# Low CD4$^+$ T Cell Count is a Risk Factor for Cardiovascular Disease Events in the HIV Outpatient Study

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***Background.*** Traditional cardiovascular disease (CVD) risk factors, human immunodeficiency virus (HIV) infection, and antiretroviral (ARV) agents have been associated with CVD events in HIV-infected patients. We investigated the association of low CD4$^+$ T lymphocyte cell count with incident CVD in a cohort of outpatients treated in 10 HIV specialty clinics in the United States.

***Methods.*** We studied patients who were under observation from 1 January 2002 (baseline), categorized them according to National Cholesterol Education Program guidelines into 10-year cardiovascular risk score (10-y CVR) groups , and observed them until CVD event, death, last HIV Outpatient Study contact, or 30 September 2009. We calculated rates of incident CVD events and identified associated baseline risk factors using Cox proportional hazard models. We also performed a nested case-control study to examine the association of latest CD4$^+$ cell count with CVD events.

***Results.*** Among 2005 patients, 148 experienced incident CVD events. CVD incidence increased steadily from 0.4 to 3.0 events per 100 person-years from lowest to highest 10-y CVR group ($P < .001$). In multivariable Cox analyses adjusted for 10-y CVR, CD4$^+$ cell count <350 cells/mm$^3$ was associated with incident CVD events (hazard ratio, 1.58 [95% confidence interval, 1.09–2.30], compared with >500 cells/mm$^3$), suggesting an attributable risk of ~20%. In the multivariable case-control analyses, traditional CVD risk factors and latest CD4$^+$ cell count <500 cells/mm$^3$, but not cumulative use of ARV class or individual drugs, were associated with higher odds of experiencing CVD events.

***Conclusion.*** CD4$^+$ count <500 cells/mm$^3$ is an independent risk factor for incident CVD, comparable in attributable risk to several traditional CVD risk factors in the HIV Outpatient Study cohort.

Studies have demonstrated increased risk for incident cardiovascular disease (CVD) among persons living with human immunodeficiency virus (HIV) infection [1–7] associated with traditional CVD risk factors (eg, tobacco use and hypertension), exposure to various antiretroviral agents [8–20], lower high-density lipoprotein cholesterol (HDL-C) levels [21], and HIV infection or its associated inflammatory state [1, 21–26]. Lower baseline and proximal CD4$^+$ T lymphocyte counts have been observed in patients who experienced incident myocardial infarction (MI), compared with patients who did not [27]. With use of data from the HIV Outpatient Study (HOPS) cohort, we evaluated the contributions of traditional cardiovascular risk factors, antiretroviral exposure, and immunologic and virologic status to risk for incident cardiovascular events.

## METHODS

The HOPS is an ongoing, prospective, observational cohort study of HIV-infected patients receiving care since 1993. For the present analyses, we analyzed data

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**Table 1. Characteristics and Antiretroviral Exposure of Patients by 10-Year Cardiovascular Disease Risk Category, HIV Outpatient Study, January 2002–September 2009**

| Characteristic | 10-Year risk of cardiovascular disease | | | | | |
|---|---|---|---|---|---|---|
| | Overall ($n$ = 2005) | LR ($n$ = 675) | MR ($n$ = 565) | MHR ($n$ = 365) | HR ($n$ = 400) | $P$[a] |
| Baseline characteristics | | | | | | |
| Age, median years | 42 | 38 | 41 | 47 | 48 | <.001 |
| Male sex | 1532 (76) | 451 (67) | 405 (72) | 350 (96) | 326 (82) | <.001 |
| Race and ethnicity | | | | | | <.001 |
| White, non-Hispanic | 1048 (52) | 304 (45) | 276 (49) | 252 (69) | 216 (54) | |
| Black, non-Hispanic | 657 (33) | 251 (37) | 199 (35) | 73 (20) | 134 (34) | |
| Hispanic | 239 (12) | 93 (14) | 71 (13) | 31 (8) | 44 (11) | |
| Other | 61 (3) | 27 (4) | 19 (3) | 9 (2) | 6 (2) | |
| Follow-up after baseline, median years | 5.5 | 5.5 | 5.5 | 5.8 | 5.1 | .32 |
| Year of HOPS entry | | | | | | <.001 |
| 1998 or earlier | 856 (43) | 247 (37) | 210 (37) | 176 (48) | 223 (56) | |
| 1999–2005 | 1149 (57) | 428 (63) | 355 (63) | 189 (52) | 177 (44) | |
| Private insurance | 1147 (57) | 420 (62) | 293 (52) | 233 (64) | 201 (50) | <.001 |
| History of IDU | 227 (11) | 37 (5) | 90 (16) | 38 (10) | 62 (16) | <.001 |
| Prior AIDS-defining illness, n (%) | 728 (36) | 209 (31) | 204 (36) | 139 (38) | 176 (44) | <.001 |
| Nadir $CD4^+$ cell count <200 cells/$mm^3$ | 1043 (52) | 319 (47) | 307 (54) | 197 (54) | 220 (55) | .025 |
| Nadir $CD4^+$ cell count, median cells/$mm^3$ | 197 | 218 | 187 | 190 | 180 | .27 |
| $CD4^+$ cell count, median cells/$mm^3$ | 395 | 396 | 358 | 401 | 415 | .002 |
| Peak viral load, median copies/mL | 5985 | 7790 | 19,712 | 1911 | 2384 | <.001 |
| Viral load, median copies/mL[b] | 419 | 745 | 908 | 200 | 200 | <.001 |
| Viral load <400 copies/mL | 987 (49) | 305 (45) | 243 (43) | 211 (58) | 228 (57) | <.001 |
| Alcohol use | | | | | | <.001 |
| Missing information | 127 (6) | 49 (7) | 32 (6) | 18 (5) | 28 (7) | |
| None | 977 (49) | 322 (48) | 284 (50) | 146 (40) | 225 (56) | |
| <7 drinks/week | 689 (34) | 242 (36) | 192 (34) | 144 (39) | 111 (28) | |
| 7–14 drinks/week | 124 (6) | 40 (6) | 30 (5) | 31 (8) | 23 (6) | |
| >14 drinks/week | 88 (4) | 22 (3) | 27 (5) | 26 (7) | 13 (3) | |
| BMI | | | | | | .005 |
| Missing information | 120 (6) | 47 (7) | 36 (6) | 21 (6) | 16 (4) | |
| ⩽25 | 909 (45) | 331 (49) | 261 (46) | 160 (44) | 157 (39) | |
| >25 | 976 (49) | 297 (44) | 268 (47) | 184 (50) | 227 (57) | |
| Hypertension | 974 (49) | 95 (14) | 351 (62) | 221 (61) | 307 (77) | <.001 |
| Diabetes mellitus | 190 (9) | 0 (0) | 0 (0) | 0 (0) | 190 (48) | <.001 |
| History of tobacco use | 1108 (55) | 164 (24) | 348 (62) | 296 (81) | 300 (75) | <.001 |
| Total cholesterol, median mg/dL | 204 | 197 | 181 | 226 | 238 | <.001 |
| LDL cholesterol, median mg/dL | 105 | 108 | 94 | 114 | 107 | <.001 |
| HDL cholesterol, median mg/dL | 37 | 44 | 35 | 35 | 35 | <.001 |
| Non-HDL cholesterol, median mg/dL[c] | 164 | 151 | 142 | 186 | 199 | <.001 |
| Triglycerides, median mg/dL | 163 | 126 | 162 | 200 | 225 | <.001 |
| Metabolic syndrome[d] | 516 (26) | 85 (13) | 157 (28) | 103 (28) | 171 (43) | <.001 |
| Cholesterol-lowering agents | | | | | | |
| Statin drug/ezitimibe | 562 (28) | 119 (18) | 109 (19) | 125 (34) | 209 (52) | <.001 |
| Fibrate | 235 (12) | 39 (6) | 53 (9) | 54 (15) | 89 (22) | <.001 |
| Fish oil | 139 (7) | 25 (4) | 42 (7) | 33 (9) | 39 (10) | <.001 |
| Cumulative years of antiretroviral use since HIV infection diagnosis[e] | | | | | | |
| NRTI, median years | 8.4 | 7.7 | 7.8 | 9.2 | 10.0 | <.001 |
| NNRTI, median years | 3.9 | 3.8 | 3.5 | 4.6 | 4.3 | .006 |
| Protease inhibitor drug, median years | 6.0 | 5.5 | 5.2 | 6.7 | 7.4 | <.001 |
| Zidovudine, median years | 5.1 | 4.7 | 4.9 | 6.0 | 5.7 | .09 |
| D-drug, median years | 5.8 | 5.3 | 5.3 | 6.4 | 6.5 | <.001 |
| Abacavir, median years | 3.3 | 3.2 | 3.3 | 3.5 | 3.5 | .69 |

**Table 1.** ***(Continued.)***

| Characteristic | 10-Year risk of cardiovascular disease | | | | | |
|---|---|---|---|---|---|---|
| | Overall ($n$ = 2005) | LR ($n$ = 675) | MR ($n$ = 565) | MHR ($n$ = 365) | HR ($n$ = 400) | $P$[a] |
| Tenofovir, median years | 3.3 | 3.2 | 3.0 | 3.5 | 3.4 | .13 |
| Any HAART, median years | 7.3 | 6.7 | 6.7 | 8.3 | 8.2 | <.001 |
| Antiretroviral use during observation | | | | | | |
| NRTI | | | | | | |
| Ever taken | 1895 (95) | 638 (95) | 539 (95) | 347 (95) | 371 (93) | .35 |
| Duration of therapy, median years | 4.6 | 4.7 | 4.6 | 5.1 | 4.0 | .007 |
| NNRTI | | | | | | |
| Ever taken | 1175 (59) | 415 (61) | 337 (60) | 209 (57) | 214 (54) | .07 |
| Duration of therapy, median years | 2.5 | 2.6 | 2.3 | 2.7 | 2.4 | .11 |
| Protease inhibitor drug | | | | | | |
| Ever taken | 1403 (70) | 456 (68) | 393 (70) | 275 (75) | 279 (70) | .07 |
| Duration of therapy, median years | 3.4 | 3.4 | 3.2 | 3.5 | 3.3 | .28 |
| Zidovudine | | | | | | |
| Ever taken | 767 (38) | 254 (38) | 218 (39) | 150 (41) | 145 (36) | .56 |
| Duration of therapy, median years | 2.5 | 2.4 | 2.7 | 2.6 | 2.2 | .13 |
| D-drug | | | | | | |
| Ever taken | 891 (44) | 275 (41) | 237 (42) | 181 (50) | 198 (50) | .004 |
| Duration of therapy, median years | 2.1 | 2.1 | 2.0 | 2.1 | 1.7 | .78 |
| Abacavir | | | | | | |
| Ever taken | 765 (38) | 241 (36) | 221 (39) | 149 (41) | 154 (39) | .38 |
| Duration of therapy, median years | 2.4 | 2.4 | 2.3 | 2.5 | 2.0 | .44 |
| Tenofovir | | | | | | |
| Ever taken | 1327 (66) | 477 (71) | 399 (71) | 237 (65) | 214 (54) | <.001 |
| Duration of therapy, median years | 3.1 | 3.2 | 2.9 | 3.3 | 3.0 | .25 |
| Any HAART | | | | | | |
| Ever taken | 1886 (94) | 636 (94) | 536 (95) | 346 (95) | 368 (92) | .28 |
| Duration of therapy, median years | 4.5 | 4.6 | 4.4 | 5.0 | 4.0 | .008 |

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. BMI, body mass index calculated as weight in kilograms divided by the square of height in meters; d-drug, didanosine, stavudine, and dideoxycytidine; HAART, highly active antiretroviral therapy; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HOPS, HIV Outpatient Study; HR, high risk, defined as >20% risk and presence of >2 risk factors; IDU, injection drug use; LDL, low-density lipoprotein; LR, low risk, defined as <10% risk and presence of 0–1 risk factor; MHR, moderate high risk, defined as 10%–20% risk and presence of >2 risk factors; MR, moderate risk, defined as <10% risk and presence of ⩾2 risk factors; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor.

[a] Likelihood ratio $\chi^2$ test for binary variables or Kruskal-Wallis test for continuous variables.

[b] For undetectable viral load results, a value equal to the lower limit of detection divided by 2 is assigned.

[c] Non-HDL cholesterol equals total cholesterol minus HDL cholesterol.

[d] Metabolic syndrome was defined as at least 3 of the following: BMI ⩾28.9 for men or ⩾24.9 for women, fasting glucose level ⩾110 mg/dL; HDL level <40 mg/dL for men or <50 mg/dL for women, blood pressure ⩾130/85 mmHg or on antihypertensives, and fasting triglyceride level ⩾150 mg/dL.

[e] Any antiretroviral exposure entered in the HOPS, including prior to HOPS enrollment.

from 10 participating HIV clinics (university-based, public, and private) in US cities (Chicago, IL; Denver, CO; Long Island, NY; Oakland/San Leandro, CA; Philadelphia, PA; Tampa, FL; and Washington, DC) participating in the HOPS on and after 1 January 2002. Patient data, including sociodemographic characteristics, symptoms and signs, diagnoses, treatments, and laboratory values were abstracted from medical charts and entered into an electronic database by trained staff. These data were reviewed for quality and analyzed centrally. Since its inception, the HOPS protocol has been reviewed and approved annually by the institutional review boards of the Centers for Disease Control and Prevention and each local site. Written informed consent was obtained from all patients.

We included patients active in the HOPS on or after 1 January 2002. Start of observation (baseline date) was 1 January 2002 or the date of the first HOPS visit thereafter, with first HOPS visit being no later than 1 October 2007 to assure a minimum follow-up time of at least 1 year after the baseline visit. We further limited inclusion to patients with data necessary to calculate baseline Framingham 10-year cardiovascular

**Table 2. Incidence of Cardiovascular Disease (CVD) Events by Select Factors at Baseline and during Observation among 2005 HIV Outpatient Study Patients, January 2002–September 2009**

| Variable | No. of patients | CVD incidence per 100 person-years | $P$[a] |
|---|---|---|---|
| Baseline characteristics | | | |
| 10-Year CVD risk category | | | |
| LR | 675 | 0.39 | Referent |
| MR | 565 | 0.91 | .013 |
| MHR | 365 | 2.29 | <.001 |
| HR | 400 | 3.04 | <.001 |
| Age[b] | | | |
| <42 years | 961 | 0.55 | Referent |
| ⩾42 years | 1044 | 2.16 | <.001 |
| Sex | | | |
| Male | 1532 | 1.51 | .09 |
| Female | 473 | 1.04 | Referent |
| Race and ethnicity | | | |
| White, non-Hispanic | 1,048 | 1.53 | Referent |
| Black, non-Hispanic | 657 | 1.11 | .12 |
| Hispanic | 239 | 1.40 | .85 |
| Other | 61 | 2.23 | .35 |
| Year of HOPS entry | | | |
| 1998 or earlier | 856 | 1.56 | .18 |
| 1999–2005 | 1149 | 1.23 | Referent |
| Insurance at baseline | | | |
| Private | 1147 | 1.16 | Referent |
| Public/none/unknown | 858 | 1.73 | .021 |
| History of IDU | | | |
| Yes | 227 | 1.80 | .28 |
| No | 1778 | 1.35 | Referent |
| History of AIDS-defining illness | | | |
| Yes | 728 | 1.47 | .65 |
| No | 1277 | 1.35 | Referent |
| Nadir $CD4^+$ cell count stratum, cells/$mm^3$ | | | |
| <200 | 1043 | 1.62 | .051 |
| ⩾200 | 962 | 1.15 | Referent |
| Baseline $CD4^+$ cell count stratum, cells/$mm^3$ | | | |
| <350 | 869 | 1.66 | .041 |
| 350–499 | 417 | 1.43 | .32 |
| ⩾500 | 719 | 1.10 | Referent |
| Baseline viral load, copies/mL | | | |
| <400 | 987 | 1.32 | Referent |
| ⩾400 | 1018 | 1.49 | .52 |
| Alcohol use | | | |
| Missing information | 127 | 1.27 | .94 |
| None | 977 | 1.22 | Referent |
| <7 drinks/week | 689 | 1.54 | .24 |
| 7–14 drinks/week | 124 | 1.60 | .54 |
| >14 drinks/week | 88 | 2.30 | .10 |
| BMI | | | |
| Missing information | 120 | 1.69 | .50 |
| ⩽25 | 909 | 1.26 | Referent |
| >25 | 976 | 1.49 | .36 |
| History of hypertension | | | |
| Yes | 974 | 2.12 | <.001 |
| No | 1031 | 0.72 | Referent |

**Table 2.** ***(Continued.)***

| Variable | No. of patients | CVD incidence per 100 person-years | $P$[a] |
|---|---|---|---|
| History of diabetes | | | |
| Yes | 190 | 2.78 | <.001 |
| No | 1815 | 1.26 | Referent |
| History of tobacco use | | | |
| Yes | 1108 | 1.80 | <.001 |
| No | 897 | 0.92 | Referent |
| Baseline total cholesterol, mg/dL | | | |
| >200 | 1051 | 1.71 | .004 |
| ⩽200 | 954 | 1.01 | Referent |
| Baseline LDL or non-HDL cholesterol above target range[c] | | | |
| Yes | 832 | 2.11 | <.001 |
| No | 1173 | 0.85 | Referent |
| Baseline HDL, mg/dL | | | |
| <40 for men or <50 for women | 1263 | 1.60 | .026 |
| ⩾40 for men or ⩾50 for women | 742 | 1.05 | Referent |
| Baseline triglyceride levels, mg/dL | | | |
| ⩽200 | 1224 | 1.07 | Referent |
| >200 | 781 | 1.87 | <.001 |
| ARV status at baseline | | | |
| ARV naive | 447 | 1.21 | .53 |
| ARV experienced, not HAART | 51 | 1.40 | >.99 |
| HAART experienced | 1507 | 1.44 | Referent |
| Receiving ARV at baseline | | | |
| Yes | 1400 | 1.37 | .72 |
| No | 605 | 1.49 | Referent |
| Cumulative antiretroviral exposures since HIV diagnosis[d] | | | |
| Exposure to NRTIs | | | |
| Yes | 1941 | 1.36 | .029 |
| No | 64 | 3.39 | Referent |
| Exposure to NNRTIs | | | |
| Yes | 1470 | 1.24 | .023 |
| No | 535 | 1.89 | Referent |
| Exposure to PIs | | | |
| Yes | 1602 | 1.38 | .88 |
| No | 403 | 1.46 | Referent |
| Exposure to zidovudine | | | |
| Yes | 1309 | 1.38 | .93 |
| No | 696 | 1.43 | Referent |
| Exposure to d-drugs | | | |
| Yes | 1222 | 1.37 | .78 |
| No | 783 | 1.46 | Referent |
| Exposure to abacavir | | | |
| Yes | 909 | 1.29 | .44 |
| No | 1096 | 1.49 | Referent |
| Exposure to tenofovir | | | |
| Yes | 1363 | 0.92 | <.001 |
| No | 642 | 2.65 | Referent |
| Exposure to HAART | | | |
| Yes | 1931 | 1.36 | .10 |
| No | 74 | 2.72 | Referent |
| Cumulative ARV exposures during observation | | | |
| Exposure to NRTIs | | | |
| Yes | 1895 | 1.32 | .002 |

**Table 2.** ***(Continued.)***

| Variable | No. of patients | CVD incidence per 100 person-years | $P$[a] |
|---|---|---|---|
| No | 110 | 3.39 | Referent |
| Exposure to NNRTIs | | | |
| Yes | 1175 | 1.21 | .047 |
| No | 830 | 1.70 | Referent |
| Exposure to PIs | | | |
| Yes | 1403 | 1.17 | .001 |
| No | 602 | 2.03 | Referent |
| Exposure to zidovudine | | | |
| Yes | 767 | 1.35 | .79 |
| No | 1238 | 1.43 | Referent |
| Exposure to d-drugs | | | |
| Yes | 891 | 1.30 | .47 |
| No | 1114 | 1.49 | Referent |
| Exposure to abacavir | | | |
| Yes | 765 | 1.31 | .58 |
| No | 1240 | 1.46 | Referent |
| Exposure to tenofovir | | | |
| Yes | 1327 | 0.96 | <.001 |
| No | 678 | 2.46 | Referent |
| Exposure to HAART | | | |
| Yes | 1886 | 1.32 | .002 |
| No | 119 | 3.27 | Referent |

**NOTE.** Baseline is defined as start of observation in this analyses (1 January 2002 or HOPS entry if thereafter). Unless otherwise specified, all factors were measured up to 1 year before baseline through 275 days after baseline. ARV, antiretroviral therapy; BMI, body mass index calculated as weight in kilograms divided by the square of height in meters; d-drug, didanosine, stavudine, and dideoxycytidine; HAART, highly active antiretroviral therapy; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HOPS, HIV Outpatient Study; HR, high risk, defined as >20% risk and presence of >2 risk factors; IDU, injection drug use; LDL, low-density lipoprotein; LR, low risk, defined as <10% risk and presence of 0–1 risk factor; MHR, moderate high risk, defined as 10%–20% risk and presence of >2 risk factors; MR, moderate risk, defined as <10% risk and presence of ⩾2 risk factors; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

[a] Likelihood ratio by $\chi^2$ test.

[b] Median baseline age, 42 years.

[c] LDL cholesterol goals by cardiovascular risk category according to the 2001 National Cholesterol Education Program III Guidelines are as follows. When serum triglycerides values are <200 mg/dL, the LDL goals are <160 mg/dL for the LR group, <130 mg/dL for MR and MHR groups, <100 mg/dL for HR group. When serum triglycerides are ⩾200 mg/dL, non-HDL goals are used instead of LDL goals. Non-HDL goals are 30 mg/dL above the LDL goals for the respective 10-year cardiovascular risk categories.

[d] Any ARV exposure entered in the HOPS, including prior to HOPS enrollment.

risk score (10-y CVR) and restricted analyses to patients who had ⩾2 outpatient encounters (eg, clinical office visit, phone contact, and laboratory visit) and who, during 12 months before and up to 9 months after baseline had ⩾2 blood pressure (BP) measurements recorded and ⩾1 fasting lipid panel measured. To assess for potential selection bias, we compared demographic and HIV-specific factors of patients included in our analysis with those of patients excluded because of inadequate data to calculate 10-y CVR.

We calculated rates of incident CVD events per 100 person-years. An incident CVD event was defined as any of the following diagnoses: myocardial infarction, nonembolic/nonhemorrhagic stroke, coronary artery disease (CAD), angina, and peripheral arterial disease. Observation time began at the baseline date and was censored at the date of CVD event for persons who developed the outcome or at the earliest of last HOPS contact, date of death, or 30 September 2009 for persons who did not experience the outcome.

We categorized HOPS patients using baseline Framingham 10-y CVR into 4 categories as defined by the 2001 National Cholesterol Education Program Adult Treatment Panel-III (NCEP III) guidelines [28], and we conducted the study during the time period when these guidelines and their updates were in force. In this analysis, major risk factors used for calculating 10-y CVR included cigarette smoking (past or current), hypertension (BP >140/90 mmHg, diagnosis of hypertension, or prescription of antihypertensive therapy with a diagnosis of hypertension regardless of BP), serum high density lipoprotein

**Table 3. Cox Proportional Hazards Models to Identify Factors Associated with Subsequent Cardiovascular Events in the Human Immunodeficiency Virus Outpatient Study, January 2002–September 2009 ($n = 2005$).**

| Baseline variable | Univariate analyses, hazard ratio (95% CI) | *P* | Multivariable analyses, hazard ratio (95% CI) | *P* | Attributable risk, % |
|---|---|---|---|---|---|
| Model 1 | | | | | |
| Age ⩾42 years | 3.91 (2.59–5.89) | <.001 | 2.86 (1.88–4.36) | <.001 | 49.2 |
| Male sex | 1.46 (0.96–2.21) | .08 | 1.20 (0.79–1.83) | .40 | 13.3 |
| Current or past tobacco smoker | 1.94 (1.37–2.76) | <.001 | 1.66 (1.17–2.36) | .005 | 26.7 |
| LDL/non-HDL greater than goal[a] | 2.50 (1.78–3.51) | <.001 | 1.66 (1.16–2.38) | .006 | 21.5 |
| HDL <40 for men or <50 for women | 1.53 (1.07–2.19) | .020 | 1.42 (0.98–2.05) | .06 | 20.9 |
| Hypertension | 2.96 (2.06–4.27) | <.001 | 2.08 (1.42–3.02) | <.001 | 34.4 |
| Diabetes | 2.20 (1.44–3.35) | <.001 | 1.26 (0.81–1.95) | .30 | 2.4 |
| $CD4^+$ cell count | | | | | |
| <350 cells/$mm^3$ | 1.51 (1.04–2.19) | .032 | 1.58 (1.09–2.31) | .017 | 20.1 |
| 350–499 cells/$mm^3$ | 1.29 (0.82–2.02) | .28 | 1.28 (0.81–2.02) | .28 | 5.5 |
| ⩾500 cells/$mm^3$ | Referent | … | Referent | … | … |
| Model 2 | | | | | |
| 10-Year CVR group | | | | | |
| HR | 7.83 (4.38–14.0) | <.001 | 7.90 (4.42–14.1) | <.001 | 57.9 |
| MHR | 5.87 (3.22–10.7) | <.001 | 5.91 (3.24–10.8) | <.001 | 47.2 |
| MR | 2.35 (1.23–4.48) | .010 | 2.27 (1.19–4.32) | .013 | 26.4 |
| LR | Referent | … | Referent | … | … |
| $CD4^+$ cell count | | | | | |
| <350 cells/$mm^3$ | 1.51 (1.04–2.19) | .032 | 1.58 (1.09–2.30) | .017 | 20.1 |
| 350–499 cells/$mm^3$ | 1.29 (0.82–2.02) | .28 | 1.29 (0.82–2.03) | .28 | 5.7 |
| ⩾500 cells/$mm^3$ | Referent | … | Referent | … | … |

**NOTE.** Cardiovascular events included myocardial infarction, coronary artery disease, angina; nonembolic nonhemorrhagic stroke, and peripheral arterial disease. CI, confidence interval; CVR, cardiovascular risk; HDL, high-density lipoprotein; HR, highest risk; LDL, low-density lipoprotein; LR, low risk; MHR, moderately high risk; MR, moderate risk.

[a] LDL cholesterol goals by CVR category according to the 2001 National Cholesterol Education Program III Guidelines are as follows. When serum triglycerides levels are <200 mg/dL, the LDL goals are <160 mg/dL for the LR group, <130 mg/dL for the MR and MHR groups, and <100 mg/dL for the HR group. When serum triglyceride levels are ⩾200 mg/dL, non-HDL goals are used instead of LDL goals. Non-HDL goals are 30 mg/dL above the LDL goals for the respective 10-year CVR categories.

cholesterol (HDL-C) <40 mg/dL for men and <50 mg/dL for women, family history of premature CVD (in men, first-degree relative with age <55 years; in women, first-degree relative with age <65 years), older age (men ⩾45 years; women ⩾55 years), and presence of a coronary heart disease (CHD) risk equivalent (eg, diabetes mellitus or prior peripheral or central arterial disease). Patients with ⩽1 major risk factor and no history of CHD risk equivalents had a 10-y CVR <10% and were categorized as being at low risk (LR). Among patients with ⩾2 major risk factors, patients with a 10-y CVR <10% were categorized as being at moderate risk (MR); those with a 10-y CVR of 10%–20% were classified as being at moderately high risk (MHR); and those with known CHD, a CHD risk equivalent, or a 10-y CVR >20% were classified as being at highest risk (HR). For each of the 4 risk categories, we calculated rates of incident CVD per 100 person-years of observation.

We categorized antiretroviral (ARV) exposures by ARV class (eg, nucleoside reverse-transcriptase inhibitors [NRTIs], nonnucleoside reverse-transcriptase inhibitors [NNRTIs], or protease inhibitors [PIs]), by individual agents (eg, zidovudine, abacavir, and tenofovir), and by groups of single agents with shared toxicity profiles (eg, the "d-drugs": stavudine, didanosine, and zalcitabine). For each category of ARV exposure, we calculated the total length of time exposed since HIV diagnosis and during observation after baseline.

We performed a cohort analysis to assess the association of baseline characteristics with subsequent CVD events. We also performed a nested case-control study to explore associations of nadir, baseline $CD4^+$ cell counts and most proximal $CD4^+$ cell count (termed latest $CD4^+$ cell count) with incident CVD events. Case patients were patients who experienced an incident CVD event during observation. For each case patient, we randomly selected 4 control subjects who were patients under observation during the calendar year in which the correspond-

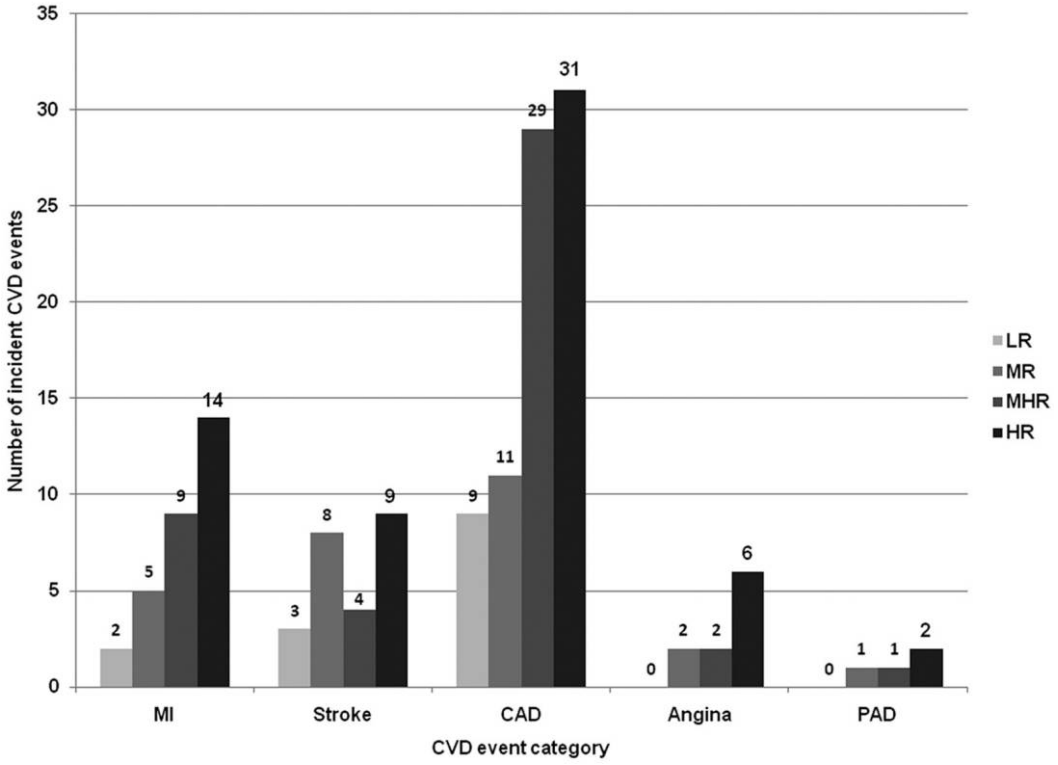


**Figure 1.** Distribution of incident cardiovascular disease (CVD) events by 10-year cardiovascular risk group. CAD, coronary artery disease; HR, high risk; LR, low risk; MHR, medium-high risk; MI, myocardial infarction; MR, medium risk; PAD, peripheral artery disease.

ing case patient's incident CVD event had occurred but who had not experienced an incident CVD event while under observation. For cases, the latest $CD4^+$ cell count was defined as the determination closest to the CVD event within the 12 months preceding the event. For control subjects, the latest $CD4^+$ cell count was defined as that value closest to the midpoint of the calendar year during which the CVD event of the corresponding case patient had occurred.

Patient characteristics were compared using the Yates corrected $\chi^2$ test or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables for 2-group comparisons. For cohort analyses, Cox proportional hazards regression was used to assess the association of various baseline clinical and demographic factors with incident CVD events. We calculated the population attributable risk (AR) associated with each factor by considering the prevalence of exposure in the study population and the multivariable hazard ratio associated with that factor using standard formulas [29]. For case-control analyses, we used logistic regression to assess the association of the following baseline factors with the odds of experiencing an incident CVD event: 10-y CVR, nadir, baseline, and latest $CD4^+$ cell count; HIV viral load (VL); injection drug use (IDU); race and ethnicity; type of health insurance: and cumulative exposure both to major classes of ARVs and to individual ARV agents.

Summaries of descriptive data, univariate analyses, and Cox proportional hazards regression modeling were performed with SAS, version 9.1 (SAS Institute). Statistical estimates with 2-sided *P*-values <.05 were considered to be statistically significant.

## RESULTS

Of 5382 patients with ⩾1 outpatient encounter in the HOPS on or after 1 January 2002, we excluded 3377 for the following reasons (applied hierarchically): 165 had <2 encounters, 896 had <1 year of observation after baseline, 154 had their first HOPS visit after 1 October 2007, 1304 had no lipids measured and recorded during the 12 months before and 9 months after baseline, and 858 had <2 BP readings. The 2162 patients who were excluded because of a lack of requisite lipid measurements or blood pressure readings were similar to the 2005 included patients by race and ethnicity, but they were significantly younger (median age, 40 vs 42 years; $P < .05$), were more likely to have been male (82% vs 76%), were more likely to have been privately insured (66% vs 57%), were less likely to have been using or have previously smoked tobacco (51% vs 55%), or to

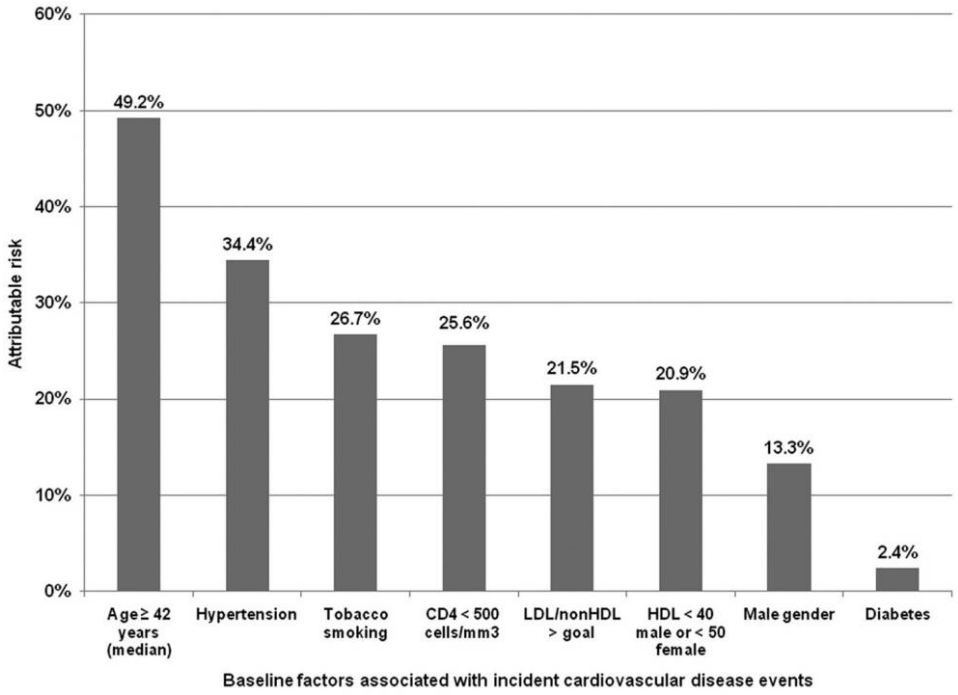


**Figure 2.** Attributable risk for factors associated with incident cardiovascular disease (CVD) events, the Human Immunodeficiency Virus (HIV) Outpatient Study, January 2002–September 2009 ($n = 2005$). HDL, high-density lipoprotein; LDL, low-density lipoprotein.

have received a diagnosis of an AIDS-defining illness (22% vs 36%), diabetes mellitus (4.6% vs 9.0%), hypertension (24% vs 49%), or to have had a body mass index >25 kg/m$^2$ (13% vs 49%) at baseline.

Of 2005 patients analyzed, we categorized 675 (33.7%) as having NCEP III–defined LR for CVD, and 565 (28.2%), 365 (18.2%), and 400 (20.0%) as MR, MHR, and HR, respectively (Table 1). The study population analyzed had a baseline median age of 42 years and was predominately male (76%) and white (52% were non-Hispanic white, 33% were non-Hispanic black, and were 12% Hispanic). At baseline, 49% of patients had hypertension, 9% had diabetes mellitus, and 55% were current or former tobacco smokers. Median values for LDL cholesterol (LDL-C), HDL-C, non-HDL cholesterol (non-HDL-C) and triglycerides (TGs) were 105, 37, 164, and 163 mg/dL, respectively. At baseline, median CD4$^+$ cell count was 395 cells/mm$^3$, and median nadir CD4$^+$ cell count was 197 cells/mm$^3$. Baseline median HIV VL was 419 copies/mL, and 49% of patients were virologically suppressed (HIV VL <400 copies/mL). Median length of subsequent follow-up was 5.5 years (interquartile range [IQR], 3.2–7.7 years) and did not differ statistically among the 4 CVR groups (Table 1).

As expected, for most of the traditional CVD risk factors at baseline, the percentage of patients with each risk factor increased significantly across categories of increasing 10-y CVR with the exceptions of distributions for race and ethnicity, follow-up time, and diabetes mellitus (all 190 individuals with diabetes mellitus were placed in the HR category). Total years of exposure to ARV classes and individual drugs increased across categories of increasing 10-y CVR (Table 1).

One hundred forty-eight individuals (7.4%) experienced an incident CVD event (Figure 1). In univariate analysis, the incidence rate for CVD events among LR patients was 0.4 cases per 100 person-years (14 CVD events); rates for patients in the MR, MHR, and HR categories were 0.9 (27 events), 2.3 (45 events), and 3.0 (62 events) cases per 100 person-years, respectively ($P < .001$ by Poisson distribution). Traditional cardiovascular risk factors measured at baseline, having public or no insurance at baseline, and baseline CD4$^+$ cell count <500 cells/mm$^3$ were all statistically associated with higher rates of incident CVD events ($P < .05$) (Table 2). Incidence of CVD did not differ statistically by race or ethnicity, history of IDU, or calendar year of entry into HOPS. Exposure to certain ARVs since receipt of HIV diagnoses and during observation, such as NRTIs, NNRTIs, and tenofovir, was associated with reduced incidence of CVD in crude analyses (Table 2). Of note, exposure to HAART during observation was also associated with reduced incidence of CVD (Table 2).

In the multivariable analyses using Cox proportional hazards models (Table 3), baseline CD4$^+$ cell counts <350 cells/mm$^3$ and 350–499 cells/mm$^3$, compared with CD4$^+$ cell count ⩾500 cells/mm$^3$, were independently associated with incident CVD

**Table 4. Nested case-control analyses of factors associated with odds of a subsequent cardiovascular event, Human Immunodeficiency Virus Outpatient Study (HOPS), January 2002–September 2009 (146 cases and 584 controls).**

| Variable | Univariate analyses, odds ratio (95% CI) | *P* | Multivariable analyses [a], odds ratio (95% CI) | *P* |
|---|---|---|---|---|
| 10-Year CVR group | | | | |
| HR | 7.57 (3.98–14.4) | <.001 | 8.72 (4.53–16.8) | <.001 |
| MHR | 5.61 (2.89–10.9) | <.001 | 6.42 (3.27–12.6) | <.001 |
| MR | 2.21 (1.10–4.42) | .025 | 2.34 (1.16–4.72) | .018 |
| LR | Reference | … | Reference | … |
| Nadir $CD4^+$ cell count, cells/$mm^3$ | | | | |
| <350 | 1.35 (0.64–2.83) | .43 | … | … |
| 350–499 | 1.46 (0.60–3.57) | .40 | … | … |
| ⩾500 | Reference | … | Reference | … |
| Baseline $CD4^+$ cell count, cells/$mm^3$ | | | | |
| <350 | 1.81 (1.19–2.75) | .006 | … | … |
| 350–499 | 1.52 (0.92–2.52) | .11 | … | … |
| ⩾500 | Reference | … | Reference | … |
| Latest $CD4^+$ cell count[b], cells/$mm^3$ | | | | |
| <350 | 2.59 (1.68–3.99) | <.001 | 3.07 (1.95–4.84) | <.001 |
| 350–499 | 2.35 (1.44–3.81) | <.001 | 2.79 (1.67–4.67) | <.001 |
| ⩾500 | Reference | … | Reference | … |
| Baseline $\log_{10}$ viral load[c], cells/mL | 1.03 (0.93–1.13) | .62 | … | … |
| White, non-Hispanic race or ethnicity | 1.07 (0.74–1.55) | .71 | … | … |
| Private insurance | 0.71 (0.49–1.02) | .06 | … | … |
| IDU risk factor | 1.42 (0.83–2.41) | .20 | … | … |
| Cumulative PI years [d] | 1.00 (0.94–1.05) | .92 | … | … |
| Cumulative HAART years | 1.00 (0.95–1.06) | .96 | … | … |
| Cumulative ARV years | 1.02 (0.97–1.06) | .46 | … | … |
| Cumulative NRTI years | 1.02 (0.97–1.06) | .45 | … | … |
| Cumulative NNRTI years | 1.01 (0.93–1.08) | .88 | … | … |
| Cumulative zidovudine years | 1.05 (1.00–1.12) | .08 | … | … |
| Cumulative d-drug years | 0.98 (0.92–1.03) | .38 | … | … |
| Cumulative abacavir years | 1.05 (0.96–1.15) | .31 | … | … |
| Cumulative tenofovir years | 1.01 (0.89–1.13) | .94 | … | … |

**NOTE.** ARV, antiretroviral therapy; CI, confidence interval; CVR, cardiovascular risk; d-drug, didanosine, stavudine, or zalcitabine; HAART, highly active antiretroviral therapy; HR, highest risk; IDU, injection drug use; LR, low risk; MHR, moderately high risk; MR, moderate risk; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

[a] Parsimonious model included only factors significantly ($P < .05$) associated with subsequent cardiovascular disease events.

[b] For patients with cardiovascular disease, the latest $CD4^+$ cell count was the value closest to the cardiovascular disease event within the preceding 12 months; for control subjects, it was the value closest to the midpoint of the calendar year in which the cardiovascular disease case arose.

[c] Per 1.0 $\log_{10}$ increase.

[d] Cumulative years of exposure to a given drug or class of antiretroviral drugs entered in the HOPS, including prior to HOPS enrollment.

in both a model that included the factors used for categorizing the four 10-y CVR groups per NCEP III (model 1) and a model that included the 4 NCEP-III categories (model 2). In the latter model, using the LR category as referent, CVD risk increased significantly with each higher 10-y CVR category ($P < .001$ for trend): MR (hazard ratio, 2.27; 95% confidence interval [CI], 1.19–4.32); MHR (hazard ratio, 5.91; 95% CI, 3.24–10.8); HR (hazard ratio, 7.90; 95% CI, 4.42–14.1). When evaluated as a continuous variable, each decrease in baseline $CD4^+$ cell count of 100 cells/$mm^3$ was also significantly associated with increased rates of CVD (hazard ratio, 1.08; 95% CI, 1.01–1.14). Association of low $CD4^+$ cell count with increased rates of CVD remained significant and without marked change after further adjustment for baseline IDU, frequency of alcohol use, and

baseline HIV VL in model 2; none of these additional covariates were independently associated with rates of CVD or appeared to act as confounders in the association between low $CD4^+$ cell count and CVD risk. In our study population, we found that the attributable risk of incident CVD events for baseline $CD4^+$ cell count <500 cells/$mm^3$ was 25.6%, a value comparable to that for tobacco smoking and dyslipidemia and greater than the attributable risks associated with male sex, hypertension, or diabetes (Figure 2). Similar relationships were observed using a cutoff value of $CD4^+$ cell count <350 cells/$mm^3$ (data not shown).

In the case-control analysis, latest $CD4^+$ cell count <500 cells/$mm^3$ was independently associated with increased odds of incident CVD (Table 4). Findings were similar in an alternate model when we analyzed latest $CD4^+$ cell count as a continuous variable per 100 cells/$mm^3$ increase (odds ratio, 1.14; 95% CI, 1.06–1.22). When introduced into the multivariable logistic regression model one at a time, no class of ARVs or individual ARV agent was associated with incident CVD events.

## DISCUSSION

We found that, in addition to traditional cardiovascular risk factors, a lower $CD4^+$ cell count was independently associated with increased risk of incident CVD events. For our population, the percentage of incident CVD events attributable to baseline $CD4^+$ cell count <500 cells/$mm^3$ (compared with ⩾500 cells/$mm^3$) was on par with that for certain traditional CVD risk factors. We did not detect associations with use of any ARVs by class or by agent.

The increased risk of CVD among HIV-infected patients has been associated with traditional factors that are highly prevalent in the HOPS cohort and in other HIV-infected cohorts [1–7, 30, 31], as well as with exposure to specific ARVs. ARV exposures have been associated directly with CVD [1, 2, 7–20, 32, 33] and with risk for intermediary conditions in the causal pathways leading to CVD, such as insulin resistance, diabetes mellitus [8, 8, 12], and elevations in lipids [3, 5, 6, 8, 9–13, 18, 20, 33]. Some agents, notably ritonavir, elevate TG levels [13–16, 18].

Lack of a direct association of ARVs with incident CVD in our study is notable. The association between certain ARV exposures and 10-y CVR in crude analyses were no longer apparent after controlling for traditional CVD risk factors and HIV disease factors. ARV therapy may alter lipids to increase the risk of CVD, but it may also reduce risk because of suppression of HIV replication or HIV-associated inflammation. This analysis was not powered to assess the contribution of individual ARV agents to cardiovascular events.

The associations of ARVs with the intermediary conditions mentioned above must be placed in the context of cholesterol metabolism in HIV infection and the lipid changes that accompany antiretroviral therapy. Untreated HIV infection is associated with abnormally reduced levels of total cholesterol (TC), LDL-C, and HDL-C and higher levels of TGs. Initiation of HAART increases TC and LDL-C levels to their premorbid levels. HDL-C improves, but it rarely returns to normal levels [34]. TGs become elevated in some patients who receive ARVs; however, in most cases, the TG elevations are modest. TG levels >400 mg/dL inhibit disposal of LDL-C by LDL-C receptors. Small or modest elevations in TGs have minimal impact on LDL-C disposal [35].

In addition, there is growing evidence that HIV or the inflammatory response to HIV infection contributes independently to the development of atherosclerosis. Both the Strategies for Management of Antiretroviral Therapy (SMART) [36] and Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) [27] studies have suggested an association between lower $CD4^+$ cell counts and incident cardiovascular events. Lower $CD4^+$ cell counts are associated with elevated levels of serum markers of inflammation and increased levels of activated $CD4^+$ T cells. Activated $CD4^+$ T cells are frequently present in atherosclerotic lesions in the general population [23]. The chronic inflammation that accompanies uncontrolled or more advanced HIV disease consists of many of the same inflammatory cells and proinflammatory cytokines that destabilize atherosclerotic plaques. The particles contained in these plaques are immunogenic and trigger an inflammatory cascade that results in plaque rupture and coronary artery thrombosis [22, 23, 37]. The chemokine receptor CCR5 resides in the intima media of arteries, directing monocytes and recruiting T cells to these arteries [38–40].

Our study has several limitations. We analyzed data collected by chart abstraction from routine clinical practice. Family history of CVD and tobacco use history may have been incompletely charted. We used stringent inclusion criteria that relied heavily on the presence of specific clinical and laboratory documentation, and patients missing required test results were excluded. Patients for whom adequate inclusion data were available were likely perceived or known to be at greater risk of CVD, and therefore our study population was probably enriched in patients more likely to experience CVD events (ie, 49% had baseline BP >140/90 mmHg), limiting generalizability of our findings and raising the possibility of selection bias. The relatively small number of incident cardiovascular events limited our statistical power and potentially limited our ability to detect some weaker associations (in particular, associations between ARV exposures and CVD events). It also prevented a more detailed analysis of risk factors (eg, separate analysis for men and women), which has been possible in larger HIV-infected and uninfected cardiovascular cohorts. Most large studies have used acute myocardial infarction or acute coronary syndrome as the outcome of interest. We chose to look at a

broader group of clinical cardiovascular events that are known to result from atherosclerosis. Therefore, it may not be possible to draw comparisons between our study and analyses that studied only myocardial infarction. We would caution about generalizing the attributable risks that we calculated, because these are specific to this population and may not be representative of all HIV-infected persons in the frequencies of the risk factors examined (eg, hypertension and tobacco smoking). Nonetheless, our data support prior observations that HIV infection in itself is a risk factor for CVD not dissimilar in magnitude to some traditional risk factors for CVD events [41, 42]. A study such as ours is observational and can only address associations, not causality, and is subject to unmeasured confounders. It is possible that levels of another laboratory marker (of inflammation) closely associated with $CD4^+$ cell count, rather than $CD4^+$ cell count itself, drove or determined the association with increased risk of CVD that we observed.

In our study, $CD4^+$ cell counts <500 cells/$mm^3$ conferred an attributable risk for incident CVD commensurate with or greater than some traditional cardiovascular risk factors. Our observations support the need for randomized controlled trials to assess whether earlier initiation of ARVs and avoidance of treatment interruptions will reduce the incidence of cardiovascular events. Like several other HIV-associated co-morbidities, CVD results from the interplay of multiple risk factors, including both traditional risk factors and those related uniquely to HIV infection. Much emphasis has been placed on avoiding ARV agents that have been associated with CVD. In addition to timely initiation of ARV therapy and selecting appropriate antiretroviral therapy in patients at substantially elevated risk of CVD, we believe that greater emphasis should be placed on improving management of traditional CVD risk factors and encouraging therapeutic lifestyle changes (eg, smoking cessation, exercise, weight loss, and dietary modification) in accordance with NCEP III guidelines.

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