HIV, HAART and the Heart: Cardiovascular Risk Associated with HIV and Antiretroviral Therapy

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Outline:

I. **Trends in Morbidity and Mortality: The Changing Face of HIV Disease**
   a. **Increased survival and aging of HIV-infected patients**
   b. **Trends in causes of death among persons with HIV/AIDS in the HAART era**

II. **Epidemiology of Cardiovascular Disease in HIV**

III. **Risk Factors and Pathogenesis of CVD in HIV**
   a. **Prevalence of Traditional CVD Risk Factors among HIV Patients (smoking)**
   b. **HAART**

IV. **Risk of AMI in the VA Population: Role of HAART, CKD and HCV**
   a. **Abacavir, Chronic Kidney Disease and Acute Myocardial Infarctions**
   b. **Hepatitis C Co-infection and Cardiovascular Risk in HIV**

V. **Potential Mechanisms of Increased Atherogenesis in HIV**

VI. **Concluding Remarks and Future Directions**

I. Trends in Morbidity and Mortality: The Changing Face of HIV Disease

a. Increased survival and aging of HIV-infected patients

Together with prophylaxis for opportunistic infections [1], the discovery and widespread use of protease inhibitors (PI) in the context of combination therapy – known as Highly Active Antiretroviral Therapy (HAART) – has had a significant impact on the survival of HIV-infected patients [2, 3]. During the second half of the 1990's decade, mortality of HIV-infected patients in the U.S. and Europe dropped to less than 1/3 of the rate of the previous half-decade [2-4]. Furthermore the HIV population is significantly aging. It is expected that by 2015, more than one-half of all HIV-infected individuals in the United States will be aged >50 years [5]. In 2007, the largest number of new HIV/AIDS diagnoses was for persons aged 40–44 years, who accounted for 15% of all HIV/AIDS cases diagnosed during that year [6].

b. Trends in causes of death among persons with HIV/AIDS in the HAART era

The increase in overall survival and aging of HIV-infected patients has been associated with a shift in underlying cause of death among these patients, with lesser representation of "AIDS-related causes" and greater representation of "non-AIDS-related" deaths. Between 1999 and 2004, the proportion of deaths due to non–AIDS-related causes increased by 33% in New York [7]. Similar trends have been observed across North America and Europe [3, 8-10]. Among the "non-AIDS-related" causes, those most commonly reported are chronic liver disease (mostly resulting from hepatitis C co-infection, cardiovascular disease (CVD), and non–AIDS-defining cancers [7-10].

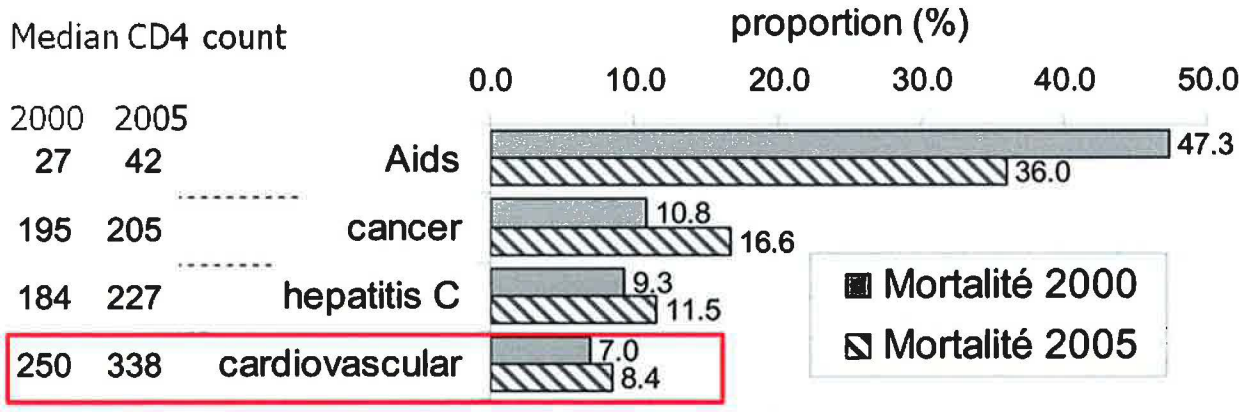


Figure 1: Underlying cause of death in HIV-infected adults: Overall distribution in 2000 (n = 964) and 2005 (n = 1042), and most recent CD4 cell count by cause; Mortalité 2000 and 2005 surveys, France [10, 16].

II. Epidemiology of Cardiovascular Disease in HIV

Several database analyses and observational cohort studies have reported a higher incidence of cardiovascular events among HIV-infected patients than HIV-negative controls [11-15]. CVDs

now account for 8% to 22% of deaths among HIV-infected patients and this percentage appears to be increasing [3, 10, 16, 17].

However, while the studies mentioned above show a relative increase over time in the proportion of HIV deaths caused by CVD [3, 16], there is to date no documented absolute increase in cardiovascular morbidity or mortality[11]. In fact rates of, and mortality from acute myocardial infarctions (AMI) among HIV patients appear to have either stabilized or are have decreased in the recent years in a number of cohort analyses [12, 16, 18]. Also, somewhat paradoxically, the impact of HIV and HAART on cardiovascular risk was seen only in the group of patients younger than 33 in one study [19]. All this should call for a re-examination of the factors potentially associated with increased cardiovascular risk among HIV-infected patients.

III. Risk Factors and Pathogenesis of CVD in HIV

a. Prevalence of Traditional CVD Risk Factors among HIV Patients (smoking)

It has already been shown that HIV-infected patients are more likely to smoke than age- and gender-matched controls [20]. Indeed, tobacco smoking appears to not only independently predict HIV infection, but also progression to AIDS [20]. A population-based cohort study in France [21], evaluated the distribution of risk factors for cardiovascular disease in HIV patients. The predicted CAD risk was greater among HIV-infected compared with the HIV-uninfected cohort. However, the estimated attributable risks due to smoking were 65% and 29% for HIV-infected men and women, respectively. Smoking was also the most prevalent cardiovascular risk factor among HIV-infected patients in the Swiss Cohort [22]. Smoking and other potential lifestyle differences can therefore account for at least part of the excess cardiovascular morbidity, but is not adequately accounted for in the most referenced cohort analyses of the impact of HAART on cardiovascular risk in HIV patients [23, 24].

b. HAART

The typical HAART regimen contains three different antiretrovirals grouped into two main components: 1) A "backbone" which typically comprises two drugs in the nucleoside reverse transcriptase inhibitor (NRTI) class. 2) An "anchor" drug which is either a ritonavir-boosted PI, non-nucleoside reverse transcriptase inhibitor (NNRTI), or an integrase inhibitor (INSTI). Currently, the two most prescribed NRTI backbones are abacavir (ABC) + lamivudine (3TC) and tenofovir (TDF) + emtricitabine (FTC). The potential impact of antiretroviral therapy (ART) on the cardiovascular risk of HIV-infected patients has been debated for over a decade now, ever since ART use has been found to be associated with metabolic complications including dyslipidemia and insulin resistance [25]. Significant differences in the rates, magnitudes and types of dyslipidemias have been reported both within classes [26, 27], and between classes of antiretroviral drugs, with the NRTI class being the least associated with dyslipidemia [28, 29].

"Preferred HAART Regimens" - DHHS Guidelines: Construct regimen by choosing one component from Column A and one component from Column B			
January 2008			
Column A			**Column B**
January 2008			
PI	*NNRTI*		*NRTI*
Atazanavir + Ritonavir	Efavirenz		Tenofovir/Emtricitabine (Truvada)
Fosamprenavir + Ritonavir BID			Abacavir/Lamivudine (Epzicom)*
Lopinavir/ritonavir (Kaletra) BID			
December 2009			
PI	*NNRTI*	*INSTI*	*NRTI*
Atazanavir + Ritonavir	Efavirenz	Raltegravir	Tenofovir/Emtricitabine
Darunavir + Ritonavir			

* for patients who test negative for HLA-B5701

Table 1: Preferred HAART Regimens: DHHS Guidelines

The link between HIV- and HAART-induced dyslipidemias and CVD appears to have been confirmed by the analysis of the D:A:D cohort (an international collaboration of 11 cohorts, following 33,347 HIV-1-infected individuals at 212 clinics in Europe, the USA, and Australia), which concluded that every year of protease inhibitor use was associated with a 16% increase in risk of AMI, while the exposure to NNRTI was not associated with a significantly increased risk [30, 31]. The PI-associated increased risk was only partly explained by dyslipidemia suggesting that ART might potentiate cardiovascular risk through other mechanisms.

An subsequent analysis of the cardiovascular risk associated with NRTIs in the same cohort found no associations between the rate of myocardial infarction and cumulative or recent (<6 months) use of zidovudine, stavudine, or 3TC (all NRTIs). By contrast, recent—but not cumulative—use of ABC or didanosine (DDI) was associated with an increased risk of myocardial infarction (compared with those with no recent use of the drugs, relative rate 1·90, 95% CI 1·47–2·45 [p=0·0001] with ABC and 1·49, 1·14–1·95 [p=0·003] with DDI), even after adjustment for predicted 10-year risk of coronary heart disease. This increased risk was not sustained beyond 6 months after cessation of exposure to the NRTIs. The authors concluded that the excess risk is a direct effect of the antiretrovirals and does not seem to be explained by underlying established cardiovascular risk factors [24]. A post-hoc analysis of the Strategies for Management of Anti-Retroviral Therapy (SMART) study [32] was concordant with these findings. It showed that cumulative – but mostly recent – use of ABC and DDI was associated with an increased risk of CVD, postulating that the drugs may cause vascular inflammation, which may in turn precipitate a cardiovascular event.

On the other hand the Danish cohort [15] analysis showed that HIV-infected patients on HAART have a significantly higher risk of hospitalization for ischemic heart disease than non-HIV patients, but this excess risk did not increase with the duration of therapy. Finally, in a recent randomized controlled trial, in which ABC/3TC or TDF/FTC were substituted for current HAART regimen in treatment-experienced, virologically suppressed patients,

ABC/3TC was associated with more serious non-AIDS events, particularly cardiovascular events (0.3 vs. 2.2 events per 100 patient-years; HR, 0.12; 95% CI, 0.02-0.98) [33].

The lack of "dose-response relationship" between duration of ABC and DDI exposure and risk of events nonetheless remains puzzling. [34]. In general, while the increased risk of AMI among HIV-infected patients is unquestioned, the association between the duration of ART or specific antiretroviral drugs with increased cardiovascular risk has not been consistently observed by other cohorts or clinical trials [11-15, 19]. Also, a corollary to the findings of an association between HAART and cardiovascular events is the expectation that the rates of CVD will continue to increase as the exposure to HAART increases among HIV populations. However, the above-mentioned recent stabilization or decline in rates of, and mortality from AMI among HIV patients [12, 16] is paradoxical given the increased use of HAART in the recent years. The discrepancy was hypothesized to be due to either better cardiovascular risk management among HIV-infected patients or safer metabolic side-effect profiles of newer antiretroviral drugs [18].

Somewhat puzzling is also the analysis of the Kaiser Permanente data including 28,513 HIV-infected patients, which showed that ART was associated in increased risk of AMI (RR: 2.06) only in the younger patients (ages 18 to 33). There were no statistically significant associations between ART exposure and CVD in other age groups [19]. One final discordant note is that HAART discontinuation in the above-mentioned SMART study led to increased incidence of cardiovascular events

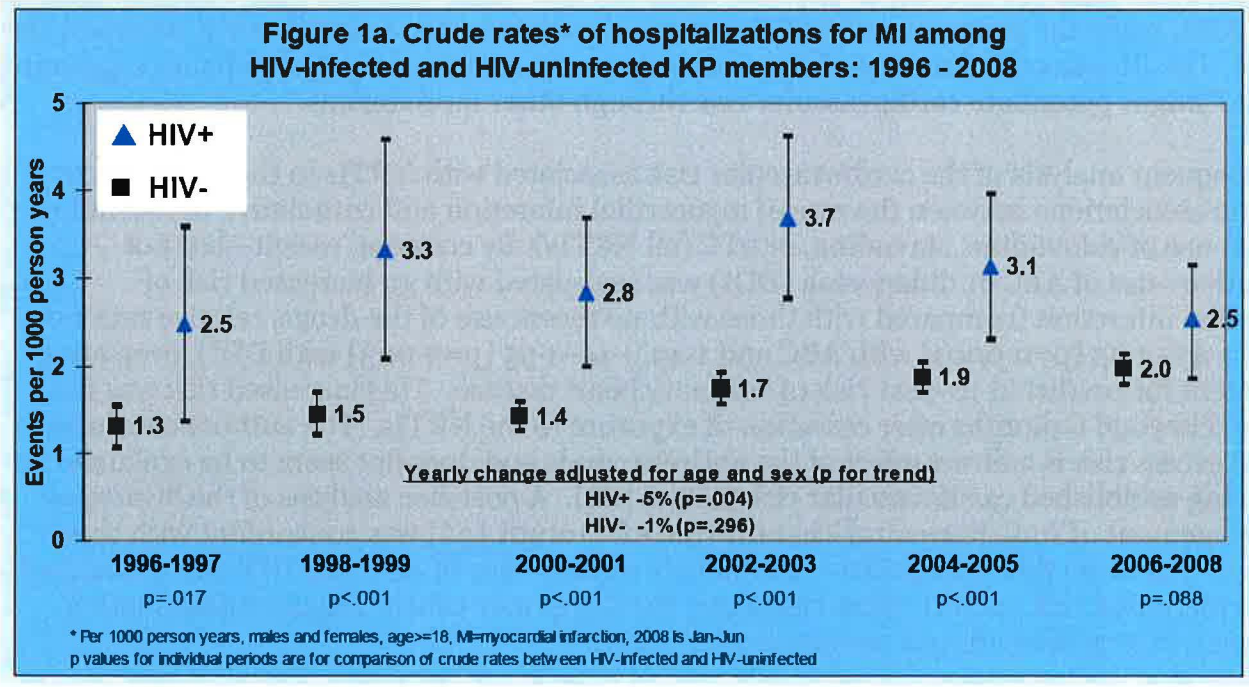


Figure 2: Crude rates of hospitalizations for AMI among HIV-infected and HIV-uninfected Kaiser Permanente members: 1996-2008 [18].

Concerns have been raised from these studies about the possibility of a "channeling bias" whereby patients deemed more at risk for CVD are disproportionately channeled to receive ABC which has been associated with fewer metabolic complications than older drugs in the NRTI class. Another possibility being that TDF is avoided in favor of ABC in patients with, or at risk for, kidney dysfunction, given the concerns for TDF-induced nephrotoxicity [35]. Nonetheless, the concerns about the cardiovascular risk associated with ABC have in part led to a change in the DHHS HIV management guidelines (see table 1 above)

IV. Risk of AMI in the VA Population: Role of HAART, CKD and HCV

a. Abacavir, Chronic Kidney Disease and Acute Myocardial Infarctions

To explore the association of antiretroviral therapy containing ABC with cardiovascular and cerebrovascular events, we utilized Veterans Affairs' Clinical Case Registry (CCR). CCR is both a registry at every VHA facility to support local care delivery and a national clinical database. Patients with AMI and cerebrovascular accidents (CVA: either ischemic strokes and transient ischemic attacks) episodes occurring after HIV diagnosis were identified by ICD-9 code. In the HAART era (1996-2004) we calculated the risk of AMI and CVA associated with cumulative use of: 1) HAART (≥ 3 antiretrovirals; containing ABC, 2) HAART with other NRTI, 3) non-HAART ART (<3 drugs concomitantly administered), and 4) no ART; exploring ART as a time-dependent variable. The impact of hepatitis C co-infection and chronic kidney disease (CKD; defined as estimated glomerular filtration rate (eGFR) of <60) on AMI risk was evaluated.

A total of 19,424 HIV-infected patients contributed 76,376 patient-years (PY) of follow-up in the HAART era (median follow-up = 3.88 years). 278 AMI and 868 CVA were diagnosed. Rates of AMI and CVD were respectively 3.69 (95% CI: 3.28 – 4.15) and 11.68 (95% CI: 10.93 – 12.48) per 1000 patient-years of observation. Rates of AMI remained relatively constant from 1996 to 2004. In univariate analysis we observed a marginal association between cumulative ABC use and AMIs. This association was further attenuated by traditional cardiovascular risk factors (model 1 in table 2 below) and renal dysfunction (model 2) prior to regimen initiation.

Exposure Category	Patient years	Unadjusted HR[1] for AMI (95% CI) P value	Model 1: Adjusting for CKD[2]	Model 2: Adjusting for traditional risk factors[3]
HAART with ABC	3,881	1.27 (0.99 – 1.62) p=0.056	1.23 (0.95 – 1.58) p=0.113	1.18 (0.92 – 1.50) p=0.191
HAART with Other NRTIs	25,077	1.09 (0.97 – 1.21) p=0.146	1.02 (0.91 – 1.15) p=0.702	0.99 (0.87 – 1.11) p=0.866
Mono & Dual ART	6,642	1.44 (1.23 – 1.67) p<0.0001	1.39 (1.18 – 1.63) p<0.0001	1.29 (1.10 – 1.52) p=0.002

1. HR: Unadjusted HR of AMI for each PY of exposure to each one of the categories
2. Most recent estimated GFR (by MDRD method; carried forward) .
3. Age, hypercholesterolemia, HTN, type 2 DM, and tobacco use.

Table 2: Cumulative ABC Use and Risk of Acute Myocardial Infarction

Furthermore, we showed that CKD was a significant risk factor for AMI in this HIV population, which the highest HR of all the factors examined, and significantly higher HR for AMI than reported in the general population [36]. Compared to patients with estimated glomerular filtration rate (eGFR) of ≥90, HR for AMI were 3.85 (2.74 – 5.42) p<0.0001 for patients with eGFR<60 and 1.33 (1.00 – 1.76) p=0.048 for patients with eGFR between 60 and 89. Similar findings have recently been published [37] in another analysis of the VA HIV population.

Renal dysfunction is a known driver for the selection of ABC vs. TDF in the treatment of HIV-infected patients and, given the known cardiovascular risk associated with kidney dysfunction in the general population [36, 38, 39]. Given the very high HR for AMI associated with CKD in our first analysis above, and the concerns for "channeling bias" discussed above, we then evaluated whether there was evidence of channeling in selecting ABC over TDF.

In a second analysis, we divided patients in 4 groups depending on whether their last recorded regimen in the database contained 1) ABC, but no TDF; 2) TDF, but no ABC; 3) both ABC and TDF; or 4) neither ABC nor TDF. A significantly greater proportion of patients initiating an ABC regimen had a baseline eGFR <60 than those initiating a TDF regimen (12.29% vs. 7.22%; p <0.0001). Estimated GFR of <60 prior to initiation of the last regimen was associated with a HR of AMI during that regimen of 3.16 (95% CI: 2.35 – 4.26). Finally, the HR of ABC for AMI was also attenuated by traditional cardiovascular risk factors and renal dysfunction prior to regimen initiation.

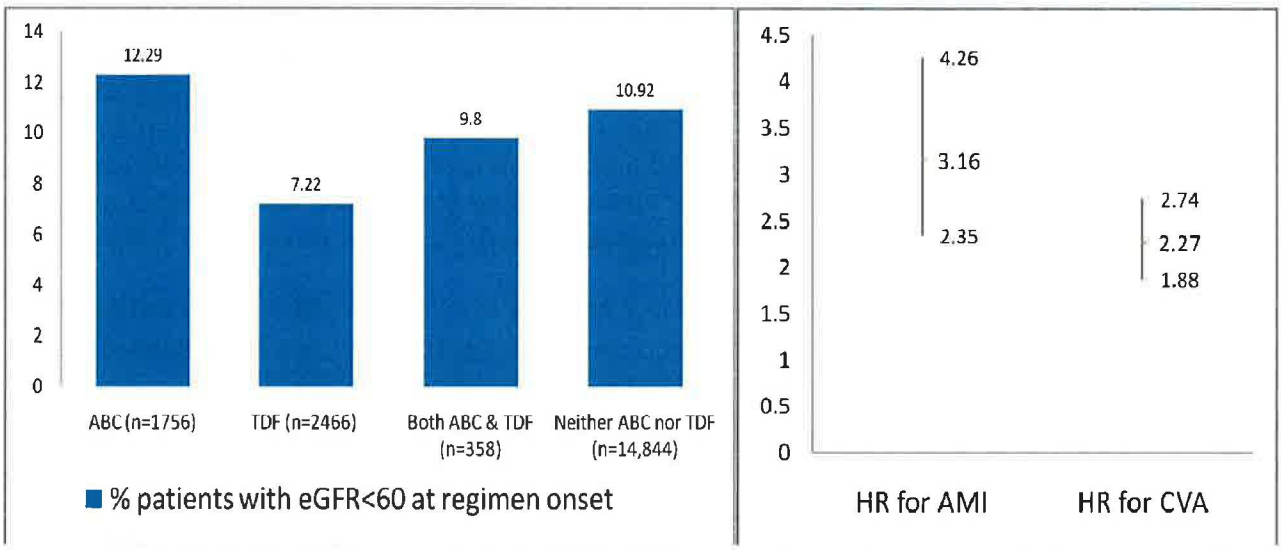


Figure 3: Impact of CKD on HAART Selection; HR of eGFR<60 at Last Regimen Onset*
*HR of eGFR <60 compared to eGFR ≥ 60 (adjusted for last ARV regimen)

We therefore showed that not only was CKD (which affects up to 15% of HIV-infected patients [42, 43]) is a significant predictor of NRTI use in the last regimen (ABC vs. TDF); CKD – but not the NRTI – significantly predicted the onset of AMI during that regimen.

Ours and most of the above-mentioned studies are observational and, as such, are not designed to definitively establish whether any associations are causal. What might increase the likelihood of the validity of any association found in such studies include the strength of the association, their consistency and a biologic plausibility. From our findings and other published observations, one can at least say that associations between ABC use and increased myocardial risk are neither strong nor consistent across studies.

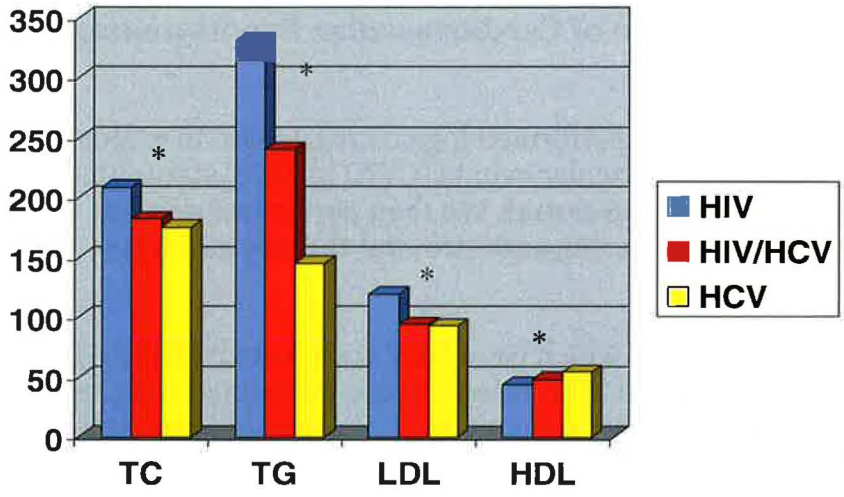
The lack of dose-response relationship between HAART exposure and CVD has been discussed above. There also remains the question of biological plausibility. In the next chapter, we will first examine the possibility of another confounder not accounted for in previous studies: hepatitis C co-infection. We will then examine possible biologic mechanisms of a direct effect of HIV infection or HAART on atherogenesis, in order to explore the biologic plausibility of the epidemiologic associations.

b. Hepatitis C Co-infection and Cardiovascular Risk

i. Impact of HCV on CV Risk Factors among HIV-infected Patients

HCV co-infection (present in 15 to 30% of HIV-infected patients [40, 41])has been found to be an independent predictor of coronary artery disease in the general population even after adjusting for traditional cardiovascular risk factors [44].

We have demonstrated a protective effect of HCV co-infection from the development of HIV- and HAART-associated dyslipidemia [45] by comparing rates of dyslipidemia among patients with HIV or HCV mono-infection and HIV/HCV co-infection at the VA North Texas Health Care System HIV and HCV clinics (figure 4; [45]); and HIV vs. HCV/HCV in CCR (table 3; [46]). Our data show that HCV co-infection was an independent predictor of lower rates of dyslipidemia in general, and hypercholesterolemia in particular, among HIV-infected patients. Although HCV co-infection predicted lower rates of hypertriglyeridemia in univariate analysis, this did not remain in multivariate analysis controlling for age, race, platelet count and ALT. These findings are in accordance with a growing body of literature in that subject [47-57].



*p<0.05

Figure 4: Impact of HCV on HIV-associated dyslipidemia

Condition	HCV status	Entire Period ('84 - '04)	Pre-HAART ('84 - '95)	HAART era ('96 - '04)	Pre-HAART vs. HAART
Hypercholesterolemia (TC>240mg/dL)	HCV+ (n=13,334)	18.2	18.4	18.0	0.497
	HCV- (n=37,208)	27.1	23.8	30.7	<0.001
	HCV+ vs. HCV-	<0.001	<0.001	<0.001	
Hypertriglyceridemia (TG>200mg/dL)	HCV+ (n=13,334)	55.1	60.0	49.6	<0.001
	HCV- (n=37,208)	59.5	63.7	55.7	<0.001
	HCV+ vs. HCV-	<0.001	<0.001	<0.001	

Table 3: Prevalence of Lipid Abnormalities by Time Period and HCV Status; adapted from [46]

Hepatitis C has also been associated with lower C-reactive protein (CRP) levels in both HIV-negative and HIV positive subjects [58, 59]. The beneficial impact of HCV co-infection on lipids and CRP – two independent predictors of cardiovascular disease – has led some to postulate that HCV co-infection may, to some extent, ameliorate the increased cardiovascular risk associated with HIV infection and HAART use [58]. However, patients with HCV co-infection appear to have higher rates of other biomarkers of endothelial dysfunction and atherogenesis [60] and higher rates of other traditional cardiovascular risk factors such as type 2 diabetes mellitus [61]. HCV seropositivity has also been associated the presence of carotid artery plaque and thickening of intima media, as well as elevated levels of biomarkers of atherogenicity (see section V below).

ii. Impact of HCV on Incidence of Cardiovascular Events among HIV-infected Patients

Using the VA CCR database described above, we performed logistic regression to evaluate acute myocardial infarction (AMI) and cerebrovascular events (CVA) by HCV status among HIV-infected US veterans in the HAART era (1996-2004). We then performed survival analyses to evaluate incident AMI and CVA, exploring antiretroviral therapy as a time-dependent variable.

A total of 19,424 HIV-infected patients (31.6% of which were HCV co-infected; [HIV/HCV]) contributed 76,376 patient-years of follow-up. HCV co-infection was associated with lower rates of hypercholesterolemia (18.0% in HIV/HCV vs. 30.7% in HIV-only patients; $p<0.001$), but higher rates of hypertension (43.8% vs. 35.6%; $p<0.0001$), type 2 diabetes (16.2% vs. 11.1%; $p<0.0001$) and smoking (36.7% vs. 24.7%; $p=0.009$).

Rates of AMI and CVA were significantly higher among HIV/HCV than HIV-only patients: 4.19 vs. 3.36 events/1000 patient-years ($p<0.001$) for AMI; and 12.47 vs. 11.12 events/1000 patient-years ($p<0.001$) for CVA. When controlling for diabetes mellitus, hypertension, age and duration of antiretroviral therapy, hazard ratios (HR) among those with HIV/HCV (vs. HIV

only) were 1.25 (95% Confidence Interval [CI]: 0.98 – 1.61; p = 0.072) for AMI and 1.20 (CI: 1.04 – 1.38; p = 0.013) for CVA. Hypertension (HR: 2.05; p <0.001), older age (HR: 1.79; p <0.001) and cumulative years of antiretroviral use (HR: 1.12; p = 0.0411) were also associated with increased risk of AMI in the adjusted model. A follow-up of this study (unpublished) shows that the impact of HCV on the rates of both AMI and CVA was significant when the period of observation was extended to the pre-HAART era.

With the very high prevalence of HCV co-infection, should it be confirmed as an independent predictor of cardiovascular events in other cohorts, it would be prudent to control for HCV infection in future studies of cardiovascular events among HIV-infected patients. Future research is needed to better elucidate the mechanisms by which HCV increases cardiovascular risk, particularly among those with HIV co-infection. Our findings also suggest it is reasonable to consider HCV co-infection, among other co-morbidities, in management decisions including timing and choice of antiretrovirals and monitoring for complications.

V. Potential Mechanisms of Increased Atherogenesis in HIV

Beyond traditional cardiovascular risk factors and HAART use, untreated HIV itself might be associated with increased risk of cardiovascular events [19, 62]. Several studies have now explored potential mechanisms by which HIV would have a direct atherogenic effect. Given the lag time between the exposure to traditional cardiac risk factors and the development of atherosclerosis and cardiac events, it's unclear whether enough time had elapsed to allow for the evaluation of HIV disease and HAART on cardiovascular morbidity when the first studies were published [31, 63-65]. The survival of HIV infected patients is just recently being lengthened by HAART, and the median duration on HAART in published studies ranging from less than two years [63] to barely over five years [31]. Finally, as mentioned above, the most recent studies are suggesting a waning of the PI effect on cardiovascular morbidity.

It is now well recognized that the sequence of events leading to acute myocardial infarction are: 1) atheroma formation and growth; 2) plaque instability and rupture, marked by endothelial activation (increased expression of adhesion molecules) and inflammation (hsCRP, IL6, TNFα); and finally 3) thrombosis [66]. HIV likely impacts all three steps. According to the D:A:D and the SMART data, only recent use of ABC (within six months or fewer) was associated with an increased risk of AMI. The rate of myocardial infarctions remained high as long as patients were receiving these drugs, but then decreased after their cessation. Should this association be true, it would signify that ABC impact the proximal events (plaque instability and rupture) triggering AMI events in patients already predisposed to develop them.

a. Cholesterol metabolism, lipid and lipoprotein alterations, impairment of Cholesterol Efflux

Several steps of HIV-1 replication critically depend on cholesterol. It has recently been demonstrate that HIV-1 impairs ATP-binding cassette transporter A1 (ABCA1)-dependent cholesterol efflux from human macrophages [67]. Impairment of cholesterol efflux leads to accumulation of intracellular cholesterol a condition previously shown to be highly

atherogenic. Also, NRTIs have also been shown to alter the expression of both mitochondrial and lipid metabolism genes [68].

b. Markers of Inflammation and Endothelial Dysfunction

Recent data suggests that endothelial dysfunction, impaired fibrinolysis, and excess inflammation may contribute to increased cardiovascular risk in HIV-infected patients with or without HAART [64, 69]. Endothelial dysfunction may be caused by the infection itself, the immunologic responses due to the HIV virus, and also by the effects of HAART through their effects on both lipid and glucose metabolism. Although intriguing, the large number of potential confounders including viral and immunologic factors, as well as treatment factors significantly hampers the study of endothelial dysfunction in HIV-associated cardiovascular morbidity [69, 70].

The SMART study reported higher levels of hsCRP and IL-6 among patients on ABC than in those receiving other NRTIs. They postulated that ABC may have pro-inflammatory properties and promoted CVD through increased vascular inflammation. However, no significant differences were observed among four other biomarkers tested, all of which have previously been associated with CVD [32].

Enhanced endothelial activation, inflammation, and increased carotid IMT occur in HIV-infected patients compared to uninfected controls, supporting a potential role of inflammation in endothelial activation and cardiovascular disease in HIV infection [71]. While these markers tend to significantly improve upon HAART initiation or re-initiation, they might not return to levels comparable to non-HIV patients even during long-term suppressive antiretroviral therapy [60, 72, 73]. It is conceivable that different antiretroviral drugs differ in their propensity to lower – or maybe increase – markers of immune activation and endothelial dysfunction in HIV patients, explaining at least in part observed differences in AMI rates.

The HEAT investigators found similar reductions in markers of inflammation (hsCRP and IL-6) and endothelial activation (VCAM-1) after initiation of ABC/3TC or TDF/FTC [74] (McComsey et al., CROI 2009; Abstract #732). Also, in a combined analysis of the MACS and WIHS cohorts, ABC use was not independently associated with elevated plasma levels of hsCRP, IL-6, and D-dimer [75]. Finally, in a study of 80 patients virologically suppressed on stable HAART who were switched to either ABC or TDF-containing regimen (BICOMBO study) there was no significant difference in changes in markers of inflammation, endothelial dysfunction, or hypercoagulability at week 48 [76].

Interestingly, HCV has also been associated with increased levels of biomarkers of inflammation and endothelial dysfunction. This highlights again the importance of controlling for HCV seropositivity in analyses of the cardiovascular risk of HIV patients, which has not been done in studies published so far. HCV is associated with increased levels of platelet-activating factor (PAF), a powerful phospholipid mediator of inflammation, and decreased plasma PAF-acetyl-hydxolase (pPAF-AH) activity (an enzyme that degrades PAF) [77]. It could therefore be hypothesized that during chronic HCV infection, the PAF/pPAF-AH system may be altered and this condition may contribute to HCV-related vascular damage. Finally, HCV co-infection during HIV treatment (but not among antiretroviral naïve subjects) is associated

with higher values for some biomarkers of early atherosclerosis, suggesting, by extension, that co-infection in treated but not untreated patients raises patients' risk for cardiovascular disease [60].

c. Flow-Mediated Dilation

There is discordant data on the impact of HAART on flow-mediated dilation (FMD). Among treatment-naive individuals with HIV, three different ART regimens were shown to rapidly improve endothelial function, as measured by FMD of the brachial artery. Benefits were similar for all ART regimens, appeared quickly, and persisted at 24 weeks [78]. FMD increased by 0.74% (IQR -0.62% to +2.74%, p = 0.003) and 1.48% (IQR -0.20% to +4.30%, p < 0.001). On the other hand , perhaps highlighting the importance of an appropriate study design, HAART in general [79], and ABC in particular [80] appeared to instead have a detrimental effect on FMD in two cross-sectional studies. Treated HIV-infected patients had significantly lower FMD (5.93 +/- 3.56) than healthy controls (10.64 +/- 3.08, P = 0.008) in an earlier study including 28 HIV-infected adults (15 receiving antiretroviral therapy and 13 naive) with low or mild cardiovascular risk and 12 healthy controls [79]. Naive patients had an intermediate FMD, but this was not statistically significant. In a more recent study of 61 subject on HAART (30 of which were receiving ABC), overall, the median FMD in the HIV-infected patients was low (3.5%; interquartile range 2.3-5.6%). The FMD was lower in the ABC-treated patients than those not on ABC (2.8 vs. 4.9%, P = 0.01).

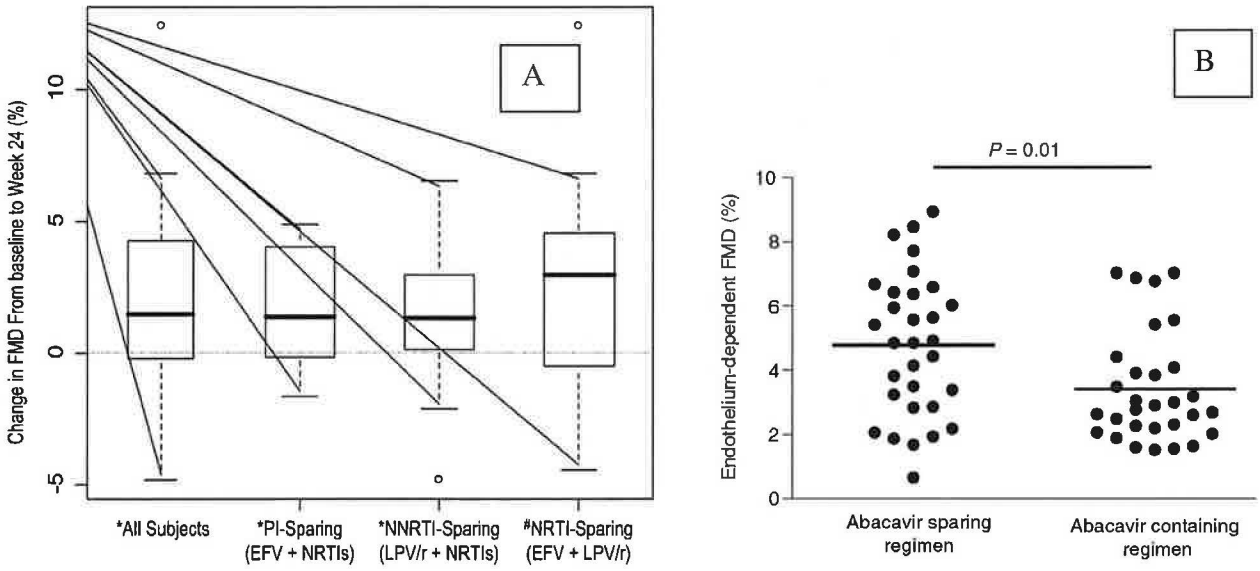


Figure 5: Flow-mediated visodilation in response to three types of "Class-sparing" HAART (panel A; [78]), and ABC-containing vs. ABC-sparing HAART (panel B; [80])

d. Intima-Media Thickness

There is also evidence that coronary atherosclerotic disease can be revealed by means of carotid intimal medial thickness (IMT) assessments in specific groups of HIV patients. Carotid IMT is higher in HIV patients than in age-matched control subjects and progresses much more rapidly than previously reported rates in non-HIV cohorts [62]. In HIV patients, carotid IMT is associated with classic coronary risk factors and with nadir CD4 count < or =200, suggesting that immunodeficiency and traditional coronary risk factors may contribute to atherosclerosis [81]. Again, multiple possible factors, including viral factors, immunologic conditions, and metabolic drug effects could affect the interpretation of these results [69].

VI. Concluding Remarks and Future Directions

a. Concluding Remarks

i. HIV disease likely promotes all three stages of atherogenesis: atheroma formation (↑ dyslipidemia, ↑ carotid intima thickness and decreased FMD); plaque instability and Rupture: endothelial activation (↑ adehsion molecules: eg VCAM-1; ↑ inflammation (hsCRP, IL-6, TNF-alpha) and thrombosis (↑D-Dimer, PAI-1).

ii. HAART use moderately (and probably transiently) ↓ markers of inflammation and endothelial dysfunction, as well as FMD. Specific antiretroviral drugs might differ in their impact on those biomarkers.

iii. The positive impact of HAART on markers of inflammation and endothelial dysfunction is likely mitigated by HCV co-infection

iv. The impact of HAART on the incidence of cardiovascular events is likely moderate; it is likely mediated at least in part by CKD and probably HCV.

v. The atherogenic potential of specific antiretroviral drugs or regimens is unclear.

b. Future Directions

i. Further explore the impact of HCV and CKD on biomarkers of cardiac dysfunction and the mechanisms of these effects

ii. Further explore the differences in impact of current and new HAART regimens on markers of endothelial dysfunction among HIV with CKD, and HIV/HCV patients.

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