Purpose of review
To report on the recent advances on lipids, diabetes, and body fat in HIV-infected patients from the perspective of aging.

Recent findings
HIV infection causes microbial translocation and inflammation that contribute to hypertriglyceridemia and insulin resistance, and quantitative and qualitative HDL-cholesterol changes that further contributes to atherosclerosis. These changes are incompletely reversed by antiretroviral therapy. Protease inhibitors have the worse lipid profile among the currently used antiretroviral drugs. Etravirine, maraviroc, and raltegravir have a lipid impact better than other antiretroviral classes. The importance of genetic background on dyslipidemia of HIV-infected patients is becoming increasingly known. Lipodystrophy is associated with inflammation, dyslipidemia, diabetes, hypertension, and functional decline. Lipohypertrophy is becoming more common in HIV-infected patients influenced by the current obesity epidemics in the general population.

Summary
Inflammation, cholesterol abnormalities, and lipodystrophy caused by both HIV infection and antiretroviral therapy may pose aging HIV-infected patients at a higher risk of comorbidities and frailty despite sustained viral suppression. Healthier lifestyles and strategies specifically addressed to diminish the impact of these pathophysiologic abnormalities will be needed for preserving the overall health in aging HIV-infected persons.

Keywords
antiretroviral therapy, diabetes, dyslipidemia, lipodystrophy

INTRODUCTION
Prevention and treatment of dyslipidemia and diabetes mellitus have become an increasingly important part in the long-term management of HIV-infected patients. Incidence of these metabolic diseases increases with age and other traditional risk factors such as obesity, smoking, and genetic predisposition. In HIV-infected patients, there may be also specific factors related to HIV infection, including chronic immune deficiency, immune activation, and inflammation, and specific antiretroviral drug’s effects on plasma lipids, insulin resistance, and probably on immune system and inflammation. This paper reviews the current knowledge on lipid disturbances, insulin-glucose homeostasis, and body fat composition in aging HIV-infected patients.

Aging is associated with changes in plasma lipids, insulin sensitivity, and body fat composition that expose older adults to a host of metabolic complications [1]. Plasma total cholesterol increases with age secondary to increasing levels of LDL-cholesterol. This increase is primarily because of a decrease in lipid metabolism which, in turn, is secondary to a decrease in both number and function of LDL receptors in the hepatic and extrahepatic cells. Although body fat increases with age and is preferentially accumulated in the abdominal region, there is a decrease in subcutaneous fat similar to but slighter than that of HIV-associated lipoatrophy [2]. With aging, there is both an increase in the release of free fatty acids from adipocytes and a decrease in the oxidative capacity of tissues. The increased nonoxidative disposal of free fatty acids leads to insulin resistance and increasing VLDL cholesterol in plasma. Older adults are at increasing risk for the development of type 2 diabetes because of the combined effects of increasing insulin resistance and impaired pancreatic islet
function with aging. Age-related insulin resistance appears to be primarily associated with adiposity, sarcopenia, and physical inactivity [3]. Aging also contributes to increasing abdominal obesity through cortisol and sexual hormones changes, decrease in physical activity, and hypercaloric diets [4**]. Major endocrinopathies seen in physiologic aging are type 2 diabetes mellitus, testosterone deficiency, sarcopenia, low bone mineral density, and thyroid deficiency [5].

GENERAL ASPECTS OF METABOLISM

It seems clear that lifestyle conditions play an important role in preventing comorbidities. Adequate nutritional supplementation is needed in addition to antiretroviral therapy to promote weight gain, improve immune response and physical activity in HIV-positive patients who present at antiretroviral therapy initiation with weight loss [6]. Exercise training increases lean mass, decreases oxidative markers, and improves immune function in virologically suppressed patients [7]. With increasing rates of obesity among HIV-infected persons similar to the pattern observed in the general population [8], efforts should be done to promote healthy lifestyles among aging HIV patients.

Metabolic syndrome in HIV persons is associated with worse clinical outcomes as in the general population, but constituents of metabolic syndrome differ between HIV and non-HIV persons. An analysis of the Nutrition for Healthy Living cohort study identified metabolic syndrome [adjusted hazard ratio 2.3, 95% confidence interval (CI) 1.1–4.7] or high triglycerides (adjusted hazard ratio 4.09, 95% CI 1.5–6.5) as independent factors for an increased risk of mortality after 36 months of follow-up [9*]. In contrast to the general population for whom insulin resistance and its surrogate markers abdominal obesity and high glucose are the most prevalent criteria of metabolic syndrome, high triglycerides and low HDL-cholesterol are the most prevalent criteria of metabolic syndrome in HIV-infected persons. Most chronic inflammatory conditions are associated with an inflammatory dyslipidemic profile [10].

In the setting of HIV infection, microbial translocation may contribute to elevated triglycerides, insulin resistance, and risk of myocardial infarction. Among HIV-infected individuals during prolonged antiretroviral therapy, greater microbial translocation was associated with lower levels of large HDL particles [11*] and with higher triglycerides, LDL-cholesterol, insulin resistance, and Framingham score [12*].

There is a relationship between CD4 cell counts and aging regarding the impact of HIV infection on morbidity and mortality of HIV-positive patients. Data from the UK Collaborative HIV Cohort Study showed that older people may be at higher risk of progression than their younger counterparts, even if their CD4+ T-cell counts are the same [13]. In addition, recent data from the same cohort have shown that age modifies the associations between CD4 count and plasma albumin and hemoglobin levels [14*]. A given reduction in CD4 count was associated with a greater reduction in hemoglobin and albumin concentrations among older people living with HIV. These findings increase our understanding of how the metabolic impact of HIV is influenced by age.

GENERAL ASPECTS OF LIPIDS

A longitudinal study of HIV-negative homosexual men in Australia confirmed that decline in HDL-cholesterol was the characteristic proatherogenic change after HIV seroconversion [15]. Interestingly, in this study, HIV seroconversion was not associated with significant changes in other lipids, markers of inflammation and coagulation, or vitamin D. These finding contribute to the gap in evidence regarding the impact of HIV infection per se, independent of antiretroviral therapy, on risk of cardiovascular disease and other comorbidities.

A large body of genetic and epidemiological evidence suggests a direct association between an elevated plasma lipoprotein (a) level and an increased risk of cardiovascular disease. Lipoprotein (a) levels are, to a major extent, regulated by genetics. Beyond plasma lipoprotein (a) levels, use of allele-specific apo(a) levels assessing the amount of lipoprotein (a) associated with a defined apo(a) allele size provides a key characteristic of the risk conveyed by lipoprotein (a). In a study with 139 white and 168 black HIV-infected
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patients, allele-specific apo(a) levels were higher in individuals with high CD4 cell counts or low plasma HIV RNA, suggesting that HIV infection activity reduced allele-specific apo(a) levels [16]. Higher allele-specific apo(a) levels associated with atherogenic small apo(a) sizes might contribute to increased cardiovascular risk in HIV-infected individuals with improved disease status.

Initiation of antiretroviral therapy with nucleoside reverse transcriptase inhibitors including zidovudine, stavudine, tenofovir, or lamivudine and nonnucleoside reverse transcriptase inhibitors nevirapine or efavirenz in African patients was associated with an increase in total cholesterol, but a greater increase in HDL-cholesterol, therefore leading to a lower total-to-HDL cholesterol ratio [17]. In an Australian study comparing lipid and vascular outcomes, initiation of antiretroviral therapy at 1 year led to greater increases in total cholesterol and triglycerides in patients treated with protease inhibitor-based regimens, and a greater elevation of lecithin:cholesterol acyltransferase (LCAT) in patients treated with regimens containing nonnucleoside reverse transcriptase inhibitors compared with patients not starting antiretroviral therapy and historic non-HIV-infected controls [18]; there were no differences in carotid intima-media thickness, pulse wave velocity, or brachial flow-mediated dilation. A Portuguese cohort study confirmed increases in total and LDL cholesterol and triglyceride levels with both protease inhibitors and nonnucleoside reverse transcriptase inhibitors in antiretroviral-naive patients after 3 years, but increase in HDL-cholesterol was higher with nonnucleoside reverse transcriptase inhibitors [19]. These studies highlight common (due to viral suppression) and differential (due to antiretroviral drugs) lipid effects on starting antiretroviral therapy (due to viral suppression) and differential (due to antiretroviral therapy, inflammation, immune system, cardiovascular disease, and the RANKL–osteoprotegerin axis).

Plasma triglycerides and HDL-cholesterol are inversely related in metabolic syndrome because of exchange of VLDL-triglycerides for HDL-cholesterol esters catalyzed by CETP. However, dyslipidemic HIV patients on antiretroviral therapy have a distinctive low HDL cholesterol plasma concentration adjusted for triglycerides [22]. HIV patients show a weak inverse relationship between HDL-cholesterol and triglycerides that is not explained by altered total CETP activity but from a non-CETP-dependent mechanism or a decrease in CETP function because of inhibitors of CETP activity in HIV patients’ plasma [23].

Lipid changes in HIV persons may have a clinical impact beyond that well known on cardiovascular disease. Patients in the Multicenter AIDS Cohort Study showing increases in total cholesterol greater than 50 mg/dl with the initiation of antiretroviral therapy had greater decreases in estimated glomerular filtration rate at 3 and 5 years relative to those showing increases or less 50 mg/dl [24]. In a small matched cohort study of HIV patients who had a low cardiovascular risk profile, serum levels of the receptor activator of the NF-κB ligand (RANKL) and osteoprotegerin in HIV patients were perturbed compared with HIV-uninfected individuals and cholesterol levels correlated significantly with the RANKL–osteoprotegerin axis in HIV infection [25], suggesting complex interplays between HIV infection, antiretroviral therapy, inflammation, immune system, cardiovascular disease, and the RANKL–osteoprotegerin axis.

Metabolomics is the unbiased identification and quantification of small molecules in biological fluids. In the context of disease, metabolomics has been used to identify novel clinical biomarkers and therapeutic targets. In a study performing untargeted metabolomic profiling of plasma from two independent cohorts of HIV-infected individuals with
late-stage disease on protease-inhibitor-based antiretroviral therapy to identify a metabolite signature that distinguishes HIV infected from healthy controls, lipid alterations were linked to markers of inflammation, microbial translocation, and hepatic function, suggesting that therapeutic strategies attenuating innate immune activation and hepatic dysfunction may be beneficial for the prevention and treatment of metabolic disorders in HIV patients [26].

Treating hypertriglyceridemia may be challenging in some HIV-infected patients. A recent study compared three different therapeutic interventions. Fibrates were more effective than fish oil or atorvastatin at lowering plasma triglycerides in HIV-infected patients with hypertriglyceridemia [27], suggesting that fibrates should be the first choice.

**LIPID EFFECTS OF ANTIRETROVIRAL THERAPY**

Antiretroviral drugs may have toxicity profiles differentially affecting the risk for or control of comorbidities. Efforts have been done in the recent past to improve our knowledge on the potential differential impact among current antiretroviral drugs on physiologic functioning of different organs or systems. A major objective of current life-lasting antiretroviral therapy is not to promote any further the development or progression of concomitant comorbidities that are part of the human aging process.

Stavudine is still used in some developing settings. A randomized clinical trial in South Africa assessed whether the reduction in stavudine dose might attenuate its toxic effects compared with tenofovir after 1 year of follow-up [28]. Although high-dose stavudine performed worse than low-dose stavudine in fasting glucose and homeostatic model assessment (HOMA), and showed a greater decrease in adiponectin than low-dose stavudine and tenofovir, both stavudine arms showed greater increases in insulin and C-peptide levels, greater decreases in skinfold thickness consistent with lipoatrophy, and a number of other mitochondrial toxicities such as neuropathy or hyperlactatemia compared with tenofovir arm. This study adds to previous evidence suggesting that stavudine even at lower doses is not a well tolerated antiretroviral therapy and should not be used.

Another study performed in Italy compared 48-week lipid effects of efavirenz or atazanavir and ritonavir, both combined with tenofovir and emtricitabine in antiretroviral-naïve patients [29]. Patients assigned to efavirenz had greater increases in total, LDL, and HDL cholesterol, and in large HDL particles, but not in total-to-HDL cholesterol ratio or indication for lipid-lowering interventions relative to patients assigned to atazanavir and ritonavir. The 96-week final results of the kivexa vs. truvada, both administered with efavirenz, in Antiretroviral-Naïve Patients (ASSERT) study suggest that tenofovir-based therapy is associated with greater increases in bone turnover and greater loss of bone mineral density, greater increases in markers of tubular dysfunction, and lower plasma cholesterol values (although no difference in total-to-HDL cholesterol ratio) than abacavir-based therapy [30]. Ritonavir-boosted atazanavir and darunavir are protease inhibitors recommended for the initial treatment of HIV infection because each has shown better lipid effects and overall tolerability than ritonavir-boosted lopinavir. A randomized clinical trial looked at the extent to which lipid effects and overall tolerability may differ between treatments with atazanavir and darunavir, and whether atazanavir-induced hyperbilirubinemia may result in more favorable metabolic effects [31]. Results at 24 weeks showed no significant differences in total cholesterol change or overall tolerability between both protease inhibitors, but there was a trend toward a lower total-to-HDL cholesterol ratio with atazanavir and ritonavir and this effect was unrelated to bilirubin. Longer follow-up is needed to ascertain whether both ritonavir-boosted protease inhibitors are similar or not regarding lipid effects. Whether different effects between antiretroviral drugs observed in clinical trials will have differential clinical consequences on comorbidities associated with aging is not yet well known.

Increasing lipid data have come from the most recently approved antiretrovirals because of their safer overall toxicity profile compared with older drugs. Switching from efavirenz or ritonavir-boosted protease inhibitors to etravirine led to a significant improvement of lipids irrespective of the presence of previous hyperlipidemia and type of antiretroviral therapy [32]. In a mouse model of genetic dyslipidemia, maraviroc reduced atherosclerotic progression by interfering with inflammatory cell recruitment into plaques and by reversing the proinflammatory profile [33]. Maraviroc also reduced both cytokine expression and secretion in human adipose cells without altering the adipogenic differentiation [34]. Switching from protease inhibitors or nonnucleoside reverse transcriptase inhibitors to maraviroc decreased total cholesterol and triglycerides in a small Spanish randomized clinical trial [35]. Switching from different class suppressive regimens to raltegravir and tenofovir and emtricitabine or abacavir and lamivudine led to improvements in plasma lipids after 48 weeks [36]. In virologically suppressed aging HIV-positive patients in whom therapy with both protease inhibitors and
nucleoside reverse transcriptase inhibitors may be challenging because of resistance, interactions or tolerability issues, there are promising results from small, short-term studies assessing dual therapy with raltegravir and a nonnucleoside reverse inhibitor such as etravirine or nevirapine [37*-39*]. Therefore, etravirine, maraviroc, and raltegravir may be preferred as antiretroviral drugs for HIV-infected patients with metabolic problems.

In contrast with etravirine, maraviroc, or raltegravir switches, switching to either darunavir monotherapy or triple therapy containing two nucleoside reverse transcriptase inhibitors showed increases in plasma lipids and decreases in flow-mediated dilation in both arms without significant differences between them [40].

**LIPID EFFECTS OF GENETIC BACKGROUND**

A longitudinal Spanish study assessed the role of 192 single-nucleotide polymorphisms (SNPs) on the incidence of dyslipidemia in 727 antiretroviral-naïve HIV patients starting antiretroviral therapy adjusting for the contribution of nongenetic factors [41**]. The authors found that one SNP in APOB was associated with an increase in LDL-cholesterol. In addition, SNPs in ABCA1/LIPC/CETP were unfavorably associated with HDL-cholesterol when antiretroviral therapy included nonnucleoside therapy. SNPs containing protase inhibitors, increasing age, and not being infected with hepatitis C were independent nongenetic factors for hypercholesterolemia. HIV impairs monocyte or macrophage cholesterol efflux by increasing ATP-binding cassette transporter 1 (ABCA1) degradation through increased monocyte ABCA1 expression in untreated HIV-infected patients that normalizes with virological suppression by antiretroviral therapy [42]; however, there is a decreased expression of cholesterol sensing, uptake, and synthesis genes in both treated and untreated HIV infection, suggesting that both HIV and antiretroviral therapy affect monocyte cholesterol metabolism in a pattern consistent with accumulation of intramonoocyte cholesterol.

Longitudinal data from men enrolled in the Multicenter AIDS Cohort Study showed that biogeographical ancestry plays an important role in the dyslipidemic responses to antiretroviral therapy [43]. Genetic influence in this study was restricted to HIV positive patients of European ancestry, not those of other geographic ancestries. In a cross-sectional study [44], glucocorticoid receptor SNPs were determined in HIV patients from the study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM) and researchers found that the Tth111I haplotype was associated with a healthier metabolic profile in African-Americans with HIV infection.

**DIABETES**

Although initiation of antiretroviral therapy may be associated with a cardioprotective lipid profile because of the higher increase in HDL-cholesterol relative to that seen in total cholesterol, it may be also associated with a tendency toward insulin resistance regardless of the type of antiretroviral regimen [17].

Among hypertriglyceridemic HIV patients on antiretroviral therapy, African-Americans and Hispanics are at increased risk of developing diabetes compared with non-Hispanic Whites. The risk seems to be higher for African-Americans with CD4 cell counts less than 300/µl and Hispanics with at least 300/µl [45].

A cross-sectional Portuguese study confirmed the association between objectively measured lipodystrophy and insulin resistance or diabetes and showed that fat mass ratio [a ratio between percentage trunk fat and percentage leg fat as measured by dual-X absorptiometry (DXA)] was a more sensitive determinant of insulin resistance and glucose disturbances than the clinical definition of lipodystrophy [46*].

A cross-sectional Spanish study demonstrated the relationship between vitamin D insufficiency and both impaired insulin sensitivity and decreased pancreatic beta-cell function in nondiabetic HIV-positive men [47].

**BODY FAT COMPOSITION**

Because of the well known development of subcutaneous lipoatrophy and abdominal obesity with physiologic aging, aging is a good reason to continue detecting body fat changes in HIV-infected patients.

Subcutaneous fat macrophages rather than adipocytes were found to be the likely source of the chronic low-level inflammation found in adipose tissue of HIV-infected individuals [48**]. Activated proinflammatory CD14+CD16+ monocytes are more prone to be HIV infected and they also associated with subcutaneous fat loss. HIV infection may modify these cells to a more proinflammatory phenotype, and these changes are not substantially modified by antiretroviral therapy. Another cross-sectional study found that CD8 T-cell activation was associated with clinical lipodystrophy and objectively measured visceral fat accumulation in virologically suppressed HIV patients [49*].
Subcutaneous fat and visceral fat are different anatomic and functional fat depots in the abdomen. A Spanish study determined the specific molecular alterations in visceral abdominal tissue (VAT) relative to subcutaneous abdominal tissue in HIV-infected patients with lipodystrophy [50]. Researchers found that mitochondrial alterations were similar in both depots, but adipogenic gene expression was decreased in subcutaneous fat and unaltered in visceral fat. Although inflammation was present in visceral fat, it was stronger and broader in subcutaneous fat.

Epidermal and thoracic periaortic fat was associated with biomarkers of immune activation, inflammation, insulin resistance, and subclinical atherosclerosis in a cross-sectional study of virologically suppressed HIV-infected patients on antiretroviral therapy [51]. Pericardial fat has been also associated with silent ischemic coronary heart disease and it was a better predictor than cardiovascular risk scores, carotid intima-media thickness, and coronary calcium to detect myocardial perfusion defects in HIV patients [52]. HIV-infected men with lipodystrophy from the Multicenter AIDS Cohort Study had higher inflammatory and insulin resistance markers than HIV-infected without lipodystrophy or HIV-uninfected men; interestingly lipodystrophy and inflammatory markers were independently associated with lower grip strength [53], suggesting that HIV-infected persons with lipodystrophy may be at increased risk for age-related functional decline and, therefore, may represent an important target population for screening aimed at disability prevention. Functional impairment in HIV-infected persons on successful antiretroviral therapy was found to be associated with low muscle mass, low bone mineral density, and low insulin growth factor-I (IGF-I) and IGF-I binding protein-3 [54]. In a small prospective study, loss of bone mineral density and gain of fat mass were correlated in HIV-infected patients starting antiretroviral therapy and this correlation was more evident among patients with protease inhibitors relative to those on nonnucleosides [55].

Different studies have shown an association between lipid abnormalities (particularly, increased small-dense LDL cholesterol/large-buoyant LDL cholesterol ratio) [56], diabetes [46*], or hypertension [57*] and fat mass ratio (a ratio between percentage trunk fat and percentage leg fat as measured by DXA). A comprehensive review of HIV-associated lipodystrophy emphasizes the increasing importance of lipohypertrophy because of both the recently recognized effects of HIV and antiretroviral therapy on visceral abdominal fat and the physiological body fat changes observed in the aging population [58**]. A retrospective cohort analysis showed that waist circumference is a limited surrogate for visceral abdominal fat as measured by computed tomography (CT) scan and DXA-derived parameters did not improved performance indices to a clinically relevant level [59], suggesting that CT scans will be needed for correctly measuring visceral abdominal fat compartment. Although detection of body fat changes may be more reliable with objective methods such as CT or magnetic resonance, these methods have limitations such as radiation and cost that prevent their generalized use in clinical practice.

Switching to lopinavir and ritonavir from either a regimen containing only nucleoside reverse transcriptase inhibitors [60] or both nonnucleoside and nucleoside reverse transcriptase inhibitors [61] led to significant limb fat gains at 96 weeks with no clinically significant lipid changes, irrespective of lopinavir and ritonavir being either alone as monotherapy [60] or combined with raltegravir [61] relative to being prescribed as triple therapy with two nucleosides. Therapy with either IGF-I or recombinant human growth hormone (rhGH) improved visceral abdominal adiposity [62,63]. IGF-I also decreased fasting insulin. The addition of rosiglitazone abrogated the adverse effects of rhGH on insulin sensitivity and glucose tolerance, whereas not significantly modifying the lowering effect of VAT. An additional study addressing the potential effects of telmisartan on visceral adiposity of HIV-positive patients found no effect on VAT, but a decrease in subcutaneous and total fat [64]. There is emerging evidence that angiotensin stimulates adipocyte differentiation and lipogenesis [65] and because of the increasing number of aging patients with hypertension treated with blockers of the angiotensin axis, it would be interesting to see whether these drugs may favorably affect body composition.

CONCLUSION

HIV-infected patients should have adequate nutrition and exercise, and more emphasis on the importance of these aspects is needed in the clinical care setting. Earlier diagnosis of HIV infection will lead to earlier initiation of antiretroviral therapy, although additional measures will likely be necessary to decrease microbial translocation, inflammation, immune deficiency, and abnormal HDL. Because of differences among antiretroviral drugs, therapy with the lowest metabolic impact should be considered for aging patients with dyslipidemia. Etravirine, rilpivirine, maraviroc, or raltegravir are metabolically well tolerated drug options and may be useful for aging HIV-infected patients. The
increasingly better known contribution of genetic background to dyslipidemia in HIV-infected patients will need to evolve from research to clinical care. Body fat changes including former lipodystrophy or more recent abdominal obesity need to be objectively measured to identify patients at higher risk of dyslipidemia, diabetes, or hypertension and should be prevented or treated if possible to improve the prognosis of those metabolic conditions.

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Conflicts of interest
M.C.: None.
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REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
■ of special interest
★ of outstanding interest
A comprehensive review on the pathophysiology of human visceral obesity.
An interesting study showing an association between metabolic syndrome and high triglycerides with mortality.
This study is concordant on emphasizing the importance of microbial translocation in the pathogenesis of metabolic abnormalities in HIV patients.
This study is concordant on emphasizing the importance of microbial translocation in the pathogenesis of metabolic abnormalities in HIV patients.
An interesting study suggesting that similar low CD4 cell counts have more negative consequences in metabolic and other health markers when HIV patients are older.
This study offers a comprehensive yet clear hypothesis on the pathophysiology of dyslipidemia in HIV-infected persons.

This pilot study offers proof of concept for simple and effective maintenance antiretroviral therapies free of both nucleoside reverse transcriptase inhibitors and protease inhibitors. This strategy looks very promising for aging HIV-infected patients.


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A large and comprehensive study on the genetic factors influencing plasma lipids adjusted for nongenetic factors.


This study together with Ref. [52] shows that fat mass ratio is not only an objective method to evaluate lipodystrophy, but also a marker for diabetes or hypertension.


An excellent study on the role of HIV and monocytes and macrophages in adipose tissue biology.


This study clearly shows a relationship between abdominal obesity and immune activation.


This study together with Ref. [41] shows that fat mass ratio is not only an objective method to evaluate lipodystrophy, but also a marker for diabetes or hypertension.


A comprehensive review on the body fat effects of different antiretroviral drugs.


