HIV-Related Metabolic Comorbidities in the Current ART Era

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KEYWORDS

- HIV
- Aging
- Comorbidity
- Multimorbidity
- Inflammation
- Immune activation

KEY POINTS

- As a consequence of earlier diagnosis and better treatment, HIV-infected persons are living longer but are also frequently exposed to effective antiretroviral therapy (ART) for longer duration.
- As patients age, they are challenged not only by HIV but also age-related diseases that may be affected by both the underlying HIV infection and ART.
- Persistent low-level inflammation likely plays a significant role in the accelerated appearance of these age-related diseases.
- Because of this complex interplay of HIV infection, ART-related factors, and traditional risk factors, HIV-infected patients are at increased risk for chronic conditions, such as cardiovascular disease, renal disease, bone disease, and diabetes mellitus, compared with uninfected persons, and may have onset of these conditions at an earlier age.

INTRODUCTION

The widespread use of potent combination antiretroviral therapy (ART) has produced significant gains in survival, resulting in an aging HIV-infected population in developed countries. In the United States, it is estimated that more than one-half of HIV-infected persons will be over age 50 years by 2015. This demographic shift to an older population has been accompanied by changing morbidity and mortality patterns, with a decline in the morbidity and mortality owing to AIDS and concomitant rise in the proportion owing to non–AIDS-related diseases.

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Aging and persistent inflammation place patients at increasing risk for many comorbidities, including cardiovascular disease (CVD), renal disease, diabetes, and low bone mineral density (BMD).\textsuperscript{13–16} Obesity and traditional risk factors, especially smoking, also play a role.\textsuperscript{17–23} Despite advances in ART, adverse effects and toxicities continue to affect long-term health, particularly with regard to dyslipidemia, insulin resistance (IR), bone loss, and renal dysfunction.\textsuperscript{24–28}

A disproportionate number of HIV-infected patients are ethnic minorities or of lower socioeconomic status, groups known to experience significant health disparities and greater risk for chronic disease.\textsuperscript{29,30} Higher rates of substance abuse may also contribute.\textsuperscript{9,31} Finally, chronic hepatitis C virus (HCV) coinfection is common among HIV-infected patients and can increase risk for diabetes mellitus, atherosclerosis, renal disease, and bone disease (Fig. 1).\textsuperscript{32–37}

Although further study is needed, the synergistic effect of the these factors seems to result in accentuated aging, in which HIV-infected patients are at increased risk for CVD, renal disease, diabetes mellitus, and low BMD compared with uninfected persons of a similar age.\textsuperscript{14,38} In addition, multimorbidity is highly prevalent among HIV-infected patients, affecting up to 65%.\textsuperscript{39–42} HIV-infected patients also seem to experience accelerated aging, in which they are risk for multimorbidity and frailty earlier in life.\textsuperscript{14,38,43}

Given the aging of the HIV-infected population, increasing morbidity and mortality owing to non–AIDS-related conditions, and the high prevalence of multimorbidity, HIV providers are increasingly called upon to balance treatment of HIV with prevention and treatment of other major chronic diseases. This paper reviews the epidemiology, pathophysiology, prevention, and treatment of important age-related comorbidities in HIV-infected patients, including atherosclerotic CVD, renal disease, obesity, diabetes mellitus, and bone disease.

![Impact on Cardiometabolic Comorbidities](image_url)

**Fig. 1.** HIV-related comorbidities.
CVD

Epidemiology

Atherosclerosis is a chronic inflammatory disease in which plaque formation is triggered by arterial wall injury, lipoprotein deposition, endothelial activation, and proinflammatory molecules, and in HIV-infected patients is likely owing to the complex interplay of HIV- and ART-related factors with traditional risk factors, although the pathophysiology is incompletely understood.44,45 CVD is a major cause of mortality among HIV-infected patients, responsible for up to 15% of deaths.3,4,9–12 HIV-infected patients are disproportionately impacted by CVD with increased carotid artery intima medial thickening, subclinical coronary artery atherosclerosis, endothelial dysfunction, and silent ischemic heart disease compared with uninfected controls.46–50 Atherosclerotic plaques in HIV-infected patients are more likely to have morphologic features associated with higher risk for rupture.51 Risk for acute myocardial infarction among HIV-infected patients is 1.5- to 2-fold greater than uninfected persons, and increased risk of cerebrovascular events has also been reported.52–57

HIV-Related Factors

HIV-related chronic immune activation and inflammation contribute to increased risk for CVD. Patterns of T-cell activation, as well as markers of monocyte and macrophage activation (soluble CD14 and CD163), have been linked to subclinical atherosclerosis.58–64 In the Strategies for Management of Antiretroviral Therapy (SMART) study, HIV-infected patients randomized to episodic rather than continuous ART had increased risk for CVD events (hazard ratio, 1.6; 95% CI, 1.0–2.5; P = .05), suggesting HIV replication is an important contributor.65 The SMART investigators subsequently demonstrated an association between elevated plasma HIV-1 RNA and interleukin-6 (IL-6), a proinflammatory cytokine involved in atherosclerotic plaque formation, and d-dimer, a biomarker of coagulation, as well as an independent association between incident CVD events and baseline markers of inflammation and coagulation (IL-6, high-sensitivity C-reactive protein, and d-dimer).45,66,67 In participants not taking ART, they observed an increase in serum procoagulants and decrease in anticoagulants compared with those on ART.68 These data indicate a relationship between HIV replication, inflammation, and CVD. In addition, there is evidence for an association between elevated plasma HIV-1 RNA and endothelial dysfunction with clear improvement in endothelial function after ART initiation.69–72

Immune activation is noted even among HIV-infected patients on ART, and although inflammatory markers decrease after ART initiation, some markers remain elevated compared with uninfected controls, indicating factors beyond HIV replication are involved.58–64 Reactivation of viral infections such as cytomegalovirus has been linked with subclinical atherosclerosis in HIV-infected patients.73–75 Early in HIV infection, there is massive depletion of CD4 cells in gut-associated lymphoid tissue, leading to increased microbial translocation, a process driving immune activation.76–78 In chronically infected patients, there is incomplete recovery of these cells after ART initiation.76 Thus, even HIV-infected patients with viral suppression on ART have significantly increased markers of microbial translocation compared with uninfected controls.79 Both lipopolysaccharide and soluble CD14 (sCD14), a lipopolysaccharide scavenger receptor on monocytes, have been associated with subclinical carotid artery atherosclerosis among HIV-infected patients.82 Lipopolysaccharide has been associated with elevated triglycerides, elevated low-density lipoprotein cholesterol, decreased insulin sensitivity, and higher Framingham risk score in HIV-infected patients.79
Finally, HIV itself is associated with dyslipidemia; a proatherogenic pattern of decreased high-density lipoprotein cholesterol, elevated triglycerides, and very low-density lipoprotein cholesterol is observed in ART-naïve patients.80

Traditional Risk Factors

Traditional risk factors such as age, smoking, dyslipidemia, hypertension, and diabetes mellitus must not be overlooked in the discussion of CVD.3,81–88 Up to 50% to 70% of HIV-infected patients are current cigarette smokers compared with 20% of the general population.20 In the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) cohort, smoking cessation was associated with a greater than 1.5-fold decline in adjusted incidence rate ratio of CVD events between the first year and more than 3 years after quitting.89 Another study on acute coronary syndrome reported a population attributable risk of 54% for smoking among HIV-infected patients as opposed to 17% in uninfected controls.90 As noted, dyslipidemia prevalence is higher with HIV than in uninfected patients, likely related to HIV and ART.40,52 Overweight/obesity is now common in the HIV-infected population and also increases risk for dyslipidemia, hypertension, and diabetes mellitus.16,91

Prevention

Two mainstays of CVD prevention among HIV-infected patients are treatment with ART to reduce HIV-related immune activation and inflammation and aggressive prevention and control of modifiable risk factors.65,92 The most recent antiretroviral guidelines recommend treatment of all HIV-infected patients with ART, regardless of CD4 count.93 Owing to the metabolic side effects of ART, all HIV-infected patients should be screened for dyslipidemia and diabetes mellitus at baseline and, thereafter, per HIV-specific guidelines.94 Routine HIV care should include counseling and pharmacotherapy for smoking cessation, counseling on physical activity, healthy dietary practices, weight loss in overweight/obese patients, and management of dyslipidemia, hypertension, and diabetes mellitus according to general population guidelines.95–97 In patients with baseline CVD risk factors or a prior history of CVD, providers should consider avoiding ART agents, which convey increased risk for dyslipidemia and IR. Whether there is a role for the anti-inflammatory effects of statins regardless of low-density lipoprotein cholesterol level is currently under study.98 As a consequence of guideline-driven care, polypharmacy is an all-too-common problem for HIV-infected persons and an area of concern as we try to balance disease prevention and medication toxicity for our aging population.14

RENAL

Epidemiology

The incidence of HIV-associated nephropathy, renal failure, and end-stage renal disease have declined thanks to improved virologic suppression with ART.99–103 Results from the SMART Study confirm the detrimental effects of uncontrolled viremia on renal function.65 Subjects who followed the treatment interruption strategy were at greater risk of developing fatal or nonfatal renal disease compared with patients randomized to continuous ART. In subsequent analyses from the same trial, treatment interruption was also associated with elevated inflammatory biomarkers, suggesting a relationship between viremia, inflammation, and renal disease.86 Despite controlled viremia, up to 30% of HIV-infected patients have prevalent renal dysfunction.15 One recent cohort identified 40% of HIV-infected patients with Stage 1 kidney disease (estimated glomerular filtration rate, <90 mL/min/1.73 m²) but only
3% with stage 2 or greater disease (estimated glomerular filtration rate, <60 mL/min/1.73 m²). Furthermore, ART-related renal toxicities have been identified: Proteinuria, renal tubular damage, interstitial nephritis, and nephrolithiasis. Other comorbidities, specifically hypertension, obesity and type 2 diabetes mellitus, are increasingly prevalent and likely increase the risk for renal disease.

Numerous antiretrovirals (ARVs) have been associated with renal dysfunction, including crystal deposition from drugs like indinavir and atazanavir. Tenofovir has been implicated to cause proximal tubular damage via mitochondrial toxicity, preventing reabsorption of filtered phosphorus, potassium, amino acids, and glucose. Tenofovir is widely recommended as a component of first-line therapy for HIV and seems to induce a modest amount of renal dysfunction in HIV-infected persons. The administration of boosted protease inhibitors can lead to decreased flux of tenofovir out of renal tubular epithelial cells and augment this tubulopathy. One study evaluated 964 patients initiating tenofovir-containing ART and 683 tenofovir-sparing ART. Exposure to tenofovir caused significantly greater glomerular filtration rate decline over 4 years. Evidence of proximal tubule dysfunction was also more prevalent among tenofovir-treated patients. The focus on tenofovir toxicity is particularly warranted given the expanding use of tenofovir for the treatment of hepatitis B infection and as a component of pre-exposure prophylaxis for HIV infection. A recent analysis from the iPREX study confirmed that creatinine clearance significantly declined among seronegative men who have sex with men who received emtricitabine/tenofovir for pre-exposure prophylaxis, although the decline was very modest and did not progress.

Prevention

Updated guidelines for screening and treating renal disease in HIV-infected persons by the HIV Medical Association of the Infectious Diseases Society of America recommend that all HIV-infected patients be screened annually for proteinuria and renal function through assessment of estimated glomerular filtration rate. Creatinine-based equations are helpful to identify persons with kidney disease, but serum creatinine may be affected by factors other than glomerular filtration, notably muscle mass, liver disease, dietary intake, age, race/ethnicity, and gender. Although the calculated equations account for some of the effects of muscle mass, age, race/ethnicity, and gender, they overestimate glomerular function for persons with lower creatinine intake or production, as can occur in persons with liver disease and possibly advanced HIV infection.

Recent data illustrate that formulae utilizing cystatin C, a small nonglycosylated protein, provide glomerular filtration rate estimates equivalent to serum creatinine-based measures that are not affected by muscle mass or decreased creatinine production. Several studies have examined cystatin C as a marker of kidney function in the setting of comorbidity and HIV-infected persons, and demonstrated that both creatinine and cystatin C were good markers of renal function; however, cystatin C was significantly associated with mortality endpoints. The authors concluded that serum cystatin C levels better reflected renal function independent of confounding factors, such as systemic inflammation or weight. Further research is needed to clarify whether cystatin C should be used to measure renal function in the setting of HIV.

Urine dipsticks and spot urine microalbumin quantification, which are used extensively in the management of diabetes mellitus, can also provide the HIV practitioner a means to monitor renal function and screen for preclinical dysfunction related to
HIV infection, its treatment, or concomitant comorbidities such as hypertension or diabetes mellitus. In 1 large cohort study, 13% of HIV-infected persons had at least trace proteinuria by urinary dipstick and 11% had urine microalbumin greater than 30 mg/dL. Considering the relatively inexpensive cost of spot urine microalbumin quantification, its integration into the routine care of HIV warrants further evaluation.

BONE DISEASE

Epidemiology

BMD, as measured by dual-energy x-ray absorptiometry (DXA) scans, serves as a surrogate marker of fracture risk and provides data to categorize persons with osteoporosis (T-score ≤−2.5) and osteopenia (T-score ≤−1.0) based on World Health Organization criteria. Similar to the data discussed for other non-AIDS comorbidities, low BMD, specifically osteoporosis and consequent fragility fractures, occur at an earlier age than is expected in HIV-infected persons. There is evidence that persons with HIV are at greater risk of having low BMD compared with non–HIV-infected persons and this change is associated with an increased risk of fracture. These findings were summarized nicely in a metaanalysis in which HIV-infected men and women, when compared with uninfected controls, had a 3.7-fold increased risk of osteoporosis (T-score ≤−2.5) and 6.4-fold increased risk of low BMD (T-score <−1.0). Effort is being taken to understand the etiology of bone loss, persons most at risk of developing fractures, and appropriate prevention and treatment strategies in HIV-infected persons. A recently published study evaluating BMD in HIV-infected adolescents and matched seronegative adolescents reported that there were striking reductions not only in BMD, as measured by DXA, but also bone strength or quality, as assessed by high-resolution computed tomography at the distal radius and tibia. This study has implications regarding long-term risk for fragility fractures for individuals who are infected early in life and fail to reach peak BMD.

Risk Factors for Low BMD

Common risk factors for osteoporosis in the general population are similarly associated with low BMD among HIV-infected persons and include older age, lower BMI, and menopausal state. In contrast with the general population, male sex has been associated with a greater risk of low BMD among HIV-infected cohorts. HCV coinfection and drug use are also associated with lower BMD and these risk factors are more common among HIV-infected persons.

The specific effects of individual ARVs is often challenging because combination therapy is the standard of care. That being said, there seems to be a catabolic window during the first 48 to 96 weeks after ART initiation in which HIV-infected individuals are particularly susceptible to bone loss, regardless of the ARVs selected, with subsequent stabilization of BMD by 96 weeks. In a recent metanalysis comparing ART-naïve, HIV-infected persons with a group on ART, the ART-treated cohort had a 2.5-fold greater risk of low BMD, largely osteoporosis. However, there was no adjustment for potential confounders. In other studies, longer ART duration has been associated with lower BMD. In the SMART study, loss of BMD was greater among patients receiving continuous ART when compared with patients on intermittent ART. Furthermore, markers of bone turnover were increased among subjects receiving continuous ART, and intermittent ART was associated with an initial decrease in bone turnover followed by stabilization. This latter stabilization occurred despite an increase in inflammatory markers and increased bone resorption cytokines. These findings support an ART-related bone toxicity.
Tenofovir is frequently implicated as a cause of bone toxicity owing to its effect at the proximal tubule leading to a Fanconi-like syndrome with phosphate wasting. Treatment with tenofovir led to significant reductions in BMD of children that were reversed with tenofovir cessation. Notably, longitudinal studies have confirmed that longer tenofovir duration is associated with greater loss of BMD. Data from pre-exposure prophylaxis studies in seronegative adults confirm the relationship between tenofovir and BMD loss.

A captivating ARV agent has recently piqued the interest among bone mavens in the HIV field: Tenofovir alafenamide fumarate (TAF), an investigational tenofovir prodrug. Data regarding changes in BMD comparing TAF versus tenofovir in combination with the same additional ARVs have confirmed the superiority of TAF over tenofovir at both total hip (−0.6% vs −2.4%; \(P<.001\)) and lumbar spine (−1.0% vs −3.4%; \(P<.001\)) BMD changes after 48 weeks of therapy.

The relationship between exposure to protease inhibitors and bone loss is also intriguing. In recently published work by Hernandez-Vallejo and colleagues, osteoblast precursor cells exposed to ritonavir boosted protease inhibitors lost proliferative capacity, demonstrated increased oxidative stress and markers of senescence and failed to differentiate into osteoblasts. These in vitro data suggest that the balance between osteoblast bone formation and osteoclast bone resorption is dysregulated by protease inhibitors, leading to excessive bone loss. The mechanism by which protease inhibitors induces loss of BMD remains unclear. Clearly, we will have numerous alternative ARV options to consider in the future.

**Fracture Risk**

The updated guidelines from the National Osteoporosis Foundation now recognize both HIV infection and ART as risk factors for osteoporosis and fragility fractures. This addition reflects the growing data on fractures and HIV. For instance, a 3-fold increased risk of incident fracture was identified among HIV-infected subjects in the HIV Outpatient Study (HOPS) when compared with a representative sample of the US population at large, with a striking increased risk among young (ages 25–54) HIV-infected persons. A similar 3-fold increased risk of any fracture was seen among HIV-infected persons in a Danish cohort. Another study evaluating fracture risk derived from US Medicare data, including 13,000 HIV-infected and 2.5 million seronegative persons, demonstrated a 50% increased risk of fracture among the HIV-infected cohort. As with low BMD, fracture risk has been reported to be increased within the catabolic window, an early period after ART initiation. Furthermore, certain ARVs have been associated with incident fractures, with exposure to tenofovir and protease inhibitors being reported most commonly. HCV has also been implicated in fracture incidence. Recently reported Medicaid data from five states demonstrated a 2-fold increase in fracture rate among HCV monoinfected, a 1.5-fold increase in fracture rate among HIV-infected, and an additive effect for coinfected persons compared with uninfected individuals. These data were confirmed in 2 other cohort studies, although data from the Veterans Aging Cohort Study failed to confirm the association of fracture with HCV. Of note, the authors of the latter study conjectured that, by controlling for fibrosis, they had mitigated the effects of HCV infection.

**Screening for Low BMD**

The appropriate time to initiate osteoporosis screening using DXA in HIV-infected persons is still slightly unclear, but current recommendations are to screen all HIV-infected postmenopausal women, HIV-infected men 50 years and older, and
younger HIV-infected persons with a recent fracture. A retrospective analysis of HIV-infected patients in Spain also helps us to understand how DXA findings may progress. In this study of mainly men with a median age of 39 and an average of 4 DXA scans, the median time to progression from normal BMD to osteopenia range was 6.7 years and occurred in approximately one-third of those with normal BMD at baseline. However, among those with a baseline T-score between −0.6 and −1.0, time to progression to osteopenia was only 1.7 years. Among those with osteopenia-range T-scores at baseline, time to progression to osteoporosis was more than 8.5 years among the 25% that progressed, shorter in those who were older (>40 years old) and with lower T-scores (<−1.8). These findings emphasize the importance of considering osteoporosis risk factors in determining overall screening rates and fracture risk. Other methods of assessing fracture risk in HIV-infected patients have been minimally evaluated. In 2 studies utilizing the World Health Organization’s FRAX calculator, fracture risk was underestimated in HIV-infected persons. However, the combined use of FRAX and the Aging Male Symptoms scale may be useful in HIV-infected men.

DIABETES MELLITUS

Epidemiology

Several cohorts of HIV-infected individuals in North America have demonstrated a high prevalence of diabetes mellitus (14%) as well as IR, a precursor for diabetes mellitus. This prevalence is similar to that demonstrated by data from the 2005 to 2006 National Health and Nutrition Examination Survey, where the crude prevalence for diabetes mellitus among the general US population was 13% and for prediabetes mellitus is 30% (either impaired fasting glucose or impaired glucose tolerance). Traditional risk factors, such as sedentary lifestyle, unhealthy diet, and obesity, were significantly associated with diabetes mellitus.

In the Multicenter AIDS Cohort Study, HIV-infected men had a greater odds of IR than HIV-negative men, regardless of ART exposure, and diabetes mellitus incidence was 4 times higher among HIV-infected men on ART compared with uninfected men. Furthermore, each additional year of nucleoside reverse transcriptase use (NRTI) increased the odds of hyperinsulinemia. A recent analysis evaluating 752 HIV-infected women enrolled in the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy and the HOPS reported that diabetes mellitus was present in 14.2% of the women. Similarly, the Women’s Interagency HIV Study demonstrated that HIV-infected women prescribed ART had greater IR as quantified by the Homeostatic Model Assessment (HOMA-IR) compared with HIV-negative women. Of note, the latter study reported that longer cumulative NRTI exposure was associated with greater HOMA-IR values.

Risk Factors

There have been many proposed etiologies for this increased risk for IR among HIV-infected persons, including ART. IR has been reported in HIV-negative subjects after brief exposure to ARVs, indicating that even short-term exposure to some, but not all ARVs, may induce IR. Multiple studies of long-term ART exposure, specifically cumulative NRTI use, have shown an association between these medications and an increased risk of IR and diabetes mellitus. Protease inhibitors, such as ritonavir, may act directly on mediators of glucose uptake, affecting glucose regulation. However, several studies in HIV-negative populations taking short-term, ritonavir-boosted lopinavir or unboosted atazanavir have reported conflicting findings.
regarding insulin metabolism, indicating that the causative pathway may be more complex and multifactorial.\textsuperscript{167–170}

Increased body mass index has a consistent association with IR. Although HIV disease is traditionally thought of as a wasting illness, patients engaged in care and treated with ART typically experience significant weight gain. A recent study illustrated that 60\% of HIV-infected patients gain weight once they engage in care.\textsuperscript{172} In a recent study of 681 HIV-infected adults, 44\% were overweight or obese (BMI >25.0 kg/m\textsuperscript{2}) and over 24 months, 20\% moved from normal to overweight/obese BMI categories.\textsuperscript{18} These data confirm the findings of other HIV cohort studies and likely reflect the obesity epidemic affecting the population as a whole in Western, industrialized nations.\textsuperscript{173} Clinicians should recognize the risk for both obesity and IR among their HIV-infected patients and develop preventive strategies.

IR and diabetes mellitus have been previously associated with HCV infection, likely mediated through impairment of hepatic glucose clearance.\textsuperscript{34} In a recent study investigating risk factors for HCV treatment failure among HIV-infected persons, IR was the strongest predictor of failure to achieve a sustained virologic response; the highest sustained virologic response rate (35\%) was in patients with an HOMA-IR of less than 2.\textsuperscript{174} IR has been shown to reduce treatment effectiveness in patients with HCV monoinfection, as well.\textsuperscript{175} Furthermore, IR is associated with steatosis and liver stiffness and possibly even increased risk of hepatocellular carcinoma, which may further complicate the management of liver disease in HIV-infected patients.\textsuperscript{34,176,177}

Thus, the strong association between HCV and IR has ramifications for treatment and long-term outcomes of both HIV and HCV infection.

Inflammation has been identified as a key player in the development of IR in the general population.\textsuperscript{178,179} A recent study in HIV-infected persons initiating ART reported that higher levels of the inflammatory markers high-sensitivity C-reactive protein, sTNFR1 and sTNFR2 were associated with an increased risk for diabetes mellitus despite suppressive ART.\textsuperscript{180} These data suggest that the inflammatory milieu of HIV infection may also contribute to development of IR. Inflammatory biomarkers are affected by other factors identified as independently associated with IR, most notably obesity and chronic HCV infection.\textsuperscript{37,181} Longer-term follow-up from prospective longitudinal cohorts will further elucidate the complex relationship between HIV-related chronic inflammation, ARV use, and IR.

\textbf{Obesity and HIV}

Before the availability of ART, AIDS wasting was a common AIDS-defining condition. However, the US obesity epidemic has spread into HIV clinics, as well. Up to two-thirds of the HIV populations in US and African populations have been found to be overweight or obese.\textsuperscript{18,172,182–187} In a rural South African population, obesity was more than 6-fold more common among HIV-infected women than men, but men were more likely to have hypertension associated with obesity.\textsuperscript{184} In a US population followed for 12 months after the initiation of ART, more weight gain occurred among women than men (8.6 vs 3.6 kg; \( P = .04 \)); among those started on PI-containing ART regimen than non–PI-containing ART regimen (9.0 vs 2.7 kg; \( P = .001 \)) and among those with lower CD4 counts (<200 cells/mm\textsuperscript{3}) than those with CD4 counts above 200 cells/mm\textsuperscript{3} (8.9 vs 0.3 kg; \( P < .0001 \)).\textsuperscript{187} These findings are supported by similar results from another US population in which HIV-infected persons with lower baseline CD4 counts (<50 cells/mm\textsuperscript{3}) and those treated with a ritonavir-boosted PI regimen had the greatest increases in BMI.\textsuperscript{18} With the comorbidities associated with obesity, including diabetes mellitus, CVD, obstructive sleep apnea, and urinary incontinence,
efforts to better understand and manage the weight gain and obesity after virologic suppression are needed.

SUMMARY

In the current ART era, the AIDS defining complications can be minimized with engagement in care and adherence to ART, yet the success of treatment has created new challenges. Particularly, the recognition of cardiometabolic comorbidities that seem to occur at an accelerated rate owing to persistent inflammation of HIV, ART toxicity, and preexisting health disparities for many HIV-infected persons. Future research will balance the aggressive guideline approach to these comorbidities with the potential complications of polypharmacy, quality-of-life issues, and alternative strategies such as exercise and dietary interventions. The next decade will see a brave, new world in the field of HIV.

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