

## Addressing Depression In People with HIV

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## Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years

Dr Cournos has no relevant financial relationships with ineligible companies to disclose. (Updated 3/31/21)

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## Learning Objectives

At the end of this presentations, learners will be able to:

- Describe the approach to the differential diagnosis and management of depressive illnesses among people with HIV.
- Differentiate the diagnosis and treatment of major depression from the diagnosis and treatment of bipolar depression.
- Cite the current evidence for the impact of depression treatment on both mental health outcomes and HIV outcomes among people with HIV.

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## Depression Among People with HIV

- Worldwide, estimates of depressive disorders among people with HIV vary widely from 6-67%, depending on the population surveyed, the approach to diagnosis, etc.
- Research generally shows that depression is the most common psychiatric disorder seen in HIV clinical settings in the U.S., with rates hovering around 30-40%.
- Among people with HIV in the U.S., depressive disorders have high rates of comorbidity with other psychiatric illnesses, such as alcohol/substance use disorders, anxiety disorders and PTSD.

Cournos, McKinnon, Wainberg, in Comprehensive Textbook of AIDS Psychiatry: A Paradigm for Integrated Care, 2017

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## Treating Depressive Illness Contains More Uncertainty than Treating HIV Infection

- Treating depressive illness currently involves more trial and error than does treating HIV infection.
- Psychiatry has no biological tests for the diagnosis of depression (nothing equivalent to detecting HIV or its associated antibody responses)
- Psychiatry has no direct biological tests for the efficacy of selecting (no phenotype, genotype, resistance testing, etc; but there are tests for drug metabolism and drug levels).
- The idea that its simple to screen for and treat depression is not yet true
- The brain is the body's most unique and least understood organ (which is why psychiatry is both difficult and fascinating)

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## Given the Frustrations of Treating Depressive Illness, Why Is Persevering So Important?

- Depressive illness is one of the most frightening and disabling of all illnesses, as described below:
- "I did not die, and yet I lost life's breath. Imagine for yourself what I became, deprived at once of both my life and death." (Dante Alighieri, The Inferno, translated by John Ciardi. Dante was born in 1265 and the DSM (1) was born in 1952, so Dante had no official DSM diagnoses. But his descriptions of depressive illness are extraordinary!)
- "I lay down fully dressed in nice clothes, in the mud...and I didn't care about standing up ever again." (Andrew Solomon, The Anatomy of Melancholy, The New Yorker)
- My next-door neighbor, Ms.O: "Of all the illnesses I've ever had, including surgery for cancer, none have been as painful or frightening as depression."
- Successfully treating depressive illness gives people their lives back.

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## Depressive Symptoms vs Depressive Illness

- Mild depressive symptoms are ubiquitous.
- Depressive symptoms can occur as part of almost any serious medical illness or neurological condition.
- Depressive symptoms can occur as part of almost any other psychiatric diagnosis or as part of ordinary distress.
- Ruling out simple stress and numerous other medical and psychiatric conditions is key to settling on a psychiatric diagnosis of depressive illness.

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## Differential Diagnosis of Depressive Symptoms

- Even though it's naive to screen patients for depressive symptoms without understanding the broad differential diagnosis for these symptoms, doing so is a common practice.
- A positive screen for depressive symptoms CANNOT BY ITSELF be used to make a psychiatric diagnosis.
- The SARS-CoV-2 pandemic has magnified this concern as we confront elevated rates of distress in the entire U.S. population.
- This talk is primarily about depressive disorders as defined in the DSM-5, and not about depressive symptoms.

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## Distinguish Between Mental Distress And Mental Disorders

### Mental Distress

Can occur in response to any adversity.

Often does not meet criteria for a psychiatric diagnosis or require specialized mental health interventions.

Often responds well to supportive strategies.

### Mental Disorders

Usually cause either persistent severe subjective distress and/or functional impairment.

Meet recognized diagnostic criteria (ICD, DSM).

Call for evidenced informed mental health interventions such as medication and psychotherapy.

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### The Two Most Commonly Used Screening Tools Used to Assess for Depressive Symptoms

- The Patient Health Questionnaire-2 (PHQ-2): Two questions
- The Patient Health Questionnaire-9 (PHQ-9): Nine questions
- A combination of the PHQ-2 and PHQ-9
- The PHQ-2 and PHQ-9 are:
  - Quick to complete
  - Free of charge to use and/or reproduce
  - Well-studied
  - Available in multiple languages
- The PHQ-2 and PHQ-9 can be accessed via the National HIV Curriculum and scored at that site using automatic calculators (Tools and Calculators); This site also offers extensive information about the sensitivity and specificity of these tools (Module 2, Lesson 5). Access these materials at [www.aidsctc.org/nhc](http://www.aidsctc.org/nhc)

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### Depression As an Illness Is Found in Two Types of Psychiatric Disorders

- Depressive disorders, which include:
  - Major depression
  - Persistent depressive disorder (includes what was previously called dysthymia)
- Bipolar disorders (depressive phase), which include:
  - Bipolar 1 (mania is/has been present)
  - Bipolar 2 (hypomania is/has been present)
  - Cyclothymia (does not meet full criteria for bipolar 1 or 2)

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### Major Depression is Best Conceptualized as a Medical Co-morbidity of HIV Infection

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|------------------------|-------------------------|
| <b>AFFECTIVE</b>       | <b>SOMATIC</b>          |
| ▪ Depressed mood       | ▪ Appetite/Weight loss  |
| ▪ Loss of interest     | ▪ Sleep disturbance     |
| ▪ Guilt, worthlessness | ▪ Agitation/retardation |
| ▪ Hopelessness         | ▪ Fatigue               |
| ▪ Suicidal ideation    | ▪ Loss of concentration |

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

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### Aim to Achieve Remission of Depressive Illness, Not Just Improvement

- Because there's no "penicillin" for depression, we largely treat patients by trial and error, monitoring tolerability to side effects and degree of improvement.
- Response to treatment (>50% reduction of symptoms) is a much less desirable outcome than remission from depressive illness (few or no symptoms).
- Depressive symptoms that persist pose a risk for relapse of depression.

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### Treatment of Unipolar Major Depression The STAR\*D Study: Overview

- STAR\*D is the largest and most inclusive clinical trial ever conducted on the treatment of non-psychotic unipolar major depression.
- This multisite, multistep, prospective, randomized, federally funded clinical trial enrolled about 4000 patients, many with medical and psychiatric co-morbidities.
- There were four sequenced treatment steps in the algorithm. The first step for everyone was treatment with the SSRI antidepressant citalopram.

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### Treatment of Unipolar Major Depression The STAR\*D Study: Overview

- There were two endpoints: response (>50% reduction of symptoms) and remission (few or no symptoms).
- If citalopram treatment was not successful, step two contained seven options for either augmentation (with another medication or cognitive behavioral therapy) or switching to another antidepressant.
- If step two failed there were further options in steps three and four.
- Since 2003, hundreds of papers have been published about the STAR\*D results.

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### Treatment of Unipolar Major Depression The STAR\*D Study: Level 2, 3, 4 Options

- **Seven Step 2 options:**
  - Switch to options: sertraline, or bupropion-SR, or venlafaxine-XR, or cognitive psychotherapy; or
  - Add-on options: bupropion-SR or cognitive psychotherapy or buspirone
- **Two Step 3 options:** Add lithium or triiodothyronine (T3)
- **Step 4 options:** Switch to the monoamine oxidase inhibitor tranylcypromine or the combination of venlafaxine-XR and mirtazapine

<https://www.nlm.nih.gov/funding/clinical-research/practical/star/d/medicationlevels.shtml>

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### Treatment of Unipolar Major Depression The STAR\*D Study: Results

- **Rates of acute remission (few or no symptoms):**
  - Step 1: 37%
  - Step 2: 31%
  - Step 3: 14%
  - Step 4: 13%
- **Rates of response (>50% reduction of symptoms):**
  - Step 1: 49%
  - Step 2: 29%
  - Step 3: 17%
  - Step 4: 16%
- Rates of medication intolerance, relapse and dropout are not shown in this slide.

Rush et al., Am J Psychiatry, 2006

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### Treatment of Unipolar Major Depression The STAR\*D Study: Implications

- It is valuable for prescribers in primary/HIV care to know how to use several antidepressants and be willing to switch patients from one to another depending on patient outcomes (symptom improvement and ability to tolerate side effects).
- If the patient does not improve sufficiently after two adequate trials, refer to mental health specialty care.
- Other reasons to refer to specialty care include bipolar depression, psychotic depression, risk for suicide and/or violence, and diagnostic uncertainty.

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### Psychotropic Medications For Depressive Disorders in People with HIV: Common Concerns

- **Antidepressants:** Most do not have problematic drug interactions with antiretroviral treatment (ART); there's a black box warning for suicide risk in patients younger than 24 years old.
- **Antipsychotics:** Most do not have problematic interactions with ART. There's a black box warning for risk of death in patients with dementia and overlapping metabolic toxicities with ART medications.
- **Mood stabilizers:** More concerns with interactions with ART medications; have various black box warnings depending on the medication selected.

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### There are Treatments For Depressive Disorders that Are Refractory to Usual Psychotropic Medications

- **Brain stimulation treatments:** Electroconvulsive therapy (ECT) was the first such treatment, but now there are two other FDA approved treatments, vagus nerve stimulation (VNS) and repetitive transcranial magnetic stimulation (rTMS).
- **Ketamine,** an agent used primarily by veterinarians for anesthesia (and sometimes as a drug of abuse), was recently approved by the FDA for refractory depression; must be used with specific safeguards.
- Patients with refractory depression should always be referred to the next level of care.

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### Distinguish Between Major Depression and Bipolar Depression

- Bipolar depression accounts for most of the time that people with bipolar disorder spend unwell.
- This may help explain why, in primary care, over 3 in 20 patients diagnosed with a depressive disorder have an unrecognized bipolar disorder.
- First line pharmacologic treatment of bipolar depression is mood stabilizers (lithium, anticonvulsants, atypical antipsychotics), whereas for major depression it's antidepressants.
- Giving antidepressants alone to people with bipolar depression works poorly and may precipitate mania.

McIntyre, et al, Curr Med Res Opin, 2019; Devaney, et al, Gen Hosp Psych, 2019

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## Diagnosing Bipolar Disorder

- There are no brief screens for bipolar disorder. The Mood Disorders Questionnaire (MDQ) is available but has 13 items.
- Ask if the patient or a close relative has ever been told s/he has manic-depressive illness or bipolar disorder?"
- Consider a few questions from the MDQ (based on the DSM-5):
  - Has there ever been a period of time when you were not your usual self, and you had much more energy than usual?"
  - Has there ever been a period of time when you got much less sleep than usual and found you didn't really miss it?
- If you get yes answers to any of the above questions, you might consider completing the MDQ ([www.aidsctc.org/hhc](http://www.aidsctc.org/hhc)) and/or referring the patient for a diagnostic evaluation.

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## Managing Bipolar Disorder

- On average, bipolar disorders are more severe illnesses than depressive disorders. This was one reason for the creation of two separate categories for these conditions in the DSM-5.
- Many people with bipolar disorder need lifetime ongoing management for this condition to maximize social/occupational functioning and well being. Evidence shows that intensive psychotherapy helps.
- Despite the associated disabilities, there's a long list of famous artists, fiction writers, inventors, politicians etc. with bipolar disorder.
- People with bipolar disorder are most amenable to treatment during the depressive phase of the illness. Those who feel euphoric and energized during (hypo)mania often reject care while in that state.

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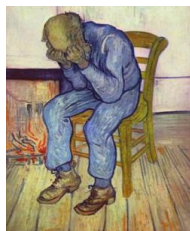
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## Many Exceptional People Have Had Bipolar Disorder: Artists



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### Many Exceptional People Have Had Bipolar Disorder: Politicians and Writers

- Winston Churchill was the Prime Minister of the UK who achieved victory during World War II. He was diagnosed with bipolar disorder in middle age and openly referred to his depression as his "black dog." He wrote voluminously and won the Nobel Prize in Literature in 1953.



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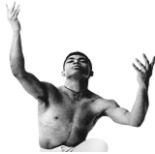
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### Many Exceptional People Have/Had Bipolar Disorder: Dancers and Entertainers

- Alvin Ailey was a renowned modern dancer and choreographer whose bipolar disorder was aggravated by his drinking and drug use. He died of AIDS in 1989, but his work lives on through the Alvin Ailey American Dance Theater.



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### Alcohol/substance use co-morbidity

- Psychiatric disorders carry a high degree of comorbidity with one another:
  - Alcohol and other substance use disorders are common co-morbidities of depressive illnesses.
  - We have yet to understand if there's an underlying biological vulnerability that could help explain why these diagnoses frequently travel together.
  - Siloed services for mental illness and substance use disorders are a major barrier to good behavioral health care
  - Most people with alcohol/substance use disorders receive no treatment for these conditions

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### Alcohol/substance use co-morbidity

- In general, outcomes tend to be significantly worse among patients diagnosed as having both major depressive disorder and an alcohol/substance use disorder, compared with patients who have only one of these diagnoses.
- A review of studies among people with bipolar disorders shows a 42% prevalence of alcohol use disorders, a 20% prevalence of cannabis use disorders and a 17% prevalence of other illicit drug use disorders.

[Iqbal et al., Focus \(Am Psychiatr Publ\), Spring 2019; Hunt, et al., J Affect Disord, 2016](#)

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### Alcohol/substance use co-morbidity

- Alcohol and substance use disorders tend to be one of the most problematic of psychiatric comorbidities among people with depressive illness and HIV because of their added negative impact on morbidity, mortality, and outcomes along the HIV care continuum.
- **In this case, two disorders = two treatments**
- Affective disorders and alcohol/substance use disorders each require their own treatment because treating only one condition doesn't usually result in sufficient improvement of the other condition.

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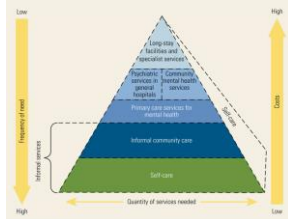
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### The World Health Organization (WHO) Pyramid of Mental Health Services



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### Activating Care along the WHO Pyramid of Mental Health Services for Depressive Illnesses

- Self care is essential with any chronic illness, including depressive and bipolar disorders.
- Depressive and bipolar disorders often occur in relapsing cycles, and self care can reduce the frequency of relapse.
- Informal care can address the social determinants of health (food, shelter, income support, etc.), which also reduces the risk of relapse.
- Specialty care can assist with stabilizing patients with depressive disorders who are being followed in HIV care.

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### What Are the Hoped-for Outcomes in the Successful Treatment of Depressive Illness

- General outcomes
  - Relief of suffering and improved quality of life
  - Reduced disability and cognitive dysfunction
  - Increased ability to function
  - Reduced mortality due to suicide or medical illness
- HIV specific outcomes
  - Improved rates of viral suppression
  - Reduced HIV-related morbidity and mortality

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### What Is the Evidence for Improved Outcomes if Depressive Illness in Treated Successfully

- People with HIV appear to achieve comparable outcomes with depression treatments as the general population.
- Evidence is mixed regarding whether successful treatment of depressive illness by itself is associated with improved rates of viral suppression; the addition of a specific adherence intervention may be needed.
- Evidence is not available regarding whether the successful treatment of depressive illness reverses the shortened life span of people with both chronic depression and HIV

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