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# Arterial Disease in Patients with Human Immunodeficiency Virus Infection: What Has Imaging Taught Us?

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## Abstract

With advances in antiretroviral therapy, individuals with human immunodeficiency virus (HIV) infection are living longer and increasingly die of non-HIV related diseases such as cardiovascular disease (CVD). Several observational studies suggest that HIV-infected patients on ART are at increased CVD risk; however, the precise mechanisms underlying the association between HIV infection and CVD risk are uncertain. Atherosclerosis and arterial disease in HIV-infected individuals is a multifactorial process with several potential targets for research and therapeutic intervention.

### Keywords

HIV; Coronary arteries; Endothelial function; Ultrasound; Carotid intima-media thickness

With the advent of potent combination antiretroviral therapy (ART), patients with human immunodeficiency virus (HIV) infection are living longer and increasingly are afflicted with chronic diseases that are common among individuals without HIV infection, such as cardiovascular disease (CVD), cancer, liver disease, and lung disease (1,2). Among HIV-infected individuals in the United States, CVD is the leading non-HIV-related cause of death, although in Europe CVD death follows cancer and liver disease among the leading causes of mortality in this patient population (1,2). Several observational studies suggest that HIV-infected patients on ART are at increased CVD risk (3-8); however, the precise



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mechanisms underlying the association between HIV infection and CVD risk are uncertain (8,9). This article critically reviews the contributions of imaging to our current understanding of arterial disease, atherosclerosis, and CVD risk in HIV-infected individuals.

## HIV and CVD Risk

Some of the increased CVD risk associated with HIV infection is due an increased burden of traditional risk factors such as cigarette smoking, which is 2-3 times more prevalent in individuals with HIV infection (10,11) and risk factors related to use of protease inhibitors, such as dyslipidemia and insulin resistance (11). In the Data Collection on Adverse Events of Anti-HIV Drugs study, exposure to protease inhibitors was an independent predictor of myocardial infarction (MI); however, the major predictors were established CVD, current or former smoking, and male sex, as well as increasing age and a family history of heart disease (12). In fully-adjusted models, diabetes mellitus, higher total cholesterol, and lower HDL cholesterol levels also were independent predictors of MI (12). In a recent observational study from the Veterans Aging Study Virtual Cohort, HIV-infected veterans (mostly men had) nearly a 50% increased relative risk of acute MI compared to those without HIV, after adjustment for traditional risk factors. In addition to HIV serostatus, other independent risk factors for incident MI were increasing age, hypertension, increasing low-density lipoprotein cholesterol, cigarette smoking, and renal disease (8). Thus, as in HIV-uninfected individuals, traditional risk factors powerfully predict CVD in those with HIV infection. However, hepatitis C co-infection, anemia, low CD4+ T-cell counts and high HIV -1 RNA levels also predicted MI risk, suggesting that certain characteristics of individuals with HIV infection, in addition to traditional risk factors, may contribute to increased CVD risk (8). Certain protease inhibitors such as lopinavir/ritonavir, indinavir, and amprenavir/fosamprenavir have been associated with increased MI risk and certain nucleoside reverse transcriptase inhibitors, most notably abacavir and possibly didanosine, also may increase MI risk, although data are conflicting (13-15). The impacts of newer classes of antiretroviral agents such as CCR5 inhibitors and integrase inhibitors which appear to have fewer lipid effects on CVD risk are largely unknown at this time.

Although use of ART has been associated with increased CVD risk, one large observational study demonstrated that HIV treatment did not increase short-term CVD risk (16). A growing body of evidence suggests that persistent inflammation and disordered immune regulation – that are present even among effectively treated HIV-infected individuals – may increase CVD risk (17). In an observational study, the odds ratio for acute MI was >4-fold higher among patients with HIV and elevated C-reactive protein compared to those without HIV and with normal C-reactive protein (18). In the Strategies for Management of Anti-Retroviral Therapy study, interruption of ART in individuals with chronic HIV infection was associated with high levels of IL-6 and D-dimers, biomarkers that were associated independently with all-cause mortality and CVD events; furthermore, ART initiation at higher CD4+ T-cell counts reduced serious non-AIDS events, which mostly were due to CVD, in a subset of participants who were ART-naive or had not been receiving ART for at least 6 months prior to participation (19,20). Indeed, although inflammation and immune dysregulation play key roles in accelerating atherosclerosis in individuals without HIV (21,22), the causes of ongoing inflammation and immune dysregulation in individuals with

treated HIV infection appear to be more complicated than in individuals without HIV in whom inflammation is driven, in large part, by visceral adiposity and the metabolic syndrome (17). Atherosclerosis and arterial disease in HIV-infected individuals clearly is a multifactorial process (Figure 1) with several potential targets for research and therapeutic intervention.

The extent by which HIV infection increases CVD risk beyond traditional risk factors and the specific contributions of ART has been difficult to determine. Most of the current data suggesting increased CVD risk among HIV-infected patients comes from observational studies that were not designed to evaluate CV endpoints and thus have important methodological limitations, including short duration of follow-up, low overall event rates, incomplete ascertainment of CVD risk factors and events, and lack of proper HIV-negative control groups. Furthermore, most HIV-infected patients are relatively young and at low short-term CVD risk, which limits the power of observational studies to more accurately quantify CVD risk, especially in the setting of traditional risk factors which may have been present longer than HIV infection itself. However, the weight of the evidence suggests a moderate degree of excess CVD risk due to HIV infection, especially in individuals over 45-50 years of age (7,8).

To overcome some of these limitations, many investigators have used arterial imaging to better understand the magnitude and contributors to increased CVD risk associated with HIV infection and its mechanisms. The dominant imaging technologies have been carotid ultrasound (to measure intima-media thickness [IMT] and to assess for plaque presence), cardiac computed tomography (to measure coronary artery calcium [CAC] or for angiography [CTA] to assess coronary plaque burden and composition), brachial artery ultrasound (for arterial reactivity testing [BART], a measure of endothelial function), and more recently, positron image tomography (PET, to assess arterial inflammation). Collectively, studies using these imaging technologies support the observational evidence that HIV infection is associated with increased CVD risk. These imaging modalities have elucidated new pathways for investigating the pathophysiology of arterial disease, atherosclerosis, and increased CVD risk in patients with HIV infection.

## Carotid Ultrasound

Increased carotid IMT is associated with prevalent CVD and risk factors as well as increased risk of future MI and stroke (23-25). Carotid plaque presence also is associated with an increased risk of future CVD events, independent of traditional risk factors (23,26). Longitudinal carotid IMT progression also has been used as a surrogate marker of change in CVD risk associated with lipid-lowering and antihypertensive medications, however its association with changes in CVD risk in the general population are less clear (27-29).

Over 20 observational studies have measured carotid IMT in individuals with HIV (30). Several also assessed for the presence of carotid plaques. In a meta-analysis that included most of these studies, the carotid IMT of individuals with HIV infection was, on average, 0.04 mm thicker (95% CI 0.02-0.06, $p<0.001$) than those without HIV infection (Figure 2) (30).

This difference in carotid IMT is of a magnitude that is consistent with the observational studies showing increased CVD risk in individuals with HIV infection. However, the studies included in the meta-analysis had widely varying population characteristics, study designs, sample sizes, length of follow-up, and different ultrasound techniques. Most of these studies measured common carotid artery IMT, although some measured IMT in the bifurcation and/or internal carotid artery segments. The finding of higher carotid IMT among those with HIV had significant heterogeneity between studies ($I^2$=86.5%), evidence for publication bias (p=0.001), confounding by male sex, and residual confounding, since a larger effect size was observed among studies with the greatest between-group demographic differences (30). Smaller studies were more likely to conclude that HIV-infected patients had thicker carotid IMT; the point estimates from larger studies were clustered around no effect. Nevertheless, a subsequent report from the cohort with the second largest number of HIV-infected patients confirmed the results of the meta-analysis (31). In the Study of Fat Redistribution and Metabolic Change, the mean difference in common carotid artery IMT between HIV-infected and uninfected controls was 0.033 mm (p=0.005), after adjustment for demographic and traditional CVD risk factors. In addition to HIV infection, these investigators also demonstrated independent effects of traditional CVD risk factors such as age, male sex, current and past smoking, diabetes mellitus, blood pressure, and total and HDL cholesterol on carotid IMT (31). Of note, directionally similar but larger effects were observed in the internal carotid artery than in the common carotid artery (31). The meta-analysis did not find higher carotid IMT for HIV-infected patients exposed to protease inhibitors, with a high degree of study heterogeneity but no evidence of publication bias (30).

Among 6 studies, the odds ratio for carotid plaque presence in HIV-infected individuals compared to uninfected controls was 1.50 (p=0.084, $I^2$=67%) with significant heterogeneity ($I^2$=67%, p=0.009). Carotid plaque tended to be more prevalent in patients on protease inhibitors, but the p value did not reach statistical significance (OR=1.71, p=0.103), possibly due to heterogeneity ($I^2$=52%, p=0.059). Thus, cross-sectional observational studies using carotid ultrasound support observational studies evaluated CVD events in demonstrating (i) traditional CVD risk factors are the primary associates of arterial injury among patients with HIV, (ii) a moderate independent association between HIV serostatus and both increased carotid IMT and plaque presence; however, it is not clear if there is an association with use of protease inhibitors.

An even smaller number of studies have looked at the effects of HIV on longitudinal progression of carotid IMT. The meta-analysis only reviewed three small to moderate-sized studies that evaluated change in carotid IMT over time (30). These studies had differing conclusions; one described a positive association between HIV serostatus and carotid IMT progression (32) but one did not (33). One study found that use of protease inhibitors was associated with more rapid carotid IMT progression (32), but two did not (33,34). Each of these studies had markedly different study designs and participant characteristics. Although they broadly agreed that traditional CVD risk factors predicted progression of carotid IMT, they had differing conclusions in regard to the directionality and magnitude of certain risk factors, including CD4 cell count (30). Two subsequent, moderate-sized studies of carotid IMT progression also had inconsistent conclusions (35,36). In one study, slower carotid IMT progression was observed among individuals with persistently suppressed HIV RNA viral

load, but with faster progression among those taking protease inhibitors compared to those taking non-nucleoside reverse transcriptase inhibitor-based based regimens (35). Increased body-mass index was the only traditional CVD risk factor that independently predicted carotid IMT progression (35). In a second study, traditional CVD risk factors, but no HIV-related measures, were associated with carotid IMT progression; however, the specific risk factors and the magnitude of their associations were inconsistent between carotid artery segments (36). In that study, waist circumference and markers of insulin-glucose metabolism appeared to be the most consistent predictors of carotid IMT progression, but these findings have not been consistently demonstrated (36). For example, another study showed that the IMT progression occurs preferentially at the carotid bifurcation region in HIV-infected individuals and is associated with levels of high-sensitivity C-reactive protein (37). Increased carotid IMT progression also has been observed after initiation of ART (38) and with tenofovir-based therapy (39,40). These studies, however, were quite small.

In regard to inflammation and markers of immune activation, the Women's Interagency Health Study demonstrated that markers of T-cell activation and senescence were associated with increased carotid plaque prevalence (41). In some studies of suppressed HIV-infected individuals, chronic inflammation has been associated with increased carotid IMT (42,43), but not in others (33,35), perhaps due to differing subject populations and imaging approaches. Recently, elevated sCD14 levels have been associated with increased carotid IMT progression in individuals with HIV (44).

In summary, traditional CVD risk factors consistently are associated with carotid IMT in HIV-infected individuals. In agreement with observational studies describing CVD events, HIV infection appears to be associated with higher carotid IMT of a magnitude that is broadly consistent with the observational studies showing an increased risk of CVD events in individuals with HIV infection. However, the effects of HIV infection, its treatments, and its associated immunological abnormalities on carotid IMT progression and plaques are unclear.

## Cardiac Computed Tomography: CAC and CTA

The presence and quantity of CAC are powerful, independent predictors of CVD risk in the general population (45-47). In one large epidemiological study, the predictive value of CAC for incident coronary heart disease and cerebrovascular disease exceed that for carotid IMT and brachial artery flow-mediated dilation (FMD) (48). The effects of HIV serostatus on CAC was addressed in the same paper that described a meta-analysis of carotid IMT and HIV serostatus (30). Seven studies were included in the CAC meta-analysis including the largest HIV experience, from the Multicenter AIDS Cohort Study (30,49). In the five studies that compared CAC among HIV-positive vs. HIV-negative individuals, the odds ratio for CAC was not significantly higher among HIV-infected patients (OR 0.95, p=0.851); however, significant heterogeneity was noted ($I^2$=65%, p=0.024). Similarly, the odds ratio for CAC among the three studies comparing HIV-infected patients with PI exposure to those not exposed to PIs also was not significant (p=0.506). In the Multicenter AIDS Cohort Study cohort of 332 HIV-negative and 615 HIV-positive men, the adjusted odds ratio for CAC prevalence was 1.35; however, the 95% confidence interval was wide (0.7-2.61) and was

similar in regard to long-term use of ART, without evidence of increased harm or benefit by treatment (49).

Subsequent observational studies have demonstrated independent associations between CAC and increasing age, hyperapobetalipoproteinemia, C-reactive protein, and metabolic syndrome in HIV-infected patients (50,51). Similarly, the Multicenter AIDS Cohort Study also demonstrated that increasing age was the strongest predictor of CAC presence among HIV-infected and uninfected individuals (49). Another study reported that in addition to traditional CVD risk factors (including age), HIV serostatus and use of cocaine were associated with CAC among African-Americans (52). Because most studies that measured CAC in HIV-infected individuals had relatively young subjects (mean age <50 years old), they would be expected to have low rates of CAC presence, since CAC is a later finding in atherogenesis than is arterial wall thickening. Accordingly, in a study that compared CAC and carotid IMT in HIV-infected individuals, more than 1/3 of HIV patients with undetectable CAC had markedly increased IMT, suggesting that in young to middle-aged HIV-infected patients, carotid IMT may be a more sensitive indicator of subclinical vascular disease than CAC (53).

CTA recently has shed significant light on CVD risk in patients with HIV infection, since it can identify non-calcified plaque as well as calcified plaque. In a cross-sectional study of 114 HIV-positive and 40 HIV-negative men, CAC scores were higher in those with metabolic syndrome, but CAC presence was not associated with HIV serostatus (54). However, CTA identified a higher prevalence of plaque in HIV-positive individuals due to an increased prevalence of non-calcified plaque segments (54). The Multicenter AIDS Cohort Study cohort described the results of CTA in 343 HIV-infected and 176 HIV-negative men (Figure 3) (55).

HIV positivity was associated independently with the extent of non-calcified plaque as well as diabetes mellitus, hypertension, and dyslipidemia and independent associations with coronary stenoses of ≥50% were identified with CD4 nadir, use of ART for >10 years, and detectable HIV RNA, even after adjustment for traditional CVD risk factors (55). Thus, an increased burden of non-calcified plaque identified by CTA appears to explain the weak and inconsistent associations previously described between CAC and HIV serostatus. Another study reported that among African-Americans with HIV infection, coronary stenoses of ≥50% were independently associated with traditional CVD risk factors, long-term cocaine use (≥15 years), and exposure to ART for ≥6 months (56). In addition to traditional CVD risk factors, HIV serostatus, use of cocaine, stavudine or lamivudine and zidovudine also have been identified as independent associates of significant coronary stenosis (52).

In summary, CAC alone appears to be an inadequate research tool for studying arterial disease burden in young adults with HIV infection. Although CAC is associated with traditional CVD risk factors, it does not appear to identify HIV-related CVD risk. Recent CTA findings consistently demonstrate increased non-calcified coronary atherosclerosis among younger patients with HIV infection, in association with traditional risk factors and HIV serostatus. The magnitude of increased CVD risk associated with the increased prevalence of non-calcified coronary atherosclerosis remains unclear because the studies

cited above were relatively small, observational, and some only included women. CTA is a valuable research tool for evaluating the causes and extent of subclinical atherosclerosis among individuals with HIV infection.

## BART

Brachial artery ultrasound can be used to assess FMD, a marker of endothelial function that predicts future CVD risk (57,58). As a sensitive and rapidly responsive biomarker, BART has played an important role in assessing the arterial pathophysiology of HIV infection and its treatments on CVD risk. Studies using BART have consistently demonstrated that patients with HIV infection have endothelial dysfunction relative to patients without HIV infection. In a case-control study of children (mean age 11 years old), brachial artery FMD was significantly lower compared to controls (p=0.02) and was worse among children treated with protease inhibitors (p=0.05) (59). In children, endothelial dysfunction was present even after adjustment for baseline diameter and traditional CVD risk factors including C-reactive protein (59). In adults, case-control studies evaluating the effects of HIV infection on FMD have had inconsistent results (60-64). Each of these studies have been relatively small with the largest including only 83 HIV-infected individuals and the population characteristics as well as imaging techniques have varied between studies (60-63). A wide range of risk factors have been associated (albeit inconsistently) with impaired FMD among patients with HIV, including lipoprotein levels, HIV viral load, nadir CD4 T-cell count, intravenous drug use, systolic blood pressure, markers of insulin-glucose metabolism, and presence of metabolic syndrome, among others. Similarly, the relationship between C-reactive protein and FMD in individuals with HIV is uncertain. One study suggested that higher C-reactive protein was associated with impaired endothelial function in HIV-infected patients (65), but four others did not (62,63,66,67). Each study had <100 HIV infected subjects with varying demographic, CVD risk factor, and HIV treatment profiles.

In a prospective, randomized clinical trial of 82 ART-naïve individuals (median age 35 years) randomized to 3 treatment-sparing initial ART regimens, FMD improved after both 4 and 24 weeks of ART, with similar changes in all arms (Figure 4) (67).

Change in FMD after 24 weeks of initiating ART was inversely associated with change in HIV RNA levels (p=0.017), despite an increase in brachial artery diameter and after adjustment (67). They suggest, as have others, that high viral load causes endothelial dysfunction and that treatment of viremia improves endothelial dysfunction associated with HIV infection (68). Collectively, BART studies suggest that in individuals with HIV infection and active viral replication, the beneficial effects of ART outweigh the potential adverse effects of specific drug classes or adverse metabolic effects such as increases in lipids or changes in insulin-glucose metabolism.

BART studies that evaluated the effects of HIV protease inhibitors on FMD also have had mixed results, likely due to small sample sizes, varying subject characteristics, and different distributions of traditional CVD risk factors (59,60,64,69). However, two randomized studies using BART evaluated the effects of switching patients from early protease inhibitors to atazanavir, a protease inhibitor with less adverse metabolic effects; they did not

show improvements in FMD despite improvements in lipids (70,71). Another randomized trial did not show improvement in FMD with raltegravir intensification in ART-suppressed patients (72). However, two randomized studies demonstrated improvements in endothelial function in dyslipidemic HIV-infected patients who received statins (73,74). Finally, observational data regarding the effects of abacavir on FMD also have had divergent results. A single center study of 61 treated and suppressed HIV-infected individuals found that those taking abacavir had lower FMD (75); however, a study of 148 individuals who initially were assigned randomly to abacavir or tenofovir did not find lower FMD among those taking abacavir.(76).

In summary, the results of BART studies suggest that untreated HIV infection and traditional CVD risk factors worsen FMD and that ART initiation and treatment of dyslipidemia with statins improve FMD. Switching patients off of protease inhibitors or intensifying ART do not improve endothelial function. Although ART initiation improves endothelial function, FMD remains abnormal even in the setting of treated and suppressed HIV infection. The long-term effects of abacavir on endothelial function remain unclear.

## Imaging Arterial Inflammation with Positron Emission Tomography (PET)

A growing body of evidence suggests that in addition to traditional CVD risk factors such as smoking, dyslipidemia, and components of the metabolic syndrome, inflammation may play a key role in increasing CVD risk among treated and suppressed HIV-infected patients. An observational study of over 70,000 individuals (487 HIV-infected) demonstrated that elevated C-reactive protein (OR 2.13, $p<0.0001$) and HIV infection (OR 1.93, $p=0.004$) were independently associated with acute MI (18). Furthermore, the Strategies for Management of Antiretroviral Therapy study found that interruption of ART in chronic HIV infection was associated with high levels of IL-6 and D-dimers, that those biomarkers were associated with all-cause mortality and CVD events, and that ART initiation at higher CD4 positive T-cell counts in a reduced non-AIDS events, which mostly were due to CVD (19,20). These observations are supported by an observed improvement in brachial FMD with ART initiation and its observed inverse association with HIV RNA load (67) as well as the association of higher markers of T-cell activation and senescence with carotid plaque prevalence (41). Furthermore, more rapid progression of carotid IMT has been associated with chronic inflammation in individuals with HIV (42,43). Ultrasound and CT, however, are unable to directly image inflammation.

18-fluorodeoxyglucose ($^{18}$FDG) uptake by arterial macrophages can been used to image arterial inflammation and early atheroma formation using PET CT technology. In a proof of concept study, 9 HIV-infected individuals with suppressed viremia on ART were compared to 5 HIV-negative individuals and were shown to have higher $^{18}$FDG uptake in the carotid arteries (77). In another cross-sectional study, 27 HIV-infected individuals were compared to two non-HIV-infected control groups, one matched for age, sex, Framingham risk score, and without atherosclerotic disease, the other matched on gender but with known atherosclerotic disease (78). Aortic $^{18}$FDG PET uptake was significantly higher in individuals with HIV compared to Framingham score-matched controls, even after adjusting for traditional CVD risk factors ($p=0.002$) and in multiple sub-analyses (Figure 5) (78).

Aortic $^{18}$FDG PET uptake was associated with levels of sCD163 (p=0.04), a marker of monocyte and macrophage activation that tracks levels of HIV RNA and is associated with cellular markers of immune activation (17,79). sCD163 levels also have been associated with non-calcified plaque, but not with CAC in ART-treated subjects with undetectable HIV viral loads compared to HIV-negative controls, whereas markers of more generalized information such as C-reactive protein and D-dimers were not associated with sCD163, coronary plaque, or $^{18}$FDG PET uptake (79).

### Summary

Arterial imaging is a useful tool for investigating CVD risk among patients with HIV infection and for exploring its causes. Carotid ultrasound, coronary CT, brachial artery ultrasound, and more recently, $^{18}$FDG PET, have provided important insights into the prevalence and pathophysiology of HIV-associated CVD risk. In general, the findings of studies using carotid ultrasound, coronary CT angiography, and $^{18}$FDG PET agree with those from observational studies of CVD events and suggest that HIV infection is associated with an increased risk of CVD. BART has been especially useful for elucidating the arterial pathophysiology of HIV infection and its treatments, as well as the arterial effects of interventions for treating HIV and dyslipidemia. $^{18}$FDG PET has been especially useful for evaluating arterial inflammation. CAC has not proven to be a useful marker of subclinical atherosclerosis in HIV-infected individuals.

Observational studies of CVD outcomes and studies using carotid IMT suggest a moderate increase in CVD risk related to HIV serostatus. Less can be said about the role of ART and specific ART therapies on CVD risk, mainly because imaging studies have had serious methodological limitations that diminish their generalizability. Studies that have harnessed the power of randomized clinical trials have been especially powerful in clarifying the relationships between ART and use of statins in HIV infected patients. The identification of improved endothelial function with viral suppression and ART, of an excess of non-calcified coronary plaque in patients with HIV infection, and of increased arterial inflammation in suppressed HIV patients have opened up new pathways for investigating the effects of persistent inflammation and immune dysregulation on CVD risk among ART-suppressed individuals. The generalizability and impact of imaging studies in HIV-infected patients will increase with greater use of randomized clinical trial designs, larger studies with longer follow-up, and with improved standardization of the imaging outcome measures.

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## Abbreviations

| | |
|---|---|
| **ART** | antiretroviral therapy |
| **BART** | brachial artery reactivity testing |
| **CAC** | coronary artery calcium |
| **CTA** | computed tomography angiography |
| **CVD** | cardiovascular disease |
| **FMD** | flow-mediated vasodilation |
| **HIV** | human immunodeficiency virus |
| **IMT** | intima-media thickness |
| **MI** | myocardial infarction |
| **PET** | positron emission tomography |

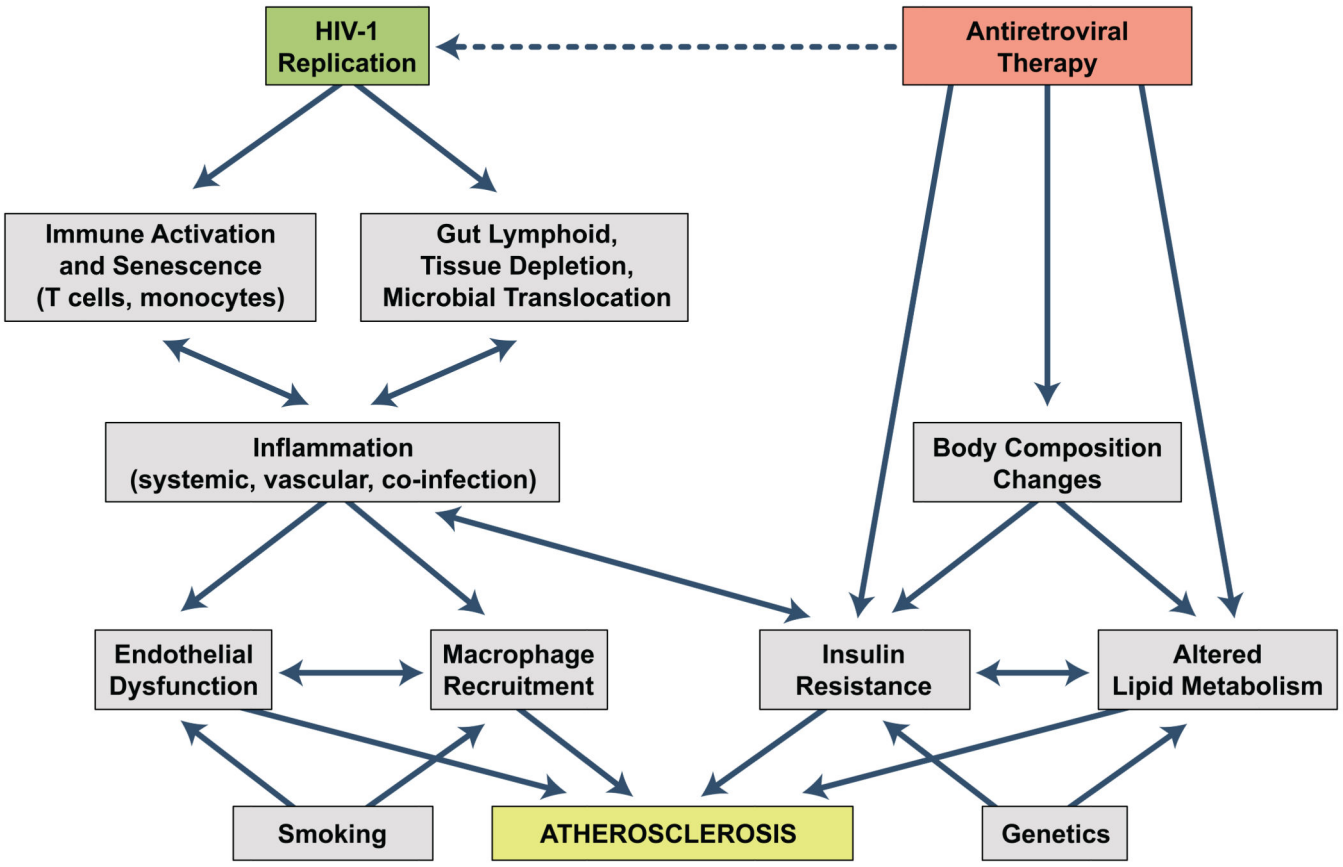


**Figure 1. Factors Contributing to Atherosclerosis and Arterial Injury in HIV-Infected Individuals**

Atherosclerosis and arterial disease in Human Immunodeficiency Virus (HIV)-infected individuals is a multifactorial process involving the virus, antiretroviral therapy, traditional risk factors for CVD and genetic predisposition. Each arrow represents a potential targets for research and therapeutic intervention.

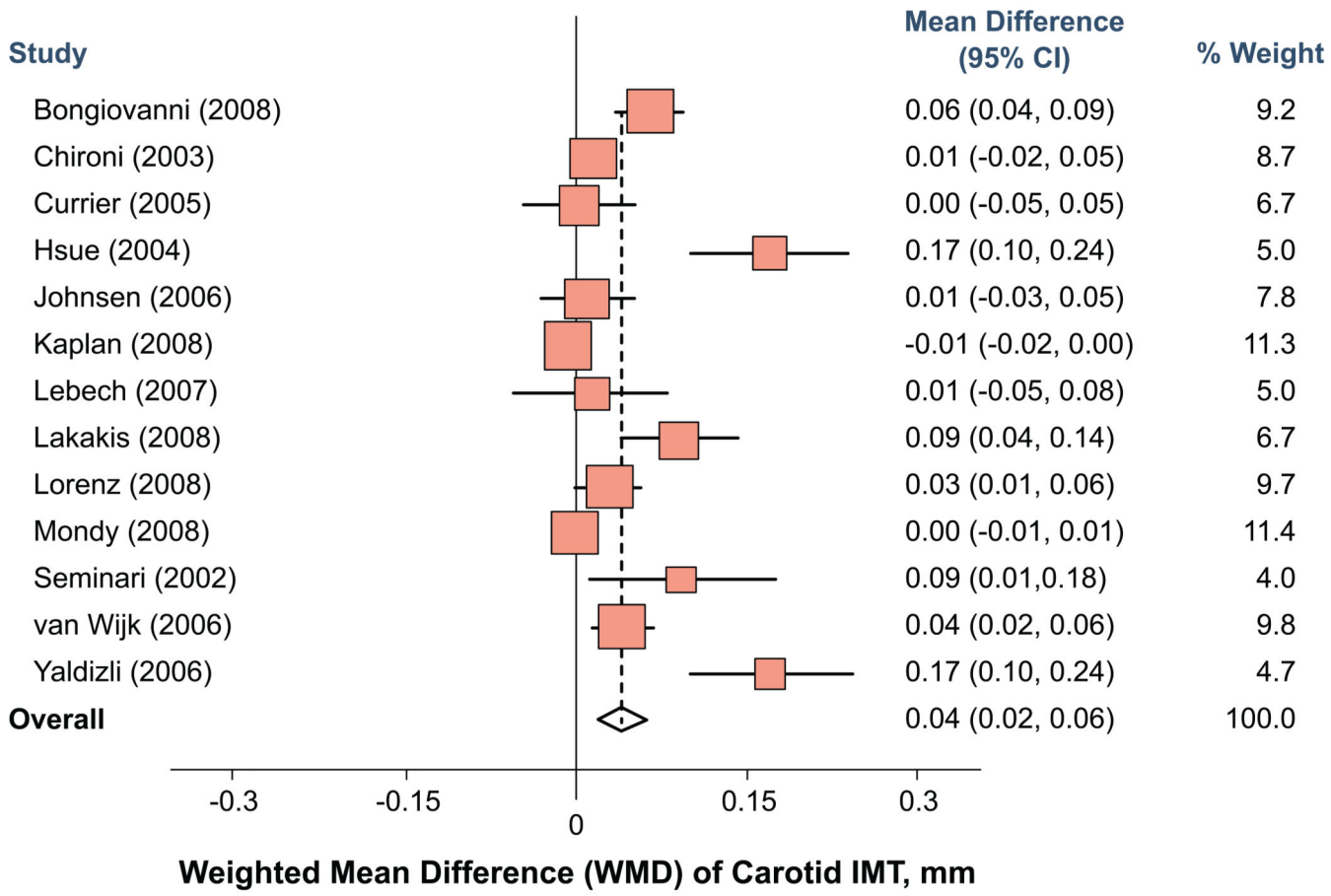


**Figure 2. Differences in Carotid IMT by HIV Serostatus (30)**

Meta-analysis of 13 studies evaluating the associations between HIV serostatus and carotid IMT. The carotid IMT of individuals with HIV infection was, on average, 0.04 mm thicker (95% CI 0.02-0.06, p<0.001) than those without HIV infection. *WMD = Weighted Mean Difference*

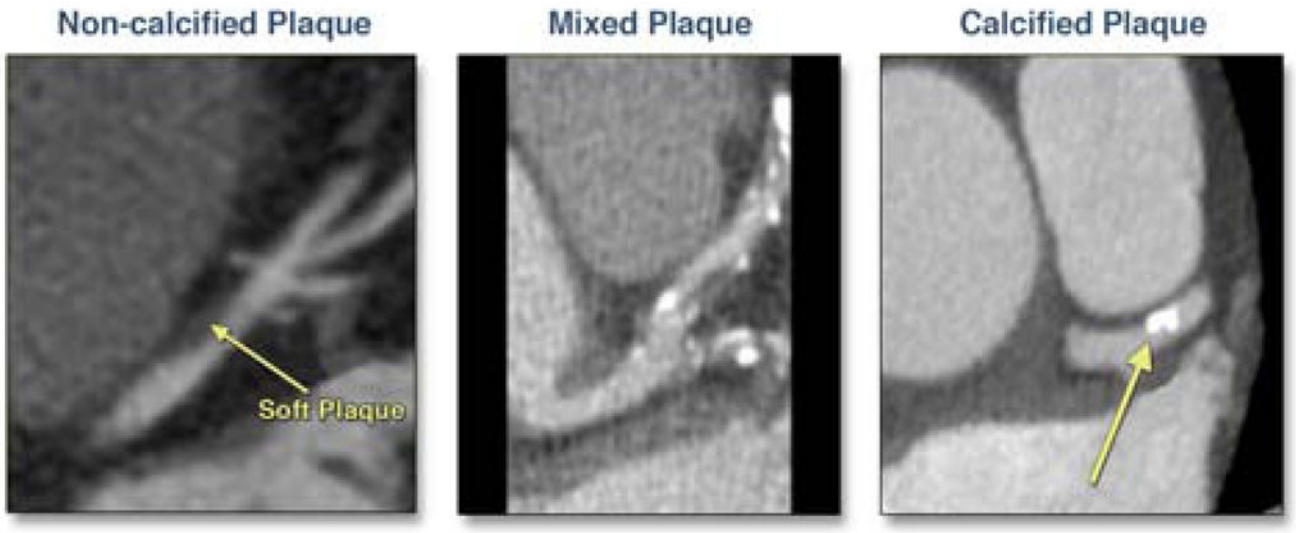


**Figure 3. Coronary Plaques Detected by Coronary CTA in the Multicenter AIDS Cohort Study (55)**

Examples of non-calcified (left panel), mixed (middle panel), and calcified (right panel) plaques detected by coronary artery computed tomography.

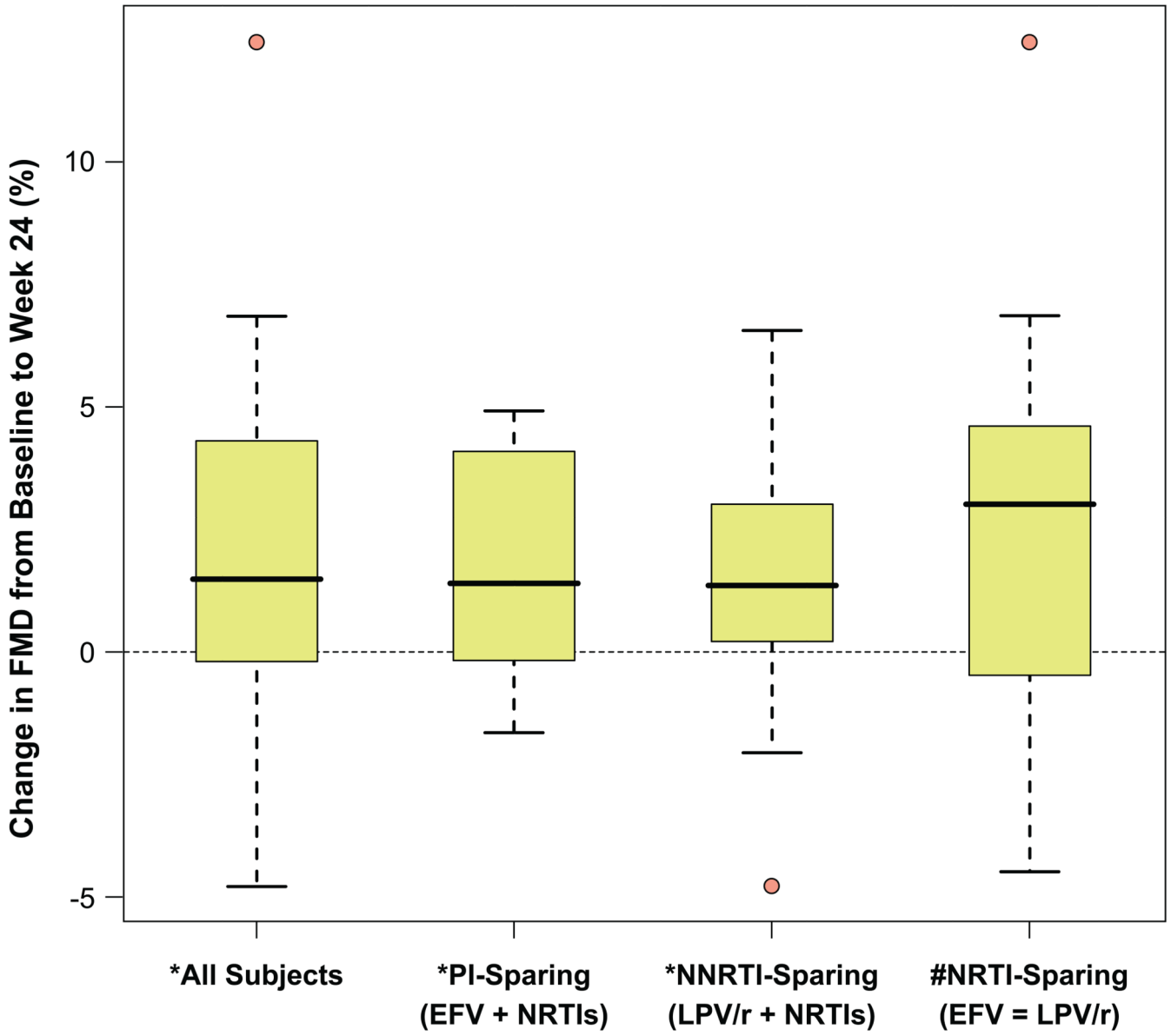


**Figure 4. Effects of 3 Class-Sparing ART Regimens on Changes in Brachial Artery FMD Over 24 Weeks (67)**

Thick bars = medians; box edges = 25$^{th}$- 75th percentiles; error bars = 95% confidence intervals. EFV = efavirenz; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

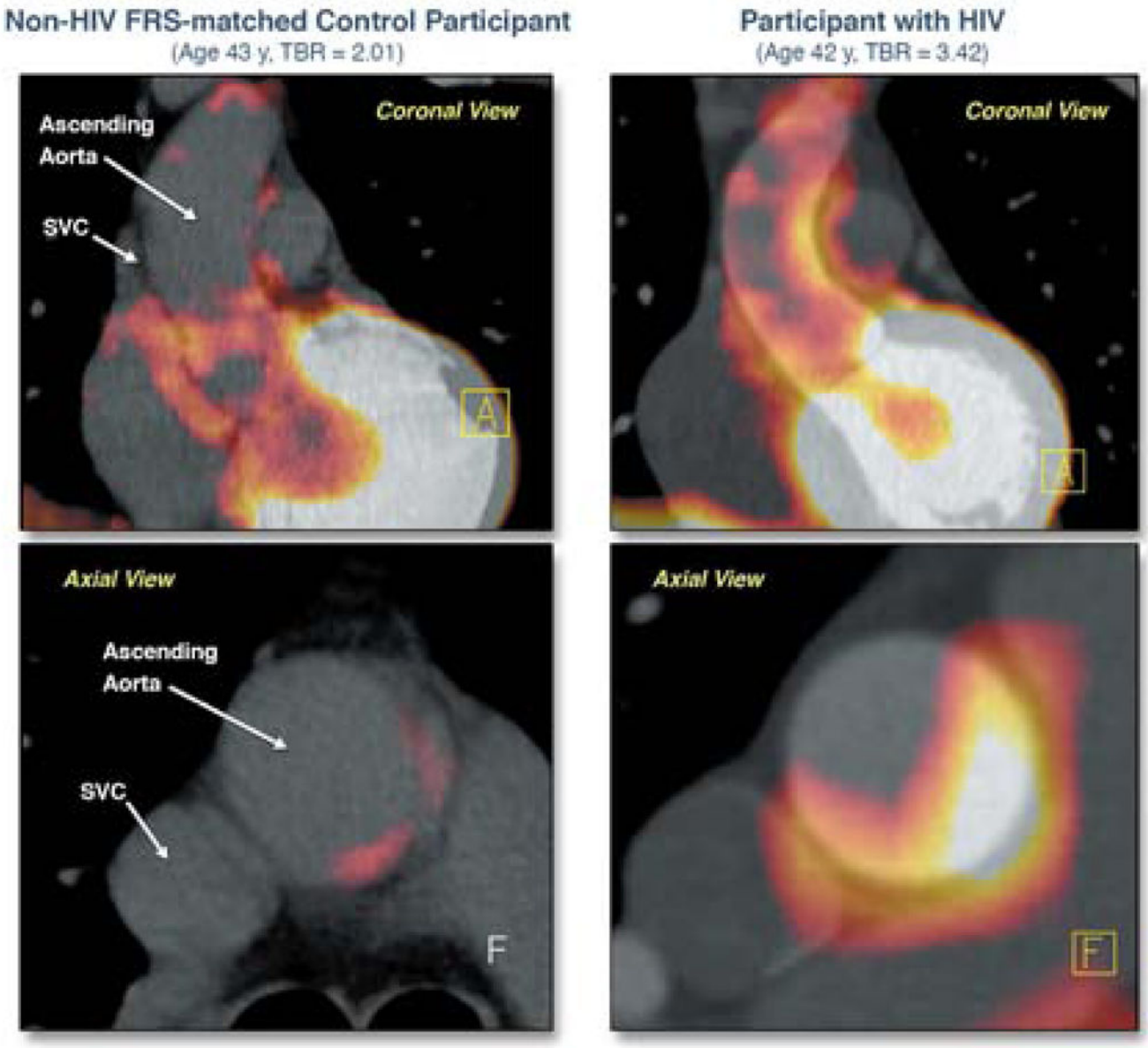


**Figure 5. $^{18}$FDG-PET/CT Aortic Imaging in HIV (78)**

Increased aortic PET-FDG uptake (red) in a HIV-infected participant compared with risk-factor matched control. A indicates anterior-posterior orientation; F, foot-head orientation. SVC = superior vena cava; TBR = target-to-background ratio.