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AIDS Rev. 2023;25:41-53

The new profile of psychiatric disorders in patients with HIV infection

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Abstract

Nowadays, HIV infection is largely considered as a chronic condition rather than a deadly disease, given that effective antiretroviral treatment allows almost complete and persistent suppression of viral replication and restoration of nearly normal CD4+ T-cell counts. Being HIV a "condition", we imply that other illnesses are more frequently seen in persons living with HIV (PLHIV), among which mental health disorders are particularly common. Despite very successful antiretroviral therapy, HIV infection may still cause a wide range of neurocognitive dysfunctions and accelerated brain ageing. Beyond direct viral effects, at least another five causes of neurological damage are more frequent among PLHIV. First, the use of neurochemical substances as sexual boosters (chemsex) has become popular in this population. Second, the rate of sexually transmitted infections as syphilis, which may affect the central nervous system, is more prevalent among PLHIV. Third, the use of certain antiretroviral drugs, such as efavirenz, has been associated with changes in mood and/or psychotic symptoms. Fourth, an increased rate of mental disorders has been reported in PLHIV, either as predisposing conditions or following the recognition of HIV diagnosis (i.e., major depression). Finally, psychosocial factors such as loneliness, isolation and stigmatization are more frequent in PLHIV and worsen their mental health. Given that the life expectancy of PLHIV has increased significantly, a new and much broader spectrum of psychiatric disorders has emerged in PLHIV. Early diagnosis and adequate management, including education and preventative interventions are warranted.

Keywords

Mental disorders. Depression. Chemsex. Substance abuse. Neurocognitive disorders. Psychosocial factors. HIV. Antiretroviral therapy.

Introduction

Mental illness makes individuals more vulnerable to HIV infection and/or acquiring other sexually transmitted diseases[1,2]. The other way around, the proportion of mental and substance abuse disorders among people living with HIV (PLHIV) is nearly 5 times greater than in the general population[3]. Despite the impressive reduction in HIV-related morbidity and mortality that highly active antiretroviral therapy (HAART) has gained, mental disorders continue to depict a high prevalence among PLHIV. Furthermore, a new and much broader range of conditions have emerged in recent years,

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Received in original form: 15-12-2022
Accepted in final form: 24-01-2023
DOI: 10.24875/AIDSRev.22000030

largely as result of exposure to risk factors and aging of this population.

The aim of this review is to raise awareness of mental health issues among HIV health professionals. Chronic diseases such as nowadays HIV infection have a well demonstrated impact on mental health. Added to the specific harm caused by HIV itself on neurocognitive function, strong data have appeared supporting a role for persistent immune activation and chronic inflammation, long-term exposure to meds, interference with social life and stigmatization, and specially the increasing use of substance abuse. Despite huge scientific advances in HIV medicine, the attention on mental disorders in PLHIV has been poor to date. Improvements in this area might result in a better quality of life of patients and favors HIV prevention and treatment.

The spectrum of mental disorders in HIV-infected patients

Severe systemic diseases are burdened with a high prevalence of mental disorders that can rise to 30-50%. Although HIV-infected patients under antiretroviral therapy (ART) infrequently suffer nowadays any acute organic complication, the long-term consequences of this infection places them at greater risk for psychiatric conditions as compared to the general population. Prevalence estimates for psychiatric disorders in PLHIV currently range between 5% and 60%, with variations depending on study designs, diagnostic methods or populations examined[3]. Of note, many of these individuals are currently diagnosed with substance use disorders[4] or had been diagnosed of cognitive impairment at earlier stages. Altogether, this can make the management and treatment of mental health abnormalities more challenging in PLHIV.

Chemsex and HIV infection

Over the last decade, "chemsex" (referring to chemicals used for the enhancement of sexual activity) has become a rising phenomenon in the community of men that have sex with men (MSM)[5,6]. The most common drugs used for chemsex experiences are combinations of crystal methamphetamine, mephedrone, gamma-hydroxybutyrate/gamma-butyrolactone (GHB/GBL) and, to a lesser extent, ketamine, and cocaine. They can be used planning to or during sexual contacts. When the administration of these drugs is done using intravenous or intramuscular injections, the term "slamming" or "slamsex" is used[7].

The prevalence of chemsex practices varies widely between different countries. Rates ranging between 3% and 29% have been reported; however, controversy exists about the reliability of these figures since sample populations are always extracted from large urban areas and frequently from patients attending sexual health clinics[5]. Anyway, chemsex has dramatically increased significantly over the last two decades.

Why a behavior with such harmful health consequences has such a high prevalence today? Mitchie et al.[8] developed a "behavior system" model to explain it, where capability, opportunity and motivation interact to generate a behavior that, in turn, fuels such risky behaviors. Opportunity is defined by all factors outside the individual that make the behavior possible or provoke it. In the case of chemsex, opportunities might include the availability of drugs, the physical spaces in which to engage (e.g., bars, cafes, discotheques, and bathhouses), and the new methods of contact that enable easy social connections, like the geospatial mobile phone app or internet based social networks. Sexual behavior is learnt, both in terms of social norms and procedures, and physical acts and techniques. Capabilities refer to the psychological and physical capacities required to conduct a behavior, which range from self-confidence to participate in group sex, to the ability to maintain an erection over prolonged sexual periods. Gay men using crystal meth at gay circuit parties in Miami highlighted the instrumental use of drugs in reducing body image anxiety, losing sexual inhibition, and facilitating social and sexual connection[9]. Drugs can be used to remove the obstacles that make these men less able to have the sex they want. Finally, motivation refers to the internal drive for a behavior. Motivations may be automatic, unmediated by conscious thought, or reflective, but always involve taking a decision and forming an intention. According to Weatherburn et al.[9] the first group of motivations for combining drugs with sex was that drugs provide these men the spirit to have the sex they desire by increasing libido, confidence, disinhibition, and stamina. The second group of motivations for promoting chemsex is that drugs enhance the qualities of the sex that these men value. Drugs make other men seem more attractive, increase physical sensations, intensify perceptions of intimacy and facilitate a sense of sexual adventure. A given clinical intervention must change one or more components of this behavioral system to become effective.

Participants may seek the desirable effects of drugs, but the disinhibiting effects may increase the level of

risk-taking behavior which subsequently may produce undesirable consequences. Although chemsex and slamsex are associated to risky sexual behaviors, they are linked to poor adherence to HIV medication and therefore may facilitate the spread of HIV and other sexually transmitted infections (STI), as seen in a follow-up study of new HIV cases among gay and bisexual men in London and Brighton. According to this Hanum et al.[10], only 3% of MSM reported injecting drugs, largely in a chemsex context, but 16% of them subsequently tested positive for HIV. Another study conducted in London collected data from anonymous self-administered questionnaires to MSM at two time points, in 2013 (n = 905) and in 2016 (n = 739)[11]. Compared to other MSM, those who participated in chemsex sessions were more likely to report HIV/STI risk behaviors within the last year, including condomless anal intercourse with HIV serodifferent partners.

The increased risk of HIV infection may be associated to the use of injected drugs such as methamphetamine. However, even without injections, drug use increases the likelihood of HIV infection or other STI, as it decreases judgment and increases impulsivity, favoring unprotected sex.

Another possible mental health consequence of chemsex is that drug effects sometimes lead to unconsciousness, making users vulnerable to sexual assault, criminal acts, or just non-consensual sex (NCS). The prevalence of NCS is known to be higher among homosexual and bisexual men compared to heterosexual men[12]. Drückler et al.[13] carried out a survey on chemsex and NCS among users of a gay dating app in Amsterdam. In this study, the overall prevalence of NCS was 18% in the past 5 years. Participants engaging in chemsex and those who did not did not differ in NCS rates in the past 5 years (58 of 237, 21.2% vs. 103 of 618, 16.7%; p = 0.109). However, when the analysis was restricted to the last year, 12.5% of chemsex users reported NCS, as compared with only a 6% of non-chemsex users (p = 0.002). Overall, participants who experienced NCS were younger (median 33 vs. 40 years old; p < 0.001), were more often crystal methamphetamine users (15.5% vs. 8.5%; p = 0.009) and reported more frequently intravenous drug use (6.2% vs. 2.1%; p = 0.008) compared with participants who did not experience NCS. Most participants in this study who had NCS reported little to no emotional distress afterwards. Among men who engage in chemsex, sexual consent can be experienced as complicated and vague, whereas the lack of distress with NCS may produce their acceptance of this ambiguity. Although sexual consent may be viewed as a human right, when drugs are involved, sexually transgressive behavior seems to occur more easily associated to Chemsex.

Those who engage in chemsex are exposed to a wide array of physical, psychological, and social adverse effects, such as the tendency to lose sleep, even staying awake for days without eating. Hospitalization may ensue on account of prolonged drug use or overdosing, that can also lead to the development of mental health issues and even neurological complications such as convulsions, stroke, coma, and death.

Driving under the influence of stimulant drugs is considered another risk behavior. Chemsex users may become addicted to these practices, what may take up a large amount of their time, in both participation and recovery from the effects of drug use. This level of dependence has negative social and laboral consequences in many instances. The unfolding of the chemsex scenario is bound to negatively affect social interrelationships and connections, as well as the ability to find or maintain gainful employment[14].

It is well known that MSM are at higher risk for a variety of mental health problems, such as depression, trauma and substance use, compared to heterosexual men[15,16]. Several studies have examined whether the practice of chemsex among MSM can negatively influence their mental health. Regarding possible associations between chemsex practices and mental health, Bohn et al.[17] conducted a survey in Germany based on a self-completed online questionnaire administered to chemsex users in the MSM community. A total of 1583 men participated, and 1050 provided information on substance use. Overall, 27% of participants (n = 280) reported that they had used methamphetamine, mephedrone, GHB/GBL, and/or ketamine in a sexual context within the past 12 months. Chemsex users showed significantly higher mean scores for depression (PHQ-9), anxiety (GAD-7), and somatization (PHQ-15) symptoms than non-chemsex users measured by scales. Although mean scores were high, they were still below the cutoff point for clinically relevant symptoms. Chemsex users reported significantly higher rates of NCS compared to non-chemsex users. Furthermore, some men using chemsex experienced adverse consequences, such as loss of money or job (49.6%), negative impacts on social functioning (33.6%), psychotic symptoms (13.2%), and physically aggressive behavior (2.9%). A last consideration refers to the recent evidence suggesting that chemsex seems to be beginning spreading among heterosexual persons having sex with multiple partners. Moreover, the

use of opiate derivatives for sexual intercourse is also on the rise in this population[18] (Fig. 1).

Substance abuse and HIV infection

Despite the increased life expectancy of PLHIV, certain personal features may impact on their health care and health-related quality of life. In this regard, substance use is an important caveat. A review on recreational drug use among PLHIV in Europe has shown that consumption rates above 50% are seen among MSM, ranging from 5.5% to 82.4%[19,20]. The ASTRA study found that 51% of 2,248 HIV+ MSM in the UK had used recreational drugs within the previous 3 months[21]. The EMIS study conducted in Spain showed that poppers (56.2%), cannabis (41.9%), cocaine (38.2%), sildenafil (32.9%), ecstasy (24.2%), and GHB/GBL (18.9%) were among the substances more frequently consumed by MSM living with HIV[22]. In contrast, the current rate of PLHIV using traditional intravenous drugs, such as heroin or crack cocaine, is lower. Trends on drug use suggest that either fewer people are taking these drugs nowadays or users have switched to new drugs[23]. Therefore, HIV and stimulant drugs have become a "double epidemic", being MSM the population at increased risk[24].

Substance use may have a negative impact on HIV care and prevention. A negative effect of illicit drug use on HIV disease pathogenesis, the acquisition of STIs and low adherence to antiretrovirals have all been reported[25].

Amphetamine-type simulants (ATS) are the second most commonly used class of illicit drugs worldwide[26]. In the period 2015-2019, methamphetamine accounted for 72% of the total amount of ATS seized globally, followed by amphetamine (19%) and "ecstasy" (4%). The rest (5%) was represented by other stimulants, including former synthetic new psychoactive substances (NPS) such as mephedrone, methylenedioxypyrovalerone (MDPV), and methylone (0.5% of total)[26,27].

Methamphetamine is a potent central nervous system (CNS) stimulator and has pervasive effects not only on the dopaminergic system, but also on noradrenergic, serotonergic, and opioidergic neurotransmitter systems throughout the brain. It is through the culmination of these complex neurochemical modulations that significant behavioral and cognitive changes result. The clinical response to methamphetamine administration at low to moderate doses (5-30 mg) includes euphoria, arousal, reduced fatigue, positive mood, tachycardia, hypertension, pupil dilation, peripheral hyperthermia, reduced appetite, behavioral disinhibition, short-term improvement in cognitive domains, and anxiety[28].

Psychotic symptoms are frequently experienced among individuals who use methamphetamine, with recent estimates of up to 40% of users. The prevalence of this disorder has increased in several countries. Although transient in a large proportion of users, acute symptoms can include agitation, violence, and delusions, and may require management in an inpatient psychiatric or other crisis intervention setting. In a subset of individuals, psychosis can recur and persist and may be difficult to distinguish from a primary psychotic disorder such as schizophrenia. The pharmacological treatment of acute methamphetamine-induced psychosis may include the use of antipsychotic medications as well as benzodiazepines, although symptoms may resolve without pharmacological treatment if the user is able to achieve a period of abstinence from methamphetamine. Importantly, psychosocial treatment for methamphetamine dependence has a convincing evidence base, and is the optimal first-line treatment approach to reducing rates of psychosis among individuals who use methamphetamines. Prevention of methamphetamine relapse is the best approach for preventing recurrence of psychotic symptoms. Long-term management of individuals who present with recurrent and persistent psychosis, even in the absence of methamphetamine use, may include both behavioral treatment to prevent resumption of methamphetamine use and pharmacological treatment targeting psychotic symptoms[29,30].

Methamphetamine can be highly addictive; when people stop the use of this drug withdrawal symptoms can include anxiety, fatigue, psychosis, intense drug cravings, and severe depression[27,28]. Depressive symptomatology has been considered the hallmark of methamphetamine withdrawal, with depressive symptoms lasting beyond two weeks of abstinence[31]. Suicide attempts or completed suicide may be a consequence of this "rebound" depression[32].

Repeated exposure to moderate to high doses of methamphetamine has been related to neurotoxic effects on the dopaminergic and serotonergic systems, leading to potentially irreversible loss of nerve terminals and/or neuron cell bodies, or astrocytosis and microgliosis[33,34]. Neurotoxic effects have been associated with behavioral and cognitive changes, such as memory and attention deficits, executive deficits, impaired psychomotor coordination, and increased aggression[27,33].

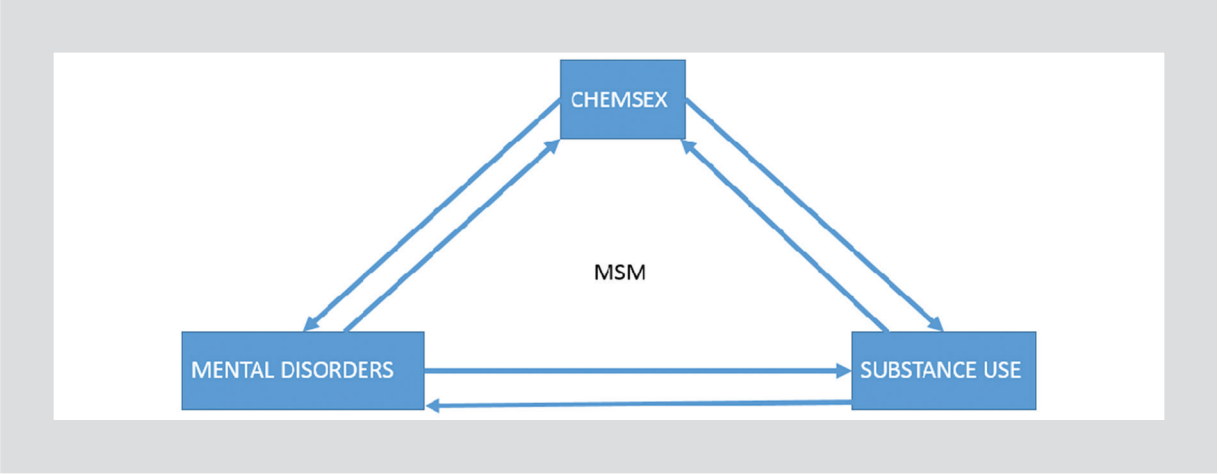

Figure 1. *Relationships between psychoactive drugs and sexual practices in people living with HIV, mostly men having sex with men. MSM: men who have sex with men.*

All ATS have similar acute and long-term effects, although here we preferentially describe methamphetamine as it is the most widely used[35,36]. The use of ATS, whether or not associated with chemsex, may be another factor in addition to the neurotoxicity of HIV itself or of certain antiretrovirals converging to cause the premature brain aging often seen in these patients.

Another drug frequently used by persons infected with HIV is GHB, also known as Fantasy, "Liquid Ecstasy" or G. Its use among gay and bisexual men has dramatically increased during recent years, as GHB is commonly regarded as a sexual-enhancement drug, causing euphoria, loss of inhibition, amnesia, and drowsiness[37]. A prospective observational study in Australian gay and bisexual men found that 19.5% of them had a history of GHB use. Overdose was reported by 14.7% of users and was more common among men who used GHB at least monthly. The abuse of GHB carries the risk of several severe adverse effects such as sedation, respiratory depression, hypothermia, coma, and even death[38].

Finally, reports of serious health effects secondary to the use of alpha- pyrrolidinovalerophenone (PVP) in the context of chemsex are on the rise. Also known as "Flakka," this is a psychoactive substance with stimulant effects. It belongs to the group of cathinones and depicts similarity with MDPV. It has a differential feature with respect to other ATS: the duration of effects may be shorter than expected. Therefore, users may repeat doses in short periods of time, thus increasing the risk of intoxication and/or death. Due to its potential euphoric highs, Flakka is known to provoke frightening delusions, paranoid psychosis and extreme agitation, among many other acute mental disorders[39,40]. It has also been linked to NCS[41].

Major depression (MD) and HIV infection

Within the HIV population, MD is the second most common psychiatric disorder, following substance abuse. MD has been reported frequently in PLHIV, but estimates concerning its prevalence have been quite divergent (from 30% to 61%), but always greater than in the general population (4-40%), in primary care settings or in subjects with other chronic medical illnesses[3]. A higher prevalence of MD has been observed in organically symptomatic versus non-symptomatic patients[42]. MD in PLHIV also impairs quality of life and adherence to or efficacy of ART[43]. MD increases the risk of acquiring HIV and of viral transmission through intensification of substance abuse and exacerbation of self-destructive behaviors, such as exposure to an increased number of sexual partners and lack of condom use. Patients with MD are also at increased risk for HIV disease progression and mortality[44].

The diagnosis of MD in HIV-infected patients is specially complicated by the high frequency of depressive symptoms associated with chronic illness, personal loss and isolation, medical treatments that may alter the mental function, comorbid neurologic illnesses, and substance abuse. HIV-associated dementia and other HIV-related CNS conditions can produce a flat, apathetic state often misdiagnosed as depression. In turn, the differential diagnosis in PLHIV reporting depressive symptoms includes MD, dysthymia, dementia, delirium, demoralization, intoxication, withdrawal, CNS injury,

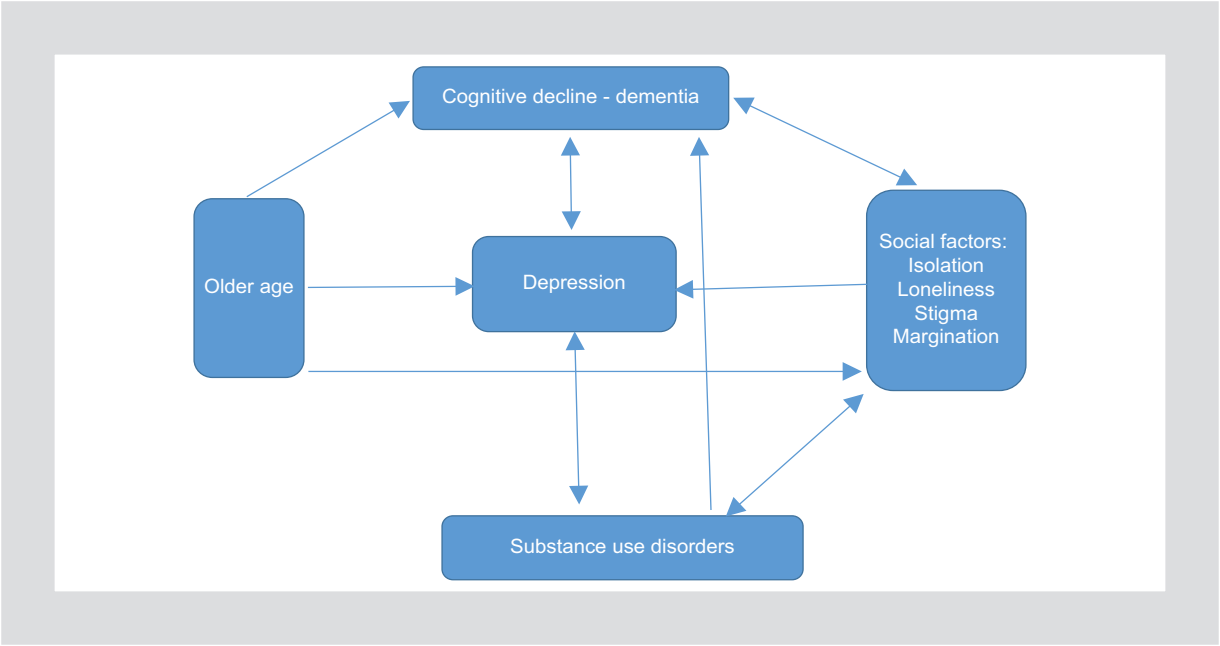

Figure 2. *Interconnections among mental disorders and HIV infection.*

CNS infection, and acute medical illness. Given that nearly 40 million people worldwide are infected with HIV[45], and that treatment with ART and control of HIV replication does not diminish the risk of depression in PLHIV, there is an urgent need to identify factors that might be targeted to prevent and treat depression in PLHIV, which is often underdiagnosed and undertreated, what favors the risk of chronicity and recurrence.

It is well-established that specific psychosocial factors contribute to higher rates of depression among PLHIV. HIV-infected individuals may suffer from isolation, lack of social support, stigmatization, discrimination, social attitudes adverse to homosexuality, violence, hopelessness, and drug abuse, all of which can contribute to depression[44] (Fig. 2).

Chronic inflammation has been postulated as an important pathophysiological factor in the pathogenesis of depressive disorders. Persistent cellular immune activation occurs in HIV infection, both at the level of the peripheral nervous system and the CNS[46]. Despite the relationship between MD and inflammation, and of MD and HIV infection, the association between chronic inflammation in PLHIV and its high prevalence of MD has not been explored in depth. Patients with major depressive disorder show increased expression of pro-inflammatory cytokines and their receptors, as well as increases in acute phase reactants such as C-reactive protein (CRP). Furthermore, experimental data show that acute activation of inflammatory signaling and the induction of inflammatory cytokines causes depressive symptoms in otherwise nondepressed adults. Moreover, a blockade of inflammatory pathways reduces depressive symptoms in patients with inflammatory disorders such as rheumatoid arthritis, psoriasis, and cancer, as well as in patients with major depressive disorder who have elevated levels of inflammation prior to treatment. Together, these findings raise the possibility that increases in inflammation take part in the pathogenesis of depression. Indeed, epidemiologic studies demonstrate that higher levels of markers of systemic inflammation such as interleukin-6 and CRP prospectively predict the development of depressive symptoms in otherwise healthy adults[46]. Given the association between inflammation and MD, it has been hypothesized that control of inflammation may provide therapeutic benefit in the overall treatment of MD, regardless of whether it is secondary to early life trauma, more acute stress response, alterations in the microbiome, a genetic predisposition, or a combination of these and other factors[47].

Despite the effectiveness of ART in blocking viral replication, PLHIV still present low-level chronic immune activation and inflammation. Systemic persistent immune activation is considered today as the driving force for CD4+ T-cell depletion. Unfortunately, the

causal link between chronic immune activation and CD4+ T-cell loss has not been formally established. This condition is the result of several factors, including thymic dysfunction, persistent antigen stimulation due to low residual viremia, microbial translocation, and dysbiosis, caused by the disruption of the gut mucosa, co-infections, and cumulative ART toxicity. All of these factors can create a vicious cycle that does not allow the full control of immune activation and inflammation, leading to an increased risk of developing non-AIDS co-morbidities[48], among which MD could be found. HIV infection can predispose to depression by several interrelated mechanisms. These include inducing chronic elevation of cytokines through activation of microglia and astrocytes; decreasing monoaminergic function; inducing neurotoxicity, especially in dopaminergic neurons; and reducing brain-derived neurotrophic factors. These viral pathways interact with psychosocial factors to create the depressive state[49].

While there is robust evidence for independent associations between these three conditions (HIV, mental disorders, and chronic inflammation), few preclinical or clinical studies have attempted to characterize their interrelationship, representing a major gap in the HIV medical literature.

The association between depression and worsening of cognitive function is another major subject of interest. Given that PLHIV currently show a higher life expectancy, a higher risk of neurodegenerative processes is a matter of concern. Executive functioning, memory and verbal fluency are negatively affected by long-term depression. Paolillo et al.[50] conducted a study aimed at examining the longitudinal associations between depressive symptoms and cognitive functioning among PLHIV. The investigators included 448 PLHIV followed longitudinally through several visits to assess possible depression and its severity (using the Beck Depression Inventory-II scale) and neurocognition (using full test battery). Participants were classified into with low (67%), medium (15%), and high (18%) depression burden. Multilevel modeling examined associations between depression burden and neurocognition over time. The study showed that acute depression had an impact on key aspects of cognitive function, including cognitive function, motor skills, and speed of thought.

One of the mechanisms by which depression causes greater cognitive impairment may be that when depressed, one engages less in intellectual, physical and socially stimulating activities, all of which are known to protect against cognitive decline in the elderly. In addition, depressed patients take less care of themselves, and this may have a negative impact on PLHIV and their healthcare[50]. More research is needed to examine how treatment for depression affects the cognitive, mental and physical health of PLHIV.

Premature aging and HIV-associated neurocognitive disorders

The Centers for Disease Control estimated that 42% of Americans living with HIV are at least 50 years-old, 25% are 50 to 55 years-old, and 6% are 55-65 years-old[51]. With longer life expectancy, PLHIV are at greater risk of developing age-related metabolic, cardiovascular, neoplastic, and neurodegenerative disorders than the general population, given the added harm of HIV on the CNS.

Before the availability of ART, HIV-associated dementia resulting from the effects of uncontrolled HIV infection on the brain was one of the most frequent diagnoses among PLHIV. Typically occurring in patients with advanced HIV disease, prognosis was often poor, with a median survival of 6 months following diagnosis of dementia. In the context of suppressive ART, HIV-associated dementia (HAD) is rare[52]. However, cognitive impairments are common in patients with HIV infection. Since these symptoms can be caused by a variety of disorders, a correct diagnosis is critical. When not attributable to an alternative cause other than HIV infection, such impairments have been collectively classified as HIV-associated neurocognitive disorders (HAND). They include a wide range of deficits defined by performance on standardized neuropsychological tests and impact on activities of daily living.

In general terms, HAD refers to severe neurocognitive deficits that lead to substantial functional impairment. Milder deficits are termed mild neurocognitive disorder if they lead to minor symptoms or impairment. Asymptomatic neurocognitive impairment refers to lack of any recognizable symptom. The definitions are applied only when the observed impairment cannot be explained by other conditions, either alternative neurological diagnoses (such as opportunistic infections, stroke, metabolic, or toxic encephalopathy) or underlying “confounding” comorbidities that might alter neuropsychological test performance (e.g., severe substance abuse, prior head trauma, hepatitis C virus coinfection with advanced liver damage, and severe psychiatric disease)[52].

HAD in its classic form, is primarily characterized by subcortical dysfunction, with attention-concentration

impairment, substantial memory deficits, impaired executive functioning, impaired psychomotor speed and precision, mental slowing, apathy, and lack of motivation. Patients with HAD may also display irritable mood, sleeplessness, weight loss, restlessness, and anxiety. Although these changes may be attributed to depression, patients with HAD are not typically dysphoric, and lack crying spells or reported sadness. However, mood changes associated with HAD may progress to psychosis with paranoid ideas and hallucinations. Furthermore, a small proportion of patients with HAD may develop mania[53].

With the introduction of ART, the pathology of HAD has shifted from subcortical regions towards a cortical pattern[54] and from a subacute, rapidly progressive disorder to a more subtle, chronic neurodegenerative process; viral levels in the CNS are now usually low or undetectable.

An estimated 30-50% of PLHIV have some degree of cognitive impairment (HAND) despite the effectiveness of ART in suppressing HIV replication. The reasons for persistent cognitive impairments among PLHIV are not entirely clear but may reflect the combined influences of chronic HIV-mediated inflammation in the CNS, lasting effects of prior HIV-related damage, as well as non-HIV factors such as substance use, cardiovascular disease, and psychiatric conditions, all of which are more prevalent in HIV populations[55,56]. As PLHIV become older, another hypothesis might be considered. HIV infection might lower the threshold for clinical presentation of age-associated neurodegenerative disease, resulting in neurocognitive dysfunction at younger ages.

Several studies have suggested that older PLHIV may experience premature or accelerated cognitive decline and greater neurocognitive morbidity than their HIV-uninfected counterparts[57,58]. According to a U.S. study by Lam et al.[52], the risk of dementia in old age increases by 58% for PLHIV compared to their HIV-negative peers, even after accounting for medical and psychiatric comorbidities and other risk factors for dementia. The authors conducted an observational cohort study of patients at an integrated health-care delivery system in California from 2013 to 2019. Participants were PLHIV on ART, ≥ 50 years old and with no prior diagnosis of dementia. Incident dementia diagnoses and baseline data on sociodemographic, smoking, alcohol use, other substance use, and clinical factors were gathered from electronic health records. The average age at the time of the diagnosis of dementia was much younger for PLHIV (67 years-old compared to 78 years old for non-HIV persons). They concluded that age-related dementia should be an increasingly important concern for PLHIV. Younger age at dementia onset among PLHIV could result in substantial health burden, reducing the benefits of improved longevity achieved with ART. Additional research on risk factors for dementia among PLHIV may help identify strategies and priority targets for dementia prevention beyond ART use alone.

A recent study Moulignier et al.[59] has advocated that HIV is an independent risk factor for silent cerebral small-vessel disease (CSVD); this entity is defined as white matter hyperintensities (WMH), silent brain infarction, or microbleeds. CSVD is responsible for future vascular events, cognitive impairment, frailty, and shorter survival. Moreover, it is the second etiology of dementia. Impact of CSVD on cognition depends on the location of lesions. Age and hypertension are known risk factors, but their association with HIV infection has not been investigated to date.

The French Microvascular Brain, Retina and Kidney Study is a cross-sectional study with prospective enrolment of treated PLHIV (n = 456). All patients are ≥ 50 years-old with HIV-RNA levels in plasma suppressed for ≥ 12 months. There is an age- and sex-matched HIV-uninfected control group (n = 154). It was designed to estimate CSVD prevalence on 3T magnetic resonance imaging. The study found that despite sustained immunovirological control, the CSVD prevalence was twice as high among middle-aged PLHIV than controls. The increasing risk of CSVD was not associated with exposure to any ART class[60].

Many case studies have suggested that small infarcts in the internal capsule, thalamus, and caudate nuclei leads to marked cognitive impairment, with damage in executive functions, language and visual construction. Depressive symptoms are also a major clinical manifestation of CSVD. However, they are largely poorly investigated[61]. WMH, lacunar infarcts, and multiple lobar cerebral microbleeds are associated with more severe depressive symptoms. Loss in white matter integrity is directly related to depressive symptoms in CSVD patients[62,63].

The contributions of HIV and CSVD on brain atrophy and cognitive impairment seem to be independent but act as an additive process. Sanford et al.[64] carried out a cross-sectional analysis of 119 treated, virologically suppressed HIV-positive and 55 HIV-negative participants. Forty-six HIV-positive and 30 HIV-negative participants were evaluated 2 years later. All participants underwent MRI and neuropsychological testing. WMH

was used as a surrogate measure of CSVD severity. Initial WMH loads and change in WMH loads were similar between the groups. However, HIV-positive participants had poorer cognition, thinner cortex and reduced subcortical volumes compared to HIV-negative controls. Higher WMH loads were associated with reduced cortical thickness and subcortical volumes and worse cognition, regardless of HIV serostatus. No significant interactions were observed between HIV and WMH loads with regard to brain volumes or cognition. This argues that optimizing vascular health may mitigate brain injury and cognitive decline, especially in virologically suppressed PLHIV on ART. In this regard, it is worth noting that protease inhibitors (PI)-based ART might be associated with more severe CSVD compared to non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART[54].

In conclusion, HIV can cause a wide variety of cognitive and motor deficits, even in the absence of opportunistic infections or malignancies that are typical of AIDS. The deleterious effects of certain ART on the CNS, psychiatric comorbidities, the consumption of substances, hepatitis C and metabolic, cardiovascular, carcinogenic, and neurodegenerative effects of aging, altogether may act synergistically to produce premature brain aging in PLHIV.

Social isolation, loneliness, marginality, and stigmatization in PLHIV

Socially disadvantaged and marginalized people are overrepresented among PLHIV (poor economical status, ethnical minorities, sexual minorities, drug users, sex workers, etc.), and they are at a greater risk for mental disorders, even before contracting HIV infection[65].

In clinical practice, we frequently see that HIV infection can lead to reduced socioeconomic status due to multiple factors, including impaired mental health. Quite often, our patients end up alone, living in marginalized environments or even in extreme destitution, far from good social, occupational, family or interpersonal functioning. In many developed countries, there are no specific social and health-care resources for attending this population with mental disorders.

Social isolation and loneliness are receiving ramping interest in the scientific community because of their impact on health. The prevalence of social isolation is increasing in contemporary societies and carries an underestimated impact on human health. Social isolation refers to objective measurable characteristics resulting in interpersonal disconnectedness: a lack of engagement with peers and the larger community. This construct is distinct from that of loneliness, which refers to subjective feelings of isolation, suggesting that loneliness and social isolation do not necessarily co-occur and should be addressed independently. Adverse consequences of isolation include lower self-rated physical health, poor mental health outcomes, chronic inflammation, cardiovascular disease and an overall increase in the likelihood of death[66,67].

The impact of social isolation in PLHIV has been poorly studied; this situation may be exacerbated by the new challenges of infection in the XXI century, such as an increased risk of frailty due to the aging of PLHIV that may make it difficult to participate in social activities; experienced or perceived stigma and discrimination that impede the establishment of social networks; and the loss of family members and friends resulting from HIV infection or simple aging. These factors can be especially detrimental in PLHIV.

Marziali et al.[68] examined the association between social isolation and mortality among a cohort of PLHIV experiencing multiple social vulnerabilities. The study population included 936 PLHIV of ≥ 19 years of age living in British Columbia, Canada, who were enrolled in the Longitudinal Investigation into Supportive and Ancillary Health (LISA) Study (2007-2010). Participants were classified as either socially connected, minimally isolated, or socially isolated (SI). Cross-sectional survey data were linked to longitudinal clinical data from a provincial HIV treatment database. They found an association between SI and all-cause mortality (adjusted OR: 1.48; 95% CI: 1.08-2.01). These results emphasize the need to mitigate the effects of social isolation among PLHIV.

Loneliness is one manifestation of inadequate social relationships and has been defined as the distress that accompanies a perceived mismatch between desired and actual social relationships. Being alone is not the same as being lonely; growing evidence has linked loneliness to various adverse health outcomes. Loneliness is associated with unfavorable cardiovascular health indicators, such as increased activation of the hypothalamic-pituitary-adrenal axis, high blood pressure, increased cholesterol levels, and coronary heart disease. Loneliness is associated with sleep disturbance and increased risk of mild cognitive impairment and dementia. Loneliness may also be detrimental to behavioral, mental, and social health throughout the lifespan, influencing outcomes such as substance misuse, suicidal ideation, anxiety, depression, and

poor subjective wellbeing. According to a 2015 meta-analysis, people with chronic loneliness had a 26% increased risk of mortality[69]. This increased risk is comparable to set up risk factors such as physical inactivity and obesity[69,70].

Large national surveys have defined epidemic levels of loneliness in the US. Longitudinal surveys over decades have reported that almost half of Americans either sometimes or always felt alone or left out, and that a quarter rarely or never feel that there are people who really understand them. Social networks have also become smaller with increasing numbers of people having no significant person that they discuss important matters with (from 10% in 1985 to 18% in 2018)[71].

Being HIV-positive can exacerbate loneliness issues for many long-term survivors and even aggravate their health problems, an issue that has not yet been sufficiently pointed out. Greene et al.[72] conducted a cross-sectional study among HIV-positive adults aged ≥ 50 years-old in San Francisco to evaluate the frequency of loneliness, main features of those who reported loneliness, and the association of loneliness with functional impairment and health-related quality of life (HRQoL). Participants (n = 356) were predominately male (85%); 57% were white; median age was 56-years-old. Overall 58% reported any loneliness, with 24% reporting mild, 22% moderate, and 12% severe loneliness. Lonely participants were more likely to report depression, alcohol and tobacco use, and have fewer relationships. Loneliness was associated with functional impairment and poor HRQoL. The authors concluded that a comprehensive care approach, incorporating mental health and psychosocial assessments with more traditional clinical assessments, will be needed to improve health outcomes for the growing older HIV-positive population.

Factors associated with loneliness in a study of almost 1000 HIV positive people, included not being in a relationship, lower financial income, poorer adherence, living alone, higher risk of smoking and comorbidities (including frailty, cognitive decline, and depression) and lower quality of life[73].

Another social factors that negatively influence health in several ways are the stigma, marginalization and discrimination experienced by many PLHIV[74]. The mentally ill also suffer particularly from these conditions[75]. Being infected with HIV and suffering from a mental disorder increases the chances of being stigmatized, marginalized, and discriminated. All result in impaired physical and mental health.

The term stigma refers to a set of attitudes, usually negative, that a social group has towards other minority groups because they present some type of differential trait or "mark" that allows them to be identified. Stigmatized people suffer from attitudes and beliefs that lead people to reject them because they are perceived as different. This can be the case for patients with mental illnesses or those infected with HIV. One consequence of stigma is discrimination; while stigma refers to an attitude or assumption, discrimination refers to behaviors that result from those attitudes or assumptions. They consists in the practice of unfavorable treatment or undeserved contempt for a certain person or group. The person stigmatized by the lack of acceptance may adopt different postures to overcome this difficulty, ranging from isolation to aggressiveness.

The mechanisms through which stigma may be experienced by PLHIV or/and mental illness include enacted stigma, anticipated stigma, and internalized stigma. Enacted stigma refers to discrimination experienced by PLHIV or with mental disorders, and may include acts of violence and marginalization. Anticipated stigma is the awareness of negative social perceptions toward PLHIV or/and mental illness and the expectation that a PLHIV or with a mental disorder will experience prejudice and discrimination in the future. Internalized stigma refers to the endorsement of negative beliefs, views, and feelings of oneself as relates to one's HIV-positive or mentally ill status[74].

HIV-related stigma and discrimination impede millions of PLHIV from accessing and benefiting from effective prevention and treatment services. As a result, approximately 50-60% of HIV-infected people regret of their serostatus, and many choose to hide it. Furthermore, HIV-related stigma and discrimination have been found to be associated with delays in seeking care and potential barriers to HIV counseling and testing, disclosure of HIV serostatus[76], retention in care and treatment, and uptake of and adherence to ART. There is also mounting evidence that HIV-related stigma and discrimination are associated with other social outcomes such as racism and poverty[77].

The double burden of HIV-related stigma and mental disorders could result in poor HRQoL in PLHIV. Previous studies have linked AIDS-related stigma and discrimination to mental wellbeing in PLHIV. Steward et al.[78] found that all forms of stigma and discrimination are ultimately associated with depressive symptoms among PLHIV in India. More recent studies have confirmed these findings and included other mental health outcomes such as anxiety, stress, or post-traumatic stress disorders (PTSD) in different populations of PLHIV in different countries around the world[79].

Concluding remarks

Tremendous biomedical advancements in HIV prevention and treatment have led to aspirational efforts to end the HIV pandemic. However, this goal will not be completed without addressing the significant mental health and substance use problems among PLHIV. These phenomena exacerbate the many social and economic barriers to accessing adequate and sustained healthcare and are among the most challenging barriers to achieve the control and end of the HIV pandemic.

Rates of mental health illnesses are higher among both people vulnerable to acquiring HIV and PLHIV compared to the general population. As a benefit of ART, the HIV population is aging, adding mental health problems typical of older age, such as cognitive impairment. The high prevalence of mental disorders in this population, including the use of toxic substances generally in association with chemsex, further influences the increasing rate of cognitive decline seen in PLHIV. Finally, psychosocial factors as isolation, perceived loneliness, stigmatization, and discrimination worsen the prognosis of these patients.

Mental health impairments increase the risk for HIV acquisition. On the other hand, among PLHIV result in negative health outcomes at each step in the medical care continuum. Given that the necessary screening tools and efficacious treatments exist to treat many mental health problems, attention should be made to earlier diagnosis[80].

In 2020 and 2021, the European AIDS Treatment Group (EATG)[81] conducted a literature review and community survey on mental health and HIV; it convened two workshops to discuss the results and implications for health care providers and community organizations. The attitudes and knowledge of healthcare professionals caring for HIV-infected patients vary with respect to mental health. HIV specialists are not necessarily comfortable asking specific questions related to mental health symptoms, and do not necessarily have the tools to conduct mental health assessments in PLHIV. In addition, they are often unaware of the potential impact of mental health on the HRQoL of HIV-infected persons, including treatment adherence and risk behaviors. Some of the recommendations of this working group are recorded below:

- Raise awareness regarding mental health issues among PLHIV, due to both the increased impact of chronic conditions in mental health, as well as to the burden of stigma and discrimination among PLHIV.
- Encourage and improve coordination between mental health services and other HIV-related care aspects and their correct referral in case of need. This also includes the need to develop different specialized services for different risk groups, including sex workers, gay men, injection drug users and the elderly, since models developed for one group often do not work for others.
- Fund mental health research, mental health service availability and use, with special emphasis on marginalized, criminalized, or underserved populations.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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