

# PRACTICE GUIDELINE FOR THE Treatment of Patients With HIV/AIDS

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*Originally published in November 2000. This guideline is more than 5 years old and has not yet been updated to ensure that it reflects current knowledge and practice. In accordance with national standards, including those of the Agency for Healthcare Research and Quality's National Guideline Clearinghouse (<http://www.guideline.gov/>), this guideline can no longer be assumed to be current. The April 2006 Guideline Watch associated with this guideline provides additional information that has become available since publication of the guideline, but it is not a formal update of the guideline.*

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# STATEMENT OF INTENT

The American Psychiatric Association (APA) Practice Guidelines are not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and practice patterns evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome for every individual, nor should they be interpreted as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available.

This practice guideline has been developed by psychiatrists who are in active clinical practice. In addition, some contributors are primarily involved in research or other academic endeavors. It is possible that through such activities some contributors, including work group members and reviewers, have received income related to treatments discussed in this guideline. A number of mechanisms are in place to minimize the potential for producing biased recommendations due to conflicts of interest. Work group members are selected on the basis of their expertise and integrity. Any work group member or reviewer who has a potential conflict of interest that may bias (or appear to bias) his or her work is asked to disclose this to the Steering Committee on Practice Guidelines and the work group. Iterative guideline drafts are reviewed by the Steering Committee, other experts, allied organizations, APA members, and the APA Assembly and Board of Trustees; substantial revisions address or integrate the comments of these multiple reviewers. The development of the APA practice guidelines is not financially supported by any commercial organization.

More detail about mechanisms in place to minimize bias is provided in a document available from the APA Department of Quality Improvement and Psychiatric Services, “APA Guideline Development Process.”

This practice guideline was approved in July 2000 and published in November 2000.

# INTRODUCTION

This practice guideline seeks to summarize data and specific forms of treatment regarding the care of patients with HIV/AIDS. The purpose of this guideline is to assist the psychiatrist in caring for a patient with HIV/AIDS.

Psychiatrists care for patients with HIV/AIDS in many different settings and serve a variety of functions. In many cases, a psychiatrist will serve as a consultant to the patient's primary care physician. This guideline reviews the treatment that patients with HIV/AIDS may need. The psychiatrist should either provide or advocate for the appropriate treatments.

To share feedback on this or other published APA practice guidelines, a form is available at [http://www.psych.org/psych\\_pract/pg/reviewform.cfm](http://www.psych.org/psych_pract/pg/reviewform.cfm).

# DEVELOPMENT PROCESS

This document is a practical guide to the management of patients—primarily adults over the age of 18—with HIV/AIDS and represents a synthesis of current scientific knowledge and rational clinical practice. This guideline strives to be as free as possible of bias toward any theoretical approach to treatment.

This practice guideline was developed under the auspices of the Steering Committee on Practice Guidelines. The process is detailed in a document available from the APA Department of Quality Improvement and Psychiatric Services: the “APA Guideline Development Process.” Key features of the process include the following:

- a comprehensive literature review (description follows) and development of evidence tables;
- initial drafting by a work group that included psychiatrists with clinical and research expertise in HIV/AIDS;
- the production of multiple drafts with widespread review, in which 14 organizations and over 60 individuals submitted significant comments;
- approval by the APA Assembly and Board of Trustees; and
- planned revisions at regular intervals.

A computerized search of the relevant literature from MEDLINE, PsycINFO, EMBASE, and AIDSLINE was conducted.

The first literature search was conducted by using MEDLINE for the period from 1966 to June 1998 and used the key words “acquired immunodeficiency syndrome,” “HIV,” “dementia,” “mood disorders,” “anxiety,” “sleep,” “depression mania,” “substance use,” and “adjustment disorders.”

The literature search conducted by using PsycINFO covered the period from 1967 to March 1998 and used the key words “acquired immune deficiency syndrome,” “adjustment disorders,” “human immunodeficiency virus,” “dementia,” and “mood disorders.”

The literature search conducted by using EMBASE covered the period from 1980 to 1998 and used the key words “acquired immune deficiency syndrome,” “adjustment disorders,” “human immunodeficiency virus,” “manic depressive psychosis,” “depression,” and “mood disorders.”

The literature search conducted by using AIDSLINE covered the period from 1980 to 1998 and used the key words “acquired immunodeficiency syndrome,” “HIV,” “adjustment disorders,” “psychotherapy,” “dementia,” “treatment,” “therapy,” “therapeutic,” and “mood disorders.”

An additional literature search was conducted by using MEDLINE for the period from 1990 to 1999 and used the key words “correctional settings,” “jail,” “women,” “minorities,” and “suicide.”

Additional, less formal, literature searches were conducted by APA staff and individual members of the work group on HIV/AIDS.



# **PART A:**

## **BACKGROUND INFORMATION AND TREATMENT RECOMMENDATIONS FOR PATIENTS WITH HIV/AIDS**

### **I. SUMMARY OF TREATMENT RECOMMENDATIONS**

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The following executive summary is intended to provide an overview of the organization and scope of recommendations in this practice guideline. Because psychiatric treatment of patients with HIV/AIDS requires the consideration of many factors, it cannot be adequately reviewed in a brief summary. The reader is encouraged to consult the relevant portions of the guideline when specific treatment recommendations are sought. This summary is not intended to stand on its own.

#### **▶ A. CODING SYSTEM**

Each recommendation is identified as falling into one of three categories of endorsement, indicated by a bracketed Roman numeral following the statement. The three categories represent varying levels of clinical confidence regarding the recommendation:

- [I] Recommended with substantial clinical confidence.
- [II] Recommended with moderate clinical confidence.
- [III] May be recommended on the basis of individual circumstances.

#### **▶ B. GENERAL CONSIDERATIONS**

All psychiatrists need to have an adequate fund of knowledge about HIV/AIDS. Because scientific knowledge regarding virology, prevention, and interventions to treat HIV infection advances rapidly, this guideline attempts to summarize current knowledge and principles of treatment with the expectation that updated information will be needed. For this reason, several pertinent web site addresses have been included both in the text and in an appendix at the end of the guideline. The reader is encouraged to use the web sites to search for additional or more current information that will supplement the information provided in this guideline. Section II provides information about the following: the pathophysiology and virology of HIV, the epidemiology of HIV/AIDS, transmission of HIV, pathogenesis of HIV, assessment and staging of HIV disease, treatment for HIV infection, impact of HIV on the central nervous system, neuropsychiatric clinical syndromes, differential diagnosis of neuropsychiatric syndromes, pediatric HIV/AIDS syndromes, and prevalence of comorbid psychiatric conditions.

Section III serves as a guide for formulating and implementing a treatment plan, and its outline is mirrored in Sections V and VI, in which the data regarding prevention and treatment, respectively, are provided. Readers may find it useful to first read Section III and then refer to Sections V and VI for the scientific evidence on which the treatment recommendations have been made.

Because there are many clinical and environmental features that may influence treatment, Section IV provides additional information on sociodemographic variables such as race/ethnicity, sexual orientation, gender, age, economic factors, and setting (urban versus rural). Specific clinical topics of suicidality, bereavement, axis II disorders, and psychoneuroimmunology are also covered. Last, information about special treatment situations such as alternative/complementary treatments, institutional settings, and health care clinician issues is included.

### **1. Psychiatric management of individuals at high risk for HIV infection**

Psychiatrists may encounter patients in the course of their clinical work who are at risk for acquiring HIV infection. Optimum management of patients at high risk for HIV infection uses a wide range of psychiatric skills such as comprehensive diagnostic evaluations, assessment of possible medical causes of new-onset symptoms, initiation of specific treatment interventions, and a keen understanding of psychodynamic issues [I]. Patients with substance use disorders, patients with severe mental illness, and victims of sexual abuse/crimes have specific risks for becoming infected with HIV [I]. Psychiatric management of individuals who, because of specific behaviors, are at risk for HIV infection involves obtaining a risk history, considering the need for HIV antibody testing, initiating risk reduction strategies, and initiating postexposure prophylaxis with antiretroviral medication when indicated. A psychiatrist will not be aware of a patient's risk for HIV infection unless risk behavior is accurately assessed [I]. Psychiatrists should be knowledgeable about which specific risk behaviors are more likely to result in HIV transmission [I]. Psychiatric units or individual practitioners who conduct HIV testing should be aware of their obligation to provide the necessary pre- and posttest counseling [I]. Because successful risk reduction requires more than knowledge of risk, ongoing discussions between patient and psychiatrist can help provide the motivating and skill-building factors that help ensure consistent changes in behavior [II].

Psychiatrists serve as primary clinicians of both medical and psychiatric care in some institutional settings. Thus, administrators of these facilities should formulate policies that support the full range of HIV prevention steps outlined in this guideline [I]. Postexposure prophylaxis is recommended for known occupational exposure, especially percutaneous or mucous membrane exposure, to blood or other body fluids [I]. The American College of Obstetricians and Gynecologists now recommends that an HIV antibody test be offered during annual exams to all women seeking preconception care, not just pregnant women [II].

### **2. Psychiatric management of HIV-infected individuals**

Specific tasks that constitute the psychiatric management of patients with HIV/AIDS include the following: establishing and maintaining a therapeutic alliance; collaboration and coordination of care with other mental health and medical providers; diagnosing and treating all associated psychiatric disorders; facilitating adherence to the overall treatment plan; providing education about psychological, psychiatric, and neuropsychiatric disorders; providing risk reduction strategies to further minimize the spread of HIV; maximizing psychological and social/adaptive functioning; considering the role of religion/spirituality; preparing the patient for issues of disability, death, and dying; and advising significant others/family regarding sources of care and support.

The development of a psychiatric treatment plan for patients with HIV infection requires thoughtful and comprehensive consideration of the biopsychosocial context of the illness [I].

When seeing a patient in consultation, it is important to gather history about cognitive or motor symptoms and conduct a mental status screening examination to determine whether neurocognitive deficits are present [I]. Psychiatrists should be knowledgeable about medication side effects and drug interactions of psychotropic agents as well as HIV-related medications in order to provide optimum patient care [I]. Psychiatric treatment of patients with HIV infection should include active monitoring of substance abuse, since it is often associated with risk behaviors that can lead to further transmission of HIV [I]. Adherence is of utmost concern with antiretroviral treatment because the regimens are so unforgiving; even minor deviations from the prescribed regimen can result in viral resistance and permanent loss of efficacy for existing medications [I]. Psychiatrists can play an important role in the promotion of patient adherence, since comorbid psychiatric disorders (e.g., substance abuse or depression) have been shown to adversely affect patient compliance with a complicated treatment regimen [II].

### **3. Treatment of psychiatric disorders that result from or are comorbid with HIV infection**

Psychiatric disorders associated with HIV/AIDS should be accurately identified and treated [I]. In adults and children with HIV infection, changes in mental status or the emergence of new psychiatric or cognitive disorders requires ruling out treatable and reversible causes; medical causes are of increasing concern if CD4 counts are low or viral load has begun to rise [I]. The more common diagnoses found in association with HIV/AIDS are dementia and the spectrum of cognitive disorders; delirium; mood disorders; substance use disorders; anxiety disorders; psychotic disorders; adjustment disorders; sleep disorders; disorders occurring in infants, children, and adolescents; and HIV-associated syndromes with psychiatric implications. Both psychopharmacologic and psychotherapeutic treatment strategies are often indicated.

Treatment of HIV-associated dementia consists of intervening with combination antiretroviral therapy that targets the underlying HIV infection, with consideration of whether the agents adequately penetrate the central nervous system (CNS); management of symptoms associated with HIV-associated dementia (e.g., agitation or fatigue) with antipsychotic or stimulant agents, respectively, should be considered [I]. Delirium in the context of HIV infection may often be caused by interactions between the many medications taken by HIV patients. Management of delirium includes the judicious use of antipsychotic medications, with many clinicians choosing atypical agents because of their lower side effect profile; benzodiazepines are relatively contraindicated [III].

The management of disturbances in mood, such as major depression or mania, for patients with HIV infection is similar to that for other patients with medical comorbidity [I]. Choice of an antidepressant or mood-stabilizing agent may be influenced by the antiretroviral regimen in place, and dose adjustments may be necessary if drug-drug interactions are likely. A wide array of antidepressant agents are effective in the treatment of HIV-associated major depression, including newer agents such as the selective serotonin reuptake inhibitors (SSRIs) [I] and medications such as psychostimulants and testosterone [II]. Psychotherapy, particularly interpersonal psychotherapy, either alone or in combination with antidepressant agents, is also an effective treatment for HIV-related depression [II]. Mania associated with HIV infection, particularly late in the course of HIV disease, may be difficult to treat; however, treatment studies suggest that traditional antimanic agents are effective and tolerated [II].

The constellation of other disorders associated with HIV infection requires treatment. Substance use disorders are prevalent among persons with or at risk for HIV infection, and treatment is a high priority [I]. Psychiatrists should be aware that by treating substance abuse, they may well be preventing HIV infection. One component of a comprehensive approach to HIV prevention among injection drug users is access to sterile syringes [I]. Treatment of anxiety and sleep disorders among HIV-infected patients has not been well studied. For patients who are taking protease inhibitors, benzodiazepines are generally contraindicated because of drug-drug

interactions [II]. Thus, benzodiazepines should be given only as a short-term intervention in most instances. Psychotic symptoms in late-stage HIV infection are generally managed with atypical antipsychotic medications at the lowest effective dose, since standard neuroleptic medications have been associated with severe and difficult-to-treat extrapyramidal side effects [I]. Adjustment disorders may require treatment with psychotherapy or medication to prevent progression to a more severe psychiatric disturbance [III]. HIV-associated syndromes with psychiatric implications encompass wasting syndrome, fatigue, pain, and sexual dysfunction. Wasting syndrome has been effectively treated with testosterone (or its derivatives), growth hormone, and thalidomide [I]. Psychostimulants are one of the main interventions used for fatigue [II]. Chronic pain from peripheral neuropathy is often treated with tricyclic antidepressants and anticonvulsant medications, but published treatment studies of pain syndromes in patients with HIV infection have not supported their use [III]. In men, HIV-related hypogonadism can be treated with testosterone replacement [II].

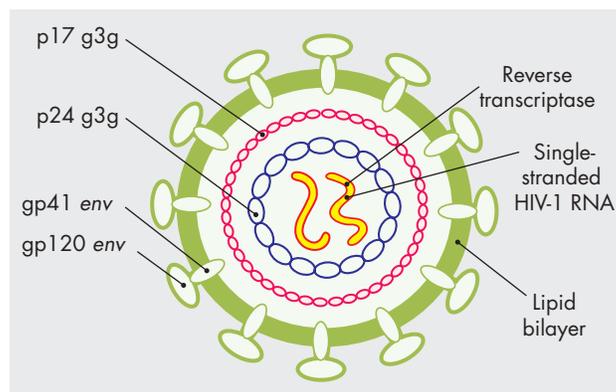
Treatment of children and adolescents with antiretroviral medications has increased survival rates and slowed progression to AIDS [I]. The effectiveness of treatment of other mental and behavioral disorders associated with HIV infection in children and adolescents is largely unstudied.

## II. DISEASE DEFINITION, EPIDEMIOLOGY, AND NATURAL HISTORY

### ▶ A. BASIC FACTS ABOUT HIV INFECTION, AIDS, AND TREATMENTS

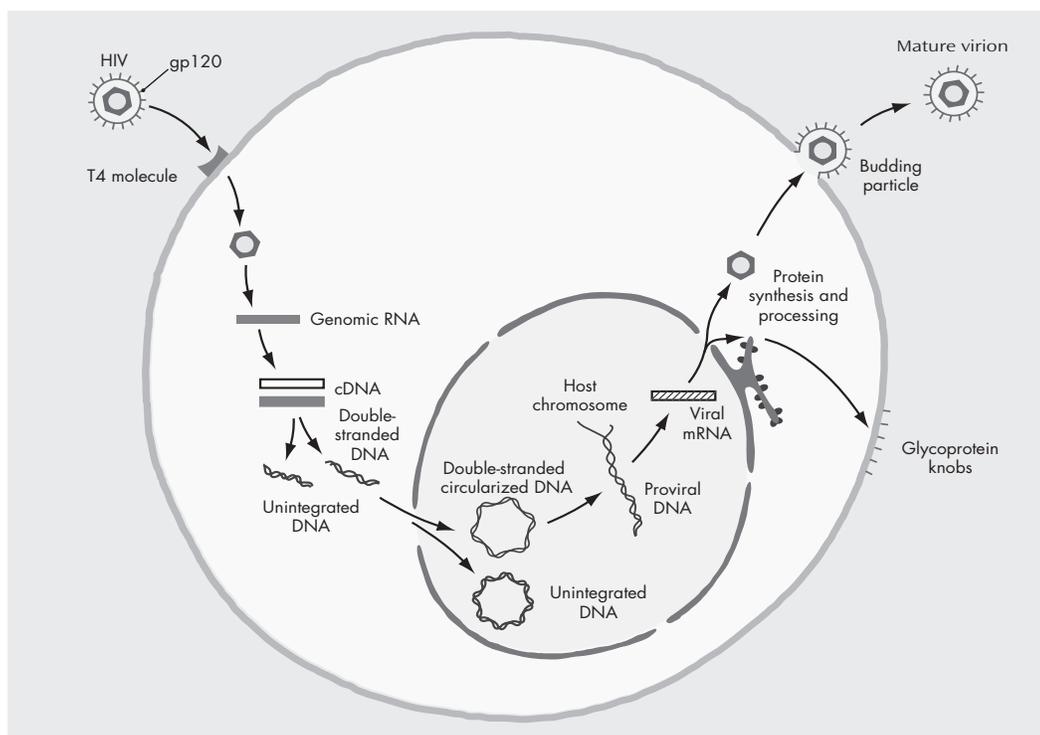
#### 1. Pathophysiology and virology

Identified in 1984, HIV is a human retrovirus (Figure 1). A retrovirus contains RNA as its genetic material as well as the enzyme reverse transcriptase required to translate RNA into DNA within the human host cell. Once HIV RNA is transcribed into human DNA through the process of replication, it becomes a functional virus capable of producing profound immune deficiency, particularly cell-mediated immune dysfunction (Figure 2).



**FIGURE 1.** The Structure of HIV.

Source. Mims C et al. *Medical Microbiology* 1993, p. 24.15.



**FIGURE 2.** The HIV Replication Cycle.

Source. Mims C et al. *Medical Microbiology* 1993, p. 24.16.

As with other retroviruses, HIV has a rapid rate of genetic mutation. HIV-1 is the form of the virus that causes disease in most of the world, including the United States, Europe, Asia, Latin America, and most of Africa. HIV-2, discovered in 1986, causes a relatively small proportion of cases clustered in West Africa. Unless specified, the term HIV used in this guideline will refer to HIV-1.

HIV selectively infects certain cells within the human body, with the primary sites being blood mononuclear cells, particularly T-helper (CD4) lymphocytes and lymphoid tissues. HIV is neuropathic, invading the CNS early during the initial period of infection.

Counter to earlier beliefs, HIV does not become “dormant” but rather engages in an extraordinary battle with the immune system that begins and continues after initial infection. Once a host is infected with HIV, the virus begins a process of rapid replication, with billions of viral particles made soon after infection (Figure 3). At the same time, the host immune system mounts a response. The capacity of HIV to infect host cells and replicate, destroying CD4 cells in the process, is counteracted by the capacity of the host immune system to produce and maintain immune surveillance over the replicating virus. Current knowledge suggests that there is a viral “set point” that varies among individuals and constitutes a balance between viral reproduction and the immune response. This viral set point has prognostic significance (1). The growth of knowledge about the virology and pathophysiology of HIV has had enormous implications for treatment interventions.

## 2. Epidemiology of HIV/AIDS

HIV infection is a global pandemic, with cases of AIDS reported in nearly every country in the world. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), as of

**TABLE 1. U.S. Prevalence of HIV Infection, AIDS Cases, and Cumulative Deaths as a Result of AIDS Through December 1999**

<b>Persons Living With HIV Infection in 1999</b>	<b>Persons Living With AIDS in 1999</b>	<b>Cumulative Deaths as a Result of AIDS</b>
113,167	299,944	430,441

*Source.* From the CDC HIV/AIDS Surveillance Report (3).

December 1999, more than 33 million people in the world are estimated to be living with HIV/AIDS, of which 95% live in the developing world. Globally, more than 16 million people have died of AIDS since the epidemic began (data available at [www.unaids.org](http://www.unaids.org)).

The Centers for Disease Control and Prevention (CDC) monitors the incidence, prevalence, morbidity, and mortality from HIV/AIDS in the United States ([www.cdc.gov/nchstp/hiv\\_aids/dhap.htm](http://www.cdc.gov/nchstp/hiv_aids/dhap.htm)). Through December 1999, a cumulative total of more than 730,000 AIDS cases have been reported to the CDC; there have been 430,441 total deaths from AIDS in the United States (Table 1). Approximately 650,000–900,000 persons in the United States are currently infected with HIV, which is about 0.3% of the population or 1 in 300 Americans.

In recent years, there has been a remarkable change in the epidemiology of AIDS in the United States. The National Center for Health Statistics has reported that age-adjusted death rates from AIDS in the United States declined an unprecedented 47% from 1996 to 1997, and AIDS fell from 8th to 14th among leading causes of death in the United States over the same time (2). For those aged 25–44, AIDS dropped from the leading cause of death in 1995 to the third-leading in 1996 and the fifth-leading in 1997 (2). The drop in deaths and AIDS incidence has been attributed to the effectiveness of antiretroviral therapy, but the declines have been less apparent among women and minorities.

At the same time, a study by the CDC found that despite the decrease in AIDS deaths and incidence, the *rate* of new HIV infections has remained the same: about 40,000 new cases a year (3). Therefore, the overall prevalence of HIV infection in the United States has increased (4). Prevention of HIV infection remains a high priority.

Approximately 70% of new infections occur among men, of which 60% are men who have sex with men, 25% are injection drug users, and 15% are men exposed through heterosexual contact (3). Among women, 75% of new infections occur through heterosexual contact and 25% through injection drug use (5). African American and Hispanic communities are two distinct populations within which women, youth, and children are especially affected.

### **3. Transmission of HIV**

HIV is transmitted through body fluids. It has been isolated from a variety of body fluids, including blood, semen, vaginal secretions, breast milk, urine, saliva, and tears. The risk of transmission through contact with a given fluid is related both to the amount of virus present in the fluid and to the type of exposure to it. HIV is found in such small concentrations in tears, saliva, and urine that transmission through casual contact with these fluids is theoretically possible but highly unlikely. On the other hand, behaviors that lead to certain types of exposure to blood, semen, vaginal secretions, and breast milk—all fluids with higher HIV concentrations—may lead to HIV transmission. HIV is spread primarily by unprotected sexual intercourse, irrespective of gender or sexual orientation, and sharing of unsterilized injection equipment for either medical or illicit purposes. It can be transmitted from an infected mother to an infant in utero during pregnancy, perinatally, or through breast-feeding.

#### **a) Sexual**

Sexual behaviors with exchange of body fluids can transmit HIV. While the rate of HIV transmission is somewhat higher for the recipient of semen than for the donating sexual partner,

**TABLE 2. Risk of HIV Transmission Associated With Various Sexual Activities**

<b>Risk Level</b>	<b>Sexual Activity</b>
<i>No risk</i>	Dry kissing Body-to-body rubbing Massage Nipple stimulation Using unshared inserted sexual devices Being masturbated by partner without semen or vaginal fluids Erotic bathing and showering Contact with feces or urine on intact skin
<i>Theoretical risk</i>	Wet kissing Cunnilingus with barrier Anilingus Digital-anal and digital-vaginal intercourse, with or without glove Using shared but disinfected inserted sexual devices
<i>Low risk</i>	Sharing nondisinfected personal hygiene items (razors, toothbrushes) Cunnilingus without barrier during or outside menstruation Fellatio and ejaculation, with or without ingestion of semen Fellatio, with or without condom Penile-vaginal intercourse with condom Penile-anal intercourse with condom
<i>High risk</i>	Penile-vaginal intercourse without condom Penile-anal intercourse without condom Coitus interruptus (intercourse with withdrawal before ejaculation)

*Source.* From Counselling Guidelines for HIV Testing (6).

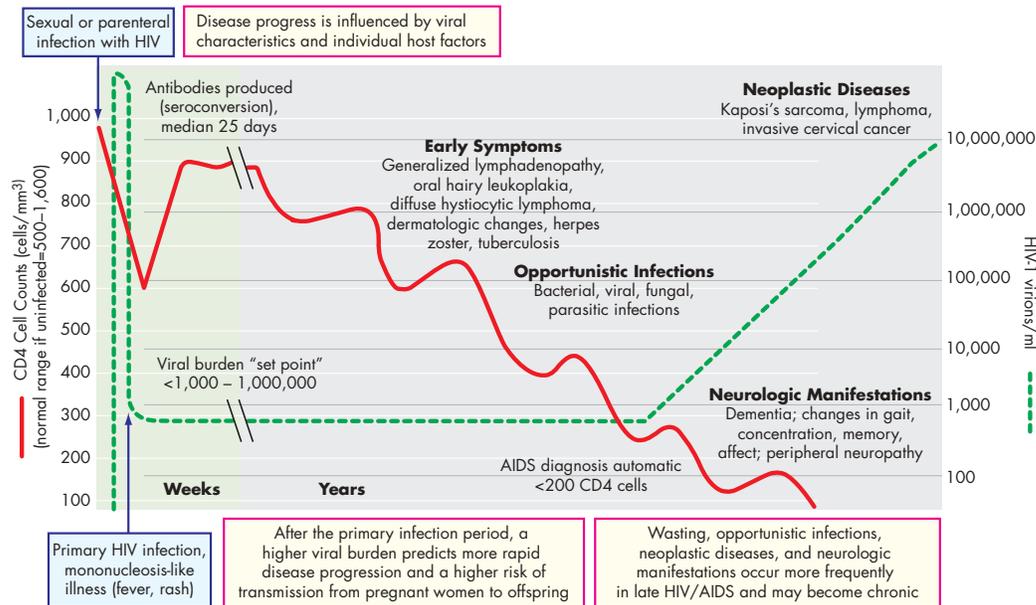
transmission has been documented in both directions. Penile-anal and penile-vaginal intercourse are considered the highest risk behaviors, with transmission more likely in the presence of other sexually transmitted diseases or genital lesions or during sexual activities that cause a rupture of tissue or bleeding (Table 2).

### **b) Injection drug use**

Sharing the equipment used to prepare and inject drugs with an HIV-infected person is a very efficient means of transmitting HIV and essentially amounts to a direct inoculation of viral particles from one person to another. The risk of transmission is directly related to the concentration of virus present in the blood and the volume of blood exchanged. Injection drug use is the second most common risk factor for HIV infection, and injection drug users account for an increasing proportion of AIDS cases (24% in 1997). It has been estimated that there are more than 1.5 million injection drug users in the United States (7).

### **c) Blood transfusion**

Blood transfusion with infected blood products remains a significant risk for acquiring HIV in some parts of the world. In the United States, donated blood has been screened for antibodies to HIV-1 since 1985 and for antibodies to HIV-2 since 1992. Therefore, the risk of transmission from a blood transfusion has become extraordinarily low—less than 0.001%. To further ensure that donated blood is not infected with HIV, since 1996 the American Red Cross has used the HIV antigen test. This test helps address the problem of false-negative HIV antibody tests in donors who may not have produced detectable antibodies after their initial infection. Before the use of lyophilized factor VIII, recurrent inoculation with pooled donated factor VIII was a major source of HIV transmission in hemophilia patients.



**FIGURE 3.** The Course of Untreated Adult HIV Infection.

Source. From the Southeast AIDS Training and Education Center, Emory University, Atlanta.

#### d) Perinatal

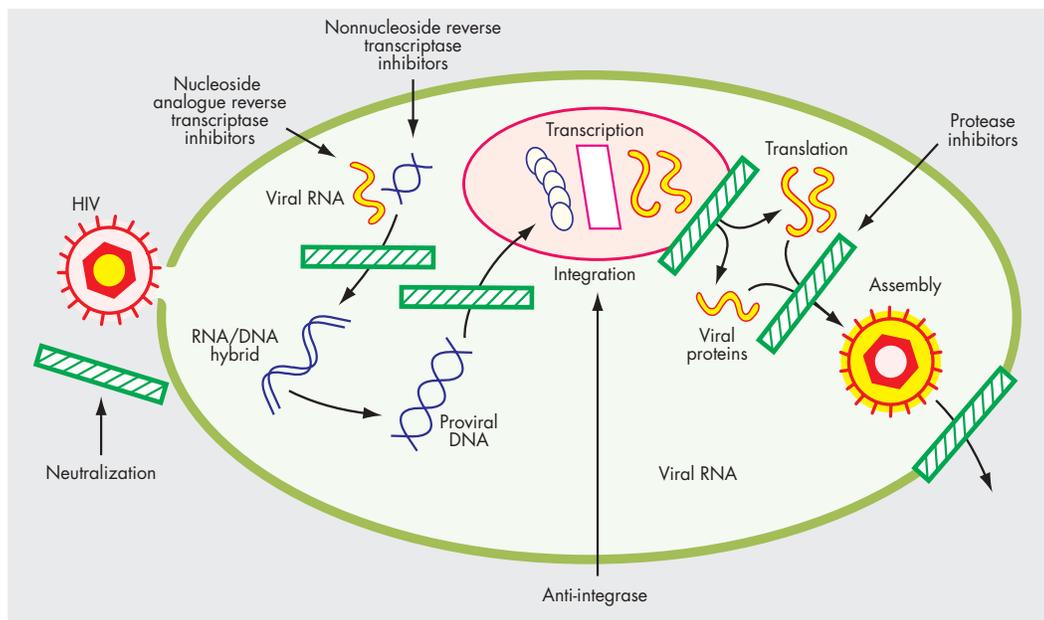
Infection from mother to infant can occur during gestation, delivery, or breast-feeding. Because breast milk contains significant numbers of lymphocytes that can lead to HIV transmission from mothers to newborns, it is recommended in the United States and other developed countries that HIV-infected mothers bottle-feed and not nurse their infants.

#### e) Cofactors for transmission

Cofactors can enhance but do not cause the transmission of HIV. *Physical* cofactors include the presence of sexually transmitted diseases (such as gonorrhea, syphilis, and chlamydia, which may cause genital lesions) or genital/mucous membrane bleeding during sexual activity. The use of mood or mind-altering substances may serve as a *behavioral* cofactor because they can lower sexual inhibitions, impair judgment, or increase impulsivity. Data are inconclusive regarding the effect of mind-altering substances on immunocompetence and HIV susceptibility or progression.

### 4. Pathogenesis of HIV

Three to 6 weeks after initial infection with HIV, there is a burst of viral replication, with wide dissemination of the virus throughout the body, particularly in lymphoid tissue and within the CNS. During this acute phase, approximately 50%–90% of people will experience a nonspecific “flu-like” syndrome of varying severity with fever, sore throat, rash, lymphadenopathy, and splenomegaly. Others do not have this seroconversion syndrome and may be unaware of their infection (8). As the host’s immune system begins to recognize the pathogen and mounts a response to control the infection, plasma viral titers may drop 100-fold within 1 or 2 months of initial infection. When the host produces circulating antibodies against HIV, the host is said to “seroconvert,” demonstrating a positive HIV antibody test. Although the immune system may



**FIGURE 4. Antiviral Therapy Targets During the HIV Replication Cycle.**

Source. Adapted from Paul (16).

appear to control the initial infection, chronic viral replication persists. There have been recent discoveries that “resting CD4 T cells” become infected rapidly after HIV transmission, and once HIV hides within resting T cells, antiretroviral therapy is unlikely to affect this sanctuary for HIV (9, 10).

The acute phase is followed by a clinically asymptomatic phase, during which the body has established a dynamic balance between the capacity of the virus to replicate and infect new CD4 cells and the capacity of the body to produce more CD4 cells. Even so, as many as 10 billion viral particles are produced daily, with a plasma virus half-life of about 6 hours. The asymptomatic phase may last for many years until symptoms arise that indicate that HIV infection is progressing. Progression to a symptomatic phase of illness may occur more rapidly in those with immune systems that are compromised before HIV infection and in infants with undeveloped immune systems. Other factors influencing disease progression include mutations of cell surface receptors and host factors such as HIV-specific cytotoxic lymphocyte response (Figure 3).

Viral load, a measurement of how many viral particles are present in a cubic millimeter of blood, is determined by several different assays that can detect as few as 20 viral particles per cubic millimeter of blood. Below that threshold, viral load is reported as “nondetectable.” This does not mean that there is no HIV in the blood. Furthermore, this method does not measure the amount of HIV in lymphoid tissue, semen, or CNS. While some studies have shown a small correlation between serum viral load and lymphoid tissue and CSF viral load, in later stages of HIV infection, plasma and CSF viral load are largely uncorrelated (11, 12). Thus, the CNS can be seen as an independent “reservoir” of HIV replication. Current practice is to use serum viral load measurements, in combination with assays of immune cells such as CD4 counts and genotypic testing for viral resistance, to guide clinical decisions about the initiation of or changes in antiretroviral medication (13–15).

**TABLE 3.** 1993 Revised Classification System for HIV Infection and Expanded AIDS Surveillance Case Definition for AIDS Among Adolescents and Adults

T Cell Count (cells/ $\mu$ l)	Clinical Categories		
	A Acute (primary) HIV or persistent generalized lymphadenopathy; patient is asymptomatic	B Patient is symptomatic, but condition does not meet criteria for category A or C	C Patient has an AIDS indicator condition <sup>a</sup>
$\geq 500$	A1	B1	C1
200–499	A2	B2	C2
$< 200^a$	A3	B3	C3

Source. From the Centers for Disease Control and Prevention (17).

<sup>a</sup>As of Jan. 1, 1993, persons with AIDS indicator conditions (categories C1–C3) as well as those with T lymphocyte counts less than 200/ $\mu$ l (category A3 or B3) were categorized as AIDS cases in the United States and its territories.

New knowledge about the life cycle of HIV and the discovery of several classes of medications that disrupt the virus at different points in the replication cycle (Figure 4) benefit many patients who receive multidrug regimens, known as potent, combination, or highly active antiretroviral treatment. However, these regimens—which involve at least three medications, with short- and potential long-term side effects, taken multiple times per day for the life of the infected person—require strict adherence. The behavioral and psychological burden of early intervention is thus a mitigating factor against such an early and aggressive treatment approach. The rapid pace of changes to potent, combination, or highly active antiretroviral treatment guidelines adds to uncertainty about such interventions. Medications that can be taken less frequently are being developed to make the regimens more manageable.

## 5. Assessment and staging of HIV disease

HIV infection usually leads to clinical diseases that affect almost every organ system and present with a wide range of symptoms and syndromes. Accurate assessment and diagnosis of systemic as well as CNS impairment requires close medical and psychiatric management, with increasing vigilance as immune competence declines and the possibility of life-threatening disorders increases.

The CDC Revised Classification system for HIV infection and AIDS used CD4 counts and staging of illness (Table 3) to establish clinical categories for HIV disease. Generally, AIDS is defined by certain conditions marking advanced immunosuppression, such as a diagnosis of opportunistic infections (e.g., *Pneumocystis carinii* pneumonia) or other conditions (e.g., dementia or wasting). AIDS-defining criteria are listed in Table 4.

## 6. Treatment for HIV infection

Most of the world's HIV-infected population has little if any access to antimicrobial therapies for consequences of immune deficiency, let alone combination antiretroviral treatment. In the United States, revised standards of care for the treatment of HIV infection have improved treatment effectiveness, increased survival for patients, and potentially lessened development of viral resistance. Treatment is accomplished through numerous combinations of antiretroviral agents from four classes: nucleoside analogue reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors, and the newest class, nucleotide analogues (Table 5). Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents are available from the HIV/AIDS Treatment Information Service (<http://www.hivatis.org>).

The current goal of antiretroviral therapy is to reduce viral load to undetectable levels and maintain such remission without interruption. Evidence suggests that the therapies suppress

**TABLE 4. AIDS-Defining Conditions That Emerge With Advancing Immunosuppression**

CD4 Cell Count (cells/mm <sup>3</sup> )	Condition
200–500	Thrush Kaposi's sarcoma Tuberculosis reactivation Herpes zoster Herpes simplex Bacterial sinusitis/pneumonia
100–200	<i>Pneumocystis carinii</i> pneumonia
50–100	Systemic fungal infections Primary tuberculosis Cryptosporidiosis Cerebral toxoplasmosis Progressive multifocal leukoencephalopathy Peripheral neuropathy Cervical carcinoma
0–50	Cytomegalovirus disease Disseminated <i>Mycobacterium avium-intracellulare</i> complex Non-Hodgkin's lymphoma Central nervous system lymphoma HIV-associated dementia

replication but do not eradicate HIV from all parts of the body, particularly lymphoid tissue and the brain. Not all patients who initiate antiretroviral therapy respond. The lack of clinical response is likely explained by problems with adherence, suboptimal antiretroviral treatment potency, and genetic mutation of HIV strains (18). Many patients experience substantial side effects, and it is not uncommon for changes to be made in antiretroviral drug regimens because of such side effects. Adverse effects include lipodystrophy (fat redistribution syndromes), hyperlipidemia, nephrotoxicity, bone marrow suppression, neuropathy, and elevation of glucose to possibly diabetes mellitus–causing levels (19). Patients often experience nausea, diarrhea, sleep disturbances, and rashes. The cost of antiretroviral drugs alone is about \$12,000 per year for a single individual, and the long-term health consequences of these agents are not known.

Adherence is of utmost concern with antiretroviral treatment because the regimens are so unforgiving; even minor deviations from the prescribed regimen can result in viral resistance and permanent loss of efficacy for existing medications. Studies of antiretroviral treatment continue to indicate that near-perfect adherence is needed to adequately repress viral replication. The potential implications of nonadherence are troubling, as evidenced by a study that found a primary viral resistance rate to antiretrovirals of 16.3% among a cohort of recently infected individuals (20). This study documented what was earlier considered a theoretical concern—namely that persons newly infected with HIV may carry viral strains already resistant to available antiretroviral agents, indicating transmission of resistant viral strains from persons who were taking nonsuppressive multiple drug therapy or who were nonadherent to treatment (21).

As the U.S. HIV epidemic spreads increasingly among disadvantaged persons with limited resources who may have multiple comorbid disorders, significantly more psychosocial stressors, and less access to ongoing primary or mental health care, these individuals are at risk of not receiving the recommended treatment for HIV infection. Services for HIV patients must balance medical interventions with the emotional, economic, and social supports required for good quality of life and prevention of further transmission.

**TABLE 5. Antiretroviral Medications**

<b>Class</b>	<b>Drug Name</b>
<i>Nucleoside analogue reverse transcriptase inhibitors</i>	Abacavir
	Didanosine <sup>a</sup>
	Lamivudine <sup>b</sup>
	Stavudine <sup>c</sup>
	Zalcitabine <sup>d</sup>
	Zidovudine <sup>e</sup>
	Lamivudine-zidovudine (combination)
<i>Nonnucleoside reverse transcriptase inhibitors</i>	Delavirdine
	Efavirenz
	Nevirapine
<i>Protease inhibitors</i>	Amprenavir
	Indinavir
	Lopinavir-ritonavir (combination)
	Nelfinavir
	Ritonavir
	Saquinavir
<i>Nucleotide analogues</i>	Adefovir

<sup>a</sup>Formerly called dideoxyinosine (ddI).

<sup>b</sup>Formerly called 3TC.

<sup>c</sup>Formerly called d4T.

<sup>d</sup>Formerly called 2'3'-dideoxycytidine (ddC).

<sup>e</sup>Formerly called azidothymidine (AZT).

## ► **B. ASSOCIATED FEATURES OF NEUROPSYCHIATRIC AND PSYCHOSOCIAL IMPORTANCE**

### **1. Impact of HIV on the CNS**

Clinical evidence for direct infection of the CNS by HIV emerged in the mid-1980s, when patients began to survive their presenting opportunistic infections but went on to develop neuropsychiatric syndromes that could not be attributed to CNS opportunistic infections or neoplasms. Additional evidence included signs of neurocognitive impairment in adults, loss or arrest of developmental milestones in children, ability to culture HIV from CSF, neuropathological lesions of the brain at autopsy, and abnormalities observed through brain imaging techniques, including cerebral atrophy.

HIV invades the CNS early in the course of infection, entering by way of macrophages, which along with microglial cells are largely responsible for HIV replication within the CNS. While HIV does not infect neurons in the CNS, it causes neuronal death by other mechanisms. It is hypothesized that HIV infection of microglial cells in the CNS causes the elaboration of neurotoxins that, in turn, cause neuronal damage (22, 23). Neuronal dysfunction usually takes place at a slow rate, and it is not clear whether the immune system plays a role in keeping HIV in the CNS under control (24). Some researchers believe that high systemic viral load may “drive” neurological disease (25), but there is converging evidence that the CNS compartment differs from that of the peripheral bloodstream, with independent viral evolution/mutation (leading to viral resistance) and different viral load decay kinetics (26, 27).

Major unanswered questions remain about the natural history of HIV in the CNS and whether current antiretroviral treatment regimens penetrate the blood-brain barrier sufficiently to reduce viral replication to the levels seen in the systemic circulation. Neuroprotective agents, immune modulators that increase macrophage activity within the CNS, and vaccines that boost immune response rather than prevent infection are all potential additional strategies to address neuropsychiatric syndromes.

## **2. Clinical syndromes**

HIV infection can lead to neuropsychiatric syndromes that can occur at various stages of infection. Clinicians need to be aware of this possibility when evaluating new patients and observing changes in the patients whom they treat (28). Symptomatic HIV infection of the brain generally affects cognitive and motor functioning. Subtle neuropsychological impairment may be found in 22%–30% of otherwise asymptomatic patients with HIV infection (29, 30); these findings may or may not have functional significance. There is ample evidence for HIV causing the disorders HIV-associated dementia and HIV-associated minor cognitive motor disorder. HIV can affect other areas of the nervous system, causing syndromes such as painful sensory peripheral neuropathy or vacuolar myelopathy of the dorsolateral columns of the spinal cord. There are limited data in support of HIV infection of the CNS resulting in syndromes such as psychosis (31) or mania (32–34).

What separates HIV-associated dementia and HIV-associated minor cognitive motor disorder from the less severe cognitive changes seen in some HIV patients are the significance and duration of the functional deficits (Table 6, Table 7). HIV-associated minor cognitive motor disorder is a less severe disorder than HIV-associated dementia but does not necessarily progress to HIV-associated dementia (36). HIV-associated minor cognitive motor disorder is important to diagnose and treat, since it is thought to involve neuronal cell dysfunction rather than actual cell death, as seen in HIV-associated dementia. Both HIV-associated minor cognitive motor disorder and HIV-associated dementia are independent risk factors that decrease survival among patients with HIV infection (37, 38).

## **3. HIV-associated dementia**

In contrast to Alzheimer's disease, which is a cortical dementia, HIV-associated dementia is classified as a subcortical dementia. HIV-associated dementia can produce different combinations of a clinical triad of progressive cognitive decline, motor dysfunction, and behavioral abnormalities. Symptoms commonly found in HIV-associated dementia include psychomotor slowing, decreased speed of information processing, impaired verbal memory and learning efficiency, and, later on, impairment in executive functioning. Behavioral manifestations vary throughout the range of HIV-related neurocognitive disorders, ranging from apathy to psychosis.

While the prevalence rate for HIV-associated dementia was estimated in the past to be 15%–20% of all AIDS patients (39), the incidence rate for HIV-associated dementia may be affected by the use of potent combination therapies. One report from the Multicenter AIDS Cohort Study (40) demonstrated declines of at least 50% in the incidence of HIV-associated dementia and CNS opportunistic complications (e.g., toxoplasmosis and primary CNS lymphoma) since the introduction of combination antiretroviral treatment in 1996. A second report has estimated that the incidence of HIV-associated dementia decreased from 21.1/1000 person-years in 1990–1992 to 14.7/1000 person-years in 1996–1997 (40). On the other hand, one group found that for patients who received combination antiretroviral treatment, the proportion of HIV-associated dementia as a percentage of all AIDS-defining illnesses rose from 4.4% to 6.5% between 1995 and 1997 (41). This shift in the rate of HIV-associated dementia is thought to reflect the decrease in rates of other AIDS-defining conditions, thereby leading to the relative rise in HIV-associated dementia cases.

**TABLE 6. Definitional Criteria for HIV-Associated Dementia**

Criterion	Description
1. Acquired abnormality in at least two of the following cognitive abilities (present for $\geq 1$ month) Attention/concentration Speed of processing Abstraction/reasoning Visuospatial skills Memory learning Speech/language	Cognitive decline verified by history and mental status examination. When possible, history should be obtained from an informant and examination should be supplemented by neuropsychological testing. The cognitive dysfunction must cause impairment of work or in activities of daily living, with impairment not attributable solely to severe systemic illness.
2. At least one of the following: Acquired abnormality in motor function or performance Decline in motivation or emotional control or change in social behavior	Abnormality verified by physical examination, neuropsychological tests, or both. Change characterized by any of the following: apathy, inertia, irritability, emotional lability, or new-onset impaired judgment characterized by socially inappropriate behavior or disinhibition.
3. Absence of clouding of consciousness during a period long enough to establish the presence of criterion 1	
4. Exclusion of another etiology by history, physical, and psychiatric examination and appropriate laboratory and radiologic tests	Alternate possible etiologies include active central nervous system opportunistic infections or malignancy, psychiatric disorders (e.g., depressive disorders), active substance abuse, or acute or chronic substance withdrawal.

*Source.* From the American Academy of Neurology (35).

**TABLE 7. Definitional Criteria for HIV-Associated Minor Cognitive Motor Disorder****Probable Diagnosis (must meet all four criteria)<sup>a</sup>**

1. Acquired cognitive/motor/behavioral abnormalities, verified by both a reliable history and by neuropsychological tests
2. Mild impairment of work or activities of daily living
3. Does not meet criteria for HIV dementia or HIV myelopathy
4. No other etiology present

*Source.* From the American Academy of Neurology (35).

<sup>a</sup>A possible diagnosis of minor cognitive motor disorder can be given if criteria 1–3 are present and either 1) an alternative etiology is present and the cause of number 1 is not certain, or 2) the etiology of criterion 1 cannot be determined because of an incomplete evaluation.

**4. Other psychiatric syndromes**

Because HIV affects subcortical areas of the brain, it has been postulated that HIV may cause syndromes relating to mood and psychosis. New-onset psychosis and mania in HIV-infected patients tend to present at later stages of HIV disease and often occur in association with cognitive motor impairment. Lyketsos and colleagues (34) have described HIV-infected patients with so-called AIDS mania who present at advanced stages of HIV infection but generally have no family or personal history of mood disorder and have higher rates of comorbid dementia.

**TABLE 8. Etiologies of Delirium in HIV/AIDS Patients**

Intracranial	Extracranial
Seizures	Medications and other drugs (not exhaustive)
Infections	Amphotericin B
Cryptococcal meningitis	Acyclovir
Encephalitis due to HIV, herpes, cytomegalovirus	Ganciclovir
Progressive multifocal leukoencephalopathy	Ethambutol
Mass lesions	Trimethoprim/sulfamethoxazole
Lymphoma	Pentamidine
Toxoplasmosis	Foscarnet
	Ketoconazole
	Sedative/hypnotics
	Cycloserine
	Opiate analgesics
	Isoniazid
	Rifampin
	Zidovudine or didanosine
	Vincristine
	Dapsone
	Drug or alcohol withdrawal
	Infection/sepsis
	Endocrine dysfunction/metabolic abnormality
	Hypoglycemia due to pentamidine, protease inhibitors
	Hypoxia due to pneumonia
	Nonendocrine organ dysfunction
	Renal failure due to HIV nephropathy or medication toxicity
	Liver failure due to comorbid hepatitis and medication toxicity
	Nutritional deficiencies
	Wasting syndrome
	Failure to replace trace elements or vitamins in total parenteral nutrition

*Source.* Adapted from Bialer et al. (50).

They hypothesized that mania in this context is directly caused by HIV brain infection. Mijch and colleagues (32) conducted a prospective case-control study to test the hypothesis put forward by Lyketsos et al. In their study of 19 HIV patients with secondary mania, they found that treatment with zidovudine, which is known to penetrate the blood-brain barrier well, provided a protective effect against the development of mania. In addition, they found the incidence rate of HIV-associated dementia in the subjects with mania to be significantly greater than in HIV subjects without mania.

New-onset psychotic symptoms have been reported in HIV-positive individuals in the absence of medical/iatrogenic causes or concurrent substance abuse (42, 43). One case-control study systematically examined patients with HIV infection that predated the onset of psychosis (31). In this study, the psychotic subjects had significantly higher rates of past stimulant and sedative-hypnotic abuse and higher mortality at follow-up. While the study was limited by a sample size of 20, the authors postulated that direct effects of HIV infection on the brain could be one possible cause of new-onset psychosis in their subjects.

**TABLE 9. Central Nervous System Manifestations of HIV-1 Infection**

Type of Manifestation	Condition
<i>Acute HIV-1 infection</i>	Viral meningitis Encephalitis Ascending polyneuropathy
<i>Opportunistic infections (late HIV-1 infection)</i>	<i>Toxoplasma</i> cerebritis Cryptococcal meningitis Progressive multifocal leukoencephalopathy Neurosyphilis <i>Mycobacterium tuberculosis</i> meningitis Cytomegalovirus encephalitis Herpes simplex encephalitis
<i>Neoplastic disease (late HIV-1 infection)</i>	CNS lymphoma Kaposi's sarcoma
<i>Other manifestations</i>	HIV-associated dementia HIV-associated minor cognitive motor disorder

## 5. Differential diagnosis of neuropsychiatric syndromes

Differential diagnosis of an acute change in mental status includes but is not limited to delirium. Delirium occurs frequently in the medically ill and is more likely when a patient's illness is more severe. Estimates of rates of delirium in HIV patients range from 43% to greater than 65% in late-stage AIDS (44–46). Definition and management of the syndrome of delirium is well described in the *APA Practice Guideline for the Treatment of Patients With Delirium* (47). Identification of the delirious state and intervention to correct underlying causes reduces morbidity and mortality. In persons with HIV infection, the most common causes are iatrogenic and psychoactive-substance-induced toxicity, infection, neoplasms, and metabolic disturbances. Some antiretroviral medications can cause delirium (e.g., zidovudine at high doses [48] or efavirenz [49]) (Table 8).

The term “HIV encephalopathy” is occasionally used to refer to acute-onset cognitive deficits in adults, but its definition and usage vary. A wide range of conditions that primarily involve the CNS needs to be considered within the psychiatric differential diagnosis, since these conditions may present with psychiatric symptoms or cause psychiatric syndromes including psychosis (with or without an affective component) and mood episodes (mania, hypomania, depression) (51) (Table 9). The same concerns exist for medications commonly used to treat conditions associated with HIV infection (Table 10).

In adults and children with HIV infection, changes in mental status or the emergence of new psychiatric or cognitive disorders requires ruling out treatable and reversible causes; medical causes are of increasing concern if CD4 counts are low or viral load has begun to rise. Psychiatrists should consider adding assessments of basic immune function and viral load, CSF examination, and brain imaging studies to the standard medical workup of new- or acute-onset psychiatric syndromes for patients with or at high risk for HIV infection (Table 11).

## 6. Pediatric HIV/AIDS syndromes

To date, the proportion of children born with HIV who survive until the age of 9 is approximately 50%, but antiretroviral interventions will increase the number of infected youth who enter adolescence. HIV-related symptoms may develop at any age, but a prospective collaborative study found that only 10% of children were symptomatic before the onset of an AIDS-defining illness (53).

Certain clinical presentations characterized by lymphadenopathy, parotitis, skin diseases, and recurrent respiratory tract infections are associated with longer survival, while lymphoid

**TABLE 10. Neuropsychiatric Side Effects of Selected Medications Used in HIV Disease**

<b>Drug</b>	<b>Target Illness</b>	<b>Side Effects</b>
Acyclovir	Herpes encephalitis	Visual hallucinations, depersonalization, tearfulness, confusion, hyperesthesia, hyperacusis, thought insertion, insomnia
Amphotericin B	Cryptococcosis	Delirium, peripheral neuropathy, diplopia
$\beta$ -Lactam antibiotics	Infections	Confusion, paranoia, hallucinations, mania, coma
Co-trimoxazole	<i>Pneumocystis carinii</i> pneumonia	Depression, loss of appetite, insomnia, apathy
Cycloserine	Tuberculosis	Psychosis, somnolence, depression, confusion, tremor, vertigo, paresis, seizure, dysarthria
Didanosine	HIV	Nervousness, anxiety, confusion, seizures, insomnia, peripheral neuropathy
Efavirenz	HIV	Nightmares, depression, confusion
Foscarnet	Cytomegalovirus	Paresthesias, seizures, headache, irritability, hallucinations, confusion
Interferon- $\alpha$	Kaposi's sarcoma	Depression, weakness, headache, myalgias, confusion
Isoniazid	Tuberculosis	Depression, agitation, hallucinations, paranoia, impaired memory, anxiety
Lamivudine	HIV	Insomnia, mania
Methotrexate	Lymphoma	Encephalopathy (at high dose)
Pentamidine	<i>Pneumocystis carinii</i> pneumonia	Confusion, anxiety, lability, hallucinations
Procarbazine	Lymphoma	Mania, loss of appetite, insomnia, nightmares, confusion, malaise
Quinolones	Infection	Psychosis, delirium, seizures, anxiety, insomnia, depression
Stavudine	HIV	Headache, asthenia, malaise, confusion, depression, seizures, excitability, anxiety, mania, early morning awakening, insomnia
Sulfonamides	Infection	Psychosis, delirium, confusion, depression, hallucinations
Thiabendazole	Strongyloidiasis	Hallucinations, olfactory disturbance
Vinblastine	Kaposi's sarcoma	Depression, loss of appetite, headache
Vincristine	Kaposi's sarcoma	Hallucinations, headache, ataxia, sensory loss
Zalcitabine	HIV	Headaches, confusion, impaired concentration, somnolence, asthenia, depression, seizures, peripheral neuropathy
Zidovudine	HIV	Headache, malaise, asthenia, insomnia, unusually vivid dreams, restlessness, severe agitation, mania, auditory hallucinations, confusion

Source. Adapted from Grant and Atkinson (52).

interstitial pneumonitis and thrombocytopenia form an intermediate survival group. The worst prognosis is associated with bacterial infections, progressive neurological disease, anemia, and fevers (54).

HIV infection that occurs at the time of birth rather than early in gestation is thought to be associated with a better prognosis. While at any given time many HIV-infected children may not experience significant HIV-related medical morbidity, their overall health outcome may be compromised by the conditions of poverty.

**TABLE 11. Evaluation of Altered Mental Status in Patients With HIV/AIDS**

**Physical/neurologic examination**

- Focal deficits may indicate space-occupying lesion (e.g., CNS lymphoma, toxoplasmosis, progressive multifocal leukoencephalopathy)
- Sensory changes, which may indicate peripheral neuropathy
- Ataxia or changes in gait, which may indicate myelopathy

**Laboratory analyses**

- CBC with differential
- Serum chemistries
- Arterial blood gas in patients with pneumonia
- VDRL, fluorescent treponemal antibody
- B<sub>12</sub>, folate

**MRI**, to rule out space-occupying lesion (progressive multifocal leukoencephalopathy)

**Lumbar puncture**, to rule out acute infection (e.g., cryptococcal meningitis, herpes, toxoplasmosis, syphilis)

**Neuropsychological testing**

- AIDS Dementia Rating Scale
- Finger Tapping Test
- Trail Making Test

*Source.* Adapted from Bialer et al. (50).

The impact of HIV on the developing nervous system of children is more significant than on the developed adult nervous system, and certain cognitive deficits may occur in some infected youth. The term “dementia” is not commonly used to describe cognitive deficits in children by pediatricians or child psychiatrists, who refer to this condition as either HIV-associated progressive encephalopathy or HIV encephalopathy. Nonetheless, “dementia due to HIV disease” in children is specifically mentioned in DSM-IV (p. 148).

HIV-associated progressive encephalopathy in children is characterized by a triad of symptoms: impaired brain growth, progressive motor dysfunction, and loss or plateau of developmental milestones (55). Progressive encephalopathy needs to be distinguished from mental retardation secondary to other causes, such as maternal drug addiction and prematurity, which can be determined only by longitudinal assessment. Despite the general fact that progressive encephalopathy is observed in the context of immunosuppression, markers of immunologic functioning (e.g., CD4 count) do not correlate with degree of neurocognitive impairment (54). The prevalence rate of progressive encephalopathy in a cohort of 128 HIV-infected children was 21% during a mean follow-up period of 24 months. Progressive encephalopathy was the first AIDS-defining condition in 67% of the group, and mean survival after diagnosis was 14 months (56).

Although many children with HIV are considered to be asymptomatic, numerous studies document at least some cognitive and language delays (57). In a sample of 36 HIV-infected children who were less than 10 years old, brain abnormalities detected by means of computerized tomography scans were significantly correlated with receptive and expressive language deficits, with expressive language more severely impaired than receptive language among those children with progressive encephalopathy (58). In addition, visual motor deficits are common and may be correlated with disease progression (59).

► **C. PREVALENCE OF COMORBID PSYCHIATRIC CONDITIONS**

Since early in the HIV epidemic, researchers have studied the prevalence of psychiatric disorders in persons with HIV infection (60–63). Often these psychiatric disorders predated HIV

infection or occurred during the course of living with the disease; they are not necessarily attributable to neuropathic effects of HIV. Psychiatric illness is generally related to poorer functioning and quality of life as well as increased use of HIV-related hospital services (64). A study conducted by researchers in California found that depression was associated with shorter survival times in men with HIV infection (65).

Prevalence rates of psychiatric disorders reported in published studies vary widely. In general, higher rates of psychiatric disorders are seen in later stages of HIV infection and are reported in studies that assess patients receiving care in HIV medical or psychiatric clinics rather than community-based samples (66). On one extreme, recent data from the national, multisite HIV/AIDS Mental Health Services Demonstration Program revealed high rates of depression (60%), dysthymic disorder (25%), and anxiety disorders (25%) among persons seeking HIV-related mental health services in the public sector (67). The study found high rates of comorbid substance use disorders, with nearly 50% of all patients also having a diagnosis of alcohol or drug dependence. These higher rates are most likely linked to characteristics of the population studied: HIV-positive individuals voluntarily seeking psychiatric care, a population that may be more reflective of patients receiving care from community mental health clinics. In contrast, prevalence studies in selected community-based samples have found much lower rates of psychiatric disorders, such as rates of major depressive disorder in the 4%–14% range (68–73).

### **III. FORMULATION AND IMPLEMENTATION OF A TREATMENT PLAN**

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#### **▶ A. INDIVIDUALS AT HIGH RISK FOR HIV INFECTION**

HIV prevention strategies are an essential component of the comprehensive treatment of specific psychiatric populations and for other psychiatric patients who manifest high-risk sexual and drug use behavior. Some psychiatric patients, such as those confined to forensic units, in long-term hospitals, and locked nursing homes have almost no access to preventive strategies other than those provided and supported by staff. Administrators and institutions should formulate policies that support the full range of HIV prevention steps outlined in this section. Primary prevention strategies are those that seek to avert initial infection. Secondary and tertiary prevention strategies target infected individuals in order to prevent further transmission and reduce HIV-related medical complications, respectively.

##### **1. Psychiatric management**

Optimum management of patients at high risk for HIV infection involves a wide range of psychiatric skills: comprehensive diagnostic evaluations, assessment of possible medical causes of new-onset symptoms, initiation of specific treatment interventions, and a keen understanding of psychodynamic issues. In some institutional settings, psychiatrists serve as primary clinicians of both medical and psychiatric care. In such situations, psychiatrists should be mindful to include HIV risk assessment and prevention as part of patients' treatment plans.

##### **a) Obtaining a risk history**

A psychiatrist will not be aware of a patient's risk for HIV infection unless risk behavior is accurately assessed. Such an assessment should be considered in every psychiatric evaluation in order to identify individuals who are at high risk due to specific behaviors. Factors such as acute episodes of psychiatric illness, stressful or traumatic life events, and the developmental stage of the patient (e.g., initiation of sexual activity in adolescents) contribute to the need for ongoing appraisal of patient risk. Psychiatrists are particularly well-placed to assess HIV risk because

**TABLE 12.** Items for Clinicians to Cover When Conducting an Assessment of HIV Risk Behavior

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Frequency of sexual intercourse (vaginal, anal, oral)
Number, gender, and known HIV risk of sex partners
Whether the patient has traded sex (for money, drugs, a place to stay, cigarettes)
Past and current symptoms of sexually transmitted infections
Use of condoms and other contraceptive methods
Use of drugs, particularly those that are injected or sniffed
Sharing of needles, syringes, or other injection equipment

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*Source.* From McKinnon et al. (74).

they often follow patients for lengthy periods of time, which allows for multiple opportunities to assess behavior (74).

At times, the clinical state of the patient may preclude an accurate assessment, such as when the patient is acutely psychotic or intoxicated. In this situation, the risk history may need to be obtained either when the patient is able to provide valid answers or with the assistance of family or friends. Psychiatrists should be knowledgeable about which specific sexual behaviors are more likely to result in HIV transmission (Table 2). When conducting an assessment of risk behavior, psychiatrists should convey a nonjudgmental attitude.

When carrying out a risk assessment, it is important to clarify the vocabulary and cultural beliefs of the patient. For instance, it is not uncommon for patients and clinicians to use different terms to describe sexual or drug use behaviors, and slang terms change quickly. The National Institute on Drug Abuse has published a community drug alert that outlines common street drugs and their slang names, which is available at [www.drugabuse.gov](http://www.drugabuse.gov). Clinicians may be able to clarify risk behavior terms by first describing a risk behavior and then asking a patient what he or she would call that behavior (Table 12).

### **b) HIV antibody testing**

Attitudes about HIV antibody testing have changed with the development of HIV treatment interventions and educational efforts. Formerly, patients were unwilling to learn their HIV status, since knowing could cause emotional distress, could engender possible discrimination, and did not lead to better clinical outcomes. Public policy now promotes earlier identification of HIV infection so that newly infected persons can be medically monitored and receive antiretroviral treatment as appropriate. Yet HIV testing still carries risks due to worries and fears associated with HIV/AIDS, as well as the possibility of physical assault by a partner or other relation after HIV diagnosis (75). Disclosure of HIV status to family, friends, or employers can be quite problematic for some patients.

Discussion of the pros and cons of a routine baseline HIV test are part of a comprehensive approach to HIV prevention in high-risk patients. Psychiatric units or individual practitioners who conduct HIV testing should be aware of their obligation to provide the necessary pre- and posttest counseling (76). Elements of pre- and posttest counseling include an explanation of the HIV test, including risks and benefits, confidentiality of the results, discussion of risk behavior and risk reduction strategies, and plans for dealing with a positive or negative test result. Federal guidelines for counseling have been established by the CDC (<http://www.cdc.gov/hiv/pubs/hivctsr.pdf>).

Clinicians should remember that the timing of when to undergo HIV testing is a distinct clinical decision. For instance, it is generally not advisable to test a patient for HIV while he or she is confused or intoxicated with alcohol or drugs. In the event that a patient cannot give informed consent, the psychiatrist should be familiar with the local legal requirements regarding HIV testing and disclosure (77). Anonymous and confidential HIV testing is often provided by state public health agencies or community-based organizations; some patients prefer ano-

nymity and may be more likely to agree to testing given this option. Many state health departments conduct “partner notification” or prevention counseling and referral services to identify and test past or present sexual partners or drug injection equipment-sharing partners of a newly reported HIV-seropositive person.

The American College of Obstetricians and Gynecologists now recommends that an HIV antibody test be offered during annual exams to all women seeking preconception care (not just pregnant women), which reflects the growing awareness that many women may not properly assess their personal risk for HIV infection (78). This recommendation goes beyond the previous recommendation that pregnant women undergo HIV antibody testing so that HIV-infected women can consider treatment with antiretroviral medication. For female patients who are at risk for HIV infection *and* for pregnancy, conducting a baseline pregnancy test along with a baseline HIV test is advised.

### **c) Risk reduction strategies**

Risk reduction strategies include education of patients about behaviors that place them at risk for HIV infection, active discussions of changes in behavior, and treatment of problems that promote risky behavior. It is important to view undergoing an HIV antibody test as a “teachable moment,” when counseling about risk for HIV can be tailored to the specific behavior of the patient and an individualized risk reduction plan can be developed.

Because successful risk reduction requires more than knowledge of risk, ongoing discussions between patient and psychiatrist can help provide the motivating and skill-building factors that help ensure consistent changes in behavior. Psychiatrists should consider unconscious motivations that may contribute to risk-taking behavior when developing risk reduction strategies. Some patients may need to be referred to community-based organizations or other clinicians who offer specific risk reduction programs (e.g., needle exchange programs or skills training groups). For some patients, risk reduction strategies can include extended counseling and case management, such as that modeled by the CDC (79).

When appropriate, psychiatrists should determine whether patients have access to condoms and the skills to use them (Table 13). Skills to discuss and negotiate safer sex with partners may need to be developed; psychotherapy can provide an opportunity to practice communication skills through role playing. Clinicians should be alert to feelings of powerlessness in sexual situations for patients with histories of sexual abuse and to the real possibility of violence for some if a sexual partner is threatened or angered.

Psychiatric conditions that could theoretically increase patient risk for engaging in high-risk behavior include impulse control disorders, untreated depression, hypersexuality associated with mania, psychotic disorders, mental disorders due to a general medical condition, binge alcohol or drug use, and personality disorders.

### **d) Postexposure prophylaxis**

The premise underlying postexposure prophylaxis is that chemoprophylaxis during a window of opportunity may prevent initial cellular infection and local propagation of HIV, thus allowing the host immune defenses to eliminate the inoculum of virus (81). Currently, postexposure prophylaxis is recommended for known occupational exposure, especially percutaneous or mucous membrane exposure, to blood or other body fluids.

Psychiatrists who serve as administrators of mental health facilities should formulate policies and protocols for the expedient treatment of health care professionals or patients who have had such exposure. The protocol requires a rapid assessment of risk and, where risk is present, beginning a multiple drug regimen as soon as 1–2 hours after exposure and not later than 24–36 hours. It further requires 4 weeks of treatment with two or three antiretroviral agents that can have significant side effects.

**TABLE 13. Condom Use**

Condoms must be used consistently and correctly to provide maximum protection. Consistent use means using a new condom with each act of intercourse. Latex condoms and polyurethane condoms provide protection; lambskin condoms should not be used. Correct condom use includes all of the following steps.

- Check the expiration date.
- Use a new condom for each act of vaginal, anal, or oral intercourse.
- Put on the condom as soon as erection occurs and before any vaginal, anal, or oral contact with the penis.
- Apply lubricant to penis before and after putting the condom on. This will provide greater satisfaction for both the insertive and the receptive partners.
- Hold the tip of the condom and unroll it onto the erect penis, leaving space at the tip of the condom, yet ensuring that no air is trapped in the tip of the condom.
- Adequate lubrication is important to prevent condom breakage, but use only water-based lubricants, such as glycerine or lubricating jellies (which can be purchased at any pharmacy). Oil-based lubricants, such as petroleum jelly, cold cream, hand lotion, or baby oil, can weaken the condom.
- Withdraw from the partner immediately after ejaculation, holding the condom firmly to the base of the penis to keep it from slipping off.

*Source.* From the CDC National Center for HIV, STD and TB Prevention, Division of HIV/AIDS Prevention (80).

The CDC has issued guidelines for the use of antiretroviral medication following health care worker occupational exposure to HIV (82). There is a National Clinicians' Postexposure Hotline (888-448-4911) that can be accessed 24 hours a day for guidance in cases of possible or known exposure to HIV. A web site ([www.ucsf.edu/hivcntr](http://www.ucsf.edu/hivcntr)) offers a wealth of information to address this issue.

Data are being gathered to evaluate the use of postexposure prophylaxis in other exposure situations, but it is being increasingly offered for known or possible sexual exposure to HIV. Public health messages should emphasize that postexposure prophylaxis should be used only when primary prevention methods such as use of condoms or avoidance of high-risk behaviors have failed. Clinicians should counsel patients who receive postexposure prophylaxis to reduce their chance of future exposure (81).

## **2. Specific treatment situations**

### **a) Patients with substance use disorders**

The best way to prevent the spread of HIV through injection drug use is effective primary prevention of drug use. For people who are already injecting opioids, eliminating this behavior through adequately dosed substitution therapy, such as methadone or a long-acting form of methadone, L- $\alpha$ -acetylmethadol (LAAM), can serve an HIV prevention function.

Harm reduction policies have received more support in the last decade due to the spread of AIDS among injection drug users. The primary purpose of harm reduction is to decrease the negative consequences of drug use (83). As opposed to a policy of abstinence, harm reduction approaches realistically assume that some individuals will continue to use drugs. In this framework, a hierarchy of goals is established, with more immediate or attainable ones achieved on the way to risk-free use or possible abstinence. Risk reduction strategies such as methadone maintenance treatment, needle education and bleach distribution, safer sex education, legal clean needle purchase, and needle exchange programs are all examples of harm reduction strategies (84).

While injection drug use has a direct role in transmission of HIV, noninjection drugs and alcohol can play a potent role as cofactors of transmission because of their effects on behavior

and cognition. The treatment success of substance use disorders varies, and the situation is further hampered because access to substance abuse services is often limited or is unwanted; relapses are common. Nonetheless, keeping substance use disorder intervention high on the list of treatment priorities is recommended for persons at risk for HIV infection.

One component of a comprehensive approach to HIV prevention among injection drug users is access to sterile syringes. The U.S. Public Health Service recommends that injection drug users who continue to inject use sterile syringes to prepare and inject drugs and obtain those syringes from a reliable source (e.g., a pharmacy). At the same time, a wide variety of laws and regulations restrict the ability of injection drug users to purchase and possess sterile syringes (7). Numerous national organizations, including the American Psychiatric Association (85), the American Medical Association, and the American Pharmaceutical Association, have recommended in policy statements and guidelines the removal of government restrictions on the availability of sterile syringes and have supported government-sponsored needle exchange programs. Cleaning drug injection equipment with bleach is an alternative that requires a multi-step cleaning process that is impractical for many injection drug users (86).

#### **b) Patients with severe mental illness**

Rates of HIV infection among psychiatric inpatients averaged 7.8% in seroprevalence studies conducted in East Coast cities (87). Men and women were equally affected, with the highest rates occurring among patients who were under 40, were black or Latino, or used substances, especially injected drugs. Rates for other geographic areas in the United States were not available.

Despite not identifying themselves as gay, 10% of men with schizophrenia have reported same-sex sexual encounters (88). Public mental health systems should implement prevention policies and practices, educate both mental and medical health care clinicians about key treatment issues, and develop effective linkages between clinicians and systems of care (89, 90).

Severe mental illness may be associated with health risks due to poor access to health care or decreased capacity to care for oneself. Despite the challenges that chronically and severely mentally ill patients face, risk reduction programs tailored to their needs have been shown to reduce risk of HIV infection (91, 92).

#### **c) Victims of sexual abuse/crimes**

Psychiatrists frequently encounter child, adolescent, and adult psychiatric patients who have histories of being sexually abused, including when treating patients with posttraumatic stress disorder (PTSD), dissociative disorders, and borderline personality disorder. Victims of sexual crimes vary from those with long abuse histories to those with a single sexual assault. Sexual coercion often results in long-term emotional damage to those that have been assaulted and may be followed by PTSD or other psychiatric disorders. These emotional scars are associated with increased vulnerability to other HIV-risk situations.

A patient with a history of sexual abuse or trauma should be asked about specific behaviors that are associated with risk for HIV transmission. Patients with such a history may be reluctant to provide information initially. Psychiatrists should determine if a psychiatric disorder is present and whether treatment is indicated. In the case of sexual assault, psychiatrists should expediently gather enough information so that the decision about the appropriateness of post-exposure prophylaxis can be made (93).

## **▶ B. HIV-INFECTED INDIVIDUALS**

### **1. Psychiatric management**

The development of a psychiatric treatment plan for patients with HIV infection requires thoughtful and comprehensive consideration of the biopsychosocial context of the illness.

Treatment decisions must balance standard recommendations for psychiatric conditions against the medical stage of HIV illness and up-to-date information about available medical interventions targeted at the underlying HIV infection. At the same time, psychiatrists should be aware that emotional reactions and conflicts can interfere with a patient's ability to follow medical recommendations and thus have a profound effect on physical status. Psychiatrists should carefully consider possible medical causes of psychiatric symptoms and whether a medical workup is indicated to rule out a potentially life-threatening illness due to HIV or HIV-related illness. Organ malfunction, synergism of side effects of drugs, and drug-drug interactions are important factors to address in the management of patients.

**a) Establish and maintain a therapeutic alliance**

Establishing an alliance involves, in part, recognition of a patient's understanding of his or her stage of illness and an evaluation of how he or she is coping with it. The exploration of cultural/ethnic beliefs regarding psychiatric and HIV illnesses can also contribute to the formation of a solid alliance. Because of the potential for the patient to feel shame and stigma associated with HIV infection and the sensitive nature of discussing risk behavior, psychiatrists should be supportive and not judgmental to encourage trust.

Issues of confidentiality should be reviewed with the patient, and the patient should be asked to consider the psychiatrist's role in assisting with the process of disclosure of HIV status to appropriate persons (94). In establishing a therapeutic alliance, it is important to discuss with the patient whether he or she wants to extend the treatment relationship to include selected communication with the family or significant other(s). Lastly, given the importance of the therapeutic alliance and the emotional impact of issues related to HIV, the psychiatrist should be aware of transference and countertransference feelings as well as personal attitudes about HIV infection and how the patient acquired the virus.

**b) Collaborate and coordinate care with other mental health and medical providers**

Managing the health care needs of a patient with HIV infection can be challenging due to the complex nature of the illness. Psychiatrists must be aware that the illness changes over time and has many different clinical manifestations. In addition, because information about HIV-related treatment is constantly evolving, psychiatrists may feel that their fund of knowledge about the most current interventions, such as antiretroviral medications, is inadequate. To keep up to date and to provide good clinical care, it is essential to collaborate with other physicians in infectious disease, primary care, and other disciplines.

Discussions of drug-drug interactions and the close monitoring and workup of unexplained somatic or psychiatric symptoms are examples of how psychiatrists and primary care physicians can assist each other in providing high-quality comprehensive care. Patients should specify their agreement for the exchange of specific information between the psychiatrist and other clinicians in a written release of information. It is often appropriate to use a multidisciplinary team approach when managing a patient with HIV, especially as the disease becomes more advanced. Access to both general medical and specialty care may need to be addressed.

**c) Diagnose and treat all associated psychiatric disorders**

A number of surveys of persons with HIV infection have shown an elevated premorbid rate of psychiatric disorders when compared to rates in the general population. In addition, psychiatric disorders can develop during any stage of HIV illness.

Psychiatric treatment of patients with HIV infection should include active monitoring of substance abuse, since it is often associated with risk behaviors that can lead to further transmission of HIV. Clinicians must not assume that patients who have relatively good immune functioning have no risk for CNS HIV disorders. Thorough evaluation and accurate diagnosis are key to selecting the appropriate intervention, whether it is risk reduction counseling, neuropsychological testing, or the use of psychotropic and antiretroviral medications.

There are no data to suggest that the psychotherapeutic management of patients with HIV infection should be different from that of other patients. Many clinicians use a variety of approaches (e.g., both time-limited and longer-term individual and group psychotherapy) and psychotherapeutic models (e.g., cognitive behavior, supportive, interpersonal, or psychodynamic/psychoanalytic).

**d) Facilitate adherence to overall treatment plan**

Adherence to a treatment regimen is profoundly important for patients with HIV infection. Research has demonstrated that less than 95% adherence to antiretroviral medications results in the development of viral resistance (95). Translated into actual practice, if medication doses are taken twice a day, a patient cannot miss more than one dose every 10 days.

Because comorbid psychiatric disorders, such as substance abuse or depression, have been shown to adversely affect patients' compliance with a complicated treatment regimen, psychiatrists and patients should actively discuss adherence to both psychotropic and HIV medications (96). Psychoeducational approaches are especially useful, since they reinforce the importance of adherence, support appropriate help-seeking, and identify barriers to adherence. Some patients who are unable to modify their behavior after educational approaches may be helped by intensive psychodynamic psychotherapy. If indicated, outreach efforts with public health nurses and services can be used to provide adherence assistance.

**e) Provide education about psychological, psychiatric, and neuropsychiatric disorders**

Mental health problems can occur at any stage of HIV illness (e.g., around the time of serologic testing) (97), or they could be precipitated by the onset of somatic symptoms. Preexisting psychiatric disorders or personality traits may be exacerbated by the onset of HIV illness. Patients may seek mental health services on their own, but it is not uncommon for other clinicians to request psychiatric consultation for patients who are in crisis or who have psychiatric symptoms.

It is often the psychiatrist's role to educate other clinicians and patients about the neuropsychiatric complications of HIV infection and to initiate and encourage treatment of current or emergent psychiatric disorders. When seeing a patient in consultation, it is important to gather history about cognitive or motor symptoms and conduct a mental status screening examination to determine whether neurocognitive deficits are present (see Section III.B.2.a on screening exams).

**f) Provide risk reduction strategies to further minimize the spread of HIV**

Psychiatrists are obligated to assess the risk for HIV transmission from their HIV-infected patients to others and to provide risk reduction counseling. This task should be a long-term treatment priority, since many HIV-infected individuals continue risk behaviors. Risk assessment should be repeated when there are changes in the patient's clinical status or social situation, such as the onset of binge drug or alcohol use or new sexual relationships. Psychotherapy may help some individuals who are unaware of motivations that promote ongoing risk behavior. When a psychiatrist cannot provide the specific risk reduction intervention that is indicated for a patient, he or she should refer patients to resources such as HIV/AIDS service organizations and support the intervention when initiated.

**g) Maximize psychological and social/adaptive functioning**

Biomedical interventions have stemmed the progression of HIV illness so that its course has increasingly resembled that of other chronic medical illnesses. Therefore, maximizing psychosocial functioning is relevant to the long-term social and economic impact of HIV infection. Psychiatrists can enhance a patient's functioning by helping him or her cope with the illness. Psychiatrists should ask about and be aware of a patient's use of alternative or complementary treatments, including herbal remedies.

Assessment of social supports, utilization of appropriate community-based services, and resolution of financial and occupational concerns are all potential fruitful domains of inquiry. Many patients find support groups for persons with HIV infection helpful in coping with their illness, whereas others may prefer individual, couples, or family therapy.

#### **h) Role of religion/spirituality**

Inquiry about the spiritual beliefs and religious faith of a person with HIV infection should be a regular part of a psychiatric assessment and treatment planning, since they can be an important source of support for many with HIV/AIDS. Facing a serious illness often serves as a catalyst for a search for meaning and a renewal of spiritual beliefs and practices. A person's religious history includes not only current beliefs and practices but also religious traditions of one's family of origin and ethnic culture.

Religious congregations have had different, sometimes negative, responses to the spiritual needs of members with HIV/AIDS that often correspond to the core beliefs of the faith communities (98). Many ethnic minorities find the religious community or body of the church to be the network that most effectively addresses their need for support in crises.

The concept of spirituality goes beyond religious considerations to encompass multidimensional and existential perspectives that are important in maintaining well-being for many persons with HIV infection. It is not uncommon for persons with HIV/AIDS to seek alternative modes of spiritual expression, such as meditation. An assessment of the spiritual needs of a patient involves questions around the person's concept of God, sources of strength and hope, significance of practices and rituals, and perceived relationship between spiritual beliefs and health status (99). Information gathered may help caregivers assist patients to better cope with their illness at all stages but particularly as a patient nears death.

#### **i) Prepare for issues of disability, death, and dying**

As HIV illness advances, a psychiatrist may be asked to help evaluate the need for reasonable work or school accommodations or the ability to return to work in line with the Americans With Disabilities Act. Patients with minor children may need assistance with disclosure of illness and the establishment of a custody plan in the event of parental death from AIDS. Psychotherapy may be very helpful in reducing the emotional distress and turmoil activated by approaching death.

The fundamental right of a patient with advancing HIV illness to make treatment decisions can be supported when issues relating to disability, death, and dying are discussed by the appropriate parties in a timely and ongoing fashion. Discussions about preferences for care should be initiated by physicians, since it has been reported that only 36% of patients with AIDS had spoken with their physician about their preferred treatment (100). It is recommended that patients with HIV infection draw up a living will to guide end-of-life decisions in addition to a durable power of attorney. Copies of these documents should be placed in a patient's medical charts and in the files of their primary and specialty physicians.

#### **j) Advice to significant others/family regarding sources of care and support**

The HIV patient's significant others—partner, family, and friends—are often collaborative partners in care and support who often shoulder a significant share of the clinical day-to-day care of an acutely or terminally ill patient with AIDS. They also are a rich source of collateral information about the clinical status of the patient. The psychiatrist needs to take care that the patient has given consent before speaking directly with family and significant others.

Intimate involvement with the patient and his or her illness can lead to mental health difficulties for the significant others as well. Referral to support groups for significant others affected by HIV may be helpful, as can encouragement to participate in HIV/AIDS advocacy organizations. Both can provide emotional validation and a degree of respite for a significant

**TABLE 14. Screening Examinations for HIV-Associated Cognitive Motor Dysfunction**

<b>Instrument</b>	<b>Administration</b>	<b>Comments</b>
Mental Alteration Test (102)	Clinician administered	Timed test; verbal version of the Trail Making Test; alternates between numbers and letters
HIV Dementia Scale (103)	Clinician administered	Five sections cover memory registration, attention, psychomotor speed, memory recall, and construction
Executive Interview Test (104)	Clinician administered	A 10-minute, 25-item bedside test of executive function, including snout reflex, word fluency, echopraxia, go/no-go task

other. Some significant others and family members may be best served by referral for psychiatric evaluation and treatment, including individual or family therapy.

## **2. Diagnosis and treatment of disorders requiring specific psychiatric intervention**

### **a) Dementia and the spectrum of cognitive disorders**

Cognitive complaints are not uncommon among psychiatric patients in general, but the evaluation of such complaints in a patient with HIV infection requires a comprehensive psychiatric assessment, formulation of a differential diagnosis, and possible medical workup. Symptoms of early cognitive changes due to HIV can be subtle and can differ from symptoms associated with cortical dementia such as Alzheimer's. For example, HIV-associated dementia, due to its subcortical localization, more commonly presents with psychomotor slowing rather than deficits in language or visual recognition. Psychiatrists need to be aware of these differences in clinical phenomenology in order to identify HIV-associated dementia at early stages.

The widely used Mini-Mental State (101) is not sensitive in picking up early HIV-associated cognitive motor symptoms. Alternative screening examinations have been proposed that identify symptoms more likely to be present with subcortical dementia (102–105). Psychiatrists should become familiar with the available screening examinations for cognitive motor impairment that are more specific for subcortical symptoms (Table 14). It has been found that patient self-assessment of cognitive status is not reliable (106). Therefore, psychiatrists should administer a baseline screening examination on every patient with HIV infection and plan to readminister the test on a regular basis as part of the treatment plan. If there is evidence of early cognitive impairment, formal neuropsychological testing is useful to more comprehensively document cognitive dysfunction as well as areas of relative cognitive strength.

Once cognitive deficits are identified, the psychiatrist should work in collaboration with infectious disease specialists, neurologists, or primary care clinicians to develop a plan for further workup. A magnetic resonance imaging scan often reveals no abnormality in patients with early dementia, so this technique is not useful in providing specific confirmation of HIV-associated dementia. The overall immunological status of the patient should be assessed if not already known.

Pharmacologic treatment of HIV-associated dementia consists of intervening with potent antiretroviral therapy that targets the underlying HIV infection with consideration of whether the agents adequately penetrate the CNS. For comorbid conditions such as depression, psychiatrists should consider prescribing antidepressant medications as they would for other medically ill patients. Last, for management of symptoms associated with HIV-associated dementia (e.g., agitation or fatigue), medications such as antipsychotic or stimulant agents, respectively, should be considered.

Psychotherapy may be helpful for patients with mild to moderate dementia in order to help them understand, mourn, and adapt to this new impairment of functioning. Both medications and psychotherapy can thus improve the quality of life both for persons with HIV-related cognitive disorders and their significant others while also improving overall clinical outcomes.

#### **b) Delirium**

The evaluation of the cause of delirium in an HIV-infected patient requires the psychiatrist to be alert to multiple possible etiologic factors and be knowledgeable about specific diseases that are associated with HIV infection. Examples are hypoxemia due to *Pneumocystis carinii* pneumonia, uremia due to HIV nephropathy, or elevated ammonia levels due to cirrhosis. One of the most important factors is the multiple medications that HIV patients typically take, which often cause delirium or contribute to delirious states because of drug-drug interactions. Problems arising from such toxicity are often reversible. Patients with AIDS who reside in either nursing homes or assisted living facilities or who have been hospitalized and who develop delirium have been shown to have significantly shorter survival than AIDS patients without delirium (107, 108). HIV-associated delirium may present with symptoms that resemble classic mania or drug intoxication, thereby bringing patients to the attention of a psychiatrist for evaluation. Delirium in the context of HIV infection should be evaluated like delirium with other medical conditions (47). A psychiatrist should advocate for a complete medical/neurological evaluation for patients with HIV infection who present with an acute onset of psychiatric symptoms with no previous psychiatric history. A complete workup should include a toxicology screen, thorough neurological examination, laboratory evaluation, and brain imaging studies. A comprehensive assessment for infectious processes should be conducted and may entail lumbar puncture.

Management of delirium in the context of HIV infection includes judicious use of antipsychotic medications for symptoms of agitation or perceptual abnormalities such as hallucinations. Many clinicians use the newer, atypical antipsychotic agents due to their lower side effect profile.

#### **c) Mood disorders**

The management of disturbances in mood such as depression or mania for patients with HIV infection is similar to that for other patients with medical comorbidity. Fatigue and insomnia, frequent complaints in otherwise asymptomatic patients, are likely related to psychological disturbances such as major depressive disorder (109). In addition, the overall medical status of the patient should be assessed to take into account possible effects of concurrent illness or side effects of medications such as efavirenz. Psychiatrists should know all medications that a patient is taking. Choice of an antidepressant or mood-stabilizing agent may be influenced by the antiretroviral regimen in place, and doses may need to be adjusted if drug-drug interactions are likely. Psychotherapy should be recommended when indicated.

Manic syndromes are difficult to treat in HIV-infected patients for several reasons. First, mania may result from HIV infection (secondary mania) (33), AIDS-associated brain infections, neoplasms, or treatment with medications like steroids. In addition, manic syndromes can be related to comorbid substance use disorders, and case reports have documented manic symptoms induced by the antiretroviral agents didanosine and zidovudine (110, 111). Patients who experience their first manic episode later in the course of their HIV disease are less likely to have personal or family histories of mood disorders and are more likely to have dementia or neurocognitive slowing (34). Although the prevalence and incidence of mania associated with HIV are not well described, treatment studies suggest that traditional antimanic agents are effective and tolerated.

#### **d) Substance use disorders**

In the United States, substance use disorders are prevalent in the population of persons with or at risk for HIV infection, and treatment is a high priority. Because drug- and alcohol-dependent

HIV-infected patients form a large reservoir for HIV in the United States, and because behavior that risks transmission of HIV is often associated with concomitant substance use, psychiatrists should be aware that by treating substance abuse, they may well be preventing HIV infection (112). Unfortunately, the number of injection drug users in the United States outnumbers the available treatment slots.

Treatment with methadone or LAAM (113) can be an important treatment component for persons with opiate dependence. Since the quality of such programs varies, psychiatrists should help identify the best program for their patients. Factors that often indicate higher quality include the use of higher doses of methadone or LAAM and a close working relationship with primary medical clinicians and associated psychosocial services. It should be noted that doses of methadone may need to be increased or decreased in accordance with the use of specific antiretroviral agents that can have an impact on the metabolism of methadone.

Psychiatrists may be primary providers of care in a variety of clinical settings for HIV-infected patients who also have a substance use disorder. Psychiatrists should either provide treatment for their patients with comorbid substance abuse or collaborate with high-quality substance abuse programs. Substance use disorders themselves are often associated with comorbid psychiatric disorders such as anxiety, depression, and psychotic symptoms. Treatment of these comorbid conditions can help stabilize patients who are attempting to achieve sobriety or abstinence.

#### **e) Anxiety disorders**

Many problems involving anxiety symptoms can arise in relationship to HIV illness. An example of a clinical anxiety problem *without* HIV infection is AIDS phobia. For persons infected with HIV, there are numerous points at various stages of the illness when anxiety about the future, physical symptoms, or clinical decisions can become overwhelming. Psychotherapeutic approaches to situational anxiety can help patients work through intense affects and provide a structure within which sound decisions can be made.

Anxiety disorders can precede HIV infection or arise as its consequence. Treatment of anxiety disorders among HIV-infected patients has not been well studied; thus, psychiatrists should apply standard pharmacologic treatments for anxiety disorders with caution. For instance, many benzodiazepines are contraindicated when patients are taking protease inhibitors, particularly ritonavir, since predicted pharmacokinetics suggest blood levels of these psychotropic agents will be greatly elevated. Thus, benzodiazepines should be given as a short-term intervention in most instances. Psychiatrists may need to adjust medication doses and consider medical setbacks when treating patients with prominent anxiety symptoms. Psychotherapy may be effective in managing anxiety while reducing the need for medications. PTSD is a possible outcome of sexual assault or abuse and may be a focus of clinical treatment for some patients with HIV infection.

#### **f) Psychotic disorders**

Psychotic symptoms in the context of HIV infection, particularly at advanced stages of illness, do not necessarily indicate a primary psychotic disorder, such as schizophrenia, but may arise from causes ranging from opportunistic infections, mania, HIV-associated dementia, or delirium. Evaluation of new-onset psychosis requires a careful medical/neurological workup.

There is no literature to suggest that the use of antipsychotic medication needs to be modified for HIV-infected patients who have good immune functioning and are not taking antiretroviral medication. For patients taking antiretroviral medications, it is important to be aware of drug-drug interactions and overlapping toxicities. In particular, the use of clozapine is problematic with both ritonavir and zidovudine, the former because ritonavir may elevate blood levels of clozapine, the latter because clozapine and zidovudine can each cause significant bone marrow suppression.

In late-stage HIV infection, atypical antipsychotic medications are the first-line treatment because standard neuroleptic medications have been associated with very severe and difficult-to-treat extrapyramidal side effects. Also, in late-stage HIV illness, the lowest effective dose of any atypical antipsychotic medication should be given, since lower doses are sufficient to achieve efficacy and necessary to help prevent side effects.

**g) Adjustment disorders**

These disorders are interspersed among other diagnostic categories and are differentiated on the basis of onset after an identifiable stressor. Adjustment disorders are associated with significant emotional or behavioral symptoms. Although they may arise from stressful life events such as testing HIV-antibody positive, they may indicate a subsyndromal state that will evolve into a severe psychiatric disorder if left untreated. Various forms of psychotherapy may be indicated to prevent progression to a more severe psychiatric disturbance.

**h) Sleep disorders**

Sleep complaints are common in HIV patients in psychiatric treatment. Sleep disturbances may arise from a psychiatric disorder such as depression or stem from complications of HIV infection. For instance, because pain is a frequent accompaniment of HIV-related illness and is often treatable, clinicians should intervene to alleviate pain that causes sleep disturbance. The antiretroviral medication efavirenz is associated with a high incidence of vivid dreams and nightmares.

**i) Disorders of infancy, childhood, and adolescence**

The presenting psychiatric problems of HIV illness in children depend upon factors such as the age and developmental stage of the child, HIV clinical stage, psychosocial situation, and individual vulnerabilities for psychiatric disorders. Although there are few studies in this area, psychiatric disorders are common among infected youth, with rates of about 30% for mood disorders and 25% for attention deficit hyperactivity disorder (114, 115). As mood and anxiety disorders are more likely to be overlooked by caregivers than disorders with prominent behavioral manifestations (externalizing disorders), extra vigilance is required by the psychiatrist.

Just as the standard of care for HIV intervention has changed for adults, so have the treatments for children infected with HIV. Children have increased survival rates and slower progression to AIDS with the use of antiretroviral medications.

Psychiatrists, especially child and adolescent psychiatrists, need to help support children who survive to adolescence to negotiate this complex developmental stage. Psychotherapy may be of particular help for adolescents who are dealing with issues of developing sexuality. For some adolescents, sexuality may be a reminder of their infection. For others, sexual risk behavior may be a reenactment of parental behaviors, a method of mastering their trauma, or a response to their anger concerning their ill health. Substance abuse is frequent (33% in one study) and is likely to involve multiple drug use (116). The issues of risk behavior and autonomy have implications for HIV prevention, adherence to treatment, and effective coping with chronic illness. The family's understanding and capacity to respond in a supportive manner are essential—these adaptations will not only help the child or adolescent cope with the attendant biopsychosocial adversity, they may also influence morbidity and mortality. The importance of family dynamics for children and adolescents with chronic illness and handicapping conditions has long been recognized (117, 118).

**j) HIV-associated syndromes with psychiatric implications**

In the case of somatic syndromes that exist at the interface of medical and psychiatric disorders, psychiatrists can serve to integrate treatment approaches and promote interdisciplinary and interspecialty dialogue. Symptoms such as fatigue, weight loss, pain, and sexual dysfunction can

be associated with HIV illness as well as psychiatric disorders. It is useful to avoid all-or-nothing, mind or body, approaches when evaluating such nonspecific symptoms. Good communication between psychiatrists and other physicians leads to better treatment decisions. Principles of palliative care apply when a patient is terminally ill and desires treatment that focuses on comfort and symptom relief.

Wasting syndrome generally occurs in patients with more advanced HIV illness and can be related to a number of physiologic disturbances, such as progressive HIV disease, hypogonadism, and gastrointestinal malabsorption. Loss of lean body mass is a strong predictor of increased mortality due to AIDS (119). Wasting is defined as loss of >10% of ideal body weight.

Fatigue is a common, often chronic symptom in HIV disease, frequently associated with depressed mood and physical disability, particularly among patients with more advanced HIV infection or AIDS (120–122).

Patients report pain at all stages of HIV illness, but complaints tend to be more frequent and more intense at advanced stages of systemic illness (123, 124). Common painful symptoms stem from headaches, herpetic lesions, peripheral neuropathy, back pain, throat pain, arthralgias, and muscle and abdominal pain (125).

Sexual dysfunction has been reported to occur in both men and women with HIV infection. In men, hypogonadism can be treated with testosterone replacement (126). As a rule, testosterone more effectively treats diminished libido than erectile dysfunction.

## IV. CLINICAL AND ENVIRONMENTAL FEATURES INFLUENCING TREATMENT

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### ▶ A. SOCIODEMOGRAPHIC VARIABLES

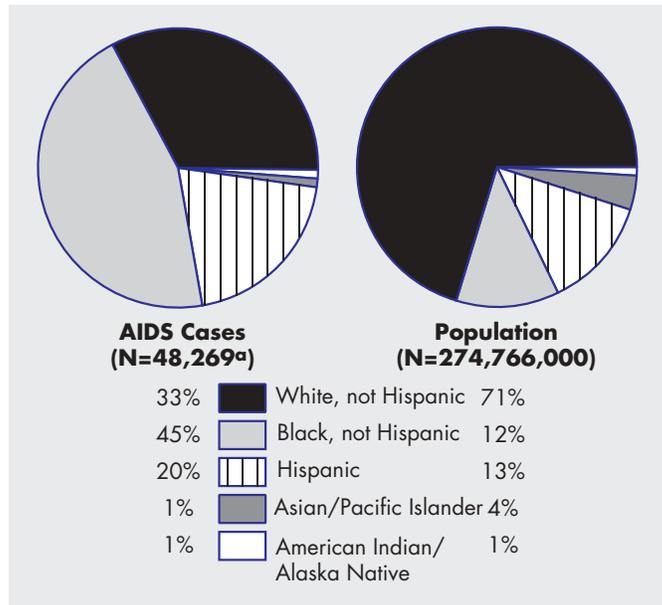
#### 1. Race/ethnicity

AIDS and HIV infection disproportionately affect both the African American and Hispanic populations in the United States. In 1998, African Americans accounted for 45% of AIDS cases reported that year while constituting only 12% of the total U.S. population. The same year, the rate of reported AIDS cases for Hispanics in the United States was 20%, although Hispanics constituted only 13% of the general population (Figure 5). In 1998, African Americans overtook whites as the group with the largest number of persons living with AIDS. The rates have been relatively constant in the Asian/Pacific Islander and American Indian/Alaska Native groups: about 1% of cases (Figure 6).

The statistics are even more skewed when classified according to both race *and* gender. For those cases of AIDS reported through 1998, 77% of all women with AIDS were black or Hispanic; 81% of all children with AIDS were black or Hispanic (127).

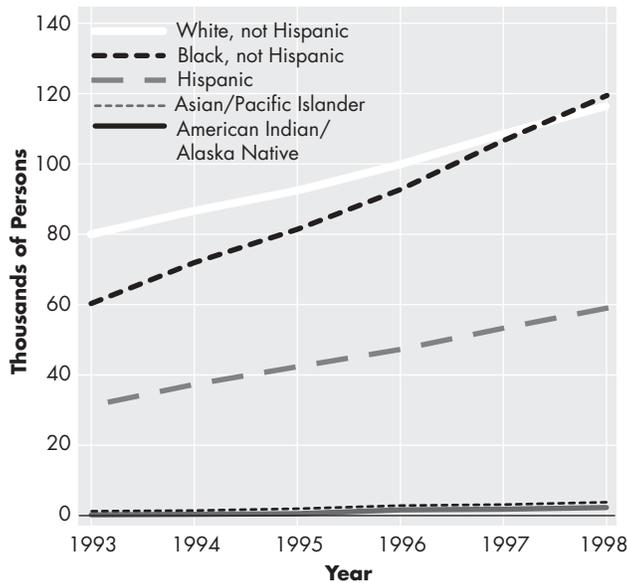
Three interrelated issues seem to account for the high rates of HIV/AIDS in minority communities: 1) inequities in the general health status in economically disadvantaged minorities, 2) problems controlling substance abuse in minority communities, and 3) the role of substance abuse in the spread of HIV sexually and perinatally.

HIV prevention efforts must be tailored for specific ethnic/cultural groups so that their effectiveness can be enhanced. This point is highlighted by the high levels of stigma associated with gay or bisexual activity in the African American and Hispanic communities. The impact of religious beliefs (Pentecostal, Catholic) in these communities may also affect HIV prevention efforts due to negative views of homosexuality.



**FIGURE 5.** U.S. AIDS Cases Reported in 1998 and Estimated 1998 U.S. Population, by Race/Ethnicity (3).

<sup>a</sup>Includes 242 persons with unknown race/ethnicity.



**FIGURE 6.** Estimated Number of Persons Living With AIDS in the United States, 1993–1998, by Race/Ethnicity (3).

Hispanics in the United States constitute a diverse group of cultures and countries of origin. Surveys have found that exposure to HIV varies in different Hispanic subgroups. For example, injection drug use is more prevalent among Hispanics from Puerto Rico, whereas the more common risk behavior for Hispanics who originate from Mexico, Cuba, and South and Central America is unsafe sex among men who have sex with men (128).

## **2. Sexual orientation**

Throughout most of the earlier years of the HIV/AIDS epidemic, men who had sex with men were disproportionately affected. Although this group still constitutes the population with the highest AIDS incidence (37% of new AIDS cases in 1998), through massive prevention interventions, rates for men who have sex with men have declined, whereas other exposure categories are increasing annually. For example, in 1998, 12% of new AIDS cases were linked to heterosexual transmission (127).

Evidence from HIV prevalence studies and risk behavior surveys supports the need to continue HIV prevention efforts among each generation of gay and bisexual men. There are cohort differences in attitudes, behavior, and perceived risk in younger and older gay and bisexual men. In one study of six urban counties, 5%–8% of adolescents and young men between the ages of 15 and 22 who were having sex with men were already infected with HIV (3).

Bisexual women have been reported to have significantly more sexually transmitted diseases and HIV risk than heterosexual women (129), and women who have sex with women constitute a group with a combination of risks for HIV infection. In general, female-to-female transmission is thought to be uncommon, although theoretically possible. The CDC writes that “of the 347 (out of 2,220) women who were reported to have had sex only with women, 98% also had another risk— injection drug use in most cases” (130). Women who have sex with women do need to know that exposure to mucous membranes, such as the vagina or mouth, or to vaginal secretions or menstrual blood could transmit HIV, especially if the concentration of the virus is high (early or late-stage HIV infection).

## **3. Gender**

The percentage of women with both HIV infection and AIDS has been steadily rising over the past decade. AIDS cases among women and adolescent girls rose 364% between 1991 and 1997. Trends in HIV diagnoses showed a 3% decrease in men but a 3% increase in women between 1995 and 1996. Heterosexual contact is the leading risk category for women (38%), with 29% of cases in women resulting from personal injection drug use (127).

The exposure category “other/not identified” represents 32% of AIDS cases in women (127). It is typical for more recently reported cases to be classified as “other/not identified,” but after medical record review and investigation, most cases are eventually attributed to one of the defined exposure categories.

African American and Hispanic women are disproportionately affected, with AIDS rates 17 and 6 times higher, respectively, than for Caucasian women. Despite the difficult socioeconomic conditions many minority women live in, a recent survey of health concerns among low-income women found that AIDS was ranked as the most important concern (131).

There are issues that are unique to women and HIV/AIDS. Male-to-female transmission is estimated to be eight times more likely than female-to-male transmission (132). Sex differences in HIV measurements such as viral load, side effects of antiretroviral medications, and access to quality health care have all been documented (133). These biological differences make recommendations for antiretroviral therapies more uncertain for women. In addition, most clinical trials of interventions to treat HIV infection have enrolled male subjects. Women, particularly HIV-positive women, have psychological, psychosocial, reproductive, and gynecological concerns that differ from men (134, 135).

#### **4. Age**

AIDS has always had the greatest impact on Americans ages 25–44. For example, in 1996, almost 75% of persons with AIDS were between the ages of 25 and 44; 21% were over age 44, and less than 4% were between the ages of 13 and 24. More recent data have shown that one in four new infections in the United States occurs in people younger than 22 years of age (127).

Because of the impact associated with new medical therapies, many people's lives have significantly lengthened, which has led to older generations of persons living with HIV/AIDS. For instance, currently one out of 10 AIDS patients in the United States is over 50 years old; in Florida, one out of every six AIDS patients is older than 50 (136).

The age of diagnosis for 11% of AIDS cases is 50 years or older, and the age of diagnosis for 3% of AIDS cases is 60 years or older (127). However, there remains a common misperception that HIV is not a risk for older people. Many HIV-related symptoms mimic the effects of aging, so clinicians may be slow to diagnose HIV infection in older people and fail to question their older patients about risk behaviors (137). This is troublesome given research findings that document that adults over the age of 50 are up to one-sixth as likely to use condoms as people in their 20s (138). A particular diagnostic challenge for mental health clinicians treating HIV-infected older persons involves neurological symptoms, for which the differential diagnosis of cognitive impairment should be broadened to include dementias seen in older age.

#### **5. Economic factors**

According to data from the first national multisite HIV/AIDS Mental Health Services Demonstration Program, of nearly 2,000 persons with HIV/AIDS seeking mental health services, a majority were socially and economically disadvantaged (i.e., marginally employed, poor, relying on public assistance, or under- or uninsured) (139). Almost half of the 2,000 patients treated in this program lacked medical insurance, and for all patients median monthly income was only \$575. Other sources of economic information yield seroprevalence data that suggest higher rates of HIV infection among the poor. For example, among Job Corps participants (who are primarily economically disadvantaged youth), HIV seroprevalence rates are twice that of youth seen at adolescent clinics and eight times higher than rates for similar age youth who apply for military service (140).

#### **6. Urban versus rural**

Although HIV has historically disproportionately affected urban areas, rural populations are increasingly at risk. Although more drug-related risk behaviors are reported by residents of large metropolitan areas, high-risk sexual behaviors have not been found to differ significantly among urban and rural residents (141). However, one recent study found rural low-income women less likely to use condoms than their urban counterparts (142). When compared to urban dwellers living with HIV/AIDS, rural inhabitants report significantly lower life satisfaction, lower perceptions of social support from family and friends, reduced access to medical and mental health care, elevated levels of loneliness, more community stigma, heightened personal fear that their HIV status might be disclosed by others, and more maladaptive coping strategies (143).

### **▶ B. CLINICAL FEATURES**

#### **1. Suicidality**

Suicide, attempted suicide, and suicidal ideation are complex clinical issues that may arise during the course of psychiatric care for HIV patients (144). Studies in the 1980s, before antiretroviral treatments, reported rates of completed suicide in HIV-positive men as high as 66 times

that of the general population (145–147). However, more recent data show suicide rates only modestly elevated and comparable to those in other medically ill populations (148), although perhaps most elevated among men who have sex with men (149). A study among U.S. military service applicants found suicide rates for both HIV-positive and HIV-negative individuals that were only marginally more elevated than those in the U.S. general population (150).

A number of risk factors for suicide in HIV patients have been described. They include psychiatric morbidity such as substance abuse (151, 152), antisocial personality disorder (153), family psychiatric history and family history of attempted suicide (154), and major depressive disorder. Numerous psychosocial factors have also been identified, such as a history of multiple HIV-related losses, lack of social support, loss of employment or insurance coverage, painful and disfiguring physical deterioration, exhaustion of financial resources, and reliance on public assistance (155, 156).

Recent evidence has shown that patients with greater levels of “fighting spirit,” a specific pattern of adjustment to life-threatening illnesses, tend to have lower levels of suicidal ideation. Evaluation of suicide risk and other violent acts is an integral part of a comprehensive evaluation for HIV/AIDS patients. Psychiatric treatments that promote greater adaptation to living with HIV infection may lower the risk of suicide for many patients (154).

## **2. Bereavement**

There are unique features to bereavement in the context of HIV/AIDS. Deaths from AIDS often disproportionately affect specific segments of the U.S. population. For example, it is not uncommon for a member of the gay community to have lost multiple persons to AIDS. At the same time, a bereaved individual may himself or herself be infected with HIV. Reports have suggested increases in high-risk sexual behavior and suicidal ideation in partners of individuals who have died of AIDS (157, 158). Bereavement is often compounded by the fact that many people die from AIDS at a young age, out of synchrony with the normal developmental sequence (159, 160).

Growing numbers of children will lose one or both parents to HIV. Psychiatrists need to explore the capacity of families to communicate about HIV and the children’s understanding of their parent’s illness. Disclosure is difficult for many parents who worry about revealing stigmatized behaviors or overwhelming a child with information (161). Permanency planning is an essential step in communication and collaboration with social agencies. For many children, bereavement is complicated by the psychosocial problems that existed before HIV that are then compounded by disintegration of the immediate family. Problem behaviors in adolescents who anticipate losing one or both parents to AIDS have been described (162). Family-based, multidisciplinary team approaches may be effective in providing access to care and needed follow-up services.

Researchers have studied the relationship of AIDS bereavement and psychological or medical variables but have not necessarily found that greater numbers of AIDS losses are associated with a higher rate of depressive symptoms or depressive disorders (163) or that distress increases in a dose-response relationship to the number of losses (164). One investigation reported changes in measures of immune function relevant to HIV disease in bereaved HIV-positive men that suggested patterns consistent with disease progression (165). Bereavement has been associated with decreased lymphocyte proliferation (164, 166) and decreased natural killer cell function (167, 168).

Group therapy is often recommended for AIDS-related bereavement (169). Group participants include partners, friends, family, and caregivers of persons who have died of AIDS. A randomized, controlled trial of support group interventions for bereaved HIV-positive and HIV-negative men demonstrated significant improvement in grief symptoms for the treatment group compared to control subjects (170).

### 3. Axis II disorders

Several studies have reported that patients with HIV infection have a prevalence of personality disorders in the range of 19%–37%, which is higher than rates found in comparable patients who are not infected (171). Personality disorders categorized (per DSM) within cluster B, such as borderline and histrionic personality disorder, are the most common (172). These data are supported by clinical reports from settings that provide care for large numbers of HIV-infected patients (173). The findings are not surprising given the association between personality disorders—especially those disorders in which “impulsivity” is prominent—and risk factors for HIV infection such as high-risk drug use and sexual behaviors. Personality disorders among those infected with HIV are associated with a higher rate of depression, maladaptive coping, and other psychiatric symptoms (174, 175) as well as with a higher rate of injection drug use (176). In fact, one study has documented that among their sample of HIV-positive and “at risk” HIV-negative gay men, persons with personality disorders were at significant risk of onset of future axis I disorders and serious functional impairment, regardless of a past history of axis I disorders (177).

No studies have assessed the efficacy of specific treatments for personality disorders among individuals infected with HIV. There is no evidence against the use of standard psychiatric treatments for personality disorders, tailored to the individual patient. Some clinicians use an approach that includes limit setting, especially limits on the inappropriate use of medical resources and medications. Other strategies for complex cases emphasize the development and maintenance of a doctor-patient relationship, treatment of comorbid conditions such as depression and substance abuse, and supportive or cognitive psychotherapy techniques (173).

### 4. Psychoneuroimmunology

The relationship of behavior and psychopathology to immune measures has been the focus of ongoing research over recent years. With regard to HIV infection, the findings are mixed. On the one hand, a number of studies have found that stressful life event burden is associated with decreased CD4 cell count (178–180), decreased cytotoxic T lymphocyte count (181), clinical HIV disease progression (182, 183), and physical symptom burden (168). In contrast, the relationship of variables such as stressful life events and depressed mood levels with markers of immunological progression has not been supported by other studies (184, 185).

There appears to be an increase in the frequency and severity of depression around the time of the onset of AIDS that persists throughout the time of severe immunodeficiency (66). Whether depressed mood levels in general are associated with decreases in immune function is not clear, since one study has shown such an association (186), whereas another has not (187). The disparity across studies attempting to elicit such natural history relationships may be due to methodological differences related to the extent to which other factors, including immunological measures and clinical disease progression, had been controlled (179).

Interventions such as cognitive behavior stress management, coping skills enhancement training, massage therapy, existential therapy, bereavement support groups, and antidepressant medication have all been evaluated with regard to their effect on immune measures (188–190). The findings are mixed, with some interventions showing modest improvements of specific immune measures, whereas others did not result in positive changes. Most interventions are safe, including those that involved the antidepressants fluoxetine and imipramine (190). At this time, these types of interventions should be regarded as investigational in terms of their immunological and health effects. However, psychotherapeutic and psychopharmacologic interventions are indicated for their alleviation of distress and enhancement of functional status.

A caveat regarding the use of such interventions is that many patients hold beliefs that may lead to inappropriate expectations of the potential for immunological and clinical health effects. Patients who do not observe these effects may come to blame themselves (and their be-

havior) for the lack of such immunological and clinical effects and for disease progression. This could actually result in increased distress. Hence, patients must be carefully prepared for understanding the context in which behavioral interventions are being offered and which outcomes should be considered primary (psychological and functional) and which might be considered secondary and investigational (immunological and clinical health). On the other hand, clinicians should not discourage use of adjunctive techniques that can potentially add to the effect of current medical management by expanding the comprehensiveness of care.

## ► C. SPECIAL TREATMENT SITUATIONS

### 1. Alternative and complementary treatment

Alternative and complementary medicine is an important part of the health care sought by many Americans. Surveys of the U.S. public in both 1990 and 1997 demonstrated that over one-third of Americans used at least one unconventional treatment in the past year, with rates rising from 34% to 42% between 1990 and 1997. It is estimated that the number of visits to nontraditional care clinicians exceeds total visits to all U.S. primary care physicians and represents \$27.0 billion in annual out-of-pocket expenditures (191, 192). More than 60% of patients who use complementary/alternative treatments do not disclose the treatments to their doctors. Depression is one of the most common conditions for which patients seek alternative/complementary therapies.

Surveys specific to the HIV-infected population report similar findings, with between 30% and 68% of respondents reporting use of some form of complementary/alternative treatment (193–196). Patients with HIV/AIDS use complementary and alternative medicine to improve general health or quality of life, prevent progression of HIV disease, treat specific symptoms, or counter side effects that result from biomedical treatments (197, 198).

According to data from the first 1,016 participants of the Alternative Medical Care Outcomes in AIDS Study, the 10 most frequently used activities are aerobic exercise (64%), prayer (56%), massage (54%), needle acupuncture (48%), meditation (46%), support groups (42%), visualization and imagery (34%), breathing exercises (33%), spiritual activities (33%), and other exercise (33%) (199). Other nontraditional treatments include nutritional, vitamin, or herbal supplements and medicinal use of marijuana and anabolic steroids. Only one research study to date has examined complementary therapy in the context of HIV infection. A multi-site project is currently being conducted in cooperation with the Office of Alternative Medicine, National Institutes of Health, to evaluate these treatments (200).

### 2. Institutional settings

Institutions that house, treat, or incarcerate have a responsibility to address issues of HIV education, prevention, and clinical services for persons served in these settings. Seroprevalence studies in institutional settings identify the scale of HIV infection and help inform policies for the institution. For example, concerns about HIV infection among institutionalized mentally retarded persons have been somewhat allayed by studies that found either no cases of HIV infection (201) or low rates (0.16%) (202). These institutions nonetheless need to maintain universal blood and body fluid precautions as well as develop prevention programs tailored to their patient population.

Some of the highest rates of HIV infection are found among jails and prisons due to the high frequency of drug-related sentences and high-risk behaviors that occur within the institutions. Prevalence rates among male inmates have been recorded between 6% and 8.5% (203, 204); one study of incarcerated women in New York found an 18.8% rate of HIV infection (205).

Despite the alarmingly high rates of HIV infection among prisoners in the United States, administrative and institutional barriers, such as not allowing the distribution of condoms, undermine prevention interventions. Collaboration between institutional staff and clinicians or researchers of HIV prevention efforts may lead to effective interventions for inmates and their partners (206). Psychiatrists working in correctional facilities may need to advocate for patients who may not receive antiretroviral medications in a timely manner due to lockdowns, solitary confinement, or other factors. Recommendations for handling HIV-related issues in psychiatric institutions can be found in policy and position statements issued by the APA Office on AIDS ([www.psych.org/aids](http://www.psych.org/aids); click on “Policy Statements”).

### **3. Health care clinician issues**

HIV creates unique demands on clinicians. Stresses that are associated with the care of HIV-infected patients include fear of contagion, the emotional impact of dying patients, stigma associated with AIDS, anxiety concerning sexual and drug risk behavior, a constantly changing knowledge base, and often inadequate treatment resources (207). Health care workers have numerous reactions to these stresses. Clinicians have reported, for example, greater anxiety, more interference with nonwork activities, and symptoms similar to PTSD when treating AIDS patients as compared to non-AIDS patients (208, 209).

Despite the stresses and demands, most clinical staff members feel positively about their work, and only a small minority experience job burnout. The frequently cited rewards of working with HIV-infected patients include a sense of personal helpfulness, increased professional mastery, altruism, and admiration for patients’ courage (210). In order to support employees, most multidisciplinary programs address issues that are likely to cause stress, such as death and dying, the management of sexuality, and fear of contagion. Interventions to address these issues range from weekly informal team meetings to leader-based staff support groups (211, 212).

Workshops that allow caregivers an opportunity to express grief, explore frustrations, and share resources may be helpful (213). Progress in HIV therapeutics requires frequent educational updates. Appropriate resolution of staff conflict and disagreement is useful in the HIV care setting, as it is in other settings that deal with chronic medical illness. One study, for example, found that HIV health care workers who perceived colleagues as significantly stressful were nearly 50% more likely to experience job burnout (214). Thus, a well-functioning HIV team may help buffer the stresses of providing care, and psychiatrists can be effective by assisting those teams.

## **PART B:**

# **REVIEW AND SYNTHESIS OF AVAILABLE EVIDENCE**

## **V. DATA REGARDING PREVENTION FOR INDIVIDUALS AT HIGH RISK FOR HIV INFECTION**

### **▶ A. HIV-RELATED RISK ASSESSMENT OF BEHAVIOR**

In a national survey of 417 practicing psychiatrists conducted in 1997 by APA, the physicians reported that over 9% of patients they treat are at risk for HIV infection (215); the rate was

derived from questions about psychiatrists' knowledge of patient risk behavior. This estimate is probably conservative, since many psychiatrists do not conduct a detailed HIV risk assessment. Nonetheless, the survey data support other findings that psychiatric patients report higher rates of HIV risk behavior than the general population (141) and underscore the important role that psychiatrists play in preventing HIV infection.

Studies of primary care clinicians who conduct HIV risk assessments among patients who express concern about HIV risk found that in 73% of the encounters, the physicians did not elicit enough information to adequately characterize patients' HIV risk status (216).

## ▶ **B. HIV ANTIBODY TESTING**

It is estimated that only two-thirds of all HIV-infected people in the United States know their serological status. Hence, many do not know until they are diagnosed with AIDS. The CDC recommends routine voluntary HIV antibody testing of patients who are admitted to hospitals that have HIV seroprevalence rates of >1% among admitted patients.

A multistate evaluation found that *anonymous* HIV testing was associated with earlier HIV testing and HIV-related medical care when compared to those who were tested *confidentially* (217). Concerns about HIV test confidentiality led to a study of testing trends in six states that initiated name-based reporting of HIV test results. The researchers did not find significant declines in the total number of HIV tests performed at counseling and testing sites other than those expected from trends present before name-based reporting (218). Moreover, Osmond and colleagues (219) surveyed nearly 2,000 HIV-seropositive patients diagnosed during 1995–1996 in five states with name-based HIV surveillance (and three without) and reported that keeping records of people infected with HIV by name does not help or hinder treatment.

Home collection testing for HIV provides a method for testing among individuals who may not otherwise seek HIV testing through publicly funded sites or medical providers. A review of data collected by test manufacturers in the first year of availability (1996–1997) reported that of 174,316 tests performed, 0.9% were positive. Most users of home collection tests were white men aged 25–34 years; HIV prevalence was highest among nonwhites, men who had sex with men (particularly bisexual men), and injection drug users. Nearly 60% of those who submitted samples and 49% of those who tested positive had never had a previous HIV test (220).

## ▶ **C. INTERVENTIONS TO REDUCE HIV RISK BEHAVIOR**

A wealth of literature addresses the issue of how to intervene to reduce HIV risk behavior at both the individual and community level. While this section will focus primarily on data concerning interventions at the individual level, macro-level changes in structure or policy can lead to powerful community-level support of specific behavior changes (221). The AIDS Community Demonstration Project is a good example of a community-level intervention. Community volunteers and “small” media were able to influence community norms about the use of condoms and disinfection of drug injection equipment by using bleach (222). Other examples of societal-level policies that influence the effectiveness of individual-level HIV risk behavior interventions are 1) laws that prohibit same-sex marriage, which hinder the establishment of long-term monogamous relationships for men who have sex with men (223), and 2) insufficient substance abuse treatment capacity, which decreases the opportunity for an injection drug user to receive treatment.

Sexual behavior is the target of most prevention efforts worldwide, but because of the diversity of sexual behavior and the influences of economics, culture, and environment, interventions to stem HIV necessarily vary as well (224). Because of the sheer size of the prevention literature and the many specific populations that have been targeted, these guidelines will not

provide more detailed information about subgroups based on gender, ethnicity, or age. A publication from the CDC entitled “Compendium of HIV Prevention Interventions with Evidence of Effectiveness” provides a useful synopsis of the research in this area (225).

## **1. Counseling strategies**

The HIV counseling and testing model has been widely used in studies that intend to promote behavior change in persons at risk for HIV infection. Yet, two large reviews of HIV counseling and testing studies (226, 227) found that HIV counseling and testing interventions do not consistently lead to risk reduction or promote help-seeking behavior in most populations studied. Both analyses found that serodiscordant heterosexual couples demonstrated the most change in risk behavior. A recent meta-analysis of the effect of HIV counseling and testing interventions found that they were more effective in secondary prevention for HIV-positive persons than as a primary prevention strategy (228).

The most widely used counseling models acknowledge that knowledge about HIV transmission and prevention is necessary but not sufficient for behavior change (229–231). More effective interventions rely on skills training and take into account individual psychosocial and cognitive strategies (232). Essential to effective counseling is helping patients perceive themselves as at risk for HIV infection, addressing motivation to reduce risk, and ensuring that patients have the skills and resources to implement risk reduction strategies. Changing peer norms with the help of peer leaders and matching the background characteristics (e.g., race, ethnicity, sexual orientation) of the leader to the targeted population often help increase intervention effectiveness.

The largest randomized, controlled HIV behavioral intervention study conducted in the United States found that even among persons served in public health settings, a small-group, seven-session risk reduction intervention cut reported high-risk sexual behaviors in half and more than doubled reported regular use of condoms (from 23% to at least 60%) (233). HIV prevention interventions have proven useful for psychiatric populations, including injection drug users and people with severe mental illness, and have been shown to be effective even when conducted in busy public clinics (234, 235).

## **2. Specific strategies for injection drug users**

The principles for preventing the spread of HIV among active drug injectors are similar to those used to modify unsafe sexual behavior. Ethnographic research has clarified how injected drugs are purchased, dissolved, filtered, transferred into syringes, and injected, and how sharing practices at each step in the process contribute to the potential spread of HIV (236). Successful interventions focus on knowledge, motivation, and behavioral skills that are tailored to realistic strategies for changing sharing practices. These programs have also engaged members of the injection drug use community as prevention leaders.

An international study found that injection drug users are capable of changing their risk behavior and providing accurate reports of their behavior. Further, these behavioral changes are associated with lower rates of HIV infection (237). A review of the research literature on HIV prevention outreach efforts concluded that most such programs have led to changes in drug-related and sex-related risk behaviors in injection drug users (238). Specific reductions in drug injection, sharing of injection equipment, and crack use and increases in needle disinfection, condom use, and entry into drug treatment were seen with such programs.

The most controversial component of HIV transmission prevention in the injection drug use population has been the use of needle and syringe exchange programs that make sterile equipment available to drug injectors. These programs have met strong political opposition in many countries, including the United States, and assessment of their effectiveness has been fraught with methodological difficulties. There are unsubstantiated concerns that exchange programs may at-

tract subjects who engage in the riskiest practices and that the number of needles or syringes in circulation may not be sufficient to ensure single-time use (239). Recent U.S. and international data make a strong argument for the benefits of needle exchange programs on reducing HIV transmission as well as other parenterally transmissible infections such as hepatitis B and C (240, 241). Nonetheless, since federal funds to date have been prohibited for use in needle exchange programs, they have had limited impact on lowering HIV transmission in the United States. Needle exchange programs that do exist are often small and cannot meet local demand.

#### ► **D. REDUCING MATERNAL-FETAL TRANSMISSION**

Before interventions with antiretroviral treatment were instituted, between 1,000 and 2,000 infants were born each year in the United States with HIV infection (242). Since recommendations were made for routine counseling and voluntary HIV testing of pregnant women, and for subsequent treatment with zidovudine for those who prove seropositive, the CDC has recorded dramatic decreases in perinatal transmission. From 1992 to 1997, cases of perinatal AIDS declined 67%, including an 80% decline in AIDS cases among infants and a 66% decline among children between the ages of 1 and 5 (243). It has been shown that elective cesarean delivery may further decrease the risk for fetal infection (244).

The protocol of administering zidovudine to a pregnant woman in the last two trimesters, followed by intravenous zidovudine during delivery, then 6 weeks of zidovudine treatment for newborns was found to reduce the incidence of HIV transmission from mother to child from 22.6% to 7.6%—a 66% reduction (245, 246). While the mechanism by which zidovudine reduces perinatal transmission is not known, research has shown that a risk factor for perinatal transmission is the amount of HIV in the pregnant woman's blood (247, 248). At the same time, the effect of zidovudine's lowering maternal HIV viral load does not fully explain the efficacy of zidovudine in reducing transmission. Another important component of protection may be preexposure prophylaxis of the fetus or infant to antiretroviral drugs. Because it has been shown to be metabolized into its active triphosphate form within the placenta, zidovudine may have distinct superiority in efficacy compared to other nucleoside analogues such as didanosine and zalcitabine (249).

There have been other studies of interventions to reduce perinatal transmission, such as short-course antenatal/intrapartum zidovudine in non-breast-feeding Thai women (250) or the combined agent lamivudine/zidovudine during gestation, intrapartum, and postpartum in African women (251). Both interventions were associated with reductions in perinatal transmission by approximately 50% (even though the group given lamivudine/zidovudine breast-fed). In the situation when the diagnosis of HIV infection is not made until near the end of gestation or during labor, treatment with the combined agent lamivudine/zidovudine or nevirapine in the intrapartum/postpartum period has been shown to be effective in reducing transmission (251, 252).

There are limited data on the effect of combination antiretroviral therapies on pregnancy outcome. A retrospective Swiss study reported that 80% of women experienced side effects to the drugs, which included reverse transcriptase inhibitors and protease inhibitors, and further, found a possible association with preterm birth (253).

Women who face decisions regarding the use of antiretroviral medications during pregnancy must consider the effects of treatment on their own health as well as on fetal or child health. These decisions are complex, since the standard of care has moved to multiple antiretroviral drugs, and yet the long-term consequences of exposure to such drugs by the infant are not known. In general, the three-stage zidovudine regimen (prenatal, intrapartum, and postpartum) alone or in combination with other antiretroviral agents should be discussed and offered to all HIV-infected pregnant women.

Antiretroviral protocols to prevent perinatal transmission are burdensome for patients and practitioners, and adherence is again a crucial factor in treatment effectiveness. A 1995 study

found that only 15% of HIV-positive mothers and their newborns received the full zidovudine treatment regimen (252). This same study found that 26% of pregnant women with HIV infection did not receive any prenatal care. Coordination of care by providers of medical, mental health, drug abuse, and social services may be required for the successful implementation of antiretroviral treatment during pregnancy.

## ► **E. POSTEXPOSURE PROPHYLAXIS**

While universal infection control precautions have become the standard of care in the U.S. health care system, as of June 1998, 54 health care workers had documented HIV infection through occupational exposure. Of the 54, 46 had percutaneous (puncture/cut injury) exposure, five had mucocutaneous (mucous membrane or skin) exposure, two had both percutaneous and mucocutaneous exposure, and one had an unknown exposure (82). The estimated risk of HIV infection in health care workers with percutaneous HIV exposure is approximately 0.3% (254).

Postexposure prophylaxis with antiretroviral agents has been shown to be safe and effective (82). The postexposure prophylaxis protocol outlines specific steps in assessing risk. First, the type of exposure—including type of material, contact surface type, volume, and severity of exposure—is determined. Next, the HIV status of the exposure source is assessed on the basis of factors such as probable viral titer (based on clinical HIV status of exposure source) and whether actual HIV status is known (it may be unknown). The exact postexposure prophylaxis recommendation—whether to intervene at all, use two agents (zidovudine and lamivudine), or use three (both of the above plus either indinavir or nelfinavir)—is based on these assessments. If done properly, postexposure prophylaxis can reduce the risk for occupational transmission of HIV infection in health care workers with known exposure, such as a needle stick injury involving blood or other body fluids, by 80% (255).

## ► **F. SPECIAL PSYCHIATRIC POPULATIONS**

### **1. Patients with substance use disorders**

HIV is spread both by sharing injection drug use equipment (most frequently practiced by opiate, cocaine, or methamphetamine users) and by engaging in unsafe sexual practices that are associated with substance use disorders. Documented sexual risk behaviors among those with substance use disorders include having multiple partners in the context of buying or selling sex for drugs or money to buy drugs; unprotected sex with injection drug users; and difficulty employing safer sex practices while intoxicated. These sexual encounters can also increase the risk of transmission of other sexually transmitted diseases that are cofactors for HIV transmission. Unfortunately, sexual risk behaviors are more resistant to change than drug-use risk behaviors in drug users (256).

Comorbidity of substance use disorders with other psychiatric disorders deserves mention. A study that used data from the 1992 National Survey of Veterans examined whether substance abuse or other mental disorders serve as risk factors for HIV infection. The investigators found that the combination of substance abuse and PTSD increased the rate of HIV infection by almost 12 times over that of those without either disorder (257).

Drug use disorders are associated with high rates of incarceration for drug-related crimes. Jails and prisons, in turn, bring people with elevated rates of HIV infection together in a confined space, increasing the chance that a sexual or injection drug use partner encountered in these settings will be infected with the virus (258, 259). Institutionalization in all-male settings also increases the likelihood of sex between men.

There are geographic differences in seroprevalence rates of HIV in injection drug use populations, with the highest rates in the United States occurring in the Northeast, on the East

Coast, and in Puerto Rico (3). Holding the risk behavior constant, the likelihood of acquiring HIV increases with its penetration into a given geographic area by increasing the chance that sexual and drug injection partners will be infected. Because substance use disorders are associated with decreased occupational functioning or disability, many of these individuals become impoverished and often cluster in urban neighborhoods that are endemic for HIV.

## **2. Patients with severe mental illness**

The severely and persistently mentally ill population is at risk for HIV infection due to factors analogous to those of patients with substance use disorders. There are high rates of substance use disorders among those with severe mental illness, and both populations share similar tendencies to reside in institutions or poor urban neighborhoods where cases of HIV infection are concentrated. Chronically mentally ill adults have been documented to have misunderstandings about AIDS transmission, to have histories of treatment for sexually transmitted diseases, and to report behaviors such as “survival sex” (in exchange for shelter, food, or money) (260). When compared to the general population, people with severe mental illness have higher rates of same-sex sexual activity and intimate contact with multiple partners (261). One study found an association of positive symptoms of psychosis and the diagnosis of schizophrenia with specific high-risk sexual behaviors (74).

Randomized, controlled trials of relatively brief AIDS prevention programs for the chronically mentally ill led to significant improvements in rates of unprotected intercourse and condom use (262) and knowledge about AIDS (263) in the intervention groups. It is not known whether such improvements persist beyond the short follow-up period.

## **3. Victims of sexual abuse/crimes**

A history of sexual abuse is highly prevalent among both women and men living with or at risk for HIV infection. One report of 408 mostly economically disadvantaged women (at least 18 years old) found a lifetime prevalence of sexual abuse of 43%; over one-half of the cases occurred during adulthood (264). A cohort of 327 homosexual or bisexual men had a 35.5% rate of childhood sexual abuse. Men with a history of childhood sexual abuse reported more lifetime male partners and a higher likelihood of unprotected receptive anal intercourse in the past 6 months (265). Women with a history of childhood sexual abuse have been found to have more sexual partners, heightened sexual activity, and more negative expectations of condom use (266). For example, a study of women in low-income housing developments found that those with a history of sexual coercion were likely to perceive that requesting a partner to use a condom would create a potentially violent situation (267).

In children, the occurrence of sexually transmitted diseases can be the first indication of sexual abuse. Although perinatal transmission of HIV accounts for the vast majority of HIV cases in children, HIV transmission has been reported to occur through childhood sexual abuse (268). Efforts to encourage active risk reduction in high-risk populations through AIDS education have found that adolescents who have been sexually abused are significantly less likely to use condoms and have much greater communication difficulties than their peers (269).

# **VI. DATA REGARDING PSYCHIATRIC TREATMENTS FOR INDIVIDUALS WITH HIV INFECTION**

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Psychiatric treatments for individuals with HIV infection follow the same principles as for any patient with a psychiatric diagnosis, but there are special considerations. As with other patients

with comorbid medical and psychiatric illnesses, it is essential to help patients cope with HIV illness and, when appropriate, with death and dying. There is also an ongoing need to determine whether new psychiatric symptoms have a medical basis that requires intervention. Examples of unique treatment issues with HIV patients include but are not limited to the following:

- working with the patient on disclosure of HIV status;
- assessing dangerousness from the perspective of HIV transmission and intervening to reduce that risk;
- helping families with dependent children arrange permanency planning;
- treating HIV-infected children who have developmental delays resulting from prenatal drug exposure or from HIV infection;
- negotiating disability status and, for some patients, a return to work;
- bereavement/loss; and
- treatment adherence.

## ▶ **A. ACCESS TO SERVICES**

Most patients are asymptomatic for many years after becoming infected. But once symptomatic with more advanced HIV disease, they may become high users of medical care, including mental health services (270). They may need frequent assessment and treatment visits, undergo many medical tests, require hospitalization, and take multiple medications (often as many as 10–15 different medications at different times of day). Many patients receive medical care from an HIV primary care or infectious disease clinic or from an infectious disease specialist in the community. A recent study reported better medical outcomes for patients with HIV infection who receive care from physicians with more experience treating HIV diseases (271).

The Ryan White CARE (Comprehensive AIDS Resources Emergency) Act was enacted in 1990 to help states, communities, and families provide care for people with HIV/AIDS who lack adequate health insurance or other resources. Since its inception, CARE Act grants have totaled \$6.4 billion and have served approximately 500,000 individuals with HIV/AIDS annually. Administered by the Health Resources and Services Administration of the U.S. Department of Health and Human Services, CARE Act grants were reauthorized in 1996 and comprise several programs. Title I grants provide funds to cities for low-income or under- or uninsured persons to cover the cost of health care and medications, as well as support services like counseling and home and hospice care. Title II grants are for the 50 states, the District of Columbia, Puerto Rico, and U.S. territories to improve the quality, accessibility, and organization of both health care and support for patients with HIV/AIDS. Title III grants are given to public or nonprofit entities that provide comprehensive primary health care services for persons with AIDS or at-risk populations. Title IV grants fund efforts to coordinate HIV services and access to research for children, youth, women, and families. An additional component of the CARE program includes training for health care professionals, grants for innovative service delivery models for special populations, and dental services.

Despite CARE Act funding, lack of access to care remains a problem that affects morbidity and mortality for certain groups. One study documented that among urban patients who receive medical care, there are no differences in HIV disease progression or survival associated with sex, race, injection drug use, or socioeconomic status. This suggests access to medical care is a main determinant of how quickly a patient develops AIDS (272). More recently, investigators from the HIV Cost and Services Utilization Study, a national population-based sample, found that African American, Hispanic, female, uninsured, and Medicaid-insured individuals all had inferior patterns of medical care (e.g., later initiation of antiretroviral medication) than did Caucasian and privately insured individuals (273).

Persons with HIV infection have higher rates of most psychiatric disorders than the general population. Psychiatric patients with common medical problems, especially those with severe mental illness, receive suboptimal medical care and suffer greater morbidity and mortality from medical illnesses than the general population. Studies are now under way to determine the access of patients with severe mental illness to HIV-related medical treatments; it can be assumed that these patients need help to access medical services.

Psychiatric disorders can be underdetected, misdiagnosed, undertreated, or treated improperly in primary care settings. For example, while a substantial majority of HIV-infected persons presenting for intake to an HIV primary care clinic suffered from depression, substance dependence, or another current psychiatric disorder, most cases were not detected by clinicians (66). Underscoring the importance of mental health care is the finding that ongoing high-risk sexual behavior is predicted by higher levels of depression and recreational drug use (274).

There are several patient barriers to meeting the mental health needs of HIV-infected persons. These barriers include adherence difficulties (e.g., missed appointments or inability to follow treatment recommendations); fear of additional stigmatization (the “double stigma” of HIV and a mental disorder); negative prior experiences with the mental health system; lack of funds for transportation, payment of care, or medications; unstable housing and frequent relocation; and the complex comorbid presentations of patients with HIV infection (e.g., depression complicated by concurrent substance dependence and a personality disorder). On the other hand, health care professionals should not assume that depression is “normal” in a person with HIV infection.

Some innovative HIV clinics integrate medical, mental health, and substance abuse treatment within their programs (275). These model programs increase the opportunities for prevention and treatment and may reach a more impaired population (276). One model uses an outpatient psychiatric consultation-liaison clinic that specializes in the treatment of HIV-infected patients. The clinic can be physically off-site from an HIV clinic but receives most of its referrals from that clinic. Other models include HIV programs within community mental health centers, programs located within residential substance abuse treatment facilities, free-standing community-based agencies, and referrals to private practitioners with expertise in treating HIV patients. All of these models appear to be effective (67).

## ▶ **B. PHARMACOLOGIC TREATMENT**

In general, the use of psychotropic agents in HIV patients follows similar principles for using these medications in such populations as geriatric patients or those with comorbid medical illnesses. This is particularly true for patients with more advanced HIV disease and those on complex antiretroviral regimens who may be more sensitive to medication dosages and side effects and are at higher risk for drug-drug interactions (277). Because some standard medications used to treat HIV infection or HIV-related conditions can potentially inhibit or induce the cytochrome P450 system, psychotropic medications that share metabolic pathways should be used judiciously; however, this concern should not preclude appropriate pharmacologic intervention.

General guidelines, particularly for patients with symptomatic HIV disease, include 1) using lower starting doses and slower titration, 2) providing the least complicated dosing schedules possible, 3) focusing on drug side effect profiles to avoid unnecessary adverse events (e.g., anticholinergic effects from tricyclic antidepressants, leukopenia from carbamazepine), and 4) maintaining awareness of drug metabolism/clearance pathways to minimize drug-drug interactions and possible end organ damage.

Published reports of adverse events and side effects can offer specific guidance for the use of some psychotropic agents in HIV-infected patients. However, clinicians must be cautioned that many studies that have examined psychotropic effectiveness in HIV patients were conducted on relatively asymptomatic patients, often did not include women or youth, and were conducted before the availability of combination antiretroviral therapy. Liver disease, in particular hepatitis C,

**TABLE 15. Cytochrome P450 Inhibition Potency of Protease Inhibitors, by Isoenzyme System**

Protease Inhibitor	Cytochrome P450 Isoenzyme Inhibited
Ritonavir	3A4, 2C9, 2D6
Indinavir	3A4
Nelfinavir	3A4, 2C19, 2D6
Saquinavir	3A4, 2C9

is becoming increasingly important as a comorbid condition. Thus, routine liver function testing is necessary when prescribing psychotropic medications for patients with HIV infection.

Combination therapy with multiple medication classes constitutes the standard of care for successful treatment of HIV infection. Although limited clinical information is available concerning drug-drug interactions involving psychotropic and antiretroviral medications, effective psychotropic medication management in the setting of HIV requires attention to possible interactions.

Potential drug-drug interactions in the setting of antiretroviral therapy include the effects of antiretroviral agents on psychotropic medications and vice versa. Protease inhibitors and nonnucleoside reverse transcriptase inhibitors are metabolized by the cytochrome P450 system and may inhibit or induce multiple isoenzymes. For example, the protease inhibitor ritonavir inhibits the cytochrome P450 isoenzymes 3A, 2D6, and 2C9/19; thus, most psychotropic medications may be affected when concomitantly used with ritonavir. Other protease inhibitors tend to only inhibit the cytochrome P450 isoenzyme 3A, thus limiting possible drug-drug interactions to psychotropic medications metabolized via this pathway (e.g., some benzodiazepines, citalopram, and nefazodone).

The nonnucleoside reverse transcriptase inhibitors also require careful attention. For example, nevirapine and efavirenz are metabolized via the cytochrome P450 isoenzymes 3A and 2B6 and induce cytochrome P450 activity, which could result in decreased psychotropic concentrations at standard doses (278). Delavirdine, another nonnucleoside reverse transcriptase inhibitor, inhibits the cytochrome P450 isoenzyme 3A and reduces hepatic clearance of psychotropic agents primarily metabolized by this pathway (279). The protease inhibitors and nonnucleoside reverse transcriptase inhibitors are among the most problematic of the antiretrovirals when coadministered with psychotropic medication. Table 15 indicates the relative rank order of inhibition potency of the currently available protease inhibitors.

For combination antiretroviral therapy that includes protease inhibitors and nonnucleoside reverse transcriptase inhibitors, an overarching concern in terms of coadministration with psychotropic agents is not only the possibility of plasma levels of psychotropic medications outside the targeted therapeutic concentration range but also the possible reduction of antiretroviral levels to the point of risking their effectiveness. While most interactions *inhibit* the cytochrome P450 system, some clinically important drug interactions also *induce* this system with medications used to treat co-occurring medical conditions in HIV disease (e.g., glucocorticoids, rifampin, phenytoin). Table 16 provides an overview of psychotropic agents and HIV therapies, routes of metabolic inhibition and induction, and potential clinical concerns.

Although the aforementioned risks for drug-drug interactions may seem substantial, to date, clinical data have not revealed severe side effects among most patients receiving antiretrovirals in conjunction with psychotropic medications (50). A few reports have documented the inhibitory effects of protease inhibitors. For example, when coadministered with ritonavir, desipramine levels have been shown to increase 145% *in vitro* (280) and to increase to some extent when coadministered with other protease inhibitors (281). In a clinical setting, coadministration of saquinavir and midazolam has caused prolonged sedation (282). These *in vitro* and *in vivo* data should lead to careful monitoring for potentially problematic or dangerous side effects in patients taking antiretrovirals.

**TABLE 16.** HIV-Related Medications and Psychotropic Agents Involving the Cytochrome P450 System

<b>Cytochrome P450 Isoenzyme</b>	<b>Common HIV-Related Medications That Inhibit Isoenzyme</b>	<b>Psychotropic Medications Primarily Metabolized by Isoenzyme</b>	<b>Possible Clinical Implications of Isoenzyme Inhibition</b>	<b>Common HIV-Related Medications That Induce Isoenzyme</b>	<b>Possible Clinical Implications of Isoenzyme Induction</b>
3A4	Protease inhibitors (especially ritonavir) Delavirdine Clarithromycin Erythromycin Itraconazole Ketoconazole Macrolide antibiotics	Benzodiazepines Buspirone Citalopram Carbamazepine Nefazodone Trazodone	Increased plasma levels and increased side effects; for benzodiazepines, sedation and decreased respiratory drive	Nevirapine Efavirenz Glucocorticoids Rifampin Rifabutin	Decreased plasma levels of psychotropic medications and decreased effectiveness
2D6	Protease inhibitors (especially ritonavir and nelfinavir)	Mirtazapine Fluoxetine Paroxetine Sertraline Fluvoxamine Tricyclic antidepressants Venlafaxine Neuroleptics, typical and atypical	Increased plasma levels and increased side effects; for tricyclic antidepressants, potential increased risk for cardiac conduction delay	None	

Drugs of abuse can also cause drug-drug interactions. MDMA, an amphetamine derivative also known as “ecstasy” that is primarily metabolized via the cytochrome P450 isoenzyme 2D6, reportedly led to a lethal overdose when taken by a patient being treated with ritonavir (283). Other drugs of abuse, particularly those metabolized via the cytochrome P450 isoenzymes 2D6 or 3A (e.g., amphetamines, ketamine, heroin, cocaine, and  $\gamma$ -hydroxybutyrate) may lead to toxic events when taken by patients being treated with protease inhibitors.

Although some drug-drug interactions may be only theoretical, it is prudent for clinicians to explain these concerns during the informed consent process of psychotropic prescribing. Because of the extent of comorbid substance abuse among some HIV patients, a general warning of the possible interactions of combining antiretroviral agents, psychotropic medications, and recreational drugs is often indicated. Web sites are available to clinicians and patients that address antiretroviral drug interactions and may be useful educational and reference tools ([www.aegis.com](http://www.aegis.com); [www.drug-interactions.com](http://www.drug-interactions.com); and [www.dml.georgetown.edu/depts/pharmacology/davetab.html](http://www.dml.georgetown.edu/depts/pharmacology/davetab.html)).

Psychiatrists should remember that HIV patients who have been clinically stable on regimens of maintenance psychotropic medications and who later initiate combination antiretroviral therapies may require adjustments or changes in their psychotropic regimen. The rational choice of psychotropic medications must also include critical considerations of adherence. Generally, it is important to minimize the number of drug doses and to tie dosing to times of the day with natural cues (e.g., meals, work schedule, bedtime). Outlined here are unique factors to consider in administering specific psychotropic agents to HIV patients, particularly those patients simultaneously receiving antiretroviral therapies.

## **1. Antidepressant agents**

The prevalence of mood disorders in HIV patients is higher than general population rates; evidence from effectiveness studies and clinical trials indicates that antidepressants are generally well tolerated by HIV patients, even those with symptomatic HIV infection or AIDS (284–290). Thus, antidepressants are commonly prescribed to HIV patients for the treatment of depression as well as for other HIV-related conditions, such as chronic pain (e.g., peripheral neuropathy) (291). However, clinicians must be cautioned that two factors may limit the generalizability of some antidepressant studies. First, many studies of antidepressants in HIV patients were conducted before the availability of combination antiretroviral therapy and thus did not take into account possible pharmacokinetic complications (292). Second, a minority of published psychopharmacology studies has included patients with advanced stages of HIV infection or AIDS. There is, to date, no evidence to suggest adverse effects of antidepressants on the immune system (293).

### **a) SSRIs**

Several studies have indicated that tricyclic antidepressants are less well tolerated than SSRIs (287, 294), leading some to recommend SSRIs over tricyclic antidepressants (277). One study found that despite efficacy for treating depression, fluvoxamine was poorly tolerated by HIV patients (295). Because similar metabolic pathways, particularly the cytochrome P450 isoenzyme 2D6, are utilized by SSRIs and ritonavir, the psychiatrist should maintain communication with other clinicians treating the patient. Although SSRIs are generally well tolerated across a broad range of blood levels, the untoward outcome of serotonin syndrome may be possible in some cases in which the cytochrome P450 isoenzyme 2D6 is inhibited (296). While the SSRIs themselves inhibit this isoenzyme, the potency of their inhibition is less than that of ritonavir. However, the potential impact of SSRI-related inhibition of the cytochrome P450 isoenzyme 2D6 should be remembered when coadministering SSRIs with other agents that are substrates of the cytochrome P450 2D6 isoenzyme.

### **b) Tricyclic antidepressants**

While tricyclic antidepressants are metabolized by other cytochromes, they rely principally on the cytochrome P450 isoenzyme 2D6 for clearance. Therefore if tricyclic antidepressants are coadministered with ritonavir, monitoring of ECG results and tricyclic antidepressant plasma levels is recommended because of the possibility of increased tricyclic antidepressant plasma levels from cytochrome P450 inhibition and associated tricyclic antidepressant side effects (e.g., delayed cardiac conduction, anticholinergic effects, orthostasis).

### **c) Other antidepressants**

Nefazodone and the protease inhibitors are both potent inhibitors of the cytochrome P450 isoenzyme 3A, and their combination may be problematic. Nefazodone administration may theoretically decrease the metabolism of some protease inhibitors, leading to increased protease inhibitor plasma levels and increased side effects. However, one study that examined the efficacy of nefazodone in HIV patients found that only one of 15 patients had a clinically significant drug interaction that was related to coadministration with ritonavir (288). Of general concern is the coadministration of nefazodone or protease inhibitors with the antipsychotic pimozide, which can cause cardiac arrhythmias at increased plasma levels (296). Other potentially dangerous interactions with inhibitors of the cytochrome P450 isoenzyme 3A include the coadministration of most benzodiazepines (respiratory depression), clozapine (seizures), ergot alkaloids (sustained systemic vasoconstriction), and sildenafil (priapism).

Venlafaxine has been reported to decrease the concentration of indinavir significantly even though a lack of such interaction was predicted based on each drug's pharmacokinetic parameters. At this time, venlafaxine should be avoided in those patients receiving indinavir, since decreases in concentration of protease inhibitors can affect treatment efficacy and increase the chances for viral resistance to develop (297).

Previously it was thought that bupropion was eliminated via the cytochrome P450 isoenzyme 2D6. However, recent data have shown that it is actually cleared via the 2B6 isoenzyme. Therefore, bupropion has been removed from the list of drugs contraindicated with ritonavir, and this is reflected in the revised product monograph.

No adverse events have been reported with the agents citalopram and mirtazapine. Citalopram has minimal inhibitory actions on the cytochrome system and may be particularly useful for patients taking multiple medications where drug-drug interactions are an ongoing concern. Mirtazapine, because of its sedating profile, may be particularly useful for depressed patients with insomnia. It may also be helpful for patients with poor appetite because of its tendency to increase appetite and also helpful for patients who may be prone to sexual dysfunction with other antidepressant agents.

## **2. Antipsychotic medications**

Generally, the use of antipsychotic medication among patients with advanced HIV infection is associated with an increased incidence of extrapyramidal side effects. High-potency standard neuroleptics (haloperidol is the most commonly used in published reports) can be associated with severe dystonia, rigidity, akathisia, and parkinsonism (31, 298–301). Low-potency standard neuroleptics can also result in severe extrapyramidal side effects but overall appear to be less problematic than high-potency neuroleptics (302–305).

A study that contrasts with the perspective that standard neuroleptics are associated with severe extrapyramidal side effects in advanced HIV infection was conducted in hospitalized patients with AIDS who were randomly assigned pharmacologic treatment for delirium; 13 received chlorpromazine, and 11 received haloperidol (46). The study stated that “no clinically significant medication-related side effects were noted.” However, patients were treated with very low doses of neuroleptic (i.e., average maintenance doses were 36 mg/day for chlorpromazine and 1.4 mg/day for haloperidol). The study is consistent with the rest of the literature in

stressing the importance of treating patients with advanced HIV infection with the lowest possible effective dose when using a typical neuroleptic.

Neuroleptic malignant syndrome has been noted with standard neuroleptics in five reports. In one case, neuroleptic malignant syndrome occurred within 24 hours; in the four other cases, neuroleptic malignant syndrome occurred within days of initiating treatment (300, 306–309). All patients recovered with usual management. Onset of tardive dyskinesia has been reported within a period as short as 6 weeks or within months (31, 310, 311). Confusion has also been reported with standard neuroleptics (312).

Most patients with extrapyramidal side effects respond to typical treatments, but one case report of a patient with parkinsonian side effects noted a slow response (299). Another patient had no response to multiple antiparkinsonian agents (313). Scurlock et al. (298) reported an AIDS patient who developed a grand mal seizure while taking chlorpromazine, and Jones et al. (314) reported a grand mal seizure in one man with symptomatic HIV infection who was taking amitriptyline and chlorpromazine.

Atypical antipsychotic agents appear to be better tolerated with fewer serious side effects, as evidenced by two case series of 30 combined patients who received risperidone (310, 315), one report of four patients who received remoxipride (298), and another of four patients who received molindone (312). Some of these patients had previously experienced severe side effects while taking typical neuroleptics. All were able to tolerate the atypical agents, and most but not all patients had a good therapeutic response. The most common side effects seen with risperidone were drowsiness and drooling (315). Extensive clinical experience suggests that olanzapine is also well tolerated for the treatment of psychosis, delirium, and behavioral disturbances among HIV patients.

It is of interest that movement disorders, including dystonia and parkinsonism, have been reported in advanced HIV infection without exposure to neuroleptics (316, 317). In the one case report of irreversible extrapyramidal side effects in a man with HIV-associated dementia following exposure to standard neuroleptics, an autopsy revealed numerous microscopic changes, including neuronal loss in the basal ganglia (313). It may be that damage to the basal ganglia is a factor that increases the susceptibility of HIV patients to extrapyramidal side effects after neuroleptic administration (318). A similar pattern of extrapyramidal side effect susceptibility in concert with neuronal damage has been described in the elderly (311, 319).

For all antipsychotic agents, the possibility of drug-drug interactions must be considered for those patients also taking antiretroviral medication. Antipsychotic dosage adjustments may be required to minimize side effects such as extrapyramidal side effects. Because of the rare dose-related side effect of agranulocytosis among patients taking clozapine, this particular agent should be monitored closely if given to any HIV patient (320). Likewise, clinicians should monitor for risk of seizures if clozapine is administered with ritonavir, since ritonavir inhibits the cytochrome P450 isoenzyme 2D6, clozapine's primary metabolic pathway. Pimozide should also be used cautiously in combination with any inhibitor of the cytochrome P450 isoenzyme 3A because of risk of fatal arrhythmias at elevated doses. Depot antipsychotic medication should be avoided in advanced HIV disease.

### **3. Psychostimulants**

Psychostimulants, such as methylphenidate and dextroamphetamine, are frequently used in HIV patients with neurocognitive impairment, fatigue, and, to a lesser extent, in some patients with depression (321, 322). These drugs are generally safe and well tolerated with no drug-drug interactions reported to date among HIV patients. The possibility of dopamine agonism inducing psychosis should be considered in vulnerable patients, such as those with a history of HIV-related CNS complications or a history of psychosis. Psychostimulants should be avoided or used judiciously among patients with a past or current history of amphetamine abuse.

## **4. Mood stabilizers**

### **a) Valproate**

Use of valproate in patients with bipolar disorder is not uncommon, particularly among HIV patients who develop mania secondary to HIV-related complications or psychoactive substance use. Concerns have been raised about the potential for valproate to possibly accelerate disease progression in HIV-positive patients. This concern is based on the fact that valproate has been shown *in vitro* to lower glutathione levels, which leads to activation of HIV replication (323). However, a retrospective review by Maggi and Halman (324) of 11 patients with HIV infection who were also treated with valproate found no evidence of increased viral load in those receiving adequate antiretroviral therapy.

The metabolic pathways of valproate are not fully delineated, but this agent has been associated with hepatotoxicity. There is a case report of valproic acid–induced hepatotoxicity when valproate was used together with ritonavir and nevirapine (325). Valproate inhibits glucuronyl transferase. Zidovudine uses glucuronyl transferase as its primary pathway of metabolic clearance. Therefore, increased plasma levels of zidovudine and associated side effects could result when the two agents are combined.

Generally, divalproex sodium is better tolerated than valproic acid, since it produces fewer gastrointestinal side effects and can be dosed less frequently (two or three times a day rather than four), particularly among HIV patients who may have preexisting gastrointestinal illness. Increased side effects may be caused by increased concentrations of free valproate in HIV patients because of factors such as the reduction of plasma protein levels, the increased percentage of free drug due to chronic illness, or drug-drug interactions that may decrease protein binding of valproate (326).

### **b) Lithium carbonate**

Lithium is commonly used in HIV patients with primary bipolar disorder. Because it does not require hepatic metabolism, it is a rational choice for many patients taking antiretroviral agents who require extensive hepatic metabolism. Lithium should be used with great caution in patients who develop HIV-related nephropathy, a generally irreversible complication that can lead to decreased lithium clearance and possible lithium toxicity. When given at doses necessary to maintain serum lithium concentrations between 0.5 and 1.5 meq/liter, lithium has been associated with signs of toxicity in some HIV patients, even among patients without renal disease (327). Thus, clinical experience suggests that lithium is best avoided in patients with probable AIDS mania or advanced HIV disease due to risk of toxicity.

### **c) Carbamazepine**

Although not absolutely contraindicated, carbamazepine is used less commonly in HIV patients because of its potential to cause bone marrow complications (e.g., leukopenia or aplastic anemia). This risk should be avoided in immunocompromised patients. Carbamazepine, like other anticonvulsants, phenobarbital, and phenytoin, is known to induce activity of the cytochrome P450 isoenzyme 3A. This induction can accelerate antiretroviral drug metabolism and possibly cause decreased plasma levels and diminished efficacy. It is recommended that carbamazepine concentrations be closely monitored.

### **d) Newer anticonvulsants**

Lamotrigine, gabapentin, and topiramate are newer anticonvulsants that have recently been used off-label to treat selected populations of patients with bipolar disorder, typically those with rapid cycling, mixed mood states, or bipolar depression. While no data currently support their use for mood disorders in HIV patients, gabapentin may offer some advantages over other anticonvulsants because it is neither protein bound nor metabolized by the liver. Gabapentin

is thus less likely than other anticonvulsants to lead to drug-drug interactions. Gabapentin has been successfully used in HIV patients to treat peripheral neuropathy, which can be both a complication of HIV disease and a side effect of some antiretroviral agents.

## **5. Anxiolytic and sedative-hypnotic medications**

### **a) Buspirone**

Buspirone is commonly used and generally well tolerated in HIV patients as a treatment for generalized anxiety disorder (328). There are no reports of HIV-related drug-drug interactions with buspirone. However, one case report describes induction of manic psychosis following a single dose of buspirone in a patient with asymptomatic HIV illness (329).

### **b) Benzodiazepines**

Benzodiazepines are commonly used in HIV patients and are best used for short periods to minimize the risk of tolerance or addiction and to maximize effectiveness. This class of drugs is generally best avoided in patients with alcoholism and those with a history of substance abuse. Benzodiazepines are metabolized primarily by the cytochrome P450 isoenzyme 3A; however, oxazepam, lorazepam, and temazepam are metabolized by direct conjugation via glucuronyl transferase, resulting in shorter elimination half-lives and less likelihood of metabolite accumulation and associated side effects.

When some benzodiazepines are coadministered with inhibitors of the cytochrome P450 isoenzyme 3A (such as protease inhibitors), one would expect a decrease in benzodiazepine clearance with increased sedation, potentially resulting in respiratory depression. Even saquinavir's relatively low-potency inhibition of the cytochrome P450 isoenzyme 3A has been shown to prolong the sedative effect of midazolam (282). Although one study that examined the chronic effect of ritonavir administration on alprazolam metabolism reported a 10%–15% decrease in expected alprazolam levels (330), a more recent study found that short-term, low-dose ritonavir administration significantly impaired alprazolam clearance (331). These studies call attention to the need for judicious use of alprazolam in combination with ritonavir.

An additional consideration when using benzodiazepines that are metabolized by glucuronidation (e.g., oxazepam, lorazepam, temazepam) involves ritonavir's inductive effect on glucuronyl transferase activity (332). The concentration of glucuronyl transferase substrates may be decreased when these agents are coadministered with ritonavir. Therefore in some cases, patients taking one of these three benzodiazepines may require higher doses for symptom control. Benzodiazepine-dependent patients may also require higher doses to avoid the onset of withdrawal (296).

## **6. Medications for HIV-related wasting**

Some patients with wasting syndrome can be helped by medications that serve as appetite stimulants to combat loss of appetite and associated weight loss. Four agents currently have been approved by the Food and Drug Administration (FDA). Two of these agents, dronabinol and oxandrolone, are Schedule II controlled substances. Because these agents have unique psychiatric side effect profiles, they should be monitored closely among patients who receive psychiatric care.

Dronabinol is a cannabinoid indicated for HIV-associated anorexia and nausea. It is a major active metabolite in marijuana and, like marijuana, has complex effects on the CNS, including sympathomimetic activity. Oxandrolone is an anabolic steroid synthetically derived from testosterone that is used for weight gain and promotion of lean body mass (333–335). Its side effect profile is similar to that of other anabolic steroids, including mood effects. Another agent, megestrol acetate, is a synthetic derivative of progesterone that increases fat rather than muscle gain. It also lowers testosterone and may produce side effects (e.g., mood disturbances) similar to those associated with glucocorticoids. Somatotropin is an injectable form of recombinant human growth hormone indicated for the treatment of AIDS wasting and cachexia (336–340). It

is an anabolic and anticatabolic treatment that combats the loss of lean body mass and is generally well tolerated by patients. The effects of somatotropin are often lost when it is discontinued.

These medications can be extremely beneficial for patients with significant anorexia, weight loss, and nausea. However, because they are usually used in more advanced stages of HIV disease, when patients are more medically frail and receiving multiple other medications, psychiatrists should actively monitor response, side effects, and drug interactions. Limited data do not indicate a high incidence of psychiatric side effects.

Thalidomide, a potent teratogen once marketed as a sedative and morning sickness agent in the 1950s and 1960s, is currently available on a restricted basis for HIV patients for the treatment of wasting syndrome (341, 342). The agent is FDA-approved as an immunomodulatory drug for the treatment of severe HIV-related oral ulcers. Prescribing physicians must register under a special restricted distribution program with the FDA. Primary psychiatric side effects include CNS depression; few data are available concerning drug-drug interactions, although thalidomide does not appear to be metabolized by the liver to any large extent.

## **7. Testosterone**

A number of clinical trials have found testosterone to be effective in the treatment of a number of HIV-related symptoms (e.g., fatigue, wasting, impaired sexual functioning, and mild depression) often associated with more advanced HIV disease (126, 343, 344). Although typically used to treat hypogonadism in the general population, clinical response to testosterone in HIV patients is not correlated with serum testosterone levels at baseline. HIV-infected men with normal levels of testosterone respond as well as those with lower than normal levels (126). The most common psychiatric side effects of testosterone are changes in mood and irritability.

## **8. Opiate analgesics**

Many HIV patients are treated with opiate analgesics for both acute pain syndromes, such as that associated with *Candida* esophagitis, as well as chronic pain conditions (e.g., neuropathic and myopathic pain syndromes). Chronic pain is also common in advanced HIV disease, particularly among cachectic patients with wasting syndrome. Because opioids are metabolized primarily via the cytochrome P450 isoenzymes 2D6 and 3A, they should be used cautiously in conjunction with antiretroviral agents that are likely to increase their plasma levels.

Some opioids, such as codeine and hydrocodone (as well as the nonopiate tramadol), must be converted into active metabolites to produce analgesic effects. This conversion can be blocked by cytochrome P450 inhibitors, which results in reduced pain control in addition to adverse reactions from the buildup of unmetabolized drug (345). Oxycodone and morphine, which are primarily glucuronyl transferase substrates, are alternatives for pain control. However, in the presence of a glucuronyl transferase inducer such as ritonavir, their analgesic effect can be diminished as well (296, 332). As HIV disease progresses, the provision of safe, effective pain control requires clear understanding of the above factors.

## **9. Drugs used in the treatment of substance use disorders**

### **a) Opioid dependence**

There is limited information available on the extent and clinical implications of drug interactions in HIV-positive patients with comorbid substance use disorders. However, several studies have been published. Methadone has been shown to significantly increase zidovudine levels, but zidovudine has not been shown to affect methadone levels (346–348). Interim results from a study of the interaction of zidovudine with LAAM, buprenorphine, or naltrexone indicate that LAAM does not affect zidovudine levels, whereas buprenorphine may decrease levels non-significantly (349). Another report indicates that abacavir, a newer nucleoside analogue reverse transcriptase inhibitor, increases methadone clearance, although the proposed mechanism re-

mains unclear (350). Preclinical studies of the coadministration of protease inhibitors and methadone revealed that ritonavir causes a twofold increase in the area under the curve for methadone level and that indinavir causes a 30% increase, compared to no increase with saquinavir (351). One case report has indicated that nelfinavir may induce cytochrome P450 enzymes leading to decreased methadone levels (352). Nevirapine and efavirenz induce cytochrome P450 enzymes important to methadone metabolism and are reported to precipitate opiate withdrawal symptoms in methadone maintenance patients (278, 353). The consequences of undetected drug interactions among opioid-dependent patients are complicated and include nonadherence with treatment regimens, the potential development of resistant HIV strains, increased illicit drug abuse, drug toxicity, and loss of efficacy. In administering methadone to HIV patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors, clinicians should adjust doses to compensate for cytochrome P450 enzyme effects.

#### **b) Alcohol dependence**

There is no clinical information regarding the use of disulfiram in patients with HIV infection. Psychiatrists should therefore follow general guidelines for the use of disulfiram cautiously. Naltrexone, an opioid antagonist, is indicated in the treatment of alcohol dependence and for the blockage of the effects of exogenously administered opioids. Because naltrexone can cause hepatocellular damage when given in excessive doses, it should be used cautiously in patients with liver disease. It should also be noted that naltrexone's opioid antagonism might block the clinical effects of some commonly used medications in HIV patients that contain opioids (e.g., antidiarrheal medications, cough and cold preparations).

### **10. Alternative/complementary agents**

Patients with HIV infection may use a wide range of alternative/complementary agents for preventive and symptomatic treatment of HIV-related complications. Of particular interest to psychiatrists are those agents used to treat psychiatric symptoms. For example, patients may take *Hypericum perforatum* (St. John's wort) or the nutritional supplement S-adenosylmethionine (or SAM-e) to treat depression, kava kava for anxiety, melatonin or valerian root for insomnia, and ginkgo biloba for memory problems. One published report found that St. John's wort, which contains an inducer of the cytochrome P450 isoenzyme 3A, dramatically lowered levels of indinavir (and presumably other substrates of the cytochrome P450 isoenzyme 3A) (354). The FDA thus issued a public health advisory that concomitant use of St. John's wort with protease inhibitors and nonnucleoside reverse transcriptase inhibitors is not recommended. There are no data regarding other alternative/complementary agents at this time.

## **▶ C. PSYCHOSOCIAL TREATMENT**

Since the beginning of the AIDS epidemic, psychosocial support has emerged as a cornerstone of the comprehensive treatment for many persons infected and affected by HIV/AIDS. For many HIV patients, psychotherapy and psychosocial interventions have been invaluable in the search for meaning during the course of living with HIV (355). Psychotherapy can be an important intervention to address conditions that may interfere with a patient's acceptance of HIV illness or their ability to work cooperatively with their health care team. With the advent of new antiretroviral treatments, new psychotherapy themes have emerged, including changes in role definitions and life trajectory as well as treatment adherence challenges (356–358).

For patients who are socially disenfranchised, psychosocial treatments may consist of basic services that assist them in gaining access to food, shelter, transportation, and child care—essential elements of a care plan that diminish health care delivery barriers and promote mental health care utilization.

Generally, psychosocial treatments are those treatments, often offered in the community, that provide direct assistance along such parameters as social adjustment, social support, coping, and overall adjustment to HIV infection. Psychosocial interventions often occur in group formats, such as informal support groups, although more formal groups may tailor their membership (i.e., women, men, mothers, caregivers) or their mission (HIV risk reduction, treatment adherence) (359, 360). Other formats include peer counseling, a supportive intervention typically offered by HIV-positive consumers based in community AIDS service organizations.

Other psychosocial treatments have been developed that incorporate a service model (e.g., psychosocial rehabilitation programs for persons with HIV/AIDS, day treatment programs for HIV-positive persons with neurocognitive impairment) or a service theme (e.g., permanency planning for parents with advanced AIDS, HIV prevention, case management, disclosure of HIV status) (67, 79, 355, 361).

Researchers have described a wide range of psychological and psychosocial sequelae from HIV/AIDS (251). In their review of empirical findings, Kalichman and Sikkema (362) showed that psychological complications include distress, anger, guilt, bereavement, and the full spectrum of psychiatric disorders. Syndromes such as depression may appear, subside, and recur during the course of living with HIV/AIDS. Moreover, certain psychosocial conditions, such as increased social support and fewer incidents of HIV-related discrimination, have been shown to predict greater life satisfaction among HIV patients (143).

Psychosocial treatment of HIV-related complications will often involve referral of patients to community AIDS service organizations that specialize in the provision of psychosocial support. While many of the treatment issues are also themes that will emerge in psychotherapy (i.e., stigma, coping strategies, or disclosure of HIV status), support groups and other interventions provide a model for structuring social support over the course of living with HIV infection (362). Psychosocial services may take on added importance for patients living in rural regions, in which more community HIV-related stigma has been documented (143).

Psychosocial interventions have been shown to enhance adaptive coping strategies, social support, perceived sense of meaning and purpose, and self-esteem and also have been shown to lower anxiety and HIV risk behaviors among HIV-positive adults (359, 363–365). Because of the spectrum of social, psychological, and neuropsychiatric consequences of HIV/AIDS, psychiatric treatment should consider the relevance for a given individual of a wide variety of potential psychosocial interventions, spanning the spectrum from individual to family or group psychotherapy as well as psychodynamic/psychoanalytic, interpersonal, behavioral, or supportive approaches.

#### ► **D. LEGAL AND ETHICAL ISSUES**

Psychiatrists caring for HIV-infected patients can be faced with complex legal and ethical issues, some of which are unique to HIV infection. The AIDS Litigation Project conducted a national review of cases that involved individuals with HIV/AIDS in the federal and state courts in the United States between 1991 and 1997. The review identified important subsets of litigation, which included issues of “testing and reporting; privacy, the duty to warn, and the right to know; physician standards of care in prevention and treatment; and discrimination and access to health care” (366).

Most U.S. states have legal requirements surrounding HIV testing that require written informed consent and a minimum amount of pre- and posttest counseling—both to those who test positive and to those who test negative. Furthermore, many states are required to report positive HIV test results to public health agencies. Some states mandate that the report include the name of the individual who tested HIV positive. All states have mandatory name reporting when a patient is diagnosed with an AIDS-defining condition.

For those infected with HIV, confidentiality of HIV status is often paramount, especially for patients who are asymptomatic or who are concerned about possible discrimination by their em-

ployers or by insurance companies. Psychiatrists are typically attuned to confidentiality issues and regard patient-doctor confidentiality as fundamental to effective treatment. Yet, there are limits to confidentiality, such as when there is potential for others to be harmed, and these limitations should be discussed with patients when treatment is initiated.

For persons infected with HIV, particularly those recently diagnosed, their recent sexual partners and/or those with whom they share injection equipment should be informed of their potential exposure to HIV. These partners can benefit from HIV counseling and testing and knowing their HIV infection status. Many health departments offer services known either as “partner notification” or prevention counseling and referral services (367–369).

Another important issue involves the dangerousness of HIV patients. A patient with HIV infection is not a danger to others in the absence of imminent threats to harm others. In general, there are no legal requirements for physicians to inform partners of HIV-infected patients of their HIV status, especially if the patient agrees to notify their partner or if they are clearly practicing “safer sex.” However, because HIV-infected patients are able to transmit the virus and potentially put others in danger of infection, psychiatrists who care for HIV patients have an ethical requirement to counsel their patients about modes of HIV transmission and promote safer behavior, such as the consistent use of condoms and/or the use of clean needles. Psychiatrists can offer to assist patients in notifying individuals at risk or help refer a patient to public health officials for partner notification, if necessary.

On the other hand, if a patient has not disclosed their HIV-positive status to a partner and continues high-risk behavior, psychiatrists may have a duty to warn identifiable sexual partners or other at-risk individuals. APA policy reads that, “If a patient refuses to change behavior that places others at risk for HIV infection or to inform individuals at ongoing risk, or if the psychiatrist has good reason to believe that the patient has failed to or is unable to cease such behaviors or to inform those at risk, it is ethically permissible for the psychiatrist to notify identifiable individuals at risk or to arrange for public health authorities to do so” (370). Psychiatrists need to be mindful that while it may be *ethically* permissible to notify, it may not be *legally* permissible, and therefore psychiatrists should obtain legal advice before breaching confidentiality.

For patients who are impulsive or psychotic, protective measures such as voluntary or involuntary psychiatric hospitalization are options for treatment of psychiatric disorders and protection of others. For antisocial individuals, hospitalization should not be used merely as a means of social control.

During the course of HIV illness, and especially after the onset of AIDS, patients may experience cognitive impairment or symptoms of dementia. Such disturbances may affect a patient’s ability to give informed consent to accept or refuse treatment. When psychiatrists are asked to conduct competency evaluations for patients with HIV/AIDS, a comprehensive mental status examination that includes an evaluation of cognition is critical, followed—if indicated—by formal neuropsychological testing and assessment of specific treatment decision-making capacity.

The opposite of a patient’s refusal of treatment is the refusal on the part of physicians to provide HIV treatment to psychiatric patients. Because antiretroviral therapies involve complex medication regimens and adherence to treatment is critical, physicians may be biased against prescribing these treatments to patients with a comorbid mental illness such as a substance use disorder. While refusal of treatment due to poor adherence is appropriate, refusal of treatment solely on the grounds of a mental illness is not. When the psychiatrist is a consultant who does not intervene directly in the care of the patient, he or she will need to work with the primary clinician to help ensure that appropriate psychiatric treatment is received (371).

## ► **E. ADHERENCE TO TREATMENT**

Potent antiretroviral treatment has given hope to patients infected with HIV yet simultaneously has increased the complexities of managing HIV illness (372). For instance, the combination

of three or more medications used in most antiretroviral treatment regimens makes adherence difficult. In addition, some medications must be taken with food, others without food; dosing is usually twice a day but sometimes can be more frequent. Side effects can be significant, requiring discontinuation or the initiation of a new combination of medications. Because antiretroviral treatment should begin as an aggressive broad attack on HIV replication, doses of the drugs are generally not titrated upward but rather are initiated at the full dose. Thus, patients may experience many initiation side effects.

Adherence to antiretroviral therapy regimens is critical, as evidenced by a study that measured adherence by using a microelectronic monitoring system (95). The authors found that 95% adherence to treatment was associated with complete viral suppression but that failure rates increased sharply with less than 95% adherence. Researchers have documented that patients who receive potent antiretroviral treatment but who are not enrolled in clinical trials show viral suppression rates one-half those of study patients, which suggests the real-world difficulty of maintaining strict adherence (373).

Adherence to any kind of medical treatment is a well-established problem. Overall adherence rates vary from 20% to 80% and average 50% (374). Psychiatrists should make every effort to treat and control psychiatric disorders that affect a patient's ability to maintain close adherence to an HIV treatment regimen. Each year, about 7% of patients with AIDS develop HIV-associated dementia (375). This condition can interfere with ability to follow and understand treatment regimens. In addition, researchers have found that depression can be a cause of nonadherence and that treatment of depression might thus improve medical outcomes (96). Strategies that have proven useful in improving adherence for both psychotropic and antiretroviral medication have been reported and are summarized below (376).

### **1. Institutional factors**

How a health care system is structured will strongly influence whether clinicians and patients can collaborate and enhance adherence. One important element is a respectful and culturally sensitive environment. The availability and continuity of clinicians over time with 24-hour/day phone coverage to handle crises that might disrupt a regimen (severe side effects, loss of medication), as well as clinician caseloads that permit time for adequate discussion with patients, all promote adherence. Hospitals do not always dispense medications on the 8- or 12-hour schedules required for antiretroviral dosing. Last, social service mechanisms such as case management for handling financial and logistical barriers to obtaining and following the regimens provide crucial support.

### **2. Physician factors**

When initiating antiretroviral treatment, it is essential for the physician to prepare the patient. Because the best chance at viral suppression occurs with the first regimen, it makes sense to wait until the patient is ready. For a psychiatrist, it is important to treat or recommend treatment for comorbid alcohol/substance use disorders, depression, psychotic illnesses, or personality disorders that are likely to interfere with adherence (377). At the same time, if the patient is motivated to begin antiretroviral treatment, this can be a good opportunity to introduce psychiatric or substance use treatment if indicated.

### **3. Clinical strategies**

Multiple approaches to enhancing adherence are often needed (Table 17). For longer-term adherence, individual medication management, in which a staff member provides assessment and problem-solving support, may improve adherence (378).

**TABLE 17. Interventions to Increase Patient Adherence to Antiretroviral Regimens**

**Prepare patients**

- Discuss use of medications before prescribing
- Outline pros and cons of therapy
- Acknowledge commitment required, consequences of noncompliance, and benefits of therapy

**Provide written instructions**

- Inform patients of expectations, including side effects
- Provide information on who patients should call if significant side effects occur
- Schedule a follow-up appointment soon after initiating therapy

**Review importance of therapy**

- Inform patients that they must continue to take all medications
- Review the effects of stopping one medication
- Outline procedure for obtaining refills

**Recognize patient lifestyle and preferences**

- Twice-daily dosing benefits may outweigh initial side effects; ritonavir may be preferred
- Consider whether patients prefer tolerability over convenience; nelfinavir or indinavir may be preferred
- Discuss midday dosing
- Recommend medication timers or calendar
- Help patients plan for away-from-home dosing
- Simplify regimens
- If possible, prioritize or eliminate medications when patients are overwhelmed

**Look for and address nonadherence**

- Consider regimens that minimize cross-resistance
- Use regimens that leave options for future effective antiretroviral therapy
- Inquire about adherence
- Inquire about medication-taking behavior at each visit
- Anticipate relapses in adherence, even after long-term use of medication

► **F. SPECIFIC SYNDROMES**

There are numerous psychiatric difficulties that can occur in the context of HIV infection, yet studies of the treatment of HIV-related psychiatric disorders are limited. This section summarizes the existing scientific literature on the treatment of specific psychiatric disorders for patients with concurrent HIV/AIDS.

**1. Dementia and the spectrum of cognitive disorders**

Most research studies on the treatment of cognitive disorders associated with HIV infection have focused on HIV-associated dementia. Fewer studies have looked at the benefits of intervention at earlier stages of cognitive decline despite the possibilities for treating disorders, such as minor cognitive motor disorder, that involve neuronal cell dysfunction rather than cell death. Treatment of neuropsychological impairment without clinical disorder has been studied to some extent, and protection against neuropsychological impairment has been studied least.

Pharmacologic treatment strategies for cognitive disorders can be divided into four types: 1) antiretroviral therapies, 2) therapies aimed at immunological measures or inflammatory mediators, 3) therapies aimed at bolstering the response of the brain to the onslaught of the infection (e.g., neurotransmitter manipulation), and 4) nutritional therapies. Most controlled studies have investigated the efficacy of antiretroviral therapies, and while these studies have advanced our knowledge about interventions for cognitive disorders, several key factors must

be kept in mind. First is the fact that most published studies to date report on the treatment strategy of administering a single antiretroviral agent. Their findings are therefore difficult to interpret in light of the multidrug regimens that are now the standard of care in developed countries. Second, the reports vary widely with regard to the study population, since some studies enrolled subjects on the basis of established criteria for HIV-associated dementia or minor cognitive motor disorder but other studies enrolled cognitively impaired subjects without specifying whether they also met criteria for a clinical disorder. Third, the range of HIV clinical severity also varied widely in study subjects.

Whether antiretroviral agents penetrate the blood-brain barrier sufficiently to adequately suppress viral replication is a key issue that requires further study (379, 380). We know that near-perfect adherence to antiretroviral therapy is required to maintain plasma viral load at undetectable levels. Even in the best-case scenario, if decreased plasma viral load is achieved and levels of antiretroviral agents in CSF or brain tissue are optimized, it is not yet known whether complete suppression of replication in the CNS can be achieved (381). Another theoretical concern is that if antiretroviral resistance develops in the CNS, it is possible that resistant HIV could then reseed the peripheral circulation. This mechanism could potentially lead to increased prevalence of neurocognitive disorders as well as systemic progression of HIV disease.

#### **a) Zidovudine treatment of cognitive disorders or dysfunction**

Two randomized, placebo-controlled clinical trials have provided evidence for the effectiveness of zidovudine in reducing neuropsychological impairment for patients with HIV infection. Sidtis and colleagues (382) treated a group of 40 homosexual men (early-stage dementia and mean CD4 cell counts of 500 cells/mm<sup>3</sup>) with 1000 or 2000 mg/day of zidovudine or placebo. They found that both treatment groups demonstrated significant combined mean neuropsychological z score improvements when compared to the placebo group. In another randomized, placebo-controlled clinical trial, Schmitt and colleagues (383) used zidovudine to treat 281 subjects who did not necessarily have clear-cut signs of neuropsychological impairment or cognitive disorder but were stratified into two groups, AIDS or early asymptomatic HIV infection, on the basis of CD4 cell count. Significant improvements were found in attention, memory, visual-motor, and simple motor function at 4 months in both groups, which led to premature discontinuation of the study.

An open study of zidovudine in injection drug users found improvements in neuropsychological functioning on a number of subtests (384). Four case control studies retrospectively examined whether zidovudine treatment was associated with outcomes such as reduced leukoencephalopathy (385, 386), lower CSF  $\beta_2$ -microglobulin levels (which are related to neuropsychological improvement) (387), or improved neuropsychological measures (388). Three of the four studies found that the zidovudine-treated patients had significantly positive findings compared to untreated patients.

While the above studies support the efficacy of zidovudine, they do not resolve the issue of optimal dosage nor zidovudine resistance (380). Doses of up to 2000 mg/day of zidovudine were used in some of the above studies, which are often associated with significant toxicity, including neutropenia and anemia. A typical zidovudine dose used now is 500–600 mg/day, and many patients cannot tolerate even these reduced doses (375). Patients can develop resistance to zidovudine, especially if used alone, and because zidovudine-resistant strains can be transmitted from one person to another, some HIV experts have considered the need for testing for zidovudine resistance before choosing which agents to use in treatment (389).

#### **b) Other antiretroviral treatments of cognitive disorders or dysfunction**

Treatment studies of antiretroviral agents other than zidovudine are fewer but illuminating. De Ronchi and colleagues (390) conducted a clinical trial (N=88) that compared zidovudine to didanosine to refusal of therapy in both symptomatic and asymptomatic HIV patients. They

found that for subjects who were *symptomatic* for HIV disease, both zidovudine and didanosine treatment resulted in better performance on all neuropsychological subtests. In general, *asymptomatic* subjects did not show significant differences in neuropsychological performance compared to the untreated group. The findings suggest differences in effectiveness based on HIV clinical status.

A more recent placebo-controlled study involved the use of abacavir, a nucleoside analogue reverse transcriptase inhibitor with good CSF penetration, in 99 subjects with moderate to severe HIV-associated dementia (391). This study did not demonstrate significant differences in neuropsychological scores between abacavir and placebo groups, but a major limiting factor in this study design was that abacavir alone was added to an already failing antiretroviral treatment regimen.

Of currently available antiretroviral agents, the CSF penetration of stavudine is relatively high (0.4 ratio with serum), but a recent study indicated that stavudine nevertheless penetrates brain tissue poorly (392). The individual protease inhibitors have not been well studied for effects on neurocognitive impairment, and all but indinavir (0.16 ratio with serum) penetrate the CSF poorly (393). Regarding the nonnucleoside reverse transcriptase inhibitors, nevirapine has been shown to have a 0.45 CSF-to-serum ratio and therefore may be a good candidate to include in future controlled studies of HIV-associated cognitive disorders (381).

Ferrando and colleagues (394) studied the effects of various combination antiretroviral therapy regimens on measures of cognitive motor function. They found that tests of attention, concentration, psychomotor speed, learning, and memory were significantly better in those subjects taking antiretroviral therapy than in those who were untreated. Furthermore, they found that those without neuropsychological impairment had lower mean viral load levels, which suggests that antiretroviral treatment benefits neuropsychological functioning through lowering viral load. A similar conclusion was offered by Sacktor et al. (40).

### **c) Antiretroviral treatments to prevent HIV-associated dementia**

A few studies have examined the use of antiretroviral medications to prevent HIV-associated dementia. Moore and colleagues (395) conducted a study of 863 homosexual men treated with zidovudine who were evaluated every 2 months for 2 years or until death. Development of HIV-associated dementia continued with zidovudine treatment but was significantly correlated with low CD4 cell count. Montforte and colleagues (396) used didanosine in a study of 1,047 subjects (median CD4 cell count of 47 cells/mm<sup>3</sup> and mean prior zidovudine treatment of 19 months). Subjects were followed every 2 months to a clinical endpoint (AIDS-defining condition, severe adverse event, or death). They reported a very low incidence of HIV-associated dementia (11 subjects, or 1%), although no formal criteria for defining HIV-associated dementia were offered. One randomized clinical trial with 32 subjects that compared zidovudine treatment to placebo found no significant difference in rate of developing dementia by treatment assignment (397). HIV-associated dementia prevention requires further study, but it appears that treatment with antiretroviral medications may prevent the development of HIV-associated dementia and other cognitive motor disorders.

### **d) Interventions that affect inflammatory mediators**

Although peptide T can be thought of as “antiretroviral,” since it blocks the binding of envelope glycoprotein to CD4 receptors, it more likely exerts its effects through decrements in the deleterious effects of inflammatory mediators known as cytokines, such as tumor necrosis factor. A multisite, randomized, placebo-controlled clinical trial with intranasal peptide T was conducted on a sample of 215 patients with HIV-associated neurocognitive impairment, most of whom were taking a single antiretroviral agent or a two-drug combination regimen (398). The study found no statistically significant differences between treatment and placebo groups on global neuropsychological z scores. However, subgroup analyses showed that subjects with a CD4

count of 201–500 cells/mm<sup>3</sup> and subjects with at least moderate neuropsychological impairment at baseline improved significantly with peptide T compared with those given placebo ( $p < 0.05$ ). In addition, peptide T was well tolerated with no clinically significant toxic effects.

Studies of inflammatory mediators are indicated because researchers have postulated that HIV-related neuronal injury involves the activation of voltage-dependent calcium channels and *N*-methyl-D-aspartate (NMDA) receptor-operated channels (399). Therefore, studies are underway using memantine (an NMDA antagonist), inhibitors of tumor necrosis factor- $\alpha$ , thalidomide, pentoxifylline, and naloxone (an inhibitor of interferon- $\alpha$ ). Mapou and colleagues (400) conducted a clinical trial with interferon- $\alpha$ -n3 in 20 asymptomatic subjects with HIV infection and reported significant improvements in neuropsychological performance in selected subtests. While interferon has been associated with neuropsychological side effects, including depression, Skillman et al. (401) reported that such side effects are minimal.

Nimodipine is a voltage-dependent calcium channel antagonist that has been postulated to prevent HIV-related neuronal injury. Two controlled studies of nimodipine, one in combination with zidovudine (402) and one with nimodipine alone (403), found no significant differences in overall neuropsychological performance.

#### **e) Treatments involving neurotransmitter manipulation**

Stimulant drugs have been used as palliative agents to help manage symptoms of fatigue, decreased concentration, or memory deficits among patients with HIV-associated dementia or minor cognitive motor disorder. With regard to the specific effect of stimulants on neurocognitive impairment, there has been one randomized, placebo-controlled clinical trial of a small sample of eight opioid-dependent patients maintained on a regimen of methadone (404). This 7-day crossover study with sustained-release methylphenidate (20–40 mg/day) resulted in non-significant neuropsychological z score improvements from baseline with methylphenidate but not placebo. Fernandez and colleagues (321) presented case reports of treating patients with HIV-related disease with methylphenidate (30–90 mg/day) or dextroamphetamine (30–60 mg/day). All patients improved significantly; however, there was no placebo control group and the sample size was small. Similar data from a small trial are offered by Holmes et al. (405).

Studies of dopaminergic agonists are supported by preliminary data in the form of case studies of carbidopa and L-dopa (303). The Dana Consortium conducted a randomized, placebo-controlled clinical trial of 36 subjects with HIV-associated cognitive motor impairment who were given L-deprenyl, a putative antiapoptotic agent, and found that deprenyl-treated subjects showed an improvement in neuropsychological test performance, specifically in verbal memory (406). Investigation of the dopaminergic agent pramipexole is currently under way.

Other neurotransmitters such as serotonin and 5-hydroxyindoleacetic acid have been found to be decreased in CSF as HIV disease progresses (407). It is possible that increasing CNS serotonin levels through administration of agents such as SSRIs may be useful in the treatment of cognitive motor impairment.

#### **f) Nutritional therapies and HIV-associated cognitive disorders**

Nutritional therapies need to be considered as potential interventions for the cognitive motor symptoms associated with HIV infection. A case report of a subject with apparent late-stage HIV-associated dementia and a low cobalamin (vitamin B<sub>12</sub>) level due to decreased intrinsic factor secretion responded over 2 months to B<sub>12</sub> replacement therapy with complete symptom resolution (408). Oxidative free radical scavengers such as vitamin E, the experimental antioxidant OPC-14117, and the trace mineral and antioxidant selenium may prove to be therapeutically useful.

## **2. Delirium**

Antipsychotic medications have been the treatment of choice in treating delirious states that develop in patients with HIV infection, with most evidence arising from case reports or uncon-

trolled trials (409, 410). For patients with HIV infection, a prominent issue is the observed increased sensitivity to side effects (299, 300). This sensitivity applies to extrapyramidal side effects with higher-potency agents and also to cognitive side effects with lower-potency antipsychotics.

To date, only one randomized clinical trial has studied the treatment of delirium associated with HIV infection. Breitbart and colleagues (46) approached 244 hospitalized AIDS patients and monitored them for the development of delirium. Among the 30 subjects who went on to develop delirium, 310 episodes of delirium occurred that met both DSM-III-R and Delirium Rating Scale criteria (411). The 30 subjects were randomly assigned to receive haloperidol (N=11), chlorpromazine (N=13), or lorazepam (N=6). Because the six subjects taking lorazepam developed signs of toxicity (oversedation, disinhibition, ataxia, and increased confusion), this treatment was terminated prematurely. Both haloperidol and chlorpromazine treatment resulted in significantly reduced scores on the Delirium Rating Scale in the first 24 hours. The researchers did not report significant problems with extrapyramidal side effects in study patients, but mean daily doses were low.

Scattered case reports or series suggest that other antipsychotic agents may be useful for treating HIV-associated delirium. For instance, molindone (312), risperidone (315), and droperidol (412, 413) have been suggested as alternatives to the standard antipsychotic medication because of differences in side effect profile, onset of action, or potency.

### **3. Mood disorders**

Disturbances of mood occur frequently in the context of HIV infection. Treatment studies are quite varied with regard to variables such as severity of mood disorder, methodology to categorize or diagnose mood disorders, outcome measures, and stage of HIV illness.

#### **a) Acute treatment of depressive disorders—somatic treatments**

Many studies, including randomized controlled trials, open-label trials, case series, and case reports, support the efficacy and safety of many antidepressants in the acute treatment of depressive disorders, including major depression, in a wide range of HIV-infected populations at all disease stages.

Wagner and colleagues (286) reported on a series of 6-week studies that used random assignment and placebo control to examine the efficacy of standard and alternative antidepressants for major depression in HIV-infected patients. The agents used at standard doses were fluoxetine, sertraline, imipramine, dextroamphetamine, and testosterone. Response rates to the different agents ranged from 70% to 93% and were significantly higher than placebo.

Similar findings were reported in a randomized, placebo-controlled clinical trial conducted by Elliot and colleagues (287) in 75 HIV patients (45% with AIDS) who had major depression. Both imipramine- and paroxetine-treated groups improved significantly compared to placebo at weeks 6, 8, and 12. The dropout rate due to side effects was higher for those receiving imipramine (48%) than it was for placebo (24%) or paroxetine (20%).

One randomized, placebo-controlled clinical trial (N=120) found that fluoxetine was an efficacious antidepressant agent among depressed HIV patients; the response rate for fluoxetine was 74% versus 47% for placebo (289). The same study reported significant differences between ethnic groups in terms of antidepressant efficacy; the response rates were 84% for white, 67% for Latino, and 50% for black subjects (414). Despite the effectiveness of fluoxetine in treating depression, because both placebo response and attrition were high, the researchers suggested that the addition of another medication in patients with serious medical illness who require multiple concomitant medications may be a significant barrier to the treatment of depression.

In a double-blind, placebo-controlled trial that compared desipramine to fluoxetine in 14 women with advanced HIV disease, both agents were linked to symptom improvement; however, for most of the women significant depressive symptoms remained after the 6-week trial

(294). These findings are consistent with those of an open-label fluoxetine trial that compared HIV-positive and HIV-negative depressed men, which found that improvement in the HIV-positive cohort was significantly delayed beyond the 8-week trial compared to the HIV-negative patients (415).

The randomized trials are supported by uncontrolled studies of depression in HIV populations and confirm the effectiveness of fluvoxamine (295) and fluoxetine (293, 416, 417) in HIV-infected *asymptomatic* patients and of paroxetine, sertraline, and fluoxetine in *symptomatic* HIV patients (285, 418). In an open trial in which HIV-positive depressed women were given either fluoxetine or sertraline, both drugs were found to be effective treatments (419). Another open-label study found nefazodone effective in the treatment of depressed HIV-positive patients (288). One open-label trial of 32 patients with advanced HIV disease found venlafaxine effective among depressed patients who also had minor cognitive motor disorder (420).

The use of psychostimulants for treatment of major depression in HIV-infected outpatients has been supported in smaller studies, including five case reports, one open-label trial, and one placebo-drug-placebo clinical trial (321, 322, 421, 422). These studies suggest that methylphenidate, up to 35 mg/day, or dextroamphetamine, up to 10 mg/day, can improve major depression.

An open trial of testosterone replacement for hypogonadal men found that of 34 study participants with major depressive disorder, 79% had significant improvement in mood (126). There is a case report of a patient with HIV infection and comorbid major depressive disorder whose depression resolved with treatment with the antiretroviral agent zidovudine (423). For patients with severe major depression who are delusional or have failed medication treatment, ECT has been found to be safe and effective (424).

#### **b) Acute treatment of depressive disorders—psychotherapy**

Several studies of psychotherapeutic treatment of depression in HIV patients have been conducted. In a randomized, controlled trial, Targ and colleagues (425) compared structured group therapy plus fluoxetine to structured group therapy with placebo in 20 asymptomatic homosexual men with major depression or adjustment disorder and Hamilton Depression Rating Scale scores  $\geq 16$ . Both groups showed significant improvements in depression after 6 weeks of treatment, but there were no differences between treatment groups (425). In contrast, another randomized, placebo-controlled clinical trial that compared the efficacy and safety of fluoxetine plus group psychotherapy versus group psychotherapy alone in 47 depressed HIV-positive men for 7 weeks found that fluoxetine in addition to group therapy was more efficacious than group psychotherapy alone. Differences were particularly apparent for patients whose initial depressive episodes were rated as severe (Hamilton depression score  $\geq 24$ ) (290).

Markowitz and colleagues (426) conducted a randomized, placebo-controlled clinical trial that compared 16-week interventions with interpersonal psychotherapy, cognitive behavior therapy, supportive psychotherapy, and supportive psychotherapy plus imipramine in 101 HIV patients with depressive symptoms (Hamilton depression score  $\geq 15$ ). Patients randomly assigned to interpersonal psychotherapy and supportive psychotherapy plus imipramine had significantly greater symptom improvement than those receiving supportive psychotherapy alone or cognitive behavior therapy.

In an earlier study (427), the Markowitz group demonstrated the benefits of interpersonal psychotherapy in HIV-positive, asymptomatic outpatients in an open study of men and women with DSM-III-R major depression or dysthymia. Twenty (87%) out of 23 patients achieved a full remission after 6 weeks by clinical assessment; mean Hamilton depression scores at baseline and follow-up were 25 and 6.8, respectively. Levine et al. (428) reported that four outpatients with major depression remained euthymic for 9 months with structured group psychotherapy after acute remission was achieved with fluoxetine, 20–40 mg/day.

Other studies such as two retrospective chart reviews (284, 429) and a prospective effectiveness study (430) support the findings from controlled and uncontrolled treatment studies of major depression that treatment with a number of different antidepressant agents is effective and generally tolerated in HIV patients.

**c) Treatment of other types of depression**

Other studies have investigated the efficacy of treatment for other types of depression in HIV patients. These studies generally use screening instruments (e.g., the Center for Epidemiologic Studies Depression Scale [CES-D Scale]) rather than structured interviews or clinical evaluations to diagnose specific depressive disorders. All involved ambulatory patients who had no significant clinical manifestations of HIV disease. In a study of patients with depression (CES-D Scale score >16) but with unknown psychiatric diagnoses, investigators compared cognitive behavior therapy and brief supportive group therapy to a waiting list control condition. Outpatients (N=68) were randomly assigned to an 8-week intervention of cognitive behavior therapy, support group, or a control group. While both types of psychotherapy were superior to the control condition, neither led to significant reductions on the CES-D Scale into the nondepressed range (431).

Eller (432) conducted a randomized, placebo-controlled clinical trial of alternative therapies for depression and assigned 81 male and female outpatients with HIV infection to guided imagery, relaxation therapy, or usual care. The sample had a mean CES-D Scale score of 19. There were no significant declines in CES-D Scale scores during treatment in any of the three groups.

**d) Treatment of mania/bipolar disorder**

One chart review (433) and one case report (434) have addressed the treatment of manic syndromes in HIV-infected patients. The chart review study identified seven male outpatients with mania who did not improve with lithium or neuroleptic treatment due to toxicity. Three patients had been treated with valproic acid (750–1750 mg/day), two with clonazepam (2 mg/day), one with phenytoin, and one with carbamazepine. All seven patients experienced remission of their manic syndrome with the agent used (433). The case report described the effectiveness of valproic acid in the treatment of acute mania in a patient with AIDS complicated by dementia (434). There are no published studies of maintenance treatments for mania or bipolar disorders in HIV-infected populations.

**4. Substance use disorders**

Clinical consensus has established the necessity of treating substance use disorders in order to produce optimal psychiatric and medical outcomes for patients with HIV infection. Despite this knowledge, remarkably few studies have investigated psychiatric treatment of substance use disorders in HIV-infected patients. This section will review the literature of the treatment of substance use disorders and associated syndromes.

**a) Entry into a treatment program**

Entry into a treatment program is probably one of the more critical steps for the assessment and treatment of substance use disorders. Guydish and colleagues (435) described a consultation-education-triage model program that referred drug users with HIV infection to follow-up care for substance use disorders. Of the 86 patients referred over an 8-month period, 81% were referred for further care to a substance use program, with 58% actually contacting the referral resource. Eighty percent had AIDS or symptomatic HIV disease; 37% of patients were dependent on alcohol, 36% were dependent on amphetamines, and 26% were dependent on heroin, marijuana, or cocaine.

#### **b) Methadone maintenance**

The Program for AIDS Counseling and Education in San Francisco is considered a model program for inner-city, poor, opiate-dependent, mostly minority men (436, 437). The program provides medical assessment and care, psychiatric treatment, methadone treatment, counseling, detoxification, and tolerance management for opiate addicts. Outcomes for patients enrolled in the Program for AIDS Counseling and Education have been reported in two conference papers. In one report, 29 opioid-dependent HIV patients with a mean of 28 days of drug use in the past month reduced their use to a mean of 5.9 days of use per month after 3 months in the program (438). The other report focused on clinical events related to drug use before and after enrollment for 62 patients in the program (439). Clinical events included medical complications and lapses in compliance with treatment. At baseline, patients experienced 0.72 clinically significant medical complications per 100 patient years, whereas the rate decreased significantly to 0.16 during enrollment in the Program for AIDS Counseling and Education. There was also a reduction in preventable HIV clinical events from 0.21 per 100 patient years to 0.02 per 100 patient years after starting the program. The reports provide some evidence that both the medical care as well as substance use behaviors of HIV-infected opioid addicts can benefit from a multidisciplinary, structured intervention.

#### **c) Pharmacologic treatment of substance use disorders**

One study of HIV-infected patients investigated the effect of antidepressant medications on symptoms of drug dependency, such as drug craving and comorbid depression. Batki (440) conducted a controlled trial that compared fluoxetine to placebo in 37 patients with cocaine and opiate dependency who were on a regimen of methadone maintenance. Of this sample, 41% also had major depression. Participants treated with fluoxetine (20–40 mg/day) had lower median measures of cocaine metabolites in urine and fewer mean days of cocaine use per week (1.6) compared to those given placebo (2.6); the fluoxetine-treated patients also reported reduced cocaine craving. Those with major depression showed significant improvement after the 12-week treatment.

#### **d) Overall outcomes of psychiatric treatment**

Lyketsos and colleagues (430) conducted a 14-month prospective effectiveness study of clinical outcomes in HIV patients who were referred to psychiatric treatment. Within the cohort, 110 patients had current (N=66) or recent (N=44) substance use disorders; there were high rates of polysubstance dependence, with only a small proportion of patients who abused alcohol. The psychiatric treatment took place within a primary care clinic and included treatment for substance abuse and concurrent psychiatric disorders. Psychiatric intervention led to a decrease in the use of substances and better clinical condition.

### **5. Anxiety disorders**

Anxiety disorders are prevalent in the population of persons who have or are at risk for HIV infection, but studies of specific treatments for anxiety disorders in HIV patients are lacking. The literature provides only one retrospective chart review and two case reports that address the management of anxiety disorders in HIV-positive patients. There are no treatment studies of PTSD among HIV-infected patients, although PTSD rates are high in some HIV-affected groups (441).

A chart review study found that bupirone was an effective anxiolytic in opioid-dependent, HIV-positive patients who were on a regimen of methadone maintenance and who also had a comorbid anxiety disorder. The study additionally showed a modest reduction of urine tests positive for substances of abuse, from 42% to 30% (328).

McDaniel and Johnson (442) found fluoxetine to be effective in the treatment of obsessive-compulsive disorder (OCD) in two HIV-positive patients. Both patients tolerated the fluoxetine with minimal side effects and responded with resolution of OCD symptoms within 6–8 weeks.

A male patient with advanced AIDS complicated by comorbid trichotillomania and major depression was reported to have responded well to sertraline at a maximum dose of 150 mg/day. The patient reported experiencing a 70%–80% decrease in hair pulling and a modest improvement in depressed mood, with minimal medication side effects (443).

## **6. Psychotic disorders**

Nine literature citations, two of them clinical trials and the remainder case reports, present evidence concerning the efficacy of psychotropic medication for the management of psychosis in the presence of HIV infection. The nine reports contain fewer than 100 subjects, approximately 90% of them male, and most with symptomatic HIV infection, usually AIDS. Where stated, the majority did not have a history of psychosis before HIV infection, and, where stated, the majority had cognitive impairment.

Antipsychotic medications were effective in treating psychosis whether or not cognitive dysfunction or delirium was present. One large case history series found that patients with manic psychosis showed more improvement than patients with schizophreniform psychosis (315). The two clinical trials (31, 444) found that positive symptoms responded better than negative symptoms. Across studies the subjects, who largely had advanced HIV disease, required lower doses of antipsychotic medication, similar to the pattern seen in the elderly. Lower doses were also useful due to increased sensitivity to side effects. If a patient did not respond to or tolerate one antipsychotic, it was useful to try another from a different class (300, 301, 310, 312).

In case reports, the use of adjunctive medications, including antianxiety drugs, antidepressants, and mood stabilizers, was a common practice and often useful in individual cases, but there have been no controlled studies on the efficacy of these combinations. Two case reports, each of a single male subject with AIDS, found that catatonia responded rapidly to lorazepam (445, 446). No side effects were noted.

Maintenance medication was not always necessary to sustain remission of psychotic symptoms (42, 312). In some cases it was specifically noted that symptoms of psychosis diminished as severe late-stage medical illness progressed (42). While it has been hypothesized that there is a window of vulnerability to psychosis or mania occurring early in the course of HIV-associated dementia (447), no data support this theory, and most patients treated for psychosis have continued their maintenance medication regimens.

There are few data on the treatment of psychosis in early-stage HIV infection or among women nor is there information concerning potential modifications in the treatment of preexisting psychotic illness, which might be necessary in the presence of advancing HIV infection.

## **7. Adjustment disorders**

Two open-label clinical trials have assessed the effectiveness of psychotropic medications in the management of adjustment disorders in HIV-positive patients. As part of a larger study that examined the effectiveness of paroxetine in the treatment of depression in the context of HIV infection, Grassi and colleagues (418) included five patients with a diagnosis of adjustment disorder with depressed mood. All five patients received paroxetine (20 mg/day) and showed significant recovery as measured by the Hamilton depression scale at the 6-week endpoint.

Five male patients with neurocognitive impairment as well as a diagnosis of adjustment disorder with depressed mood were treated as part of a larger study of the effectiveness of psychostimulants in patients with HIV-associated dementia. Four of the five patients who received methylphenidate had moderate to marked improvement in symptoms; the one patient with minimal response was switched to dextroamphetamine and subsequently had a moderate response (405).

## **8. Sleep disorders**

Numerous reports have documented disrupted sleep and altered sleep architecture in HIV patients (29, 448, 449), including one study which linked fatigue and sleep disturbances to morbid-

ity and disability in homosexual men (450). While the etiologies remain unclear, some investigators have documented growth hormone dysregulation associated with sleep pathology (451), and one study found obstructive sleep apnea due to adenotonsillar hypertrophy to be a primary cause of sleep disruption in a cohort of HIV patients with excessive daytime sleepiness (452).

The treatment of sleep disorders in HIV-positive persons has been examined in only one open-label clinical trial of flurazepam in 12 patients (453). All patients were given a one-time dose of flurazepam, 30 mg, to examine changes in the patients' electroencephalographic recordings during sleep. Flurazepam mainly affected non-REM parameters, such as reduction of times awake during the night and increases in stage two and effective sleep time. As this study did not address treatment with flurazepam beyond a one-time dose, actual treatment recommendations cannot be made.

## **9. Disorders of infancy, childhood, and adolescence**

Since HIV infection in childhood is associated with developmental delays or loss of acquired skills, it is hoped that early treatment will promote normal development. Currently, it appears that antiretroviral drug therapy reduces morbidity in children, especially in those with HIV-associated neurocognitive impairment. Several studies have reported a significant increase in mental ability, as measured by the WISC-R, the McCarthy Scales of Children's Abilities, or the Bayley Scales of Infant Development, in over 450 children during 12- and 36-month trials with zidovudine (58, 246, 454, 455). None of the studies included a control group.

The safety of zidovudine for children is similar to that for adults, although up to 40% of children experience hematological side effects that require dose alterations (246). The one published study of 54 children that did not find a significant improvement in cognitive functioning with zidovudine treatment did find a significant decrease in CD4 levels over the treatment period. No data were provided on adherence to treatment or zidovudine resistance (456). Other antiretroviral agents, such as didanosine, have been studied, with a multisite project showing that combination zidovudine and didanosine therapy was superior to either used as monotherapy for most of the CNS outcomes evaluated (457). Although combination antiretroviral therapy with three agents is standard practice with adults, there is only one case report of its use with a child (458). Caregivers noted the positive impact of this regimen on an 8-year-old boy's neurocognitive development.

The effectiveness of the treatment of other mental and behavioral disorders associated with HIV infection in children and adolescents is largely unstudied. Case reports of single patients suggest that attention deficit disorders and depressive disorders in those with HIV infection may be treated by using regimens that are standard for those without HIV infection (459). As in the treatment of adults, children with HIV infection may be especially sensitive to some treatment side effects, such as insomnia or appetite suppression associated with psychostimulant use.

Pain frequently accompanies pediatric HIV and can involve multiple organ systems (460). Clinicians should be aware that the inadequate verbal skills of younger children or the fact that some children are from non-English-speaking families can lead to the underrecognition and undertreatment of pain (461).

## **10. HIV-associated syndromes with psychiatric implications**

A number of HIV-associated clinical syndromes have psychiatric implications, such as wasting syndrome, fatigue, pain, and sexual dysfunction. Because there are overlapping symptoms with these conditions and psychiatric disorders, it is useful for psychiatrists to be aware of treatment studies for such syndromes so that overall clinical outcomes can be improved.

### **a) Wasting syndrome**

Several studies have focused on the use of testosterone for treatment of wasting syndrome in both patients with low testosterone levels and patients with "clinical hypogonadism" (normal

hormone levels). Grinspoon and colleagues (462) conducted a double-blind, placebo-controlled study of hypogonadal HIV-positive men with wasting syndrome that demonstrated the safety and efficacy of testosterone replacement therapy (300 mg i.m. every 3 weeks). The treatment resulted in a significant increase of lean body mass, overall quality of life, and self-perception of appearance in treated subjects. Similar findings have been reported by Rabkin and colleagues (126, 343, 463), who conducted several randomized, placebo-controlled trials as well as open trials of testosterone replacement in men with clinical hypogonadism that led to significant positive effects on mood and weight (lean body mass). Another study that used oxymetholone, a testosterone derivative, demonstrated weight gain in cachectic men with AIDS (464). A controlled study of hypogonadal *women* with HIV infection that used transdermal testosterone replacement also reported improvement in lean body mass and quality of life (465).

Wagner and colleagues (466) reported an additional improvement of measures on the Brief Symptom Inventory and nutritional status for patients who exercised in addition to receiving testosterone replacement. In a double-blind, randomized, placebo-controlled trial, researchers found that resistance exercise in addition to testosterone and the anabolic steroid oxandrolone substantially increased lean body mass (467). Two open-label studies have reported that oxandrolone, 20 mg/day, in HIV patients with wasting syndrome led to significant weight gain, in particular, increases in body cell mass (334, 335).

Several clinical trials have used the recombinant growth hormone somatotropin for treatment of HIV-related wasting (336, 340). A large multicenter, double-blind, placebo-controlled study that used growth hormone in patients with AIDS wasting reported significant improvement in overall quality of life and weight gain, with no negative effect on virological or immunological markers (339). Treatment was well tolerated.

Since tumor necrosis factor- $\alpha$  has been postulated to have a role in the pathogenesis of wasting syndrome, the effect of thalidomide, a selective inhibitor of tumor necrosis factor- $\alpha$ , has been studied in patients with AIDS wasting syndrome. Two reports (a mail survey of thalidomide users and a small randomized, placebo-controlled clinical trial) have supported the positive effects of thalidomide on weight gain, appetite, and quality of life (341, 342).

## **b) Fatigue**

Breitbart and colleagues (468) conducted a randomized, placebo-controlled clinical trial that used two psychostimulant medications, methylphenidate and pemoline, in treating fatigue among HIV patients. They found that both treatments were superior to placebo, with a stronger effect in the methylphenidate group. In addition, they reported that improvement in fatigue was associated with improvement in depressive symptoms and psychological distress. In an open trial of depressed patients with CD4 counts below 200, dextroamphetamine administration led to improvement of fatigue in 95% of patients along with reduction in depression scores (322). Testosterone replacement with dehydroepiandrosterone (DHEA) in HIV-infected hypogonadal men has also been found to improve symptoms of fatigue (469).

## **c) Pain**

Studies of the frequency and adequacy of treatment for pain among patients with AIDS find wide variations in the effectiveness of interventions to manage pain. A study by Breitbart et al. (123) found that 85% of HIV patients in their ambulatory sample treated at a cancer center received inadequate pain therapy. Yet a different study reported that only 20% of their sample of AIDS patients treated in the hospital, home care, or nursing facility did not receive effective pain control (470).

While agents such as tricyclic antidepressants and anticonvulsant medications are often used to manage chronic pain from peripheral neuropathy, published treatment studies for HIV-associated peripheral neuropathy have not supported their use. Two randomized, controlled trials have focused on HIV-associated peripheral neuropathy; both trials used the agent mexiletine,

an antiarrhythmic drug with local anesthetic properties that had been used in the treatment of diabetic neuropathy (317, 471). Neither study found pain relief different from that of placebo. Furthermore, Kiebertz et al. (317) did not find that treatment with amitriptyline provided significant pain relief compared to placebo. Shlay and colleagues (472) conducted a randomized, controlled trial that compared acupuncture, amitriptyline, and placebo for pain due to HIV-related peripheral neuropathy and found that neither acupuncture nor amitriptyline was more effective than placebo.

#### **d) Sexual dysfunction**

Sexual dysfunction is experienced commonly by HIV patients, both men and women, particularly with HIV disease progression. While no treatment trials are currently published, a cautionary note regarding sildenafil is clinically important. Sildenafil should be used judiciously in patients with erectile dysfunction who are also taking protease inhibitors, since the primary route of sildenafil metabolism is via the cytochrome P450 isoenzyme 3A4. One death has been reported in a 47-year-old male taking ritonavir and saquinavir who was administered 25 mg of sildenafil (473). The manufacturer of sildenafil has recommended that patients receiving ritonavir should not take more than a single sildenafil dose of 25 mg in a 48-hour period.

## **PART C:**

### **FUTURE RESEARCH NEEDS**

Considerable progress has been made in understanding HIV, AIDS, and treatment for these conditions. However, further studies are needed regarding specific, effective treatments for patients, including women and children, with HIV/AIDS. Areas of specific concern include:

1. The impact of antiretroviral therapy on the incidence of CNS opportunistic diseases and neuropsychiatric disorders.
2. The specific etiology of HIV-associated dementia and minor cognitive motor disorder and effective interventions to prevent or ameliorate these conditions.
3. The clinical significance of drug-drug interactions of psychotropic agents and HIV-related medications.
4. Whether HIV is directly linked to the occurrence of psychosis, mania, depression, or other psychiatric disorders in persons with HIV infection.
5. Whether the CNS serves as a reservoir of HIV-resistant strains and the clinical implications if it does.
6. The effectiveness of psychiatric care in critical areas of treatment adherence, prevention of HIV infection, and psychosocial adaptation.
7. Information about the impact of HIV infection on development in children, with possible differences in clinical course due to whether infected in utero or perinatally or due to type of treatment received.
8. More effective interventions for HIV risk reduction in specific psychiatric populations, particularly for primary prevention of HIV infection.
9. The need for more data about the effectiveness of psychiatric treatments such as psychotherapy, pharmacotherapy, and psychosocial services for adults, adolescents, and children with HIV/AIDS.
10. Investigating possible gender differences in the problems associated with HIV/AIDS and treatment for these conditions.

## APPENDIX 1. HIV/AIDS Electronic Resources

Resource	Organization	URL
General information	AIDS Action Committee (AAC)	<a href="http://www.aac.org">www.aac.org</a>
	AIDS Daily Summary	<a href="http://www.cdcpin.org/news/start.htm">www.cdcpin.org/news/start.htm</a>
	AIDS Education Training Centers (AETC)	<a href="http://www.service.emory.edu/SEATEC/AETCdir.html#USA">www.service.emory.edu/SEATEC/AETCdir.html#USA</a>
	AIDS Virtual Library	<a href="http://www.planetq.com/aidsvl/index.html">www.planetq.com/aidsvl/index.html</a>
	American Medical Association	<a href="http://www.ama-assn.org">www.ama-assn.org</a>
	American Psychiatric Association	<a href="http://www.psych.org/aids">www.psych.org/aids</a>
	Business and Labor Resource Service	<a href="http://www.brta-hta.org">www.brta-hta.org</a>
	Centers for Disease Control and Prevention (CDC)	<a href="http://www.cdc.gov">www.cdc.gov</a>
	CDC National Prevention Information Network (CDCNAC)	<a href="http://www.cdcpin.org">www.cdcpin.org</a>
	CDC National AIDS Funding Database	<a href="http://www.cdcpin.org/db/public/fundmain.htm">www.cdcpin.org/db/public/fundmain.htm</a>
	CMV Retinitis Education and Treatment Information	<a href="http://www.piv.org">www.piv.org</a>
	Food and Drug Administration (FDA)	<a href="http://www.fda.gov">www.fda.gov</a>
	FDA/OASHI: HIV/AIDS	<a href="http://www.fda.gov/oashi/aids/hiv.gov">www.fda.gov/oashi/aids/hiv.gov</a>
	FDA Medical Bulletin	<a href="http://www.fda.gov/medbull/contents.html">www.fda.gov/medbull/contents.html</a>
	Healthcare Communications Group	<a href="http://www.healthcg.com">www.healthcg.com</a>
	Healthfinder	<a href="http://www.healthfinder.gov">www.healthfinder.gov</a>
	HIVdent	<a href="http://www.hivdent.org">www.hivdent.org</a>
	Human Retroviruses and AIDS Sequence Database	<a href="http://hiv-web.ianl.gov">hiv-web.ianl.gov</a>
	Johns Hopkins AIDS Service	<a href="http://www.hopkins-aids.edu">www.hopkins-aids.edu</a>
	Infectious Diseases Society	<a href="http://www.idsociety.org">www.idsociety.org</a>
	Insights in HIV Disease Management	<a href="http://www.meniscius.com/hiv">www.meniscius.com/hiv</a>
	Medical Matrix	<a href="http://www.medmatrix.org/index.asp">www.medmatrix.org/index.asp</a>
	National Academy of Sciences	<a href="http://www.nas.edu">www.nas.edu</a>
	National AIDS Treatment Advocacy Project (NATAP)	<a href="http://www.natap.org">www.natap.org</a>
	National Hemophilia Foundation (NHF)	<a href="http://www.infoahf.org">www.infoahf.org</a>
	National Institutes of Health (NIH)	<a href="http://www.nih.gov">www.nih.gov</a>
	National Science Foundation	<a href="http://www.nsf.gov">www.nsf.gov</a>
	New York Online Access on Health	<a href="http://www.noah.cuny.edu/aids/aids.html">www.noah.cuny.edu/aids/aids.html</a>
Pharmaceutical Research Manufacturers Association of America (PhRMA)	<a href="http://www.phrma.org">www.phrma.org</a>	

**APPENDIX 1. HIV/AIDS Electronic Resources (continued)**

<b>Resource</b>	<b>Organization</b>	<b>URL</b>
<b>General information (continued)</b>	The Access Project	204.179.124.69/network/access/index.html
	The Body	www.thebody.com
	University of California HIV/AIDS Program	hivinsite.ucsf.edu
	USP Pharmacopeia Practitioners Reporting Network	usp.org/index
	Yahoo: Health Medicines HIV/AIDS	www.yahoo.com/Health/Medicine
	Webber's AIDS/HIV Law and Policy Resource	www.critpath.org/aidslaw
<b>Alternative treatments</b>	American Chiropractic Association	www.amerchiro.org/aca
	ATDN's Alternative Treatments	204.179.124.69/network/altx.html
	Bastyr University AIDS Research Center	www.bastyr.edu/research/busrc
	Herb Research Foundation	www.herbs.org
	Homeopathic Educational Services	www.homeopathic.com
	Institute for Traditional Medicine	www.europa.com/-itm
<b>Clinical trials</b>	Adult AIDS Clinical Trials Group (ACTG)	aactg.a-3.com/links.com
	AIDS Clinical Trial Information Services	www.actic.org
	AIDS Treatment Information Service	www.atis.org
	American Foundation for AIDS Research (amFAR)	www.amfar.org/td
	Canadian HIV Trials Network	www.hivnet.ubc.ca/ctn.html
	Pediatric AIDS Clinical Trials Group	pactg.s-3.com/links.htm
	The Body	www.thebody.com/treatclintri.html
	USA HIV Clinical Trials/Trial Search	hivinsite.ucsf.edu/tsearch
	Vanderbilt Vaccines	www.mc.vanderbilt.edu/adl/aids_project/vac
<b>Harm reduction/ needle exchange</b>	Center for AIDS Prevention Studies (UCSF)	www.caps.ucsf.edu/capsweb
	The Lindesmith Center	www.lindesmith.org
	The XCHANGE POINT	members.aol.com/xchangept/aids.html
	North American Syringe Exchange Network	www.nasen.org
	Safe Works AIDS Project	www.safeworks.org

**APPENDIX 1. HIV/AIDS Electronic Resources (continued)**

<b>Resource</b>	<b>Organization</b>	<b>URL</b>
<b>Recreational drugs and anti-HIV drug information</b>	National AIDS Manual	<a href="http://www.nam.org/uk/atu/atu51.trt">www.nam.org/uk/atu/atu51.trt</a>
	Notes from the Underground	<a href="http://www.aidsinfonyc.org/pwahg/notes/38.html">www.aidsinfonyc.org/pwahg/notes/38.html</a>
	Positively AWARE	<a href="http://www.tpan.com/library/pa/mayjun97/p.32.htm">www.tpan.com/library/pa/mayjun97/p.32.htm</a>
	The Toronto Hospital	<a href="http://www.tthhivclinic.com/recreation.htm">www.tthhivclinic.com/recreation.htm</a>
	POZ	<a href="http://www.thebody.com/poz/survival/6_98/warning.html">www.thebody.com/poz/survival/6_98/warning.html</a>
	CATIE (Community AIDS Treatment Information Exchange)	<a href="http://www.catie.ca">www.catie.ca</a>
	University of California, San Francisco	<a href="http://Hivinsite.ucsf.edu/topics/substance_use/hiv_aids_medications_and_interventions_with_legal_and_illegal_drugs/">Hivinsite.ucsf.edu/topics/substance_use/hiv_aids_medications_and_interventions_with_legal_and_illegal_drugs/</a>
	Medscape	<a href="http://www.medscape.com/medscape/hiv/clinicalmgmt/can/drug/public/toccm.drug.html">www.medscape.com/medscape/hiv/clinicalmgmt/can/drug/public/toccm.drug.html</a>
	NO/AIDS Task Force	<a href="http://www.crescentcity.com/noaids">www.crescentcity.com/noaids</a>
	Project Inform	<a href="http://www.projinf.org/fe/drugin.html">www.projinf.org/fe/drugin.html</a>
San Francisco AIDS Foundation	<a href="http://www.afa.org/treatment/beta/b34/b34piint.html">www.afa.org/treatment/beta/b34/b34piint.html</a>	

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American Academy of Family Physicians  
American Academy of Psychiatry and the Law  
American Group Psychotherapy Association, Inc.  
American Psychiatric Nurses Association  
American Society of Addiction Medicine  
American Society of Clinical Psychopharmacology, Inc.  
APA Commission on Psychotherapy by Psychiatrists  
Association for Academic Psychiatry  
Association of Gay and Lesbian Psychiatrists  
Black Psychiatrists of America  
National Association of Social Workers  
PacifiCare Behavioral Health  
Royal Australian and New Zealand College of Psychiatrists  
San Francisco AIDS Foundation

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The following coding system is used to indicate the nature of the supporting evidence in the references:

- [A] *Randomized clinical trial.* A study of an intervention in which subjects are prospectively followed over time; there are treatment and control groups; subjects are randomly assigned to the two groups; both the subjects and the investigators are blind to the assignments.
  - [B] *Clinical trial.* A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally; study does not meet standards for a randomized clinical trial.
  - [C] *Cohort or longitudinal study.* A study in which subjects are prospectively followed over time without any specific intervention.
  - [D] *Case-control study.* A study in which a group of patients and a group of control subjects are identified in the present and information about them is pursued retrospectively or backward in time.
  - [E] *Review with secondary data analysis.* A structured analytic review of existing data (e.g., a meta-analysis or a decision analysis).
  - [F] *Review.* A qualitative review and discussion of previously published literature without a quantitative synthesis of the data.
  - [G] *Other.* Textbooks, expert opinion, case reports, and other reports not included above.
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