

*Invited Review***Addressing Depressive Disorders Among People With HIV****Andres Fuenmayor, MD; Francine Cournos, MD**

Columbia University, New York, New York

Depressive disorders are the most common psychiatric disorders among people with HIV. Depressive disorders cause great suffering and disability and, among people with HIV, are associated with numerous negative HIV outcomes, including nonadherence to anti-retroviral medication and increased morbidity and mortality. This article is focused on the detection, differential diagnosis, and management of depressive disorders among adults in HIV primary care settings in the United States. Because of the siloed nature of HIV primary health care and behavioral health care in the United States, this paper is geared toward clinicians who are not behavioral health specialists and who are working in HIV care settings that have limited access to behavioral health services and still seek to treat depressive disorders. In clinical settings that are fortunate enough to have well-integrated behavioral health services, HIV primary care clinicians may be able to depend on this specialist workforce, but these settings tend to be the exception and not the rule.

Keywords: HIV, depression, treatment, primary care

Epidemiology of Depression Among People with HIV and Steps to Care

Depressive disorders are the most common psychiatric disorders among people with HIV infection.¹ The

Author Correspondence

Send correspondence to Andres Fuenmayor, MD, Herbert Pardes Building, 1051 Riverside Dr, New York, NY, 10032, or email af3237@cumc.columbia.edu.

lifetime rates of depressive disorders among people with HIV who are seen in HIV care settings in the United States are much higher than rates in the general US population. In 2019, it was estimated that 7.8% of adults in the general US population have had at least 1 major depressive episode,² whereas these rates hover around 30% to 40% among people with HIV. Moreover, among people with HIV in the United States, depressive disorders have

Major depression among people with HIV is associated with increased morbidity, mortality, and worse outcomes along the entire HIV care continuum

high rates of comorbidity with other psychiatric illnesses, such as alcohol and substance use disorders, anxiety disorders, and posttraumatic stress disorder (PTSD). Worldwide, estimates of depressive disorders among people with HIV vary widely from 6% to 67%,³ depending on the population surveyed, the approach to diagnosis, and other factors.

The World Health Organization (WHO) classifies major depression as the second most common cause of disability worldwide.⁴ Depressive disorders are strongly linked to mortality, through suicide and as a result of suboptimal outcomes in the care and treatment of other medical conditions. Major depression among people with HIV is associated with increased morbidity, mortality, and worse outcomes along the entire HIV care continuum. In all countries, the number of behavioral health practitioners is insufficient to treat the number of people with depressive disorders. This has led to a strong focus

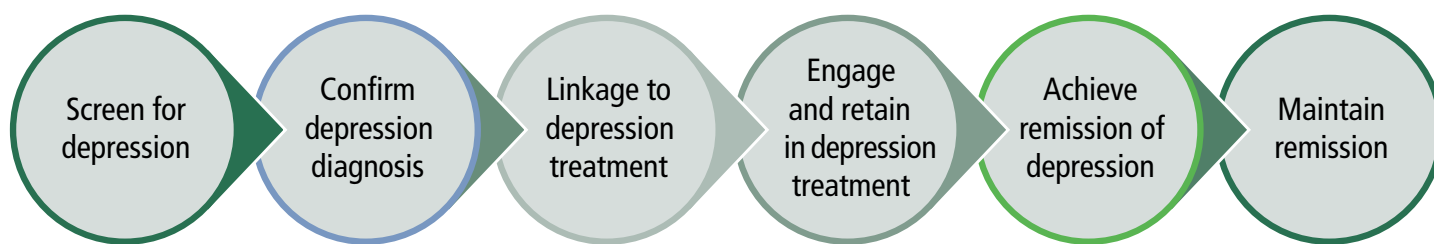


Figure 1. Model of health care continuum care for depressive disorders.

on detecting and treating depressive disorders in primary/HIV care settings. The continuum we use for HIV detection, care, and treatment can be readily adopted to depressive disorders (Figure 1).

Screening for Depression

The US Preventive Services Task Force reports that depression is undetected in up to 50% of all cases in primary care,³ which has led to a recommendation for depression screening. In primary care settings, the Patient Health Questionnaire-2 (PHQ-2) and the Patient Health Questionnaire-9 (PHQ-9) are the most commonly used tools to screen for major depression, and in some settings, these tools are built into the electronic medical record. The PHQ-2 assesses for the 2 primary affective symptoms of depression: depressed mood and loss of interest or pleasure for at least 2 weeks. Sensitivity and specificity of the PHQ-2 for diagnosing major depression is best estimated at 91% and 67%, respectively, with a score of 2 or higher, and 72% and 85%, respectively, with a score of 3 or higher.⁵ The PHQ-9 begins with the same 2 questions as the PHQ-2, but it adds 7 other questions that parallel the symptoms of major depression as described in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. At a score of 10 or higher, the sensitivity and specificity of the PHQ-9 for major depression are best estimated at 85% and 85%, respectively.⁶ The PHQ-2 is sometimes used as the initial screen and, if positive, is then followed by the PHQ-9.

The PHQ-2 and PHQ-9 can be conveniently accessed via the National HIV Curriculum⁷ and scored at its website using automatic calculators. This website also offers information about the sensitivity and specificity of these tools.

The PHQ-2 and PHQ-9 have gained wide acceptance because they are briefer than many other depression rating scales; they can be administered in person by a clinician, by telephone, or self-administered by the patient; they can provide an assessment of symptom severity and be used to track symptom improvement; and they are quick to complete, free of charge, available in a variety of languages, and well-validated worldwide.

Unfortunately, screening tools for major depression cannot be used to establish a definitive diagnosis of this disorder by themselves, because there are too many false negative and false positive results. Nor are there currently available biologic tests for major depression that can be used to confirm the diagnosis. There are research tools used to assess for major depression that are more accurate than clinical screening tools, but these are too time-consuming to be used in a busy clinical practice. Moreover, a positive screen for major depression requires a differential diagnosis to rule out other conditions.

Differential Diagnosis of Depressive Symptoms

Depressive symptoms can occur as part of almost any serious medical, neurologic, or psychiatric illness. Among people with HIV, depressive symptoms may occur as part of a large variety of common comorbid medical conditions; as a result of the adverse effects of antiretroviral drugs and other prescribed medications; from the use of alcohol and recreational drugs; and in response to various social determinants of health, including loneliness and loss, homelessness, food insecurity, and the experience of interpersonal violence. It is always essential

to assess depressive symptoms with an awareness of this complex differential diagnosis and the many contributing factors, and to plan a response that

Symptoms of depression have become ubiquitous components of stress and distress during the SARS-CoV-2 pandemic among the general population worldwide

takes into account as many of these variables as possible.

Complicating matters further, symptoms of depression have become ubiquitous components of stress and distress during the SARS-CoV-2 pandemic among the general population worldwide.⁸ The number of available behavioral health care practitioners is always limited when compared with the number of people in distress. To best utilize these limited resources, it is essential to distinguish people in distress from those who meet the criteria for mental disorders (Table 1).

A General Approach to Depressive Symptoms

The WHO has outlined an excellent general approach to mental health care, including the management of depressive symptoms, through its pyramid of mental health services. The pyramid captures all of the levels of care that are needed to manage mental health problems, and offers a helpful way of conceptualizing a response to the increased incidence of major depression and other mental disorders during the SARS-CoV-2 pandemic⁸ worldwide (Figure 2).⁹ The base of the pyramid is the key role of self-care, which has been widely promoted for patients and their health care practitioners. This includes implementing personal strategies such as maintaining social connections through virtual means, carving out time for rest and pleasurable activities, ensuring adequate sleep, and engaging in mindfulness and

Table 1. Key Elements That Distinguish Mental Distress and Mental Disorders

Mental disorder	Mental distress
<ul style="list-style-type: none"> • Usually cause either persistent severe subjective distress • Meet recognized diagnostic criteria (ie, International Classification of Disease, Diagnosis and Statistical Manual of Mental Disorders) • Call for evidence-informed mental health interventions such as medication or psychotherapy 	<ul style="list-style-type: none"> • Can occur in response to any adversity • Often does not meet the criteria for a psychiatric diagnosis or require specialized mental health interventions • Often responds well to supportive strategies

meditation. Self-care is an essential ongoing component in the prevention and management of all medical and psychiatric illnesses.

The next level up in the pyramid is the key role of informal care. This can include reaching out to social supports in the community including family, friends, neighbors, houses of worship, and community-based organizations. As the use of technology has expanded, the availability of support through virtual means has increased. Informal care is another essential element of mental illness prevention and treatment.

The middle level of the WHO pyramid is primary care. It is at this level that most people with mental health symptoms will first appear within the medical system. Moreover, a recent US study found that 45.7% of antidepressants are prescribed in primary care.¹⁰ Primary care, including HIV primary care, is in a crucial position with regard to the recognition of mental health problems, hence the importance of depression screening in this setting. It is also at the primary care level that decisions are often made regarding who warrants referral to specialty mental health care (Figure 2).⁹

Considerable emphasis has been given to integrating the treatment of uncomplicated major depression into primary care, but numerous educational and health system barriers make achieving this goal difficult. HIV primary care settings that

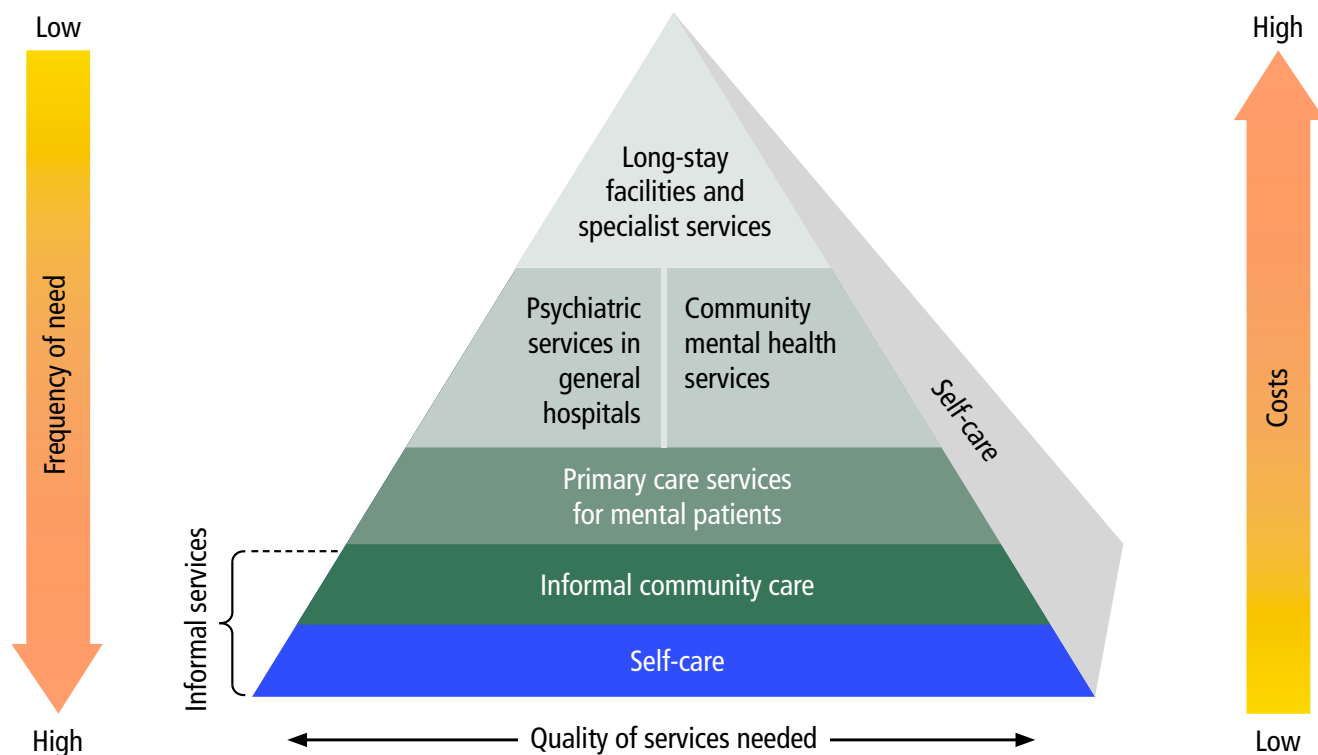


Figure 2. Model for improving health systems and services for mental health. Adapted from the World Health Organization.⁹

have no behavioral health practitioners often consider prescribing antidepressants as the only realistic option for treating depression. This approach is safest and most effective when the prescribing clinicians assess and address contributing medical and psychosocial problems. Moreover, the overuse and the underuse of antidepressants are common problems in the United States. Although a PHQ-9 score of 10 or higher is suggestive of major depression, ruling out bipolar depression is important before prescribing any antidepressant medication.

Depressive Disorders versus Bipolar Disorders

In the most recent version of the *Diagnostic and Statistical Manual of Mental Disorders*, the *DSM-5*,¹¹ a decision was made to create separate categories for depressive disorders and bipolar disorders. Symptoms of depression are prominent in both conditions.

The most common depressive disorder is major depressive disorder, and the PHQ-2 and the PHQ-9

screen for this condition. Major depression can be conceptualized as a medical comorbidity of HIV infection, with affective symptoms (such as depressed mood, loss of interest, guilt, worthlessness, and suicidal ideation) and somatic symptoms (such as appetite/weight loss, sleep disturbance, motor agitation/retardation, fatigue, and loss of concentration). Persistent depressive disorder shares similar symptomatology with major depressive disorder but can vary in the severity of symptoms and has a longer duration of at least 2 years.¹¹ The previous diagnosis of dysthymia is now subsumed in this category.

Bipolar disorders are characterized by switching between depressive and elevated moods. The distinguishing feature of bipolar disorders is periods of abnormal and persistently elevated, expansive, or irritable moods and high amounts of energy, referred to as the (hypo)manic phase of the illness, lasting at least 1 week and alternating with periods of depression. The severity of these elevated states determines whether the illness is called bipolar 1 (full mania) or bipolar 2 (hypomania). Cyclothymia is

defined as at least 2 years (1 year in youth) of numerous periods of hypomania and depression that do not fully meet the requirements for mania, hypomania, or major depressive episodes.¹¹

Episodes of depression or (hypo)mania that are induced by substance use or medications are specifically listed as “substance/medication-induced”

A 2019 systematic review and meta-analysis of studies concluded that more than 3 in 20 patients managed in primary care settings for depression have unrecognized bipolar disorder

in the *DSM-5*. The screening instruments recommended in this article are based on *DSM-5* diagnoses, and readers are encouraged to review the full criteria for these disorders.

Accurately distinguishing between bipolar disorders and depressive disorders can be challenging, and bipolar disorders are often underdetected. A 2019 systematic review and meta-analysis of studies concluded that more than 3 in 20 patients managed in primary care settings for depression have unrecognized bipolar disorder.¹² This occurs in part because people with bipolar disorders spend most of their unwell time in a depressed state and are more likely to seek help when depressed. Evidence suggests that the treatment of bipolar depression with antidepressant monotherapy is not effective, and it may precipitate mania, especially in people with bipolar 1 diagnoses.¹³ Mood stabilizers, including atypical antipsychotics, specific anticonvulsants, and lithium, are the psychotropic medications of choice to treat bipolar depression.

What is Known About Effective Treatment for Depression Among People With HIV?

There are some studies that specifically focus on the treatment of depressive disorders in people with HIV,

but it is important to look for guidance from more general evidence on the treatment of depressive disorders. Current guidelines for the treatment of depression in adults from the American Psychiatric Association describe effective psychotherapies and medication treatments for depressive disorders.¹⁴ Strong evidence suggests that specific psychotherapies, especially cognitive behavioral therapy and interpersonal therapy, are effective treatments for mild to moderate depression.¹⁴

However, in HIV primary care settings that do not have access to clinicians who are trained to provide psychotherapy to patients with depressive disorders, prescribing antidepressant medication is often the most immediately available option. However, it is important to bear in mind that although

Primary care physicians often initiate pharmacologic interventions more frequently than any other treatment option in their patients with newly diagnosed depression... psychotherapy is often a patient preference

primary care physicians often initiate pharmacologic interventions more frequently than any other treatment option in their patients with newly diagnosed depression,¹⁵ current research and treatment recommendations indicate that psychotherapy is often a patient preference.¹⁶ Primary care programs that have on-site staff who can offer brief evidence-based psychotherapies for depression are at a distinct advantage for engaging patients in depression treatment.

Aim to Achieve Remission of Depression Using a Stepped Care Approach

Outcomes in the treatment of episodes of major depression are often referred to as either response, defined by at least a 50% reduction in symptoms,

or remission, defined as few or no symptoms. Remission is a much more desirable outcome than response because it is associated with better functioning and prognosis.¹⁷ Moreover, depressive symptoms that persist pose a risk for relapse of major depression.

It helps to understand the trial-and-error nature of prescribing antidepressants. Unlike the treatment of HIV and other infectious diseases, there are no biologic markers that allow matching an antidepressant medication to whether a specific person will

Using suboptimal doses of antidepressant medication is one of the common reasons for failure of antidepressant trials in primary care

improve on that particular medication. Liver enzyme levels can be measured to assess whether a person will be a slow or rapid metabolizer of a specific antidepressant, but this is currently not a part of routine clinical practice. As a result, giving an antidepressant involves monitoring the patient's degree of improvement and the tolerability of its adverse effects. Of course, it is always useful to obtain the patient's past history of successes and failures on previous antidepressant trials and use that as a guide.

Starting at a low dose reduces adverse effects, which can be important for people with HIV, especially those who are older or medically complicated. At the same time, it is important to escalate the dose as needed to achieve remission if the patient requires a higher dose and can tolerate the adverse effects. Using suboptimal doses of antidepressant medication is one of the common reasons for failure of antidepressant trials in primary care.¹⁸ An antidepressant may need to be stopped quickly if a patient cannot tolerate it. When this is not the case, a typical antidepressant trial requires 6 to 8 weeks to determine efficacy.

There are many antidepressant studies that illustrate the above points in the treatment of major

depression. Of special interest is the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study. This large study of stepped care for the treatment of nonpsychotic major depressive disorder evaluated patients with comorbid medical conditions and was conducted with funding from the National Institute of Mental Health (NIMH) rather than with funding from pharmaceutical companies. The study involved a series of randomized controlled trials that examined the acute and longer-term treatment outcomes associated with the steps needed to achieve an adequate benefit using a measurement-based stepped care approach (Table 2). The study enrolled adult patients who were candidates for the first treatment step. Patients who did not achieve remission or could not tolerate a treatment step were encouraged to proceed to the next step.¹⁹

There were 2 endpoints: response (>50% reduction of symptoms) and remission (few or no symptoms). There were 4 sequenced treatment steps in the algorithm. The first step for everyone was treatment with the selective serotonin reuptake inhibitor (SSRI) antidepressant citalopram. If citalopram treatment was not successful, step 2 contained 7 switch or add-on options as follows: switch to sertraline; to bupropion-slow release (SR); to venlafaxine-extended release (XR); to cognitive psychotherapy; or use an add-on option: add bupropion-SR, add cognitive psychotherapy, or add buspirone. If step 2 failed, steps 3 and 4 involved other switching and add-on options, including using classes of less-frequently prescribed antidepressants, lithium, tri-iodothyronine (T3), and various antidepressant combinations. These latter steps are unlikely to be used in the primary care setting.

The STAR*D study illustrates the importance for prescribers in HIV primary care to learn to use several antidepressants and to be willing to switch patients from one to another depending on patient outcomes (symptom improvement and ability to tolerate adverse effects). In the STAR*D study, steps 1 and 2 each had about a one-third chance of achieving acute remission. This may sound disappointing, but given the suffering and disability caused by major depression, the value of persistence in finding an effective treatment cannot be underestimated.

The low rates of success in steps 3 and 4 suggest that after the failure of 2 adequate antidepressant trials, patients should be referred to mental health specialty care for further treatment. Other reasons to refer to specialty care include bipolar depression, psychotic depression, risk for suicide or violence, and diagnostic uncertainty.

Selecting an Antidepressant Medication

As the STAR*D study indicates, many different antidepressant medications are available for treating major depression and are variably successful in terms of efficacy and tolerability for any particular person. The literature about antidepressants is too extensive to be summarized here, but some general principles are helpful. It is always important to consider overlapping toxicities and drug interactions with prescribed medications the patient is already taking, and this information can be readily accessed using online resources. Primary care prescribers can select a few of the common SSRIs and serotonin and norepinephrine reuptake inhibitor antidepressants and learn enough about their profiles to become comfortable prescribing them. It is also helpful to know that antidepressants work as anti-anxiety medications, and may improve the symptoms of anxiety disorders and PTSD. For people with depressive illness and comorbid alcohol or other substance use disorders, it is best to presume that these 2 disorders require separate treatments, and to know that treatments for depression and alcohol or substance use disorders can be administered simultaneously depending on the patient's motivation and the resources available.

Referring Patients to Behavioral Health Care

Although treating uncomplicated major depression in HIV primary care is essential to reaching all people with HIV who suffer from this condition, it is important to identify people with HIV who need referral to specialty care. Common reasons for referral include the failure of 2 adequate trials of antidepressant treatment, suspicion of bipolar disorder, psychotic

symptoms, suicide risk, and diagnostic uncertainty. There is a growing literature on the relationship between depression and medical conditions that increase inflammation, such as HIV infection. Studies

Common reasons for referral to behavioral health specialty care include the failure of 2 adequate trials of antidepressant treatment, suspicion of bipolar disorder, psychotic symptoms, suicide risk, and diagnostic uncertainty

concerning the potential use of anti-inflammatory agents to treat depression or enhance the therapeutic effects of antidepressants are underway, but the evidence is not yet strong enough to make specific clinical recommendations. Novel agents such as ketamine are also being studied and may be available in some specialty behavioral health care settings.²⁰

People with HIV who are on a stable medication regimen for depression that was originally prescribed in a psychiatric setting can often be followed up for maintenance in a HIV primary care setting.

Outcomes of the Treatment of Depression in People With HIV

The key outcomes of successfully treating depressive disorders among people with HIV are relief from suffering, improvement in quality of life, and restoration of function. Depression is a remarkably painful state that robs people of a sense of being fully alive. Dante offers a succinct summary of this state in *Inferno*: "I did not die, but yet I lost life's breath. Imagine for yourself what I became, deprived at once of both my life and death."²¹

Although depressive disorders are associated with increased mortality among people with HIV, it is not known if successful depression treatment reverses this shortened lifespan. Interestingly, there is some evidence that successful treatment of

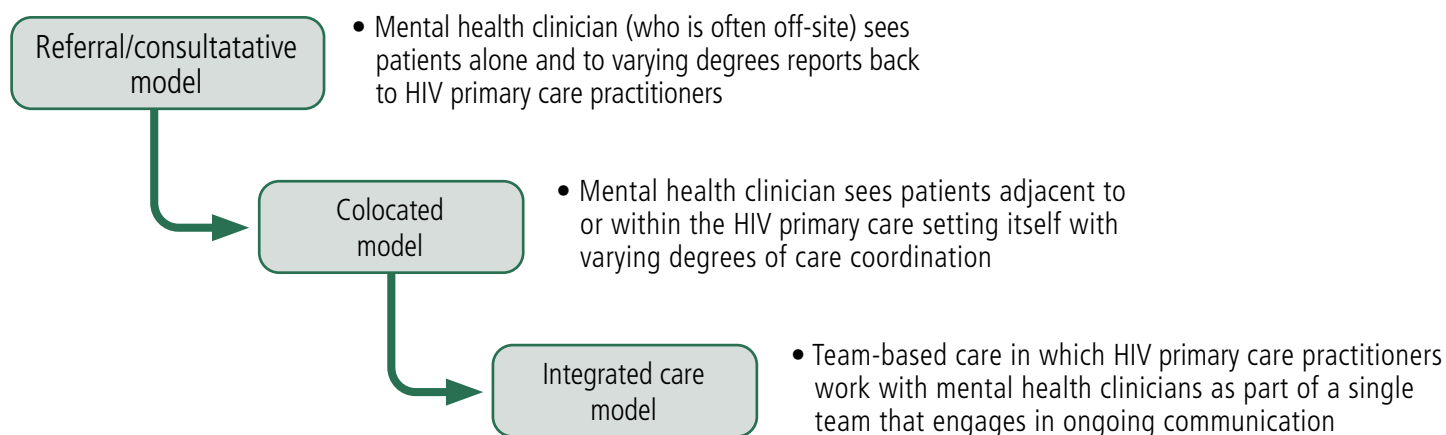


Figure 3. Overall model for linkage to care.

depression prolongs life in a number of other medical conditions.^{21,22}

Linkage to Depression Treatment

For HIV primary care practitioners who refer some or all of their patients with depression to behavioral health care practitioners for treatment, there are many models for conceptualizing this collaboration. The schematic in Figure 3 offers a simple summary of these models.

One integrated care model that has received particular attention is the collaborative care model.²³ In this model, a team within the primary care setting manages patients with depression, and a psychiatrist is available as a consultant to the team rather

Taking antidepressants is associated with adherence to antiretroviral therapy

than as someone who directly assesses and treats the patients. Although many excellent models exist for integrating depression treatment into primary care, implementing these models has often proven difficult.²³ Most HIV primary care programs use an approach that seems realistic for their particular circumstances.


Engagement and Retention in Depression Treatment

Adherence to medication over time is very difficult for all patients and for all conditions, and adherence to antidepressants is no exception.²⁴ A recent review of studies suggests that patients taking antidepressants are more likely to adhere to antiretroviral therapy,²⁵ but it is difficult to know if this simply reflects that these patients are more generally adherent to treatment, or if the treatment of depression directly influences adherence to antiretroviral therapy.

Maintaining Remission

Depression tends to be a recurrent disorder, and taking antidepressant medication continuously is often recommended for chronic and recurrent episodes of major depression. Usually, attempts are made to use the lowest possible doses of medication that keep people well. The literature on the success of discontinuing antidepressants in chronic or recurrent depression is limited and is plagued with confusion between the withdrawal effects of discontinuing antidepressants and actual relapse.²⁶ At present, patients and their clinicians do best when they engage in joint decision making about which course of action to take.

Conclusion

Depressive disorders are common among people with HIV. HIV primary care settings have a critical role to play in detecting and treating these conditions, because doing so is critical to the quality of life and functioning of people with HIV. Therefore, it is well worth the time and effort required to conduct the needed differential diagnosis and to persist in seeking treatments that achieve remission from depression. Because the brain and the body form a single integrated system, it is essential to overcome treatment silos and achieve care integration in the long run. 

This article is based on a presentation given at the Ryan White HIV/AIDS Program CLINICAL CONFERENCE by Dr Cournos on October 5, 2021: <https://youtu.be/N4M2Y-qHx39M>. This article was prepared by Dr Fuenmayor and Dr Cournos in January 2022.

The IAS–USA has identified and resolved ahead of time any possible conflicts of interest that may influence this continuing medical education (CME) activity with regard to exposition or conclusion. The Accreditation Council for Continuing Medical Education (ACCME) defines ineligible companies (formerly described as commercial companies) as those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients. All financial relationships with ineligible companies for the authors and planners/reviewers are listed below. To view the financial relationships of the *Topics in Antiviral Medicine* Editorial Board, please see the front material of this volume.

Financial affiliations with ineligible companies in the past 24 months: Dr Fuenmayor has no relevant financial relationships with ineligible companies. (Updated May 10, 2022) Dr Cournos has no relevant financial relationships with ineligible companies. (Updated May 10, 2022)

Planner/reviewer 1 has been a consultant to Antiva Biosciences, Gilead Sciences, Inc., and Merck and Co, Inc. (Updated on May 10, 2022)

Planner/reviewer 2 has no relevant financial relationships with ineligible companies to disclose. (Updated on May 10, 2022)

Reviewer 3 has no relevant financial relationships with ineligible companies to disclose. (Updated on April 27, 2022)

All relevant financial relationships with ineligible companies have been mitigated.

Additional References Cited in Text

1. Nanni M, Caruso R, Mitchell A, Meggiolaro E, Grassi L. Depression in HIV infected patients: a review. *Curr Psychiatry Rep.* 2015;17(1):530.
2. National Institute of Mental Health. Major depression. <https://www.nimh.nih.gov/health/statistics/major-depression>. Accessed on January 4, 2022.
3. Cournos F, McKinnon K, Wainberg M. Epidemiology of psychiatric disorders associated with HIV and AIDS. In: Cohen M, Gorman J, eds. *Comprehensive textbook of AIDS psychiatry*. Second ed. New York: Oxford University; 2017;29-45.
4. Thornicroft G, Chatterji S, Evans-Lacko S, et al. Undertreatment of people with major depressive disorder in 21 countries. *Br J Psychiatry.* 2017;210(2):119-124.
5. Levis B, Sun Y, He C, et al. Accuracy of the PHQ-2 alone and in combination with the PHQ-9 for screening to detect major depression: systematic review and meta-analysis. *JAMA.* 2020;323(22):2290-2300.
6. Arroll B, Goodyear-Smith F, Crengle S, et al. Validation of PHQ-2 and PHQ-9 to screen for major depression in the primary care population. *Ann Fam Med.* 2010;8(4):348-353.
7. AIDS Education and Training Center Program. National HIV curriculum. <https://aidsetc.org/nhc>. Accessed on January 4, 2022.
8. Santomauro D, Mantilla Herrera A, Shadid J, et al. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet.* 2021;398(10312):1700-1712.
9. World Health Organization (WHO). Improving health systems and services for mental health: mental health policy and service guidance package. *World Health Organization.* 2021.
10. Ohayon M, McCue M, Krystal A, et al. A longitudinal study to assess antidepressant treatment patterns and outcomes in individuals with depression in the general population. *CNS Spectrums.* 2021;26(2):180.
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing, 2013.
12. Daveney J, Panagioti M, Waheed W, Esmail A. Unrecognized bipolar disorder in patients with depression managed in primary care: a systematic review and meta-analysis. *Gen Hosp Psychiatry.* 2019;58:71-76.
13. Gitlin M. Antidepressants in bipolar depression: an enduring controversy. *Int J Bipolar Disord.* 2018;6(1):25.
14. American Psychological Association. Clinical practice guideline for the treatment of depression across three age cohorts. <https://www.apa.org/depression-guideline>. Published February 2019. Accessed on January 4, 2022.
15. Robinson W, Geske J, Prest L, Barnacle R. Depression treatment in primary care. *J Am Board Fam Pract.* 2005; 18(2):79-86.

16. Dorow M, Lobner M, Pabst A, Stein J, Riedel-Heller S. Preferences for depression treatment including internet-based interventions: results from a large sample of primary care patients. *Front Psychiatry*. 2018;9:181.
17. Keller M. Remission versus response: the new gold standard of antidepressant care. *J Clin Psychiatry*. 2004;65 Suppl 4:53-59.
18. Al-Harbi K. Treatment-resistant depression: therapeutic trends, challenges, and future directions. *Patient Preference Adherence*. 2012;6:369-388.
19. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905-1917.
20. Lima TM, Visacri MB, Aguiar PM. Use of ketamine and esketamine for depression: an overview of systematic reviews with meta-analyses. *Eur J Clin Pharmacol*. 2022;78(3):311-338.
21. Krivoy A, Balicer R, Feldman B, et al. Adherence to antidepressants is associated with lower mortality: a 4-year population-based cohort study. *J Clin Psychiatry*. 2016;77(5):e566-e572.
22. Gallo J, Morales K, Bogner H, et al. Long term effect of depression care management on mortality in older adults: follow-up of cluster randomized clinical trial in primary care. *BMJ*. 2013;346:f2570.
23. Lavakumar M, Makurumidze G, Bradley M, Avery A. Integrated and collaborative care. In: Bourgeois J, Cohen M, Makurumidze G, eds. *HIV Psychiatry*. Springer, Cham; 2022:499-521.
24. Ji N, Hong Y. Effect of income level on adherence to antidepressant treatment in first onset depression outpatients. *PLoS One*. 2020;15(9):e0238623.
25. El-Halabi S, Cooper D, Cha D, et al. The effects of antidepressant medications on antiretroviral treatment adherence in HIV-positive individuals with depression. *J Affect Disord*. 2021;300:219-225.
26. van Leeuwen E, van Driel M, Horowitz M, et al. Approaches for discontinuation versus continuation of long-term antidepressant use for depressive and anxiety disorders in adults. *Cochrane Database Syst Rev*. 2021;4:CD013495.

Top Antivir Med. 30;(2):454-463

©2022, IAS–USA. All rights reserved.