Background

In the United States, people living with HIV infection have a high prevalence of concomitant mental disorders, including alcohol and substance use disorders, as well as other mental illnesses.[1,2] These co-morbidities of HIV infection, especially major depression and alcohol/substance use disorders, are associated with many negative HIV-related outcomes, including sexual and injection drug-use risk behaviors that may forward HIV transmission and problems engaging in care along the entire HIV clinical care continuum, including with adherence to antiretroviral regimens. People with mental illnesses are also overrepresented among those who suffer from powerful social determinants of poor health, including poverty, homelessness, incarceration and additional stigma. Alcohol and substance use disorders, major depression, and many other mental illnesses shorten the lifespan of persons with HIV infection independent of adherence to HIV care and treatment.

Challenges in Evaluating Mental Disorders in Persons with HIV Infection

Persons living with HIV may also experience neurocognitive deficits. In particular, HIV-associated neuropsychiatric disorder (HAND) is an increasing concern for the aging HIV-infected population and HAND often complicates the care of older persons (and some younger persons) living with HIV infection. The aging of people living with HIV infection, and the neurocognitive problems associated with many of the comorbidities associated with HIV, such as substance use and hepatitis C, contribute to the complexity of diagnosing and managing cognitive problems. Therefore, clinicians caring for individuals living with HIV should be aware of the multitude of challenges implicit in the screening, diagnosis, and management of mental disorders and neurocognitive deficits and should assist their patients in obtaining access to appropriate, integrated neuropsychiatric treatment.

Delirium

The presence of delirium, a common neuropsychiatric disorder among people with HIV infection, requires a careful evaluation to rule out the possibility of life-threatening medical conditions. Clues to the presence of delirium include sudden onset, fluctuating level of consciousness and abnormal vital signs. Virtually any life threatening condition can cause delirium, including the failure of any major organ system (liver, kidneys, lungs, heart, brain), any severe febrile illness, head trauma, blood loss, metabolic conditions, intoxication, alcohol withdrawal, accidental or intentional poisoning, etc. A sudden change in mental status should be considered a medical emergency until proven otherwise, even among people known to have other preexisting mental disorders. Delirium in persons with HIV infection will not be addressed in this review.

Overview

This Topic Review will emphasize screening recommendations and tools for identifying depression, bipolar disorders, common anxiety disorders and PTSD, as well as neurocognitive disorders, among
persons living with HIV in the United States. Detailed discussions of definitions, diagnostic criteria, and treatment for particular DSM-5 conditions are beyond the scope of this review. Screening tools for Alcohol/Substance Use Disorders are addressed in the topic Substance Use Disorders. It is, however, important to recognize that alcohol and other substance use disorders are highly comorbid with other mental illnesses, especially in the US, and this comorbidity complicates diagnosis and treatment.
Estimates of Mental Disorders in Persons Living with HIV

Definition

The term mental disorders, as used in DSM-5, includes, among other conditions, alcohol and other substance use disorders; anxiety and depressive disorders; severe mental illnesses such as bipolar disorders and schizophrenia; and neurocognitive disorders.

Increased Prevalence of Mental Disorders in Persons with HIV Infection

Early estimates of the prevalence of selected mental disorders among people with HIV infection were based on data from the HIV Cost and Services Utilization Survey (HCSUS), a nationally representative, longitudinal survey of persons with HIV infection who were receiving medical care for HIV in early 1996.[1] This study found that persons with HIV infection screened positive for mental disorders significantly more often than persons in the general population (using the same screeners for depression, anxiety, and panic attacks as used in the 1994 National Household Survey on Drug Abuse).[1] Screening alone without further diagnostic interviews overestimated the prevalence of mental disorders in persons living with HIV, but subsequent studies also reported relatively higher prevalence rates of various mental disorders among persons living with HIV.[2,3,4] For example, the National Epidemiologic Survey of Alcohol and Related Disorders reported a 12-month prevalence of major depressive disorder and bipolar disorder among persons with HIV infection was 9.0% and 10.8% compared to a 12-month prevalence of 6.2% and 3.7% among those without HIV infection.[5,6] A recent study examined the excess burden of depression among a nationally representative sample of more than 4000 people with HIV infection receiving medical care in the U.S. and compared these rates to the general U.S. population; among those with HIV infection, 25.6% had current depression, a rate almost three times greater than the 9.1% rate of current depression in the general population (Figure 1).[7] In addition, posttraumatic stress disorder (PTSD) is also more prevalent among persons with HIV infection compared to those without HIV infection; in particular, women with HIV suffer high rates of PTSD (up to 30% in several studies, which is five times the prevalence reported among women without HIV infection);[8,9] these rates are even higher in low-income women with HIV infection.[10]
Mental Disorders and Risk of HIV Acquisition and Transmission

HIV Acquisition Risk

An extensive body of medical literature has documented an increased risk of HIV acquisition among individuals with mental illness, especially among women. For example, bipolar disorder is associated with increased impulsivity, impaired judgment, risk-taking, substance use, and homelessness—all factors that may increase high-risk behaviors such as injection drug use, needle sharing, multiple partner sex, condomless sex, transactional sex, and sex under the influence of psychoactive substances. Social impairments associated with severe mental illness also increase HIV acquisition risk by interfering with the ability of an individual to maintain healthy sexual relationships and to negotiate condom use with casual or anonymous partners. An early study that examined the overlap of mental illness and HIV found that 1 out of every 18 patients admitted to two psychiatric hospitals in New York City were individuals with HIV infection; a follow-up study in New York City found an HIV prevalence of approximately 5% among patients with severe mental illness at two public psychiatric hospitals. In a later retrospective review at Duke University, HIV infection was present in 1.2% of the psychiatric outpatients, approximately 4 times the rate of HIV in the general population in the United States. Similarly, a seroprevalence study conducted across four states found that the rate of HIV infection among individuals being treated for a severe mental illness in both inpatient and outpatient settings was 8 times the rate of the general U.S. population. Further, a recent meta-analysis reported a 6% prevalence of HIV infection among people with severe mental illness in the United States, and a separate multisite cross-sectional study found an HIV prevalence of 4.8% after performing HIV testing on 1,061 people in mental health settings. Taken together, these studies clearly suggest that mental illness is associated with HIV acquisition.

HIV Transmission Risk

Mental disorders increase HIV transmission risk primarily through poor medication adherence and increased sexual risk behavior, often in the context of substance use. In addition, close to 100% of people who inject drugs have a mental disorder, most commonly opioid addiction and other substance use disorders, and HIV transmission in this population occurs through both unsafe drug injection and sexual risk behavior. Persons living with HIV who regularly take antiretroviral therapy markedly reduce the risk of transmitting HIV to sexual partners; accordingly, persons living with HIV who are not taking antiretroviral therapy miss out on this major prevention mechanism. Major depression has been linked to increased rates of nonadherence to antiretroviral therapy, thus raising the likelihood of HIV transmission to partners. In addition, anxiety and depression have been linked to increased sexual risk-taking, possibly as a means to cope with psychological stress, whereas bipolar disorder may lead to increased sexual risk behavior through pathways of impulsivity, mania, and hypersexuality. The association between mood disorders and increased sexual risk behavior is inconsistent across studies, and co-existing substance use disorders likely influence this link. Treatment for mental disorders, especially depression and substance use disorders, need to be considered in efforts to prevent forward transmission of HIV. A psychiatry group at Duke has generated a conceptual model outlining the impact of mental health treatment on HIV transmission risk behavior in persons living with HIV.
Impact of Mental Disorders on HIV Disease Outcomes

Negative Impact on the HIV Continuum of Care

The presence of mental disorders in persons living with HIV has correlated with decreased initiation of antiretroviral therapy, reduced medication adherence, and lower rates of virologic suppression, all of which have significant implications for individual health as well as for HIV prevention efforts.[36] Studies have established a relationship between antiretroviral therapy nonadherence and symptoms of depression, posttraumatic stress disorder (especially in those patients with concomitant depression), and bipolar disease.[23, 24, 37] The relationship between posttraumatic stress disorder and nonadherence has been inconsistent,[38] perhaps because the high rates of comorbid depression are the determining factor. Patients with bipolar disorder present particular challenges with respect to antiretroviral adherence, as these patients frequently demonstrate poor insight, mood fluctuations, housing instability, and poor adherence to psychiatric medications.[23] One study involving persons with HIV infection reported those with bipolar disorder had significantly lower adherence with antiretroviral therapy when compared with those who did not have bipolar disorder (47.7% versus 90.9%), with adherence defined in this study as the proportion of correctly taken doses over 30 days using electronic monitoring devices.[25] Overall, however, a systematic review failed to find any consistent association between adherence and non-addictive mental disorders other than depression, and this remains an area of active study.[26] Discrepancies in various study findings may in part be explained by differences in control of the underlying psychiatric illness during the study, but more importantly very little research has been funded in this domain.

Benefit of Engagement in Care for Mental Disorders

Notwithstanding the data that suggest reduced antiretroviral adherence among persons with HIV infection who have mental disorders, treatment of mental disorders can mitigate psychiatric symptoms as well as improve adherence to antiretroviral therapy.[39] In some patients, a diagnosis of a mental disorder may facilitate closer monitoring and medical scrutiny, which fosters engagement in care and improved adherence rates. A longitudinal study of five outpatient sites in the United States found that individuals with a psychiatric disorder who attended at least 6 visits for their mental disorder were less likely to discontinue antiretroviral therapy in the first 2 years of treatment compared to individuals who had no health visits for their mental disorder, and that a dose-response relationship may exist, such that individuals with frequent mental health visits derive the greatest benefit in adherence rates.[40] These findings corroborate results from previous studies, such as the Women's Interagency HIV Study, that found individuals who used mental health services had a 20% increase in the adjusted odds of utilizing antiretroviral therapy compared to those who did not access mental health services, and the HIV Cost and Services Utilization Study finding that among persons with HIV infection who had a psychiatric disorder, those who received care from a psychiatric provider had a 50% increase in the odds of receiving antiretroviral therapy.[40]

HIV Disease Outcomes

Mental disorders have been shown to predict adverse outcomes in some groups of individuals with HIV infection who were living with a psychiatric condition. In particular, untreated depression significantly worsens adherence to antiretroviral medication, decreases the likelihood of full virologic suppression or CD4 cell recovery, and appears to increase the risk of disease progression and death;[41] however, some of this effect may be mitigated if depression is treated, particularly with the use of selective serotonin reuptake inhibitors (SSRIs).[42] In a large, multi-state retrospective cohort study of more than 3,000 persons with HIV infection, investigators reported individuals with depression who were treated with SSRIs had better adherence to antiretroviral therapy, improved virologic suppression, and a greater rise in CD4 cell count compared to their counterparts who did not receive SSRI treatment.[42] Posttraumatic stress disorder has also been shown to predict
increased HIV symptomatology among both men and women with HIV infection, high rates of emergency room utilization, and increased HIV-related morbidity.\[^{43,44}\]

**Morbidity and Mortality Considerations**

Although not often thought of in this way, many mental illnesses are best conceptualized as systemic diseases affecting both the brain and other organs of the body. As a group, people with mental disorders experience increased morbidity and mortality when compared to comparable people who do not have these conditions.\[^{45}\] Certain health problems are inherent in the disease process itself, such as the well-established association of major depression with heart disease. Other health problems are caused by the harms of having the disorder, such as liver disease associated with alcoholism and cancer associated with tobacco smoking. Treatment of mental illness can itself cause harm, such as the obesity associated with taking antipsychotic medication. For these and other reasons, the treatment of physical and mental disorders is inseparable, and this is particularly important in HIV care.
Overview of Screening Tools for Common Mental Disorders

History of Mental Disorders Screening Tools

In the early 1990s, Drs. Robert Spitzer, Janet B.W. Williams, Kurt Kroenke, and coworkers developed the 26-item Primary Care Evaluation of Mental Disorders (PRIME-MD) patient questionnaire as a screening tool for five of the most common psychiatric disorders: (1) depression, (2) anxiety, (3) somatoform, (4) alcohol use disorder, and (5) eating disorders. Although the PRIME-MD emerged as a groundbreaking mental health screening tool, its utility in clinical practice settings has been limited by the long administration time required by the clinician to complete the 26-item survey. These same investigators subsequently developed and validated a self-administered form of the PRIME-MD known as the Patent Health Questionnaire (PHQ). The development of the PHQ led to shorter, more practical screening tools, such as the PHQ-9 screening tool for depression and the generalized anxiety disorder 7 (GAD-7) screening tool. Online toolkits are available to screen for common mental disorders. See the screening tools for Mental Disorders Screening category of the Tools & Calculators section of this website.

Barriers to Usefulness of Screening Tools

It is important to note that the primary barrier to the usefulness of screening tools for mental disorders is the low rates of further diagnostic evaluation and linkage to and retention in mental health care that follow the initial screening. This problem has been well demonstrated for depression. Barriers to treatment have led to a number of new team-based models for delivering mental health services within primary care; studies of these new models are promising, although they are rarely conducted in HIV settings.

Use of Mental Disorders Screening Tools in Primary Care

Ideal Aspects of Mental Disorder Screening Tools

Practical screening tools for use in the primary care setting should be brief, easily scored, free, evidence-based, and accessible to a range of providers without specific training. The principles that define a good screening test are not unique to persons with HIV infection but rather apply to screening more generally. An ideal screening test for a mental disorder will accurately identify individuals with the clinical condition of interest without diagnosing individuals who do not have the condition. In addition, screening tests should be limited to conditions for which there is available, effective treatment that can directly target the disease and improve prognosis and outcomes. Most of the common mental disorders seen among people with HIV infection have effective treatments.

Follow-Up for a Positive Screen

A positive screen for a mental disorder usually needs to be followed by a further diagnostic evaluation to clarify that the condition crosses the threshold for a true mental disorder. Unfortunately, there are no biological tests that can be conducted in clinical care settings to clarify the presence of the vast majority of mental disorders. However, tests for medical conditions causing delirium and dementia, and tests for the presence of alcohol and other drugs, can contribute to diagnostic accuracy. There are research instruments for the diagnosis of many mental disorders, but these are too long and cumbersome for use in primary care. Several screening tools for the most common mental disorders in primary care are described below, with links provided to the screening tool.
Depression Screening Tools

The United States Preventive Services Task Force (USPSTF) has recently upgraded the strength of its recommendation for depression screening in the general adult population to a Grade B recommendation based on accumulating evidence that screening offers a moderate to substantial benefit. The USPSTF recommendation specifically stated “screen for depression, with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up.” Given the increased prevalence of depression in persons living with HIV, the HIV Primary Care Guidelines recommend screening for depression at the initial visit and at periodic visits thereafter.

Patient Health Questionnaire-9 (PHQ-9)

The Patient Health Questionnaire-9 (PHQ-9) is a self-administered questionnaire, which scores each of the 9 DSM-5 criteria as “0” (not at all) to “3” (nearly every day) for items in the survey during the most recent 2 weeks. The PHQ-9 was designed to serve as a multipurpose instrument tool for screening, diagnosing, monitoring, and measuring the severity of depression. In addition, the ninth question screens the patient for the presence and duration of suicide ideation. The PHQ-9 has been shown to have diagnostic validity comparable to the original physician-administered PRIME-MD, but is a much more practical tool for use in the clinic setting. In addition, the PHQ-9 has also been validated across diverse patient populations, including among African Americans, Chinese Americans, Latinos, and non-Hispanic whites.

- **Interpretation**: The PHQ-9 score ranges from 0 to 27. Increasing scores with the PHQ-9 clearly correlate with greater likelihood of major depression. In addition, a cumulative score of 10 points or higher has 88% sensitivity and specificity for major depression and scores of 5 to 9, 10 to 14, 15 to 19, and 20 and higher correlate with mild, moderate, moderately severe, and severe depression, respectively. For patients who have a score of 1 or greater on any question, an additional tenth question is asked that evaluates how these problems impact function at home, at work, and with others. The authors of a recent review of studies using the PHQ-9 concluded that it has acceptable diagnostic properties at a cutoff score of 10. By contrast, looking at very similar results, other authors conclude that the PHQ-9 shows suboptimal results for diagnostic purposes and recommend further diagnostics. The Mitchell paper suggests that using the two-step procedure of starting with the PHQ-2 and following up with the PHQ-9 gives better diagnostic results and saves clinician time. We recommend using this two-step approach in most clinical settings of HIV clinical care, since it provides a realistic strategy for broadly screening for depression.

- **Recommendation**: Individuals who reach the threshold for a positive screen (a score of 5 or higher) should ideally be offered a full diagnostic interview using standard diagnostic criteria from the DSM-5. Unfortunately, not every clinical setting has the resources to offer further diagnostic evaluation. In such situations the primary care clinician should use good clinical judgment taking into account the duration and severity of the depression, its impact on functioning, and the treatment preferences of the patient. Some authors, but not all, conclude that a PHQ-9 score of 10 or higher is acceptable for diagnostic purposes, and most patients who screen positive for moderately severe depression or severe depression warrant treatment using antidepressants, psychotherapy, and/or a combination of both. In addition, any positive response on question 9 (presence and duration of suicide ideation) warrants immediate further evaluation to determine if there is imminent risk of self-harm. Suicide screening instruments, including the PHQ-9, have not been shown to significantly predict near-term outcomes, so additional risk stratification may be necessary.

Patient Health Questionnaire-2 (PHQ-2)
The Patient Health Questionnaire-2 (PHQ-2) is a 2-item, validated screening tool that uses the first two questions of the PUQ-9 that ask about the frequency of depressed mood and anhedonia (the first two DSM-5 criteria for diagnosing major depression).[62] The PHQ-2 focuses the time frame to the past 2 weeks and grades answers on a 4-point scale; the PHQ-2 is distinct from the 2-Item PRIME-MD, which uses a 4-week time frame and a yes or no response to questions.

- **Interpretation:** The PHQ-2 score ranges from 0 to 6. Using a cutoff score of 3, the PHQ-2 has a sensitivity of 83% and specificity of 90% for major depressive disorder. In one study, investigators concluded a cutoff score of 3 was the optimal cut point for screening purposes, with the qualification that moving the cut point to 2 would enhance sensitivity and moving to 4 would increase specificity (Figure 5).[62]
- **Recommendation:** The PHQ-2 functions as a brief, practical, first-step screening tool, intended to identify individuals who require additional evaluation with another instrument, such as with the PHQ-9, or a direct diagnostic psychiatric interview; the PHQ-2 should not be used as a final diagnostic tool for depression.

2-Item PRIME-MD

This 2-item PRIME-MD is based on the 27-item PRIME-MD. The 2-item PRIME-MD inquires about the frequency of depressed mood and anhedonia over the past 4 weeks using two of the questions from the 27-item PRIME-MD.[63] The following two questions are asked in the 2-item PRIME-MD: (1) “During the past month, have you often been bothered by feeling down, depressed, or hopeless?” and (2) “During the past month, have you often been bothered by little interest or pleasure in doing things?”[64] The two questions are scored based on a “yes” or “no” response. A positive (“yes”) answer to both of these questions has been shown to have a sensitivity of 97% and a specificity of 57% for diagnosing major depression.[64] A positive answer to the first question alone is 93% sensitive and 62% specific, and a positive answer to the second question alone is 79% sensitive and 72% specific.[64]

- **Interpretation:** A “yes” answer to either one or both of the screening questions is considered a positive screening result.
- **Recommendation:** Similar to the PHQ-2, the 2-item PRIME-MD is a brief and practical initial screening tool, and persons who have a positive screening result on the 2-item PRIME-MD require additional evaluation with the PHQ-9, or a direct psychiatric interview that uses diagnostic criteria from the DSM-5.[60]

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) was developed in 1983 to assess anxiety disorders and depression among patients attending hospital-associated clinics that were not psychiatric clinics. The HADS includes 14 questions, 7 about depression and 7 about anxiety, with each answer scored from 0 to 3. The focus is on psychological complaints and does not relying on somatic symptoms that overlap with those seen in medical conditions. The HADS has also been studied in various clinical populations, including persons with multiple sclerosis, traumatic brain injury, cancer, and renal failure receiving dialysis.[65,66,67,68] Interestingly, the HADS has not been found to perform well in patients with hepatitis C.[69] There are no studies evaluating the HADS performance in persons with HIV infection in the United States.

- **Interpretation:** With a cutoff score of at least 8 points, the sensitivity and specificity is approximately 80% for both the HADS-A (anxiety subscale) and HADS-D (depression subscale).[70]
- **Recommendation:** As with other depression screeners, individuals who reach the threshold for a positive score should be referred for a full diagnostic interview that uses diagnostic criteria from the DSM-5. Compared to several other screening tools, the HADS is not as useful in primary care settings.
Anxiety Disorder Screening Tools

Two of the most common anxiety disorders are generalized anxiety disorder (GAD) and panic disorder. Screening for these disorders, combined with evidence-based treatment approaches, has been shown to improve patient outcomes, yet there are no formal recommendations for screening primary care clients, regardless of HIV status.[71] Some experts recommend screening all primary care patients for these two anxiety disorders, or at the very least, those with risk factors.

Generalized Anxiety Disorder-7 (GAD-7)

The 7-item Generalized Anxiety Disorder-7 (GAD-7) anxiety scale is a brief, self-administered questionnaire that has been validated in the general population to identify patients with probable generalized anxiety disorder.[72,73,74] The questionnaire includes questions about anxiety symptoms occurring in the past 2 weeks.

**Interpretation:** The GAD-7 scores can range from 0 to 21. A major study identified a cut-point score of 10 as having the optimized sensitivity (89%) and specificity (82%) for diagnosing generalized anxiety disorder (Figure 6).[74] Scores of 0-4, 5-9, 10-14, and 15-19 correlate with minimal, mild, moderate, and severe levels of anxiety, respectively. A more recent meta-analysis suggested using a cutoff score of 8 to optimize sensitivity without compromising specificity.[75]

**Recommendation:** Individuals who meet the threshold for a positive GAD-7 screen (a score of 8 or above) ideally should have a complete diagnostic evaluation.

Patient Health Questionnaire for Panic Disorder (PHQ-PD)

This 5-item screening instrument is one subset of questions (questions 3a-d and questions 4 a-k) derived from the longer Patient Health Questionnaire (PHQ), which itself is a short, self-reported instrument derived from the physician-administered PRIME-MD interview. The PHQ-PD, also called the panic module of the PHQ, has been found to be a valid screening instrument with sensitivity of 44 to 66% and specificity of 87 to 95%, depending on the scoring algorithm that is applied.[76] Using a single screening question taken from the PHQ-PD module (e.g., question 3a: “In the last 4 weeks, have you had an anxiety attack—suddenly feeling fear or panic?”) improves sensitivity to 71% but drops specificity to 84%.

**Interpretation:** A positive score on the original panic module is indicated with a positive (“yes”) answer on all four questions 3a-d plus a positive (“yes”) answer on at least four items from questions 4a-k. Modified versions of the test improve sensitivity by requiring only 2 or 3 positive answers for questions 3a-d. The most sensitive version of the panic module screener is the single screening question 3a—“yes” answer to this single question is considered a positive screen.

**Recommendation:** Many experts recommend using the single screening question (question 3a) since it has better psychometric properties than the full PHQ-PD algorithm.[76] Moreover, because primary care settings do not usually screen for panic disorder, adding only one question minimizes any additional burden to screening procedures already in place. Individuals who screen positive require follow-up with a formal diagnostic procedure.
Posttraumatic Stress Disorder (PTSD) Screening Tools

There is limited evidence to support screening the civilian primary care population for post-traumatic stress disorder, and the United States Preventive Services Task Force does not address PTSD screening. In contrast, other organizations, including the National Institute of Health Care and Excellence in the United Kingdom (NICE-UK), recommend screening for PTSD when there is a known exposure to a traumatic stressor, such as following a natural disaster or after experiencing an accident, injury, or significant illness.[77] HIV infection and the events surrounding its acquisition may qualify as such an exposure given that people with HIV infection have considerably higher rates of PTSD than the general population, approximating 30% for women in the United States.[8,9]

Multiple PTSD screening instruments are available, including the 5-item Primary Care PTSD Screen from DSM-5 (PC-PTSD-5), the 17 item PTSD Checklist, the 4-item Startle-Physiologic Arousal-Anger-Numbness (SPAN), the 7-item Breslau's scale, the 10-item Trauma Screening Questionnaire, and the Single-Item PTSD Screener.[77,78,79] Among these screening tools, the PC-PTSD-5 test (five items) appears to be the best single screening test for PTSD for use in primary care, based on data from the similar older 4-item Primary Care PTSD screen related to the number of items in the screening tool and diagnostic accuracy.[78] The PTSD checklist can also be used but it has more items.

Primary Care Posttraumatic Stress Disorder (PC-PTSD)

The Primary Care PTSD for DSM-5 (PC-PTSD-5) screening test is a 5-item scale that includes questions about symptoms unique to PTSD (re-experiencing, avoidance, numbness, hyperarousal and feelings of guilt or blame).[79] One study found that the previously used 4-item PC-PTSD was more effective when used in combination with the General Health Questionnaire-12 (GHQ-12), which is a set of 12 questions used to screen for nonpsychotic psychiatric disorders and graded on a 4-point response scale.[80]

- **Interpretation**: Different studies recommend different cut-off scores for a positive screen. A study involving 398 Veterans patients at a primary care clinic patients found a score of 3 correlated with 95% sensitivity and 85% specificity for the diagnosis of PTSD (Figure 7).[78,79] Another large study that used data extracted from clinical databases for Veterans Affairs primary care patients used a score of 2 or greater as the cutoff for a positive PC-PTSD screen.

- **Recommendation**: Individuals who screen positive on the PC-PTSD screening test qualify for additional evaluation from the primary care provider or a mental health practitioner that includes an interview evaluating PTSD criteria from the DSM-5.
Bipolar Disorder Screening Tool

Bipolar disorder encompasses a spectrum of clinical disorders (bipolar I disorder, bipolar II disorder, and cyclothymic disorder) consisting of episodes of manic, hypomanic and depressive symptoms. The heterogeneous presentation of bipolar disorder can make it difficult to detect this disorder, through screening, and subsequently, estimates of lifetime prevalence of bipolar disorder vary widely across studies.[81] The National Comorbidity Survey estimates that the lifetime and 12-month prevalence for bipolar I disorder is 1.0% and 0.6%, respectively; for bipolar II disorder these numbers are 1.1% and 0.8%.[82] There are no formal recommendations for screening for bipolar disorder; however, some experts recommend that primary care physicians implement selective screening for bipolar disorder in patients with known depression, anxiety, or substance use disorders.[81]

Mood Disorders Questionnaire (MDQ)

The Mood Disorders Questionnaire (MDQ) can be used to screen for lifetime history of mania or hypomania. The MDQ consists of 13 “yes” or “no” questions based on DSM-5 criteria for bipolar disorder with two additional items to assess frequency and severity of “yes” responses. In primary care the question of whether a patient has bipolar disorder arises most frequently in the context of beginning an antidepressant medication because these medications can precipitate mania in vulnerable individuals. The MDQ is not a practical screening tool for most primary care clinicians, primarily because of the need to ask so many questions. Accordingly, some clinicians may find that asking a couple of pointed questions during history taking can be useful in ruling out a history of mania: (1) “Have your ever told you that you have manic-depressive illness or bipolar disorder?” and (2) “Has there ever been a period of time when you were not your usual self and you had much more energy than usual?” These questions parallel two of the items on the MDQ. Yes answers would then lead to further inquiry.[83,84]

- **Interpretation:** In the primary care setting, a score of 7 on the MDQ has a sensitivity of 43% and a specificity of 95% for detecting any type of bipolar disorder. In the mental health setting, diagnostic characteristics are better overall: for a score of 7, sensitivity is 81% and specificity is 85% (Figure 8).[84]
- **Recommendation:** Based on data showing low sensitivity but high specificity (and high negative predictive value), bipolar disorder screening tools, such as the MDQ, may be most appropriately utilized to rule out bipolar disorder in patients presenting with depression, rather than as a general screening tool.[85] A large review on the MDQ’s performance found that the MDQ is limited in its ability to detect bipolar disorder II (which is characterized by episodes of hypomania rather than mania), is less sensitive and has lower positive predictive value in the primary care population compared to the psychiatric population, and cannot be recommended for routine screening for bipolar disorder due to the lack of studies examining the benefits of improved detection against the risk of over diagnosis.[86] A subsequent meta-analysis on the accuracy of various bipolar disorder screening instruments, including the MDQ as well as the Hypomania Checklist (HCL) and Bipolar Spectrum Diagnostic Scale (BSDS), confirmed these tools have lower sensitivity for detecting bipolar disorder in primary care settings compared to mental health settings and that a clinical psychiatric diagnostic interview is essential in confirming any positive screen.
Neurocognitive Disorders in Persons Living with HIV

Estimates of Neurocognitive Disorders in Persons with HIV Infection

Cognitive disorders are widespread in the general population, with prevalence estimated to be 5 to 7% in most parts of the world; age is the major predictive factor for the development of dementia and the prevalence of dementia nearly doubles every 10 years after age 60.[87] Overall, adults living with HIV have poorer cognitive performance compared with those without HIV infection, regardless of age.[4,88,89] One cross-sectional observational study of persons with HIV infection reported neuropsychological impairment in 52% of study participants whereas other studies report prevalence rates ranging from 25 to 60%.[88,90] Similar to the general population, increasing age remains a strong predictor of poor neurocognitive performance in persons living with HIV; other risk factors include low nadir CD4 count, previous central nervous system (CNS) injury, detectable plasma HIV RNA levels, and comorbid conditions, such as hypertension, insulin resistance, viral hepatitis, and substance use disorder.[4,88,91] In addition, major depression, another common comorbid condition in persons living with HIV, carries a significant burden of cognitive impairment that is reversible in part with treatment of depression.[92,93] In this section we look at screening tools for both neurocognitive disorders in general as well as HIV-associated neurocognitive disorders in particular.

HIV-Associated Neurocognitive Disorder (HAND)

The term HIV-associated neurocognitive disorder (HAND) is used to describe the spectrum of neurocognitive dysfunction that includes (1) asymptomatic neurocognitive impairment, (2) mild neurocognitive disorder, and (3) HIV-associated dementia.[94] These three conditions have been classified based on criteria established by consensus research definitions, referred to as the Frascati Criteria, and are not readily applied to clinical settings.[95] The Multicohort AIDS Study (a prospective study with gay and bisexual men) found that asymptomatic neurocognitive impairment doubles the risk of developing symptomatic HAND compared to a diagnosis of normal cognition.[90] Asymptomatic neurocognitive impairment and mild neurocognitive disorder involve mild neuropsychological impairment in at least two domains that is not attributable to comorbid conditions; mild neurocognitive disorder is differentiated from asymptomatic neurocognitive impairment by the presence of functional decline in activities of daily living. The third and most serious HAND diagnosis is HIV-associated dementia, which is characterized by neuropsychological impairment of at least moderate severity and major functional decline in at least two domains.[88,95] In the observational study noted above, only 2% of participants met the criteria for HIV-associated dementia, which is a significant drop from the 10 to 15% prevalence of HIV-associated dementia prior to the availability of effective antiretroviral therapy.[88] By contrast, the prevalence of milder forms of HAND has not declined despite effective antiretroviral therapy, though the study results are complicated by a CD4 nadir below 200 cells/mm$^3$ in 70% of the participants. In addition to low nadir CD4 count, other risk factors linked to poor neurocognitive performance include increasing age, previous CNS injury, detectable HIV RNA, and comorbidities such as hypertension, viral hepatitis, substance use disorder and depression.[88,91]

Differential Diagnosis

Although HAND describes a spectrum of neurocognitive impairment from mild to severe, it is important to recognize that persons living with HIV continue to be at risk for other causes for neurocognitive decline, including cerebrovascular disease, severe psychiatric disorders, Alzheimer’s disease, metabolic disorders (such as hypothyroidism), abuse of alcohol, side effects of psychotropic drugs, neurotoxicity related to certain antiretroviral medications, previous or current central nervous system opportunistic infections (and their sequelae), or other neurological diseases.[4,96,97,98,99] Treatable causes of neurocognitive disorder, such as depression, thyroid disease, B12 deficiency, syphilis, opportunistic infection and tumor should be identified and addressed.
Neurocognitive Screening Tools

Recommendations to Screen for Neurocognitive Disorders

The United States Preventive Services Task Force (USPSTF) has found insufficient evidence to recommend for or against screening for cognitive impairment in older adults in the general population in the absence of known impairments.\[100\] Considering that as many as 50% of persons living with HIV have some form of HIV-associated neurocognitive disorder, most experts recommend that persons with HIV infection should ideally have a baseline neurocognitive assessment, with follow-up screening every 6 to 12 months for individuals at high risk for HAND and every 12 to 24 months in persons at lower risk.\[101\] From a practical standpoint, however, this recommendation is often not implemented because existing clinical screens do not perform well in identifying milder forms of HAND. Therefore, identifying and developing practical screening tools for individuals with HIV infection that can detect milder forms of HAND and discriminate among the different HAND disorders is essential.

Screening Tools for Neurocognitive Disorders

Among the tools that are currently available, no consensus exists on which screening tool to use. The primary care literature offers four brief screening tools that are not specific to the diagnosis of HAND but are validated for general use in the primary care setting (Mini-Mental State Examination, General Practitioner Assessment of Cognition, Memory Impairment Screen, and Mini-Cognitive Assessment Instrument). The American Academy of Neurology acknowledged in its 2001 report on early detection of neurocognitive impairment that more research is needed to help clinicians differentiate among available screening instruments.\[102,103,104\] Several HIV-specific neurocognitive screening tools have been developed, but a consensus panel of experts on HIV neurocognitive disorders has concluded no single screening test is appropriate in all clinical situations—the choice of test may vary with patient population, provider experience and preference, cost, and time—and further acknowledges that all of the available tools are less sensitive for detecting milder forms of cognitive impairment.\[101\] At the present time, a comprehensive neuropsychological assessment remains the gold standard for diagnosing HIV-associated neurocognitive disorders.

General Population Neurocognitive Screening Tools

Mini-Mental State Exam (MMSE)

The MMSE is among the oldest screening tools for cognitive impairment. The MMSE, which takes approximately 5 to 10 minutes to administer, includes a series of questions that cover 7 cognitive domains: orientation, registration, attention and calculation, recall, language, and construction.\[105,106\] A score of 24 points or lower (out of a total of 30 points) represents cognitive impairment. Most experts agree the MMSE is a weak tool for diagnosing HAND.\[107,108\] Despite free available versions of the MMSE, Psychological Assessment Resources (PAR) now holds exclusive rights to the MMSE and claims that any use of the MMSE requires their permission and ordering through them. Due to poor performance for evaluation of HAND in persons living with HIV and the logistical problems obtaining this test, we do not recommend using MMSE as a neurocognitive screening tool for HAND.

Mini-Cognitive Assessment Instrument (Mini-Cog)

The Mini-Cog is a test consisting of three-word registration, followed by a clock-drawing test, and then followed by three-word recall.\[109\] Patients receive 0 to 3 points based on the number of items recalled, and 0 or 2 points for clock drawing (a correct clock should have all the numbers placed appropriately, with the hands pointing to the time designated by the examiner). A total score of 0 to 2 indicates dementia. The test has sensitivity ranging from 76 to 99% and specificity ranging from
73 to 93% across studies.[102,110] Because of its speed, accuracy, and the fact it does not require patient fluency in English, some primary care providers suggest using this test as the initial screen.[102] Again, the Mini-Cog is not specific to HAND.

**The General Practitioner Assessment of Cognition (GPCOG)**

The GPCOG consists of 6 initial questions involving registration and recall, time orientation, clock drawing, and historical questions.[111] A two-part version of the GPCOG with an additional 6 questions can be used if the examiner knows the patient well enough to validate the historical questions. A score of 9 or above is considered normal, and a score of 4 or lower indicates cognitive impairment. For patients scoring in the 5 to 8 range who have a longstanding relationship with their provider, the second part of the GPCOG asks providers questions about the patient’s current functional status compared to 5 years ago. Using a cutoff of 7 points for dementia, the sensitivity and specificity for the GPCOG is 82% and 70%, respectively; the two-part GPCOG increases the specificity to 83%.[102]

**Memory Impairment Screen (MIS)**

The MIS is a 4-minute, 4-item delayed, free and cued recall test.[112] The patient is given a piece of paper with the names of four different items (an animal, vegetable, city, and musical instrument). The patient then counts from 1 to 20 and then back to 1, and is asked to recall the items. A total of 2 points are given for items recalled without cueing, and 1 point is given for items recalled with cueing. As a screening tool for dementia, based on a cutoff score of 5, the sensitivity of the MIS is 86% and the specificity is 91%.[102]

**Montreal Cognitive Assessment (MOCA)**

The MOCA is a free, online, validated instrument that is available in many languages to screen for mild cognitive impairments. The MOCA takes approximately 10 to 15 minutes to administer and consists of 30 items that measure function in 8 cognitive domains.[113] A score of 26 points or lower (out of a maximum of 30) indicates cognitive impairment. The MOCA has been found to be more sensitive than the Mini-Mental Status Exam (MMSE) at detecting mild cognitive impairment in the general population.[103,114] Among individuals with HIV infection, the MOCA has only moderate sensitivity and poor specificity for detecting mild cognitive impairment.[113]

**HIV-Specific Neurocognitive Screening Tools**

**HIV Dementia Scale (HDS) and Modified HIV Dementia Scale (M-HDS)**

The HIV Dementia Scale (HDS) is a test consisting of 4 items that address 4 cognitive domains: memory/recall, attention/learning, psychomotor functioning, and eye movements (visuocostruction); the maximum score on the HDS is 16.[113,115,116] The HDS was originally developed in 1995 and found to be superior to the Mini-Mental Status Exam (MMSE) for identifying HIV-associated dementia; in this study, using an HDS cutoff score of less than or equal to 10 for identifying HIV dementia, performed with sensitivity of 80%, specificity 91%, and positive predictive value 78%.[115] The HDS has been found to have inadequate sensitivity and specificity for detecting milder forms of cognitive impairment.[113,117] A modified version of the HDS (M-HDS) is a more practical screening tool for clinicians and non-neurologists.[118] The modified test eliminates evaluation of antisaccadic eye movements, a process deemed difficult for non-neurologists.

**International HIV Dementia Scale (IHDS)**

In 2005, an International HIV Dementia Scale (IHDS) was developed by Sacktor and colleagues and adopted for use in global settings to address culturally specific elements of the original HIV Dementia Scale and trouble administering the anti-saccadic errors test.[119,120] The IHDS test has three tasks
that evaluate motor speed, psychomotor speed, and memory-recall: timed finger tapping, timed alternating hand sequence test, and 4-item recall at 2 minutes. The maximum score is 12 points. Patients with a score of 10 or lower should undergo further evaluation for possible dementia. A meta-analysis showed this test performed well when screening for dementia, but had low accuracy for milder HAND conditions.

**European AIDS Clinical Society (EACS) Cognitive Screen**

The European AIDS Clinical Society recommends initial screening for cognitive impairment using 3 questions related to memory loss, reasoning, and attention. The questions are graded as “never”, “hardly ever”, or “yes, definitely”; an answer of “yes, definitely” on at least one question is considered to be an abnormal screen.
Models for Integrating Screening for Mental Disorders and Neurocognitive Disorders into HIV Primary Care

Integrating Mental Disorders Screening in Primary Care

Models for integrating the evaluation and management of mental disorders into the primary care setting have focused primarily on depressive disorders; key elements of this integrative approach are highlighted in the recent United States Preventive Services Task Force (USPSTF) recommendation that endorses routine screening for depression in the general adult population, including pregnant and postpartum women.[53] The USPSTF statement outlines that implementation of the screening recommendation is best realized through a collaborative model of multidisciplinary, team-based care developed by the Community Preventive Services Task Force. This model uses case managers to connect primary care providers, patients, and mental health providers with stated goals of increasing screening and evidence-based treatment as well as improving clinical and community support for patient engagement in self-management. In this model, providers are responsible for screening patients, initiating treatment, and ensuring proper referral while the case managers provide patient education, tracking, and management of the treatment plan. A Cochrane review has also found that collaborative care based on chronic disease models is associated with significant improvement in depression and anxiety outcomes.[121]

Integrating Mental Disorders Screening in HIV Care Settings

Given the high prevalence of mental disorders, particularly depression, among persons living with HIV, collaborative care models that allow for mental health treatment within the HIV medical home are paramount.[122] A depression treatment cascade, mirroring the well-known HIV treatment cascade, has been published and it highlights the attrition along the continuum from depression diagnosis to effective treatment; according to this cascade, 18% of individuals with HIV infection and depression are receiving any treatment for depression, 7% are receiving adequate treatment, and only 5% are in remission (Figure 9).[122] There is also interplay between the two cascades since depression is recognized to decrease engagement in HIV care and adherence to antiretroviral medication.[122] Despite the recognized mental health treatment gap, there is limited data related to evidence-based strategies that can be integrated into HIV primary care. Some proposed solutions include co-located services and the use of embedded mental health providers. Just as initiation of HIV care is more likely when diagnosis occurs at a site that offers co-located medical care, mental health treatment is also more likely when it is co-located within the familiar setting of a patient’s medical home.[123,124] Collaborative care models to link antiretroviral and antidepressant management have also been tested in clinical trials. One such collaborative model, termed measurement-based care, has reported improvement in depression among participants. Measurement-based care is a decision support model for integrating antidepressant management into routine HIV care, in which depression case managers use metrics to give HIV primary care clinicians antidepressant treatment recommendations.[122,125]
Summary Points

- Screening tools for identifying mental disorders, including HIV-associated neurocognitive disorders, among persons living with HIV infection in the United States are important given the high prevalence of these conditions among adults with HIV infection.
- The prevalence of depression, anxiety, and posttraumatic stress disorder is significantly higher among adults with HIV infection than in adults without HIV infection.
- There is an increased risk for HIV acquisition and HIV transmission associated with certain mental disorders, and co-existing substance use disorders often mediate this link.
- Mental disorders have been associated with decreased utilization of antiretroviral therapy and predict worse HIV disease outcomes.
- Practical screening tools for use in the primary care setting should be brief, easily scored, free, evidence-based, and accessible to a range of providers without requiring specific training.
- Screening tools for some of the most common mental health diagnoses encountered in primary care include: 2-Item PRIME-MD, PHQ2, and PHQ-9 (depression); GAD-7 (generalized anxiety disorder), PHQ-PD (panic disorder); and PC-PTSD-5 (posttraumatic stress disorder). A positive result on any screening test requires confirmation with a formal diagnostic interview.
- HAND likely affects 50% of persons living with HIV infection, with age representing the greatest risk factor.
- Additional risk factors for HAND include low nadir CD4 count, previous central nervous system injury, detectable plasma HIV RNA levels, and comorbidities such as hypertension, insulin resistance, viral hepatitis, depression, and substance use disorder.
- HAND is subdivided into three categories based on severity of disease: (1) asymptomatic neurocognitive impairment, (2) mild neurocognitive disorder, and (3) HIV-associated dementia.
- Screening tools for neurocognitive disorders include, among others, the MMSE, Mini-Cog, GPCOG, MIS, MOCA, European AIDS Clinical Society Cognitive Screen, HIV Dementia Scale, and International HIV Dementia Scale. None of these screens can reliably detect milder forms of HIV-associated neurocognitive impairment. Rather, with regard to HAND, these tools work best at screening for HIV-associated dementia, with the last two tools having been specifically developed for this purpose.
- Co-located services, the use of embedded mental health providers, collaborative care, and decision support tools may all help to integrate mental health care into HIV primary care and improve the HIV treatment cascade.
Citations


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References


Figures

Figure 1 Prevalence of Depression in Persons with HIV and in General Population


*Estimates based on data from Medical Monitoring Project (MMP), 2009
^Estimates based on data from Behavioral Risk Factors Surveillance System (BRFSS), 2006 and 2008
Figure 2 HIV Prevalence in General Outpatient Psychiatric Population

These data were obtained through general outpatient psychiatric clinics at Duke University Medical Center during 2001-2004.

Figure 3 Positive Prevention Model Showing Hypothesized Effects of Mental Health Treatment on HIV Transmission Risk Behavior

Figure 4 PHQ-9 Scores and Likelihood Ratio for Major Depression

These data are based on surveys from 580 patients who completed the PHQ-9 and had a structured interview by a mental health professional to determine the presence or absence of major depression.

Figure 5 Operating Characteristics of PHQ-2 for Major Depression

This table shows the sensitivity, specificity, positive predictive value, and likelihood ratios for the range of PHQ-2 scores in diagnosing major depressive disorder. These data are based on surveys from 580 patients who completed the PHQ-2 and had an independent mental health professional interviews.


<table>
<thead>
<tr>
<th>PHQ-2 Score</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Likelihood Ratio</th>
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<tbody>
<tr>
<td>1</td>
<td>97.6</td>
<td>59.2</td>
<td>15.4</td>
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<tr>
<td>2</td>
<td>92.7</td>
<td>73.7</td>
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<td>3</td>
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<td>90.0</td>
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<tr>
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<tr>
<td>6</td>
<td>26.8</td>
<td>99.4</td>
<td>78.6</td>
<td>48.2</td>
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Figure 6 Operating Characteristics of GAD-7 for Generalized Anxiety Disorder

This table shows the sensitivity, specificity, and likelihood ratios for the GAD-7 scores in the range of 8 to 15 as a diagnosis for generalized anxiety disorder. These data are based on 995 patients who completed the GAD-7 and underwent structured psychiatric interviews by a mental health professional as an evaluation for generalized anxiety disorder.


<table>
<thead>
<tr>
<th>GAD-7 Score</th>
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<th>Specificity</th>
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<tr>
<td>15</td>
<td>48</td>
<td>95</td>
<td>8.7</td>
</tr>
</tbody>
</table>
**Figure 7 Diagnostic Characteristics for the Primary Care PTSD Screen for DSM-5 (PC-PTSD-5)**

These data are based on surveys from 399 adult Veterans seen at a primary clinic. The Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) screening tool was used.


<table>
<thead>
<tr>
<th>Cut-off Score</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Likelihood Ratio</th>
</tr>
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<td>-</td>
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<td>97</td>
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Figure 8 Operating Characteristics of the Mood Disorder Questionnaire

This graphic is based on data from 198 individuals seen at five out-patient clinics. A score of 7 or higher (gray vertical line) was chosen as the optimal cutoff.

**Figure 9 Depression Treatment Cascade for Patients with HIV Infection**

This graphic shows that among all HIV patients with a major depressive episode in the past year, the estimated proportion of patients that have: the depression recognized clinically, receiving any treatment, receiving adequate treatment, and achieved remission.