ARTIGO DE CONSENSO

# Gestão clínica de comorbilidades no envelhecimento da população que vive com VIH: uma revisão de peritos – Parte II

# *Clinical management of comorbidities in the aging population living with HIV: an expert review – Part II*

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## / Resumo

**Introdução:** O número de pessoas com 50 ou mais anos que vive com VIH tem aumentado. Tal deve-se principalmente à implementação da terapêutica antirretrovírica combinada que conduziu ao aumento da qualidade de vida e da longevidade desta população. Contudo, em idades mais avançadas, estes indivíduos apresentam pelo menos uma comorbilidade, sendo necessário um tratamento personalizado.

**Objetivos:** Este trabalho constitui a segunda parte de uma revisão especializada e tem como objetivo expor os pontos mais importantes sobre a prevenção, diagnóstico e tratamento das comorbilidades mais comumente observadas na população portuguesa que vive com VIH.

**Métodos:** Um comité científico independente coordenou painéis compostos por peritos de diferentes áreas clínicas que discutiram as principais comorbilidades associadas à infeção por VIH, na população portuguesa.

**Resultados:** As comorbilidades mais frequentemente associadas à infeção por VIH foram identificadas e as principais indicações para prevenção, diagnóstico e tratamento destas foram resumidas neste documento.

**Conclusões:** O envelhecimento das pessoas que vivem com VIH levou a um aumento da prevalência de comorbilidades pertencentes a diversas especialidades clínicas. Recomendações específicas para cada uma destas áreas foram reunidas neste documento, com o objetivo de melhorar a qualidade de vida da população que vive com VIH.


**Palavras-chave:** Envelhecimento; vírus da imunodeficiência humana; comorbilidade


## / Abstract

**Introduction:** *The number of people living with HIV with 50 years or older has been increasing. This is mainly due to the implementation of combination antiretroviral therapies which allowed the increase in longevity and quality of life of this population. However, most of the aging population living with HIV has at least one comorbidity and thus need a personalized treatment.*

**Aims:** *This work is the second part of a specialized review. The main goal is to highlight the most relevant issues on prevention, diagnosis and treatment of the comorbidities commonly observed in the Portuguese population living with HIV.*

**Methods:** *An independent scientific committee coordinated specialized panels, where specialists of different clinical areas analyzed the main comorbidities associated with HIV infection in the Portuguese population.*

**Results:** *The most common comorbidities associated with HIV infection were identified and the main recommendations for their prevention, diagnosis and treatment are summarized in this paper.*

**Conclusions:** *Aging of the population living with HIV led to an increase in the emergence of comorbidities belonging to different clinical specialties. Specific recommendations for each one of these areas were compiled in this document with the goal of improving the quality of life of people living with HIV.*


**Keywords:** *Aging; human immunodeficiency virus; comorbidities*

## / Introduction

In Portugal, in 2019, 24.1% of newly diagnosed HIV cases occurred in individuals which were 50 years or older.[1] Worldwide, the number of people living with HIV, which were 50 years or older, increased from 8% in 2000 to 16% in 2016.[2] The development of antiretroviral therapies (ART) has promoted the increase in longevity and the improvement of quality of life of people living with HIV.[3,4] However, the increased life expectancy, together with the premature aging associated with HIV infection due to increased immunosenescence and chronic inflammation conditions, can also trigger the onset of age-related comorbidities.[3-5] Accordingly, it has been shown that non-infectious comorbidities are more common in people living with HIV than in the general population.[4] Moreover, individuals living longer with HIV show higher incidence of multiple comorbidities.[6] A Portuguese study enrolling 401 adults living with HIV aged 59 or older during 2019 found that hypercholesterolemia, arterial hypertension and chronic depression/anxiety were the most frequent comorbidities in this population.[7] Even though awareness regarding the increasing number of older individuals living with HIV is growing, there is still a need for specific guidelines on how to better assist these patients.[8] Sensitizing physicians for the prevention, diagnosis and management of comorbidities in this population is essencial.[9,10]

Part I of this expert review comprised the current state-of-the-art on clinical management of the comorbidities most commonly observed in the Portuguese healthcare system, in people aged 50 years or older living with HIV.[11] Moreover, the expert panel discussion methodology followed for this work was described.[11] In this work, part II of the expert review, the key points on prevention, diagnosis and treatment considerations of these comorbidities are presented, with the aim of improving their management and, consequently, improving the quality of life of the Portuguese aged population living with HIV.

## / Methods

The methodology employed in this work has been extensively described in part I of this expert review.[11] Briefly, seven physicians specialized in Cardiology, Nephrology, Endocrinology, Neurology, Urology, Oncology and Psychiatry performed a literature review, focused on their respective fields of expertise, which included both evidence-base data and current experience in clinical practice. After the first draft, all authors discussed the structure and content of the document in an expert meeting coordinated by two infectious disease experts. The resulting document describes a comprehensive care plan for the most common comorbidities observed in the Portuguese population living with HIV.

### Endocrinology

***Diabetes mellitus (DM)*** comprises a group of metabolic disorders, characterized by the presence of high levels of sugar in the bloodstream over long periods of time.[12] It can result from a deficiency in producing insulin, insufficient insulin action or both.[12] Factors such as aging, obesity, genetics, co-infection with hepatitis C virus (HCV), being male and being non-Caucasian increase the risk of developing DM.[13] Moreover, ART can also increase the prevalence of DM.[14] Protease inhibitors are associated with insulin resistance and can cause pancreatic β-cells apoptosis[14]. Nucleotide/nucleoside analogs reverse-transcriptase inhibitors can affect the distribution of adipose tissue and are associated with insulin resistance[14] whilst integrase inhibitors are associated with weight increase.[15] Thus, screening for pre-DM and DM should be performed 6 to 12 months before starting ART and 3 months after starting or changing regimens.[14] If results do not reveal anomalies, the assessment should be annual.[14] Diagnosis is based on plasma glucose criteria and, usually, two tests are needed to confirm the diagnosis.[14] For individuals with a pre-DM diagnosis, a lifestyle change that includes physical exercise and diet for weight loss could prevent the development of the disease. For individuals diagnosed with DM, a lifestyle change will also be beneficial together with pharmacological therapy.[16] Metformin, if tolerated, is the first-line therapy for DM.[17] If the patient presents or is at high risk of developing atherosclerotic cardiovascular disease (CVD), glucagon-like peptide-1 receptor agonists (GLP-1RA) or renal sodium-dependent glucose co-transporter 2 inhibitors (SGLT2i) should also be prescribed.[18] If the patient presents or is at high risk of developing chronic kidney disease (CKD) or heart failure (HF), an SGLT2i should be preferentially prescribed.[18] If after introduction of the lifestyle changes and metformin treatment (either alone or concomitant to other drugs due to underlying CVD, CKD or HF) the target values of glycemia are not reached, clinical referral is advised.

***Metabolic syndrome (MS)*** comprises metabolic risk factors, which seem to promote the risk of developing atherosclerotic CVD and type 2 DM (T2DM).[19] Individuals with these characteristics are in a pro-thrombotic and pro-inflammatory state. Aging and lifestyle influence the onset of MS and can promote risk factors such as obesity, particularly abdominal obesity, hypertriglyceridemia, hypertension, hyperglycemia and high cholesterol levels.[19] Diagnosis of MS can be performed using the criteria from the International Diabetes Federation and from the National Cholesterol Education Program-Adult Treatment Panel.[19] Briefly, abdominal obesity, hypertriglyceridemia, lipoprotein levels, arterial blood pressure and fasting glucose levels are assessed.[19] Since the main goal of treatment is to reduce the risk of atherosclerosis, a lifestyle change is the priority.[14,19] Exercise, a healthy diet and smoking cessation should decrease risk factors.[19] If the risk of developing disease is high, pharmacological therapy can be added to modulate arterial hypertension, hyperglycemia and to decrease triglycerides or low-density lipoproteins.[14,19] If the risk factors are not lowered after introducing lifestyle changes and pharmacological therapy, clinical referral is advised.

**Osteoporosis** is characterized by the loss of bone density, which may result in bone fractures.[20] Risk factors include aging, low body mass index (BMI), a sedentary lifestyle, previous bone fractures, smoking, alcohol abuse, use of glucocorticoids, hypogonadism, menopause, hypovitaminosis D, co-infection with hepatitis B virus (HBV) or HCV, CKD and DM.[20] Moreover, specific risk factors associated with HIV-infection such as ART, low levels of $CD4^+$ T cells and chronic inflammation can also contribute for the development of osteoporosis.[20,21] The risk of fractures can be diagnosed using the FRAX® tool that integrates clinical risk factors as well as bone mineral density at the femoral neck.[22] Moreover, the existence of fragility fractures in the absence of other bone metabolism anomalies can also be an indicator of osteoporosis.[23] First line pharmacological treatment for this condition includes biphosphonates (e.g. alendronic, risedronic, ibandronic and zoledronic acids) and denosumab (RANK ligand inhibitors).[22,24] Lifestyle improvement and consumption of appropriate levels of vitamin D and calcium are also helpful in ameliorating this condition.[21] Patients are advised to maintain an active lifestyle that includes weight-bearing, balance and resistance exercises and older patients should be taught strategies to reduce the risk of falls.[23] If a patient under treatment continues to have recurrent fractures or bone loss, experiences discomfort using the available pharmacological options or has osteoporosis with unusual characteristics or associated diseases such as CKD or hyperparathyroidism, clinical referral is recommended. Furthermore, referral to a specialist is advised when there are osteoporosis indicators such as a hip, spine, humeral or forearm fractures without trauma or the existence of fragility fractures.

**Vitamin D** increases calcium and phosphorus absorption, both important for skeletal mineralization.[25] In individuals living with HIV, vitamin D deficiency has been associated with bone disease, depression, neurocognitive disease, CVD, arterial hypertension, MS, T2DM, infections and autoimmune diseases such as type 1 DM and neoplasms.[26] One of the causes of vitamin D deficiency is insufficient sun exposure. The quantity of vitamin D absorbed is influenced by daily schedule, geographical localization, apparel, the use of sunscreen, skin pigmentation and BMI.[26] However, other factors such as aging and the presence of other diseases can influence the rate of production and absorption of vitamin D.[26] Moreover, and although vitamin D exists in fish oils and in enriched foods, it is naturally sparse in the diet.[25] Vitamin D deficiency is diagnosed by quantifying serum levels of 25-hydroxy vitamin D.[22] If these levels reveal insufficiency of vitamin D, levels of the parathyroid hormone, calcium, phosphate, and alkaline phosphatase should also be assessed.[22] To increase the levels of vitamin D, cholecalciferol can be prescribed.[22,26]

### Urology

As **erectile dysfunction (ED)** is more frequent in older men, the premature aging due to HIV and its treatment might induce the onset of ED. [27,28] Common risk factors for ED are aging, hypogonadism, MS, obesity, DM, dyslipidemia, hypertension, peripheral neuropathy, lifestyle, endothelial dysfunction, and low-grade chronic inflammation.[27,29,30] People with HIV have additional risk factors such as the psychological burden and sexual aspects related to the condition, ART, other medications, substance abuse (if existent), alterations of body image and CVD.[31] In order to diagnose ED it is necessary to collect the clinical history of the patient, focusing especially on the sexual component.[30] Validated questionnaires such as the International Index of Erectile Function-5 (IIEF-5) can be employed to quantify ED.[32] Regarding the biological component, a lipid panel, glycemia and total testosterone should be assessed.[33] Moreover, a color Doppler ultrasound assessment of penile vascular function can be performed.[33] Treatment of ED includes lifestyle changes, switch of drugs that negatively impact ED (e.g., antihypertensive drugs and antiretrovirals) and/or prescription of phosphodiesterase type 5 inhibitors or alprostadil cream.[34] If the patient does not notice improvements after taking the maximum tolerated dose at least 8 times, clinical referral is recommended.

**Hypogonadism** is characterized by asthenia, mood swings, reduced libido and ED. Less frequent symptoms are reduced muscle mass, weight loss, body hair loss, changes of sleep pattern and concentration, and memory impairment.[35,36] Hypogonadism diagnosis in people living with HIV is more difficult. Levels of the sex hormone-binding globulin are usually increased in these patients, masking the existence of hypogonadism in patients with normal levels of total testosterone but reduced levels of free testosterone.[36] Therefore, besides determining the levels of total testosterone, it is essential to determine the levels of the bioavailable fraction.[36,37] Hypogonadism can be treated with hormonal replacement therapy, prescribed by an urologist.[36]

**Voiding dysfunction** in people with HIV can be of neurogenic nature or occur due to infection or obstruction.[38] The most common symptoms are urinary retention, detrusor hyperactivity and infravesical obstruction.[38] Identification of the cause is usually achieved by performing a urodynamic study.[39] Treatment should be prescribed by an urologist and should take into account the associated risks such as sepsis due to the use of vesicular probes in immunodepressed patients.[39,40]

People living with HIV can also suffer from other disorders such as ejaculatory dysfunction and reduction of libido, orgasmic function or sexual arousal.[34] These are typically related to psychological distress due to the stigma associated with HIV infection, concern with transmission as well as the depression and anxiety that affects this population.[34]

### Oncology

People living with HIV are more prone to develop certain cancers, especially in later stages of life, when they are older and have been infected for longer.[41,42] The higher risk is associated with the

reduced response of the immune system to oncogenic virus such as the Epstein-Barr, responsible for Hodgkin and some non-Hodgkin lymphomas, and HBV and HCV that can cause hepatocellular carcinoma.[41,42] Moreover, these patients have a lower survival rate, probably due to late diagnosis and to a more limited access to suitable oncologic treatments.[43] Lifestyle factors such as smoking and alcohol consumption also increase the risk of developing cancer.[42] Lung, colorectal, penile and testicular cancers, and non-Hodgkin lymphoma are the most frequent oncological disorders that concur with HIV.[41] Prostate cancer has been reported to be less prevalent in individuals living with HIV than in the general population, but that might be due to an usually lower rate of cancer screening in these patients, that leads to underdiagnosis, as the patients might remain asymptomatic for many years.[41] Generally, all oncological patients should maintain ART during chemotherapy unless it reduces treatment compliance due to toxicity or treatment interactions.[42] Patients should be clinically referred to an oncologist as soon as there are reasons to suspect of cancer.

**Lung cancer** diagnosis is based on the size of lung nodules. Nodules smaller than 8mm should be monitored to assess if there are alterations whilst nodules bigger than 8mm should be subject to endobronchial or transthoracic biopsy.[44,45] Cancer staging is achieved through computed tomography (CT) and fluorodeoxyglucose positron emission topography (FGD-PET).[44] Treatment depends on cancer stage, histological results, and biomarkers' levels, but systemic treatment is considered safe.[45]

**Prostate cancer** diagnosis requires transrectal biopsy to exclude infectious pathologies, which could be misdiagnosed as this oncological disorder.[46] Moreover, for localized tumors, the Gleason score and levels of prostate-specific antigen should also be determined.[46] Staging can be determined by bone scintigraphy and pelvic magnetic resonance imaging (MRI).[46] The most recent therapeutic agents for this disorder include abiraterone acetate, enzalutamide and cabazitaxel,[47] which seem to be safe for individuals living with HIV.

**Colorectal cancer** diagnosis is achieved through histological studies.[48] Cancer staging is determined through abdominal, pelvic and thoracic CT.[48] An ecoendoscopy to locally evaluate the tumor is necessary for rectal tumors.[49] Although systemic therapies based on fluoropyrimidines, oxaliplatin or irinotecan are considered safe, their interaction with ART is a possibility.[48,49] Regarding the treatment of metastasized cancer, monoclonal antibodies such as bevacizumab or cetuximab/panitumumab are also regarded as safe.[49]

**Non-Hodgkin lymphoma** diagnosis is achieved through an excisional biopsy in a reference laboratory with experience in morphological analysis and in molecular biology techniques.[50] Staging is determined by performing an FGD-PET.[50] Treatment of this disorder includes rituximab together with chemotherapy.[50] However, the use of this antibody can increase HIV-infection related complications and, thus, close monitoring should be performed.[51]

**Penile and testicular cancer** diagnosis is achieved through biopsy[52] and treatment guidelines should contemplate the lower tolerance to chemotherapy and radiotherapy of HIV patients that can result in lower efficacy.[42]

### Cardiology

CVD comprises different cardiopathies such as coronary disease, heart failure, and arrhythmias. Usually, acquired cardiopathies increase exponentially in patients that are older than 50 years. Besides aging, risk factors include dyslipidemia, hypertension, DM, smoking, obesity, genetics and structural heart disease.[53] The increased longevity of HIV patients has made the appearance of these disorders more common.[54] Moreover, chronic inflammation, opportunistic pathogens and deleterious effects of ART increase the risk of HIV patients developing CVD.[54] Screening for CVD can be performed using the Systematic Coronary Risk Evaluation (SCORE), which estimates the risk of atherosclerotic events in the following 10 years.[55] Also, behaviors such as having a healthy diet (rich in fruit, vegetables and cereals, and low on salt and saturated fats), regular exercise, moderate alcohol consumption and no smoking can help lower the risk of developing CVD.[53]

**Coronary disease** is diagnosed by screening for risk factors according to the guidelines of the European Society of Cardiology, identifying symptoms of myocardial ischemia and through specific exams such as an ECG, cardiac stress test or coronary CT angiogram.[53] Besides the lifestyle changes mentioned above, antiplatelet, lipid lowering and anti-ischemic therapies, myocardial revascularization (angioplasty and/or surgery) and cardiac rehabilitation could be adopted to treat coronary disease.[54] Moreover, it is important to assess the impact of ART on dyslipidemia, insulin resistance or DM and an adjustment might be needed.[54]

**Heart failure (HF)** can cause fatigue, dyspnea and edema and it is important to identify typical symptoms according to the guidelines of the European Society of Cardiology.[53] Additionally, is important to assess the levels of N-terminal-pro-brain natriuretic peptide (NT-proBNP) and perform an echocardiography to check for structural cardiac disease and left ventricular ejection fraction (LVEF).[56] Treatment involves controlling for cardiovascular risk factors and the prescription of diuretic agents. In cases where LVEF is reduced, treatment with beta-blockers, angiotensin-converting-enzyme-inhibitors, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, angiotensin receptor-neprilysin inhibitors, and cardiac resynchronization therapy might be necessary.[56] Additionally, it might be necessary to implant a cardioverter-defibrillator.[56] If the patient has reduced LVEF with or without HF, has HF without reduced LVEF after hospitalization or has HF associated with structural cardiac disease, clinical referral is recommended.

**Arrhythmia** occurs when there is a dysregulation in the electrical impulses that synchronize heartbeats.[57] Typical symptoms include palpitations, syncope and HF.[58] Diagnosis of arrhythmia can be achieved by performing an electrocardiogram or by Holter monitoring.[58] In order to control the rhythm, catheter ablation, cardioversion and antiarrhythmic agents may be used.[59] To control the heart rate, treatment with beta-blockers or implantation of a pacemaker or of a cardioverter-defibrillator might be needed.[59] To prevent stroke when the patient presents atrial fibrillation, oral anticoagulation therapy can be prescribed.[60] If the patient presents atrial fibrillation and there are indications of structural heart disease or if the patient has bradyarrhythmia and/or tachyarrhythmia, clinical referral is recommended.

### Nephrology

Kidney disease is one of the main complications that arise from HIV infection with a prevalence between 2.7 and 15%.[61,62] Aging, coexistence of DM and/or arterial hypertension, ethnicity, coinfection with HBV and/or HVC, direct or indirect action of HIV on kidney structures and kidney toxicity of ART contribute to the decline in health.[62,63]

**HIV-associated nephropathy (HIVAN)** is characterized by progressive renal failure and high levels of proteinuria resulting in a need for hemodialysis or kidney transplant.[62,64] It is more frequent in black individuals due to the higher incidence of two coding variants (G1 and G2) in the apolipoprotein L1 gene.[62] Immune complex nephritis is characterized by progressive renal failure, arterial hypertension, proteinuria, hematuria and hypocomplementemia.[64] A renal biopsy is the only procedure to diagnose both HIVAN and immune complex nephritis.[61] However, if proteinuria levels are higher than normal, if there are renal tubular lesions together with an incomplete Fanconi syndrome, when there are predominant hyperphosphaturia and hypophosphatemia, and if there is kidney failure with a glomerular filtration rate below 60 mL/min using the CKD-EPI (chronic kidney disease epidemiology study group) formula, clinical referral to a Nephrology consultation is recommended.

**Nephrotoxicity** has been associated with nearly all classes of antiretrovirals.[62] Besides direct effects in the kidneys, antiretrovirals can also have cardiovascular and metabolic effects that indirectly contribute to the development of kidney disease.[62,65] Given this, renal imaging and glomerular and tubular function should be assessed before starting ART and monitored at least every six months.[65] If a change in therapeutic regimen occurs, a new assessment should be performed.[65] The choice of ART should take into account the renal function.[65]

**Coinfection with hepatitis B and C viruses** causes a rapid decline of renal function and glomerular filtration rate, contributing to the rapid evolution to stage 5 CKD.[65] As there are options for effective treatment of HBV and HCV infection, this should be a priority.[65] Coinfection with HBV or HCV increases the probability of the patient being considered a candidate for kidney transplant, as they increase the risk of progressive CKD 2- to 3-fold.[65] Most transplantation units do not include individuals who are older than 65 years and newly infected with HIV in their active kidney transplant waiting lists. However, if the patients were already waiting when they reach that age and do not present significant CVD, they might be subjected to kidney transplantation and often with excellent outcomes.[64,65] These patients, together with the ones that do not satisfy the conditions set for renal transplantation, should start dialysis upon entering stage 5 CKD.[64,65]

### Neurology

Aging, low levels of $CD4^+$ T cells, high HIV loads, and ART are risk factors for neurological disorders.[66,67] Thus, older HIV patients have a higher risk of developing neurological disease. Cerebrovascular disorders, neurocognitive deterioration, epilepsy, and peripheral neuropathy are the most common neurological disorders in HIV patients.

For **cerebrovascular disorders**, high blood pressure, excessive body weight, DM, smoking and excessive alcohol intake are also risk factors.[66,67] Diagnosis of stroke or transient ischemic attack (TIA) is suspected upon the onset of symptoms such as hemiparesis, ocular paralysis, dysarthria, homonymous visual field defects and cortical function deficits in various combinations.[68] If these symptoms appeared in the last 24 hours, patients should be referred to the Stroke Fast Track. In the emergency room setting, a CT scan is usually the preferred diagnostic exam.[68] Intravenous contrast might be needed to identify the nature of the cerebral lesion and/or to perform a CT angiography to screen for arterial endoluminal thrombus.[68] If the symptoms appeared in the previous weeks or months, an MRI should be performed. Moreover, the cause of stroke/TIA and vascular risk factors should be assessed by performing a 12-lead electrocardiogram, transthoracic echocardiogram, carotid Doppler test (if possible, a transcranial Doppler as well), and blood tests for lipid profile, thyroid stimulating hormone, free T4, creatinine, urea, electrolytes, liver enzymes, syphilis, and a basic coagulation study.[68] A Holter monitor test might also be needed to check for paroxysmal atrial fibrillation.[68] Non-pharmacological interventions such as physical exercise and a healthy diet contribute for the prevention of stroke.[69] Moreover, secondary prevention of stroke includes statins together with an anticoagulant (if there is atrial fibrillation or if the patients have mechanical heart valves and/or anti-phospholipid syndrome) or a platelet aggregation inhibitor (for the remaining cases).[69] Newer oral anticoagulants should be considered in patients with non-valvular atrial fibrillation as alternatives to older vitamin K antagonists.[69] If there is significant luminal stenosis (>70% in the Doppler ultrasound, >50% in catheter angiography) of the symptomatic internal carotid artery, urgent referral for Vascular Surgery is recommended. If patients

have symptoms and a carotid stenosis between 50 and 69% (in the Doppler ultrasound), or do not have symptoms but present a carotid stenosis of at least 70% (in the Doppler ultrasound) referral to a Neurology consultation is advised. Moreover, if patients do not have risk factors or the cause for the cerebrovascular disorders cannot be identified, they should also be referred to a Neurology specialist. In case of motor deficits, ataxia, balance problems, dysphagia or speech problems, referral to a Physical Medicine and Rehabilitation consultation is recommended.

**Cognitive deterioration** diagnosis can be challenging, as unspecific cognitive difficulties might occur as a result of attention deficits due to anxiety and depression, which levels are usually higher in individuals living with HIV.[70] Thus, the priority is to screen for treatable causes. For this, blood tests (hemogram, serum levels of B12 vitamin and folic acid, quantification of indicators for renal, hepatic and thyroid functions and screen for syphilis) and a structural brain imaging exam, preferentially a MRI, should be performed.[71,72] When a MRI is not possible, a CT should be obtained.[71] This allows to scan for HIV-associated complications such as cerebral lymphoma and progressive multifocal leukoencephalopathy and is especially important if symptoms progress during weeks/months or if the patient loses autonomy due to cognitive deterioration.[71,72] Lumbar puncture and analysis of the cerebrospinal fluid should be considered in a case-by-case basis, and is mandatory if infection of the central nervous system is suspected.[71,72] If the patient presents symptoms indicative of obstructive sleep apnea such as excessive daytime sleepiness, morning headaches, concentration difficulties throughout the day or breathing pauses during sleep (reported by the partner) it is advised to perform a polysomnography[73] or to refer the patient to a specialized consultation. If all other causes are excluded and symptoms such as memory and concentration impairment are present, the patient may have HIV Associated Neurocognitive Disorder (HAND), which is caused by a direct pathogenic effect of HIV in the brain.[70] If the patient has cognitive complaints without a specific cause, but presents functional deterioration or other non-explained neurological deficits such as language disorder or ataxia, a referral to a Neurology consultation is recommended. Similarly, if the patient presents a fast, unexplained cognitive deterioration, which occurs in weeks or months, referral to a Neurology specialist is also advised. Additionally, if the diagnostic process mentioned above does not allow for the identification and treatment of the condition, and the value obtained in the Mini Mental State Examination[72] is below the cut-off value for the Portuguese population, referral to a Neurology consultation is recommended. If there are substantiated suspicions that the condition is due to depression or anxiety, referral to a Psychiatry consultation is advised. Treatment with cholinesterase inhibitors or memantine should only be prescribed by neurologists or psychiatrists, and is approved solely in patients diagnosed with Alzheimer's disease or Lewy body dementia.[71] These drugs should not be used to treat other causes of cognitive deterioration, including HAND.

**Epilepsy** is characterized by recurrent, unprovoked seizures.[74] It is diagnosed through solid clinical data such as direct observation by an eyewitness. Brain imaging, preferentially MRI, should be obtained (although CT can also be used in an emergency setting).[74] Electroencephalography is not recommended to screen for epilepsy.[74] Patients should be treated with an anti-epileptic drug (AED) if the risk of recurrence is considered high (e.g., permanent structural brain lesions).[74] Levetiracetam is probably the best cost/benefit/risk ratio AED for HIV patients; the dose should be adjusted to renal clearance.[75] If the diagnosis of epilepsy is uncertain, the cause for epilepsy cannot be established after brain imaging, treatment with the first AED is not successful (in cases where there is good treatment adherence and the triggers were eliminated), or if the patient does not recover to the pre-seizure condition, referral to Neurology is recommended.

**Peripheral neuropathy** is the most common neurological disorder in HIV, usually distal symmetric sensory polyneuropathy.[76] Screening in asymptomatic patients is not recommended. However, if the patients have neuropathic pain, paresthesia, dysesthesia, hypoesthesia or decreased deep tendon reflexes, peripheral neuropathy is the plausible cause.[76] Other factors that can cause these symptoms, such as excessive alcohol intake, vitamin B12 or folate deficiency, DM or monoclonal gammopathy should be excluded.[76] Electromyography (EMG)[76,77] and clinical referral to Neurology is recommended if patients present neurologic deficits unexplained by known lesions, if there is evidence of severe peripheral motor dysfunction such as muscle atrophy or fasciculations, if symptoms present asymmetrically, or if there is evident progression of the deficits for weeks or months. If compressive radiculopathy is suspected clinically or in EMG, an MRI should be performed at the appropriate spinal level – if confirmed, referral to Neurosurgery or Orthopedics should follow, according to local protocols.[78] If sensitive and/or motor deficits emerge acutely or subacutely, a spinal tap and examination of the cerebral spinal fluid should be carried out in order to rule out infectious or auto-immune (Guillain-Barré syndrome) neuropathy.[78] The treatment of HIV-associated sensory neuropathy is solely symptomatic.[76] Positive symptoms such as pain, paresthesia and dysesthesia can be improved with antiepileptic drugs (gabapentin, pregabalin, lamotrigine), antidepressants (duloxetine), or opioids (tramadol).[76,77] Non-steroidal anti-inflammatory drugs, paracetamol and amitriptyline are ineffective,[76,77] and clinical referral to a specialized pain clinic might be necessary in refractory cases.

### Psychiatry

Mental suffering can precede infection with HIV, be a consequence of its action in the central nervous system or be a consequence of the impact of the disease in the life and psychology of the patient.[79,80] An effective psychological assistance is essential for treatment success, ameliorating the prognosis and helping in the

epidemic control.[79] HIV patients frequently develop **anxiety**, **depression**, and **insomnia**.[79,81-83] The development of these conditions depends on the history of mental illness and socio-demographic factors such as educational level, employment situation, age and gender.[79] Additionally, some medications can also induce psychological disorders as side-effects.[81] More frequently though, it is the HIV infection itself that has a negative impact in the mental health of patients.[80] The stigma and discrimination that is still associated with the disease and the inability to deal with suffering, disease and/or death contribute to mental health issues.[79,80] In order to diagnose these disorders, specific factors should be assessed. Therefore, symptoms such as chest pain, sweating, dizziness, gastrointestinal alterations and/or headaches without underlying medical causes (e.g., withdrawal of psychotropic substances, respiratory problems, and CVD) are common in anxiety.[84] For both anxiety and depression, life events should be analyzed, and the Hospital Anxiety and Depression Scale can be used.[84] In insomnia, elevated cortisol levels can explain the inability to sleep and behaviors such as excessive time in bed, fear of not sleeping, napping, and coffee and alcohol consumption can perpetrate the problem.[79,82] When these perturbations are mild, psychological education (including sleep hygiene training) and cognitive/behavioral therapy might be sufficient.[82] If these prove ineffective, psychopharmacological therapy (e.g., benzodiazepines and antidepressants) should be added.[82,83] If it is difficult to reach a definite diagnosis, if the physician has limited experience in prescribing psychotropic drugs, or if the patients are not responding to psychiatric medications, are experiencing severe psychiatric disorders such as suicide ideation, are consuming illicit drugs, and/or have other relevant psychiatric comorbidities and/or sleep pathologies, clinical referral is recommended.

## / Conclusions

The introduction of ART and the resulting increase in longevity of HIV patients has led to the onset of age-related comorbidities. Given the distinct characteristics of HIV infection, specific diagnosis and treatment approaches must be followed. The choice of ART should take into account the presence of comorbidities and consequently, concomitant medications. Similarly, therapeutic approaches for comorbidities should take into consideration the antiretroviral regimen in use. Finally, the follow-up of these patients should integrate different specialties in a multidisciplinary approach, due to the coexistence of HIV infection with other diseases. In this work, the key points on the diagnosis and treatment of the most common comorbidities associated with HIV infection were described. Incorporation of these indications in clinical practice will improve the overall health status of patients and contribute to the improvement of their quality of life.

## / Conflicts of interest

NM received fees for lectures, advisory boards, travel grants or consultancy from Merck Sharp & Dohme, Abbvie, Gilead Sciences, Janssen-Cilag and ViiV Healthcare. AH, FC and JF received fees from Merck Sharp & Dohme. AF received fees for lectures, advisory boards, travel grants or consultancy from Abbvie, Astellas, AstraZeneca, Baxter, Bial, Fresenius Medical Care, Genzyme, Janssen-Cilag, Merck Sharp & Dohme, Mundipharma and Vifor Pharma. JM received advisor honoraria from Bial, Biogen, Merck Sharp & Dohme, Roche and Zambon, as well as financial support to speak or attend meetings from Abbvie, Bial, Boston Scientific, GE Healthcare, Medtronic, Novartis, Roche and Roche Diagnostics. MB received financial support for advisory boards from Abbott Laboratories, AstraZeneca, Bial, Janssen-Cilag, Jaba Recordati, Angelini and Merck Sharp & Dohme. FM received financial support for consultancy services, meetings and teaching, research and publications from Abbvie, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme and ViiV Healthcare. JSC received financial support from Merck Sharp & Dohme, Gilead and Janssen-Cilag. RSC participated in advisory boards and lectures for Abbvie, Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme and ViiV Healthcare. ARS received fees from Merck Sharp & Dohme, Gilead Sciences, Janssen-Cilag and ViiV Healthcare. Other co-authors (NT and PF) have no conflicts of interest to disclose.

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