# HIV AIDS Clinical Care: Neuropsychiatric Disorders

Quantum Units Education
Affordable. Dependable. Accredited.

www.quantumunitsed.com

# Introduction

HIV/AIDS clinical care has improved dramatically over the decades, given the availability of new medications and a better understanding of how best to use antiretrovirals and deliver primary care to persons living with HIV/AIDS. Positive change on such a massive scale, however, brings with it new demands on clinicians.

Along with innovations in HIV drug therapies, HIV/AIDS care has become more complex than ever before due to increasing comorbidities that are attributable to HIV treatment and the aging of the HIV-infected population in the United States. Patient needs also have expanded across a broad spectrum of medical, psychological, behavioral, and social issues. Notably, significant numbers of infected individuals are identified and enter care late in the course of their HIV disease, confronting clinicians with complex and immediate care challenges.

Since the early days of the epidemic, clinicians have received training in HIV/AIDS clinical care through the AIDS Education and Training Centers (AETCs) Program – the clinical training arm of the Ryan White HIV/AIDS Program that is administered by the Health Resources and Services Administration (HRSA) and its HIV/AIDS Bureau (HAB). The AETC network conducts more than 14,000 training events each year with approximately 143,000 health care providers in attendance.

The *Guide for HIV/AIDS Clinical Care* is a pillar of the Ryan White HIV/AIDS Program's mission to continuously improve HIV/AIDS clinical care. The *Guide* was first published in 1993 as a collaborative effort of several regional AETCs. It was subsequently updated and expanded in 2006 and 2011. The version before you incorporates many new insights, but the time-tested format has been retained – easy access to crucial facts for a busy clinician.

The developers of the *Guide* strive to be responsive to how HIV/AIDS clinical care is provided today.

- With more routine HIV testing in medical settings, a large number of individuals are entering care via primary care sites that have relatively limited experience managing HIV/AIDS disease.
- A notable proportion of HIV/AIDS primary care in the United States is provided by advanced practice nurses and physician assistants.
- Shortages in the health care work force are worsening. Experienced staff members are aging and retiring, a limited number of new clinicians are entering primary care and specializing in HIV/AIDS care, and fewer clinicians are available in geographic areas with limited resources.

As a result, front line primary care providers may be less familiar with management of HIV/AIDS disease, as outlined in U.S. Department of Health and Human Services treatment guidelines (available at aidsinfo.nih.gov) and clinical practices presented in this *Guide*.

By presenting best practices in the clinical management of HIV/AIDS disease, the *Guide* can help us continue the remarkable advances in HIV/AIDS care that have made the Ryan White HIV/AIDS Program a model for health care delivery for our Nation and for the world.

— Laura W. Cheever, MD, ScM
*Associate Administrator*
*HIV/AIDS Bureau*
*U.S. Department of Health and Human Services*
*Health Resources and Services Administration (HRSA)*

# Abbreviations for Dosing Terminology

**BID** = twice daily

**BIW** = twice weekly

**IM** = intramuscular (injection), intramuscularly

**IV** = intravenous (injection), intravenously

**PO** = oral, orally

**Q2H, Q4H, etc.** = every 2 hours, every 4 hours, etc.

**QAM** = every morning

**QH** = every hour

**QHS** = every night at bedtime

**QID** = four times daily

**QOD** = every other day

**QPM** = every evening

**TID** = three times daily

**TIW** = three times weekly



**Important Notice**

The U.S. Department of Health and Human Services (HHS) HIV/AIDS Bureau is committed to providing accurate information on the care of HIV-infected persons. It is important to be aware that management options and protocols change over time. Forthcoming HHS guidance on certain topics may differ from recommendations contained in this *Guide*. Readers are encouraged to check for updates to treatment guidelines at AIDS Info (aidsinfo.nih.gov) and for updates to drug information at Drugs@FDA (www.accessdata.fda.gov/scripts/cder/drugsatfda).

# Pain Syndrome and Peripheral Neuropathy

## Background

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage." Pain is subjective, it is whatever the patient says it is, and it exists whenever the patient says it does. Pain is a common symptom in people with HIV infection, especially those with advanced disease. It occurs in 30-60% of HIV/AIDS patients and can diminish their quality of life significantly. Like cancer patients, HIV patients experience an average of 2.5 to 3 types of pain at once. Pain in HIV-infected patients may have many causes (as discussed below).

Pain is significantly undertreated, especially among HIV-infected women, because of factors ranging from providers' lack of knowledge about the diagnosis and treatment of pain to patients' fear of addiction to analgesic medications. Pain, as the so-called fifth vital sign, should be assessed at every patient visit.

### Peripheral Neuropathy

Pain from HIV-associated peripheral neuropathy is particularly common, and may be debilitating. Peripheral neuropathy is clinically present in approximately 30% of HIV-infected individuals and typically presents as distal sensory polyneuropathy (DSP). It may be related to HIV itself (especially at CD4 counts of <200 cells/μL), to medication toxicity (e.g., from certain nucleoside analogues such as stavudine or didanosine), or to the effects of chronic illnesses (e.g., diabetes mellitus). Patients with peripheral neuropathy may complain of numbness or burning, a pins-and-needles sensation, shooting or lancinating pain, and a sensation that their shoes are too tight or their feet are swollen. These symptoms typically begin in the feet and progress upward; the hands also may be affected. Patients may develop difficulty walking because of discomfort, or because they have difficulty feeling their feet on the ground. Factors associated with increased risk of peripheral neuropathy include the following:

- Previous peripheral neuropathy
- Low CD4 count (<200 cells/μL)
- Previous AIDS-defining opportunistic infection or neoplasm
- Vitamin B12 deficiency
- Exposure to stavudine or didanosine
- Use of other drugs associated with peripheral neuropathy (e.g., isoniazid, dapsone, metronidazole, hydroxyurea, thalidomide, linezolid, ribavirin, vincristine)
- Use of other neurotoxic agents (e.g., alcohol)
- Diabetes mellitus

Patients should be assessed carefully before the introduction of a potentially neurotoxic medication (including stavudine or didanosine), and the use of these medications for patients at high risk of developing peripheral neuropathy should be avoided.

## S: Subjective

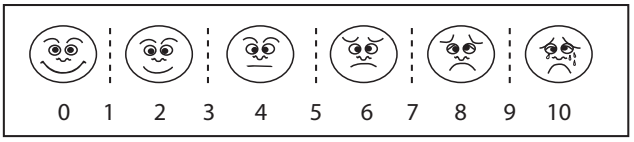
Self-report is the most reliable method to assess pain.

The patient complains of pain. The site and character of the pain will vary with the underlying cause. Ascertain the following from the patient:

- Duration, onset, progression
- Distribution, symmetry
- Character or quality (e.g., burning, sharp, dull)
- Intensity
- Severity (using the 0-10 scale; see Figure 1)
- Neurologic symptoms (e.g., weakness, cranial nerve abnormalities, bowel or bladder abnormalities)
- Exacerbating or relieving factors
- Response to current or past pain management strategies
- Past medical history (e.g., AIDS, diabetes mellitus)
- Psychosocial history
- Substance abuse and alcohol use history (amount, duration)
- Medications, current and recent (particularly zalcitabine, didanosine, stavudine, and isoniazid)
- Nutrition (vitamin deficiencies)
- Meaning of the pain to the patient

**Measuring the severity of the pain:** Have the patient rate the pain severity on a numeric scale of 0-10 (0 = no pain; 10 = worst imaginable pain), a verbal scale (none, small, mild, moderate, or severe), or a pediatric faces pain scale (when verbal or language abilities are absent). Note that pain ratings >3 usually indicate pain that interferes with daily activities. Use the same scale for evaluation of treatment response.

**Figure 1. Faces Pain Rating Scale (0-10)**




**Quick screen for peripheral neuropathy:** Ask about distal numbness and check Achilles tendon reflexes. Screening for numbness and delayed or absent ankle reflexes has the highest sensitivity and specificity among the clinical evaluation tools for primary care providers. For a validated screening tool, use the ACTG Brief Peripheral Neuropathy Scale (BPNS) to scale and track the degree of peripheral neuropathy (see www.hiv.va.gov/provider/manual-primary-care/peripheral-neuropathy.asp#S4.2X).

## O: Objective

Measure vital signs (increases in blood pressure, respiratory rate, and heart rate can correlate with pain). Perform a symptom-directed physical examination, including a thorough neurologic and musculoskeletal examination. Look for masses, lesions, and localizing signs. Pay special attention to sensory deficits (check for focality, symmetry, and distribution [such as "stocking-glove"]), muscular weakness, reflexes, and gait. Patients with significant motor weakness or paralysis, especially if progressive over days to weeks, should be evaluated emergently.

**To evaluate peripheral neuropathy:** Check ankle Achilles tendon reflexes and look for delayed or absent reflexes as signs of peripheral neuropathy. Distal sensory loss often starts with loss of vibratory sensation, followed by loss of temperature sensation, followed by onset of pain. Findings are usually bilateral and symmetric.

## A: Assessment

Pain assessment includes determining the type of pain, for example, nociceptive, neuropathic, or muscle spasm pain.

**Nociceptive pain** occurs as a result of tissue injury (somatic) or activation of nociceptors resulting from stretching, distention, or inflammation of the internal organs of the body. It usually is well localized; may be described as sharp, dull, aching, throbbing, or gnawing in nature; and typically involves bones, joints, and soft tissue.

**Neuropathic pain** occurs from injury to peripheral nerves or central nervous system structures. Neuropathic pain may be described as burning, shooting, tingling, stabbing, or like a vise or electric shock; it involves the brain, central nervous system, nerve plexuses, nerve roots, or peripheral nerves. It is associated with decreased sensation and hypersensitivity.

**Muscle spasm pain** can accompany spinal or joint injuries, surgeries, and bedbound patients. It is described as tight, cramping, pulling, and squeezing sensations.

Although pain in HIV-infected patients can result from opportunistic infections, neoplasms, or medication-related neuropathy, it is important to include non-HIV-related causes of pain in a differential diagnosis. Some of these other causes may be more frequent in HIV-infected individuals. A partial list for the differential diagnosis includes:

- Anorectal carcinoma
- Aphthous ulcers
- Appendicitis
- Arthritis, myalgias
- Candidiasis, oral or esophageal
- Cholecystitis
- Cryptococcal disease
- Cytomegalovirus colitis
- Dental abscesses
- Gastroesophageal reflux disease (GERD)
- Ectopic pregnancy
- Herpes simplex
- Herpes zoster
- Kaposi sarcoma
- Lymphoma
- Medication-induced pain syndromes (e.g., owing to growth hormone, granulocyte colony-stimulating factor)
- Medication-induced peripheral neuropathy (e.g., owing to didanosine, stavudine, isoniazid, vincristine)
- Other causes of peripheral neuropathy: diabetes, hypothyroidism, B12 deficiency, syphilis, cryoglobulinemia (especially in patients with hepatitis C coinfection)
- *Mycobacterium avium* complex
- Myopathy
- Pancreatitis
- Pelvic inflammatory disease
- Toxoplasmosis

## P: Plan

Perform a diagnostic evaluation based on the suspected causes of pain.

### Treatment

Treatment should be aimed at eliminating the source of pain, if possible. If symptomatic treatment of pain is needed, begin treatment based on the patient's pain rating scale, using the least invasive route. The goal is to achieve optimal patient comfort and functioning (not necessarily zero pain) with minimal medication adverse effects. Use the three-step pain analgesic ladder originally devised by the World Health Organization (WHO); see Figure 2.

### Nonpharmacologic interventions

The following interventions can be used at any step in the treatment plan:

- A therapeutic provider-patient relationship
- Physical therapy
- Exercise
- Relaxation techniques
- Guided imagery
- Massage
- Biofeedback
- Reflexology
- Acupuncture
- Thermal modalities (hot and cold compresses or baths)
- Transcutaneous electrical nerve stimulation (TENS)
- Spiritual exploration
- Prayer
- Deep breathing
- Meditation
- Enhancement of coping skills
- Self-hypnosis
- Humor
- Distraction
- Hobbies

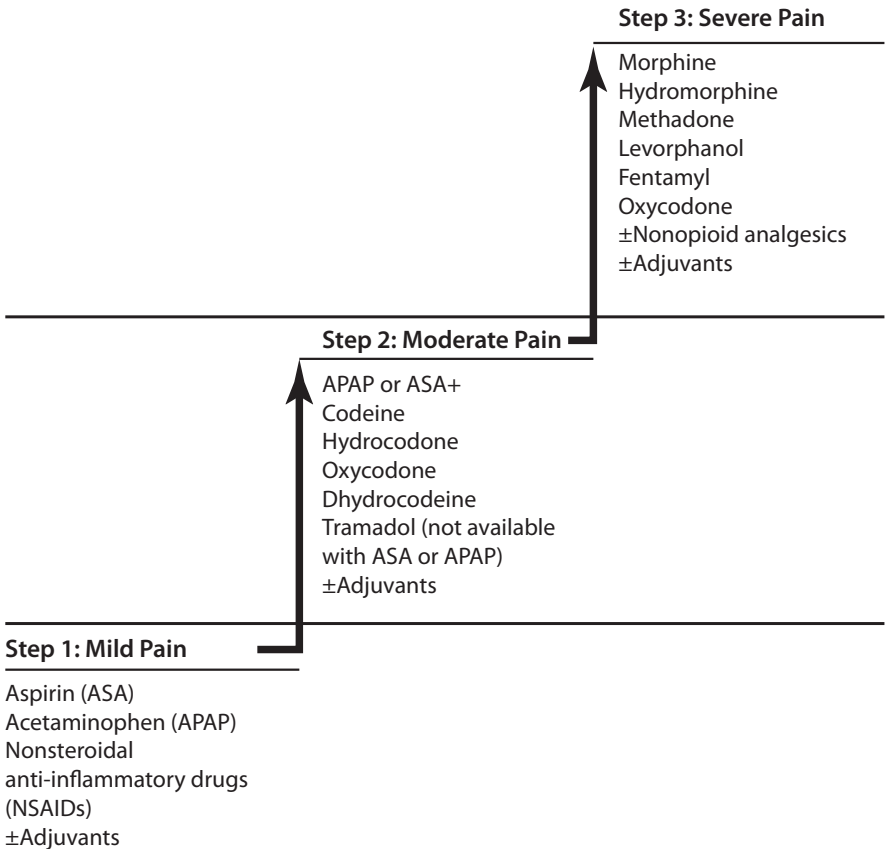
## Pharmacologic interventions

### Principles of pharmacologic pain treatment

- The dosage of the analgesic is adjusted to give the patient adequate pain control.
- The interval between doses is adjusted so that the pain control is uninterrupted. It can take 4-5 half-lives before the maximum effect of an analgesic is realized.
- Chronic pain is more likely to be controlled when analgesics are dosed on a continuous schedule rather than "as needed." Sustained-release formulations of opioids should be used whenever possible.
- For breakthrough pain, use "as needed" medications in addition to scheduled-dosage analgesics. When using opiates for both scheduled analgesia and breakthrough pain, a good rule of thumb is to use 10% of the total daily dosage of opiates as the "as needed" opiate dose for breakthrough pain.
- Oral administration has an onset of analgesia of about 20-60 minutes, tends to produce more stable blood levels, and is cheaper.
- Beware of the risk of prolonged analgesic half-lives in patients with renal or hepatic dysfunction.
- Caution when using combination analgesics that are coformulated with ingredients such as acetaminophen, aspirin, or ibuprofen. Determine the maximum daily dosage of all agents.

The following three steps are adapted from the WHO analgesic ladder. Agents on higher steps are progressively stronger pain relievers but tend to have more adverse effects.

**Figure 2. Pharmacologic Approaches to Pain Management: WHO Three-Step Ladder**




Adapted from World Health Organization. *Cancer Pain Relief and Palliative Care, Report of a WHO Expert Committee.* Geneva: World Health Organization; 1990.
Note: "Adjuvants" refers either to medications that are coadministered to manage an adverse effect of an opioid or to so-called adjuvant analgesics that are added to enhance analgesia.

## Step 1: Nonopiates for mild pain (pain scale 1-3)

- The most common agents in this step include acetaminophen (650-1,000 mg PO Q6H as needed) and nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen 600-800 mg PO TID with food, and cyclooxygenase-2 (COX-2) inhibitors such as celecoxib and rofecoxib.
- A proton-pump inhibitor (such as omeprazole) can decrease the risk of gastrointestinal bleeding when using NSAIDs.
- Acetaminophen has no effect on platelets and no antiinflammatory properties; avoid use in patients with hepatic insufficiency, and in general limit to 4 g per day in acute use (or 2 g per day for patients with liver disease). Monitor liver function tests in chronic use.
- NSAIDs and acetaminophen can be used together for synergism.
- Note that COX-2 inhibitors have been associated with an increased risk of cardiovascular events and should be used with caution.

### Step 2: Mild opiates with or without nonopiates for moderate pain (pain scale 4-6)

- Most agents used to treat moderate pain are combinations of opioids and Step 1 agents. The most common agents are acetaminophen combined with codeine, oxycodone, or hydrocodone. Codeine can be dosed as codeine sulfate, separately from acetaminophen. Beware of acetaminophen toxicity in these combination drugs.
- Other agents include buprenorphine (partial opiate agonist).
- Tramadol (Ultram) is a centrally acting nonopiate that can be combined with NSAIDs. As with opiates, it is prone to abuse. Tramadol lowers the seizure threshold; avoid use for patients with a seizure history. Avoid coadministration with selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) because of the risk of serotonin syndrome.

### Step 3: Opioid agonist drugs for severe pain (pain scale 7-10)

- Morphine is the drug of choice in this step. Start with short-acting morphine and titrate the dosage to adequate pain control, then divide the 24-hour total in half to determine the dosing for the sustained-release morphine, given Q12H. When converting from IV to PO morphine, PO dosage is about two to three times the parenteral dosage.
- Other agents used are oxycodone, hydromorphone, fentanyl, levorphanol, methadone, codeine, hydrocodone, oxymorphone, and buprenorphine.
- Avoid meperidine because of the increased risk of delirium and seizures.
- Around-the-clock, sustained-release PO dosing will achieve optimum pain relief.
- Patients unable to take PO therapy may use transdermal fentanyl patches or do rectal administration of sustained-release tablets such as long-acting morphine. Note that the onset of analgesia with fentanyl patches can take more than 12 hours, and the analgesic effect can last more than 18 hours after the patch is removed.
- Anticipate and treat complications and adverse effects of opioid therapy, such as nausea, vomiting, and constipation. Constipation often leads to nausea and can be prevented with prophylactic stool softeners (such as docusate) and stimulant laxatives (such as senna).

### Adjunctive treatments

The addition of antidepressant medications can improve pain management, especially for chronic pain syndromes. These agents, and anticonvulsants, usually are used to treat neuropathic pain (discussed in more detail below), but should be considered for treatment of other chronic pain syndromes as well.

### Treatment of neuropathic pain

Assess the underlying etiology, as discussed above, and treat the cause as appropriate. Review the patient's medication list for medications that can cause neuropathic pain. Discontinue the offending agents, if possible. For patients on stavudine or didanosine, in particular, switch to another nucleoside analogue if suitable alternatives exist, or at least consider dosage reduction of stavudine to 30 mg BID (consult with an HIV expert). For patients on isoniazid, ensure that they are taking vitamin B6 (pyridoxine) regularly to avoid isoniazid-related neuropathy.

### Nonpharmacologic interventions for neuropathic pain

The nonpharmacologic interventions described above can be useful in treating neuropathic pain.

### Pharmacologic interventions for neuropathic pain

Follow the WHO ladder of pain management described above. If Step 1 medications are ineffective, consider adding antidepressants, anticonvulsants, or both before moving on to opioid treatments.

### Antidepressants

Antidepressant medications often exert analgesic effects at dosages that are lower than those required for antidepressant effects. As with antidepressant effects, optimum analgesic effects may not be achieved until several weeks after starting therapy.

- **Tricyclic antidepressants (TCAs):** Note that ritonavir and other protease inhibitors, and the pharmacokinetic booster cobicistat, may increase the level of TCAs, so start at the lowest dosage and titrate up slowly. Dosages may be titrated upward every 3-5 days, as tolerated. In general, TCAs are best avoided in elderly patients.
  - **Nortriptyline (Pamelor):** Starting dosage is 10-25 mg QHS. Usual maintenance dosage is 20-150 mg QHS.
  - **Desipramine (Norpramin):** Starting dosage is 25 mg QHS. Usual maintenance dosage is 25-250 mg QHS.
  - **Imipramine:** Starting dosage is 25 mg QHS. Usual maintenance dosage is 25-300 mg QHS.
  - **Amitriptyline (Elavil):** Starting dosage is 10-25 mg QHS. Usual maintenance dosage is 25-150 mg QHS. Amitriptyline has the highest rate of adverse effects among the TCAs, so other agents typically are preferred.

Adverse effects include sedation, anticholinergic effects (e.g., dry mouth, urinary retention), altered mental status, QT prolongation, arrhythmias, and orthostatic hypotension. Monitor TCA levels and EKG at higher dosage levels. There is a significant risk of overdose if taken in excess.

- **SSRIs:** See chapter *Major Depression and Other Depressive Disorders* for dosing, side effects, and drug interactions associated with this class of agents. SSRIs are less effective than TCAs in treating chronic pain.
- **Venlafaxine (Effexor):** Starting dosage is 37.5 mg daily. Usual maintenance dosage is 75-300 mg daily in divided doses or by extended-release formulation (Effexor XR). Note that there are limited data on using venlafaxine for patients with HIV infection.
- **Duloxetine (Cymbalta):** Starting dosage is 30-60 mg daily. Dosages of >60 mg per day are rarely more effective for either depression or pain treatment. Note that there are limited data on using duloxetine for patients with HIV infection.

### Anticonvulsants

The following agents may be effective for neuropathic pain:

- **Gabapentin (Neurontin):** Considered first-line for HIV sensory neuropathy for its tolerability. Starting dosage is 100-300 mg QHS; may be increased every 3-5 days to BID or TID to achieve symptom relief. Monitor response and increase the dosage every 1-2 weeks by 300-600 mg/day. Usual maintenance dosage is 1,200-3,600 mg/day in divided doses. Adverse effects include somnolence, dizziness, fatigue, weight gain, and nausea. To discontinue, taper over the course of 7 or more days.
- **Pregabalin (Lyrica):** Starting dosage is 25-50 mg TID; may be increased by 25-50 mg per dose every 3-5 days as tolerated to achieve symptom relief. Maximum dosage is 200 mg TID. Adverse effects are similar to those of gabapentin. To discontinue, taper over the course of 7 or more days.
- **Lamotrigine (Lamictal):** Starting dosage is 25 mg QOD; titrate slowly to 200 mg BID over the course of 6-8 weeks to reduce the risk of rash (including Stevens-Johnson syndrome). Adverse effects include sedation,

dizziness, ataxia, confusion, nausea, blurred vision, and rash. Note that lopinavir/ritonavir (Kaletra) may decrease lamotrigine levels; higher dosages may be needed. To discontinue, taper over the course of 7 or more days.

- Although phenytoin and carbamazepine have some effectiveness in treating neuropathy, they have significant drug interactions with protease inhibitors and nonnucleoside reverse transcriptase inhibitors, and their use with HIV-infected patients is limited. Topiramate and valproic acid have been used for migraine prophylaxis and anecdotally may be useful for treating peripheral neuropathy, but have not been well-studied in HIV-related neuropathies.

## Topical therapy

- **Capsaicin cream** (0.075%, 0.1%): Capsaicin inhibits the secretion of substance P and has been found to be effective for the management of pain associated with arthritis and neuropathy. It may be applied BID or TID. Patients must be instructed to wash their hands well after applying to avoid spreading the residual cream to sensitive areas such as the nose or eyes. It may cause burning.

### Treatment of Muscle Spasm Pain

Stretching, heat, and massage may help the pain of muscle spasm. This pain also can respond to muscle relaxants such as baclofen, cyclobenzaprine, tizanidine, benzodiazepines, as well as intraspinal infusion of local anesthetics for spinal injuries.

### Substance Abuse, HIV, and Pain

Some health care providers hesitate to treat pain in patients with current or past substance abuse because of concern about worsening these patients' dependence on opioids or suspicion that such patients are seeking pain medications for illicit purposes. However, the following points should be considered:

- Many patients with current or past substance abuse do experience pain, and this pain should be evaluated by care providers and treated appropriately.
- Failure to distinguish among addiction, tolerance, and dependence can lead to undertreatment of chronic pain by health care providers.
- Addiction (substance abuse) is a complex behavioral syndrome characterized by compulsive drug use for the secondary gain of euphoria.
- Pharmacologic tolerance refers to the reduction of effectiveness, over time, of a given dosage of medication.
- Physical dependence is the consequence of neurophysiologic changes that take place in the presence of exogenous opioids.
- Aberrant use of pain medications, if it develops, is best managed by an interdisciplinary team of providers from HIV clinical care, psychiatry, psychology, pharmacy, social services, and drug addiction management.
- Drug-drug interactions between certain antiretroviral medications and methadone can decrease methadone serum concentrations (see chapter *Drug-Drug Interactions with HIV-Related Medications*). If this occurs, methadone dosages may need to be increased to prevent opiate withdrawal.
- As part of chronic pain management in patients with substance abuse, consider establishing a written pain-management

contract to be signed by the clinician and the patient. The contract should:

- Clearly state limits and expectations for both the patient and provider.
- Identify a single clinician responsible for managing the pain regimen.
- Tell the patient what to do if the pain regimen is not working.
- Describe the procedure for providing prescriptions (e.g., one prescription given to the patient, in person, for a limited period of time, such as 1 month).
- List the rules for dealing with lost medications or prescriptions.

## Patient Education

- Pain management is part of HIV treatment, and patients should give feedback to allow the best treatment decisions. If pain persists for more than 24 hours at a level that interferes with daily life, patients should inform their health care provider so that the plan can be changed and additional measures, if needed, can be tried.
- Patients should not expect full pain relief in most cases, but enough relief that they can perform their daily activities.
- "Mild" pain medications (e.g., NSAIDs, aspirin, acetaminophen) usually are continued even after "stronger" medications are started because their mechanism of action is different from that of opiates. This combination of pain medication has additive effects, so that pain may be controllable with a lower narcotic dosage.
- Patients taking "around-the-clock" medications should take them on schedule. Those taking "as needed" medications should take them between doses only if they have breakthrough pain.
- Patients who are prescribed opiates should be advised to take no more than the prescribed dosages. Misuse or inappropriate use can result in overdose.
- Opiates may cause severe constipation. Patients must remain hydrated and will likely need stool softeners, laxatives, or other measures. They should contact their health care provider promptly if constipation occurs.
- Patients taking opiates should avoid driving and operating machinery.

## References


- American Academy of HIV Medicine. *Pain Management.* In: *AAHIVM Fundamentals of HIV Medicine (2007 ed.).* Washington, DC: American Academy of HIV Medicine; 2007.
- Association of Nurses in AIDS Care. *Pain.* In: Kirton C, ed. *Core Curriculum for HIV/AIDS Nursing, 2nd Edition.* Thousand Oaks, CA: Sage Publications; 2003;143-155.
- Breitbart W. *Suicide Risk and Pain in Cancer and AIDS.* In: Chapman CR, Foley KM, eds. *Current and Emerging Issues in Cancer Pain: Research and Practice.* New York: Raven Press; 1993;49-66.
- Cherry CL, Wesselingh SL, Lal L, et al. *Evaluation of a clinical screening tool for HIV-associated sensory neuropathies.* Neurology. 2005 Dec 13;65(11):1778-81.
- Gonzalez-Duarte A. Robinson-Papp J, Simpson DM. *Diagnosis and management of HIV-associated neuropathy.* Neurol Clin. 2008 Aug;26(3):821-32, x.
- Hahn K, Arendt G, Braun JS, et al. *A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies.* J Neurol. 2004 Oct;251(10):1260-6.
- McArthur J, Brew B, Nath A. *Neurological complications of HIV infection.* Lancet Neurol. 2005 Sep;4(9):543-55.
- O'Neill WM, Sherrard JS. *Pain in human immunodeficiency virus disease: a review. Pain.* 1993 Jul;54(1):3-14.
- Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.* Department of Health and Human Services. Available at aidsinfo.nih.gov/guidelines. Accessed December 1, 2013.
- Singer EJ, Zorilla C, Fahy-Chandon B, et al. *Painful symptoms reported by ambulatory HIV-infected men in a longitudinal study.* Pain. 1993 Jul;54(1):15-9.
- Slaughter A, Pasero C, Manworren R. *Unacceptable pain levels.* Am J Nurs. 2002 May;102(5):75, 77.
- Swica Y, Breitbart W. *Treating pain in patients with AIDS and a history of substance use.* West J Med. 2002 Jan;176(1):33-9.
- Weinreb NJ, Kinzbrunner BM, Clark M. *Pain Management.* In: Kinzbrunner BM, Weinreb NJ, Policzer JS, eds. 20 *Common Problems: End-of-life Care.* New York: McGraw Hill Medical Publishing Division; 2002:91-145.
- U.S. Department of Health and Human Services. *A Guide to the Clinical Care of Women with HIV – 2013 Edition.* Rockville, MD: U.S. Department of Health and Human Services; 2013. Available at hab.hrsa.gov/deliverhivaidscare/files/womenwithaids.pdf. Accessed March 1, 2013.
- U.S. Department of Health and Human Services. *Management of Cancer Pain.* Rockville, MD: Department of Health and Human Services; 1994.
- World Health Organization. *Cancer Pain Relief and Palliative Care, Report of a WHO Expert Committee.* Geneva: World Health Organization; 1990.

# HIV-Associated Neurocognitive Disorders

## Background

HIV is a neurotropic virus that directly invades the brain shortly after infection. HIV replicates in brain macrophages and microglia, causing inflammatory and neurotoxic host responses. HIV may cause cognitive, behavioral, and motor difficulties. These difficulties may range in severity from very mild to severe and disabling.

The American Academy of Neurology (AAN) recognizes three categories of HIV-associated neurocognitive disorder (HAND) (see Table 1, below).

- **Asymptomatic neurocognitive impairment** (ANI) is determined by neurocognitive testing and is not apparent clinically.
- **Mild neurocognitive disorder** (MND) is a diagnosis of exclusion; it may be made clinically if neurocognitive testing is not available, and it involves mild functional impairment.
- **HIV-associated dementia** (HAD) involves moderate to severe functional impairment.

[In the *Diagnostic and Statistical Manual of Mental Disorders (*DSM-5) section on cognitive disorders, MND correlates with mild neurocognitive disorder, and HAD with major neurocognitive disorder.]

Both MND and HAD are AIDS-defining conditions (listed as "Encephalopathy, HIV Related" in the classification system used by the U.S. Centers for Disease Control and Prevention), and they are risk factors for death. Neurocognitive disorders associated with HIV are among the most common and clinically important complications of HIV infection. However, they are diagnoses of exclusion, and other medical causes must be ruled out.

Risk factors for developing an HIV-associated neurocognitive disorder include the following:

- Older age
- Female gender
- More advanced HIV disease (including CD4 count of <100 cells/μL, wasting)
- High plasma HIV RNA (viral load)
- Comorbid conditions (especially anemia and infection with cytomegalovirus, human herpesvirus 6, and JC virus)
- History of injection drug use (especially with cocaine)
- History of delirium

With the advent of ART, HAD prevalence has declined and MND prevalence has increased.

As people with HIV live longer and become older, the risk of developing cognitive impairment increases. The use of effective antiretroviral therapy (ART) that maintains the plasma HIV RNA at undetectable or low values is important for preventing and treating HIV-related neurocognitive disorders. In people with neurocognitive impairment, however, there may be some benefit in using antiretroviral (ARV) agents that penetrate the CNS. However, recent research suggests that neuroinflammation rather than the HIV viral load in the CNS is primarily responsible for cognitive impairment in HIV-infected individuals. In choosing an ART regimen, it is important to take into consideration resistance testing, CNS penetration, and adherence issues.

### Minor Neurocognitive Disorder

MND is characterized by mild impairment in functioning and may escape diagnosis by the clinician. The onset and course of MND can vary dramatically. The more demanding the activities of a particular individual, the more likely that person would be to notice the difficulties in functioning.

### HIV-Associated Dementia

HAD is characterized by symptoms of cognitive, motor, and behavioral disturbances. There is often a progressive slowing of cognitive functions, including concentration and attention, memory, new learning, sequencing and problem solving, and executive control. HAD also can present with behavioral changes, which mainly take the form of apathy, loss of motivation, poor energy, fatigue, and social withdrawal. Motor changes, including slowing, clumsiness, unsteadiness, increased tendon reflexes, and deterioration of handwriting may occur.

## S: Subjective

If a neurocognitive disorder is suspected, obtain a history of the patient's symptoms (see below). Whenever possible, obtain a parallel history of the patient's past history and recent mental status changes from significant others or caretakers.

Patient self-reports of cognitive problems and bedside cognitive status tests may be insensitive, particularly to subtler forms of impairment. Often, other people may observe changes in the person's behavior or mood that indicate some change in cognitive functioning.

To help clarify factors that may be causing the changes in mental status, inquire about the following:

- Acuity of onset
- Recent changes or events
- Medications, particularly new medications
- Drug and alcohol use
- Symptoms of opportunistic illnesses, other infections
- HIV history, including duration, CD4 cell count, HIV viral load, history of ART
- History of other medical and psychiatric disorders

**Table 1. AAN Criteria for HIV-Associated Neurocognitive Disorder**

| **HIV-Associated Asymptomatic Neurocognitive Impairment (ANI)** |
|---|
| • Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1 SD below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills.<br>• The cognitive impairment does not interfere with everyday functioning.<br>• The cognitive impairment does not meet criteria for delirium or dementia.<br>• There is no evidence of another preexisting cause for the ANI. |
| **Mild Neurocognitive Disorder (MND)** |
| • Acquired impairment in cognitive functioning, involving at least two ability domains, documented by performance of at least 1 SD below the mean for age/education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language, attention/working memory, abstraction/executive, memory (learning and recall), speed of information processing, sensory–perceptual and motor skills.<br>• The cognitive impairment produces at least mild interference in daily functioning (at least one of the following):<br>  • Self-report of reduced mental acuity, inefficiency in work, homemaking or social functioning<br>  • Observation by knowledgeable others that the individual has undergone at least mild decline in mental acuity with resultant inefficiency in work, homemaking, or social functioning<br>• The cognitive impairment does not meet criteria for delirium or dementia.<br>• There is no evidence of another pre-existing cause for the mild neurocognitive disorder. If the individual with suspected mild neurocognitive disorder also satisfies criteria for a severe episode of major depression with significant functional limitations or psychotic features, or substance dependence, the diagnosis of mild neurocognitive disorder should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month after cessation of substance use. |
| **HIV-Associated Dementia (HAD)** |
| • Marked acquired impairment in cognitive functioning, involving at least two ability domains; typically the impairment is in multiple domains, especially in the learning of new information, slowed information processing and defective attention/concentration. The cognitive impairment must be ascertained by neuropsychological testing with at least two domains being 2 standard deviations or greater below that of demographically corrected means.<br>• The cognitive impairment produces marked interference with day-to-day functioning (work, home life and social activities).<br>• The pattern of cognitive impairment does not meet criteria for delirium.<br>• There is no evidence of another, pre-existing cause for the dementia (e.g., other CNS infection, CNS neoplasm, cerebrovascular disease, pre-existing neurologic disease or severe substance abuse compatible with CNS disorder). |

Adapted from Antinori A, Arendt G, Becker JT, et al. *Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007* Oct 30;69(18):1789-99.

Additionally, the AAN specifies that, for patients with severe depression or substance dependence who are suspected of having HAD, the neurocognitive assessment should be deferred until the depression or substance use is in remission.

Although the AAN criteria include assessment via neuropsychological testing, in the absence of such testing, it is acceptable to make a presumptive diagnosis of MND or HAD on the basis of clinical signs and symptoms once all other possible causes of changes in mental function have been ruled out.

## O: Objective

- Check temperature and other vital signs (MND and HAD are not associated with fever).
- Perform a complete physical examination with special attention to signs of opportunistic illnesses.
- Perform a thorough neurological examination, including funduscopy. Rule out focal neurologic deficits.
- Perform Mini-Mental State Examination (note that this is not sensitive for HIV-associated neurocognitive disorders; negative results do not rule out these conditions).

Consider a neuropsychological screening test such as the Modified HIV Dementia Scale (see Figure 1), International HIV Dementia Scale, or the Montreal Cognitive Assessment. Others are noted in "Laboratory and Diagnostic Evaluation," below.

## A: Assessment

A differential diagnosis includes the following medical conditions, which may present with cognitive changes or delirium:

- Substance use: intoxication or withdrawal from alcohol, opioids, stimulants, etc.
- Psychiatric disorders, especially major depression
- Metabolic or systemic disorders, including hepatic encephalopathy, vitamin B12 or folate deficiency, uremia, endocrine disorders (e.g., hypogonadism)
- Central nervous system (CNS) opportunistic infections, such as cytomegalovirus encephalitis, cryptococcal meningitis, tuberculous meningitis, CNS toxoplasmosis, and progressive multifocal leukoencephalopathy (PML)
- Systemic infections
- Brain tumors, including CNS lymphoma and metastatic disease
- Other causes of cognitive impairment and dementia (e.g., neurosyphilis, substance-induced dementia, vascular dementia, brain injury, Alzheimer disease, and hydrocephalus)
- Medication adverse effects: ARV medications (especially efavirenz), psychotropic medications, interferon, anticholinergics, and others
- Poisoning with toxic substances

## P: Plan

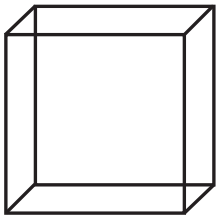
### Laboratory and Diagnostic Evaluation

A change in the mental status of an HIV-infected person should prompt a thorough search for underlying biological causes. As noted above, HIV-related neurocognitive disorders are diagnoses of exclusion, and other causes of the patient's symptoms should be ruled out.

Perform the following tests:

- Laboratory tests: Complete blood count, electrolytes and creatinine, liver function, thyroid function, vitamin B12, rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL).
- Toxicology tests if substance use is suspected (e.g., opioids, ethanol, amphetamines).
- Brain imaging studies (computed tomography [CT] scan or magnetic resonance imaging [MRI]); rule out space-occupying masses and other lesions; cortical atrophy may be seen in advanced HAD; this finding is not specific.
- Cerebral spinal fluid (CSF) tests if CNS infection is suspected.
- Consider tests for neurocognitive impairment as noted in the table below; most of these can be found on the website of the New York State Department of Health AIDS Institute at www.hivguidelines.org/clinical-guidelines/hiv-and-mental-health.
- Refer to an HIV-experienced neuropsychologist, neurologist, or psychiatrist, if available.

**Figure 1. Modified HIV Dementia Scale**

| Maximum Score | Score | Exercise |
|---|---|---|
| N/A | N/A | **Memory/Registration:** State four words for the patient to recall (dog, hat, green, peach), pausing 1 second between each. Then ask the patient to restate all four. |
| 6 | (___) | **Psychomotor Speed:** Ask the patient to write the alphabet in upper case letters horizontally across the page; record time: ____seconds.<br>≤21 sec = 6<br>21.1 - 24 sec = 5<br>24.1 - 27 sec = 4<br>27.1 - 30 sec = 3<br>30.1 - 33 sec = 2<br>33.1 - 36 sec = 1<br>> 36 sec = 0 |
| 4 | (___) | **Memory Recall:** Ask the patient to restate the four words from Memory/ Registration above. Give one point for each correct response. For words not recalled, prompt with a "semantic" clue, as follows: animal (dog); piece of clothing (hat), color (green), fruit (peach). Give 1/2 point for each correct after prompting. |
| 2 | (___) | **Construction:** Copy the cube below; record time:____seconds.<br>(<25 sec = 2; 25 – 35 sec = 1; >35 sec = 0)<br>  |

Maximum score: 12 points; a score of <7.5 points suggests possible HAD (note, this test is not specific)
Adapted from McArthur JC. *Minor cognitive motor disorder: Does it really exist?* Hopkins HIV Rep. Nov 1996;8(4):8.

| Table 2. Tests for Identifying and Staging HIV-Related Neurocognitive Impairment | |
|---|---|
| **HIV Dementia Scale** | • Screens for the memory and attention deficits and psychomotor slowing that are typical of HAD<br>• Requires training to administer and, therefore, may not be ideal for a clinic setting |
| **Modified HIV Dementia Scale** | • Designed specifically for use by non-neurologists and, therefore, may be more useful than the HIV Dementia Scale for a primary care setting<br>• Requires approximately 5 minutes to administer<br>• See Figure 1, above |
| **Mental Alternation Test** | • Useful for assessing patients with early dementia, who will show impairments in timed trials |
| **Memorial Sloan-Kettering (MSK) Scale** | • Can be used for assessing severity<br>• Combines the functional impact of both cerebral dysfunction (dementia) and spinal cord dysfunction (myelopathy); the two entities can be separated and staged independently |
| **Trail Making Test, Parts A and B (from the Halstead-Reitan Neuropsychological Battery)** | • May be used as a screening tool, but results require interpretation by a neuropsychologist<br>• May be used at the bedside to track a patient's response to ART over time |
| **Grooved Pegboard (dominant and nondominant hand)** | • May be used as a screening tool and does not require literacy |

## Treatment

There are no specific treatments for HIV-associated neurocognitive disorders, but ART may reverse the disease process, and a number of therapies may be helpful. The treatment of MND and HAD ideally utilizes a multidisciplinary approach that may involve HIV specialists, neurologists, psychiatrists, psychologists, nurse practitioners, social workers, substance-use counselors, case managers, and others.

Neurocognitive impairment in patients with HIV infection often is multifactorial. In addition to treating HIV-associated neurocognitive disorders themselves, it is important to correct, as much as possible, all medical conditions that may adversely affect the brain (e.g., psychiatric comorbidities, endocrinologic abnormalities, adverse medication effects). For patients using alcohol or illicit or nonprescribed drugs, implement strategies to reduce their use; these agents can further impair cognition.

### Pharmacologic Management of HIV-Associated Neurocognitive Disorders

- **ART:** Maximal suppression of HIV replication via ART may partially or fully reverse HIV-associated neurocognitive disorders, and ART is the treatment of choice for both treatment and prevention of HIV-associated neurocognitive disorders, including dementia. In general, ART regimens that effectively suppress HIV RNA in the serum also suppress HIV in the CNS. However, ARV medications vary in their ability to penetrate the blood-brain barrier and, therefore, in their ability to act directly on the HIV in the CNS. Limited data suggest that using ARVs with good CNS penetration may be important in treating or preventing neurocognitive disorders, and some experts recommend the use of these ARVs, if otherwise appropriate, for patients with HIV dementia. ARVs with the best CNS penetration include the nucleoside reverse transcriptase inhibitors (NRTIs)

abacavir, emtricitabine, and zidovudine (AZT, ZDV); the nonnucleoside reverse transcriptase inhibitor (NNRTI) nevirapine; the protease inhibitors (PIs) indinavir/ritonavir and lopinavir/ritonavir; and the CCR5 antagonist maraviroc. The integrase inhibitor raltegravir has reasonably good CNS penetration. There currently is no role for testing levels of HIV RNA in the CSF outside research settings.

- **Stimulants:** Stimulant medications (e.g., methylphenidate, dextroamphetamine) have been used as palliative agents to help manage symptoms of fatigue, decreased concentration, and memory deficits among patients with MND and HAD. Starting dosages of both is 5 mg/day; maximum dosage is 60 mg/day. The response to stimulants is idiosyncratic and varies from patient to patient; begin with the lowest dose of 5 mg QAM and titrate upward as needed. If BID dosing is required as a result of afternoon fatigue, the afternoon dose should be taken before 2 p.m. to prevent interference with sleep. Consider referral to a psychiatrist or neurologist for evaluation and initiation of treatment; after a stable dosage is achieved, treatment may be continued. These medications should be used with caution for patients who have a history of stimulant abuse.
- For comorbid depression, consider prescribing antidepressant medications as for other medically ill HIV-infected patients (see chapter *Major Depression and Other Depressive Disorders*).
- Antipsychotic medications may be useful in treating agitation and hallucinations but should be used for patients with dementia only when nonpharmacologic measures are insufficient for patient management; consult with a psychiatrist. All antipsychotic medications increase the risk of death in elderly patients with dementia. Start antipsychotic medications at the lowest possible dosage and increase slowly as needed.
- Many agents are being studied for either their neuroprotective effects or their therapeutic effects on HIV-associated neurocognitive disorders. The data are not sufficient at present to make specific recommendations. Patients with dementia often are sensitive to medication side effects; follow closely.
- Benzodiazepines have been shown to increase confusion and decrease concentration, and generally should be avoided.

### Nonpharmacologic Management of MND and Mild HAD

- Encourage patients to remain appropriately active
- Explain the benefits of structured routines
- Encourage good nutrition
- Use strategies to minimize use of alcohol and illicit drugs
- Use memory aids such as lists
- Simplify complex tasks, especially drug regimens
- When giving instructions, do the following:
  - Repeat information
  - Write instructions to provide structure for patients and caregivers
  - Ask patients to express the information and instructions in their own words
- Adherence to medical regimens, including ART, often is particularly difficult for patients with neurocognitive disorders. Encourage use of medication adherence tools such as pill boxes, alarms, and, if available, packaged medications (e.g., blister packs) or prefilled medi-sets. Encourage patients to enlist adherence support from family members and friends.
- Cognitive skills building can be helpful (e.g., reading, solving puzzles, intellectual conversation).

### Nonpharmacologic Management of Moderate to Severe HAD

The strategies noted above should be utilized, but additional measures are needed.

Management of patients with severe or late-stage HAD requires an evaluation of their safety and a determination of the environment and level of supervision that are needed. The clinician should attend to the following:

- Help determine whether patients can be left alone at home or whether doing so would present the risk of them wandering away or sustaining an injury in the home (e.g., from the use of an appliance such as the oven).
- For patients who cannot be left alone at home, assess options for support (e.g., help from family members or paid home attendants).
- Utilize fall prevention strategies.
- For patients who smoke, decide whether smoking can be done safely; if smoking is deemed unsafe, consider smoking cessation programs or supervision.
- If lesser measures fail, explore options for placement in a skilled nursing facility.

Additional helpful strategies for managing patients who are confused, agitated, or challenged by their experience include the following:

- Keep their environments familiar to the extent possible (e.g., in terms of objects, people, locations).
- Redirect or distract patients from inappropriate behavior.
- Remain calm when patients become confused or agitated; refrain from confronting an agitated patient; reorient confused or agitated patients.
- Provide a clock and calendar in the room to help keep patients oriented to time and to day of the week.
- Provide lighting that corresponds with day and night.
- Emphasize routines.
- Ensure that patients who require eyeglasses or hearing aids wear them to help lessen confusion and disorientation.
- Prepare patients for any planned changes.
- Ensure that patients are receiving their prescribed medications.
- Protect wandering patients.
- Supervise any cigarette smoking.
- Offer activities that keep patients' minds alert.
- Educate family members about the nature of dementia and methods for helping patients maintain activities of daily living.
- Suggest that patients or their family members make arrangements for financial, health, and other matters in the event they become unable to make decisions about their affairs (e.g., advance health care directives, durable powers of attorney, wills).

## Patient Education

- Advise patients that ART can be effective in preventing and treating HIV-related neurocognitive impairment.
- Inform patients and family members of the many other strategies that may aid in managing neurocognitive impairment. Such strategies may help patients maintain the highest possible level of skills and independence.
- Family members and significant others can be important sources of support (e.g., by providing assistance with medication adherence).
- Advise patients with advanced HAD that placement in a residential facility may be the best option for ensuring their safety.

## References


- American Academy of Neurology. *Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus-type 1 (HIV-1) infection. Report of a Working Group of the American Academy of Neurology AIDS Task Force.* Neurology. 1991 Jun;41(6):778-85.
- Antinori A, Arendt G, Becker JT, et al. *Updated research nosology for HIV-associated neurocognitive disorders.* Neurology. 2007 Oct 30;69(18):1789-99.
- Brew B, Pemberton L, Cunningham P, et al. *Levels of human immunodeficiency virus type 1 RNA in cerebrospinal fluid correlate with AIDS dementia stage.* J Infect Dis. 1997 Apr;175(4):963-6.
- Cherner M, Cysique L, Heaton RK, et al.; HNRC Group. *Neuropathologic confirmation of definitional criteria for human immunodeficiency virus-associated neurocognitive disorders.* J Neurovirol. 2007;13(1):23-8.
- Cohen MA, Gorman JM. *Comprehensive Textbook of AIDS Psychiatry.* New York: Oxford University Press; 2008.
- Evers S, Rahmann A, Schwaag S, et al. *Prevention of AIDS dementia by HAART does not depend on cerebrospinal fluid drug penetrance.* AIDS Res Hum Retroviruses. 2004 May;20(5):483-91.
- Goodkin K, Fernandez F, M Forstein, et al. *A perspective on the proposal for neurocognitive disorder criteria in DSM-5 as applied to HIV-associated neurocognitive disorders.* Neuropsychiatry (London). 2011 Oct 1;1(5):431-440.
- McArthur JC, McClernon DR, Cronin MF, et al. *Relationship between human immunodeficiency virus-associated dementia and viral load in cerebrospinal fluid and brain.* Ann Neurol. 1997 Nov;42(5):689-98.
- New York State Department of Health AIDS Institute. *Mental Health Care for People with HIV Infection: Clinical Guidelines for the Primary Care Practitioner.* Available at www.hivguidelines.org/clinical-guidelines/hiv-and-mental-health. Accessed December 1, 2013.
- Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.* Department of Health and Human Services. Available at aidsinfo.nih.gov/guidelines. Accessed December 1, 2013.
- Power C, Selnes OA, Grim JA, et al. *HIV dementia scale: a rapid screening test.* J Acquir Immune Defic Syndr Hum Retrovirol. 1995 Mar 1;8(3):273-8.
- Price RW, Epstein LG, Becker JT, et al. *Biomarkers of HIV-1 CNS infection and injury.* Neurology. 2007 Oct 30;69(18):1781-8.
- Rippeth JD, Heaton RK, Carey CL, et al.; HNRC Group. *Methamphetamine dependence increases risk of neuropsychological impairment in HIV infected persons.* J Int Neuropsychol Soc. 2004 Jan;10(1):1-14.
- Schifitto G, Navia BA, Yiannoutsos CT, et al.; Adult AIDS Clinical Trial Group (ACTG) 301; 700 Teams; HIV MRS Consortium. *Memantine and HIV-associated cognitive impairment: a neuropsychological and proton magnetic resonance spectroscopy study.* AIDS. 2007 Sep 12;21(14):1877-86.
- Shiu C, Barbier E, Di Cello F, et al. *HIV-1 gp120 as well as alcohol affect blood-brain barrier permeability and stress fiber formation: involvement of reactive oxygen species.* Alcohol Clin Exp Res. 2007 Jan;31(1):130-7.

# Major Depression and Other Depressive Disorders

## Background

**HRSA HAB Performance Measures**

Percentage of patients aged 12 years and older **screened for clinical depression** on the date of the encounter using an age-appropriate standardized depression screening tool AND, if positive, a follow-up plan is documented on the date of the positive screen

(Adult and Adolescent measure)

Major depression is the most prevalent psychiatric comorbidity among people with HIV infection and commonly has a significant impact on health. The etiology may be multifactorial, as with depression in HIV-uninfected persons, but HIV infection may bring additional complexity. A diagnosis of HIV may cause a psychological crisis, but also may complicate underlying psychological or psychiatric problems (e.g., preexisting depression, anxiety, or substance abuse). Direct viral infection of the central nervous system (CNS) can cause several neuropsychiatric syndromes. In addition, both HIV-related medical conditions and HIV medications can cause or contribute to depression.

Patients with untreated depression experience substantial morbidity and may become self-destructive or suicidal. They are at continuing risk of engaging in unsafe behaviors that may lead to HIV transmission and poor adherence to care and treatment.

Major depression in persons with comorbid medical illness, including HIV infection, has been associated with the following:

- Decreased survival
- Impaired quality of life
- Decreased adherence to antiretroviral therapy (ART)
- Increased risk behaviors
- Suicide
- Longer hospital stays and more frequent medical visits (e.g., emergency room, medical clinics)
- Higher treatment costs

Stress and depressive symptoms, especially when they occur jointly, are associated with diminished immune defenses in HIV-infected individuals, and severe depression is associated with higher mortality rates. Anxiety symptoms are common among people with major depression (see chapter *Anxiety Disorders*). Psychotic symptoms may occur as a component of major depression and are associated with an increased risk of suicide. Even one or two symptoms of depression increase the risk of an episode of major depression.

All clinicians should do the following:

- Maintain a high index of suspicion for depression and screen frequently for mood disorders.
- Elicit any history of psychiatric diagnoses or treatment.

Rule out medical conditions that may cause mood or functional alterations.

Refer for psychiatric evaluation and psychosocial support, including, as appropriate, to substance abuse counselors and domestic violence service providers.

A screening test for depression such as the Patient Health Questionnaire-2 (PHQ-2) should be administered yearly or whenever a patient's complaints or symptoms suggest depressive disorders.

**Patient Health Questionnaire-2 (PHQ-2)**

Over the past 2 weeks, how often have you been having little interest or pleasure in doing things?

0 = Not at all
1 = Several days
2 = More than half the days
3 = Nearly every day

Over the past 2 weeks, how often have you been feeling down, depressed, or hopeless?

0 = Not at all
1 = Several days
2 = More than half the days
3 = Nearly every day

Calculate the total point score: ____

**Score interpretation: Patient Health Questionnaire-2 (PHQ-2)**

| Score | Probability of major depressive disorder (%) | Probability of any depressive disorder (%) |
|---|---|---|
| 1 | 15.4 | 36.9 |
| 2 | 21.1 | 48.3 |
| 3 | 38.4 | 75.0 |
| 4 | 45.5 | 81.2 |
| 5 | 56.4 | 84.6 |
| 6 | 78.6 | 92.9 |

Depression is diagnosed, as in HIV-uninfected individuals, according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-5.

## Major Depression

The patient may complain of either or both of two cardinal symptoms:

- Diminished interest or pleasure in activities
- Depressed mood, sadness

If either or both of these are present, other complaints may be used to diagnose major depression, including the following:

- Decreased ability to concentrate
- Appetite changes with weight changes (increase or decrease)
- Fatigue or loss of energy
- Feelings of worthlessness or guilt
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Recurrent thoughts of death or suicide

The diagnosis of major depression is made if five of the above symptoms occur on most days for at least 2 weeks. Depressed mood or diminished interest or pleasure must be one of the five symptoms present.

Other subjective symptoms of depression may include the following:

- Hopelessness
- Helplessness
- Irritability or anger
- Somatic complaints in addition to those noted above

## Other Depressive Disorders

- **Persistent depressive disorder:** A new DSM category that subsumes dysthymia and chronic major depressive disorder. This is another very common depressive disorder found among HIV-infected patients. Treatments for major depression and persistent depressive disorder are similar.

  Dysthymia has been characterized by more chronic but less severe symptoms than those

found in major depression. The diagnosis is made when a person has had a depressed mood for most of the day, for more days than not, for at least 2 years. While depressed, the patient exhibits two or more of the following symptoms:

- Poor appetite or overeating
- Insomnia or hypersomnia
- Low energy or fatigue
- Low self-esteem
- Poor concentration or difficulty making decisions
- Feelings of hopelessness

In addition, the symptoms must cause clinically significant distress or impairment in functioning, and there can have been no major depressive episode during the first two years of the disturbance.

- **Bipolar disorder:** Major depression may be a manifestation of bipolar disorder. Bipolar disorder should be ruled out before giving an antidepressant to a patient with major depression, as bipolar disorder usually requires the use of mood stabilizers before, or instead of, beginning antidepressant medications (antidepressant therapy may precipitate a manic episode). Bipolar disorder should be suspected if a patient has a history of episodes of high energy and activity with little need for sleep, has engaged in risky activities such as buying sprees and increased levels of risky sexual behavior, or has a history of taking mood stabilizers (lithium and others) in the past. If bipolar disorder is suspected, refer the patient to a psychiatrist for further evaluation and treatment.
- **Other forms of depression** include adjustment disorder with depressed mood (acute reaction to a life crisis, such as the loss of a job), premenstrual dysphoric disorder, disruptive mood dysregulation disorder, and depressive disorder not otherwise specified.

## S: Subjective

- Inquire about the symptoms listed above, and about associated symptoms.
- Take a careful history of the timing and duration of symptoms, their relationship to life events (e.g., HIV testing, loss of a friend, onset of physical symptoms), and any other physical changes noted along with the mood changes.
- Elicit personal and family histories of depression, bipolar disorder, or suicidal behavior.
- Probe for suicidal thoughts, plans, and materials to execute the plans (see chapter *Suicide Risk*).
- Inquire about hallucinations, paranoia, and other symptoms.
- Ask about current and past medication use and substance abuse.

## O: Objective

Perform mental status examination, including evaluation of affect, mood, orientation, appearance, agitation, or psychomotor slowing; perform thyroid examination, inspection for signs of self-injury, and neurologic examination if appropriate.

## A: Assessment

### Partial Differential Diagnosis

Rule out nonpsychiatric causes of symptoms, which may include the following:

- Hypothyroidism or hyperthyroidism
- Hypotestosteronism (hypogonadism) – very common with HIV disease in both men and women
- Other endocrine disorders such as Addison disease
- Substance-induced mood disorder (intoxication or withdrawal)
- Medication adverse effects (e.g., from steroids, efavirenz, isoniazid, or interferon-alfa)

- HIV dementia or minor cognitive motor disorder
- HIV encephalopathy
- Neurosyphilis
- Opportunistic illnesses affecting the CNS (e.g., toxoplasmosis, cryptococcal disease, CNS cytomegalovirus, progressive multifocal leukoencephalopathy)
- Vitamin B12, folate (B6), zinc, vitamin A, or vitamin D deficiency

## P: Plan

### Evaluation

The diagnosis is based on clinical criteria as indicated above. Rule out medical and other causes. An initial screening includes the following:

- Complete blood count, electrolytes, creatinine, blood urea nitrogen (BUN), glucose
- Thyroid function tests (thyroid stimulating hormone [TSH], T4)
- Vitamin B12, vitamin D, and folate levels
- Testosterone (both in men and women)
- Other tests as suggested by history and physical examination

### Treatment

Refer immediately for psychiatric evaluation or treatment if the patient is:

- Hopeless
- Suicidal (see chapter *Suicide Risk*)
- Displaying psychotic symptoms
- Debilitated or functionally impaired by severe symptoms
- Not responding to treatment

The combination of psychotherapy and antidepressant medication is more effective than either treatment modality alone. Social support interventions (e.g., community-based HIV support groups) also can help; refer to available resources. Patients should be encouraged to discontinue alcohol or substance use, and should be referred for treatment as indicated.

### Psychotherapy

Individual psychotherapy with a skilled, HIV-experienced mental health professional can be very effective in treating depression. Several specific types of individual and group psychotherapies for depression (e.g., interpersonal therapy, cognitive-behavioral therapy, behavioral activation, supportive psychotherapy, coping effectiveness) have been shown to be effective for HIV-infected individuals.

### Pharmacotherapy

For most patients, a selective serotonin reuptake inhibitor (SSRI) or a serotonin-norepinephrine reuptake inhibitor (SNRI) is the most appropriate initial treatment for depression. For patients who experience treatment failure with these agents (or have an incomplete response) at a customary therapeutic dosage, consultation with a psychiatrist is recommended.

When selecting antidepressant medications, consider their side effect profiles as a means to manage other symptoms the patient may be experiencing. For example, activating antidepressants (taken in the morning) may help patients who complain of low energy; antidepressants that increase appetite may be useful for patients with wasting syndrome; sedating antidepressants (taken at bedtime) may help patients with insomnia. Medications that may be lethal if overdosed (e.g., tricyclic antidepressants) should not be prescribed to patients for whom suicidality may be a concern.

The information below describes specific antidepressant medications, with information on dosage and possible adverse effects.

Most antidepressants should be started at low dosages and gradually titrated upward to avoid unpleasant side effects that might lead to nonadherence. Antidepressant effect usually is not noticed until 2-4 weeks after starting a medication. If there is no improvement in symptoms in 2-4 weeks, and there are no significant adverse effects, the dosage may be increased.

A therapeutic trial consists of treatment for 4-6 weeks at a therapeutic dosage. If the patient's symptoms have not improved, an increase in dosage or a switch to another medication should be considered. Patients who remain depressed should be referred to a psychiatrist.

Monitor all patients closely after starting them on antidepressant medications. Depressive symptoms may continue to worsen while on medication; improved energy is the initial effect of antidepressants, whereas hopelessness and sadness improve later. In addition, some young persons are at risk of worsening depression caused by antidepressants. Black-box warnings advise that antidepressants may cause increased risk of suicidality in children, adolescents, and young adults (<24 years of age) with major depressive or other psychiatric disorders, especially during the first month of treatment.

Medications should be continued for 6-9 months beyond the resolution of symptoms, to reduce the risk of recurrence. After this time, treatment may be tapered down gradually if the patient wishes, with careful monitoring for depressive symptoms. The risk of recurrence is higher if the first depressive episode is inadequately treated or if the patient has had multiple depressive episodes. For patients with recurrent depression, consider long-term maintenance antidepressant treatment. See "Discontinuing antidepressant medication," below.

### Potential ARV Interactions

Interactions may occur between certain ARVs and agents used to treat depression. Some combinations may be contraindicated and others may require dosage adjustment. Refer to medication interaction resources or consult with an HIV expert, psychiatrist, or clinical pharmacist before prescribing.

Some ARV medications (particularly protease inhibitors [PIs]) and the pharmacokinetic booster cobicistat may affect the metabolism of some antidepressants via cytochrome P450 interactions. For example, ritonavir can significantly increase serum levels of tricyclic antidepressants, increasing the risk of tricyclic toxicity. In the case of most other antidepressants, interactions with ARVs generally are not clinically significant, but most antidepressants used concomitantly with PIs or cobicistat should be started at low dosages and titrated cautiously to prevent antidepressant adverse effects and toxicity. On the other hand, some PIs may decrease levels of paroxetine, sertraline, and bupropion, and efavirenz also lowers sertraline and bupropion levels; these antidepressants may require upward titration if used concurrently with interacting ARVs. Further information is presented under individual agents and classes, below.

For patients who are starting ARV medications (particularly PIs) or cobicistat and are on a stable antidepressant regimen, monitor carefully for adverse effects and for efficacy of the antidepressant; dosage adjustments may be required.

The available antidepressant medications (SSRIs and SNRIs), including therapeutic dosages and possible positive and negative effects, are listed in Table 1.

**Table 1. SSRI and SNRI Antidepressant Medications and Possible Positive and Negative Effects**

| Medication/Usual Dosage | Possible Positive Effects | Possible Negative Effects |
|---|---|---|
| **SSRIs** | No anticholinergic or cardiovascular effects, nonfatal in overdose; may help treat anxiety | • Sexual dysfunction (men and women)<br>• Serotonin withdrawal syndrome if discontinued abruptly |
| Citalopram (Celexa): 10-60 mg QD | May have lower risk of significant drug-drug interactions than other SSRIs | Mild nausea, possible sedation |
| Escitalopram (Lexapro): 10-20 mg QD | May have lower risk of significant drug-drug interactions than other SSRIs | Mild nausea, possible sedation |
| Fluoxetine (Prozac): 10-40 mg QD | Rarely sedating, often energizing, lower risk of SSRI withdrawal syndrome if discontinued abruptly | Insomnia, agitation, nausea, headache, sexual dysfunction in men and women, long half-life |
| Paroxetine (Paxil): 10-40 mg QD | May be sedating (for patients experiencing sedation with paroxetine, dose at bedtime; can be useful with depression-associated insomnia) | Insomnia, agitation (for patients experiencing these effects, administer dose in mornings), nausea, headache, higher risk of SSRI withdrawal syndrome, weight gain |
| Sertraline (Zoloft): 50-200 mg QD | May have lower incidence of significant drug-drug interactions compared with fluoxetine and paroxetine | Insomnia, agitation, nausea, headache |
| **SNRIs** | | • Nausea, headache, nervousness, sexual dysfunction (men and women)<br>• Serotonin withdrawal syndrome if discontinued abruptly |
| Duloxetine (Cymbalta): 30-60 mg QD | May be used also for pain management and neuropathy; may have lower risk of significant drug-drug interactions compared with SSRIs | Nausea, somnolence |
| Venlafaxine (Effexor): 37.5-75 mg BID or TID<br>OR<br>Venlafaxine XR (Effexor XR): 75-375 mg QD | May have lower risk of significant drug-drug interactions compared with SSRIs | Hypertension (monitor blood pressure at higher dosages)<br><br>Higher risk of SSRI/SNRI withdrawal syndrome |
| Desvenlafaxine (Pristiq): 50 mg QD | May have lower risk of significant drug-drug interactions compared with SSRIs | Higher risk of SSRI/SNRI withdrawal syndrome |

## Other agents

- **Bupropion (Wellbutrin and others):** Bupropion is available in immediate-release form (requires TID dosing), sustained-release (SR) (requires BID dosing), or extended-release (XL) (QD dosing) formulations. At higher bupropion dosages, there is an increased risk of seizures, and this drug is contraindicated in patients who have risk factors for seizures. For patients taking PIs, caution should be used as the dosage approaches 300-400 mg per day because of possible increases in levels of bupropion (however, tipranavir and efavirenz may decrease bupropion levels). Bupropion may have an activating effect, which some patients may experience as agitation, insomnia, or both, and also may have an appetite suppressant effect. It usually does not cause sexual dysfunction, and therefore may be helpful for individuals with depression who experience adverse sexual effects with other antidepressant agents.
- **Mirtazapine (Remeron):** (15-45 mg QPM) May have lower risk of significant drug-drug interactions compared with SSRIs; can be useful when weight gain and sleep induction are needed. Potential adverse effects include sedation, increased appetite, weight gain, constipation, and dry mouth. Note that the higher dosages may result in increased activation owing to increased norepinephrine (NE) receptor antagonism.
- **Tricyclics:** Tricyclic antidepressants may be effective, but generally are not recommended for treatment of depression because they have a higher risk of adverse effects than do SSRIs and SNRIs. They also are more dangerous (potentially fatal) in overdose. Adverse effects include anticholinergic effects, sedation, and cardiac conduction abnormalities. Levels of tricyclics are increased by ritonavir, so lower dosages may be needed for patients taking ritonavir or ritonavir-boosted PIs.

**Routine monitoring of blood levels of tricyclics should be performed on patients receiving higher doses *(e.g., 100 mg per day; 50 mg for nortriptyline)*, those on concurrently on ritonavir, and those with risk factors for cardiac conduction abnormalities.** A routine electrocardiogram should be performed before prescribing tricyclics, and this class of drugs should not be prescribed to patients with cardiac conduction problems.

The adverse effects of tricyclics can be used to treat insomnia or diarrhea, for example, and tricyclics can be effective for neuropathic pain.

- **Imipramine (Tofranil):** FDA indications for depression and chronic pain. The full recommended dosage for either problem is 150-300 mg QHS. Starting dosage: 25-75 mg PO QHS.
- **Doxepin (Sinequan):** FDA indications for depression and anxiety at adult dosages of 150-300 mg QHS. Starting dosage: 25-75 mg PO QHS.
- Three other available tricyclics have an FDA indication for depression only: **nortriptyline (Pamelor)** at dosages of 50-150 mg QHS; **desipramine (Norpramin)** at dosages of 50-200 mg a day; and **protriptyline (Vivactil)** at dosages of 5-10 mg, either TID or QID.
- **Tricyclics need to be started at low dosages and titrated gradually.** Lower dosages (or alternative agents) often are more appropriate for patients who are elderly, medically ill, or taking ritonavir or a ritonavir-boosted PI.

- **Trazodone:** a highly sedating antidepressant that is rarely used at an antidepressant dosage. Rather, it is often given at lower dosage for insomnia associated with depression, at a dosage of 25-50 mg 1-2 hours before bedtime. Ritonavir and other PIs can increase trazodone levels significantly; start at low dosage and use the lowest effective dosage; monitor for adverse effects.
- **Nefazodone (Serzone):** an antidepressant that usually should be avoided in people with HIV infection. Little information on interactions with ARVs is available, but it appears that nefazodone may increase levels of maraviroc and saquinavir, and that ritonavir may increase nefazodone levels. It has a black-box warning for severe liver toxicity. If the patient has ever had liver toxicity from the drug, restarting it is contraindicated.
- **St. John's wort:** an herbal antidepressant that can significantly decrease serum concentrations of PIs, NNRTIs, and maraviroc; it is contraindicated for use by patients taking those ARVs.

Treatment may involve antidepressant combinations, including psychostimulants; consult with a psychiatrist.

### Discontinuing antidepressant medication

Antidepressant medication generally should be continued for at least 6 months following resolution of a first episode of major depression. Longer term, and even indefinite, maintenance treatment may be necessary for people with recurrent major depression. When discontinuing antidepressants, it is important to taper them gradually to avoid withdrawal symptoms or rebound depression. Abrupt discontinuation of SSRI and SNRI antidepressants often precipitates unpleasant withdrawal symptoms such as confusion, agitation, irritability, sensory disturbances, and insomnia. This is particularly true for paroxetine and venlafaxine. Fluoxetine, because of its long half-life, is uncommonly associated with withdrawal symptoms.

### Brain stimulation treatments

There are a variety of brain stimulation treatments that usually are reserved for patients who have inadequate responses to medication. Electroconvulsive therapy (ECT) is the best known of these treatments and, despite the stigma associated with it, is more effective than antidepressant medication. Newer brain stimulation treatments also are available. These treatments require referral to the specialty care locations that offer them. Antidepressant medication often is used for maintenance after stabilization with ECT, but for some people, maintenance ECT is needed to prevent the relapse of depression.

## Patient Education

- Providers should explain to patients that illness (physical or emotional) is not a character flaw or a moral or spiritual weakness. It is a common aspect of HIV infection. Sadness is a normal part of life, but major depression always is abnormal and often can be alleviated with medication, psychotherapy, or both.
- Providers should help patients identify the symptoms of depression and the factors that led them to seek treatment. Patients will need to monitor themselves for recurrences or exacerbations and get help if the symptoms recur. Patients should be told to contact providers if they notice changes in their sleep, appetite, mood, activity level, or concentration, or if they notice fatigue, isolation, sadness, or feelings of helplessness.
- When starting an antidepressant medication, patients should expect that it will take 2-4 weeks for them to notice any improvement. Their symptoms should continue to decrease over the following weeks. If they do not have much improvement in symptoms, providers may choose to adjust the dosage of the medication or to change medications. Patients must continue taking their medications so that the symptoms of depression do not return.
- Providers should let patients know that St. John's wort can lower levels of ARVs and cannot be taken if they are on ART.
- Antidepressants typically are given for a long time, usually for a year or longer, to help patients with the chemical imbalances associated with major depression. Patients should be told that they should not suddenly stop antidepressants they have been taking for a long time, and that these medications need to be discontinued gradually.
- Some patients develop problems with sexual function while they are taking antidepressants. They should report any problems to their prescribers. (Note: Providers should let patients know that sexual well-being is fundamental to quality of life and can be talked about and addressed in the clinical setting.)

## References


- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing; 2013.
- Himelhoch S, Medoff DR, Oyeniyi G. *Efficacy of group psychotherapy to reduce depressive symptoms among HIV-infected individuals: a systematic review and meta-analysis.* AIDS Patient Care STDS. 2007 Oct;21(10):732-9
- Ickovics JR, Hamburger ME, Vlahov D, et al.; HIV Epidemiology Research Study Group. *Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women: longitudinal analysis from the HIV Epidemiology Research Study.* JAMA. 2001 Mar 21;285(11):1466-74.
- Leserman J, Petitto JM, Perkins DO, et al. *Severe stress, depressive symptoms, and changes in lymphocyte subsets in human immunodeficiency virus-infected men. A 2-year follow-up study.* Arch Gen Psychiatry. 1997 Mar;54(3):279-85.
- Maye TJ, Vittinghoff E, Chesney MA, et al. *Depressive affect and survival among gay and bisexual men infected with HIV.* Arch Intern Med. 1996 Oct 28;156(19):2233-8.
- New York State Department of Health AIDS Institute. *Mental Health Care for People with HIV Infection: Clinical Guidelines for the Primary Care Practitioner.* Available at www.hivguidelines.org/clinical-guidelines.
- Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.* Department of Health and Human Services. Available at aidsinfo.nih.gov/guidelines. Accessed December 1, 2013.
- Schatzberg AF, Nemeroff CB, eds. *Essentials of Clinical Psychopharmacology.* Washington: American Psychiatric Press; 2006.
- Sikkema KJ, Hansen NB, Ghebremichael M, et al. *A randomized controlled trial of a coping group intervention for adults with HIV who are AIDS bereaved: longitudinal effects on grief.* Health Psychol. 2006 Sep;25(5):563-70.
- Stober DR, Schwartz JAJ, McDaniel JS, et al. *Depression and HIV disease: prevalence, correlates and treatment.* Psych Annals. 1997;27(5):372-377.
- Wainberg ML, Faragon J, Cournos F, et al. *Psychiatric Medications and HIV Antiretrovirals: A Guide to Interactions for Clinicians, 2nd Edition*. Laminated booklet produced by the New York/New Jersey AIDS Education and Training Center, U.S. Health Resources and Services Administration; 2008.

# Suicide Risk

## Background

Transient suicidal thoughts are common for some people throughout the course of HIV disease and often do not indicate significant risk of suicide. However, persistent suicidal thoughts with associated feelings of hopelessness and intent to die are very serious and must be assessed promptly and carefully. Compared with people at high risk of suicide who are not HIV infected, people living with HIV have significantly increased frequency and severity of both suicidal ideation and thoughts of death. The risk of suicide is especially high for patients who are depressed and for those at pivotal points in the course of HIV infection. Stigma, quality of life concerns, and issues regarding disclosure may be contributing factors.

**HRSA HAB Performance Measures**

Percentage of patients aged 12 years and older **screened for clinical depression** on the date of the encounter using an age-appropriate standardized depression screening tool AND, if positive, a follow-up plan is documented on the date of the positive screen

(Adult and Adolescent measure)

Suicidality may be the direct physiological result of HIV (e.g., owing to the impact of HIV in the brain), a reaction to chronic pain, or an emotional reaction to having a chronic and life-threatening illness (e.g., major depression as a result of physical illness or psychiatric side effects caused by medications used to treat HIV infection and associated comorbidities). Many events may trigger suicidal thoughts among people with HIV. Such events include learning of their positive HIV status, disclosing to family and friends, starting antiretroviral therapy (ART), noticing the first symptoms of infection, having a decrease in CD4 cell count, undergoing a major illness or hospitalization, receiving an AIDS diagnosis, losing a job, experiencing major changes in lifestyle, requiring evaluation for dementia, and losing a significant relationship.

Evaluation of suicide risk must be included as part of a comprehensive mental health evaluation for HIV-infected patients. Note that asking patients about suicidal thoughts does not increase their risk of suicide.

**Risk factors for suicide attempts include the following:**

- Previous suicide attempts
- Abandonment by or isolation from, family, friends, or significant others
- Age >45 for men, >55 for women; or teen years
- Male gender
- Gay sexual orientation
- Transgender
- Any acute change in health status; worsening of HIV-related illness or other physical illnesses
- Family history of completed suicide
- Alcohol and other substance misuse, abuse, or dependence
- Relapse into drug use after significant recovery
- Severe anxiety, depression, psychotic disorder, or other mental health disorder
- Domestic violence
- Social isolation (e.g., being single, divorced, or alone, or experiencing the death of a spouse)
- Multiple losses or recent stressors
- Financial difficulty, unemployment

- Hopelessness and lack of pleasure
- Impulsivity
- Pain
- Perception of poor prognosis
- Perception of poor social support
- Planning for death
- Stigmatization associated with illness, sexual orientation, substance use history, or other factors
- Fear of HIV-associated dementia

**Protective factors include the following:**

- Strong psychosocial support
- Evidence of good coping mechanisms
- Cultural and religious beliefs against suicide
- Reasons for living
- No specific plan for suicide

## S: Subjective

**The patient expresses or exhibits, or a personal care giver discloses, the following:**

- Active suicidal ideation with intent and plan, such as giving away significant personal belongings, saying goodbye, acquiring the means (e.g., gun, pills), writing a suicide note
- Depressed mood, hopelessness, agitation, intoxication with alcohol or other drugs
- Passive withdrawal from therapy or medical care or decreased adherence (e.g., stopping medications, missing appointments)
- A desire for HIV disease to progress more rapidly

**Inquire about the following during the history** *(again, note that asking patients about suicidal thoughts does not increase their risk of suicide)***:**

- Previous suicide attempt(s) – one of the best predictors of eventual death by suicide
- Friend or family member who has committed suicide
- Personal or family history of depression
- Previous episode of psychosis
- Presence of risk factors described above

**Probe for other depressive symptoms and the immediacy of potential suicidal intent. Sample questions may include the following:**

- "It sounds as if you're in great pain. Have you ever thought that life is not worth living?"
- "Do you often think of death?"
- "Do you think about hurting yourself?"
- "How might you do that?"
- "Do you have a plan?" Ask whether the patient has access to the components of the plan (e.g., gun, pills)
- "Is this something you feel you might do?"
- "What would prevent you from doing this?"
- "Have you ever attempted suicide? What did you do?"

## O: Objective

- Perform a mental status examination and suicide assessment.
- Look for signs of self-inflicted injuries such as wrist lacerations or neck burns.
- Look for signs of depression, agitation, or intoxication.

## A: Assessment

See chapter *Major Depression and Other Depressive Disorders* for differential diagnosis of possible causes of depression and suicidality.

## P: Plan

### Evaluation

Evaluate the patient for depression, risk factors for suicide, and contributing psychiatric illnesses or situational stressors. Determine the immediacy of potential suicidal intent. If a mental health professional is available on site or can be summoned, an urgent consultation often is helpful in making these determinations.

### Treatment

- If the patient exhibits active suicidal ideation with a plan, hospitalize the patient immediately, preferably in a psychiatric facility.
- If suicidal thoughts are passive, refer for evaluation for specific psychiatric disorders and refer for psychotherapy with an HIV-experienced mental health provider.
- Encourage the patient to contact you or another specified clinician for help, or to go to a hospital if suicidal ideation worsens or patient worries about acting upon suicidal thoughts.
- Note that making a contract with a patient against suicide is not recommended; research shows it is not effective, and it can provide a false sense of security.
- Inform patients about local suicide prevention resources, including suicide hotlines, emergency response (e.g., 911), and local emergency departments.
- Contact the patient between appointments. Enlist the help of significant others (if the patient agrees); invite them to accompany the patient on the next visit and see all of them together. Consider a support group or peer referral, if available.
- Consider dispensing medications on a weekly basis for the following purposes:
  - Monitoring emotional status and treatment adherence
  - Preventing the availability of lethal doses of medications
- Perform appropriate follow-up. In consultation with a skilled mental health provider, be sure that the patient is receiving appropriate ongoing treatment for underlying or persisting psychiatric illness. Assess at each visit for adherence to mental health care and for recurrence of symptoms.

## Patient Education

- Suicidal ideation and severe depression are not normal aspects of HIV infection, and usually can be treated effectively.
- Patients should report suicidal thoughts to their health care provider.
- Inform patients about local suicide prevention resources, including suicide hotlines, emergency response (e.g., 911), and local emergency departments.

## References


- Cournos F, Lowenthal D, Cabaniss D. *Clinical Evaluation and Treatment Planning: A Multimodal Approach.* In: Tasman A, Kay J, Lieberman JA, et al., eds. *Psychiatry, Third Edition*. Hoboken, NJ: John Wiley & Sons; 2008;525-45.
- Gielen AC, McDonnell KA, O'Campo PJ, et al. *Suicide risk and mental health indicators: Do they differ by abuse and HIV status?* Women's Health Issues. 2005 Mar-Apr;15(2):89-95.
- Goldstein RB, Black DW, Nasrallah A., et al. *The prediction of suicide: Sensitivity, specificity and predictive value of a multivariate model applied to suicide among 1906 patients with affective disorders.* Arch Gen Psychiatry. 1991 May;48(5):418-22.
- Kelly B, Raphael B, Judd F, et al. *Suicidal ideation, suicide attempts, and HIV infection.* Psychosomatics. 1998 Sep-Oct;39(5):405-15.
- Kessler RC, Borges G, Walters EE. *Prevalence of and risk factors for lifetime suicide attempts in national comorbidity survey.* Arch Gen Psychiatry. 1999 Jul;56(7):617-26.
- Komiti A, Judd F, Grech P, et al. *Suicidal behaviour in people with HIV/AIDS: a review.* Aust N Z J Psychiatry. 2001 35(6):747-57.
- Mountain Plains AIDS Education and Training Center. *HIV and Suicide: Risk Assessment and Intervention*. 2007.
- New York State Department of Health AIDS Institute. *Mental Health Care for People with HIV Infection: Clinical Guidelines for the Primary Care Practitioner.* Available at www.hivguidelines.org/clinical-guidelines. Accessed December 1, 2013.
- Robertson K, Parsons TD, Van Der Horst C, et al. *Thoughts of death and suicidal ideation in nonpsychiatric human immunodeficiency virus seropositive individuals.* Death Stud. 2006 Jun;30(5):455-69.
- Roy A. *Characteristics of HIV patients who attempt suicide.* Acta Psychiatr Scand. 2003 Jan;107(1):41-4.
- Wainberg ML. *Mental Health Issues in HIV-Positive Patients.* Presentation at the 3rd annual Mountain-Plains AIDS Education and Training Center Faculty Development Conference, Keystone, CO. Mountain Plains AIDS Education and Training Center; 2005.

# Anxiety Disorders

## Background

Anxiety symptoms are common and can develop or recur for many reasons, including a patient's worries about HIV infection and treatment, or issues unrelated to HIV. Symptoms can range from mild distress to full-blown anxiety disorders. Symptoms of anxiety can mimic symptoms of physical illness, and an appropriate workup should be performed to rule out other illnesses. Use of illicit drugs (e.g., amphetamines, cocaine) or alcohol can cause or substantially worsen anxiety symptoms; all patients should be screened for substance use.

**HRSA HAB Performance Measures**

Percentage of patients aged 12 years and older **screened for clinical depression** on the date of the encounter using an age-appropriate standardized depression screening tool AND, if positive, a follow-up plan is documented on the date of the positive screen

(Adult and Adolescent measure)

Anxiety disorders include generalized anxiety disorder, specific phobia, and social phobia; related disorders include posttraumatic stress disorder (PTSD) and panic disorder. This chapter focuses primarily on anxiety symptoms and generalized anxiety disorder. See chapters *Panic Disorder* and *Posttraumatic Stress Disorder* for further information about these conditions.

## S: Subjective

The criteria for a diagnosis of generalized anxiety disorder include unrealistic or excessive worry about two or more life circumstances for ≥6 months, and at least three of the following subjective complaints:

- Restlessness or feeling keyed-up or on edge
- Difficulty concentrating or mind going blank
- Irritability
- Muscle tension
- Being easily fatigued
- Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)

Other subjective complaints may include the following:

- Shortness of breath or smothering sensations
- Palpitations or accelerated heart rate
- Dizziness or lightheadedness
- Exaggerated startle response
- Trembling, twitching, or feeling shaky
- Dry mouth
- Flushes or chills
- Frequent urination
- Muscle aches or soreness
- Nausea, diarrhea, or other abdominal distress
- Skin rashes
- Sweating or cold, clammy hands
- Trouble swallowing or "lump in the throat"

Ask about the symptoms indicated above, and about the following:

- Anxiety patterns (e.g., constant or intermittent; timing, duration, precipitants)
- Onset: sudden or gradual
- Caffeine intake
- Recreational drug or alcohol use (current or recent)
- Concomitant illnesses (e.g., cardiac, pulmonary, endocrine)

- Family history of similar problems
- Medications, supplements, and herbal preparations
- History of previous episodes
- Recent stressors
- Sleep disturbances
- Other physical symptoms

## O: Objective

Measure vital signs, with particular attention to heart rate (tachycardia) and respiratory rate (shortness of breath, hyperventilation).

Perform a physical examination, including mental status and neurologic, cardiopulmonary, and thyroid examinations.

## A: Assessment

A differential diagnosis may include the following medical conditions:

- Substance use (e.g., amphetamines, cocaine)
- Substance or medication withdrawal (e.g., alcohol, benzodiazepines)
- Excessive caffeine intake
- Electrolyte imbalances
- Heart disease, arrhythmias
- Hyperthyroidism
- Hypoglycemia
- Immune disorders
- Respiratory disease, hypoxia
- Medication adverse effects (e.g., with efavirenz, isoniazid, corticosteroids, theophylline, or stimulants)
- Sleep disturbances or sleep deprivation
- Allergic reactions
- Anemia
- Central nervous system (CNS) or opportunistic infections or malignancies
- Systemic or other infections
- Vitamin B12 deficiency

## P: Plan

### Diagnostic Evaluation

Perform the following tests:

- Blood glucose, electrolytes
- Thyroid function tests (TSH, T4)
- Electrocardiogram (EKG) if patient has shortness of breath or palpitations
- Arterial blood gases (if difficulty breathing is not self-limited)
- Other tests as indicated by symptoms and physical examination

### Treatment

Once medical disorders have been ruled out, and the diagnosis of an anxiety disorder is established, several options are available:

#### Psychotherapy

Options include cognitive-behavioral therapy, interpersonal therapy, exposure therapy, a stress-management group, relaxation therapy, visualization, guided imagery, supportive psychotherapy, and psychodynamic psychotherapy. Long-term psychotherapy may be indicated if experienced professionals are available and the patient is capable of forming an ongoing relationship. If possible, refer to an HIV-experienced therapist. The type of psychotherapy available to the patient often depends on the skills and training of the practitioners in a given health care system or region. In addition, the patient may be referred to available community-based support.

#### Pharmacotherapy

Medications, with or without psychotherapy, may alleviate symptoms of anxiety. Patients with advanced HIV disease, like geriatric patients, may be more vulnerable to the CNS effects of certain medications. Medications that affect the CNS should be started at low

dosage and titrated slowly. Similar precautions should apply to patients with liver dysfunction.

### Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are effective in treating patients with anxiety. They are favored for long-term use when a specific anxiety disorder is present and persistent. These medications do not cause tolerance or pose a risk of addiction. Below is a list of antidepressants approved by the U.S. Food and Drug Administration (FDA) for specific anxiety disorders, and their usual recommended dosages. FDA recommendations are based on availability of specific study data, but all SSRIs (regardless of whether they have an FDA indication for anxiety) may be helpful for a broad range of anxiety disorders.

Common adverse effects of SSRIs and SNRIs include sexual dysfunction, sleep disturbance, and nausea. For patients who are medically ill, these medications should be started at low dosage and titrated up slowly; a low dosage may be effective. These medications also should be down-tapered slowly; SSRI/SNRI discontinuation syndrome may occur if they are discontinued abruptly.

See chapter *Major Depression and Other Depressive Disorders* for further information about antidepressant medications, including adverse effects.

SSRI antidepressants:

- Fluoxetine (Prozac): FDA indication for panic disorder with a recommended dosage of 20 mg QD. Also recommended for obsessive-compulsive disorder, but higher dosages are needed, sometimes up to 80 mg daily.
- Escitalopram (Lexapro): FDA indication for generalized anxiety disorder at a dosage of 10 mg QD.
- Citalopram (Celexa): Does not have specific FDA indications for anxiety disorders. Suggested dosage: start at 10 mg QD and titrate as needed; maximum dosage: 60 mg daily.
- Paroxetine (Paxil): FDA indications for obsessive-compulsive disorder and panic disorder both at a recommended dosage of 40 mg QD. Also indicated for social anxiety disorder at a dosage of 20-40 mg daily. Usual starting dosage: 10 mg daily.
- Sertraline (Zoloft): FDA indications for panic disorder and PTSD at dosages of 50-200 mg QD. Usual starting dosage: 25 mg daily.

SNRI antidepressants:

- Venlafaxine timed-release formulation (Effexor XR): FDA indication for generalized anxiety disorder, at recommended dosages of 75-225 mg per day. Note: There is a risk of hypertension at the higher dosages of venlafaxine; monitor blood pressure.
- Duloxetine (Cymbalta): FDA indication for generalized anxiety disorder at a recommended dosage of 60 mg QD.

Other antidepressants:

- Some sedating antidepressants are effective, nonaddictive agents that are helpful when taken at bedtime for both insomnia and anxiety symptoms. These include trazodone 25-100 mg QHS or imipramine (Tofranil) 25 mg QHS. Note that imipramine and other tricyclics must be used with caution but are not contraindicated for use by patients taking ritonavir (including ritonavir-boosted protease inhibitors [PIs]).
- Gabapentin (Neurontin), which sometimes is used as a mood stabilizer, may be given at dosages of 200-400 mg BID to QID and may help to diminish anxiety.

### Anxiolytics

Short-term use of benzodiazepines sometimes is appropriate for mild and brief situational anxiety symptoms, even without the presence of a specific anxiety disorder. For longer-term use, non-benzodiazepines (e.g., buspirone [see below], SSRIs, or SNRIs) are preferred.

- Buspirone (BuSpar) is a nonaddictive anxiolytic. Start at 5 mg PO TID. If symptoms persist, the dosage can be increased by 5 mg per dose each week to a maximum of 10-15 mg TID (for a total daily dosage of 30-45 mg). It will take several weeks for patients to notice a decrease in anxiety; low-dose benzodiazepines may be used during this interval. The major potential adverse effects of buspirone are dizziness and lightheadedness.
- Consider intermediate half-life benzodiazepines such as lorazepam (Ativan) 0.5 mg PO Q8H or oxazepam (Serax) 10 mg PO Q6H if buspirone is not tolerated or to alleviate anxiety symptoms until buspirone takes effect. Longer-acting benzodiazepines such as clonazepam (Klonopin) also may be useful at dosages of 0.25-0.5 mg PO BID.
- Benzodiazepines generally should be used only for acute, short-term management because of the risk of tolerance and physiologic dependence. These risks are even more problematic for patients with a history of addiction.

#### Potential ARV Interactions

Interactions may occur between certain ARVs and agents used to treat anxiety. Some combinations may be contraindicated and others may require dosage adjustment. Refer to medication interaction resources or consult with an HIV clinical pharmacist, HIV specialist, or psychiatrist before prescribing.

**Antidepressants**

- Some ARV medications (particularly PIs) and the pharmacokinetic booster cobicistat may affect the metabolism of some antidepressants via cytochrome P450 interactions. For most SSRIs and SNRIs, interactions with ARVs generally are not clinically significant; in the case of tricyclics, their levels may be significantly increased by ritonavir. On the other hand, some PIs may decrease levels of paroxetine and sertraline, and efavirenz also lowers sertraline levels. See chapter *Major Depression and Other Depressive Disorders* for further information.

**Anxiolytics**

- PIs, nonnucleoside reverse transcriptase inhibitors (NNRTIs), and cobicistat may raise blood concentrations of many benzodiazepines. Consider using a benzodiazepine metabolized by glucuronidation (e.g., lorazepam, oxazepam), particularly in patients with liver disease. For benzodiazepines metabolized by the CYP system (e.g., clonazepam), start at low dosages and titrate slowly. Given the very long half-life of both the parent drug and its metabolites, diazepam is best avoided in patients receiving ART. Other CNS depressants and alcohol should be avoided in patients taking these benzodiazepines.
  - Midazolam (Versed) and triazolam (Halcion) are contraindicated for use with all PIs and with cobicistat, delavirdine, and efavirenz.
- Buspirone levels may be increased by ritonavir-boosted PIs and cobicistat, and may be decreased by CYP inducers. Monitor patients for adverse effects and for efficacy.

## Patient Education

- Behavioral interventions can help to reduce anxiety, but may take practice. Patients should seek help from a therapist or another experienced source.
- Advise patients that misuse of alcohol or illicit drugs can cause or substantially worsen anxiety symptoms; advise patients to decrease or eliminate use. Refer for substance abuse treatment if indicated.
- Inform patients that they may develop problems with sexual function because of antianxiety medications. Patients should report any problems to their prescribers. (Note: Providers should let patients know that sexual well-being is fundamental to quality of life and can be talked about and addressed in the clinical setting.)

## References


- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing; 2013.
- New York State Department of Health AIDS Institute. *Mental Health Care for People with HIV Infection: Clinical Guidelines for the Primary Care Practitioner.* Available at www.hivguidelines.org/clinical-guidelines. Accessed December 1, 2013.
- Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.* Department of Health and Human Services. Available at aidsinfo.nih.gov/guidelines. Accessed December 1, 2013.
- Wainberg ML, Faragon J, Cournos F, et al. *Psychiatric Medications and HIV Antiretrovirals: A Guide to Interactions for Clinicians, 2nd Edition.* Laminated booklet produced by the New York/New Jersey AIDS Education and Training Center, U.S. Health Resources and Services Administration; 2008.

# Panic Disorder

## Background

Panic disorder is an anxiety disorder whose essential feature is the presence of recurrent, unexpected panic attacks. Panic attacks are discrete, sudden-onset episodes of intense fear or apprehension accompanied by specific somatic or psychiatric symptoms (e.g., palpitations, shortness of breath, fear of losing control). A patient is diagnosed as having panic disorder when he or she has experienced such attacks, and at least one of the attacks has been followed by ≥1 month of persistent concern about additional attacks, worry about the implications or consequences of the attack, or a significant change in behavior related to the attack.

The symptoms of panic disorder usually begin in late adolescence to the mid-30s and may coincide with the presentation of major depressive disorder, social phobia, or generalized anxiety disorder. Panic disorder can interfere with the ability to conduct activities of daily living. Patients with panic disorder have an increased incidence of suicide.

Symptoms may mimic those of various physical illnesses or be caused by other medical conditions (e.g., hyperthyroidism, brain tumors, adrenal tumors, heart arrhythmias, hypoglycemia, anemia). Substance or alcohol intoxication or withdrawal also may cause panic symptoms. Patients with panic symptoms should be evaluated for other causative conditions.

Major depressive disorder occurs in 50-65% of people with panic disorder. Major depression may precede or follow the onset of panic disorder. Patients with panic disorder therefore should be screened for depression initially and periodically thereafter (see chapter *Major Depression and Other Depressive Disorders*). Anxiety also commonly is experienced by persons with panic disorder; see chapter *Anxiety Disorders* for further information about this condition.

## S: Subjective

The patient complains of discrete periods of intense fear or discomfort in which four or more of the following symptoms developed abruptly and reached a peak within 10 minutes:

- Shortness of breath or smothering sensation
- Sweating
- Trembling or shaking
- Dizziness, lightheadedness, faintness, or feeling of unsteadiness
- Numbness or tingling sensations
- Chest pain or discomfort
- Palpitations or accelerated heart rate
- Hot flashes or chills
- Sensation of choking
- Depersonalization or derealization
- Fear of dying
- Fear of going crazy or losing control
- Nausea or abdominal distress

Other subjective complaints may include the following:

- Apprehension about the outcome of routine activities and experiences
- Anticipation of a catastrophic outcome from a mild physical symptom or from medication side effects
- Discouragement and demoralization

Panic attacks are, by definition, self-limited and they peak quickly. Symptoms that persist continuously for longer periods suggest other causes.

Ask about the symptoms indicated above and about the following:

- Frequency, duration, and onset of panic episodes
- Possible precipitants, (e.g., settings in which attacks occur), situations (e.g., being alone outdoors), relationship to food or hunger
- Current medications, herbal products, and supplements; recent medication changes
- Multiple visits to health care providers with complaints suggesting panic attacks
- Family history of mood and psychiatric illnesses, particularly anxiety and panic
- Use of recreational drugs (especially stimulants such as cocaine or amphetamines), alcohol (current and recent), and caffeine
- Sleep disturbances
- Concomitant illnesses (e.g., endocrine, cardiac, pulmonary)
- Any associated or concurrent symptoms that could suggest a medical etiology
- Screen for depression (see chapter *Major Depression and Other Depressive Disorders*)

## O: Objective

Measure vital signs, with particular attention to heart rate (tachycardia) and respiratory rate (shortness of breath, hyperventilation). Perform a complete physical examination, including thyroid, cardiac, pulmonary, and neurologic evaluation.

During actual panic attacks, patients may have increases in heart rate, respiratory rate, or systolic blood pressure.

## A: Assessment

A differential diagnosis may include the following conditions:

- Congestive heart failure, myocardial ischemia, arrhythmias
- Hyperthyroidism
- Intoxication with or withdrawal from psychoactive substances (e.g., amphetamines, cocaine, hallucinogens, caffeine, medications)
- Hypoglycemia
- Hypoxia
- Hyperparathyroidism
- Medication side effects
- Pheochromocytoma
- Adrenal disorders, Cushing syndrome, electrolyte abnormalities
- Respiratory infection
- Seizure disorder
- Vestibular dysfunction
- Allergic reactions
- Posttraumatic stress disorder
- Social phobia or specific phobia (specific phobia is a response to a specific stimulus, whereas a patient with panic attacks is unsure when they will recur and what will trigger them)
- Agoraphobia
- Obsessive-compulsive disorder
- Separation anxiety disorder

# P: Plan

## Diagnostic Evaluation

Perform the following tests:

- Electrolytes, blood glucose
- Thyroid function tests (thyroid stimulating hormone [TSH], T4)
- Arterial blood gases if the patient has persistent shortness of breath
- Electrocardiogram if chest pain or other cardiac symptoms are present
- Other tests as indicated by symptoms and physical examination

## Treatment

Once other diagnoses have been ruled out, consider the following treatments:

### Psychotherapy

Options include cognitive-behavioral therapy, interpersonal therapy, exposure therapy, a stress-management group, relaxation therapy, visualization, guided imagery, supportive psychotherapy, and psychodynamic psychotherapy. Long-term psychotherapy may be indicated if experienced professionals are available and the patient is capable of forming an ongoing relationship. If possible, refer to an HIV-experienced therapist. The type of psychotherapy selected often will depend on the skills and training of the practitioners available in a given health care system or region. In addition, refer the patient to available community-based support. Emergency referrals may be needed for the most anxious patients and those with comorbid depression.

### Pharmacotherapy

Patients with advanced HIV disease and geriatric patients may be more vulnerable to the central nervous system (CNS) effects of certain medications. Medications that affect the CNS should be started at low dosage and titrated slowly. Similar precautions should apply to patients with liver dysfunction.

#### Options

A number of medications have an approved indication by the U.S. Food and Drug Administration (FDA) for panic disorder. These include the serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine extended-release, and benzodiazepines listed below. For most patients, SSRIs are preferable to benzodiazepines for the treatment of panic disorder because they do not have the potential for addiction and they do not pose the same level of risk if drug interactions cause an elevation of their levels. Other medications used to treat anxiety disorders, such as SNRIs may be considered, and some of them are less likely to interact with ARV medications. See chapter *Anxiety Disorders* for descriptions of these medications.

**SSRI antidepressants** approved for panic disorder include the following:

- Fluoxetine (Prozac), recommended dosage 20 mg PO QD (usual starting dosage 10 mg daily)
- Paroxetine (Paxil), recommended dosage 40 mg PO QD (usual starting dosage 10 mg daily)
- Sertraline (Zoloft), recommended dosage 50-200 mg PO QD (usual starting dosage 25 mg daily)

**SNRI antidepressant** approved for panic disorder:

- Venlafaxine (Effexor XR), recommended dosage 75-225 mg PO QD (usual starting dosage 37.5 mg daily)

**Benzodiazepines** approved for panic disorder include the following:

- Clonazepam (Klonopin), recommended dosage 0.5-2 mg PO BID
- Alprazolam (Xanax), recommended dosage 0.5-3 mg PO TID or Xanax XR at a recommended dosage of 3-6 mg PO QD; start at low dosage, may increase every 3-4 days in increments of ≤ 1 mg/day if tolerated

**Potential ARV Interactions**

Interactions may occur between certain ARVs and agents used to treat panic. Some combinations may be contraindicated and others may require dosage adjustment. Refer to medication interaction resources or consult with an HIV expert or clinical pharmacist before prescribing.

Some ARV medications (particularly protease inhibitors [PIs]) and the pharmacokinetic booster cobicistat may affect the metabolism of some SSRIs via cytochrome P450 interactions. These generally are not clinically significant, but SSRIs used concomitantly with PIs or cobicistat should be started at low dosages and titrated cautiously to prevent antidepressant adverse effects and toxicity. On the other hand, some PIs may decrease levels of paroxetine and sertraline, and efavirenz also lowers sertraline levels; these antidepressants may require upward titration if used concurrently with interacting ARVs.

PIs and cobicistat can significantly elevate the levels of clonazepam and alprazolam, resulting in the potential for severe sedation or respiratory depression. For patients receiving clonazepam or alprazolam, it is recommended that these medications be used at the lowest dosages for the shortest duration possible.

## Patient Education

- Inform patients that behavioral interventions can help to reduce the frequency and severity of panic attacks.
- Some antidepressants and antianxiety medications can prevent or reduce the severity of panic attacks.
- Advise patients that they may develop problems with sexual function because of the medications. Patients should report any problems to their prescribers. (Note: Providers should let the patient know that sexual well-being is fundamental to quality of life and can be talked about and addressed in the clinical setting.)

## References


- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing; 2013.
- New York State Department of Health AIDS Institute. *Mental Health Care for People with HIV Infection: Clinical Guidelines for the Primary Care Practitioner.* Available at www.hivguidelines.org/clinical-guidelines. Accessed December 1, 2013.
- Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Department of Health and Human Services. Available at aidsinfo.nih.gov/guidelines. Accessed December 1, 2013.
- Wainberg ML, Faragon J, Cournos F, et al. *Psychiatric Medications and HIV Antiretrovirals: A Guide to Interactions for Clinicians, 2nd Edition.* Laminated booklet produced by the New York/New Jersey AIDS Education and Training Center, U.S. Health Resources and Services Administration; 2008.

# Posttraumatic Stress Disorder

*Francine Cournos, MD; and Milton Wainberg, MD*

## Background

Symptoms of posttraumatic stress disorder (PTSD) can develop after exposure to a traumatic event. A traumatic event may be a single instance, such as a car accident or experience of a natural disaster, or an ongoing pattern of events, such as continuous neglect, physical or sexual abuse, or chronic exposure to war or violent conflict. PTSD causes intrusive memories, hyperarousal, and psychological numbing or avoidance, among other symptoms. It may impair an individual's psychological and physical functioning, decreasing immune system function and increasing susceptibility to illness. Untreated PTSD can increase the risk of HIV transmission or acquisition and worsen the course of HIV treatment.

Individuals with PTSD may experience depression, anxiety, social isolation, impairments in trust and attachments, and feelings of anger, and PTSD often coexists with depression, anxiety, or other psychiatric illnesses. PTSD may be associated with increased risk-taking behavior (e.g., substance abuse, unsafe sex).

The rate of PTSD among individuals with HIV infection (in whom the lifetime prevalence is possibly as high as 42%) is higher than that of the general population (1.3%-7.8%). Women experience PTSD at a higher rate than men. The likelihood of developing PTSD increases in relation to the severity of or proximity to the traumatic event. A history of traumatic experiences may increase an individual's risk of developing PTSD after a new trauma. Although a diagnosis of HIV may trigger PTSD symptoms, a history of trauma or abuse often is present as well. A personal or family psychiatric history may increase the likelihood of developing PTSD.

PTSD is diagnosed, as in HIV-uninfected individuals, according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-5 (see "References," below). It is treatable through diverse therapies and psychopharmacology.

## S: Subjective

The following reflect DSM-5 diagnostic criteria; include them in the history.

- The person experienced, witnessed, or was confronted with an event or events that involved actual or threatened death, serious injury, or sexual violence, or a threat to the physical integrity of self or others.
- The person's response involved intense fear, helplessness, or horror.
- The person complains of persistently reexperiencing the event in one or more of the following ways:
  - Recurrent and intrusive distressing recollections of the event, including images, thoughts or perceptions
  - Recurring distressing dreams of the event
  - Acting or feeling as if the traumatic event were recurring (includes a sense of reliving the experience, illusions, hallucinations and dissociative flashback episodes, including those that occur when awakening or intoxicated)
  - Intense psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event
  - Physiological reactivity on exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event

- The person makes efforts to avoid thoughts or reminders of the trauma.
- The person has disturbances in mood or cognition that began or worsened after the traumatic event.

Other complaints may include the following:

- Overwhelming emotions caused by memories of the event
- Emotional numbness
- Disruptions in consciousness, memory, or identity
- Depersonalization (i.e., a feeling of watching oneself act, while having no control over a situation)
- Derealization (i.e., alteration in the perception or experience of the external world so that it seems strange or unreal)
- Feelings of estrangement from others
- Episodes of lost time

The patient may experience the following:

- Recurrent distressing recollections of the event
- Recurrent distressing dreams of the event
- Illusions/hallucinations of the event actually occurring
- Psychological distress triggered by cues reminiscent of the event
- Avoidance of thoughts, feelings, or conversation associated with the event
- Avoidance of activities, places, or people associated with the event
- Inability to recall important aspects of the event
- Diminished interest in significant activities
- Detachment
- Restricted range of affect
- Difficulty falling or staying asleep
- Irritability or outbursts of anger
- Difficulty concentrating
- Hypervigilance

Ask about the duration of symptoms (PTSD is characterized by symptoms that last for more than 1 month).

Also screen for the following:

- Clinical depression
- Anxiety disorders
- Alcohol or other substance-use disorders

## O: Objective

- Check vital signs, with particular attention to heart rate (tachycardia) and respiratory rate (shortness of breath, hyperventilation).
- Perform a physical examination, including mental status and neurologic examination (tremor, hyperreflexia, focal abnormalities).
- Look for signs of physical trauma or sexual assault.

## A: Assessment

A differential diagnosis may include the following:

- Substance use (e.g., amphetamines, cocaine)
- Substance withdrawal (e.g., alcohol, benzodiazepines)
- Electrolyte imbalances
- Excessive caffeine intake
- Hyperthyroidism
- Medications effects (e.g., efavirenz, isoniazid, steroids, theophylline)
- Allergic reactions
- Head trauma
- Hypoglycemia
- Sleep disturbances or sleep deprivation
- Central nervous system (CNS) or opportunistic infections or malignancies

- Systemic or other infections
- Respiratory disease
- Heart disease, arrhythmias
- Anemia
- Vitamin B12 deficiency

# P: Plan

## Evaluation

Perform the following tests:

- Complete blood count, electrolytes, creatinine, blood urea nitrogen, glucose
- Thyroid function tests (thyroid stimulating hormone [TSH], T4)
- Vitamin B12 levels
- Other tests as suggested by history and physical examination

## Treatment

Once other diagnoses have been ruled out and the diagnosis of PTSD is established, several treatment options are available.

### Psychotherapy

Options include individual cognitive-behavioral therapy, cognitive processing therapy, exposure therapy, eye movement desensitization and reprocessing, interpersonal therapy, a stress-management group, relaxation therapy, visualization, guided imagery, supportive psychotherapy, and other forms of therapy. Long-term psychotherapy may be indicated if experienced professionals are available and the patient is capable of forming an ongoing relationship. If possible, refer to an HIV-experienced therapist. The specific psychotherapy often depends on the skills and training of the practitioners available in a given health care system or region.
In addition, refer the patient to available community-based support.

### Pharmacotherapy

#### Antidepressants

Most antidepressants should be started at low dosages and gradually titrated upward to avoid unpleasant side effects. Therapeutic effects may not be noticed until 2-4 weeks after starting a medication. If there is no improvement in symptoms in 2-4 weeks, and there are no significant adverse effects, the dosage may be increased. Before prescribing a medication, always remember to check for drug-drug interactions, particularly with concurrent antiretrovirals (ARVs). See "Potential ARV Interactions," below, and chapter *Major Depression and Other Depressive Disorders* for further information about antidepressants, including possible adverse effects and interactions with ARVs.

- **Selective serotonin reuptake inhibitors** (SSRIs) have the strongest evidence for efficacy and tolerability for PTSD and are first-line medication treatment. Two SSRI antidepressants have a specific indication for PTSD approved by the U.S. Food and Drug Administration (FDA): sertraline (Zoloft) at recommended dosages of 50-200 mg QD (usual starting dosage: 25 mg daily) and paroxetine (Paxil) at recommended dosages of 20-50 mg QD (usual starting dosage: 25 mg daily). Other SSRIs include fluoxetine (Prozac), citalopram (Celexa), and escitalopram (Lexapro).
- The **serotonin norepinephrine reuptake inhibitor** (SNRI) antidepressants such as venlafaxine (Effexor), desvenlafaxine (Pristiq), and duloxetine (Cymbalta), as well as the antidepressant mirtazapine (Remeron), are second-line treatments if SSRIs prove ineffective or are not well tolerated.
- **Tricyclic antidepressants** (TCAs) may be employed if the individual has had a good response to them in the past and they do not cause severe side effects, or if the individual

has failed to respond to or cannot tolerate SSRIs or SNRIs. TCAs in low dosages also may be used for sleep; see chapter *Insomnia*.

### Anxiolytics

Antianxiety medications have not been shown to be effective treatments for PTSD when used alone but may be effective, as adjunctive therapy, in reducing anxiety symptoms. Benzodiazepines can reduce anxiety rapidly, often within hours, but may have counterbalancing side effects early in the course of their use that include sedation and incoordination. In addition, physical dependency may develop in patients who use them for more than a few weeks. Benzodiazepines are not recommended for people who have a history of alcohol abuse or dependence. Benzodiazepines ideally would be used only briefly and intermittently to quell acute and severe anxiety symptoms. Levels of many benzodiazepines may be increased by certain protease inhibitors and nonnucleoside reverse transcriptase inhibitors; see "Potential ARV Interactions," below.

Buspirone (BuSpar) is a nonaddictive anxiolytic. It usually must be taken for at least 1-2 weeks before anxiety symptoms begin to lessen. Starting dosage is 5 mg PO TID. If symptoms persist, the dosage can be increased by 5 mg per dose each week to a maximum of 10-15 mg PO TID (for a total daily dosage of 30-45 mg). Low-dose benzodiazepines may be used during the initial weeks of buspirone therapy, until the effects of buspirone are felt. The major potential adverse effects of buspirone are dizziness and lightheadedness.

### Anticonvulsants

Mood stabilizers such as valproate (Depakote), carbamazepine (Tegretol), lamotrigine (Lamictal), and topiramate (Topamax) may be added for patients with a partial response to an antidepressant. They may be helpful for those who have considerable irritability, anger, or hostility, as well as those with reexperiencing symptoms (e.g., flashbacks, intrusive memories). Gabapentin (Neurontin) 200-400 mg BID or QID sometimes helps to diminish anxiety. Treatment with these agents usually should be done by or in consultation with a psychiatrist.

### Antipsychotics

Older and newer antipsychotics (aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone) may be suitable for individuals with psychotic features of PTSD or those who have a comorbid psychotic illness. These medications also may be helpful for some individuals who have not benefited from medications indicated for PTSD. Adverse effects may include dyslipidemia, hyperglycemia, weight gain, and sudden cardiac death. Consultation with a psychiatrist is recommended.

### Other medications

A variety of other medications have been used as adjunctive treatment when insomnia and nightmares persist despite adequate use of psychotropic medications. Research is still quite limited, but suggests that the antihypertensive drugs clonidine (Catapres) and prazosin (Minipress) may help with the insomnia and nightmares of PTSD.

Patients with advanced HIV disease and geriatric patients may be particularly vulnerable to the CNS effects of certain medications. Medications that affect the CNS should be started at low dosage and titrated slowly. Similar precautions should apply to patients with liver dysfunction.

### Potential ARV Interactions

Interactions may occur between certain antiretrovirals and agents used to treat PTSD. Some combinations may be contraindicated and others may require dosage adjustment. Refer to medication interaction resources or consult with an HIV expert or pharmacist before prescribing.

**Antidepressants**

- Levels of many SSRIs and SNRIs may be increased or decreased by certain protease inhibitors (PIs) or NNRTIs and by the pharmacokinetic booster cobicistat. These interactions generally are not clinically significant, but most agents should be started at low dosages and titrated cautiously while monitoring efficacy and adverse effects. See chapter *Major Depression and Other Depressive Disorders*.
- Tricyclic levels can be increased substantially by ritonavir and cobicistat. If they are used for patients taking ritonavir, ritonavir-boosted PIs or cobicistat, they should be started at low dosage, patients should be followed closely, and tricyclic levels should be monitored.

**Anxiolytics**

- PIs, cobicistat, and nonnucleoside reverse transcriptase inhibitors may raise blood concentrations of many benzodiazepines. If benzodiazepines are used, they should be started at low dosage, and other CNS depressants should be avoided. Consult with a clinical pharmacist before prescribing. See chapters *Anxiety Disorders* and *Insomnia* for additional information.
  - Midazolam (Versed) and triazolam (Halcion) are contraindicated for use with all PIs or cobicistat and with delavirdine and efavirenz.
- Buspirone levels may be increased by ritonavir-boosted PIs or cobicistat and may be decreased by CYP inducers. Monitor patients for adverse effects and for efficacy.

**Anticonvulsants**

- Most anticonvulsants may have significant interactions with certain ARVs and other medications; check for drug-drug interactions before prescribing.

**Antipsychotics**

- Potential interactions vary according to the specific medications used; consult with a pharmacist or psychiatrist.

## Patient Education

- Explain to patients that illness (physical or emotional) is not a character flaw or a moral or spiritual weakness.
- Inform patients that both behavioral interventions and medication can be very helpful in treating PTSD. If one strategy is not successful, many others are available.
- Advise patients that psychiatric medications are often given for a long time, usually for a year or longer.
- Advise patients that, when they start taking an antidepressant medication for PTSD, they should expect that it will take 2-4 weeks for them to notice any improvement. Their symptoms should continue to decrease over the following weeks. If they do not have much improvement in symptoms, providers may choose to adjust the dosage of the medication or to change medications. Patients must continue taking their medications so that symptoms do not return.
- Advise patients that they may develop problems with sexual function because of psychiatric medications. They should report any problems to their prescribers.

## References


- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing; 2013.
- Cohen M, Hoffman RG, Cromwell C, et al. *The prevalence of distress in persons with human immunodeficiency virus infection*. Psychosomatics. 2002 Jan-Feb;43(1):10-5.
- Essock SM, Dowden S, Constantine NT, et al.; Five-Site Health and Risk Study Research Committee. *Risk factors for HIV, hepatitis B, hepatitis C among persons with severe mental illness*. Psychiatr Serv. 2003 Jun;54(6):836-41.
- McNicholl I. HIV InSite Database of Antiretroviral Drug Interactions. San Francisco: UCSF Center for HIV Information. Available at hivinsite.ucsf.edu/insite?page=ar-00-0. Accessed December 1, 2013.
- New York State Department of Health AIDS Institute. *Mental Health Care for People with HIV Infection: Clinical Guidelines for the Primary Care Practitioner.* Available at www.hivguidelines.org/clinical-guidelines. Accessed December 1, 2013.
- New York State Department of Health AIDS Institute. *Trauma and Post-Traumatic Stress Disorder in Patients with HIV/AIDS*; 2007. Available at www.hivguidelines.org/clinical-guidelines. Accessed December 1, 2013.
- van Liempt S, Vermetten E, Geuze E, et al. *Pharmacotherapeutic treatment of nightmares and insomnia in posttraumatic stress disorder: an overview of the literature.* Ann N Y Acad Sci. 2006 Jul;1071:502-7.

# Insomnia

## Background

Insomnia is a common accompaniment to HIV infection, especially as the disease progresses and complications worsen. Once present, insomnia tends to be chronic, unlike the transient disturbances of sleep that are a normal part of life. Most insomnia related to HIV can be characterized by the amount, quality, or timing of sleep. Insomnia may cause progressive fatigue and diminished functioning.

### S: Subjective

The patient may complain of the following:

- Difficulty initiating sleep
- Early-morning awakening
- Mind-racing thoughts (e.g., "I can't turn off my thoughts.")
- Difficulty maintaining sleep
- Nonrestorative sleep (i.e., although the amount of sleep is adequate, the patient does not feel rested upon awakening)
- Nighttime restlessness

Ask about the symptoms above, and about the following:

- Determine the patient's bedtime sleep habits; request additional history from a sleep partner, if possible
- Try to quantify how long the patient actually sleeps each night

Ask about the following:

- Alcohol and recreational drug use
- Caffeine intake (quantity, times of day)
- Nightmares, life stressors
- Concurrent medications that may cause insomnia as an adverse effect (e.g., efavirenz, corticosteroids, pseudoephedrine, and decongestants)
- Medications (prescription or over-the-counter) or supplements used to promote sleep
- Shift work, exercise, nighttime reflux or heartburn, snoring, and periods of apnea (not breathing)
- Collar size (size >16 more often associated with sleep apnea)

Screen for depression and anxiety.

### O: Objective

Perform a general symptom-directed physical examination, including evaluation of body habitus, neurologic status, and mental status.

### A: Assessment

A partial differential diagnosis includes the following:

- Alcohol intake (interferes with sleep 2-4 hours after ingestion, may cause nocturnal awakening)
- Caffeine intake
- Recreational drug use
- Anxiety disorder
- Major depression (insomnia is a primary symptom)
- Transient insomnia related to acute stress
- Cognitive impairment
- Disturbance of the sleep/wake cycle because of excessive time in bed or inadequate sleep hygiene (e.g., noise in the bedroom)
- Medication adverse effects (e.g., from steroids, efavirenz)

- Other identifiable sleep disorders (e.g., obstructive sleep apnea, periodic leg movements)
- Pain
- Underlying systemic medical conditions that can interfere with sleep, such as delirium, lung disease, congestive heart failure, renal failure, diarrhea, and incontinence

## P: Plan

### Evaluation

The diagnosis usually is based on history. A sleep evaluation (including polysomnography) may be indicated when a physiologic cause (e.g., obstructive sleep apnea) is suspected or insomnia is severe.

### Treatment

Treat underlying illnesses that may be causing or contributing to insomnia.

- Manage correctible medical conditions that may interfere with sleep.
- Treat depression and anxiety disorders. These are very common contributors to insomnia among people with HIV infection. See chapters *Major Depression and Other Depressive Disorders*, *Anxiety Disorders*, and *Panic Disorder.*
- If the patient is suspected of having sleep apnea, periodic limb movements in sleep, or restless limb syndrome, refer to a specialist in sleep medicine for evaluation.

The following options are available for treatment:

#### Behavioral strategies

- To correct deleterious sleep habits, patients should do the following:
  - Establish a bedtime routine.
  - Avoid stimuli before bedtime.
  - Avoid vigorous exercise within 3-4 hours of bedtime.
  - Reduce or eliminate daytime napping.
  - Avoid eating, reading, watching TV, or working in bed.
  - Wake up at the same time each day regardless of total hours of sleep.
  - Have a dark, cool, quiet, comfortable environment conducive to sleep.
  - Place the bedroom clock out of sight.
- If unable to fall sleep after 15-20 minutes, the patient should get up, go into another room for nonstimulating activity in dim light (such as reading), and not go back to bed until sleepy.
- The patient should discontinue use of caffeine, central nervous system stimulants, alcohol, and tobacco, with tapering if necessary, to avoid withdrawal symptoms.
- Teach or refer the patient for relaxation techniques.

## Pharmacotherapy

### Choosing a pharmacologic agent for insomnia

A number of medications may be effective in treating insomnia. In selecting a medication for an individual patient, consider the following about a specific medication:

- Is it likely to improve symptoms that may be contributing to the patient's insomnia (e.g., depression, anxiety, psychosis, neuropathic pain)?
- Does it pose risks to the patient based on comorbid medical conditions (e.g., benzodiazepines should not be given to patients with sleep apnea, tricyclic antidepressants should not be given to patients with cardiac conduction problems)?
- Does it have adverse interactions with other medications (e.g., zolpidem [Ambien], zaleplon [Sonata], and eszopiclone [Lunesta] should be used with caution in patients taking protease inhibitors [PIs])?
- Is it the optimal agent for a patient with a current or past history of alcohol or sedative abuse/dependence?
- Is it affordable (e.g., formulary or co-pay issues)?

## Treatment considerations

There are limited data to guide the frequency (nightly, intermittently, as needed) and duration (brief, intermediate, long-term) of hypnotic medications. Hypnotics should be prescribed at the lowest effective dosage for the shortest possible period. The greater the degree of physical illness, the more likely the patient will need a low dosage of a hypnotic agent. When long-term treatment is necessary, benzodiazepines pose the greatest risk of tolerance, abuse, and dependence.

Possible adverse effects of all hypnotics include excess sedation, daytime grogginess, impaired judgment, behavior changes, and disruption of the sleep architecture. In addition, persons taking hypnotics may engage in overnight activities or behaviors without being fully awake, and may not remember these activities afterwards (e.g., walking, driving, eating); they also may have impairment in cognition and motor skills the next morning.

Interactions may occur between certain antiretrovirals (ARVs) and agents used to treat insomnia. Some combinations may be contraindicated and others may require dosage adjustment. Refer to medication interaction resources or consult with an HIV expert, psychiatrist, or pharmacist before prescribing.

### Agents with FDA-Approved Indications for Insomnia

**Antihistamines**

- The antihistamines diphenhydramine, doxylamine, and hydroxyzine, given at doses of 25-50 mg QHS, can be used for sleep. Adverse anticholinergic effects often interfere with long-term use.

**Antidepressants**

- Trazodone, 25-50 mg; maximum dose: 200 mg QHS.
  - Trazodone, a triazolopyridine derivative antidepressant and sedative, is the only antidepressant with a U.S. Food and Drug Administration (FDA) indication for insomnia, and it is widely used for this purpose. However, levels may be increased by ritonavir-boosted PIs and by the pharmacokinetic booster cobicistat. Do not use with saquinavir/ritonavir; use lower dosages for patients receiving other PIs or cobicistat. Trazodone may (rarely) cause priapism. Trazodone can be used for an indefinite period of time as it is not associated with tolerance or addiction.

**Non-benzodiazepine hypnotics (agonists of the benzodiazepine receptor)**

- Zolpidem (Ambien) 5 mg for women, 5-10 mg for men, 5 mg for geriatric patients; zolpidem-CR (Ambien-CR) 6.25 mg for women, 6.25-12.5 mg for men; zaleplon (Sonata) 5-10 mg; and eszopiclone (Lunesta) 2-3 mg QHS.
  - These newer hypnotic agents are benzodiazepine receptor agonists with shorter half-lives than benzodiazepines and may be less likely to result in day-after drowsiness. They may have decreased addiction potential compared with benzodiazepine hypnotics. Higher doses and extended-release formulations appear to increase the risk of next-morning impairment. Patients should be advised to use these hypnotics on an as-needed basis rather than nightly; it is easier for patients to discontinue a drug that they are not taking every day. The inhibition of CYP 3A4 enzyme activity by PIs or cobicistat may increase levels of these benzodiazepine receptor agonists, particularly eszopiclone; this may cause excessive sedation or respiratory depression.

**Melatonin agonists**

- Ramelteon (Rozerem), 8 mg QHS.
  - The first of a new class of melatonin agonists to receive FDA approval, ramelteon may have some advantages over sedative/hypnotic agents, such as reduced dependence and overuse. However, it may have severe adverse reactions, including hypersensitivity reactions such as anaphylaxis and angioedema. Long-term interactions with ARV agents are unknown.

**Benzodiazepine hypnotics**

- A number of benzodiazepines have FDA-approved indications for the short-term treatment of insomnia. They carry a risk of addiction and residual drowsiness the following day.
- Metabolized by glucuronidation; predicted to have few drug interactions with ARVs:
  - Temazepam (Restoril) 7.5-30 mg; intermediate half-life
  - Lorazepam (Ativan), 1-2 mg; intermediate half-life.
- Metabolized by CYP 34A; PIs and cobicistat may prolong their duration, resulting in excessive daytime somnolence. These may be most beneficial for use with patients whose insomnia is associated with anxiety:
  - Flurazepam (Dalmane) 15-30 mg
  - Quazepam (Doral) 7.5-15 mg
  - Estazolam (ProSom) 1-2 mg
- Clonazepam (Klonopin) at a dose of 0.5-2 mg has been approved for treatment of periodic leg movements. PIs and cobicistat may prolong its duration and increase risk of adverse effects; start at low dosage and titrate slowly.
- Triazolam (Halcion), another approved agent for insomnia, is contraindicated for use with all PIs, some nonnucleoside reverse transcriptase inhibitors (NNRTIs) (delavirdine, efavirenz), and cobicistat because of potentially life-threatening reactions (e.g., respiratory depression)

**Agents Used for Sedating Side Effects (no FDA indication for insomnia)**

**Antidepressants**

- Tricyclic antidepressants at doses of 10-50 mg can be beneficial for sleep, but they have longer half-lives than short-acting hypnotic agents, and potential adverse effects include cardiac dysrhythmias and pulmonary complications. Tricyclics generally should be avoided for geriatric patients. Levels of tricyclics are elevated by ritonavir and by cobicistat, and lower dosages may be needed for patients taking ritonavir or ritonavir-boosted PIs or cobicistat. Routine testing of tricyclic blood levels should be performed on patients receiving higher doses (e.g., 100 mg per day; 50 mg for nortriptyline), those concurrently on ritonavir, and those with risk factors for cardiac conduction abnormalities. A routine electrocardiogram should be performed before prescribing tricyclics, and this class of drugs should not be prescribed to patients with cardiac conduction problems. However, tricyclic antidepressants also have characteristics that may benefit some patients, including treatment of chronic pain, promotion of weight gain, and reduction of diarrhea. Amitriptyline (Elavil) and doxepin (Sinequan) are the most sedating of the tricyclic antidepressants and therefore are the drugs in this class most often used for sleep.
- The tetracyclic antidepressant mirtazapine (Remeron) is sedating and has been effective in treating insomnia at low dosages (7.5-15 mg). Higher dosages may result in increased activation owing to increased norepinephrine (NE) receptor antagonism.
- The selective serotonin reuptake inhibitor (SSRI) antidepressants are not sufficiently sedating to be used as sleeping agents, but when insomnia is caused by depression, sleep will improve as the depression lifts.

**Anticonvulsants**

- Gabapentin (Neurontin) can be useful for patients with insomnia and has been demonstrated to be particularly beneficial for patients with alcohol and other substance-use disorders; it is widely prescribed for neuropathic pain.

## Patient Education

- Instruct patients in behavioral interventions that can help to reduce insomnia.
- Additional interventions are available when behavioral interventions are not sufficient.
- Patients should be warned strongly about risks associated with medications used to treat insomnia, including the risk of sleepwalking and other overnight activities and next-morning impairment in cognition and coordination.
- Patients should report new or worsening symptoms to their health care provider. These may be not only signs of worsening insomnia, but also of symptoms of anxiety, depression, medications, or changes in medical conditions

## References


- FDA Drug Safety Communication: Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist). January 10. 2013. Available at www.fda.gov/Drugs/DrugSafety/ucm334033.htm.
- Ford DE, Kamerow DB. *Epidemiologic study of sleep disturbances and psychiatric disorders.* An opportunity for prevention? JAMA. 1989 Sep 15;262(11):1479-84.
- *Insomnia and HIV: A Biopsychosocial Approach*. In: *Comprehensive Textbook of AIDS Psychiatry*; Cohen MA, Gorman JM, eds. New York: Oxford University Press; 2008;163-72.

- Kuppermann M, Lubeck DP, Mazonson PD, et al. *Sleep problems and their correlates in a working population.* J Gen Intern Med. 1995 Jan;10(1):25-32.
- McNicholl I. HIV InSite Database of Antiretroviral Drug Interactions. San Francisco: UCSF Center for HIV Information. Available at hivinsite.ucsf.edu/insite?page=ar-00-02. Accessed December 1, 2013.
- Ohayon MM, Roth T. *Place of chronic insomnia in the course of depressive and anxiety disorders.* J Psychiatr Res. 2003 Jan-Feb;37(1):9-15.
- Reid S, Dwyer J. *Insomnia and HIV infection: a systematic review of prevalence, correlates, and management.* Psychosom Med. 2005 Mar-Apr;67(2):260-9.
- Schutte-Rodin S, Broch L, Buysse D, et al. *Clinical guideline for the evaluation and management of chronic insomnia in adults.* J Clin Sleep Med. 2008 Oct 15;4(5):487-504.
- *Sleep and Sleep-Wake Disorders.* In: *Psychiatry, 3rd Edition*. Tasman A, Kay J, Lieberman JA, et al., eds. London: J. Wiley & Sons, 2008:1626-57.
- *Sleep and Wakefulness Disorders.* In: *The Merck Manual of Diagnosis and Therapy, 18th ed.*; Beers MH, Porter RS, Jones TV, eds. Whitehouse Station, NJ: Merck & Co.; 2006:1834-40.
- Wainberg ML, Faragon J, Cournos F, et al. *Psychiatric Medications and HIV Antiretrovirals: A Guide to Interactions for Clinicians, 2nd ed.* Laminated booklet produced by the New York/New Jersey AIDS Education and Training Center, Health Resources and Services Administration; 2008.