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Fat Matters: Understanding the Role of Adipose Tissue in Health in HIV Infection

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Abstract

More than one-third of adults in the United States are obese, and obesity-related disease accounts for some of the leading causes of preventable death. Mid-life obesity may be a strong predictor of physical function impairment later in life regardless of body mass index (BMI) in older age, highlighting the benefits of obesity prevention on health throughout the lifespan. Adipose tissue disturbances including lipodystrophy and obesity are prevalent in the setting of treated and untreated HIV infection. This article will review current knowledge on fat disturbances in HIV-infected persons, including therapeutic options and future directions.

Keywords

HIV; obesity; inflammation; adipose tissue; lipodystrophy; HIV/AIDS; HIV infection; obesity and HIV; BMI; antiretroviral therapy; review

Introduction

More than one-third of adults in the United States are obese, and obesity-related disease accounts for some of the leading causes of preventable death [1]. Longitudinal studies suggest that mid-life obesity may be a strong predictor of physical function impairment later in life regardless of body mass index (BMI) in older age [2, 3], highlighting the benefits of obesity prevention on health throughout the lifespan. Adipose tissue disturbances including lipodystrophy and generalized obesity are prevalent in the setting of treated and untreated HIV infection. This article will review current knowledge on fat disturbances in HIV-infected persons, including therapeutic options and future directions.

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Discussion

Clinical Implications of Obesity and Body Fat Changes in HIV

The prevalence of obesity is increasing among HIV-infected persons, with up to 65% classified as overweight or obese [4-7]. ART initiation is often associated with weight gain partially attributed to a “return to health” phenomenon, with greater increases in weight seen in persons with the highest pre-ART HIV-1 RNA or lowest CD4+ T lymphocyte counts [8, 9]. In an AIDS Clinical Trial Group (ACTG) study (A5175) of ART initiation in resource-diverse settings, more than 25% of participants were overweight or obese at entry, and approximately 40% of participants were overweight or obese by week 144 [10]. These findings are consistent with prior observational studies on anthropomorphic changes in both resource-limited and resource-plentiful settings [11-13].

Weight gain following ART initiation has been associated with both beneficial and detrimental outcomes. While some weight gain may be beneficial particularly in wasted persons, there is likely a “tipping point” where weight gain begins to have a negative impact. For example, weight gain among underweight persons has been associated with a decline in high-sensitivity C-reactive protein (hs-CRP)levels, while weight gain among overweight or obese individuals has been associated with a significant increase in soluble CD14 (sCD14) levels (2015 Conference on Retroviruses and Opportunistic Infections, Seattle, WA; Erlandson, et al. Abstract 778). Similarly, a recent Veterans Aging Cohort Study analysis observed improved survival with weight gain in the first year of ART among underweight or normal weight but not overweight or obese participants [14]. Furthermore, overweight or obese HIV-infected individuals have a ≥67% prevalence of multi-morbidity [15]. In contrast, weight loss or failure to gain weight following ART initiation may be a poor prognostic sign or marker of concomitant infection or severe wasting [16].

Obesity is associated with hormone and cytokine imbalances, and chronic inflammation, all of which may contribute to its detrimental effects on multiple systems, including muscle [17]. Obesity and the metabolic syndrome are well-established risk factors for the development of physical function impairment or frailty among geriatric HIV-uninfected populations [18] and middle-aged or older HIV-infected adults [19-21]. Similarly, obesity is a known risk factor for diabetes mellitus and cardiovascular disease (CVD), and increased CVD risk has been described among obese and lipohypertrophic, HIV-infected adults [22].

While overall changes in body weight can have significant negative health impacts, the location of weight change may be of even greater importance. Adipose tissue accumulation in the trunk and viscera (lipohypertrophy) is well described following ART initiation. Up to 70% of HIV-infected individuals on ART may have abdominal or visceral obesity [8, 23-25], with changes not limited to older ART regimens. Indeed, in the recently completed ACTG study A5260, participants randomized to raltegravir or ritonavir-boosted darunavir or atazanavir with a backbone of tenofovir/emtricitabine had a mean visceral adipose tissue (VAT) gain of >30% after 96 weeks of therapy (2015 Conference on Retroviruses and Opportunistic Infections, Seattle, WA; McComsey, et al. Abstract 140). Discernment of lipohypertrophy in persons who are overweight or obese may be challenging, but a diagnosis of lipohypertrophy imparts important consequences and management considerations. In

particular, changes in VAT of as little as 5% are believed to affect metabolic syndrome risk [26], and a large study of body composition and HIV in the US demonstrated that increased central fat was associated with greater five-year mortality [27].

In addition to metabolic and inflammatory consequences, body fat changes are stigmatizing and may impact self-esteem and overall health perception. These negative perceptions can impact ART adherence and quality of life [28-31]. In one study, two-thirds of HIV-infected participants reported that they would be willing to trade a year of life not to have lipodystrophy [32].

Finally, given associations between chronic inflammation and the development of comorbid disease [33-35], there is an urgent need to better understand the causes of and develop interventions to attenuate the effects of chronic inflammation and immune activation in people living with treated HIV infection, including addressing adipose tissue and obesity-associated inflammation.

How Adipose Tissue Contributes to Inflammation

In the setting of weight gain, adipocytes may increase in number (hyperplasia) or volume (hypertrophy). Large, hypertrophied adipocytes may become hypoxic or accumulate toxic ceramides or other lipids; hypertrophied adipocytes also recruit pro-inflammatory immune cells, primarily activated macrophages, and cell death may result [36-38]. Activated macrophages stimulate a type 1 immune response leading to the production of tumor necrosis factor (TNF)-α and interferon (IFN)-γ; activated macrophages also lose the ability to store iron, which is then deposited in adipose tissue and associated with reactive oxygen species production and mitochondrial dysfunction [39]. Ultimately, adipocyte hypertrophy is associated with higher systemic levels of pro-inflammatory cytokines including TNF-α, interleukin (IL)-6, IL-8, IFN-γ, and lower levels of the anti-inflammatory cytokine IL-10.

Imbalance in the production of adipokines (adiponectin and leptin) and infiltration of immune cells into adipose tissue exacerbate the pro-inflammatory environment. Adipocyte hypertrophy and VAT accumulation suppress adiponectin, stimulate transforming growth factor (TGF)-β production [40] and trigger pro-fibrotic processes. Pericellular fibrosis limits adipocyte size (particularly in omental adipose tissue) in an attempt to curb further adipose tissue expansion [41]. While adipose tissue fibrosis is a normal, compensatory response to fat gain, it has unintended consequences. First, adipose tissue fibrosis does not reverse with weight loss [41], making prevention key. Second, while fibrosis limits adipocyte hypertrophy, when overfeeding continues and adipocytes cannot expand, ectopic fat deposition into sites such as the viscera and skeletal muscle occur. Ectopic fat deposition is associated with additional inflammation and metabolic dysregulation. Awareness of adipose tissue as an inflammatory and endocrine organ has improved understanding of the role of adipose tissue dysfunction and the development of diseases of inflammation, including insulin resistance and CVD [42].

Data on adipose tissue disturbances in HIV-infected persons are limited and generally restricted to lipodystrophy rather than generalized obesity. Central lipohypertrophy is associated with increased adipose tissue inflammation and apoptosis [43], while

dorsocervical lipohypertrophy is associated with adipose tissue fibrosis without inflammation, increased small adipocyte numbers and decreased vascularity [44]. A brown fat phenotype has been observed in dorsocervical subcutaneous adipose tissue (SAT) in association with protease inhibitor (PI) use and lipohypertrophy [44]. The shift to a brown fat phenotype, which is more metabolically active, may be an adaptive response to prevent further VAT expansion [45, 46], a hypothesis that is supported by the relative lack of inflammation in dorsocervical vs abdominal SAT in ART-treated patients irrespective of lipodystrophy status [47].

The known effects of specific antiretroviral agents on adipocytes are summarized in Table 1.

Cumulatively, these data support the hypothesis that adipose tissue physiology in HIV infection varies by fat type, anatomic location, and ART use rather than lipodystrophy status or fat volume alone. Impaired adipocyte differentiation has been reported with the older PIs (ritonavir, saquinavir) and the non-nucleoside reverse transcriptase inhibitors (NNRTIs, efavirenz, rilpivirine, and nevirapine) while newer therapies (including darunavir, maraviroc and raltegravir) appear to have minimal impact on adipogenesis or mitochondria. Growing evidence suggests depletion of mitochondrial DNA (mtDNA) in the adipose tissue of ART-treated and -untreated HIV-infected persons [47, 56, 57, 60-64]. Among ART-treated persons with lipodystrophy, mtDNA is depleted in both VAT and SAT, metabolism and adipogenesis markers are decreased in SAT, and less pro-inflammatory gene expression occurs in VAT, potentially protecting it from depletion [62]. Finally, SAT pro-inflammatory cytokines increase more with efavirenz (vs lopinavir-ritonavir) in combination with tenofovir and emtricitabine [59].

HIV-1-specific factors may also contribute to adipose tissue inflammation. The HIV accessory protein viral protein R (Vpr) may induce adipose tissue dysfunction by inhibiting peroxisome proliferator-activated receptor (PPAR)-γ and activating glucocorticoid genes, leading to lipolysis, macrophage infiltration into adipose tissue, loss of white adipose depots and hepatic steatosis [65]. Additionally, adipose tissue may serve as a reservoir for HIV [66], and longer duration of both HIV and ART use were positively associated with higher levels of TNF-α, caspase-3 and TGF-β [43].

Gut mucosal destruction following HIV infection and subsequent persistent microbial translocation are well described. Drainage of microbial products to the liver may cause local inflammation, increased synthesis of triglycerides and fat droplet accumulation in hepatocytes, contributing to visceral adiposity [67, 68]. Additionally, both HIV infection and obesity are independently associated with gut microbiome alterations and increased intestinal permeability that further promote local and systemic inflammation [69-75]. Although a recent study demonstrated higher levels of monocyte activation and systemic inflammation in obese vs non-obese HIV-infected persons, additional research is needed to determine whether HIV and obesity have a synergistic effect on the burden of inflammation-related metabolic disease.

Finally, the pro-inflammatory, pro-atherogenic and pro-thrombotic renin angiotensin system may be activated in HIV infection and/or by ART [76, 77]. Renin angiotensin activity

increases with VAT volume irrespective of HIV serostatus [76], but studies have been inconclusive as to whether renin angiotensin system inhibition may have beneficial effects on VAT or inflammation in HIV [78-80].

Implications of Ectopic Fat

Ectopic fat deposition is associated with inflammation and adverse metabolic impact beyond that seen with generalized obesity [81]. Associations between intra-abdominal VAT and increased metabolic disease risk (including CVD) are well described both in cross-sectional and longitudinal studies [81, 82]. In a cross-sectional study of nearly 600 HIV-infected men on stable ART, greater VAT, liver fat, and epicardial fat were independently associated with CVD after adjusting for traditional CVD risk factors [83]. HIV-infected participants in the CHARTER study with increased visceral adiposity (estimated by waist circumference ≥88 cm in women or ≥102 cm in men) had significantly worse neurocognitive function. Furthermore, an association between higher interleukin (IL)-6 levels and poorer neurocognitive function was found only among those with the largest waist circumferences, supporting a link between visceral adiposity, inflammation, and neurocognitive function in HIV-infected persons [84].

Similar adverse outcomes are found in other ectopic fat sites: in an older, HIV-uninfected population, skeletal muscle lipid content was a better predictor of insulin resistance than BMI, waist-to-hip ratio, or total body fat [85, 86]. Similarly, computed tomography (CT)-estimated paraspinal fat was a significant predictor of metabolic syndrome in women after adjustment for BMI and VAT [87]. Furthermore, skeletal muscle fat had functional consequences: greater thigh skeletal muscle fat was independently associated with lower muscle strength, slower chair rise time, and slower gait speed [88-90]; and fatty infiltration of the trunk muscles has been cross-sectionally and longitudinally associated with impaired physical function [91]. Surprisingly, HIV-infected participants in the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) Study had significantly lower intermuscular adipose tissue (by magnetic resonance imaging) compared to HIV-uninfected controls, a finding that was attenuated but persisted in multivariate analyses [92]. In contrast, a greater amount of mid-thigh muscle bundle fatty infiltration (estimated by CT scan) was found among middle-aged, HIV-infected vs HIV-uninfected men after multivariable adjustment including VAT and SAT. Furthermore, the fatty infiltration increased over time among HIV-infected compared to HIV-uninfected men (2015 Annual Meeting of the Endocrine Society; San Diego, CA; Natsag et al. Abstract FRI-229). Among younger, HIV-infected persons with lipodystrophy syndrome, greater CT-estimated fatty infiltration of the psoas muscle but not BMI, SAT, lean body mass, or ART, was associated with insulin resistance [93]. These findings suggest that skeletal muscle may be a clinically relevant ectopic fat location in HIV-infected persons, impacting both metabolic and physical function outcomes. In summary, fat location may be a better marker of metabolic risk than overall adiposity, but further studies are needed to compare deposition sites among HIV-infected individuals with and without lipodystrophy.

Adipose Tissue Quality vs Quantity

Normal, healthy adipocytes are small, well differentiated and contain a modest lipid droplet. During weight gain, adipocytes become larger, less well differentiated and engorged with lipids [94, 95], making them less dense. During wasting, adipocytes become smaller and contain fewer lipids [96, 97], increasing density. Thus, changes in adipose tissue health appear to relate to changes in adipose tissue density; however, a direct comparison of (CT-quantified) adipose tissue density and histopathology has only been reported in non-human primates to date. In that study, denser VAT was associated with smaller adipocytes, lower serum leptin, and higher adiponectin levels, but not with levels of monocyte chemoattractant protein (MCP)-1, IL-6, CRP or T lymphocyte or monocyte gene expression [98].

Adipose tissue health has important implications: First, fat is an active immune and endocrine organ, and adipocyte dysfunction has been linked to pro-inflammatory cytokine expression and inflammatory diseases including insulin resistance and CVD [99]. Second, determination of adipose tissue health may aid understanding of physiologic phenomena such as metabolically healthy obesity (described below). Third, HIV-associated and ART-associated adipose tissue dysfunction are well documented and contribute to comorbid disease. Adipose tissue health in HIV remains understudied; however, ongoing ACTG and Multicenter AIDS Cohort Study investigations may help clarify how best to assess adipose tissue quality and its potential clinical implications in HIV-infected persons.

Is Fat Always Bad? Metabolically Healthy Obesity and Obesity in Older Age

Although obesity is generally associated with the development of metabolic disorders, a state of obesity without overt cardiometabolic disease, “metabolically healthy obesity”, has been described. Metabolically healthy obesity has been variably-defined in differing populations [100-102], leading to prevalence estimates ranging from 6-40% [103]. The existence of metabolically healthy obesity is controversial, but supported by the fact that metabolic dysregulation is a heterogeneous process that also occurs in the absence of obesity. Persons with metabolically healthy obesity may have less VAT and systemic inflammation and more favorable immune profiles than the metabolically unhealthy obese [104-106], further supporting a spectrum of metabolic health within obesity. In contrast, some studies have suggested increased mortality, increased CVD risk, and differences in body composition and fat distribution in HIV-uninfected persons meeting criteria for metabolically healthy obesity, suggesting that this state is not entirely benign [103, 107-112]. It is unknown whether metabolically healthy obesity exists in HIV-infected persons. Given the prevalence of metabolic syndrome in HIV (up to 45% vs 25% in the general population [113]), the metabolic effects of HIV and ART, and the persistent immune activation and inflammation associated with even virologically-suppressed HIV, it is possible that metabolically healthy obesity may not exist in HIV-infected persons, and/or that metabolic health in this population must be defined differently (2015 International Workshop on Co-morbidities and Adverse Drug Reactions in HIV; Barcelona, Spain; Lake et al. Abstract ADRLH-33).

Another paradox is that an overweight or obese body weight among older adults is associated with improved survival, and weight loss late in life can portend a poor prognosis.

A strong association between mortality and weight loss has been well-described among older, HIV-uninfected adults independent of underlying disease or comorbid illnesses [114-117]. One longitudinal study observed an increased risk of death among older adults (mean age 73) who experienced any appreciable weight loss after the age of 21 and among underweight older adults in the 3rd-8th decades of life [115]. Reports among HIV-infected adults are more limited but similar in implication: in the Nutrition for Healthy Living cohort, weight loss from baseline and weight loss ≥5% over a 6-month period were significant predictors of mortality [118, 119].

Interventions to Modify Adipose Tissue in HIV

ART selection—ART initiation is associated with a gain in overall body weight that may contribute to VAT gains or lipohypertrophy [8, 23, 120-122]. Therefore, initiation of or switch to more "fat friendly" regimens is an appealing option, but should not be based upon changes in body weight only (see *Implications of Ectopic Fat).* For example, in ACTG study A5175, participants were randomized to efavirenz with either FTC/TDF or 3TC/ZDV. The FTC/TDF arm had significantly greater increases in overall weight as well as waist, hip, mid-arm, and mid-thigh circumferences. However, all cases of lipoatrophy occurred in the 3TC/ZDV arm, which also had greater gains in waist-hip ratio (suggestive of subtle hip lipoatrophy with relative VAT gain). Among more contemporary regimens, these differences are less apparent [10]. In ACTG study A5224s, participants randomized to ATV/r had a small but significantly greater increase in body weight than participants randomized to EFV-based therapy [123], with no significant differences seen by NRTI backbone (ABC/3TC or TDF/FTC). Although integrase inhibitors have generally been associated with smaller changes in weight and fat distribution, ACTG study A5260 observed no significant differences between raltegravir and two contemporary ritonavir-boosted PIs, darunavir or atazanavir, all with an FTC/TDF backbone (2015 Conference on Retroviruses and Opportunistic Infections; Seattle, WA; McComsey, et al. Abstract 140).

Similarly, switching ART may not reverse VAT accumulation [124-127]: HIV-infected women with central adiposity on ART switched to raltegravir from PI or NNRTI-based therapy had no significant changes in SAT or VAT area but did have significant reductions in sCD14 [126]. In the SPIRAL-LIP sub-study, participants randomized to switch from a boosted PI to raltegravir had no significant change in total adipose tissue or VAT, whereas those continuing boosted PI therapy for 48 weeks had significant increases in both [124]. In the SPIRAL parent study, switch to raltegravir was associated with significant reductions in hs-CRP, monocyte chemotactic protein (MCP)-1, IL-6, and TNF-α but not IL-10 or adiponectin, and it is not clear to what extent changes in adipose tissue explain the changes in inflammatory markers [128]. In contrast, a switch to raltegravir from stavudine therapy among lipodystrophic individuals resulted in improvements in whole body and limb fat quantity, trunk/limb fat ratio and fat mass index, with restoration of mtDNA and adiponectin levels [52].

Growth hormone (GH) axis therapies—Adiposity significantly reduces both GH secretion and pulsatility [129], thus, therapies targeting the GH axis have been of interest for obesity and lipodystrophy. Although GH has effectively decreased VAT in HIV-uninfected

and -infected populations, with some studies also reporting a simultaneous reduction in CRP, reduction in VAT was at the expense of insulin resistance, multiple side effects, and loss of SAT. Thus the clinical utility of GH for obesity treatment has been limited. Of note, many initial studies administered supra-physiologic doses of continuous GH, and subsequent trials have attempted to more closely mimic physiologic levels or the pulsatile nature of GH. A subsequent, low-dose GH trial in HIV titrated doses to achieve insulin-like GH levels within the normal range, and resulted in marginally but significantly improved VAT and worsened glucose tolerance [130]. A GH releasing hormone analogue, tesamorelin, was FDA approved in 2010 after clinical trials demonstrated significant reductions in VAT with less impact on insulin resistance and no significant difference in side effects vs placebo outside of injection site reactions and edema. In contrast to the low-dose GH study where no significant changes in adiponectin or other cytokines were observed, tesamorelin use has been associated with significant improvements in adiponectin, tissue plasminogen activator (tPA) and plasminogen activator inhibitor (PAI-1) that corresponded to reductions in VAT [131, 132]. Recently, tesamorelin has also been shown to reduce VAT in obese, HIV-uninfected persons [133].

Exercise—In epidemiologic studies, regular physical activity is associated with reduced risk of inflammation-associated disease, including dementia, cancer, CVD, and insulin resistance. In contrast, prolonged physical inactivity is associated with VAT accumulation and elevation of multiple pro-inflammatory cytokine levels. Some of the benefit of exercise may be explained through alteration in systemic cytokines [134, 135], however, few recent studies have explored the impact of exercise on markers of inflammation or immune activation in HIV-infected adults, particularly in regards to body composition changes. A systemic review published in 2010 summarized the effects of exercise in HIV-infected adults, with prior studies primarily focused on wasting or lipodystrophy: aerobic exercise generally led to improvements in BMI, triceps SAT, waist circumference, and waist-to-hip ratio [136]. Since then, a factorial intervention of lifestyle modification with or without metformin among HIV-infected adults with the metabolic syndrome observed a trend towards greater VAT reductions (without SAT loss) in the metformin group, and significantly greater reductions in intra-myocellular lipid content and hs-CRP in the lifestyle modification group [137]. In a small study of 18 HIV-infected participants with lipodystrophy randomized to 16 weeks of strength or endurance training, significantly greater decreases in total and limb fat mass were seen in the strength training group, while significantly greater reductions in systemic inflammation (hs-CRP, IL-6, TNF-α, and IL-18) were observed in the endurance group, suggesting that the reduction in inflammation was not due to changes in fat mass alone [138]. Thirty-five older adults completing a 12-week intervention of endurance with or without strength training demonstrated significant decreases in IL-6, hs-CRP, d-dimer, and IL-18 (2014 Conference on Retroviruses and Opportunistic Infections; Boston, MA; Longo, et al. Abstract 763). Finally, strength training led to decreases in trunk fat and triglyceride levels, but neither strength nor cardiovascular exercise decreased lipopolysaccharide levels (a marker of microbial translocation) [139].

Other interventions—Recently, nutritional interventions, including those targeting the intestinal microbiome, have gained traction as potential therapies for adipose tissue

dysfunction. In an animal model of diet-induced obesity, arginase inhibition ameliorated obesity-induced adipose tissue inflammation by reducing macrophage infiltration into adipose tissue, improving adipose tissue monocyte profiles, and decreasing pro-inflammatory cytokine expression [140]. Several studies have suggested that probiotic supplementation may help improve adipose tissue dysfunction by "resetting" the gut microbiome, which could help restore gut mucosal integrity, decrease microbial translocation, and decrease systemic inflammation. In the recent Probio-HIV study, ART-treated, HIV-infected adults treated with probiotics demonstrated reduced CD4+ T lymphocyte activation and reduced plasma levels of lipopolysaccharide binding protein and hs-CRP [141]. Similar studies have demonstrated improvements in d-dimer, IL-6 and lipopolysaccharide binding protein [142, 143]. An upcoming ACTG study will study the effect of the probiotic Visbiome on markers of microbial translocation, inflammation and immune activation in adults on suppressive ART.

Recent data suggest that trimethoprim sulfamethoxazole use at the time of ART initiation may improve some markers of microbial translocations without restoring the gut blood-barrier, a finding the authors hypothesized was mediated through modulation of the gut microbiome [144]. Finally, in an animal model of obesity, maraviroc therapy was associated with simultaneous improvements in gut *Enterobacteriales*, body weight gain, insulin sensitivity and liver fat [145].

Conclusions

While data on the contribution of adipose tissue dysfunction to health in treated HIV infection are emerging, many questions remain unanswered, including how adipose tissue physiology may be unique in HIV infection and/or with ART selection, the trajectory of body weight and hip/waist circumference throughout the lifetime of an HIV-infected person and/or the effects of obesity duration in HIV-infected compared to uninfected populations. Additionally, whether these associations differ by ART era and timing of ART initiation also remains unknown. Although multiple ongoing studies aim to address some of these questions, additional research is needed, particularly in regards to tissue-level physiology and the effects of newer antiretroviral agents.

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Table 1
Known effects of specific antiretroviral agents on adipocytes

Type of Adipose Tissue Disturbance	Implicated Antiretroviral Agents
Impaired adipogenesis or adipocyte differentiation or function	Lopinavir/ritonavir [48, 49], ritonavir [48], efavirenz [50, 51], rilpivirine [50], stavudine [52]
Pre-adipocyte autophagy and apoptosis	Atazanavir [53]
Impairment of lipid and/or glucose metabolism	Atazanavir/ritonavir [54], lopinavir/ritonavir [48, 49], ritonavir [48], ± darunavir [48, 49], NNRTIs [54], efavirenz [50], NRTI [54]
Impairment of mitochondrial function	Atazanavir [53], azanavir/ritonavir [48], saquinavir [55], lopinavir/ritonavir [48], ritonavir [48], NRTIs [52, 56-58]
Pro-inflammatory	Atazanavir/ritonavir [48] lopinavir/ritonavir[48], ritonavir [48], efavirenz [50, 51, 59], rilpivirine [50]
Prelamin A accumulation	Protease inhibitors [44]