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The Association of CD4+ T-Cell Count on Cardiovascular Risk in Treated HIV Disease

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Introduction

Since the advent of highly active antiretroviral therapy (HAART) in 1996, HIV-related mortality has decreased dramatically [1]. In fact, the risk of non-AIDS related mortality may now exceed the risk of AIDS-related mortality in individuals with CD4 counts > 200 cells/μl [2]. Of particular concern are increased rates of early atherosclerosis, coronary events and mortality compared with non-infected controls [3-6]. The etiology of these abnormalities in HIV infection is not well established. While long-term exposure to protease inhibitors and abacavir use are associated with increased risk of cardiovascular events in some studies [3, 7, 8], randomized studies indicate that HAART is associated with improved cardiovascular outcomes when compared with intermittent therapy [9]. Although treated disease is associated with less short-term risk of cardiovascular complications than untreated disease, it remains unclear if a delay in initiating HAART until later in the disease process is associated with residual cardiovascular risk even after long-term suppression of viral replication has been achieved.

We previously demonstrated that lower nadir CD4+ T-cell count was associated with increased arterial stiffness in a cohort of long-term HAART treated men [10]. We now extend our work in this same cohort by measuring endothelial function, as assessed by brachial artery flow-mediated dilation (FMD). Whereas arterial stiffness reflects structural and functional changes in the vascular tree, brachial artery FMD assesses intrinsic nitric oxide bioavailability and vasodilation [11]. Thus, while both vascular measures predict cardiovascular risk, the information they provide is considered complementary.

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Methods

Study Design and Participants

We conducted a cross-sectional study of HIV-infected men who were on stable HAART for > 1 year with undetectable plasma HIV RNA levels [10]. Study subjects were recruited from two ongoing prospective cohort studies at San Francisco General Hospital: the SCOPE Study and the Options Project [12, 13]. SCOPE enrolls subjects who entered care with chronic HIV disease. The Options Project enrolls subjects with early acute HIV infection, and participants are offered an "early treatment" option (initiation within 6 months of the estimated date of HIV infection). We excluded subjects with cardiovascular disease, exposure to immunomodulatory drug therapy, or any changes in statin, anti-hypertensive, or diabetic regimen within 4 months. The University of California, San Francisco Committee on Human Research approved the study. All subjects provided written informed consent.

Data Collection

Subjects underwent a detailed interview and structured questionnaire covering socio-demographic characteristics, HIV disease history, co-morbid conditions, health-related behaviors, and medication exposure. Laboratory evaluation included serum creatinine, CD4+ T-cell count, HIV RNA level, high-sensitivity C-reactive protein (hs-CRP), and plasma markers of vascular function (asymmetric dimethylarginine, ADMA; arginine; N-tyrosine) (details in Supplemental Digital Content).

Assessment of Endothelial Function

In brief, high-resolution ultrasound of the right brachial artery was performed using a 10 MHz linear array probe and the GE Vivid7 Imaging System (GE, Milwaukee, Wisconsin, USA) according to established guidelines (details in Supplemental Digital Content) [14]. A blood pressure cuff was inflated to suprasystolic pressures on the forearm for 5 minutes, and the change in brachial artery diameter was measured during reactive hyperemia one minute following cuff deflation (FMD) [15]. Nitroglycerin mediated dilation (NMD) was measured 3 minutes after administration of 0.4 mg sublingual nitroglycerin. Repeated measurements of 10 scans in a blinded manner showed a correlation coefficient of 0.998. Ten patients underwent repeat scans within 14 days of enrollment, with a difference in FMD of 0.005% (−0.06 to +0.04%, $p = 0.99$).

Statistical Analysis

Nadir CD4+ T-cell count was stratified *a priori* by groups below versus at least 350 cells/μl, according to most recent treatment guidelines for HAART initiation [16]. Associations of nadir and current CD4+ T-cell count with FMD were assessed using linear regression with robust standard errors to account for non-normally distributed residuals [17]. CD4+ T-cell counts were also analyzed continuously (log-transformed). Analyses were first adjusted for demographics (age and race/ethnicity) and study cohort. Bayesian Model Averaging was used to select candidate covariates; predictors with posterior probabilities >35% were retained in the model [18]. Covariates considered included BMI, hypertension, diabetes mellitus, current smoking, hyperlipidemia, HIV, HAART, and PI duration. Finally, we constructed a model forcing age, race, cardiovascular risk factors, HIV and HAART duration, as these covariates clinically were suspected to be potential confounders. Additional analyses evaluated CRP, ADMA, N-tyrosine, and eGFR [19] as potential mediators of the association of CD4+ count and endothelial function. Bayesian Model Averaging was performed using the BMA package for the R statistical computing language (R Development Core Team, Vienna, Austria). Other analyses were conducted using SAS, version 9.2 (SAS Institute, Inc., Cary, NC).

Results

We enrolled 74 HIV-infected men on HAART with undetectable plasma HIV RNA and without known cardiovascular disease. The median age was 47 years (IQR 42-55). Traditional cardiovascular risk factors were common: 28% had hypertension, 32% hyperlipidemia, and 14% were current smokers. The median duration of HIV infection was 7 (5-15) years, and current and nadir CD4+ T-cell counts were 659 (542-845) and 314 (150-490) cells/μl, respectively. Compared to participants with nadir CD4+ T-cell counts ≥ 350 cells/μl, those with lower nadir CD4+ T-cell counts were older, had a worse cardiovascular risk profile, with longer HIV and HAART duration (Table 1).

CD4+ T-cell Count and Endothelial Function

Nadir CD4+ T-cell count < 350 cells/μl was associated with lower FMD in age-, and race-adjusted analyses (p=0.014). After accounting for traditional cardiovascular risk factors and HIV-related characteristics, nadir CD4+ T-cell count remained independently associated with FMD (Table 2). Specifically, individuals with a nadir CD4+ T-cell count < 350 cells/μl had a 1.22% lower FMD (95% CI −2.20 to −0.19, p-value 0.02) compared with those with higher CD4+ T-cell counts. In a stepwise model considering traditional cardiovascular risk factors and HIV-related characteristics, nadir CD4+ T-cell count was the only clinical variable that was significantly associated with FMD. Nadir CD4 count showed similar associations with FMD when analyzed as a continuous variable, although the association did not reach statistical significance (+0.21% per doubling of nadir CD4, 95%CI: −0.03 to 0.44, p=0.08). By contrast, proximal CD4+ T-cell count < 350 cells/μl was not associated with FMD (p>0.05).

In secondary analyses accounting for ever-smoking and total number of pack-years, results were not materially different. Further analyses adjusted for ACE-inhibitor, beta-blocker, and statin use, all of which can influence FMD. This also did not materially change primary results.

Role of Inflammation and ADMA

In secondary analyses, we examined the effect of potential mediators on the association of nadir CD4+ T-cell count < 350 cells/μl and lower FMD. The association remained significant (p<0.05) after adjusting for CRP as a marker of inflammation, ADMA, and L-arginine/ADMA levels.

Discussion

In this cohort of long-term effectively-treated HIV-infected men, a low nadir CD4+ T-cell count was the strongest clinical predictor of endothelial dysfunction as assessed by brachial artery FMD. Specifically, a nadir CD4+ T-cell count < 350 cells/μl was associated with a 1.2% decrease in FMD. When compared with previous studies in non-infected individuals, this reduction in FMD represents a greater impairment than is observed in the presence of diabetes, smoking, or prevalent cardiovascular disease [20]. These findings suggest that delaying the initiation of antiretroviral therapy until late in the disease process (as defined by nadir CD4+ T-cell counts) may be associated with adverse cardiovascular consequences. Although most guidelines now recommend starting therapy before this threshold is reached, a substantial proportion of individuals enter care with more advanced disease, and many if not most treated individuals have a low nadir CD4+ T-cell count.

Endothelial dysfunction plays a central role in the development and progression of atherosclerosis, and predicts future cardiovascular events in non-HIV infected patients [21, 22]. HIV-infected patients have impaired endothelial function when compared with non-

infected controls [23]. The mechanism of endothelial dysfunction in HIV disease is unclear. Previous studies have shown worse endothelial dysfunction with higher viral load [23, 24], and others have demonstrated improved endothelial function with HAART treatment [25, 26]. One study demonstrated significant improvement in endothelial function in antiretroviral-naïve individuals within 4 weeks of HAART initiation [27]. Our study extends these findings to a cohort of effectively-treated adults on stable HAART, and suggests that the degree of immunological compromise prior to initiation of HAART is associated with endothelial dysfunction. Our results also suggest that immunological recovery as assessed by proximal CD4+ T-cell does not abrogate the cardiovascular risk linked to low nadir CD4+ T-cell counts.

The role of HIV disease in the pathogenesis of early atherosclerosis is supported by the consistent observation that both CD4+ count and viral load influence this disease. The CD4+ count nadir predicts subclinical carotid atherosclerosis and vascular stiffness in our investigations [5, 10], and a low CD4+ count on HAART has been associated with cardiovascular risk [28-30]. The association of low CD4+ T-cell count with cardiovascular disease is not well understood, and may be due to chronic inflammation [31] or direct viral effects [32]. Inflammatory markers have also been associated with subclinical atherosclerosis [33], mortality, and cardiovascular disease in HIV-infected individuals [34]. In secondary analyses, the association of low nadir CD4+ T-cell count and endothelial dysfunction was not mediated by inflammation as measured by CRP in our study.

Several limitations deserve mention. Potential confounding factors are a challenge in our observational study design, and only a randomized controlled clinical trial of early versus late initiation of HAART can address the issue definitively. In the absence of such a study, observational cohorts provide the best available evidence to address the question. Although we adjusted for differences in identifiable cardiovascular risk and HIV associated factors, unmeasured factors remain a possible explanation for the observed greater endothelial dysfunction in subjects with lower nadir CD4+ counts. Therefore, our results must be interpreted with caution, as the cross-sectional nature of the study precludes any causal inferences. Clearly, prospective longitudinal studies are needed to evaluate the effect of early HAART initiation on cardiovascular outcomes. Our study is of modest size, which limits complex analyses examining mediators of the observed association of nadir CD4+ T-cell count and vascular function. It is also unclear whether the association of endothelial dysfunction and nadir CD4+ T-cell count extends beyond a threshold of 500 cells/μl, as few participants met these criteria. Despite these limitations, the strengths of the study were a contemporary sample of treated HIV-infected individuals with HAART initiation both early and late in the course of HIV infection, and rigorous assessment of endothelial function.

In conclusion, a nadir CD4+ T-cell count < 350 cells/μl was associated with worse endothelial function in HIV-infected men on stable HAART. The association of nadir CD4+ T-cell count and vascular function was greater than that of traditional cardiovascular risk factors. Although causal inferences cannot be drawn from this cross-sectional study, our study provides compelling evidence that earlier initiation of HAART at higher nadir CD4+ T-cell counts may have a favorable impact on cardiovascular risk. Future prospective studies examining early HAART initiation with respect to cardiovascular outcomes are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Baseline characteristics of HIV-infected men by nadir CD4+ T-cell count

Characteristic	Nadir CD4+ T-cell count < 350 cells/μl N=39	Nadir CD4+ T-cell count ≥ 350 cells/μl N=35	p-value
Clinical			
Age, years	52 (44-58)	44 (38-49)	0.001
Race, n (%)			0.83
Caucasian	32 (82)	29 (83)	
African American	2 (5)	3 (9)	
Latino/other	5 (13)	3 (9)	
Diabetes mellitus, n (%)	5 (13)	1 (3)	0.20
Hypertension, n (%)	14 (36)	7 (20)	0.20
Anti-hypertensive use, n (%)	13 (33)	7 (20)	0.29
ACE-inhibitor, n (%)	7 (18)	4 (11)	0.52
Beta Blocker, n (%)	4 (10)	0	0.12
Hyperlipidemia, n (%)	19 (49)	5 (14)	0.003
Statin use, n (%)	21 (54)	5 (14)	0.0005
BMI, kg/m^2	25 (23-27)	24 (22-26)	0.30
Cigarette smoking, n (%)			
Current	4 (10)	6 (17)	0.72
Ever	18 (46)	17 (49)	0.84
HIV-related			
Duration of HIV infection, years	14 (7-19)	5 (3-7)	<0.0001
Current CD4+ T-cell count, cells/μl	598 (471-686)	810 (637-1020)	<0.0001
Nadir CD4+ T-cell count, cells/μl	180 (53-253)	500 (391-707)	<0.0001
HAART duration, years	8.7 (3.9-10.7)	4.0 (2.5-5.6)	0.0007
PI use, n (%)	29 (74)	18 (51)	0.05
PI duration, years	8.6 (4.2-10.8)	3.1 (1.8-5.6)	0.02
Laboratory			
hsCRP, mg/L	1.1 (0.6-2.2)	1.8 (0.7-3.3)	0.55
eGFR, ml/min	82 (74-99)	91 (81-108)	0.04
Measures of Vascular Function			
FMD, %	3.3 (2.4-4.8)	4.1 (2.7-5.6)	0.14
NMD, %	12.1 (6.8-17.4)	15.6 (12.9-18.0)	0.07
Baseline brachial arterial diameter, mm	4.4 (4.2-5.0)	4.5 (4.1-4.7)	0.32
Serum L-arginine, μM	92 (82-108)	79 (68-107)	0.16
ADMA, μM	0.45 (0.39-0.51)	0.46 (0.41-0.51)	0.58
N-tyrosine, μM	45 (34-74)	39 (32-55)	0.29

Values are represented as medians (inter-quartile range), unless otherwise noted.

ACE, angiotensin converting enzyme; BMI, body-mass index; HAART, highly active antiretroviral therapy; PI, protease inhibitor; hsCRP, highly sensitive C-reactive protein; eGFR, estimated glomerular filtration rate; FMD, flow-mediated vasodilation; NMD, nitroglycerin-mediated vasodilation; ADMA, asymmetric dimethylarginine;

Table 2

Nadir CD4+ T-cell count is associated with endothelial dysfunction independent of other risk factors

	Beta	95% CI	p-value
Nadir CD4+ count < 350 cells/μl	-1.22	-2.20 to -0.19	0.02
Age (per decade)	0.19	-0.30 to 0.69	0.44
African-American vs Caucasian	-0.17	-1.53 to 1.19	0.80
Latino/other vs Caucasian	-1.92	-2.70 to -1.13	<0.0001
Study (Options vs SCOPE)	-0.84	-2.00 to 0.34	0.16
Hypertension	0.00	-0.96 to 0.96	0.99
Diabetes mellitus	0.88	-0.54 to 2.30	0.22
Hyperlipidemia	0.29	-1.19 to 1.77	0.70
Current smoking	-0.42	-1.67 to 0.84	0.52
Past smoking	0.14	-0.78 to 1.06	0.77
HIV duration (per year)	-0.05	-0.16 to 0.06	0.36
HAART duration (per year)	0.05	-0.10 to 0.21	0.49

Beta-coefficient represents the change in % FMD with the presence versus absence of dichotomous predictors, and per unit change as noted for continuous predictors.