Atherosclerosis in the HIV and non-HIV setting: detecting and modifying cardiovascular risk

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Atherosclerotic vascular disease in HIV: It is not just ART that Hurts the Heart!

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Abstract

Purpose of review: Although potent combination antiretroviral therapy (cART) has heralded an unparalleled improvement in the treatment of HIV-1 infected patients, the now well-known metabolic complications of treatment, which include dyslipidemia, insulin resistance and changes in body fat distribution are thought to contribute to an increased risk of atherosclerotic (cardio)vascular disease (CVD). Atherogenic changes in plasma lipids as well as some evidence of increased atherogenesis, however, had already been described in HIV-1 infected patients prior to the availability of cART and even prior to that of suboptimal antiretroviral therapy. In this review we will summarize the various possible factors and mechanisms involved in atherogenesis in HIV-1 infected individuals, with a focus on those mechanisms related to the infection itself and its immunological consequences.

Recent findings: Recent data suggest that a treatment strategy involving repeated cycles of CD4+-cell-guided cART interruption is associated with a higher risk of CVD than continuous treatment aimed at optimal viral suppression.

Summary: Apart from the effects of cART-associated metabolic derangements, HIV-1 infection directly or indirectly, for instance by being associated with a state of chronic immune activation, may contribute to atherogenesis.
1. Introduction

Although potent combination antiretroviral therapy (cART) has heralded an unparalleled improvement in the treatment of HIV-1 infected patients, the now well-known metabolic complications of treatment, which include dyslipidemia, insulin resistance and changes in body fat distribution are thought to contribute to an increased risk of atherosclerotic (cardio)vascular disease (CVD). Atherogenic changes in plasma lipids as well as some evidence of increased atherogenesis, however, had already been described in HIV-1 infected patients prior to the availability of cART.

2. HIV-1 infection and atherosclerosis

Almost ten years ago, it was first suggested that use of HIV protease inhibitors is associated with premature coronary artery disease.¹ Subsequently, several studies, of which the D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study is the largest prospective observational study, have been performed to address this question. The primary analysis of the D:A:D study, which involved over 23,000 HIV-1-infected patients, patients, indeed reported a 26% relative increase in the rate of myocardial infarction (MI) per year of exposure to cART, which was independent of the risk exerted by classical CVD risk factors.² A more recent updated analysis from the same study involving a longer follow-up of more patients (almost 100,000 person years of follow-up), demonstrated that the previously reported association between cART exposure and CVD could indeed be attributed to the exposure to HIV protease inhibitors. This association was not found for exposure to non-nucleoside reverse transcriptase inhibitors (NNRTI). Part, but not all of the risk of protease inhibitor exposure could be explained by dyslipidemia associated with exposure to PI-containing cART regimens.³ Apart from the potentially atherogenic effect of cART and HIV protease inhibitors in particular there is evidence, some of it quite recent, which suggests that HIV-1 infection either by itself or through its effects on the immune system may also contribute to acceleration of the atherosclerotic process. The initial indication for a possible role of HIV-1 infection in accelerating atherosclerosis came from studies dating back to long before the era of potent cART or even suboptimal dual combination therapy for that matter. As far back as the early 1990’s, autopsy studies reported extensive atherosclerotic lesions in the coronary arteries of young HIV-seropositive adults with a mean age of 27⁴ and 32⁵ years, respectively, and similar findings were reported even earlier in paediatric patients before the introduction of zidovudine.⁶ More specifically, Tabib et al. reported findings from a small series of eight autopsies demonstrating significant coronary lesions in young (23-32 year old) HIV-infected patients.⁴ None of these patients were known to have a positive family history for coronary heart disease or other known CVD risk factors. All 8 subjects showed fibrosis of their coronary arteries with foam cells, which
was widely disseminated and causing 40-50% occlusion of the coronary arterial lumen similar to what can be found in older individuals from the general population.

More recently, results from the SMART (Strategies for Management of Antiretroviral Therapy) trial, in which continuous antiretroviral therapy (the viral suppression arm or VS) was compared with episodic use of antiretroviral therapy guided by the peripheral blood CD4+ T cell count (the drug conservation arm or DC) have provided novel additional evidence that uncontrolled HIV-1 infection may contribute to the pathogenesis of coronary artery disease. Although the average proportion of time spent on antiretroviral therapy during follow-up was almost three times longer in the viral suppression than in the drug conservation arm (93.7% vs 33.4%, respectively) simply by virtue of the two treatment strategies being compared in SMART, the rate of fatal or nonfatal cardiovascular disease was found to be statistically significantly higher in the drug conservation group (hazard ratio 1.6 (95% CI 1.0-2.5) for DC versus VS arm). The concept that uncontrolled HIV replication and the cellular immunodeficiency and chronic immune activation associated with it may contribute to cardiovascular risk is also supported by a study using ultrasonographic measurement of the carotid artery intima-media thickness (cIMT), which is a validated and accepted marker for generalized atherosclerosis and vascular disease risk. In this study, mean IMT was significantly increased in 148 HIV-1-infected adults when compared to 63 HIV-1-negative age and sex-matched control subjects at study entry, and also progressed more rapidly over a one year follow-up period in those who were infected with HIV-1. In a multivariate analysis, both classic CVD risk factors as well as being HIV-1-infected were found to be independent predictors of increased cIMT at baseline, and a nadir CD4+ T cell count of ≤ 200 cells/mm³ was independently associated with cIMT progression.

In this review, the various ART-and non-ART associated factors and mechanisms thought to be involved in atherogenesis in HIV-1-infected individuals will be summarized, with a focus on those mechanisms related to the infection itself and its immunological consequences.

3. Metabolic complications of cART

The introduction of cART has heralded an unparalleled improvement in the treatment of HIV-1-infected patients, with AIDS-associated mortality rates being reduced to less than a fifth of that in the pre-cART era in a sustained manner. These therapies however have been found to be associated with now well known metabolic complications, which include dyslipidemia, insulin resistance and changes in body fat distribution each of which are thought to potentially contribute to an increased risk of atherosclerotic (cardio)vascular disease (CVD).

Insulin Resistance

Insulin resistance and type 2 diabetes mellitus are well-known risk factors for atherosclerotic vascular disease in the general population. In previously treatment-naive HIV-1-infected indi-
Atherosclerotic vascular disease in HIV individuals, evidence of insulin resistance was observed in 13 percent during the first year of cART.14 HIV-1 infected patients with cART-associated lipodystrophy not only exhibit reduced uptake of glucose by skeletal muscle,15 but also have been found to be insulin resistant at the level of the liver and adipose tissue.16 Although both lipoatrophy and intraabdominal lipohypertrophy associated with cART likely contribute to reduced insulin sensitivity, it has been shown that a minor degree of reduction in insulin sensitivity may already occur early on following the initiation of protease inhibitor-containing cART and prior to demonstrable alterations in body fat distribution.17 These early changes may be related to the inhibitory effect of PI’s on the activity of the cellular glucose transporter 4 (GLUT-4).18 Interestingly, a recent study conducted in healthy uninfected volunteers has provided evidence that the NRTI stavudine may also directly induce insulin resistance, which was shown to be associated with reduced mitochondrial function in skeletal muscle.19 Thus, a variety of factors and mechanisms are likely to contribute to the pathogenesis of insulin resistance which may be observed in HIV-1-infected patients treated with cART.20

**Dyslipidemia**

In addition to insulin resistance, cART has been suggested to enhance atherogenesis by inducing dyslipidemia, characterized predominantly by the elevation of circulating triglyceride-rich lipoproteins such as Very Low Density Lipoproteins (VLDL) and chylomicrons, that occurs shortly after the initiation of treatment.21 A recent meta-analysis showed that after 48 weeks of treatment with protease inhibitors, the proportional elevation in concentrations of total cholesterol, triglycerides, and low density lipoprotein cholesterol (LDL) were 66%, 80%, and 37%, respectively.22 In the D:A:D study triglyceride levels >200 mg/dL were present in 40% of PI-treated patients, 32% of those treated with NNRTIs, 23% of NRTI-treated patients, and 15% of the untreated patients.23 High density lipoprotein cholesterol (HDL) < 0.9 mmol/L was found in 27%, 19%, 25% and 26%, and increased total cholesterol >6.2 mmol/L in 27%, 23%, 10% and 8% in PI-, NNRTI-, NRTI-treated and untreated patients respectively. These data show that a PI-based antiretroviral regimen generally is associated with a more atherogenous lipid profile when compared to NNRTI-based regimens.

Apart from PI’s and NNRTI’s, use of the thymidine analogue NRTI’s, stavudine and to a lesser extent lamivudine may also affect lipid profiles. In a study of approximately 600 ART naive patients who were randomized to tenofovir DF or stavudine (combined with the NNRTI efavirenz and the NRTI lamivudine in all patients) the use of stavudine was associated with significant higher increases in fasting triglycerides (+1.51 vs +0.01 mmol/L), total cholesterol (+1.50 vs +0.78 mmol/L), LDL (+0.67 vs 0.36 mmol/L) and a significantly lower increase of HDL (+0.16 vs. +0.23 mmol/L).24 In another study, including over 500 ART naive patients randomized to either stavudine plus lamivudine or tenofovir DF plus emtricitabine, plus efavirenz in both arms,25 patients randomized to stavudine/lamivudine had a significantly higher increase in fasting total cholesterol (0.91 vs 0.54 mmol/L), and LDL (0.52 vs 0.34 mmol/L). Somewhat surprisingly,
HDL levels showed a significantly greater increase in the zidovudine-treated patients: 0.23 vs. 0.16 mmol/L. The difference in increase of triglycerides was not statistically different between the two groups. Stavudine is known to be more toxic in terms of mitochondrial toxicity than zidovudine, and tenofovir has not been demonstrated to exhibit mitochondrial toxicity.26,27 The effects of thymidine analogue NRTI on the lipid profile may be the result of direct toxic effects of these drugs on mitochondria and inhibition of beta-oxidation of fatty acids25, and indirectly may also be affected by the association between the use of these drugs and the occurrence of both lipoatrophy and insulin resistance.28

In terms of mechanisms, it has been suggested that elevation of circulating VLDL early in the course of cART is caused by the combination of impaired VLDL clearance, already present in untreated HIV-1 infected patients, as well as by a cART-mediated increase in VLDL secretion by the liver.29

Similar to what is the case for the pathogenesis of insulin resistance, the pathophysiological mechanisms behind dyslipidemia induced by the different components of cART remain to be fully elucidated. This is complicated by the fact that HIV-1 infection by itself also affects levels of plasma lipids. In the early nineties it was already shown that triglycerides and free fatty acids were increased in patients with untreated HIV-1 infection, while plasma levels of HDL and LDL apolipoprotein-AI (apoAI) and apoB levels were decreased.30 These findings were confirmed in a cohort study of 50 documented HIV-1 seroconverters, which showed a decrease in total, HDL and LDL levels after seroconversion when compared to pre-infection values.31 After initiation of cART in these patients HDL levels hardly changed, but total and LDL levels increased. These increases therefore, at least partially, might reflect a restoration to pre-infection levels.

4. Immune activation

The observation that the atherosclerotic process is accelerated in patients infected with HIV-1 was made well before cART became available. As mentioned before, severe atherosclerotic lesion were found in the coronary arteries of chronically infected HIV-1-patients which could not be explained by classical risk factors.4,6 This is a strong indication that other mechanisms, in addition to the abovementioned metabolic complications of HIV treatment, are involved. In addition, HIV-1 infection was identified as an independent predictor of atherosclerosis progression in a study measuring cIMT in HIV-1 infected patients treated with cART.8 The authors suggested that the chronic immune activation associated with HIV-1 may explain these findings. In a recently published cross-sectional study comparing 93 HIV-infected and 37 uninfected adults, these same authors indeed presented evidence that the HIV-infected patients had higher CD4 and CD8-T cell activation and higher cytomegalovirus (CMV)-specific interferon-γ CD8 T-cell responses. Of note, the latter was independently associated with IMT, in the sense that for every 10-fold increase in the percentage of CMV-specific CD8 T-cells there was a 14 per-
cent increase in carotid IMT. The contribution of chronic low-grade immune activation and the chronic inflammation associated with it to the pathogenesis of atherosclerosis is well recognized. HIV-1 infection is indeed strongly associated with chronically increased immune activation and more pronounced in patients with more advanced cellular immunodeficiency. It is characterized by the presence of chronically activated T-cells, B-cells and monocytes/macrophages, as well as by increased expression of various leukocyte activation markers, production of pro-inflammatory cytokines and a rise in cell proliferation. Although the degree to which the immune system is activated may diminish with cART, it is not completely reversed even after years of sustained cART-induced viral suppression. Interestingly, it was recently suggested that depletion of gastrointestinal CD4+ T cells, which occurs very early after HIV-1 infection, compromises the integrity of the intestinal mucosal barrier and leads to increased translocation of bacteria from the intestinal lumen. As such bacteria and bacterial components subsequently stimulate innate immune cells systemically, creating the proinflammatory milieu associated with chronic HIV-1 infection. As a result of subsequent leukocyte activation, cytokine production and increased biomarkers HIV-1 infection may exert distinct pro-atherogenic effects on the vasculature of HIV-1 infected patients, similar to what can be seen in other systemic inflammatory conditions. Indeed, enhanced atherogenesis has also been observed in patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and Crohn’s disease (CD). As such, systemic inflammation has emerged as an universal risk factor for atherothrombotic disease. Several mechanisms secondary to systemic inflammation have been proposed which may explain the increased occurrence of atherothrombotic disease in patients with a condition associated with chronic immune activation and inflammation such as chronic HIV-1 infection.

Lipoproteins

A systemic inflammatory state induces dyslipidemia characterized by increased levels of triglycerides and decreased levels of HDL. Although initiation of cART has also been shown to induce dyslipidemia, this is preceded by dyslipidemic changes associated with HIV-1 infection itself, as we have outlined above. This notion is corroborated by various studies reporting dyslipidemia in HIV-1 infected patients in the pre-cART era and more recently by the Multicenter AIDS Cohort Study. In this study, serum samples of 50 male HIV-1 seroconverters were available from the following time points: pre-seroconversion (sample from the last seronegative visit), after seroconversion but before cART initiation and at several time points after cART initiation. Interestingly, HIV-1 infection itself resulted in notable declines in mean serum TC (–30 mg/dL [-0.78 mmol/L]), HDL (–12 mg/dL [-0.31 mmol/L]), and LDL values (–22 mg/dL [-0.57 mmol/L]). Unfortunately, changes in levels of triglycerides, insulin, and glucose were not quantified. Although initiation of cART resulted in increases in mean TC and LDL values, these levels, observed after years of cART, at least partially represented a return to preinfection serum lipid levels after accounting for expected age-related changes.
Although it has been well established that HDL plays a pivotal role in atheroprotection, this is of particular relevance in HIV-1 infected patients with acute coronary syndromes (ACS), since these were reported to have significantly lower HDL levels compared with HIV-uninfected ACS patients. HDL is well known as a negative acute phase protein and systemic inflammation can have a major negative effect on HDL levels. In the pre-cART era, decreased plasma concentrations of HDL in HIV-1 infected individuals were shown to be associated with immune activation. In line with this, in the D:A:D study, the risk of having decreased HDL was highest among patients with low CD4+ T cell count and high plasma HIV-1 RNA viral load. Indeed, HDL correlates negatively with current and peak viral load and positively with current and nadir absolute and percent CD4+ T cell count and CD4 percentage. Thus, considering HDL levels are reduced proportionally to the severity of HIV-1 infection, it appears this plays a major role in reducing HDL levels. It has been suggested that the effect of HIV-1 infection on HDL levels is greater than the cART effect. A relation between immune activation and dyslipidemia was also demonstrated in other studies. Taken together this implies that HIV-1 infection and HIV-1 associated chronic immune activation both have a significant atherogenic impact on lipid profiles. Of note, the non-nucleoside reverse transcriptase inhibitor nevirapine plays an interesting role as it may directly oppose infection- and immune activation-mediated reductions of HDL. A randomized trial in treatment-naive patients showed that a nevirapine-based cART regimen led to a prominent increase of both HDL (49%) and apoAI (19%) which was significantly greater than the changes in these levels seen in patients randomized to either an indinavir or lamivudine-based cART regimen, which in all arms was combined with the NRTI combination of stavudine and didanosine. These differences remained, after adjusting for changes in HIV-1 plasma RNA and CD4+ T-cell levels, indicating an effect of nevirapine on HDL and apoAI over and above that which may be explained by suppression of HIV-1 infection. It is still unknown whether this is a specific nevirapine effect or whether this might be a class-specific effect, since cART including the NNRTI efavirenz also increases HDL levels, albeit to a lesser extent than nevirapine-based treatment. The potential mechanisms underlying these changes remain speculative but unravelling thereof could contribute to understanding the lipoprotein disturbances in HIV-1 infected patients.

In addition to lowering HDL levels, a systemic inflammatory state may also affect the biochemical composition and thereby function of HDL. HDL is composed of various enzymes and other proteins which contribute significantly to its atheroprotective capacity such as the anti-oxidative enzyme paraoxonase (PON) or the anti-inflammatory protein apoAI. During an inflammatory state HDL may shed some of these components and take up other proteins such as serum amyloid A and oxidized lipids. The combination of these compositional alterations negatively affect the anti-atherosclerotic effect of HDL and may even result in the formation of pro-inflammatory HDL. Although it has already been shown in chronic inflammatory disorders such as SLE and RA that a significant proportion of HDL in these patients is proinflammatory, this remains to be evaluated in HIV-1 infection. HIV-1 infection may nonetheless directly
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affect HDL functioning. The anti-atherogenic function of HDL is attributed to its role in reverse cholesterol transport (RCT), whereby excess cholesterol is transported from peripheral cells to HDL particles for subsequent delivery to the liver. The protein crucial for the initial step of RCT, is the ATP binding cassette transporter A1 (ABCA1). Recently it was shown that HIV-1 impairs ABCA1-dependent cholesterol efflux from human macrophages.60 The Nef protein, a protein encoded by one of accessory genes of HIV-1, induced post-transcriptional down-regulation of ABCA1 and caused redistribution of ABCA1 to the plasma membrane and inhibited internalization of apoAI. Infection with HIV-1 may thus impair removal of excess cholesterol resulting in augmented accumulation of cholesterol in macrophages, thereby accelerating the atherosclerotic process.

**Endothelium**

The endothelium constitutes the barrier that leukocytes need to cross prior to the formation of an atherosclerotic plaque. It is likely that the endothelium is affected by both HIV-1 infection itself as well as antiretroviral treatment. Indeed, cART may exert direct toxic effects on endothelial cells. For instance, it was shown that the HIV protease inhibitor ritonavir is able to directly cause endothelial mitochondrial DNA damage and cell death *in vitro*.61 HIV-1 itself may also exert direct atherogenic effects on the endothelium. HIV-1 can directly bind to the endothelium and reach the subendothelium by penetrating between endothelial cells via transcytosis.62 In addition, endothelial activation may also occur in HIV-1 infection either by cytokines secreted in response to mononuclear or adventitial cell activation by virus or else by the effects of the secreted HIV-1 proteins, gp120 (envelope glycoprotein) and Tat (transactivator of viral replication) on endothelium.63 Indeed, exposure of endothelial cells to gp120 results in increased expression of adhesion molecules and monocyte adherence which facilitates leukocyte recruitment to the subendothelium and thus atherosclerotic plaque growth. In addition, gp120 in the subendothelium may further facilitate atherothrombosis as it has been shown to activate human arterial smooth muscle cells to express tissue factor, the initiator of the coagulation cascade.66 Similarly, HIV-1 Tat has been shown to induce expression of adhesion molecules in endothelial cells and to increase the adhesion of monocytes and T-cells to the endothelium.68 Endothelial activation in HIV-1 infected patients has been confirmed by several studies showing increased levels of soluble adhesion molecules correlating with immunological state and progression of HIV-1 infection.69,70 In line with this, there is a relationship between deterioration of endothelial function in HIV-1 infected patients, as assessed by flow mediated dilation (FMD), and plasma HIV-1 RNA levels.71

**Coagulation**

Under physiological conditions the endothelium protects against atherothrombosis by producing vasodilators such as nitric oxide and anti-coagulatory mediators. From the abovementioned endothelial dysfunction it can be deduced that the balance between stimulation and
inhibition of coagulation may also be disturbed. In a recent systematic review of ten epidemiological studies, the incidence of venous thromboembolic complications in HIV-1 infected patients was increased two- to tenfold compared with a HIV negative population of the same age. This hypercoagulable state in HIV-1 patients is suggested to result from a disturbed balance between increased procoagulatory (tissue factor, antiphospholipid antibodies, activated platelets) and reduced anticoagulant factors (protein S, protein C, antithrombin III, heparin cofactor II). These abnormalities correlate with severity of HIV-associated immunosuppression, as evidenced by CD4 T-cell counts which might suggest that the higher immune activation that accompanies more severe immunodeficiency in HIV-1 infection underlies a hypercoagulable state in these patients. Although the mechanism of hemostatic changes thus appears to be a result of HIV-related triggering of the immune system, the coexistence of procoagulant conditions associated with HIV-1 infection such as superimposed (opportunistic) infections and malignancies, may also contribute to the hypercoagulable state.

5. HIV-1 and immunomodulation

The association between chronic immune activation and systemic inflammation in HIV-1 infection and acceleration of the atherosclerotic process is further strengthened by the observation that immunomodulation of HIV-1 can attenuate atherogenesis. For example, the chemokine receptor CCR5 plays an interesting role in this regard. A 32-bp deletion in the CCR5 gene (CCR5Δ32) results in a nonfunctional receptor, and individuals that are homozygous for this deletion are not only resistant to infection with HIV-1 but are also protected against atherosclerotic vascular disease. Interestingly, treatment with a CCR5 antagonist (TAK-779) was shown to not only exert potent and selective anti-HIV activity in Chinese hamster ovary cells but to also attenuate atherosclerotic lesion formation by blocking the influx of T-helper 1 cells into the plaque.

A second immunomodulatory agent with potential atheroprotective effects is mycophenolate mofetil (MMF), a produg of mycophenolic acid (MPA). MMF specifically inhibits lymphocyte proliferation and has been applied in studies in HIV-1 infected patients, since it is found to have both virological and immunological effects. Treatment with MMF resulted in a decrease of the reservoir of latently infected CD4 T-cells. After discontinuation of MMF in patients treated with cART in another study, there was a temporary increase in Ki67 expression and apoptosis, indicating that MMF reduced the level of activation even in these patients. Interestingly, MMF has also been suggested to exert several anti-atherosclerotic functions and has been shown to reduce atherosclerotic lesion formation in animal studies. MMF inhibits the transfer of mannose and fucose to glycoproteins, some of which are adhesion molecules. MMF was shown to downregulate surface expression of adhesion molecules on endothelial cells and leucocytes and can therefore attenuate recruitment of circulating leukocytes to the
site of inflammation such as the atherosclerotic plaque. Two studies showed that New Zealand White rabbits which were fed a high cholesterol diet showed significantly larger areas of atherosclerotic plaques in the abdominal and thoracic aorta as compared to the MMF treated group. In the latter group, this reduction in atherosclerosis was associated with reduced number of macrophages and T-lymphocytes infiltrating the atherosclerotic plaque. The contention that immunomodulation in HIV-1 infection may not only be beneficial to attenuate HIV-mediated pathophysiology but also may translate into atheroprotection is an area of research that deserves further attention.

Figure 1  Schematic representation of enhanced atherogenesis in HIV

The use of cART is associated with insulin resistance, body fat changes and dyslipidemia. One regimen (ritonavir) has also been shown to induce cytotoxicity of human endothelial cells. Furthermore, exposure of endothelial cells to HIV-associated proteins results in increased expression of adhesion molecules and monocyte adherence. Moreover, HIV can penetrate the endothelium via transcytosis and has been shown to impair RCT and to activate human arterial smooth muscle cells (SMC) to express tissue factor (TF). Finally, systemic inflammation mediated by HIV-1 infection may also contribute to atherothrombotic disease by inducing dyslipidemia, activation of coagulation and endothelial dysfunction. It has been suggested that translocation of bacteria and bacterial components from the intestinal lumen, stimulate innate immune cells systemically, creating the proinflammatory milieu with inflammatory mediators (infl med) associated with chronic HIV infection.
6. Conclusion

The increased risk of atherosclerotic cardiovascular disease observed in patients on cART, and particularly on PI-containing cART, may be understood in terms of the dyslipidemia, insulin resistance and changes in body fat distribution associated with these treatments. However, HIV-1 infection by itself and by way of the chronic immune activation associated with the infection likely contributes to the risk of atherothrombotic disease through both direct and indirect mechanisms (see figure). Suppression of HIV replication by cART partly abrogates the state of chronic immune activation and may thus exert an atheroprotective effect. Further research is needed to unravel the role of these various treatment- and infection-associated factors towards the increased incidence of cardiovascular disease observed in HIV-1 infected patients in the era of cART. In the meantime prevention of cardiovascular disease by appropriately addressing traditional CVD risk factors in these patients is essential.
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