

## Aging with the HIV-AIDS Disease

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### Abstract

The paradigm of diagnosis, treatment and follow-up of the patients' with HIV disease has changed. If in its beginning death was certain, now with the development of Highly Active Antiretroviral Therapy (HAART) it is a chronic disease like Diabetes Mellitus (DM) or Arterial Hypertension (AH). With these changes, patients became older and with more morbidity, some associated with the infection and persistent inflammation, some with the therapy and another group has emerged-HANA (HIV non-associated AIDS conditions), affecting all organs and systems. The approach of these patients includes a multidisciplinary team. There is no manuscript regarding to this theme in the Portuguese reality.

**Keywords:** Elderly; HIV-AIDS; Acquired Immunodeficiency; Secondary Immunodeficiency

### Introduction

The first time that the world heard about human immunodeficiency virus (HIV) was in the 80's, in the United States of America (USA), San Francisco in homosexual men and intravenous (IV) drugs users. Only 10 years later, USA and Western Europe, had the first effective combination antiretroviral therapy (cART) or previously called highly active antiretroviral therapy (HAART). The paradigm of living with HIV has changed [1-20]. The mortality felt down in the USA starting in the year 1996, but only in 2012 with the widespread of cART, the death range worldwide also declined [1,2,4]. Similar patterns are reported in European countries, North America, Australia and Asia [6].

If in the 90's people died very young with opportunist infections, tumours and undernutrition. Nowadays the reality is very different. With the adequate treatment, compliance and follow-up; they can live their disease in a successful way, allowing them to age [1-3]. There are a couple of challenges that appeared in the HIV aging people, such as accelerated

aging, HIV associated non-AIDS conditions (HANA), geriatric syndromes and frailty [1,2]. In the general population, the "cut-off point" for old age is 60-75 years, but in the HIV, the limit falls to 50 years old [1-5].

### Discussion

#### Epidemiology

The age of people infected with HIV-AIDS rose during the past 30 years [1,2]. It is estimated that 3,6 million of the 35,6 million people living worldwide with HIV are over the age of 50 years, and it is expected that this trend keeps rising. In the USA, in the year 2012 approximately 40% of the people living with HIV were over 50 years and 11% were 60 or more years [1,3,4]. Data shows that around 18% of new cases are diagnosed in patients with 50 years, also allowing to have older people with this syndrome [1]. Early in the HIV epidemic, older patients acquired HIV from blood transfusions, but now they have the same risk factors as younger people—men who have sex with men (MSM), intravenous drugs users and women who have sex with infected men [3].

#### HIV and aging

Universally aging is defined as "the time-dependent functional decline that affects most living organisms". Many factors are known in this process (genetic, lifestyle and environment exposures [1,7] and it is also known that they work more intensely in the HIV positive patients. Many mechanisms are described such as genetic instability, telomere shortening, epigenetic alterations, loss of proteostasis, dysregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem-cell exhaustion and altered intercellular communications (abnormal endocrine and neuroendocrine signalling—insulin, insulin-like growth factor, growth hormone [1] as well as immune dysregulation), chronic inflammation ("InflammAging") with high markers such as interleukin (IL)-6, D-dimers, fibrinogen [1,4-7,9,11], C-reactive protein (CRP), tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) and high white

blood cells count (WBC)–neutrophils, monocytes and CD8+ T-cells [2].

The literature shows that HIV positive, ART-treated women have a higher state of immune activation, exhaustion and senescence than uninfected age-matched controls. The simplest and safest intervention to reduce inflammation and grant health ageing is moderate exercise and low caloric intake, beyond disease control [5].

Inflammation in HIV may be increased by tissue and peripheral blood virus, chronic reactivation of herpes virus such as cytomegalovirus (CMV) [1,2], microbial translocation (more evident in the gut), immune dysregulation and senescence (with depletion of CD4+ cells and increased CD8+ and monocytes). Some of these mechanisms are also described in the HIV negative patients like part of the physiological process of aging [1,5,11].

### Frailty and geriatric syndromes

Frailty, present in almost 25% of the patients with more than 85 years, is a clinical syndrome initially characterized in geriatric population with a hallmark of age-related declines in physiological reserve (and complexity in resting dynamics involving multiple physiological systems), function (with progressive decline) and increased vulnerability (due to maladaptive responses to everyday or acute stressors) to adverse health outcomes (like acute illness, falls, cognitive decline, hospitalization, disability, dependency and mortality) [1].

In the process of aging with HIV many mechanisms and cascades are involved, such as increased rates of chronic morbidities, increased rates of geriatric syndromes (conditions

that associated with aging predict adverse outcomes, like falls, urinary incontinence, slow gait, sensory deficits and neurocognitive impairment, present in 25-56% of older patients) and frailty (evaluated frequently by the Fried criteria), senescent immune changes, persistent increased inflammatory markers [1,2,4-6,7,9,11,17-19,21]. Still is controversial, even though HIV may be a risk factor for morbidities, does not appear to accelerate their occurrence over time. Patients with the risk of frailty (low current and nadir of CD4+ cells, central obesity, Hepatitis C virus [HCV] co-infection, other geriatric syndrome and lower education) will increase and adequate strategies to slow down are needed, starting in the beginning of the disease [1].

### Diagnosis, treatment and prevention of comorbidities

HIV is underdiagnosed in older patients. In 2011, 16% of the 1.1 million Americans living with HIV didn't know they had the disease. Around 18% of the patients had 50 years or older at the time of diagnosis [1,3-5]. Problems regarding to underdiagnosed infection are: provider and clinical recognition (frequently symptoms that may relate to an HIV infection or its progression may be misconstrued as relating to the aging process), insight and information about HIV prevention and transmission, lack of HIV-prevention education targeting older patients, disclosure because of the family/social stigma of HIV infection (3,4), lack of insurance or access to medical care [4].

The active screening may be considered in all older adults, as shown in the **Table 1**. Treatment should be offered to all, as early as possible, except if there is a pharmacological and/or medical contraindication [1,6].

**Table 1** Screening in HIV.

Screening in the HIV Patients [1,3,4,7,10]	
Parameter	Description
Hyperlipidaemia	Before and 1 to 3 months after starting cART, with attention to interactions with antidiabetic drugs and cART, preferring pravastatin, pitavastatin and low dose atorvastatin and rosuvastatin [1,3,7].
Haemoglobin A1c	Every 6 months [1,3,7].
Bone Density	With dual-energy x-ray absorptiometry – DXA, every 2 years and assess the need of bisphosphonate therapy [1,3].
Kidney disease	Due to cART, HIV, diabetes and hypertension, evaluating serum creatinine and urinary protein excretion [1,4].
Co-infections	Hepatitis A to D [1] Attention that live attenuated vaccines should be avoided in HIV infected with low CD4+ counts, unless the benefits clearly outweigh risks. Immunologic response to vaccines should be assessed when possible [7].
Neoplasms	Breast, cervical cancer, colorectal and prostate. Especially in the patients with the HIV-HCV co-infection, for the high risk of cirrhosis and hepatocellular carcinoma and in women with human papillomavirus (HPV) infection [1].
Medical evaluations	Dentist and ophthalmologist at least annually [4].
Vaccines	Hepatitis, tetanus, varicella, meningitis vaccine, influenza vaccination and pneumococcal should be administered [1].
Other screenings	Maintain patients' independence (for example – calendars, pill boxes, alert bracelets or alarms, optimize the older patients' residency) and reduce social isolation [4].
	Screening of other medical conditions like osteoporosis, diabetes, sexual dysfunction, polypharmacy, depression screening [1].
	Sexual screening/evaluation [10].

## HIV non-associated aids conditions

HIV patients have a higher number of comorbidities when comparing with the one HIV negative. They may appear in all ages, in high rates, but as expected are more frequent in older persons [1,3-9,11,15-18,21].

**Cardiovascular Disease (CVD):** Before HAART, it was more frequent myocarditis and dilated cardiomyopathy (especially with low CD4 nadir). Nowadays coronary artery disease (higher risk in 50%), interstice myocardial fibrosis, intracardiac fat infiltration, arrhythmic disorders, congestive heart failure and ischemic stroke are more frequent. Some drugs may enhance the cardiovascular risk such as the protease inhibitors. Other cardiovascular risk conditions are commonly seen such as insulin resistance and diabetes, obesity, hypertension, smoking. Therefore, there is an increased status of inflammation and thrombosis [1,3-5,7,9,12,13,21]. All together they make a mismatch between the chronological age and the vascular age. Note that traditional models for cardiovascular risk prediction may underestimate risk in HIV-infected patients, because atherosclerosis is driven mainly by the HIV-HAART related risk factors. Drugs like lopinavir/ritonavir, indinavir and abacavir are also associated with higher cardiovascular risk [5].

**Arterial hypertension:** Regarding to arterial hypertension, a relationship between higher systolic blood pressure and duration of HIV has been reported, being greatest after 5 years or more of ART, especially with protease inhibitors and non-nucleoside reverse transcriptase inhibitor regimens [12].

**Heart failure:** HIV infection is associated with a 1,8-fold risk of developing heart failure (HF). A metanalysis showed that systolic dysfunction was present in 8,3% (secondary to chronic inflammation, tobacco smoking and history of myocardial infarction) and diastolic dysfunction in 43,4% (due to age and hypertension) [12].

**Stroke:** Stroke is a leading cause of death and disability worldwide. HIV patients have an increased risk of stroke, predominantly the ischemic type. Some mechanisms are being pointed as an explanation—vasculopathy, thrombophilia, cardioembolic events and opportunistic infections [12].

**Pulmonary disease:** Obstructive lung disease (OLD) has been reported in positive HIV populations since the pre-HAART era. Different types can occur - fixed airway obstruction, emphysema, diffusing capacity for carbon monoxide (DLCO) impairment, chronic bronchitis, bronchial hyper-responsiveness, and asthma. OLD is the most common type and the obstruction is more severe with a quicker progression in patients with higher HIV viral levels. Pulmonary Arterial Hypertension (PAH) is one of the most severe complications of HIV infection, carrying high mortality. Its incidence has not changed with HAART and its severity doesn't correlate consistently with the immunosuppression degree [12].

**Insulin resistance and diabetes mellitus:** Diabetes Mellitus (DM) is present in 3% of the HIV positive patients who have never received HAART, but glucose intolerance increases to the range of 10 to 25% in those who have started it. Lipodystrophy

and hyperlipidaemia are also present in patients with a chronic use of protease inhibitor [3,4,7]. The incidence of diabetes is 4 times higher among HIV-infected men on HAART, especially with a ritonavir scheme [9]. In the diabetes mellitus treatment, besides metformin that causes lactic acidosis, there are no other significant interactions. Diet, exercise, eviction of smoking cannot as non-pharmacological measures cannot be forgotten [7,9,21].

**Kidney disease:** Kidney dysfunction is very frequent in ageing and more in HIV patients (around 3,5% to 9,7% in stage 3 or higher) [1,5]. HIV nephropathy (HIVAN) was initially described in the first years of the disease, especially in Afro-Americans. HAART has decreased its incidence and prevalence [1,9,21]. Risk factors known HIVAN are age, afro American, history of diabetes mellitus and hypertension, low CD4 counts, high viral loads, inflammatory markers and drugs like tenofovir [1] (with kidney lesion like proteinuria, renal tubular damage, interstitial nephritis, nephrolithiasis [9]) and hepatitis C virus infection (HCV) [4].

**Neurological disease:** At the beginning of the disease, in the 80s, both neurologic disease and dysfunction were secondary to opportunist or sexually transmitted infections (more frequent if  $CD4 \leq 200$  cells), leading to HIV associated dementia, myelopathy and peripheral neuropathy. Nowadays it is described HAND (HIV-associated neurocognitive disorders), that is present in around half of them [1,3,4,5,14,15,21]. It may be asymptomatic (in most cases, in 50%—Asymptomatic Neurocognitive Impairment [ANI]) but can be mild (minor neurocognitive disorder [MND], in 20%) or severe (in only 2% of the cases—HIV associated dementia [HIV-D]) [3,14,15,21]. They can appear besides the good HIV control and it can be present among other comorbidities as CVD and sleep disturbances [3,14]. In the pre-HAART era, the HAND took the form of motor skill and cognitive deficits, but today patients have much less obvious decline in executive functioning or memory [4]. The risk of dementia is more than three-fold, with structural changes in the brain like decreased brain volume [1], blood brain barrier abnormalities and altered permeability [5]. Clinically is indolent and the first changes can be psychomotor, difficulty in multitasking and apathy. Bad control of the HIV disease may take to disorders like central nervous system toxoplasmosis, cryptococcal meningitides, progressive multifocal leukoencephalopathy and primary central system lymphoma [3].

**Psychiatric disease:** Depression is very common in older adults and no less so in patients' HIV positive [4,5]. It may be initiated or worsened by social circumstances -isolation, loss of friends or loved ones, stigma or rejection or substance abuse. It may be subtle, and appear as sleeplessness, poor adherence to treatment regimens, poor hygiene, forgetfulness, weight loss or gain, sadness and anhedonia. Its treatment is multimodal and should be made by routine, with both social, psychological and pharmacological interventions [4,7].

**Bone disease:** Bone mineral density as measured by DXA (Bone densitometry) scans (each 2-3 year, from the 50 years), serves as a surrogate marker of fracture risk and provides data to categorize persons with osteoporosis. In fact, FRAX® (World

Health Organization Fracture Risk Assessment Tool) has not been validated in HIV-infection and may underestimate the 10-year risk in these patients [17]. Dietary, lifestyle and HAART modifications allied to DXA screening is indicated in higher risk older patients [16].

Deterioration of the bone structure related with osteopenia and osteoporosis is often asymptomatic, multifactorial and increased in this population, due to substance abuse (alcohol), smoking, low body weight and vitamin D deficiency (present in 60 to 75% of the HIV-infected elderly) [1,4,5,16,17] hypogonadism [3,4,5], lactic acidemia [7], post-menopause state [9]. Drugs like the protease inhibitors—tenofovir predispose to low bone density (bone mineral density decreases by 2 to 6% in the first two years starting this regimens) [1,7,9,17,18,21]. If there is severe osteoporosis an alternative is changing to regimens with raltegravir or abacavir associated with bisphosphonates [18]. The expected risk of fracture is around three-fold [1,3,5,7], more frequent in the vertebrae, forearms or hips (7) with severe medical, functional and economic consequences [16].

**Neoplasms/malignancy:** With aging, the risk of having cancer is higher. In both HIV-positive and HIV-negative, the incidence of lung, colorectal, prostate and breast cancers will increase. HIV patients are in higher risk for malignancy, at first with Kaposi's sarcoma (1000 times), non-Hodgkin B cell lymphoma (100 times), invasive squamous cell carcinoma of the cervix (6 times higher), known as AIDS-defining cancers [1,3,19,21]. The last ones are reduced after the HAART era [19]. Several oncogenic viruses have been implicated in these cancers, such human herpesvirus 8 (HHV8), hepatitis B virus (HBV), HCV, HPV and Epstein-Barr virus (EBV) [4].

**Mortality:** Many factors contribute to the mortality in patients with HIV, such as the time of diagnosis, CD4+ nadir, virologic suppression and the use of drugs, especially the IV (but also the smoking and other substances abuse). Other contributors are also pointed like lifestyle factors, HAART therapy, socioeconomic status, risk factors for co-morbidities, nutritional status, safe environment, ethnicity, social isolation and other active infections like herpes viruses and hepatitis. The life expectancy in a HIV positive patient is around less 20 years than the HIV negative patient [1-3,7,8].

Besides all the improvement of care and refined treatments, the mortality in this group is 1,7 to 7,0 times higher than those who are not infected. The mortality may be near to the non-infected if the CD4+ nadir is persistently above 350-500 cells/ $\mu$ L and the viral load is suppressed [1]. Cancer is responsible for one third of the deaths in HIV patients [19] CVD is the second major cause of mortality among HIV infected patients, responsible for 15% of the deaths [7,9].

The literature shows that the causes of death in the HIV group has changed from infections and malignancy in the late 90's to HANNA. This conditions still exist but in patients with delayed or ineffective treatment due to non-adherence, drug resistance, poor CD4 recovery.

## Conclusion

The number of elderly people living with HIV reflect enormous treatment successes, and present new challenges related to aging. This increase is attributed to the effectiveness of HAART that increase longevity of life but also to the increased risk of acquiring HIV in this population. Comorbidities are more common because of aging and HIV status. This increase in age and comorbidities will increase the need for multiple professional competences, and the sharing of specialist medical skills. New screening test strategies for malignancies should be developed for older HIV-infected patients.

Near of forty years after the identification of HIV, a cure for HIV infection is still to be achieved. Advances of combined antiretroviral therapy in recent years transformed HIV infection into a chronic disease when treatment is available. Physiological changes associated with aging alter drug metabolism in these patients who in most cases experience polypharmacy exposing them to drug toxicities and drug to drug interactions. Special designed preventive measures and screening programs should be designed to target elderly individuals. Clinicians should also suspect HIV early in these patients to minimize late presentation and pay attention to the principles of geriatric prescribing recommendations to minimize complications from multiple medication use. As people with HIV live longer and with more complex health and social care needs, the concept of frailty could be useful for identifying vulnerable individuals, for organizing care and for comprehensively measuring the impact of illness and treatment on overall health status. As research for a cure for HIV infection continues, there is a vital need to examine the aging population, since any drug or vaccine must now work on an older population.

## Conflict of Interest

The authors don't have any conflict of interest.

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