Overview of the neuropsychiatric aspects of HIV infection and AIDS

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INTRODUCTION

The high prevalence of neuropsychiatric disorders in individuals infected with HIV, is related to a wide variety of factors including direct effects of the virus, preexisting psychiatric conditions, personality vulnerabilities, affective disorders, addictions, and personal responses to the social isolation and disenfranchisement associated with the diagnosis of HIV. Furthermore, many HIV-infected persons experience difficulty with treatment adherence due to their behavior patterns as well as acquisition of specific neuropsychiatric disorders associated with HIV disease progression. Studies have shown that patients with neuropsychiatric conditions have poorer outcomes and less benefit from antiretroviral therapy; however, psychiatric treatment improves HIV-related outcomes [1].

Neuropsychiatric care in HIV disease ranges from supportive psychotherapy for grief and loss issues to treatment of specific HIV-associated neuropsychiatric conditions (eg, HIV-associated dementia, minor cognitive motor disorder [MCMD], acquired immunodeficiency syndrome [AIDS] mania), as well as management of unique clinical presentations of other psychiatric disorders such as depression and schizophrenia. The availability of effective psychiatric care to HIV-infected patients is critical for their treatment and also for controlling the HIV epidemic.

Mental disorders that are commonly comorbid with HIV disease include:

- Delirium

- MCMD
- HIV-associated dementia
- Major depression
- Bipolar disorder (including AIDS mania)
- Schizophrenia
- Substance abuse or dependence
- Posttraumatic stress disorder

An overview of the range of neuropsychiatric conditions associated with HIV infection will be presented here. More detailed reviews of these specific conditions are discussed separately. (See "HIV-associated neurocognitive disorders: Epidemiology, clinical manifestations, and diagnosis" and "Depression, mania, and schizophrenia in patients with HIV" and "Substance use disorder in patients with HIV".)

DELIRIUM

Delirium, a state of global derangement of cerebral function, occurs frequently in medically ill, brain-injured, or metabolically unstable patients. Delirium is characterized by inattention, disorganized thinking, confusion, emotional liability, and fluctuations in level of consciousness. Hallucinations and delusions are also common. The etiology of delirium is typically multifactorial, including elements of pharmacological toxicity, metabolic derangements, and sensory isolation due to illness and limited environmental stimulation. It is associated with high morbidity and mortality and should be diagnosed promptly and investigated thoroughly. In addition, delirium is associated with postdelirium psychiatric conditions such as posttraumatic stress disorder, suggesting a need for follow-up after an episode of delirium. (See "HIV-associated neurocognitive disorders: Epidemiology, clinical manifestations, and diagnosis".)

Due to the complexity and number of comorbid disorders, delirium is highly prevalent in HIV disease. The differential diagnosis of delirium in HIV-infected patients includes HIV-associated dementia, AIDS mania, minor cognitive motor disorder, major depression, bipolar disorder, panic disorder, and schizophrenia. Delirium can usually be distinguished by its rapid onset, fluctuating level of consciousness, and link to a medical etiology. Common etiologies include:

- Toxic (eg, poisoning or medication toxicity, especially medications with potent anticholinergic activity)
- Metabolic
- Infectious, especially central nervous system (CNS) infection
- Endocrine (eg, thyroid and adrenal axes)

- CNS neoplasm
- Cardiovascular (eg, myocardial infarction or arrhythmia)
- Neurologic (eg, seizure or stroke)
- Pulmonary (eg, hypoxia or hypercapnia)
- Traumatic (eg, head injury or burns)
- Withdrawal from alcohol or medications

DEMENTIA

HIV infection is associated with multiple cognitive impairments. Early in the epidemic (1980s), a progressive subcortical dementing illness that was fatal was described and later termed AIDS-dementia. With the advent of effective antiviral therapy, rates of this condition diminished in developed settings with effective treatment, but patients are still found to have cognitive impairment. The nosology was revised, such that the term HIV-associated neurocognitive disorder is used to describe the entire spectrum of HIV-associated neurocognitive impairment with subcategories of asymptomatic neurocognitive impairment, mild neurocognitive disorder, and HIV-associated dementia based on severity. With the advent of antiretroviral therapy (ART), HIV-associated neurocognitive disorder is more often multifactorial and involves both **cortical** and **subcortical** changes in function [2].

HIV-associated dementia must be distinguished from other causes of dementia including cytomegalovirus encephalitis, progressive multifocal leukoencephalopathy, cerebral toxoplasmosis, cryptococcal meningitis, and central nervous system lymphoma. (See "Approach to the patient with HIV and central nervous system lesions" and "Toxoplasmosis in patients with HIV" and "Epidemiology, clinical manifestations, and diagnosis of Cryptococcus neoformans meningoencephalitis in patients with HIV" and "HIV-related lymphomas: Epidemiology, risk factors, and pathobiology".)

HIV-associated dementia usually occurs in patients with a CD4 count nadir <200 cells/microL. Risks factors for HIV-associated dementia include high serum or cerebrospinal fluid HIV viral load [3], low educational level, advanced age (see "HIV infection in older adults"), anemia, illicit drug use, and female sex. Since the introduction of potent ART, the incidence of HIV-associated dementia has declined, although not as much as some of the opportunistic infections. (See "HIV-associated neurocognitive disorders: Epidemiology, clinical manifestations, and diagnosis".)

MINOR COGNITIVE MOTOR IMPAIRMENT

Minor cognitive motor impairment (MCMD), cognitive impairment that approaches but does not meet diagnostic criteria for dementia [4], is less severe than HIV-associated dementia and emerges earlier in HIV disease. Symptoms of MCMD are subtle and often overlooked. It is not known whether MCMD predisposes to HIV-associated dementia. Some patients continue to have only minor problems while others progress to full dementia.

MAJOR DEPRESSION

Comorbid major depression (table 1) is common with HIV disease, both in those with HIV dementia and others, and depression hinders effective treatment of HIV-infected individuals, such that these patients are at significantly increased risk for HIV-disease progression and mortality [5-10]. Furthermore, depressive symptoms in patients with HIV worsen antiretroviral therapy adherence, while adherence to antidepressant therapy in HIV-positive individuals with depression reverses this trend [11,12]. HIV also increases the risk of developing depression through direct damage to subcortical brain areas, chronic stress, worsening social isolation and intense demoralization. Indeed, patients with symptomatic HIV disease are significantly more likely to undergo a major depressive episode than patients with asymptomatic HIV disease, or HIV-negative control study subjects [13]. Unfortunately, depression is underdiagnosed and undertreated in most medical clinics and has thus emerged as one of the most significant factors in the HIV/AIDS epidemic. (See "Depression, mania, and schizophrenia in patients with HIV".)

The differential diagnosis in HIV patients reporting depressive symptoms includes major depression, persistent depressive disorder (dysthymia), dementia, delirium, demoralization, intoxication, withdrawal, central nervous system (CNS) injury, CNS infection, and acute medical illness. HIV-associated dementia and other HIV-related CNS conditions can produce a flat, apathetic state often misdiagnosed as depression.

MANIA

Mania (table 2), which occurs in HIV-infected patients both as a component of bipolar illness and as the unique entity of AIDS mania, is associated with impulsivity, impaired judgment, and risk taking, all of which can lead to behavior that accelerates HIV-disease progression. Bipolar illness is broad in spectrum, ranging from a severely crippling and chronic mental illness to a mild disorder with alternating experiences of elevated or depressed mood. It is thus difficult to accurately measure the prevalence and incidence of bipolar disorder and it has also been difficult historically to distinguish severe bipolar illness from schizophrenia. Investigators

looking at the relationship between HIV and mental illness have thus often simply employed the term "chronically mentally ill" for patients with severe disability from either schizophrenia or bipolar disorder. (See "Depression, mania, and schizophrenia in patients with HIV".)

AIDS mania is uniquely associated with late stage HIV infection. AIDS mania is characterized by typical mania and additional cognitive impairment in the setting of a lack of previous personal or family history of bipolar illness. AIDS mania has less euphoria and more irritability than the mania associated with illness, and is also far more chronic. In contrast to bipolar mania, AIDS mania usually does not remit if left untreated. The prevalence of AIDS mania has dropped significantly since the onset of potent antiretroviral therapy.

SCHIZOPHRENIA

Severe and chronic mental illness, historically encompassing schizophrenia (table 3) and bipolar I disorder, is estimated at prevalence rates from four to 19 percent in HIV patients. No evidence suggests that HIV causes schizophrenia, but data do suggest that schizophrenia contributes to high-risk behavior associated with HIV infection [14,15]. (See "Depression, mania, and schizophrenia in patients with HIV".)

SUBSTANCE ABUSE AND ADDICTION

Substance abuse adds a complex dimension to HIV-infected patients since addiction can serve as a primary vector for the spread of the virus but also greatly complicate treatment of HIV [7,8]. Extensive psychiatric, psychological and medical comorbidities are associated with substance abuse and addiction in HIV disease. (See "Substance use disorder in patients with HIV".)

POSTTRAUMATIC STRESS DISORDER

The relationship between posttraumatic stress disorder (PTSD) and HIV infection is also complex. PTSD exacerbates HIV risk behaviors and worsens health outcomes. HIV risk behaviors, such as prostitution and drug abuse, may increase exposure to trauma associated with increased likelihood of developing PTSD, and likewise, PTSD from early trauma predisposes individuals to engage in sex or drug behaviors that increase the risk of HIV infection. For example, PTSD often coexists with depression and cocaine/opioid abuse [16], both of which are risk factors for HIV. Substance abuse may be either a relief strategy in response to traumatic

experience, or a lifestyle that increases exposure to traumatic events like robbery or assault [17].

PERSONALITY DISTURBANCE IN HIV DISEASE

Personality disorders are more prevalent among HIV-infected (19 to 36 percent) and HIV at-risk (15 to 20 percent) individuals [18-20] than the general population (10 percent) [21]. Antisocial personality disorder is the most common personality disorder among HIV infected individuals [22], and has been shown to significantly increase risk of HIV infection [23].

Dimensional nature of personality — Patients with HIV can be characterized along the dimensions of extroversion-introversion and emotional stability-instability [24,25], rather than the personality disorders described in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) [26]. The dimensional approach emphasizes the assets as well as the vulnerabilities of extremes of personality and helps in understanding the behavior exhibited by patients. It also suggests intervention strategies and is less stigmatizing. Furthermore, a classification system based on a continuum approach is a better predictor of HIV risk behavior than DSM-5 categories [27].

The extroversion-introversion dimension refers to the individual's tendency to respond to stimuli with either excitation or inhibition. Extroverted individuals are present-oriented, feeling-directed and reward-seeking. Feelings dominate thoughts. Their primary motivation is reward-seeking or relief from discomfort and their chief focus is the immediate emotional experience [28,29]. By contrast, introverted individuals are future and past oriented, cognition-directed and consequence-avoidant. Logic and function predominate over feelings in their decisions. Introverts are motivated by appraisal of past experience and avoidance of future adverse consequences.

The second dimension of personality, stability-instability, describes the degree of emotional lability. Stable individuals respond to emotional stimuli slowly and require intense stimuli for significant emotional arousal. They also have predictable emotional responses and will usually respond the same way to the same stimulus over time. By contrast, unstable individuals experience intense mercurial emotions that are easily aroused, require only modest provocation for intense reactions, and are unpredictable, in that the same stimulus may produce very different responses when encountered at different times. The juxtaposition of these two personality dimensions allows classification of individuals into four personality types: unstable extroversion, stable extroversion, unstable introversion and stable introversion.

Although this classification scheme is not the method used in the DSM-5, various forms have been used extensively in research and we have found it to be more useful in the description and treatment of HIV-infected individuals.

For example, extreme extroverts, who may be among the most highly represented personality disorders in patients seen in HIV consultative services, are vulnerable when it is important for them to avoid consequences and focus on the future, like adhering to a complex daily antiretroviral therapy regimen. As most healthcare professionals tend to be on the introverted side (ie, consequence-avoidant), they are often puzzled by the extrovert's insensitivity to consequence and thus may face significant difficulty in communicating with these patients as they stress the long-term negatives while patients are focused on their immediate goals. We have found the following approaches to be particularly useful in aligning with unstable extrovert patients to optimize their treatment:

- Describe behaviors in terms of rewards. Reframe consequence avoidance to describe the benefits likely to be garnered from a particular course of action as opposed to describing the negative results that will ensue. For example, reframing "If you don't stop shooting drugs, you'll get sicker" as "If you get off drugs you'll feel better" places the emphasis on getting the patient to choose the desired behavior directly linked to the reward.

- Appeal to the patient's cognitive side, whenever possible, to help patients learn to recognize their vulnerabilities (ie, impulsiveness, short temper). Instruct them to remove themselves from potentially problematic situations or to have a planned response that does not rely on these feelings.

- Describe the treatment plan clearly and with firm limits. This provides all clinicians with a unified set of goals and expectations, and increases the likelihood of persuading a patient to adhere to the clinician's treatment goals.

Ultimately, these approaches can help unstable extroverted patients with HIV to change how they respond to problems by redefining their goals towards health and function, and thus gradually changing their lives in a fundamental way.

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer

short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: HIV-associated neurocognitive disorders (The Basics)")
- Beyond the Basics topics (see "Patient education: Delirium (Beyond the Basics)")

SUMMARY

- The most prevalent psychiatric disorders associated with HIV disease are delirium, minor cognitive motor disorder (MCMD), HIV-associated dementia, major depression, bipolar disorder (including acquired immunodeficiency syndrome [AIDS] mania), schizophrenia, substance abuse or dependence, posttraumatic stress disorder (PTSD), and personality disorders and traits. (See 'Introduction' above.)
- Delirium is characterized by inattention, disorganized thinking, confusion, emotional liability, and fluctuations in level of consciousness. The differential diagnosis of delirium in HIV-infected patients includes HIV-associated dementia, AIDS mania, MCMD, major depression, bipolar disorder, panic disorder, and schizophrenia. Delirium can usually be distinguished by its rapid onset, fluctuating level of consciousness, and link to a medical etiology. (See 'Delirium' above.)
- HIV-associated dementia usually occurs in patients with a CD4 count nadir <200 cells/microL. Risks factors for HIV-associated dementia include high serum or cerebrospinal fluid HIV viral load, low educational level, advanced age, anemia, illicit drug use, and female sex. Since the introduction of potent antiretroviral therapy (ART), the incidence of HIV-associated dementia has declined. (See "HIV-associated neurocognitive disorders: Epidemiology, clinical manifestations, and diagnosis".)
- MCMD is cognitive impairment that approaches but does not meet diagnostic criteria for dementia. MCMD is less severe than HIV-associated dementia and emerges earlier in HIV disease. It is not known whether MCMD predisposes to HIV-associated dementia. (See

"HIV-associated neurocognitive disorders: Epidemiology, clinical manifestations, and diagnosis".)

- Comorbid major depression (table 1) is common with HIV disease and hinders effective treatment of HIV-infected individuals, such that these patients are at significantly increased risk for HIV-disease progression and mortality. (See 'Major Depression' above and "Depression, mania, and schizophrenia in patients with HIV", section on 'Major depression'.)

- Mania (table 2) occurs in HIV-infected patients either as a component of bipolar illness, or as the unique entity of AIDS mania associated with late stage HIV infection. AIDS mania is characterized by typical mania and additional cognitive impairment in the setting of a lack of previous personal or family history of bipolar illness. The prevalence of AIDS mania has dropped significantly since the onset of potent ART. (See 'Mania' above and "Depression, mania, and schizophrenia in patients with HIV", section on 'Mania'.)

- No evidence suggests that HIV causes schizophrenia (table 3), but data indicate that schizophrenia contributes to high-risk behavior associated with HIV infection. (See "Depression, mania, and schizophrenia in patients with HIV", section on 'Schizophrenia and psychotic episodes'.)

- Substance dependence can serve as a primary vector for the spread of HIV and complicate HIV treatment. Numerous comorbidities are associated with substance use disorders in HIV disease. (See "Substance use disorder in patients with HIV".)

- PTSD exacerbates HIV risk behaviors and worsens health outcomes. HIV risk behaviors (sex and drug use) may increase exposure to trauma associated with increased likelihood of developing PTSD. Likewise, PTSD from early trauma predisposes individuals to engage in behaviors that increase the risk of HIV infection. (See 'Posttraumatic stress disorder' above.)

- Personality disturbance in patients infected with HIV can be classified according to personality disorders as well as the dimensional constructs of extroversion-introversion (tendency to respond to stimuli with either excitation or inhibition) and emotional stability-instability (degree of emotional lability). Antisocial personality disorder is the most common personality disorder among HIV infected individuals. (See 'Personality disturbance in HIV disease' above.)

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