecting the cytochrome P450 pathway and therefore not interacting with antiretroviral agents.

### Conclusions

Peripheral nerve disease is common in HIV infection. Other infectious causes are infrequent but important to recognize, as they are potentially treatable. HIV-SN is the most prevalent neuropathy associated with HIV infection and is now the most common neurological complication of HIV disease. Two forms of HIV-SN exist, distal sensory polyneuropathy (DSP) related to macrophage and cytokine dysregulation resulting from HIV infection and antiretroviral toxic neuropathy (ATN), produced by mitochondrial dysfunction. ATN can require alteration of antiviral regimens at the risk of reducing virologic control and may act to trigger or unmask clinically silent HIV-mediated neuropathy.

*Dr. Polydefkis is an Assistant Professor of Medicine in the Department of Neurology, Johns Hopkins University, School of Medicine. ▲*

Prevalence of HIV-associated Neurological Conditions Johns Hopkins HIV Clinical Cohort per 100 persons





## Introduction

Since 1989, approximately one-third of all AIDS cases in the United States have been among active or former injection drug users (IDUs) [MMWR2001; 50(21): 430]. Although the major risk factor for HIV infection in the United States among men is same-sex contact, the major risk factor among women with AIDS is either IDU or heterosexual contact with an injection drug user [CDC, *HIV/AIDS Surveillance Report* 2002;13]. Once HIV enters any IDU population, the virus can spread very quickly. For example, in the Northeast of the United States, where injection drug use is prominent, the prevalence of HIV among IDUs entering drug treatment centers from the period of 1998-1997 was 28% compared to only 3% in the West [CDC National Serosurveillance, 1993-1997]. It has been estimated that at least 55% of the patients seen in the Johns Hopkins AIDS Service (JHAS) in Baltimore are injection drug users.

Injection drug users engage in two behaviors that put them at risk for HIV infection: needle sharing and having multiple injection partners. However, substance abuse can play a major role in HIV transmission even among non-injection drug users. Addiction and high-risk sexual behavior have been linked across a wide range of settings. For example, women who use crack cocaine are more likely to engage in unprotected sex in exchange for money or drugs [Edlin BR, et al. *N Eng J Med* 1994; 331(21):1422-7; Astemborski J, et al., *Am J Public Health* 1994;84:382-87]. Men who use crack cocaine are more likely to engage in unprotected anal sex with casual male contacts [deSouza CT, et al. *J Acquir Immune Defic Syndr* 2002;29(1):95-100]. Alcohol intoxication has been associated with high-risk sexual behavior as well as more needle sharing among drug users [Stein MD, *J Subst Abuse Treat* 2000;18:359-63, Rees V, *J Subst Abuse Treat* 2001;21:129-34].

Even though it is evident that a high proportion of IDUs are infected with HIV, there has been little research on how to improve treatment accessibility and outcome in this population. It is estimated that the approximately 80% of IDUs in the United States are not in drug treatment [National Association of State Alcohol and Drug Abuse Directors, unpublished data]. Adherence to

treatment in this population is difficult because of the high prevalence of psychiatric, cognitive and social problems. This article will examine the nature of drug addiction, its interaction with HIV and psychiatric comorbidities, assessment and screening of the drug user, and the types of treatments that may be useful for these patients.

## A Model for Understanding Addiction

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) divides substance use disorders into two main categories: substance dependence and substance abuse.

In order to satisfy the criteria for substance dependence, an individual must have at least three of the following criteria:

1. Tolerance: need for use of increasing amounts of the substance in order to achieve intoxication.
2. Withdrawal symptoms typical for the substance.
3. Substance taken in larger amounts or over a longer period of time than intended.
4. Desire to cut down or control use.
5. Great deal of time spent on using, obtaining, or recovering from the substance.
6. Reduced social, occupational or recreational activities because of substance use.
7. Continued use despite adverse physical or psychological consequences.

According to the DSM-IV criteria, tolerance and withdrawal are not sufficient or even necessary to make a diagnosis of substance dependence. Compulsive cannabis use, for example, can occur in the absence of significant tolerance or withdrawal symptoms. Likewise, surgical patients can experience tolerance and withdrawal from opioid pain medications without showing signs of compulsive use.

Substance abuse is defined by one of the following criteria:

1. Recurrent substance use resulting in failure to fulfill role obligations at work, school, or home.
2. Recurrent use in physically hazardous situations.
3. Recurrent substance-related legal problems.
4. Continued use despite social or interpersonal problems caused by the substance.

To better understand the nature of habitual substance use, various models of addiction have been developed. Currently, the most popular model for understanding substance addiction is to view it as a chronic disease, akin to diabetes or asthma, in which behavioral interventions and treatment compliance play a part in controlling a lifelong illness [Leshner AI, *Hosp Practice* 1997;6-8; McLellan AT, et al. *JAMA* 2000; 284(13):1689-95]. Although the medical paradigm has done much to lessen the stigma and has resulted in improved treatment services, it is inadequate in that it fails to address the importance of psychosocial and cognitive learning variables in addiction. On the JHAS Psychiatry Service, we have used a “motivated behavior” model for understanding addiction [McHugh PR, *The Perspectives of Psychiatry*]. This model takes into account the individual’s free will, biological drive, and conditioned learning, which interact to produce addictive behavior.

### • Drive

All motivated behaviors (eating, sleeping, and sex) are driven, in part, by biological mechanisms. In the case of addiction, abused substances have been found to cause increased levels of dopamine in the nucleus accumbens, a part of the mesolimbic dopamine system found in the ventral tegmental area of the brain. These structures are among the most primitive areas of the brain and are powerful motivators when stimulated. Animals will perform a task (such as a lever press) several thousand times in order to receive an electrical or chemical stimulus to the nucleus accumbens. This biological “reward system” is modulated not only by dopamine but also by opioid receptors. Cocaine and stimulants directly cause elevated levels of dopamine, while alcohol and opiates increase the firing rate of dopaminergic neurons by acting on opioid receptors.

### • Conditioned Learning

Conditioned learning shapes behavior by way of psychological and environmental variables. Society can also play a role in initiating and sustaining addiction. This was convincingly illustrated in a study of 898 U.S. servicemen enlisted in Vietnam, where 21% were addicted to heroin while in Vietnam, but only 1% remained addicted upon their return to the U.S. [Robins LN, *Arch Gen Psychiatry* 1975;32:955-61].



## Substance Abuse and HIV

Easy access to opiates in Southeast Asia and a culture of opiate use may have been factors contributing to the high rate of heroin use.

Learning is also shaped by reinforcers provided by the drug itself. In the earlier stage of addiction, the “high” or euphoria provided by the drug serves as the positive reinforcer. In later stages, negative reinforcement becomes more important as the addict develops tolerance to the drug. Long-term heroin addicts continue to use the drug not because it makes them “high” but to avoid withdrawal sickness.

A highly conditioned behavior eventually becomes more stereotypical and compulsive in nature. Moreover, environmental cues can trigger “cravings” or urges to use the drug in a Pavlovian fashion. This is best illustrated in nicotine dependence, when smokers experience strong cravings when performing activities usually associated with cigarette smoking. In short, addiction results when biological mechanisms and environmental conditioning combine to produce a new “drive” or hunger to use drugs without the normal checks and balances that usually keep natural drives under control.

### • Choice

Finally, choice involves the free will of the individual to initiate and continue using the drug. While it is true that choice becomes narrower as addiction progresses, it is by choice that an individual enters treatment resulting in a lifestyle change.

### Medical Implications

Ongoing substance abuse has grave medical implications for HIV-infected individuals. Many physical symptoms of HIV infection overlap with those of substance abuse and withdrawal, including malaise, fatigue, weight loss, fever, diarrhea and night sweats. The accumulation of medical sequelae from chronic substance use may accelerate HIV infection itself. HIV-seropositive IDUs, for example, are at higher risk for developing bacterial infections such as pneumonia, sepsis, soft tissue infections and endocarditis than seronegative drug users [Selwyn PA, et al. *N Eng J Med* 1992;24:1697-703]. Tuberculosis and hepatitis C infection are found more commonly in this population as well [O'Connor PG, et al. *N Eng J Med* 1994;331:450-59]. Because high-risk sexual behavior and drug use are often linked, these

patients are also at risk for contracting and spreading a variety of STDs.

Neurological symptoms due to HIV infection and substances of abuse can overlap. For instance, both AIDS dementia and drug intoxication can present with apathy, disorientation, aggression, and an altered level of consciousness. Drug withdrawal can present with seizures and neurovegetative symptoms, as can opportunistic infections of the CNS.

With respect to medical treatment, HIV-infected active IDUs tend to be less compliant with medical appointments, medications, and in obtaining regular laboratory testing [Arici C, et al. *HIV Clin Trials* 2002;3(1):52-7]. Substance use is associated with poor antiretroviral medication adherence, resulting in higher viral loads and lower CD4 cell counts [Lucas GM, et al. *AIDS* 2002;16(5):767-74].

Because the HIV-infected patient is likely to be on a variety of antiretroviral medications and prophylactic agents for opportunistic infections, the clinician must be especially mindful of interactions between these medications and methadone treatment. Decreased plasma levels of methadone can occur with concurrent administration of ritonavir, nelfinavir, efavirenz, and nevirapine, necessitating adjustments in methadone dosage if withdrawal symptoms occur [Gourevitch MN, *The Mt Sinai J Med* 2000;67:429]. Medications used to treat opportunistic infections and seizures such as rifampin, phenytoin, phenobarbital, and carbamazepine can also cause decreased methadone levels.

### Concurrent Psychiatric Disorders

The term “dual diagnosis” refers to a patient who has both a drug use disorder and another psychiatric disorder; “triple diagnosis” refers to a dual diagnosis patient who also has HIV. Such patients are over-represented in treatment settings because of their symptom severity and chronicity. In a study of 50 new entrants to the JHAS, 44% of the patients had a diagnosis of current or previous substance use disorder, and 24% of those patients had both a comorbid primary psychiatric diagnosis and substance use disorder [Lyketsos CG, et al. *Int J Psych Med* 1994; 24(2):103-113].

Personality disorders, especially antisocial personality disorder, are commonly found in

the substance abusing population. Although the DSM-IV uses a categorical approach to diagnosing personality disorders in which patients need to meet a certain set of criteria to qualify for a diagnosis, it is often more helpful to view personality traits as existing along a continuum. Thus, more or less of a particular personality trait can predict habitual adaptive or maladaptive responses to life circumstances.

One model that we use on the JHAS Psychiatry Service depicts personality as existing around the axes of stability-instability and introversion-extroversion [see Hutton, *HHR* 2001,13(6):5]. The combination of the personality traits of instability and extroversion are often seen in patients being treated in the HIV clinic. Persons with extreme traits of instability have very strong and reactive emotional responses that tend to be overpowering, easily taking control of the person's judgment and behavior. Persons with extreme traits of extroversion have emotional responses that are quick and changeable, focused in the present, and tend to be predominantly reward-seeking rather than harm-avoiding. These traits are generally found in the so-called cluster B personality disorders in the DSM-IV (antisocial, borderline, narcissistic, and histrionic), which can be found in as many as 49% of all substance abusers [Kokkevi A, et al. *Addictive Behaviors* 1998; 23(6):841-53].

Unstable extroversion has important implications for the HIV-infected addict. Not only do these traits result in a vulnerability to addiction and other risky behaviors that predispose to HIV infection, but they also pose significant barriers to treatment. These patients tend to act on strong, impulsive feelings rather than on carefully considered treatment instructions. Their behavior will tend to be driven by the transient, immediate rewards of drugs rather than by their lasting future consequences. Such patients tend to become bored easily. They tend to “want what they want when they want it” rather than when it may be good for them. Studies have shown that drug users with a diagnosis of antisocial personality disorder are more likely to engage in HIV risk behaviors such as needle sharing and injection drug use

*continued on page 10*



## Substance Abuse and HIV

continued from page 9

[Brooner RK, et al. *Am J Psychiatry* 1993;140:309] and to have a greater number of sexual partners [Kelley JL, *J Subst Abuse Treat* 2000;19:59-66]. They are also less likely to stop high-risk sexual behaviors after being educated about HIV prevention [Comptom WM, et al. *Drug and Alcohol Dependence* 2000;58(3):247-57]. It is critical to identify such personality vulnerabilities in this patient population, because they can have a profound effect on treatment engagement and prognosis.

Mood disorders, especially major depressive disorder, are also found in these patients, with studies estimating a prevalence of 15% to 30% [Ahmad B, et al. *J Pak Med Assoc* 2001;51(5):183-6; Brooner BK, et al. *Arch Gen Psychiatry* 1997;54(1):71-80]. Diagnosing affective disorders in drug users can be difficult and even controversial. This controversy stems from the problem of determining the causal or even chronological relationship between drug disorders and affective disorders.

In making the diagnosis of a primary mood disorder, it often becomes necessary to observe the patient over a period of abstinence, ideally in a confined environment. Careful consideration should be given to whether the symptoms are isolated or whether they meet the full criteria for a major depressive syndrome. The temporal relationship of symptoms to substance use should also be considered. Patients with a family history of psychiatric disorders are more likely to have a comorbid psychiatric diagnosis than those who do not. Finally, collateral informants such as family members and friends who have knowledge of a patient's premorbid functioning can be invaluable in determining the longitudinal course of a patient's symptoms.

The importance of identifying affective disorders early on lies not only in their own well-known sequelae, including suicide, but also in their complex interactions with addiction. Depression is associated with worsening of addiction and resistance to treatment. Depressed patients are also more difficult to engage in and maintain in treatment given their energy, hopelessness, and negativism. Given the high prevalence of overlapping addictive and affective disorders in clinical settings, as well as the poor prognosis associated with untreated affective disorders, a treatment approach

should necessarily emphasize simultaneous and equal treatment of both entities.

### Assessment and Evaluation

Because of societal stigma attached to both substance abuse and HIV, a patient may be reluctant to disclose information in an initial evaluation. Forming a close therapeutic alliance is the first step to effective history taking. If necessary, it can be spread out over several sessions. The clinician should take a nonjudgmental and empathetic approach to interviewing the patient and move from more comfortable topics of discussion (employment, family, friends, hobbies) before introducing questions about drug use and sexual behavior. Confidentiality should be assured, as in other types of medical settings. In many cases collateral sources of information can be helpful in eliciting accurate histories. These may include old medical records, family members, friends, and health care providers (both previous and current).

A careful substance abuse history should contain specific information not only about the type of substances used but also about routes of administration, duration, frequency of use, date of first use, most recent use, and the highest/usual amount used of each drug. The patient should also be asked about periods of abstinence and relapse and the respective conditions surrounding each one.

A drug treatment history should also be obtained, including the types and period of detoxification, outpatient drug treatment, methadone maintenance, attendance at AA/NA meetings, and residential drug treatment. This information is helpful in ascertaining which methods of treatment may have been helpful in the past and which treatment modalities have failed.

To assess patients for drug dependency, questions related to drug craving, loss of control of drug use, withdrawal symptoms, medical complications, and impairment in psychosocial functioning should be explored with patients. A simple screening tool for alcoholism is the CAGE questionnaire, which has a 75% sensitivity and 96% specificity for two or more positive answers [Bush B, et al. *Am J Med* 1987;82:231]. CAGE is a mnemonic for:

1. Have you ever felt you ought to *Cut down* drinking?
2. Have people *Annoyed* you by criticizing your drinking?

3. Have you ever felt *Guilty* about your drinking?

4. Have you ever had a drink first thing in the morning (*Eye opener*)?

A complete physical examination should include a careful search for physical evidence of drug abuse, including injection marks, scars, burns, nasal septum erosion or perforation, skin abscesses, cellulitis, and soft-tissue infection. Stigmata of alcohol abuse include hepatosplenomegaly, ascites, and physical trauma. A careful neurological assessment, including a complete mental status examination is essential in order to assess for the presence of both substance intoxication and the neuropsychiatric manifestations of AIDS.

### Treatment

#### • Role Induction and Motivation to Change

The initial and often most daunting task of treating the addict is engagement and induction of the patient role. The general rule is that addicts and treatment providers begin with differing agendas—addicts tend to come to treatment settings seeking comfort and immediate crisis relief, whereas physicians and other health providers look at long term goals of improvement in a patient's health and overall functioning. One of the clinician's initial goals should be to gradually bring the patient's attitudes in line with the treatment plan.

An important first step is to identify where the patient is in terms of his or her motivation to change. Addiction experts use a "transtheoretical stages of change" model to evaluate a patient's motivational state [Prochaska JD, et al. *Psychotherapy: Theory, Research, and Practice* 1982;19:276-88]. A patient is viewed as progressing through several different stages:

1. Precontemplation: The patient has no intention to change his/her addictive behavior.
2. Contemplation: The patient is considering change because of the negative consequences of drug use but is ambivalent about it.
3. Preparation: The patient shows intention to change and takes initial steps to seek treatment.
4. Action: The patient decides to modify behavior, environment and circumstances in order to relinquish the addictive lifestyle.



## Substance Abuse and HIV

5. Maintenance: The patient works to prevent relapse and maintain abstinence.

The most difficult task faced by most clinicians is in moving a patient from a precontemplative or contemplative stage to an action stage. Change is more effective and sustained when the patient is able to verbalize self-motivational statements that indicate readiness to enter treatment (“I’ve got to do something about this problem.”). A technique known as “motivational interviewing,” developed by Miller and Rollnick, uses five main techniques to help the patient resolve ambivalence about needing treatment:

1. Expressing empathy through reflective listening.
2. Developing discrepancy between a patient’s goals or values and his/her current behavior.
3. Avoidance of argumentation.
4. Adjusting to patient resistance rather than opposing it directly.
5. Supporting the patient’s self-efficacy and the perception that s/he has the ability to change.

Once a patient has decided to change his or her addictive behavior, the clinician’s role is to then help the patient decide on a plan and to facilitate entry into treatment. This can include helping the patient make phone calls to treatment facilities, working out a child care plan for single mothers, or arranging transportation from the patient’s home to the treatment site.

### • Detoxification

In order for intoxicated patients to understand and process the cognitive steps needed for recovery, detoxification is the first step. Many HIV-infected substance abusers benefit from a brief hospital stay to stabilize their psychiatric and medical co-morbidities and to give them respite from the social chaos that is often such a prominent part of their lives. This is usually accomplished by either slowly tapering the drug of dependence or using a cross-dependent drug that has a similar pharmacological mechanism of action.

Alcoholics are detoxified through the use of a long-acting benzodiazepine, such as diazepam (*Valium*) or chlordiazepoxide (*Librium*). Patients who have liver abnormalities or are more prone to delirium can be detoxified using oxazepam (*Serax*), which has no active metabolites.

Detoxification from short-acting benzodiazepines such as lorazepam (*Ativan*), alprazolam (*Xanax*) can be accomplished by converting the patient to an equivalent dosage of a longer acting benzodiazepine, such as clonazepam, or by using a phenobarbital taper. Opioid dependent individuals are commonly detoxified through a methadone or buprenorphine taper. Clonidine, an alpha-2 adrenergic agonist, can be used alone or adjunctively to alleviate the autonomic symptoms of heroin withdrawal.

### • Treatment of Comorbid Psychiatric Conditions

Many patients with HIV and addictions often have comorbid psychiatric conditions, which need to be treated in order to maximize treatment compliance. Conditions such as major depression, bipolar disorder, and schizophrenia are best managed pharmacologically and if necessary, a psychiatric referral should be made early in the course of treatment. Because these patients tend to have multiple medical complications, it is important to remember to start psychotropic medications at low dosages and to titrate slowly to minimize the risk of developing adverse side effects and delirium.

Disorders of personality are managed with cognitive-behavioral psychotherapy. Unstable extroverts may sabotage treatment by engaging in staff splitting, doctor shopping, general noncompliance and manipulative behavior. Therapy should help the patient focus on thoughts instead of feelings and should emphasize rewards resulting from the desired behavior. Firm limit setting and a devotion to consistency on the part of all health care providers involved are essential. To this end, the treatment staff should work on a documented treatment plan with clear goals agreed upon by all. The treatment plan should be reviewed with the patient at the initiation of treatment so that he understands clearly what is expected of him and what he can expect from his treatment providers if these goals are adhered to.

### • Maintenance Treatment and Relapse Prevention

Long-term treatment is necessary for patients to begin the process of lifestyle change and recovery. Treatment settings can be inpatient, outpatient, or a combination of the two. Whether a patient can be maintained on an inpatient or outpatient

basis depends on the availability of social supports in the community, presence of medical and/or psychiatric comorbidities, likelihood of relapse, number of previous failed treatment attempts, and the need for inpatient medical monitoring for withdrawal symptoms.

An integrated approach to treatment is most effective because the complexity of this patient population makes it especially vulnerable to recidivism. To this end a “one-stop shopping” model is needed to maintain treatment engagement. Thus, a treatment center catering to HIV infected addicts should ideally include medical providers, psychiatrists, social workers, housing counselors, and day care workers on site. Directly observed therapy of antiretroviral and psychotropic medications at substance abuse treatment facilities can improve adherence and compliance. This has proven to be successful in a number of JHAS patients who also attend the 911 Broadway Center (a Hopkins-based outpatient substance abuse treatment facility), where medications are administered to patients when they arrive for their daily methadone treatment or substance abuse groups.

It is important to remember that addiction treatment is “active” rather than “passive” and entails transforming previously held beliefs, attitudes, and personal identity into a new way of life. To this end, group therapy is a necessary part of all substance abuse treatment. In group therapy, the more experienced members of the group provide both confrontation and support for the newly initiated member. Group support also provides the newly recovering addict with a hopeful view of the benefits to be achieved with recovery. A commitment to a community of recovery protects the patient from the influences of the drug community and provides the patient with new bonds that help maintain a sense of purposefulness and hopefulness.

The individual health care provider can assist the patient during this phase of recovery by helping the patient identify and avoid triggers to possible relapse and increasing the patient’s sense of self-efficacy and ability to cope without drugs. It is important to realize that relapse is often the rule and not the exception, and plans should

*continued on page 12*



## Substance Abuse and HIV

continued from page 11

be in place for early intervention. Random urine and serum drug toxicology screens and *Breathalyzer* tests can be used to monitor a patient's continued abstinence. When a relapse or "slip" does occur, the health care provider should immediately facilitate the patient's re-entry into drug treatment before old patterns of behavior become reestablished.

Pharmacological treatments should be seen as enhancements to the overall treatment plan and not as a replacement for them. For example, studies have shown that in the treatment of alcohol dependence, naltrexone in conjunction with supportive and coping skills therapy was much more effective than treatment with naltrexone alone [O'Malley SS, et al. *Arch Gen Psychiatry* 1992; 49:881-87]. Likewise, patients had better outcomes in methadone treatment when they had access to regular counseling, on-site psychiatric/medical services, and family therapy [McLellan AT, et al. *JAMA* 1993;269(15):1953-59].

In alcoholics, disulfiram can be very effective. It is taken once daily at dosages from 250 mg to 500 mg and causes a very unpleasant reaction when alcohol is ingested due to the build up of acetaldehyde in the body. Symptoms include nausea, flushing, headaches and hypotension. Liver enzymes

should be monitored because of the risk of hepatotoxicity. Another medication, which has been more recently available to clinicians, is naltrexone administered at dosages of 50 to 100 mg/day. Naltrexone has been shown to reduce alcohol cravings and the subjective feeling of alcohol intoxication [Volpicelli JR, et al. *Arch Gen Psychiatry* 1992;49: 876-880; Volpicelli JR, et al. *J Clin Psychiatry* 1995;56(suppl 7): 39-44; Swift RM, *J Clin Psychiatry* 1995; 56(suppl 7): 24-29].

In opiate dependent individuals, pharmacotherapy includes both opioid agonist and antagonist medications. Methadone is the opioid agonist most often used for maintenance treatment and has been very effective in reducing the spread of HIV. This medication is usually given to the patient at varying dosages from 40 to 100 mg daily; however, patients tend to do best at dosages above 60 mg/day. The medication is administered daily under supervision until the patient has established a pattern of abstinence, at which time take-home dosages are allowed. Buprenorphine, a partial agonist, is currently being considered for FDA approval for sublingual administration and may be a useful alternative to methadone. Naltrexone is an opioid antagonist that has a high affinity for

blocking mu receptors. The medication blocks the euphoric effects of opioids when taken at dosages of 50 to 100 mg/day. Before the medication is started, the patient must have been abstinent from opioids for a period of time, usually 5-10 days, because it precipitates rapid withdrawal in individuals who still have opioids in their system. As with disulfiram, liver function tests must be monitored because of the risk of hepatotoxicity.

### Conclusion

Working with the HIV-infected substance abuser is a challenging and often frustrating task. An integrated treatment team approach consisting of medical providers, psychiatrists, substance abuse counselors, therapists and social workers is essential in unraveling and addressing the variety of problems these patients face which make them vulnerable to nonadherence. Early identification and rapid accessibility to treatment is essential in improving both their mental and physical well-being and in halting further spread of HIV.

*Jeffrey H. Hsu, M.D. is an Instructor in the Department of Psychiatry, Johns Hopkins University, School of Medicine. ▲*

## THE HOPKINS HIV REPORT

The Johns Hopkins University AIDS Service  
The Hopkins HIV Report Distribution  
P.O. Box 651266  
Potomac Falls, VA 20165-1266

ADDRESS SERVICE REQUESTED

Non-Profit Org.  
U.S. Postage  
**PAID**  
Dulles, VA  
Permit No. 056