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REVIEW ARTICLE

Human Immunodeficiency Virus as a Chronic Disease: Evaluation and Management of Nonacquired Immune Deficiency Syndrome-Defining Conditions

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In the modern antiretroviral therapy (ART) era, motivated people living with human immunodeficiency virus (HIV) who have access to therapy are expected to maintain viral suppression indefinitely and to receive treatment for decades. Hence, the current clinical scenario has dramatically shifted since the early 1980s, from treatment and prevention of opportunistic infections and palliative care to a new scenario in which most HIV specialists focus on HIV primary care, ie, the follow up of stable patients, surveillance of long-term toxicities, and screening and prevention of age-related conditions. The median age of HIV-infected adults on ART is progressively increasing. By 2030, 3 of every 4 patients are expected to be aged 50 years or older in many countries, more than 80% will have at least 1 age-related disease, and approximately one third will have at least 3 age-related diseases. Contemporary care of HIV-infected patients is evolving, and questions about how we might monitor and perhaps even treat HIV-infected adults have emerged. Through key published works, this review briefly describes the most prevalent comorbidities and age-associated conditions and highlights the differential features in the HIV-infected population. We also discuss the most critical aspects to be considered in the care of patients with HIV for the management and prevention of age-associated disease.

Keywords. aging; cardiovascular disease; frailty; HIV; polypharmacy.

Cardiovascular morbidity and mortality is increasing among people aging with human immunodeficiency virus (HIV) [1]. Several cohort studies have shown that this population exhibits, among other cardiovascular diseases, excess risk of ischemic heart disease and heart failure [2]. Most studies suggest that HIV-infected subjects are at 1.5- to 2-fold-increased risk of acute myocardial infarction (MI) [3, 4], and the impact of cardiovascular disease is likely to increase because the median age of people living with HIV is progressively increasing in most countries with unrestricted access to antiretroviral therapy (ART) [5].

DYSLIPIDEMIA

Lipid abnormalities are frequently found in patients infected with HIV. Patients on ART may show modest improvements of lipids when switching to a regimen with more favorable lipid profile, especially when switching from old boosted protease inhibitors (PIs) to newer ones (ie, darunavir and atazanavir), and especially to integrase inhibitors and rilpivirine, which have more neutral effects on lipids [6]. The mainstay of treatment of dyslipidemia is the use of statins, which have been shown to decrease mortality in cohort studies [7]. In addition, given its anti-inflammatory effects, statins might even prove beneficial for several age-associated conditions such as chronic kidney disease (CKD) [8] and atherosclerosis [9], which seem to be more prevalent in the aging HIV-infected population. Drug interactions with ART is the most common clinical problem. For example, the use of sinvastatin is contraindicated with ritonavir or cobicistat. Atorvastatin, rosuvastatin, and pitavastatin, at starting doses of 10, 10, and 4 mg, respectively, are 3 reasonable options. Pitavastatin might be the drug of choice in patients receiving boosted PIs, given the absence of significant interactions with these agents. The experience with atorvastatin in patients not receiving boosted PIs is wide, and although emerging data suggest that rosuvastatin has positive effects in other surrogate markers of disease progression in HIV-infected patients (ie, carotid intima-media regression [9] and coronary calcium [10]), the potential for mild insulin resistance increase and new-onset diabetes mellitus stills exists [11].

ARTERIAL HYPERTENSION

It is unclear whether HIV infection or its treatment is associated with increased incidence of hypertension [12]. In general, blood

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pressure measurements slightly rise after ART initiation [13], which might be attributable to the weight gain and improvement of overall status. Special attention is needed when initiating calcium channel blockers, indapamide, and doxazosine given the risk of potential drug-to-drug interactions. Maraviroc is associated with orthostatic hypotension, which needs to be considered when initiating antihypertensive drugs.

ISCHEMIC HEART DISEASE

Primary prevention of cardiovascular events is crucial in the general management of patients infected with HIV. Hence, cardiovascular risk stratification is warranted to define clinical objectives. The previous versions of the American College of Cardiology/American Heart Association (ACC/AHA) guidelines relied on low-density lipoprotein (LDL) cholesterol level thresholds as clinical objectives to be met according to an individual's CVD risk categorization [14]. A number of equations have been calibrated to predict the risk of adverse cardiovascular outcomes in specific populations, such as SCORE, for European individuals. Even more, a risk equation developed from HIV-infected populations is available [15]. Overall, the Framingham risk equation [16] is the most widely implemented, and it classifies patients at high risk when the 10-year predicted risk of MI exceeds 20%. In this situation, the European AIDS Clinical Society recommends an aggressive management of cardiovascular risk factors and proactive ART swithcing to regimens with the most favorable metabolic profile [17].

The 2013 ACC/AHA guidelines have abandoned LDL and non-high-density lipoprotein cholesterol thresholds and goals and instead identify 4 groups likely to benefit from statin therapy. Benefit groups include the following individuals: age 21 or older with clinical atherosclerotic cardiovascular disease (ASCVD); age 21 or older with LDL 190 mg/dL or higher; age 40–75 with diabetes and LDL 70–189 mg/dL; and age 40–75 with a 10-year ASCVD risk score—that is, percentage risk of nonfatal MI, coronary death, nonfatal/fatal stroke within the next 10 years—7.5% or higher by the Pooled Cohort Equations calculator [18].

Given that HIV infection implies an additional, significant CVD risk factor not included in these equations, several studies have addressed the performance of CVD risk equations and collectively suggest that in HIV-infected patients, the equations underestimate the actual risk [15, 19–23]. A recent study evaluated the presence of high-risk morphology coronary plaque without known CVD, and the study found that although the 2013 ACC/AHA cholesterol guidelines recommend statin therapy for a higher percentage of subjects with and without high-risk plaque relative to 2004 guidelines, statin therapy still would not be recommended for the majority (74%) of HIV-infected subjects with high-risk plaques [21]. Although the performance of cardiovascular risk equations might not be optimal and outcome studies are needed to determine the utility of new statin recommendations among HIV-infected subjects, these equations provide at least a starting point for assessing the risk.

Primary prevention of ischemic heart disease is based on the screening and early detection of subclinical disease and aggressive management of cardiovascular risk factors, including exercise and diet modifications, smoking cessation, diagnosis and management of dyslipidemia, diabetes and hypertension, and aspirin use, when indicated. In secondary prevention, besides the strict control of cardiovascular risk factors, antiplatelet and/or anticoagulant therapy, beta blockers, and arterial vasodilators (calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers) are generally recommended. Hence, a number of drugs are commonly needed, and a thorough assessment of potential interactions with ART must be routinely performed [17, 24, 25].

ATRIAL FIBRILLATION

There is no evidence of excess risk of atrial fibrillation or arterial embolization in HIV-infected patients. However, it must be noted that boosted PIs and elvitegravir/cobicistat show clinically relevant interactions with the majority of drugs used for the management of this condition. More importantly, their concomitant use with rivaroxaban is contraindicated given the increased risk of major bleeding. First-generation nonnucleoside reverse-transcriptase inhibitors (efavirenz, etravirine, and nevirapine) also show potential interactions with acenocoumarol, warfarin, rivaroxaban, and clopidogrel, warranting close clinical monitoring. Raltegravir, dolutegravir, and maraviroc do not significantly interact with antiplatelet or anticoagulant agents; therefore, integrase inhibitors are a better choice in these situations.

HEART FAILURE

Human immunodeficiency virus-associated myocardiopathy is a common complication in low-income countries. Although the prevalence of systolic dysfunction has decreased, the prevalence of diastolic dysfunction is increasing after the introduction of highly active ART (HAART) in 1996. There are no specific recommendations for the management of heart failure in the HIV-infected patient beyond the assessment of drug interactions with ART [26]. Diuretics do not show significant interactions with antiretroviral drugs. Boosted PIs significantly increase digoxin levels via P-glycoprotein inhibition [27]. Tolvaptan, a vasopressin V2-receptor antagonist, and eplerenone, an aldosterone receptor antagonist, can potentially interact with antiretroviral drugs with effects on liver CYP3A4 activity.

STROKE

Stroke events have been classically more difficult to analyze in HIV populations because the pathogenesis of cerebral infarction is more diverse than that of MI, and its diagnosis is harder to validate. For coronary heart disease, traditional risk factors have classically been more prevalent among patients infected

with HIV, and additional conditions, including infections and substance abuse, might also play a role.

There is evidence suggesting that HIV infection can increase an individual's risk of stroke [28, 29]. Several cohort studies have analyzed specific risk factors among HIV-infected populations. Beyond classic risk factors, the risk appears to be higher among subjects with detectable HIV ribonucleic acid (RNA), low CD4 counts, drug use, non-Hispanic blacks, and, according to recent data, in women [30–32]. In a recent study in Spain, marked differences in stroke incidence trends were reported when HIV-monoinfected and hepatitis C virus (HCV)-coinfected individuals were compared [33]. Stroke incidence was initially much higher in monoinfection and declined throughout the study period, whereas the opposite trend was seen in coinfection. By the end of the study period, incidence of both hemorrhagic and ischemic stroke had become higher in coinfected individuals. Overall, these studies highlight stroke as another very relevant comorbidity in HIV, for which uncontrolled viral load, low CD4, drug use, and HCV infection are important factors. For many other non-acquired immune deficiency syndrome (AIDS)-defining conditions, this risk might approach that of the general population in the subgroup of patients with long-term suppressed viremia and high $CD4^+$ T-cell counts [29, 34]; therefore, beyond the control of traditional risk factors, early ART initiation and prolonged control of HIV replication are critical interventions to decrease the risk of stroke.

NONACQUIRED IMMUNE DEFICIENCY SYNDROME-DEFINING CANCERS

Non-AIDS-defining cancers have emerged as a leading cause of mortality among people aging with HIV and are likely to gain importance in the forthcoming years as the median age of HIV-infected patients continues to increase [5, 35, 36]. It has been estimated that 10% of HIV-infected patients develop cancer [37]. Although during the pre-HAART era AIDS-defining cancers (Kaposi sarcoma, cervical cancer, and non-Hodgkin lymphoma [HL]) were the most prevalent malignancies, several non-AIDS-defining cancers now account for the overall excess risk of cancer [38]. However, not all non-AIDS-defining cancers show increased prevalence in the HIV-infected population. Although some are dramatically increased, ie, anal cancer (from 10-fold to 30-fold higher risk) or lung cancer, melanoma and hepatocellular carcinoma ([HCC] from 2-fold to 5-fold higher risk), for reasons that remain poorly understood HIV-infected patients might be protected against some cancers, ie, prostate, breast, and colorectal cancer [38, 39]. A higher burden of risk factors, such as tobacco use or alcohol consumption, and a higher prevalence of coinfections associated with cancer, such as human papillomavirus, HCV, or Epstein-Barr virus (EBV), are likely determinants of the increased risk of cancer. In contrast, as it has been observed in other inflammatory conditions (ie, rheumatoid arthritis [40]), the sustained proinflammatory state associated with chronic infection might protect against the development of some neoplasias. The incidence and standardized incidence ratios of cancers most commonly diagnosed in HIV-infected individuals in the post-HAART era is summarized in Table 1. Note that the risk of many of these cancers is highly dependent on the risk factors of the population studied (ie, HCV coinfection in the case of liver cancer or tobacco use in the case of lung cancer). In the sections below, we will focus on the non-AIDS-defining cancers whose risk is more prominently increased in treated HIV-infected patients.

Anal Cancer

Albeit uncommon in the general population, anal cancer is an emerging cancer in patients infected with HIV. This excess risk is especially marked in (1) men who have sex with men (MSM), (2) women with a history of receptive anal intercourse, (3) women with a history of abnormal cervical Pap smear, and (4) men and women with genital warts, although there is increased risk of anal cancer regardless sexual orientation [52, 53]. Given the success of cervical cytology in preventing cervical cancer, screening for anal cancer is supported by HIV-specific clinical guidelines with digital rectal examination and anal cytology in at-risk populations, including HIV-infected (1) MSM, (2) women with a history of receptive anal intercourse, (3) women with a history of abnormal cervical Pap smear, and (4) men and women with genital warts. As recommended by experts, high-resolution anoscopy with biopsy should be performed if available in the presence of cytologic abnormalities [17]. High-grade squamous intraepithelial lesions (HSIL) can progress to anal cancer, although the rate of progression is low (estimated in 1 of 377 per year) [54]. Hence, treatment should be offered to patients with anal HSIL, and a variety of modalities are

Table 1. Cancer Event-Rates per 100 000 Persons-Year and Standardized Incidence Ratios in HIV-Infected Individuals After 1996

Event	Events-Rate per 100 000 Persons-Year	Standardized Incidence Ratio
Any Non-AIDS-defining cancer [37, 39, 41, 42]	670–724	1.7–2.7
Anus [37, 43–46]	60–130	20–79
Hodgkin lymphoma [37, 43, 47, 48]	47–60	11.5–31.7
Lung [42, 44, 45, 48–50]	64	1.1–3.0
Prostate [37, 42, 48]	60–97	+0.5
Colorectal [42, 43, 45]	48	0.3–1.4
Liver [39, 42, 43]	8–26	3.0–7.7
Melanoma [41–45, 48, 51]	10–60	0.5–1.5
Oropharyngeal [42, 43, 45, 47, 48]	37	0.9–1.6
Breast cancer [42, 43, 47, 48]	18	0.7–3.2
Cervix [42, 44, 47]	11–24	24
Vagina/vulva [43, 47]	10–16	5.9–6.8

Abbreviations: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.

available, including topical therapy, immune modulation with imiquimod, infrared coagulation, and anoscopy-directed lesion ablation. However, given the limitations of current screening methods and the lack of clinical trials assessing the efficacy and safety of current diagnostic and therapeutic approaches, the Centers for Disease Control and Prevention does not routinely recommend anal cancer screening with anal cytology in persons living with HIV [55]. The Anchor Study (NCT02135419) is an ongoing trial of anal cancer screening and prevention, which will address many of the key issues.

Hodgkin Lymphoma

Hodgkin lymphoma is among the most frequent non-AIDS-defining cancers, with an incidence 15- to 30-fold higher than in the general population [56]. Although the risk of other immunodeficiency-related conditions has clearly decreased with the use of ART, it seems, however, that the incidence of HL has not declined among HIV-infected subjects. There is even conflicting evidence suggesting a potential increase of HL in the ART era [57, 58]. Risk factors include advanced infection, with CD4 counts typically below 100 cells/mL or a history of low nadir CD4, and high viral loads. Because most patients infected with HIV show seropositivity for EBV, some HL might be a consequence of persistent defects of the adaptive immunity to control this pathogen, which is able to exert lymphoproliferative effects. Most HIV-associated HL show unfavorable histology, with a predominance (approximately 60% of cases) of mixed cellularity HL [59] and more advanced disease at diagnosis. Treatment of advanced HL includes initiation of ART and the use of a standard chemotherapy regimen such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) [60].

Lung Cancer

Patients infected with HIV show approximately 2- to 4-fold increased risk of lung cancer [43, 56, 57, 61]. Tobacco use is the main risk factor for lung cancer in the general population and among patients infected with HIV [62], and the prevalence of smoking is increased in the HIV-infected population [63]. Patients infected with HIV lose more life years through smoking than through HIV [62], but HIV infection is associated with excess risk of cancer even after adjustment for tobacco use [49]. Human immunodeficiency virus infection might also influence the clinical course of lung cancer, because non-small cell lung cancer seems to behave more aggressively among patients infected with HIV [64]. For these reasons, patients infected with HIV can particularly benefit from smoking cessation, which should be aggressively pursued among this cohort as the most effective measure to prevent lung cancer. Many expert groups now advocate for lung cancer screening with annual low-dose computerized tomography in patients with high-risk criteria, ie, age 55 to 74 years, a history of smoking at least 30 pack-years and, if a former smoker, having quit within the previous 15 years [65–68], although there is a significant risk of overdiagnosis and unnecessary invasive studies. Lung cancer screening in HIV-infected patients fulfilling these high-risk criteria might be especially justified given the additional risk independently associated with HIV infection, but there are no specific data for lung cancer screening in patients infected with HIV.

Hepatocellular Carcinoma

The incidence of HCC is 8-fold higher in patients infected with HIV compared with the general population [44], and it is an emerging cancer in different cohorts of patients infected with HIV [69–71]. For example, in Spain the incidence of this cancer increased from 0.1 to 1.1/1000 persons-years between 1999 and 2009 [70]. Compared with individuals with HCV infection alone, HIV/HCV coinfection is associated with accelerated progression of liver fibrosis to cirrhosis and HCC and to excess mortality [72].

All HIV-infected patients should be screened for HCV infection using enzyme immunoassays to detect anti-HCV antibodies. In addition, any HIV-infected patient with cirrhosis, regardless the etiology, should be systematically screened at 6-monthly intervals with hepatic ultrasound or computerized tomography, in the case of nodules [17, 24, 25]. Of note, the first preventive measure for HCC is HCV eradication. Recent data from trials assessing the efficacy of new anti-HCV therapies in HIV/HCV-infected patients suggest that HCV cure would be achieved in the majority of subjects with access to new treatments in a near future [73, 74].

Risk of Drug Interactions Between Chemotherapy and Antiretroviral Therapy During Treatment of Cancer

Initiation of chemotherapy in the HIV-infected patient has classically been challenging given a number of additive toxicities and drug interactions. Because most ART-associated toxicities aggravated with chemotherapy were associated with older drugs (such as neurotoxicity with didanosine and stavudine, bone marrow suppression with zidovudine, or hepatotoxicity with first nucleoside reverse-transcriptase inhibitors zidovudine, didanosine, and stavudine), most problems seen today with modern and safer ART are mainly driven by a wide spectrum of drug interactions with chemotherapy agents given the narrow therapeutic window, or they are determined by the diverse effects of antiretroviral drugs on the cytochrome P450 system as substrates, inhibitors, or inducers. Consultation of reference databases of drug interactions helps to guide clinical decisions [24]. There is a low level of evidence to guide clinical decisions regarding ART and chemotherapy given that HIV-infected patients with cancer have been classically excluded from clinical trials. Nonetheless, it is generally recommended to maintain ART given the significant risks associated with stopping ART [75]. A close collaboration between the HIV specialists and the oncologist is mandatory for the optimal management of these patients. It is common clinical practice to

switch ART regimens to minimize drug interactions. Raltegravir, dolutegravir, and maraviroc have low risk of interactions and are reasonable options [76].

KIDNEY DISEASE

There is a higher than expected risk of renal disease among HIV-infected individuals relative to age- and sex-matched populations. Although the risk of acute kidney injury is decreasing, the prevalence and incidence of chronic and end-stage kidney disease is projected to rise, as the prevalence of HIV infection and the median age of the HIV-infected population continues to rise [77, 78]. This excess risk is driven by both HIV-related conditions, including HIV-associated nephropathy, immune complex-mediated glomerulonephritis, drug toxicities, and glomerulonephritis due to HCV coinfection, and by HIV-unrelated conditions, including traditional cardiovascular risk factors (such as diabetes and hypertension) and incomplete recovery from an episode of acute kidney failure [77–79]. Human immunodeficiency virus-related factors for progressive CKD include HCV coinfection and high HIV RNA loads [80]. Although ART seems to slow the rate of renal function decline, tenofovir disoproxil fumarate (TDF) and boosted PIs have been shown to impair kidney function [81–85].

Patients infected with HIV should be screened for early identification of CKD [17, 25, 86]. Individuals infected with HIV should have their glomerular filtration rate (GFR) evaluated at least twice yearly using a creatinine-based estimate. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) GFR equation seems to be the most accurate for use in HIV-positive adults on stable ART [86–88]. Several common drugs in HIV management, including cobicistat, dolutegravir, rilpivirine, and cotrimoxazole, can decrease creatinine tubular secretion, so creatinine changes of <0.1 mg/dL after initiation of these drugs with respect to baseline values would probably lack clinical significance. Patients should also have a urinalysis or quantitative measurement of urine protein excretion at least once yearly. The definitions of the most prevalentmodalities of kidney impairmentin HIV-infected patients are summarized in Table 2. The estimated incidence of acute kidney impairment is approximately 6–10 cases per 100 patients-year in outpatients [89], and it is generally driven by concomitant conditions (fever, sepsis, dehydration).

The prevalence of CKD (defined by GFR <60 mL per minute/1.73 m^2) among patients infected with HIV in North America and Europe ranges from 4.7% to 9.7%, and higher rates have been reported when CKD was defined by either reduced GFR or proteinuria [82, 90, 91]. Glomerular harm is usually reflected by albuminuria, whereas tubular abnormalities cause low-grade albuminuria, as reflected by an albumin/protein urine ratio <0.4. Albumin-to-creatinine ratio in random urine samples (ideally the first morning sample) is the preferred marker for staging CKD [92].

Proximal tubular dysfunction, with or without estimated GFR (eGFR) impairment, is usually due to direct drug toxicity on tubular epithelial cells, as observed with tenofovir. Tenofovir disoproxil fumarate has been consistently associated with proximal tubular dysfunction and progressive eGFR decline. In the presence of concomitant risk factors for kidney impairment, it is usually challenging to elucidate the extent of renal impairment driven by TDF. Several candidate biomarkers are under evaluation and may help to anticipate TDF-induced proximal tubular dysfunction.

Clinical efforts should focus on the prevention of kidney disease by early detection and aggressive treatment of risk factors, including diabetes, hypertension, and smoking. The clear association between high plasma HIV RNA levels and low $CD4^+$ T-cell counts with excess risk of kidney disease also provides a rationale for early ART initiation. Clinical recommendations for the management of particular situations of kidney impairment are summarized in Table 3.

Table 2. Definitions to Characterize the Presence of Kidney Function Impairment

Condition	Definition
Acute kidney impairment	Significant (>25%) and rapid (<2–7 d) eGFR decline. It is generally driven by concomitant conditions (fever, sepsis, dehydration)
Chronic kidney disease	Estimated eGFR that persists below 60 mL/min/1.73 m^2 (CKD stages 1–2) for more than 3 months or the presence of proteinuria (protein/creatinine ratio >300 mg/g) even in the presence of eGFR >60 mL per min/m^2
Proximal tubular dysfunction, with or without eGFR impairment	At least 2 of the kidney alterations observed in the Fanconi syndrome: euglycemic glycosuria, phosphaturia, uricosuria, decreased fractional phosphate excretion, and/or uric acid or hypophosphatemia

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

OSTEOPENIA, OSTEOPOROSIS, AND CALCIUM DISORDERS

Osteopenia and Osteoporosis

There is increasing awareness of a higher prevalence of low bone mineral density (BMD) and excess risk of bone fractures among patients infected with HIV, either ART-treated or untreated. In the HIV Outpatient Study (HOPS), a prospective cohort at 10 HIV clinics throughout the United States, age-adjusted fractures were 2.0–3.7 times higher than in the general population [95]. The prevalence of osteopenia and osteoporosis in a meta-analysis including 884 HIV-infected patients demonstrated that 67% had osteopenia and 15% had osteoporosis [96]. The pathogenesis of osteoporosis is usually multifactorial, and traditional risk factors likely act in concert with HIV-related risk factors. Human immunodeficiency virus particles activate osteoclasts, alter vitamin D metabolism, and induce increased systemic

Table 3. Clinical Recommendations in the Setting of Kidney Impairment

Condition	Recommendation
Proteinuria with preserved eGFR (>60 mL/min)	- Rule out glomerulonephritis, especially in the presence of high-grade proteinuria (>1 g/24 h) or concomitant hematuria. - Collect 24-hour urine to determine proximal tubular dysfunction - Consider with a nephrologist the indication of a renal biopsy. - Consider angiotensin-converting enzyme inhibitors to decrease proteinuria.
Progressive tubular dysfunction	- Evaluate and treat risk factors - Discontinue tenofovir with long-term follow-up (recovery often slow and incomplete).
Progressive eGFR decline	- Evaluate and treat risk factors. - Investigate the use of nephrotoxic agents. - Collect 24-hour urine to determine proximal tubular dysfunction. - Consider tenofovir discontinuation.
Chronic kidney disease with eGFR <60 mL/min	- Consider TDF discontinuation (especially if coadministered with boosted PI). - Adjust NRTI dose (required for all with the exception of abacavir) or maraviroc. No dose adjustment is necessary for NNRTI, PI, or integrase inhibitors).
End-stage kidney disease (eGFR <10 mL/min or dialysis)	- Similar management to that of HIV-uninfected individuals, with special consideration to avoidance of nephrotoxic agents, including TDF.
Kidney transplant	- Similar indications than in the general population in ART-treated patients without overt immunosuppression (ie, $CD4^+$ T cells <200/mm^3 or AIDS). - Similar survival rates after transplantation, although some have suggested higher incidence of acute rejection [93, 94]. - Consider switching ART to raltegravir, dolutegravir, and maraviroc-based regimens might be optimal ART choices given the narrow therapeutic index and interactions of most immunosuppressive agents and the need for dose adjustments

Abbreviations: AIDS, acquired immune deficiency syndrome; ART, antiretroviral therapy; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitors; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate.

inflammation, which negatively impact on BMD [97, 98]. In addition, a biphasic BMD loss is usually appreciated after ART initiation, with a faster decline during the first 6 months and a slower but sustained decay thereafter. Tenofovir elicits greater BMD loss than other antiretrovirals of the same class (such as abacavir). Protease inhibitors might also cause BMD loss, although the evidence supporting this association is weaker [99].

Dual-energy x-ray absorptiometry (DXA) is recommended as the test of choice for screening of osteoporosis in all HIV-infected post-menopausic women and men older than 50 years [100]. The optimal time for rescreening is controversial, and it seems reasonable to base the time on the results of baseline DXA. A diagnostic workup should exclude secondary causes of osteoporosis. Therefore, the following laboratory parameters should be measured: complete blood count, albumin, calcium, phosphorus, creatinine, alanine transaminase, alkaline phosphatase, 25-OH-vitamin D, intact parathyroid hormone (PTH), thyroid-stimulating hormone, morning total testosterone (in men), and 24-hour urine calcium and creatinine. Measuring 25-hydroxyvitamin D levels, which indicate the body's vitamin D stores, may be especially useful given the high prevalence of vitamin D insufficiency reported in the HIV-infected population.

Treatment of osteoporosis and osteopenia does not differ from recommendations in the general population, although it is less supported by the few clinical trials in patients infected with HIV [100]. According to the National Osteoporosis Foundation guidelines, pharmacologic treatment of osteoporosis is recommended for postmenopausal women and men >50 years with a T-score of the femoral neck or lumbar spine less than or equal to −2.5, patients with a history of fragility fracture of the spine or hip, or patients with low bone mass (T-score between −1 and −2.5 at the femoral neck or lumbar spine) and high probability of a major fracture, based on the World Health Organization's Fracture Risk Assessment Tool (FRAX) (a significant risk includes a 10-year probability of fracture that is >3% for the hip or >20% for any major osteoporotic fracture) [101]. Encouraging life-style changes is important to minimize the impact of secondary causes, including avoiding smoking cessation, performing weight-bearing exercise, and consuming a diet rich in calcium and vitamin D. Bisphosphonates are generally considered the first-line pharmacological therapy for osteoporosis [102–104]. There are studies in HIV-infected patients supporting the efficacy and safety of weekly alendronic acid by mouth, and, more recently, annual intravenous zoledronic acid showed efficacy in 2 small studies [105, 106]. However, pharmacologic therapy for osteoporosis in patients infected with HIV warrants careful considerations before initiation, given the lack of prospective data on fracture in this population and the lack of data regarding long-term safety. There is no evidence that switching ART regimen from tenofovir or PI-containing regimens will decrease the risk of bone fractures in those with established osteoporosis, although it seems reasonable to discontinue tenofovir when other options are available.

Hypophosphatemia, Hyperparathyroidism, and Calcium Metabolism Disorders

Impaired parathyroid (PTH) secretion and action has been described in patients infected with HIV [107], independently of vitamin D levels [108]. However, the clinical significance of this observation is uncertain. In contrast, hyperparathyroidism usually reflects vitamin D deficiency (<20 ng/mL) or insufficiency (<30 ng/mL), which can be found in more than two thirds of individuals. In addition to classic risk factors for low vitamin D levels [109], patients initiating ART that includes efavirenz have been found to have a 5 ng/mL reduction in vitamin D levels compared with patients starting ART without efavirenz [110, 111]. Potential mechanisms are efavirenz-induced inhibition of CYP2RI, an enzyme implicated in the 25-hydroxilation of vitamin D, and up-regulation of the catabolism of vitamin D into its inactive metabolites. Hypocalcemia

has been described in 6.5% of individuals infected with HIV after adjusting for serum albumin, in relation with vitamin D deficiency [112]. Hyperparathyroidism can also be due to hypophosphatemia, which is relatively common during both untreated (approximately 10%) and treated (20%–30%) HIV disease. Tenofovir disoproxil fumarate has been associated with hypophosphatemia by altering phosphate tubular reabsorption in the setting of proximal tubular dysfunction and Fanconi syndrome. A urine phosphate excretion >100 mg/24 hours and a fractional excretion of phosphate ≥5% indicate phosphate urine loss, which is a cause of secondary hyperparathyroidism (PHT levels >65 pg/mL).

Although the prevalence of vitamin D insufficiency is higher among patients infected with HIV, it is challenging to make recommendations for its monitoring given the lack of evidence showing a clinical benefit of vitamin D supplementation in the absence of low BMD. The Osteo Renal Exchange Program recommends that vitamin D status should be determined by serum 25-hydroxy vitamin D levels in (1) HIV-infected patients with a history of low BMD and/or fracture and in (2) patients with any of the major risk factors for low vitamin D levels, including dark skin, dietary deficiency, avoidance of sun exposure, malabsorption, obesity, CKD, or treatment with regimens containing efavirenz, although the health benefit of identification and correction of vitamin deficiency in these groups is unclear [17]. Supplementary vitamin D should be given to HIV-infected patients with vitamin D insufficiency or deficiency, particularly if the deficiency is associated with compensatory hyperparathyroidism. Vitamin D intake should be titrated to achieve a serum 25-hydroxy vitamin level of approximately 30 ng/mL, and a suitable maintenance dose should be administered thereafter to sustain this level. Vitamin D deficiency can blunt bone response to bisphosphonate treatment; therefore, the target serum 25-hydroxy vitamin D level of 30 ng/mL should be achieved before initiating therapy with an antiresorptive drug [100]. Clinical trials assessing the optimal dose in patients infected with HIV are not available. In accordance with the Institute of Medicine of the National Academies, at least 800 international units of vitamin D should be administered daily, as recommended for older HIV-seronegative adults [113].

HUMAN IMMUNODEFICIENCY VIRUS-ASSOCIATED NEUROCOGNITIVE DISORDERS

Neurocognitive impairment has been commonly observed since the beginning of the AIDS epidemic among HIV-infected individuals. Although more characteristic of advanced stages of the disease, these conditions, ranging from mild neuropsychological deficits to profoundly disabling dementia, can also occur in patients with asymptomatic HIV infection. The pathophysiology of HIV-associated neurocognitive disorders (HAND) is an area of ongoing debate. It has been proposed that brain macrophages, microglial cells, and astrocytes, which can support HIV infection, are involved in the pathogenesis of HAND [114]. Some studies have suggested that even despite years of ART-mediated viral suppression, chronic activation of the innate immunity in the periphery [115, 116] and latent or persistent HIV infection in the brain may sustain chronic macrophage and microglia activation [117, 118]. Whether HIV infection is associated to increased prevalence of HAND independently of ART use or disease stage remains unclear [119–121]. The widespread of ART has been associated with a decrease in the prevalence of more severe neurocognitive deficits. However, overall neurocognitive deficits remain common in various cohort studies (20%–69%) even in the setting of HIV suppression [122, 123].

In clinical settings, HAND is mainly characterized by cognitive deficits, including attention, executive functioning, and speed of informational processing [124]. In 2007, the HIV Neurobehavioral Research Center published a classification scheme commonly referred as the "Frascati criteria", which has been validated and widely adopted [125], and include the following conditions, for which an alternative cause explaining the neurocognitive defects must be ruled out (Table 4).

The European AIDS Clinical Society recommends assessing for the presence of symptoms of neurocognitive impairment in all HIV-infected patients with no confounding conditions, and HAND screening can be performed quickly during a clinical visit [17], as described in Table 5.

Effective ART is the principal treatment of HAND. Other issues to be considered during the therapeutic approach include management of associated psychiatric conditions, central nervous system drug penetration, and the possibility of central nervous system viral escape. In the case of ART-treated patients diagnosed with HAND, a diagnostic work-up including magnetic resonance imaging and cerebrospinal fluid (CSF) examination is recommended for assessment for additional causes of HAND. If technically available, some experts recommend measuring HIV RNA and HIV genotype in CSF to evaluate HIV escape (either CSF HIV RNA >50 and plasma HIV RNA

Table 4. Classification Scheme of HAND Based on the "Frascati Criteria"

Condition	Definition
Asymptomatic neurocognitive impairment	A score of at least 1 standard deviation below the mean on at least 2 cognitive areas of standardized neuropsychological testing without this deficit causing an observable functional impairment
Mild neurocognitive disorder	A score of one standard deviation below the mean on at least 2 cognitive areas of standardized neuropsychological testing with at least mild impairment of daily functioning
HIV-associated dementia	A score of at least 2 standard deviations below the mean on at least 2 cognitive areas of standardized neuropsychological testing with marked associated impairment in activities of daily living

Abbreviations: HIV, human immunodeficiency virus.

Table 5. HAND Screening During a Clinical Visit Recommended by the European AIDS Clinical Society[a]

Action	Description
Rule out confounding conditions	Severe psychiatric conditions Abuse of psychotropic drugs Alcohol abuse Sequelae from previous opportunistic infections
Screen for HAND	Three questions: 1. Do you experience frequent memory loss (eg, do you forget the occurrence of special events even the more recent ones, appointments, etc)? 2. Do you feel that you are slower when reasoning, planning activities, or solving problems? 3. Do you have difficulties paying attention (eg, to a conversation, book, or movie)?

Abbreviations: AIDS, acquired immune deficiency syndrome; HAND, HIV-associated neurocognitive disorders; HIV, human immunodeficiency virus.

[a] For each question, answers could be as follows: (a) never, (b) hardly ever, or (c) yes, definitely. Persons who are HIV positive are considered to have an "abnormal" result when answering "yes, definitely" on at least 1 question, which would require further evaluation [17].

<50 c/mL or both CSF and plasma HIV RNA >50 c/mL, with CSF HIV RNA >1 $\log_{10}$ higher than plasma HIV RNA). Given the differential ability of antiretroviral drugs to cross the blood-brain barrier to penetrate the central nervous system, if CSF escape is confirmed, a switch to regimens with greater CSF penetration should be considered. Drugs with demonstrated adequate CSF penetration include zidovudine, abacavir, efavirenz, nevirapine, lopinavir/ritonavir, darunavir/ritonavir, dolutegravir, and maraviroc [17].

MULTIMORBIDITY, POLYPHARMACY, AND FRAILTY

Multimorbidity

As described, patients infected with HIV experience increased risk of a variety of non-AIDS comorbidities, which seem to be accentuated and/or accelerated by HIV [126–129]. Cohort studies have shown that, for a given age stratum, HIV infection represents an independent risk factor for the risk of comorbidities, and the number of comorbidities is higher in treated HIV-infected individuals compared with age- and sex-matched HIV-uninfected population and approach the prevalence of comorbidities observed among persons 10 years older [35, 130]. The increasing awareness of multimorbidity in HIV has raised 2 new concerns: the harm associated with polypharmacy and the development of frailty.

Polypharmacy

Among emerging clinical problems in the aging HIV-infected population, polypharmacy is likely an overlooked source of harm. It has been repeatedly shown how polypharmacy negatively impacts on medication adherence and increases the risk of adverse outcomes, including drug toxicities, drug interactions, hospitalization, geriatric syndromes, and mortality [131, 132]. Although polypharmacy has multiple definitions, it is most commonly considered as (1) the use of 6 or more medications or (2) the use of a potentially inappropriate drug for which the medication does not match the diagnosis. Risk factors for clinically significant drug interactions with ART include regimens with 3 or more antiretroviral drugs or a PI [133]. The consequences of polypharmacy are notable in older subjects living with HIV, and although the actual prevalence of adverse drug events and drug-drug interactions in this subset of patients has not been well studied, the modeling study by Smit et al [5] suggest that in 2030, 40% of patients could have complications with the currently recommended first-line regimens due to drug interactions or to contraindications.

The list of relevant interactions with concomitant ART is overwhelming and beyond the scope of this review. It is common in clinical practice to consult updated databases to check for interactions with ART [24]. The list of medications must be thoroughly reviewed, and a drug simplification effort should be pursued at every visit. In general, many physicians often hesitate to stop medications, especially if other health provider initiated treatment. Simplicity might be a solution, and ideally the number of physicians addressing patient's care should be minimized [131].

Frailty

As the HIV-infected population ages, recognition of frailty has become increasingly important. Most definitions of frailty describe a syndrome characterized by loss of function, strength, physiologic reserve, and increased vulnerability to stressors due to age-associated declines across neuromuscular, metabolic, and immune systems [134, 135]. In general, frail subjects often suffer fluctuating disability, falls, delirium, and alterations in mobility, strength, endurance, nutrition, and physical activity [135]. Human immunodeficiency virus disease can contribute to this frail phenotype through direct and indirect effects. The most studied contribution to the aging process implicated the immune systems. Many, but not all, of the immunologic alterations that persist during treated HIV infection are similar to those observed in the elderly [136, 137], and it is now widely accepted that HIV-related immunosenescence contributes to disease progression and adverse outcomes [138, 139]. Mitochondrial dysfunction, a common adverse effect of first antiretrovirals [140], can contribute to sarcopenia [141], which is a common finding among HIV-infected individuals [142]. Inflammation persists in patients on long-term ART, and inflammation is associated with anorexia and catabolism of skeletal muscle and adipose tissue, which might contribute to the nutritional and functional impairment that characterize frailty [143, 144]. The CD4/CD8 ratio, a surrogate marker of immunosenescence, correlates with a frailty phenotype in HIV-infected women [145] and with the risk of non-AIDS-associated mortality [137, 146–148]. Other risk factors for frailty include polypharmacy, multimorbidity, and social isolation. Human immunodeficiency virus disease is now a chronic

disease with many of these factors. For example, HIV disease is associated with accumulation of comorbidities in multiple systems, which ultimately lead to geriatric syndromes, including frailty, polypharmacy, and even falls an average of 15–20 years earlier than the general population [130, 149–151]. Hence, treated HIV disease is now a chronic condition with many risk factors for frailty. Several studies have shown that frailty is more frequent in treated HIV disease than in the general population [152, 153]. A hypothesized model illustrating how direct and indirect HIV-effects might impact on the development of frailty is illustrated in Figure 1.

Screening of frailty is rarely performed in most HIV clinics. However, the growing burden of HIV disease in geriatric populations [134] might demand new models for healthcare delivery. Screening of frailty would identify patients at high risk of adverse clinical outcomes who might benefit from closer monitoring, with the goal of preventing loss of independence. Over the past several years, a plethora of frailty screening tools have been developed and used to identify elderly at risk of adverse events, such as the 5-item FRAIL (fatigue, resistance, ambulation, illnesses, and loss of weight) questionnaire, to allow physicians to objectively recognize frail individuals [154].

However, there is limited evidence on interventions designed to improve prognosis in frail patients. Exercise is believed to be the best strategy to improve quality of life and functionality in the elderly [155]. Many researchers in the field believe that this simple but difficult to implement intervention might improve clinical outcomes in treated HIV-infected subjects [156]. Recent data have shown that higher physical activity improves psychomotor and executive functioning [157, 158] and inflammatory (interleukin-6, high-sensitivity C-reactive protein), metabolic (leptin), and cardiovascular (hyperemic velocity) markers [159]. Hormonal and supplemental interventions, including testosterone replacement [160], growth hormone [161], and vitamin D [162] supplementation have been investigated in the general population. Overall, data are very limited to recommend its clinical use to attenuate frailty, and none of these interventions have been investigated in patients infected with HIV.

FINAL CONSIDERATIONS

Mounting evidence suggest that persons infected with HIV might have close to normal lifespans [163–165], and the impact of HIV on the ageing process might be smaller than expected [36], especially among patients who initiate ART early [166]. As recently illustrated by the Strategic Timing of Antiretroviral Treatment (START) study, in which early ART initiation was associated with a 57% reduction of both serious AIDS and non-AIDS illnesses, initiating ART soon after HIV infection remains a priority to improve long-term outcomes [167]. The benefits of early ART initiation might be even greater in the subgroup of older patients diagnosed with HIV, who were not well represented in START study, who typically display greater

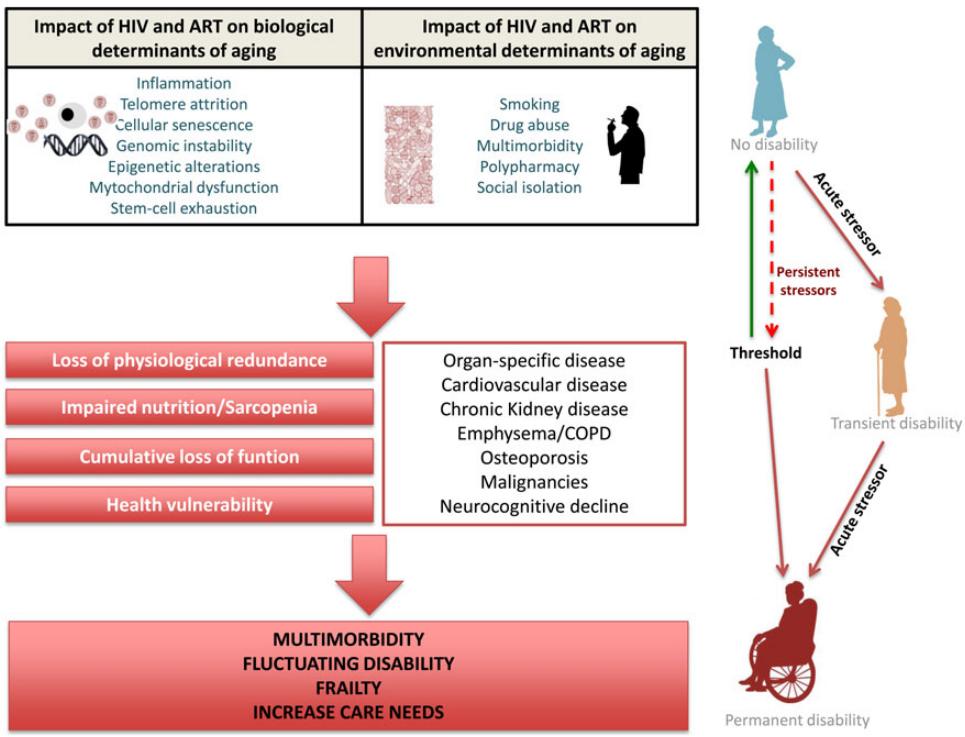

Figure 1. A model of the pathophysiology of frailty in human immunodeficiency virus (HIV)-disease. ART, antiretroviral therapy; COPD, chronic obstructive pulmonary disease.

Table 6. Proposed Assessment of Comorbidities in Stable HIV-Infected Patients >50 Years

Assessment	Tool	Follow-up Frequency	Comment
Lifestyle and prevention			
Diet	Dietary survey	Annual	
Body composition	Body mass index	Annual	
Exercise			Advise to engage in aerobic physical activity to reduce LDL-c, non-HDL-c, and blood pressure. Frequency: 3–4 sessions a week. Intensity: moderate to vigorous. Duration: 40 min on average
Tobacco use	Guided assessment	At each visit	Pursue smoking cessation in smokers.
Alcohol and illicit drugs	Guided assessment	At each visit	
Pharmacology			
Polipharmacy	Guided assessment	At each visit	
Optimize comedications	Clinical judgment	At each visit	
Drug-drug interactions	Interaction checker	At each visit	For example, at www.hiv-druginteractions.org
Comorbidities			
Cardiovascular disease			
Risk assessment	Framingham/ASCVD/ SCORE		
Hypertension	Blood pressure	Annual	
Diabetes	Serum glucose	Annual	Consider oral glucose tolerance test/HbA1c if fasting glucose levels of 5.7–6.9 mmol/L (100–125 mg/dL)
Lipids	TC, HDL-c, LDL-c, TG	Annual	
Liver disease			
Liver function	ALT/AST, ALP, Bilirubin		
Staging of liver fibrosis	FibroScan, serum fibrosis markers		In HCV and/or HBV-coinfected persons
Portal hypertension assessment	Hepatic ultrasound	6 mo	In HCV-coinfected persons with liver cirrhosis Child Pugh class A or B and Child Pugh class C awaiting liver transplantation; and in HBV-coinfected persons irrespective of fibrosis stage
Pulmonary disease			
Lung Imaging	Chest x-ray	As indicated	
Lung function	Spirometry	As indicated	
Kidney			
glomerular filtration rate	CKD-EPI	6 mo	
Kidney damage	Urine dipstick analysis, Urine albumin/creatinine ratio, protein/creatinine ratio	Annual	In individuals treated with tenofovir disoproxil fumarate, more specific markers of tubular function (ie, fractional excretions of phosphate and uric acid, urine concentrations of low molecular weight proteins) and more frequent monitoring may be needed, particularly in patients at high risk of renal toxicity.
Bone disease			
Bone profile	ALT, calcium, phosphate, vitamin D	6–12 mo	Due to cost constraints, it is controversial to universally screen vitamin D levels. In patients with low BMD or with tubular dysfunction, it seems reasonable to measure 25-OH-vitamin D levels and, eventually, parathyroid hormone levels before vitamin D supplementation.
Osteopenia/osteoporosis	Dual-energy x-ray absorptiometry	Every 10 y if BMD T score <−1.5 SD. Every 5 y if T score >−1.5 to −1.99). Every 1–2 y if T score < −2.5.	Recommended in all HIV-infected patients above 50 y.
Neurocognitive impairment			
Screening questionnaire	HIV Dementia Score	2 y	
Depression			
screening questionnaire	PHQ-2 questionnaire	As indicated	
Cancer screening			
Anal	Rectal exam, anal citology and eventually high-resolution anoscopy	Annual	In MSM or women with history of high-grade cervical, vulvar, vaginal dysplasia, or cancer. Evidence of benefit unknown.

Table 6 continued.

Assessment	Tool	Follow-up Frequency	Comment
Lung	Low-dose radiation chest scan	Annual	Controversial. Promoting smoking cessation is likely to have a greater impact on cancer prevention. High-risk criteria for participation in the NLST were age 55 to 74 y, a history of smoking at least 30 pack-years and, if a former smoker, had quit within the previous 15 y. Lung cancer is commonly diagnosed earlier in HIV-infected patients, who might benefit from initiating screening at earlier age.
Cervical	Cervical Papanicolay	1–3 y	
Breast	Mammography	1–3 y	
Prostate	PSA	2 y	Controversial. Discuss the small risk reduction against the potential harms.
Liver	Ultrasound and α-foetoprotein	6 mo	Controversial. Patients with cirrhosis and persons with HBV irrespective of fibrosis stage
Colorectal	Fecal occult blood testing, sigmoidoscopy, or colonoscopy at age 50 y. The risks and benefits of these screening methods vary.	As indicated	If average risk: screen in >50 y and continue up to 75 y. The risks and benefits depends upon the method used.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; ASCVD, arteriosclerotic cardiovascular disease; AST, aspartate aminotransferase; BMD, bone mineral density; CKD-EPI, chronic kidney disease epidemiology collaboration; HBV, hepatitis B virus; HCV, hepatitis C virus; HDL-c, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-c, low-density lipoprotein cholesterol; MSM, men who have sex with men; NLST, National Lung Screening Trial; PHQ-2, Patient Health Questionaire-2; PSA, prostate-specific antigen; SD; standard deviation; TC, total cholesterol; TG, triglycerides.

defects in the innate and adaptive immunity repeatedly associated with age-associated conditions [136].

CONCLUSIONS

Still, severe age-associated diseases are highly and increasingly prevalent among treated HIV-infected adults. In the framework of increasing health problems and multimorbidity in the aging HIV population, there is now a vivid debate about how the care should be delivered. Arguably, management of AIDS-defining conditions is no longer the dominant problem in many parts of the world, and HIV care warrants new skills. In the following years, HIV specialists will still require expertise on ART use, yet they will also need specific knowledge in the screening, prevention, and management of age-associated conditions. We think that the HIV specialist should ideally provide integrative care and bring together the screening, prevention, and treatment of most frequent comorbidities. Although this approach is increasingly observed in clinical guidelines [17], it can become unfeasible in routine care due to time and resource constrictions. We propose a model in which at-risk patients, ie, those older than 50 years, with 2 or more comorbidities or polypharmacy periodically undergo a directed and specific assessment (Table 6). In a near future, studies aimed at treating persistent inflammation, such as the REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV; ACTG5332) trial evaluating the effect of statins in HIV-infected subjects with no indication or statin use on the incidence of cardiovascular events or the ACTG5336 to reduce inflammation in treated subjects, will probably shed new light on how to prevent non-AIDS comorbidities linked with chronic HIV.

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APPENDIX

PANEL OF EXPERTS CONSULTED FOR THE ELABORATION OF THIS REVIEW

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