The association of CD4$^+$ T-cell counts and cardiovascular risk in treated HIV disease

Jennifer E. Ho[a], Rebecca Scherzer[b], Frederick M. Hecht[c], Kristinalisa Maka[d], Van Selby[d], Jeffrey N. Martin[c,e], Peter Ganz[d], Steven G. Deeks[c] and Priscilla Y. Hsue[d]

Objective: HIV-infected individuals are at high risk of developing cardiovascular disease. Whether earlier initiation of HIV therapy at higher CD4$^+$ cell counts has any effect on cardiovascular risk as assessed by endothelial function is unknown.

Design: Cross-sectional study of 74 antiretroviral-treated men with undetectable plasma HIV RNA levels.

Methods: Participants underwent noninvasive assessment of endothelial function using brachial artery flow-mediated dilation (FMD). The association of nadir and current CD4$^+$ T-cell count with FMD was assessed using multivariable linear regression.

Results: The median age was 47 years [interquartile range (IQR) 42–55], median current CD4$^+$ T-cell count was 659 cells/μl (IQR 542–845), and nadir CD4 cell count was 314 cells/μl (IQR 150–490). Twenty-eight percent had hypertension, and 32% hyperlipidemia. Nadir CD4$^+$ T-cell count less than 350 cells/μl was associated with lower FMD in age-adjusted and race-adjusted analyses and remained an independent predictor of FMD after adjustment for cardiovascular risk factors (hypertension, diabetes, smoking, hyperlipidemia) and HIV-related characteristics (HIV duration, HAART duration). After multivariable adjustment, individuals with nadir CD4$^+$ T-cell count less than 350 cells/μl had a 1.22% lower FMD compared with those with higher T-cell counts [95% confidence interval (CI) −2.20 to −0.19, $P = 0.02$]. Proximal CD4$^+$ T-cell count showed little association with FMD.

Conclusion: Among treated HIV-infected individuals, nadir CD4$^+$ T-cell count less than 350 cells/μl is independently associated with lower FMD, suggesting that delayed therapy results in sustained harm to endothelial function. Our data support future prospective studies evaluating cardiovascular effects of HAART initiation at higher CD4$^+$ cell counts.

AIDS 2012, **26**:1115–1120

Keywords: cardiovascular diseases, CD4 cell, HIV, risk factors, vasodilation

[a]Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts, [b]Veterans Administration Medical Center, [c]Positive Health Program, [d]Division of Cardiology, Department of Medicine, San Francisco General Hospital, and [e]Department of Epidemiology and Biostatistics, University of California, San Francisco, California, USA.

Correspondence to Priscilla Y. Hsue, MD, Room 5G1, Division of Cardiology, Department of Medicine, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, CA 94110, USA.

Tel: +1 415 206 8257; fax: +1 415 206 5100; e-mail: phsue@medsfgh.ucsf.edu
Received: 30 November 2011; revised: 15 February 2012; accepted: 21 February 2012.

DOI:10.1097/QAD.0b013e328352ce54

Introduction

Since the advent of 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 cell counts more than 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 cause of these abnormalities in HIV infection is not well established. Although 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, although both vascular measures predict cardiovascular risk, the information they provide is considered complementary.

Methods

Study design and participants

We conducted a cross-sectional study of HIV-infected men who were on stable HAART for more than 1 year with undetectable plasma HIV RNA levels [10]. Study participants were recruited from two ongoing prospective cohort studies at San Francisco General Hospital: the Study of the Consequences of the Protease Inhibitor Era (SCOPE) cohort and the Options Project [12,13]. SCOPE enrolls participants who entered care with chronic HIV disease. The Options Project enrolls participants 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 participants with cardiovascular disease, exposure to immunomodulatory drug therapy, or any changes in statin, antihypertensive, or diabetic regimen within 4 months. The University of California, San Francisco Committee on Human Research approved the study. All participants provided written informed consent.

Data collection

Participants underwent a detailed interview and structured questionnaire covering sociodemographic characteristics, HIV disease history, comorbid conditions, health-related behaviors, and medication exposure. Laboratory evaluation included serum creatinine, $CD4^+$ T-cell count, HIV RNA level, high-sensitivity C-reactive protein (CRP), and plasma markers of vascular function (asymmetric dimethylarginine, ADMA; arginine; and N-tyrosine) (details in Supplemental Digital Content, http://links.lww.com/QAD/A211).

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, http://links.lww.com/QAD/A211) [14]. A blood pressure cuff was inflated to suprasystolic pressures on the forearm for 5 min, and the change in brachial artery diameter was measured during reactive hyperemia 1 min following cuff deflation (FMD) [15]. Nitroglycerin-mediated dilation (NMD) was measured 3 min 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 vs. 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 nonnormally 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 of more than 35% were retained in the model [18]. Covariates considered included BMI, hypertension, diabetes mellitus, current smoking, hyperlipidemia, HIV, HAART, and protease inhibitor 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 estimated glomerular filtration rate [19] as potential mediators of the association of $CD4^+$ cell 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, North Carolina, USA).

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 (interquartile range 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 cells/μl (150–490), respectively. Compared to participants with nadir CD4$^+$ T-cell counts of at least 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 less than 350 cells/μl was associated with lower FMD in age-adjusted 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 less than 350 cells/μl had a 1.22% lower FMD [95% confidence interval (CI) −2.20 to −0.19, $P = 0.02$] 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 cell 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 less than 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 angiotensin converting enzyme inhibitor, β-blocker, and statin use, all of which can influence FMD. This also did not materially change primary results.

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
White	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
Antihypertensive use, *n* (%)	13 (33)	7 (20)	0.29
ACE inhibitor, *n* (%)	7 (18)	4 (11)	0.52
β-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 (μmol/l)	92 (82–108)	79 (68–107)	0.16
ADMA (μmol/l)	0.45 (0.39–0.51)	0.46 (0.41–0.51)	0.58
N-tyrosine (μmol/l)	45 (34–74)	39 (32–55)	0.29

Values are represented as medians (interquartile range), unless otherwise noted. ACE, angiotensin-converting enzyme; ADMA, asymmetric dimethylarginine; eGFR, estimated glomerular filtration rate; FMD, flow-mediated vasodilation; hsCRP, highly sensitive C-reactive protein; NMD, nitroglycerin-mediated vasodilation; PI, protease inhibitor.

Table 2. Nadir CD4$^+$ T-cell count is associated with endothelial dysfunction independent of other risk factors.

	β	95% CI	*P*-value
Nadir CD4$^+$ cell 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. white	−0.17	−1.53 to 1.19	0.80
Latino/other vs. white	−1.92	−2.70 to −1.13	<0.0001
Study (Options Project 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

β-Coefficient represents the change in percentage flow-mediated dilation with the presence vs. absence of dichotomous predictors, and per unit change as noted for continuous predictors. CI, confidence interval; SCOPE, Study of the Consequences of the Protease Inhibitor Era.

Role of inflammation and asymmetric dimethylarginine

In secondary analyses, we examined the effect of potential mediators on the association of nadir CD4$^+$ T-cell count less than 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 less than 350 cells/μl was associated with a 1.2% decrease in FMD. When compared with previous studies in noninfected individuals, this reduction in FMD represents a greater impairment than that 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 noninfected 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$^+$ T-cell count and viral load influence this disease. The nadir CD4$^+$ T-cell count predicts subclinical carotid atherosclerosis and vascular stiffness in our investigations [5,10], and a low CD4$^+$ T-cell 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 vs. 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 participants with lower nadir CD4$^+$ cell 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 less than 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.

Acknowledgements

J.E.H., S.G.D., F.M.H., P.G., and P.Y.H. were responsible for the study's conception and design; J.E.H., K.M., and V.S. were involved in the study performance; R.S. did the statistical analyses; J.E.H. wrote the manuscript; and all authors participated in critical review and substantial input to the final manuscript.

The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

This research was supported by grants from the NIH/University of California, San Francisco-Gladstone Institute of Virology and Immunology Center for AIDS Research, P30-AI027763 (J.E.H); from the NIH, 5R01-HL095130, and 5K23-AI066885 (P.Y.H.); from the National Institute of Allergy and Infectious Diseases, K24-AI069994 (S.G.D.), CFAR Network of Integrated Clinical Systems, R24 AI067039; and the UCSF Clinical and Translational Science Institute, UL1 RR024131-01.

P.Y.H. has received honoraria from Gilead, and grant support from Pfizer. S.G.D. has received grant support from Merck and Gilead and honoraria from Glaxo-SmithKline, ViiV, and Tobira.

Conflicts of interest

There are no conflicts of interest.

References

1. Centers for Disease Control and Prevention (CDC). **Epidemiology of HIV/AIDS – United States, 1981–2005.** *MMWR Morb Mortal Wkly Rep* 2006; **55**:589–592.
2. Lau B, Gange SJ, Moore RD. **Risk of non-AIDS-related mortality may exceed risk of AIDS-related mortality among individuals enrolling into care with CD4+ counts greater than 200 cells/mm3.** *J Acquir Immune Defic Syndr* 2007; **44**:179–187.
3. Friis-Møller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P, *et al*. **Combination antiretroviral therapy and the risk of myocardial infarction.** *N Engl J Med* 2003; **349**:1993–2003.
4. Holmberg SD, Moorman AC, Williamson JM, Tong TC, Ward DJ, Wood KC, *et al*. **Protease inhibitors and cardiovascular outcomes in patients with HIV-1.** *Lancet* 2002; **360**:1747–1748.
5. Hsue PY, Lo JC, Franklin A, Bolger AF, Martin JN, Deeks SG, *et al*. **Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection.** *Circulation* 2004; **109**:1603–1608.
6. Solages A, Vita JA, Thornton DJ, Murray J, Heeren T, Craven DE, *et al*. **Endothelial function in HIV-infected persons.** *Clin Infect Dis* 2006; **42**:1325–1332.
7. Group DADS, Sabin CA, Worm SW, Weber R, Reiss P, El-Sadr W, *et al*. **Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multicohort collaboration.** *Lancet* 2008; **371**:1417–1426.
8. Group DS, Friis-Møller N, Reiss P, Sabin CA, Weber R, Monforte A, *et al*. **Class of antiretroviral drugs and the risk of myocardial infarction.** *N Engl J Med* 2007; **356**:1723–1735.
9. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, *et al*. **CD4+ count-guided interruption of antiretroviral treatment.** *N Engl J Med* 2006; **355**:2283–2296.
10. Ho JE, Deeks SG, Hecht FM, Xie Y, Schnell A, Martin JN, *et al*. **Initiation of antiretroviral therapy at higher nadir CD4+ T-cell counts is associated with reduced arterial stiffness in HIV-infected individuals.** *AIDS* 2010; **24**:1897–1905.
11. Ganz P, Vita JA. **Testing endothelial vasomotor function: nitric oxide, a multipotent molecule.** *Circulation* 2003; **108**:2049–2053.
12. Kelley CF, Barbour JD, Hecht FM. **The relation between symptoms, viral load, and viral load set point in primary HIV infection.** *J Acquir Immune Defic Syndr* 2007; **45**:445–448.
13. Hecht FM, Busch MP, Rawal B, Webb M, Rosenberg E, Swanson M, *et al*. **Use of laboratory tests and clinical symptoms for identification of primary HIV infection.** *AIDS* 2002; **16**:1119–1129.
14. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, *et al*. **Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force.** *J Am Coll Cardiol* 2002; **39**:257–265.
15. Lieberman EH, Gerhard MD, Uehata A, Selwyn AP, Ganz P, Yeung AC, *et al*. **Flow-induced vasodilation of the human brachial artery is impaired in patients <40 years of age with coronary artery disease.** *Am J Cardiol* 1996; **78**:1210–1214.
16. Hammer SM, Eron JJ, Reiss P, Schooley RT, Thompson MA, Walmsley S, *et al*. **Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel.** *JAMA* 2008; **300**:555–570.
17. Huber PJ. **The behavior of maximum likelihood estimates under nonstandard conditions.** In: *Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability*, 1967; Berkeley, California, USA. Berkeley, California: University of California Press, vol. 1; 1967. pp. 221–223.

18. Hoeting J, Madigan D, Raftery A, Volinsky C. **Bayesian model averaging: a tutorial.** *Stat Sci* 1999; **14**:382–401.
19. Cockcroft DW, Gault MH. **Prediction of creatinine clearance from serum creatinine.** *Nephron* 1976; **16**:31–41.
20. Benjamin EJ, Larson MG, Keyes MJ, Mitchell GF, Vasan RS, Keaney JF Jr, *et al*. **Clinical correlates and heritability of flow-mediated dilation in the community: the Framingham Heart Study.** *Circulation* 2004; **109**:613–619.
21. Yeboah J, Folsom AR, Burke GL, Johnson C, Polak JF, Post W, *et al*. **Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multiethnic study of atherosclerosis.** *Circulation* 2009; **120**:502–509.
22. Davignon J, Ganz P. **Role of endothelial dysfunction in atherosclerosis.** *Circulation* 2004; **109**:III27–III32.
23. Solages A, Vita JA, Thornton DJ, Murray J, Heeren T, Craven DE, *et al*. **Endothelial function in HIV-infected persons.** *Clin Infect Dis* 2006; **42**:1325–1332.
24. Blum A, Hadas V, Burke M, Yust I, Kessler A. **Viral load of the human immunodeficiency virus could be an independent risk factor for endothelial dysfunction.** *Clin Cardiol* 2005; **28**:149–153.
25. Charakida M, Donald AE, Green H, Storry C, Clapson M, Caslake M, *et al*. **Early structural and functional changes of the vasculature in HIV-infected children: impact of disease and antiretroviral therapy.** *Circulation* 2005; **112**:103–109.
26. Blanco JJ, García IS, Cerezo JG, de Rivera JM, Anaya PM, Raya PG, *et al*. **Endothelial function in HIV-infected patients with low or mild cardiovascular risk.** *J Antimicrob Chemother* 2006; **58**:133–139.
27. Torriani FJ, Komarow L, Parker RA, Cotter BR, Currier JS, Dubé MP, *et al*. **Endothelial function in human immunodeficiency virus-infected antiretroviral-naive subjects before and after starting potent antiretroviral therapy: the ACTG (AIDS Clinical Trials Group) Study 5152 s..** *J Am Coll Cardiol* 2008; **52**:569–576.
28. Lichtenstein KA. **HIV Outpatient Study Cohort (HOPS): low CD4 associated with new cardiovascular events [abstract]**. In: *International AIDS Conference on HIV Pathogenesis and Treatment*, 2008; Mexico.
29. Baker JV, Peng G, Rapkin J, Abrams DI, Silverberg MJ, MacArthur RD, *et al*. **CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection.** *AIDS* 2008; **22**:841–848.
30. Kaplan RC, Kingsley LA, Gange SJ, Benning L, Jacobson LP, Lazar J, *et al*. **Low CD4+ T-cell count as a major atherosclerosis risk factor in HIV-infected women and men.** *AIDS* 2008; **22**:1615–1624.
31. Lau B, Sharrett AR, Kingsley LA, Post W, Palella FJ, Visscher B, *et al*. **C-reactive protein is a marker for human immunodeficiency virus disease progression.** *Arch Intern Med* 2006; **166**:64–70.
32. Ehrenreich H, Rieckmann P, Sinowatz F, Weih KA, Arthur LO, Goebel FD, *et al*. **Potent stimulation of monocytic endothelin-1 production by HIV-1 glycoprotein 120.** *J Immunol* 1993; **150**:4601–4609.
33. Hsue PY, Hunt PW, Sinclair E, Bredt B, Franklin A, Killian M, *et al*. **Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses.** *AIDS* 2006; **20**:2275–2283.
34. Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, *et al*. **Inflammatory and coagulation biomarkers and mortality in patients with HIV infection.** *PLoS Med* 2008; **5**:e203.