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Initiation of Antiretroviral Therapy at High CD4 Counts: Does it Reduce the Risk of Cardiovascular Disease?

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Abstract

Purpose of review—Inflammation and immune activation associated with untreated HIV infection may increase the risk for cardiovascular disease (CVD) and are not entirely reversed by antiretroviral therapy (ART). While older ART regimens were associated with drug-specific risks for CVD, this may not be true for modern ART. Thus, with regard to CVD risk, the net benefit of initiating antiretroviral therapy at higher CD4+ T-cell counts remains unclear.

Recent findings—In addition to the well-established risk of coronary heart disease, emerging evidence now suggests that chronic HIV infection is associated with higher risk of ischemic stroke, heart failure, and arrhythmias. These epidemiologic studies have associated immunodeficiency and active viral replication with higher CVD risk. Novel methods of imaging subclinical vascular disease continue to implicate inflammation and immune activation as likely mediators of CVD among patients with HIV. Newer generation protease inhibitors, CCR5 antagonists, and integrase inhibitors do not appear to be associated with the adverse cardiometabolic risks of older drugs.

Summary—Recent evidence suggests that treating HIV infection with ART may reduce the risk of CVD, even at higher CD4 T-cell counts; however, the definitive answer to this question will come from clinical trials and long-term observational studies.

Keywords

Cardiovascular disease; Heart Failure; Sudden cardiac death; Immune activation; Antiretroviral therapy

Introduction

Over the past 15 years, a large body of literature has emerged regarding the risk of cardiovascular disease (CVD) among patients infected with HIV. Strong evidence exists for

an effect of chronic HIV infection on the risk of coronary heart disease that is independent of many traditional risk factors(1-3). Recent evidence now suggests a similarly increased risk for ischemic stroke(4), heart failure(5, 6), atrial fibrillation(7), and sudden cardiac death(8). In these studies, HIV-infection is generally associated with a 1.5 to 2-fold higher risk. Fortunately, the absolute rate of death from CVD appears to be declining due to increased access to evidence based care(9, 10); however, the burden of subclinical disease detected by non-invasive imaging remains high(11-13). The proposed mechanisms of elevated risk are many and broadly include the effects of active viral replication and immunodeficiency(14), drug effects of antiretroviral therapy (ART)(15), and chronic inflammation and immune dysregulation(16).

Despite the epidemiologic and mechanistic studies—most of which have examined surrogate markers of risk—it remains unclear whether treating HIV with ART definitively reduces the risk of CVD, particularly for those with higher CD4 counts. The answer to this question hinges on the balance of CVD-specific ART treatment risk vs. CVD-specific risk of uncontrolled viral replication, together in the context of competing risks from HIV-related and other non-HIV-related comorbidities over a given time period (i.e. 10-year vs. lifetime). Because of these complexities, we believe that this question is best answered with clinical trials (for short term risk) complemented by long-term observational research. In the Strategies for the Management of Antiretroviral Therapy (SMART) trial, treatment interruption at CD4 counts above 350cells/mm³ was associated with a higher risk of death and CVD compared to continuous viral suppression(17), although the number of CVD events was small and events were not clearly related to treatment interruption per se(18). Initiation of ART at CD4 counts above 500 cells/mm³ has been associated with a lower risk of mortality in a large observational cohort study, but CVD-specific risk was not reported(19). The clinical trial designed to answer this question, the Strategic Timing of Anti-Retroviral Treatment (START) trial, is ongoing and will include CVD as a pre-defined secondary outcome(20).

The current US Department of Health and Human Services guidelines on the use of antiretroviral therapy acknowledge that “no study has demonstrated that initiation of ART prevents CVD” [p. E7] (21), although they suggest that given the weight of current evidence, it is reasonable to use early ART as a strategy to reduce CVD risk. In this review, we will examine the most recent evidence on this topic.

The Role of Immunodeficiency, HIV Replication, Inflammation and Immune Dysregulation

How HIV itself influences CVD risk is complex and may involve direct and indirect pathways. In this section, we will examine the links between CVD risk and (1) T-cell immunodeficiency, (2) HIV viral replication, and (3) inflammation, coagulation, and immune dysregulation.

Immunodeficiency

One would logically hypothesize that if lower CD4 counts are associated with higher CVD risk, then ART initiated at higher CD4 counts may be cardioprotective; however, whether immunodeficiency is a cause of cardiovascular disease or a marker for other mediators is unclear(16). Advanced immunodeficiency is a risk factor for poor immunological recovery after ART-initiation(22), and patients with the worst immunological recovery (CD4 T-cells <200cells/ μ L) after 2 years of suppressive ART appear to have the highest risk of cardiovascular events(23). CD4 decline despite viral suppression on therapy was recently associated with a dramatic 12-fold higher incidence of CVD in a large Danish cohort(24). In epidemiologic studies of specific cardiovascular diseases, recent CD4 <200cells/ μ L was associated with higher risk of MI(2, 14) and atrial fibrillation(7), but not stroke(4) or heart failure(5). In a case control study from the French Hospital Database, lower CD4 was associated with MI independent of ART use(25).

The association of CVD risk with CD4 count appears to remain at higher CD4 strata. For example, time-updated recent CD4 <500cells/ μ L was predictive of CVD events in the HIV Outpatient Study(26). The attributable risk of CD4 <500cells/ μ L for CVD events was similar to smoking and greater than lipoprotein concentrations or diabetes. In another study of patients with baseline CD4 count >500cells/ μ L, nadir CD4 count was an independent predictor of non-AIDS events (of which, 25% were CVD-related)(27).

Not all studies have shown consistent associations of CVD with current or nadir CD4 counts(18, 28, 29). Neither latest nor nadir CD4 count was associated with MI in D:A:D(29). There was an association of low CD4 <100cells/ μ L with stroke (adjusted HR 2.26); although the exclusion of “stroke-like events” attenuated this relationship. This study highlights the importance of outcome adjudication for all observational studies, and suggests that differences in definitions of CVD end-points may partly explain discordant findings.

Mechanistic imaging studies have helped elucidate the pathophysiology linking immunosuppression to CVD events. Using carotid ultrasound, lower current CD4 has been associated with higher prevalence of carotid plaque in the Women's Interagency Health Study (WIHS) and the Multi-center AIDS Cohort Study (MACS)(30), and lower nadir CD4 has been associated with carotid intima-media thickness (IMT) progression(31). Both lower current CD4(32) and nadir CD4(33) have been associated with increased vascular stiffness. Current CD4 counts have been positively correlated with circulating endothelial progenitor cells, which are important regulators of vascular homeostasis(34), and lower nadir CD4 has been associated with worse endothelial function(35), higher left-ventricular mass(36), and prevalent HTN(37).

In contrast, higher CD4 count may be associated with more CAC(38, 39) and CAC progression over time(40). Additionally, in treated patients, higher CD4 counts have been associated with higher amounts of epicardial adipose tissue(41, 42), a highly pro-inflammatory visceral fat depot that may mediate CVD through direct effects on the coronary arteries. The reasons for why coronary calcification may increase with ART are not entirely clear, although calcification of vascular lesions may represent a more mature

form of atherosclerosis as compared to non-calcified plaques that have been associated with inflammation and immune activation(43).

HIV replication

Plasma HIV-1 RNA level reflects the degree of ongoing viral replication and was prognostic of AIDS-related outcomes in the pre-combination ART era(44). Effective combination ART is now able to reduce viral replication to extremely low levels in most patients, although some viral replication persists. The evidence for an association between viral replication and CVD events in large epidemiologic studies appears even more robust than the link with immunosuppression. In fact, plasma viral load was associated with higher incidence of MI(2, 14), stroke(4), heart failure(5), and atrial fibrillation(7).

The strength of this association in patients on treatment is unclear, however, because viral replication is reduced to very low levels in most patients. In the French Hospital Database, plasma viremia was associated with MI independent of ART use(25). In the DAD study, however, viral load >2.6 log copies/ml was not associated with CVD-related death among those on ART [OR(95%CI) 1.19 (0.89-1.59)], though it was associated with all-cause death [OR 1.55 (1.41-1.71)](9). Higher viral load was associated with both all-cause and CVD-related death in patients off ART(9). Similarly, in patients from the EuroSIDA cohort with CD4 counts >500cells/ μ L, CVD events were not higher in those with higher levels of viremia after adjustment for ART use(45). In the Dutch ATHENA cohort, in which 90% of CVD events occurred in patients on ART, higher levels of viremia (>400 copies/ml) were associated with cardiovascular events, but lower levels of viremia (50—400 copies/ml) were not(46). Finally, participants in the drug conservation arm of the SMART trial had more CVD events than those in the viral suppression arm, though these events were not related to the most recent, time-updated viral load or the maximum viral load since baseline(18).

Mechanistic studies may again shed light on the pathologic effects of viral replication on CVD risk. Lower baseline viral load and maintenance of viral suppression during follow-up was associated with slower IMT progression in the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN)(47), and viral load prior to ART initiation was associated with carotid plaque in ACTG 5260(48). Additionally, endothelial activation and endothelial function measured by brachial artery reactivity studies rapidly improves with viral suppression during the initiation of ART(49, 50).

Although few in number, HIV “elite controllers” (ECs)— patients who are able to maintain a high degree of viral suppression in plasma without ART—serve as an important comparison group that may clarify the separate effects of ART and viral replication on CVD risk. Non-calcified coronary plaque burden is higher(51) and carotid IMT is thicker(52) in two studies that compared a small number of ECs to HIV-negative controls. Elite controllers also had higher biomarkers of inflammation and immune activation in both studies.

Inflammation, Coagulation, and Immune Dysregulation

Recent investigation has focused on whether CVD risk in patients with HIV may be explained by residual levels of chronic inflammation, altered coagulation, and immune activation, and whether residual elevated levels in patients with suppressed viremia on ART

may continue to confer increased risk. The INSIGHT SMART study group has comprehensively evaluated plasma biomarkers of inflammation and recently published results of their associations with CVD in the SMART trial(53). Compared to subjects in the lowest quartile (Q1), subjects with the highest quartile (Q4) of interleukin-6 (IL-6) and high sensitivity C-reactive protein (hs-CRP) had higher risk of CVD events (adjusted HR 4.7 and 2.1, respectively). The hazard associated with elevated hs-CRP was similar to that of a prior study of MI(54). Hs-CRP has been associated with carotid IMT progression(55), but is also associated with mortality independent of IMT(56). With regard to heart failure risk, hs-CRP was associated with left ventricular systolic dysfunction in a meta-analysis of echocardiographic studies in the HAART era(57). In small studies, IL-6 has been associated with IMT(58, 59), carotid plaque(48), and epicardial adipose tissue(42). In contrast, neither of these generalized markers of inflammation was associated with measures of coronary atherosclerosis by CT angiography(43).

D-dimer was also a strong predictor of CVD events in the SMART trial (adjusted HR 2.1, Q4 vs. Q1)(53) and has been associated with incident CVD events in HIV patients enrolled in NIH protocols(28). In a study that examined a large number of biomarkers of inflammation, coagulation, and oxidative stress, d-dimer was the only marker independently associated with endothelial function(60). Although not associated with coronary atherosclerosis by CT angiography(43), there was a borderline significant association of d-dimer with vascular inflammation in a small study that examined aortic wall uptake of ¹⁸fluorine-2-deoxy-D-glucose by positron emission tomography (PET-CT)(61).

Cellular markers of immune activation are also promising biomarkers of CVD events in treated HIV infection. CD4 and CD8 T-cell activation as measured by co-expression of CD38 and HLA-DR by flow cytometry have been associated with higher prevalence of carotid plaque (CD8+)(58, 62) and decreased carotid distensibility (CD4+)(63). Inflammatory monocyte subsets (CD14+CD16+) are elevated in HIV-infection, only partially attenuated by ART treatment, and similar to HIV-uninfected adults with acute coronary syndromes(64); though they do not appear to be associated with carotid disease(58).

Soluble CD14, a soluble marker of monocyte activation linked to translocation of bacterial lipopolysaccharide (LPS) from a damaged gut, or microbial translocation, was predictive of mortality in SMART and VACS(65, 66), though attempts to show a relationship between plasma levels of sCD14 and carotid disease(58, 59), brachial endothelial function(67), and coronary atherosclerosis(12, 43) have been largely negative. Higher levels of sCD14 (but not LPS) were associated with pathologic IMT in an Italian cohort(68). One longitudinal study associated sCD14 with carotid IMT progression in HIV-infected patients but not HIV-uninfected patients(69).

Another marker of monocyte activation, soluble CD163, is elevated in HIV-infected individuals, decreases with ART (though not to HIV-negative levels), and correlates with CD14+CD16+ monocytes and CD8+CD38+HLA-DR+ T-cells(70). It has been associated with non-calcified coronary plaque(43), low attenuation “vulnerable” plaque(12), and aortic inflammation(61), but not carotid IMT or plaque(11). Soluble CD163 is strongly related to

obesity and insulin resistance in seronegative patients(71), and appears to be modestly correlated to epicardial adipose tissue volume in ART-treated individuals without clinical lipodystrophy(42).

Adjunctive therapies may reduce CVD risk in HIV-infection by decreasing inflammation and immune activation. The anti-inflammatory drugs salsalate(72, 73) and pentoxifylline(74) failed to improve endothelial function or were poorly tolerated; however, recent studies have shown that both statins(75, 76) and aspirin(77) reduce immune activation. Additionally, retrospective studies suggest that statins may have significant effects on mortality(78), especially among those with comorbidities(79). Several trials evaluating the effect of statins on surrogate markers of CVD risk in HIV-infected patients on ART are ongoing.

In summary, the bulk of evidence suggests that advancing immunodeficiency, ongoing viral replication, and the immune dysregulation that occurs in untreated HIV-disease is associated with abnormal vascular structure and function, subclinical atherosclerosis in multiple vascular beds, and higher risk of CVD events. We will now explore whether treatment with ART effectively decreases these effects without worsening CVD risk through other pathways.

The Role of Antiretroviral Therapy

The cardiovascular risk of individual ART drugs and drug classes has been long-debated, and updated meta-analyses that span studies from the entire treatment era have been recently published(80, 81). Although both studies suggest possible associations of certain ART with CVD, they once again highlight the limitations of the current observational literature. Perhaps most importantly, antiretroviral therapy has evolved, such that many drugs of proven toxicity are no longer used in resource-rich settings. For example, the more metabolically-friendly PI atazanavir was not associated with the risk of MI seen with other PIs (e.g. indinavir and lopinavir) in an updated analysis of the D:A:D study(82). The risk of abacavir remains controversial because of the initially reported association with MI in D:A:D(83) and mechanistic studies suggesting an association with endothelial dysfunction(84), worse inflammation profile(85, 86), and increased platelet activation(87, 88). Subsequent reports from other trials and observational cohorts have been conflicting(89-91). In 2012, a United States Food and Drug Administration (FDA) sponsored trial-level meta-analysis of randomized studies failed to demonstrate an association of abacavir and MI(92); however, it was underpowered because the included trials were small and of short duration.

The detrimental effects of ART on cardiometabolic risk factors are well-documented(93). Recent studies of lipid processing have suggested that patients on ART have high-density lipoprotein particles that are larger, less stable, and dysfunctional(94), and higher pro-atherogenic levels of allele-specific apolipoprotein(a) levels(95). Interestingly, ART use may also be associated with hypertension; however, it appears that the effect is greatest when ART is initiated at lower CD4 counts(37).

Sudden cardiac death is a common cause of death in HIV-infected patients relative to the general population(8) and appears to be associated with cumulative PI use in the DAD study; although, a small association with current PI use was not statistically significant(96). These observations have sparked renewed interest in pro-arrhythmic effects of PIs. The FDA warns that ritonavir boosted lopinavir(97) and saquinavir(98, 99) may be associated with prolongation of the QT interval and elevated risk of polymorphic ventricular tachycardia; however, PI use had minimal effect on the QT interval in SMART after adjusting for race(100). Atazanavir has been associated with a lower risk of QT prolongation, adding further evidence of its favorable CVD risk profile(101). It also appears that PIs as a class may be associated with pathologic prolongation of the PR interval(100). PR prolongation >200ms is a risk factor for atrial fibrillation and all-cause mortality in the general population (102, 103).

Two newer antiretroviral drug classes, CCR5 antagonists and integrase inhibitors, may have more favorable CVD risk profiles than older agents. CCR5 is a chemokine receptor expressed on immune cells that is used by most strains of HIV-1 virus to enter the cell. It is also expressed on endothelial cells and serves to facilitate immune cell migration through the endothelium in the presence of inflammation, thus playing an important role in the progression of atherosclerosis. CCR5 blockade with maraviroc may slow progression of atherosclerosis in an inflammatory ApoE^{-/-} mouse model(102). Maraviroc treatment may be associated with larger and more rapid declines in systemic inflammation and immune activation compared to efavirenz-based ART(86) and appears to prevent left ventricular diastolic dysfunction in an SIV model(104).

Raltegravir and other agents in its class inhibit integration of HIV-1 viral DNA into the human chromosome. Switching a boosted PI regimen to raltegravir-based ART improved overall lipid profile, and caused a shift toward less atherogenic LDL subclasses(105). The switch also dramatically decreased hs-CRP and IL-6 by over 40%(106), but did not improve endothelial function(107). In a separate trial, raltegravir intensification did not improve T-cell activation or endothelial function(108).

In summary, ART clearly influences CVD risk; however, the magnitude of its effect relative to unchecked viral replication and associated inflammation remains unclear. Clinical trials are needed to determine whether newer agents will have definite advantages over traditional agents with regard to hard CVD events.

Does Treating HIV Reduce CVD Risk: The Bottom Line

The question remains-- does treatment with ART initiated at higher CD4 counts reduce CVD risk in HIV-infected patients? In light of recent evidence, we feel that the scale tips in favor of early treatment for two principle reasons. First, the bulk of evidence suggests that uncontrolled viral replication contributes more than ART treatment to the characteristic immune dysregulation that appears to be an important driver of atherosclerosis in chronic HIV infection. Despite the limitations of existing observational data, we believe that multiple pathways of immune dysfunction (e.g. generalized inflammation, T-cell activation, and monocyte activation) contribute to CVD risk in this population. Treating HIV likely

reduces CVD risk through reconstitution of the immune system and reduction of HIV viremia, inflammation, and immune dysfunction. Second, modern ART is certainly less metabolically toxic than older regimens, and, in some cases, may yet prove to be cardioprotective. Although we eagerly await the results of the START trial for short-term CVD outcomes, we recognize that additional observational research will be needed to answer this question with regard to long-term outcomes.

The degree of residual CVD risk in patients who initiate treatment at high CD4 counts and achieve viral suppression remains uncertain. Inflammation due to low-level ongoing viral replication may confer significant CVD risk over time; one study suggests that a cumulative measure of HIV replication in ART-treated patients predicts mortality(109). The impact of CVD on treated and suppressed HIV-infected patients in the long term is a question central to this population's care.

Conclusions

As the HIV-infected population ages, CVD prevalence will certainly rise. If it is not overshadowed by competing risks from co-morbidities, individual lifetime risk of coronary disease, stroke, arrhythmias, and heart failure in this population will remain high. Innovative and evidence-based adjunctive therapies such as statins and possibly anti-inflammatory drugs or immunomodulatory agents may be needed to improve outcomes. As tailored interventions are being developed, earlier treatment with ART is one strategy likely to decrease CVD risk for patients with HIV.

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Key Points

1. Strong evidence exists for an effect of chronic HIV infection on the risk of coronary heart disease that is independent of many traditional risk factors. Recent evidence now suggests a similarly increased risk for ischemic stroke, heart failure, atrial fibrillation, and sudden cardiac death.
2. In epidemiologic studies, lower current and nadir CD4 T-cell counts have generally been associated with a higher risk of CVD. Additionally, plasma viremia appears to be associated with increased risk after adjustment for ART use.
3. Novel biomarkers of inflammation and immune activation are associated with abnormal vascular structure and function detected by carotid ultrasound, brachial artery reactivity testing, CT coronary angiography, and PET-CT of large arteries.
4. Newer ART agents including CCR5 antagonists and integrase inhibitors have a more favorable cardiometabolic risk profile; although further studies are needed to determine their effect on hard CVD endpoints.