Introduction

Severe mental illness makes individuals more vulnerable to HIV infection and/or acquiring other sexually transmitted diseases\(^5\). On the other hand, the proportion of mental and/or substance-abuse disorders among people living with HIV/AIDS is nearly five-times greater than in the general population\(^6\). Despite the impressive reduction in HIV-related morbidity and mortality that antiretrovirals have gained, neuropsychiatric repercussions of this disease are expected to become more relevant in the coming years. For these reasons, a multidisciplinary approach involving evaluation, counseling, and treatment of mental disorders in HIV patients is becoming more important\(^7\).

Late recognition of mental disorders in HIV patients is related, among others, with diminished coping capacity at diagnosis\(^8\)-\(^12\), failure at primary prevention, poorer antiretroviral adherence\(^13\)-\(^18\), impairment in quality of life\(^19\)-\(^22\), greater social burden\(^23\),\(^24\), overall increases in healthcare costs\(^25\)-\(^27\), and higher mortality\(^28\).

Diagnosis of neuropsychiatric disorders

The recognition of clinical manifestations of neuropsychiatric disorders in HIV patients is currently a major challenge. Not infrequently, psychiatric symptoms may be viewed as a “natural” reaction to HIV diagnosis. The detection of mental disorders usually needs proactive investigation as symptoms may be subtle enough to remain unnoticed or underreported.

Patients presenting with acute or subacute changes in their mental state should be evaluated in a protocol-wise fashion. Neuropsychiatric evaluation should include medical and psychiatric anamnesis, mental status examination, and the use of various psychopathological assessment instruments. Additional tests (Table 1) are required for discarding central nervous system (CNS) organic diseases\(^29\) such as:

- Neoplasms (i.e. lymphoma)
- Infections (i.e. toxoplasma, tuberculosis, cytomegalovirus)
- Systemic illnesses (anemia, diabetes, testosterone deficiency, dysthyroidism, malnutrition)
- Cerebrovascular disease
- Alcohol abuse or addiction to illicit drugs
Neuropsychiatric disorders in HIV-infected patients

Severe systemic diseases are burdened with a high prevalence of mental disorders, which could rise to 30-50%. Although HIV-infected patients under antiretroviral therapy infrequently suffer acute organic complications, the chronicity of the disease places them at greater risk for psychiatric comorbidity than the general population. Prevalence estimates of psychiatric disorders among HIV-infected individuals range between 5-30%, with variations depending on study designs, methods of diagnosis, or populations studied, and are significantly associated with the presence of lifetime psychiatric disorders prior to HIV infection diagnosis. The main neuropsychiatric disorders observed in HIV patients are described in the following sections.

Delirium (confusional states)

This is the most common neuropsychiatric diagnosis in hospitalized or critically ill HIV patients, with an estimated frequency of 40-65%. This condition may be observed as soon as during acute HIV infection or, most frequently, in late stages associated to infections, malignancies, metabolic abnormalities, hypoxemia, or anemia.

Delirium is characterized by anxiety, disorientation, hallucinations, delusions, and incoherent speech, with oscillations in the level of consciousness. It is important to differentiate delirium from dementia, and even in some cases to detect delirium superimposed on dementia. At medical interview, delirium has an abrupt onset, within hours, while dementia accompanies memory impairment and decreased functioning within months. Resolution of delirium depends on treatment of the underlying cause.

HIV-associated neurocognitive disorders

HIV-associated dementia (HAD) is the most severe form of HIV-associated neurocognitive disorders (HAND), which typically occurred in severely and prolonged immunosuppressed patients when antiretrovirals were not available. Onset is insidious and the clinical syndrome results from subcortical dementia. In later stages, the clinical and radiological picture shares features of cortical and subcortical dementia. The main symptoms include neurocognitive impairment, such as decreases in psychomotor speed,
attention and concentration, memory and learning, information processing, or executive function. There may also be motor slowing, lack of coordination, or tremor that may progress to disabling weakness, spasticity, extrapyramidal movement disorders, and paraparesis. In addition, there may be behavioral affects such as apathy and irritability. Psychomotor retardation may more rarely occur.

However, the spectrum and severity of HAND has changed in the era of antiretroviral therapy. To deal with this novel scenario, the diagnostic criteria first developed by the American Academy of Neurology in 1991 were refined in 2007. A working group assembled in Frascati, Italy, established that the current essential feature of HAND is cognitive disturbance. In fact, the possibility of HIV neurocognitive disorders being diagnosed on the basis of neuromotor and non-cognitive psychiatric conditions (i.e., changes in personality or mood) was excluded. Three different mental conditions were defined, depending on the severity of symptoms: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD) (Table 3). Despite these evolutions, the prevalence of HAND remains today as it used to be in around 30-50% of patients on regular follow-up.

Some important differences between past and current presentation of HAND are greater CD4 counts and lower HIV-RNA plasma concentrations in most recent cases. A disconnection between HIV-RNA in plasma, usually undetectable, versus cerebrospinal fluid (CSF), commonly detectable, seems to be a key feature. Besides being diagnostic criteria, this finding may indicate that patients with HAND have developed an independent HIV reservoir in the CNS, less responsive to antiretrovirals, that provokes this disconnection and mental impairment. The ability of antiretrovirals to diffuse through the blood-brain barrier is strongly related with the risk for HAND. Table 4 categorizes antiretrovirals in accordance to blood-brain barrier penetration.

Common HIV comorbidities, such as antiretroviral toxicity, and common coinfections, like syphilis or chronic hepatitis, cardiovascular or metabolic diseases, illicit drugs abuse or mental disorders, may worsen HAND symptoms. Finally, the increased life expectancy in HIV patients may add cerebrovascular or degenerative encephalitides to the causative spectrum of HAND. Although for the moment HAND is usually mild and survival is not compromised, it may negatively impact on quality of life, independence in daily activities, employment, driving, or treatment adherence.

**Acute stress reactions**

Emotional reactions may include anger, guilt, fear, denial, and despair. In many cases somatic symptoms,
### Table 3. Classification of HIV-associated neurocognitive disorders

<table>
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<tr>
<th>Asymptomatic neurocognitive impairment (ANI)</th>
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<tr>
<td>– Acquired impairment in cognitive functioning, involving ≥ 2 ability domains, documented by performance of ≥ 1 SD below the mean for age/education-appropriate norms on standardized neuropsychological tests including: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills.</td>
</tr>
<tr>
<td>– The cognitive impairment does not interfere with everyday functioning, or meet criteria for delirium or dementia.</td>
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<tr>
<td>– No evidence of another preexisting cause.</td>
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<th>Mild neurocognitive disorder (MND)</th>
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<tr>
<td>– Acquired impairment in cognitive functioning, as defined for ANI.</td>
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<tr>
<td>– At least mild interference in daily functioning, including ≥ 1 of the following:</td>
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<tr>
<td>• Self-reported reduced mental acuity, inefficiency in work, homemaking, or social functioning.</td>
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<tr>
<td>• Observation by knowledgeable others of at least mild decline in mental acuity, resulting in inefficiency at work, homemaking, or social functioning.</td>
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<tr>
<td>– The cognitive impairment does not meet criteria for delirium or dementia.</td>
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<tr>
<td>– There is no evidence of another preexisting cause.</td>
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<th>HIV-associated dementia (HAD)</th>
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<tr>
<td>– Marked acquired impairment in cognitive functioning, involving ≥ 2 ability domains (typically, multiple domains), especially in learning of new information, slowed information processing, and defective attention or concentration. The cognitive impairment must be ascertained by neuropsychological testing with ≥ 2 domains ≥ 2 SD than demographically corrected means.</td>
</tr>
<tr>
<td>– Marked interference with day-to-day functioning (work, home life, social activities).</td>
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<tr>
<td>– Does not meet criteria for delirium (e.g. clouding of consciousness is not a prominent feature); or, if delirium is present, criteria for dementia need to have been met on a prior examination when delirium was not present.</td>
</tr>
<tr>
<td>– No evidence of another, preexisting cause for the dementia (i.e. other CNS infection, CNS neoplasm, cerebrovascular disease, preexisting neurologic disease, or severe substance abuse).</td>
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SD: standard deviation; CNS: central nervous system.
Adapted from Antinori A, et al. 2007.

### Table 4. Penetration of antiretrovirals through blood-brain barrier

<table>
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<th>Penetration score</th>
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<tr>
<td>4</td>
</tr>
<tr>
<td>NRTI</td>
</tr>
<tr>
<td>NNRTI</td>
</tr>
<tr>
<td>PI</td>
</tr>
<tr>
<td>ENI</td>
</tr>
<tr>
<td>INI</td>
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*Boosted with low doses of ritonavir
NRTI: nucleoside or nucleotide reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor; ENI: entry inhibitor; INI: integrase inhibitor.
Adapted the CHARTER cohort study.

suicidal ideation or even attempts, substance abuse, and high-risk activities are associated. Acute stress reactions may occur in any phase of HIV infection, especially coinciding with changes in the individual's clinical stage. They are more common immediately after the diagnosis of the infection or at initiation of antiretroviral therapy. The management of psychological reactions is based on pre- and post-event counseling.
Adjustment disorders

These are defined as the inability to cope with or maladaptive reaction to an identifiable stressful life event (i.e. divorce, family crises, health problems). Symptoms must occur within three months of the stressor, and persisted for no longer than six months. The clinical picture may be dominated by symptoms of anxiety, insomnia, or depression.

Adjustment disorders, which normally follow a benign course, are rather frequent in HIV individuals (4-10%)\(^45,85-87\) and one of the most common diagnoses in those referred to mental health services (around 30%)\(^88\).

Anxiety disorders

Episodes of anxiety lasting for one to several months are frequent in HIV-infected patients. Its prevalence is significantly lower if rigorous criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR) are used, which require a minimum of six months of symptoms, and which may explain differences in prevalence across studies (4-40%)\(^40,43,85-89,93\). Symptoms of anxiety may increase HIV fatigue and physical functional limitations\(^84\). The rates of other major anxiety disorders in HIV patients, such as panic and obsessive compulsive disorders, do not appear to be markedly elevated above community standards.

Affective disorders

While periods of sadness, anxiety, or anger may be part of adaptation to or coping with HIV disease, major depression should never be tolerated as a normal reaction.\(^1\) In this second case, low mood may be accompanied by a constellation of symptoms such as anhedonia, hopelessness or guilt, neurovegetative symptoms, or thoughts of death. Recognizing depression in the context of HIV disease is often complicated by the overlap between physical symptoms and low mood, specifically fatigue, anorexia, insomnia, and pain. Major depression has been reported frequently in subjects with HIV infection, but estimates concerning its prevalence have been quite divergent (30-61%)\(^45,46,48-57\), always greater than in the general population (4-40%)\(^45,63\). When hospitalized patients or patients at advanced stages are considered, these rates may be much higher\(^95\). The evidence suggests that HIV-infected women are more likely to become depressed than HIV-infected men\(^96,97\). Depression has been associated with a lower likelihood of receiving antiretrovirals\(^98,99\) and poor adherence\(^100,101\), which leads to a worse outcome in HIV-infected persons\(^102-105\) and increased mortality\(^106\).

Suicidal ideation is common among HIV-infected persons. Also, there are an increased rates in autolysis attempts (21.4%) and suicide deaths (3.3%)\(^107-109\). The burdens of coping with the insidious onset of functional limitations related to advanced HIV disease and the ever-present threat of death may partially explain this elevated suicide rate among HIV-positive persons prior to antiretroviral therapy\(^110\). The suicide rate declined in the ART era, but still remains more than three-times higher among HIV-positive persons than in the general population\(^111,112\).

Some risk factors associated with suicide attempts in HIV patients are: (i) HIV-related symptoms, (ii) psychiatric morbidity or substance abuse, (iii) personal or family history of suicide, (iv) multiple losses in relation to HIV infection (v) insufficient support network, (vi) higher neuroticism scores, (vii) external locus of control, and (viii) current unemployment\(^107,113\).

Mania or hypomania (characterized by the presence of increased energy, decreased sleep, restlessness, pressured speech, flight of ideas, elevated, expansive, or dysphoric mood, delusions or hallucinations) may be the result of a bipolar disorder, substance or alcohol abuse, primary HIV encephalitis, progression to AIDS, or side effects of medications (i.e. zidovudine, ganciclovir, acyclovir, interferon, efavirenz, steroids, meperidine)\(^114-117\).

Rates for mania among HIV-infected individuals are similar to community samples during early HIV infection, but increase after the onset of AIDS to become the main cause for psychiatric hospitalization. Most cases of new-onset mania occur in advanced HIV disease and they are often associated with the presence of substantial cognitive impairment\(^118\). In addition, patients with secondary mania were significantly more likely to have paranoid delusions, visual and auditory hallucinations and pronounced irritable mood, with increased severity and persistent course besides cognitive slowing and dementia. Antiretroviral agents capable of penetrating the CNS have been shown to be effective for the prevention of manic reactions\(^119\).

Substance and/or alcohol use disorder

These diagnoses are not based on the type or quantity of the drug used, but on maladaptive patterns, cognitive, behavioral, and physiological symptoms, as...
well as significant consequences related to drug or alcohol use. Lifetime rates for alcohol use disorder in HIV patients are in the range of 22-64%, and for substance use disorders from 30-56%. The prevalence of any current substance abuse, including alcohol, has been set to be 20-73%.[40-43,85,87-92,120] Comorbidity with other mental disorders is common[85,121]. Substance abusers are prone to have high-risk sexual behaviors, as there is a higher rate of non-inhibition, impaired judgment, and impulsivity[122-125]. For these same reasons, they tend to be less compliant with antiretroviral regimens[126]. Also, substance and/or alcohol use can accelerate HIV disease progression[127]. Mounting evidence suggests that these patients have accelerated and more severe neurocognitive dysfunction compared with non-drug abusing HIV-infected populations[12,128].

Alcohol can modify the pharmacokinetics of antiretrovirals by multiple mechanisms, including altering gastric emptying, changing liver P450 metabolism, or reducing liver function through fibrosis, which mostly affect protease inhibitors and nonnucleoside analogs by reducing their plasma levels[129-131]. Abacavir and ethanol share alcohol dehydrogenase in their metabolic pathway, with an elevation in the half-life of the antiretroviral[132]. Alcohol may potentiate the hepatotoxic profile of nevirapine, particularly in patients with chronic viral hepatitis[133]. Illicit drugs may affect the pharmacokinetics of alcohol by altering gastric emptying and inhibiting gastric alcohol dehydrogenase. However, alcohol dependence should not be a contraindication for the prescription of antiretrovirals[139].

Antiretrovirals also interact with other drugs of abuse. Overdoses secondary to interactions between the “rave” drugs methylene-dioxy-methamphetamine (MDMA) or γ-hydroxybutyrate (GHB) and protease inhibitors have been reported. These antiretrovirals may also inhibit metabolism of amphetamines, ketamine, lysergic acid diethylamide (LSD), and phencyclidine (PCP). Interactions between cocaine and antiretrovirals have not been described. No significant interaction between tetrahydrocannabinol (THC), the active principle of smoked marijuana, and antiretrovirals has been described[129,134].

Other mental disorders

HIV infection is a risk factor for sexual dysfunction (39-59%)[40,135-137], primarily due to a higher risk of erectile dysfunction in men with AIDS[138,139], but also comprises in almost all cases hypoactive sexual desire disorder (97%)[40,139]. Psychotic symptoms may be part of a major depressive disorder, schizophrenia, mania, obsessive-compulsive disorder, or secondary to drug or alcohol abuse, CNS complications, or medications[140]. Psychotic disorder, with a prevalence of 0.2-15%, is found most often in late stages of the disease, particularly in subjects with neurocognitive disorders[87,141-143].

Personality disorders are often an associated diagnosis, which can be detected in up to 30% of HIV-positive subjects[144-146]. Borderline, antisocial, dependent, histrionic and not otherwise specified are in this order the most frequent personality disorders among HIV individuals[30,144-146]. Evidence suggests that the presence of personality traits or disorders may potentiate risk of HIV infection and transmission, adversely affect adherence to HIV treatments, and contribute to disease progression[121,147].

Sleep disorders, primarily insomnia disorders, are prevalent in the HIV population[148,149]. Poor quality of sleep is associated with higher levels of depression, anxiety and physical symptoms, daytime sleepiness, and functional impairment[150,151]. Some possible causes of sleep disorders are: (i) certain compounds (efavirenz, zidovudine, testosterone therapy, new antidepressants, ephedrine, ginseng)[152], (ii) recreational substances (caffeine, alcohol, amphetamines, cocaine), (iii) HIV-associated neurocognitive disorder, (iv) mental disorders, (v) stressful life events or, (vi) medical conditions (i.e. pain, sleep apnea). A polysomnographic study of patients with HIV compared to uninfected controls revealed HIV-infected patients to have longer sleep onset latency, shorter total sleep time, reduced sleep efficiency, more time spent awake, more time in stage 1 sleep, and decreased REM latency, which correlated with increased levels of depression[153].

Triple diagnosis

Patients with a dual diagnosis (substance abuse and another psychiatric disorder) have more frequent and more severe psychiatric symptoms, which are associated with negative outcomes, such as poorer adherence and more frequent hospitalization[154-157]. We define triple diagnosis as dual diagnosis added to HIV infection[158], with a prevalence of 26-79%[141,159].

Conclusions

HIV infection is associated with a high prevalence of neuropsychiatric disorders. Many of these conditions show differential clinical features as compared with
HIV-uninfected individuals. Current HIV management needs multidisciplinary teams with the incorporation of mental health specialists, for early detection and treatment of neuropsychiatric disorders. Particular attention should be paid to substance abuse, triple diagnosis, and HIV-associated neurocognitive disorders. Appropriate psychiatric interventions may also contribute to prevent the spread of HIV from and among the mentally ill.

References


