

Review of Studies Addressing Cardiovascular Disease Risk in HIV Infection and/or Treatment

I Studies assessing or estimating risk of cardiovascular, cerebrovascular or coronary heart disease

1. Bozzette and colleagues examined the association between treatment for HIV infection and cardiovascular and cerebrovascular disease.

The authors used anonymous databases of the Department of Veterans Affairs (VA) to construct a large retrospective cohort of 36,766 patients who received care for HIV infection between January 1993 and June 2001. 21,659 were alive at the end of the study period. The authors followed the study population over the period of 8.5 years for the following 5 outcomes: admission for cardiovascular disease, admission for cardiovascular and cerebrovascular disease, admission for or death from cardiovascular or cerebrovascular disease, death from any cause and admission for any cardiovascular or cerebrovascular disease or death from any cause. The type and duration of antiretroviral drug exposure was also analyzed. The trends in the rates of cardiovascular and cerebrovascular disease and relation between the risk of disease and the use of antiretroviral therapy were evaluated. 1.9% of patients were female, 52.3% were Black and 71.3% were between 35 and 55 years of age.

70.2 percent of the patients received antiretroviral therapy for a mean of 15 months each. All of these received nucleoside analogues, 41.6 percent received protease inhibitors, and 25.6 percent received nonnucleoside reverse transcriptase inhibitors for a median of 17 months, 16 months, and 9 months, respectively. Approximately 1000 patients received combination therapy with a protease inhibitor for at least 48 months, and approximately 1000 patients received combination therapy with a nonnucleoside reverse transcriptase inhibitor for at least 24 months.

Overall there were 1207 admissions for cardiovascular disease, 1704 admissions for cardiovascular or cerebrovascular disease and 2006 admissions for or deaths from cardiovascular or cerebrovascular disease. The rates of these events remained constant or declined (death from any cause) during the 8.5 years of observation. After the introduction of antiretroviral therapy the rate of admission for cardiovascular or cerebrovascular disease decreased from 1.7 (in 1995) to 0.9 per 100 patient-years (in 2001). The rate of death from any cause decreased from 21.3 (in 1995) to 5.0 deaths per 100 patient-years (in 2001). No relation between the use of antiretrovirals and rate of cardiovascular or cerebrovascular events was revealed by patient level analyses, but the use of antiretroviral drugs was associated with a decreased hazard of death from any cause. Hazard for admission was significantly higher with increasing age, more advanced HIV disease, presence of an AIDS defining illness, history of treatment for a cardiovascular risk factor or preexisting vascular disease, and earlier date of first care for HIV at a VA facility. Using a 24 month of exposure to antiretrovirals model, the hazard ratio (HR) for death from any cause ranged from 0.36 to 0.67 depending on the combination of treatment ($p < 0.0001$ in each case) and the HR for admission for cardiovascular or cerebrovascular disease or death from any cause from 0.38 to 0.69 ($p < 0.0001$ in each case).

The authors concluded that the use of newer therapies for HIV was associated with a large benefit in terms of mortality that was not diminished by any increase in the rate of cardiovascular or cerebrovascular events or related mortality. Fear of accelerated vascular disease need not compromise antiretroviral therapy over the short term. However, prolonged survival among HIV-infected patients should be accompanied by longer-term observation and analysis.

Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA. Cardiovascular and Cerebrovascular events in patients treated for human immunodeficiency virus infection. New England Journal of Medicine 2003;348:702-710.

1A. Krause and colleagues analyzed the impact of protease inhibitors (PI) on the risk of myocardial infarction (MI) among men. The authors utilized the French Hospital Database on HIV (FHDH) for a retrospective analysis of the risk factors for MI.

FHDH is a clinical epidemiological network started in 1992 in 68 French university hospitals. Data on HIV-1 and HIV-2 patients is collected using a standardized collection form and a follow up form is completed every 6 months.

The authors included 34,976 men, enrolled in FHDH after January 1996, with a follow up corresponding to 88,029 patient years. Factors associated with the risk of MI were analyzed using univariate and multivariate Cox proportional hazards models. The following variables were assessed for their impact on the risk of myocardial infarction during the period 1996-1999: age, HIV exposure group, initial CD4 cell count, CD4 cell count below 50/mm³, AIDS-associated illnesses, and antiretroviral regimens.

MI was diagnosed in 60 men including 49 cases (39023 PY) of men exposed to PI. The estimated incidence of MI was 8.2 per 10 000 PY (95% CI=4.7-11.7) in patients exposed to PI for less than 18 months (group 1), 15.9 (95% CI=7.9-23.9) in those exposed between 18 and 29 months (group2) and 33.8 (95% CI=15.4-52.1) in patients exposed for 30 months or more (group 3). The expected incidence in the French general male population (FGMP) was 10.8 cases per 10,000 PY. No significant difference in incidence was observed between the general population and patients treated with PI for less than 18 months. The risk of MI was increased, but not significantly, among patients treated with PI for between 18 and 29 months. In contrast, the risk of MI among patients exposed to PI for 30 months or more was three times that of the general population [Standardized morbidity ratio (SMR)=2.9, 95% CI=1.5-5.0]. Compared to patients exposed to PI for less than 18 months, those treated for 18 months or more were at an increased risk of MI (SMR=1.9, 95% CI=1.0-3.1 and SMR=3.6, 95% CI=1.8-6.2 for exposure groups 2 and 3, respectively).

In the multivariate Cox model, adjusted for age, CD4 cell count, treatment with NRTI, NNRTI, exposure to PI was associated with a higher risk of MI (RH=2.56, 95% CI=1.03-6.34).

The authors concluded that there is a duration related effect relationship between PI use and MI, with a higher MI incidence rate among men exposed to PI for 18 months or more.

Mary-Krause M, Cotte L, Partisani M, Simon A, Costagliola D. Impact of treatment with protease inhibitor (PI) on myocardial infarction (MI) occurrence in HIV infected men. . 8th Conference on Retroviruses and Opportunistic Infections 2001; Abstract 80-657.

Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV infected men. AIDS 2003; in press.

1B. Currier and colleagues examined the relationship between antiretroviral treatment (ART) exposure and CHD incidence.

The investigators examined the Medi-Cal claims (from July 1995 to June 2000) for CHD incidence rates in HIV-infected individuals receiving and not receiving ART. HIV was defined if claims used ICD-9 codes 042, V08 or 079.5. CHD was identified as ICD-9 codes 410, 411, 413, 414.0 and 429.2. Subjects without an HIV diagnosis and <30 days of ART, or evidence of cocaine use were excluded. Subjects were ART-exposed if they had at least one prescription for ART. Subjects were free of CHD for 1 year prior to inclusion. The relative risk of CHD by ART use was determined using multivariate log-linear regression analysis. The evaluation was controlled for the comorbid covariates of diabetes, hyperlipidemia, kidney disease and hypertension. Duration and ART class were not assessed.

The investigators identified 28 513 individuals with HIV. The incidence of CHD (unadjusted for co-morbidities) per 100 patient years by age category was: 1.08 (in age group 18-33 years), 1.74 (in age group 34-49 years), 3.13 (in age group 50-65 years) and 4.90 (for above 66 years). For individuals receiving ART compared with those not receiving ART, the relative risk of CHD, controlling for co-morbidity covariates, was

2.06 (18-33 years) ($P < 0.001$), 1.08 (34-49 years) ($P > 0.30$), 0.79 (50-65 years) ($P > 0.05$), and 1.15 (above 66 year) ($P > 0.60$). Co-morbidities, especially hyperlipidemia and hypertension, were associated with a significant increase in the relative risk for CHD across all age groups.

The authors concluded that ART was associated with an increased risk of CHD in young (18-33 years) but not older individuals with HIV infection adjusting for co-morbidities. Co-morbid conditions associated with CHD in the general population were important predictors of CHD in this population.

Currier J, Taylor A, Boyd F, Kawabata H, Maa J, Dezii C, Burtcel B, Hodder S. Coronary heart disease in HIV-infected individuals: associations with antiretroviral therapy. 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV 2002; Abstract 54.

2. The Data collection on Adverse Events of anti-HIV Drugs (D:A:D) study is a multinational, tri-continental collaboration between ongoing HIV cohort studies. D:A:D was initiated in 1999 and will continue at least until the first quarter of 2005. The primary objectives of this study are to detect incidence of myocardial infarction (MI), and identify whether exposure time to combination antiretroviral therapy (CART) is independently associated with the risk of developing MI.

The analysis was based on prospective follow up of patients (from the eleven participating cohorts) during their visits to outpatient clinics scheduled as a part of their regular medical care. Standardized data collection forms providing information from physical examination, patient interview and patient case notes were completed every eight months from the time of enrollment. Data on HIV disease, risk factors for MI and incidence of MI were extracted from these forms, standardized and merged into a central data base. The data analysis was based on an incidence rate approach and the relative rate (RR with 95% confidence interval) from Poisson regression models was reported.

81% of the total study population (23,468 patients) had been exposed to at least one antiretroviral drug and 75% to CART, with a median cumulative exposure of 1.9 years (0-3.2).

A total of 126 patients developed a MI; 36 (28%) of these events were fatal. The incidence of MI increased with longer exposure to CART, with a RR of 1.26 (1.12-1.41) per year of exposure. Other independent predictors for MI were older age, smoking (current or history of), history of cardiovascular disease, male sex, total cholesterol level and a diagnosis of diabetes mellitus. Other factors which were included in the model(s) but not significantly associated with increased risk were family history of cardiovascular disease, race, body mass index, HIV infection risk group and cohort. Lipodystrophy was associated with a reduced RR. Overall, exposure to CART was associated with a 26% relative increase in the rate of MI per year of exposure over the first 4-6 years of use. Additional analyses in progress include the association of risk for MI with stage of disease, time since infection, CD4 cell counts, and HIV-1 RNA levels.

The authors concluded that the treatment associated risk for MI needs to be balanced against the marked effectiveness of CART in preventing HIV-related complications. The absolute risk for MI remains low and the current results should not lead to withholding of CART when appropriately indicated.

Friis-Møller N, Weber R, Reiss P, Thiebaut R, Kirk O, D'Arminio Monforte A, Pradier C, Morfeld L, Calvo G, Law M, El-Sadr W, Wit SD, Sabin CA, Phillips AN, Lundgren JD. Cardiovascular Disease Risk Factors in HIV Patients – Association with Antiretroviral Therapy. Results from the D:A:D Study. AIDS 2003; In Press.

Friis-Møller N, Weber R, D'Arminio Monforte A, El-Sadr W, et al. Exposure to HAART is associated with an increased risk of myocardial infarction: the D:A:D study. 10th Conference on Retroviruses and Opportunistic Infection 2003; Abstract 130.

3. Coplan and colleagues conducted a retrospective analysis of 30 Phase II and Phase III randomized clinical trials involving a total 10986 HIV-positive patients. The aim of the

study was to assess the incidence of myocardial infarction (MI) among HIV patients receiving protease inhibitors (PI) plus or minus nucleoside reverse transcriptase inhibitors (NRTIs) compared to NRTIs only. The studies involved the first four licensed PI drugs: indinavir, nelfinavir, ritonavir, and the hard-gel formulation of saquinavir. Person-years (PY) of follow up were calculated from the treatment initiation to the diagnosis of MI, or to the end of the studies for PI containing regimens or to the end of the randomized phases for NRTI-only therapy. In most studies, the participants were offered combination therapy with a PI plus NRTI in extension phases after ending the blinded phase. Only MIs occurring during the randomized phases were attributed to NRTI-only therapy. A MI that developed after starting PI therapy during an extension phase was counted as a PI case.

A total of 7,951 patients received PI therapy for an average duration of one year and there were a total of 8,789 PY of exposure to the PI containing therapy including the randomized and the randomized plus extension phases. 10 MIs (1.31/1000 PY) were documented in the randomized phases and 19 MIs (1.63/1000 PY) in the randomized plus extension phases. The overall stratified relative risk [95% CI] of MI for PI-containing regimen vs NRTI only regimens was not significantly increased 1.69 [0.54, 7.48]; the absolute difference [95% CI] in MI incidence between PI-containing and NRTI-only groups was +0.77 [-0.71, 2.26] cases per 1000 PY.

The authors concluded that compared to the NRTI - only therapy, patients receiving PI-containing regimens for an average of one year did not have significantly more MIs. However, based on the upper limit of the 95% CI, there maybe up to 2.3 additional cases of MIs per 1000 PY. Studies with longer duration of PI therapy are needed to assess the later increase in MI.

Coplan PM, Nikas A, Japour A, Cormier K, Maradit-Kremers H, Lewis R, Xu Y, DiNubile MJ. The Incidence of Myocardial Infarction in Randomized Clinical Trials of Protease Inhibitor-Based Antiretroviral Therapy: An Analysis of Four Different Protease Inhibitors. AIDS Research and Human Retroviruses 2003; in press (June 2003).

4. Illoeje and colleagues analyzed the association between PI exposure and subsequent cardiovascular disease (CVD) and coronary heart disease (CHD) events in a retrospective analysis of a prospectively collected database of HIV-1 positive patients from 8 US clinical sites (HIV InsightTM, a combination of the CDC's HIV Outpatient Study with additional physician offices and clinics funded by Cerner, IncTM). The patients were followed between January 1996 and June 2002 for the first CVD event (acute myocardial infarction (AMI), angina, coronary artery disease, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG), cerebrovascular accident (CVA), transient ischemic attack (TIA), and peripheral vascular disease (PVD) or censored at end of study follow-up. Coronary heart disease was defined as any of the following: AMI, angina pectoris, CAD, PTCA and CABG. Covariates included age, gender, race, weight, PI exposure, hyperlipidemia, CVD, diabetes mellitus, hypertension, smoking status, IV drug use (IVDU), and cocaine use.

A total of 6,711 patients were studied with a median follow-up of 2.8 yrs. 77.3% were exposed to PI treatment. The cardiovascular risk factor distribution was as follows: current smokers 36.6%, past smokers 13.9%, cocaine use 1.9%, hypertension 5.2%, diabetes mellitus 1.1%, pre-existing CVD 0.1%, and pre-existing hyperlipidemia 6.5%. The CVD-event rate was found to be 1.64% for patients in the PI group and 0.52% for non-PI patients. Unadjusted hazard ratio (HR) for PI exposure for all CVD events was 2.1 [95% CI 1.03-4.4]; the adjusted HR 1.99 [95% CI 0.95-4.14], $p=0.07$. In a model based on CHD events only, the unadjusted HR was 2.3 [95% CI 0.97-5.18]; the adjusted HR for PI exposure was 2.13 [95% CI 0.91, 4.95], $p=0.08$. In a model where PI exposure was defined as greater than 60 days, the adjusted HR for PI was 2.10 [95% CI 1.00, 4.40], $p=0.05$. In patients aged 45 to 65 years, the HR for CVD was 5.8 [95% CI 1.4-24.3] and for CHD 4.3 [95% CI 1.0 – 17.9]

The authors concluded that PI exposure doubled the risk of developing both CVD and CHD events in this analysis, and the risk is more evident in middle-aged patients. The

absolute event rates remain low; however, prolonged exposure to PI may lead to greater CVD event rates as this population continues to age.

Iloeje U, Yuan Y, Tuomari A, L'Italien G, Mauskopf J, Moore R. Protease Inhibitors May Increase Risk of Cardiovascular Disease in HIV-infected Patients. 10th Conference on Retroviruses and Opportunistic Infections 2003; Abstract 746.

5. Holmberg and colleagues analyzed patients from the HIV Outpatient Study (HOPS) to investigate whether the use of protease inhibitors (PI) was associated with an increased frequency myocardial infarction (MI). HOPS is an ongoing observational cohort in which patients have been continuously recruited and followed up since 1992. The authors identified 5672 patients infected with HIV-1 and enrolled in HOPS between the year 1993 and 2002. Two groups were formed with 3247 patients in the PI group and 2425 patients in the non-PI group.

19 patients in the PI group had a myocardial infarction as compared to 2 in the non-PI group. The adjusted odds ratio (OR) [95% CI] for use of PI was 4.92 [1.3, 32.3]. Left-censored Cox proportional hazard analysis also showed a strong relation between incidence of MI and PI use, with an unadjusted hazards ratio [95% CI] of 8.06 [1.14, 56.8]. In an adjusted model, also controlling for hypertension, smoking, diabetes mellitus, age, sex and evidence of dyslipidaemia, the hazard ratio was 6.51 [0.89, 47.8]. There were also 15 cases of angina, 11 among the 3247 individuals taking protease inhibitors and 4 among the 2425 patients not taking protease inhibitors.

The authors concluded that, although infrequent, use of protease inhibitors is associated with increased risk of myocardial infarction and perhaps angina, in patients with HIV-1. *Holmberg SD, Moorman AC, Williamson JM, Tong TC, Ward DJ, Wood KC, Greenberg AE, Janssen RS, HIV Outpatient Study (HOPS) investigators. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. The Lancet 2002; 360:1747-1748.*
Holmberg SD, Moorman AC, Ton TC, Ward DJ, Wood KC, Greenberg AE, Janssen RS. Protease Inhibitor drug use and myocardial infarctions in ambulatory HIV-infected

persons. 9th Conference on Retroviruses and Opportunistic Infections 2002; Abstract 698-T.

6. Klein and colleagues are analyzing the effect of HIV positivity, and the use of protease inhibitors (PI) on the incidence of coronary heart disease (CHD) in male HIV-1 positive patients and male HIV-1 negative controls using the Kaiser Permanente Northern California database. Currently, the study is in the seventh year of follow-up (6.5 years on Dec 31st 2002). All HIV-1 positive patients in the database were followed; 10% of age matched presumed HIV-1 negative male member patients served as the control group. The investigators are also tracking traditional CHD risk factors in both populations.

CHD and MI events were collected based on hospital admissions with a primary discharge diagnosis of CHD (ICD 9 codes 410-414). Results are expressed as event rates per 1000 PY of follow-up.

Based on the latest analysis (2003), a total of 4,408 HIV-1 positive cases, contributing to 17,716 patient ears (PY) of follow-up have been included. 39,425 HIV negative controls have contributed 211,221 PY of follow-up. The results indicate a higher age adjusted CHD rates in HIV positive cases vs controls (6.6 [95% CI 5.0,8.1] vs 3.3 [95% CI 3.0, 3.5], $p < 0.0001$). Similarly, a significant difference in MI event rates were reported (3.8 [95% CI 2.7,5.0] vs 2.6 [95% CI 2.4,2.8] $p = 0.03$). There was no clear linear relationship between event rate and duration of PI exposure, although those with greater than 1 year exposure had higher event rates than those with less than one year exposure (p value for trend not provided). Annual counts and crude rates of CHD/MI events among all active HIV-1 positive members were found to be variable and somewhat lower in the years prior to the introduction of PIs in 1996. Among HIV positive cases, CHD and MI event rates in the PI and non-PI groups were found to be similar.

The authors concluded that there is no significant effect of PI use on CHD or MI hospitalization rates among HIV positive men. However, CHD rates continue to be higher among HIV-1 positive vs HIV-1 negative men in the HAART era. The authors plan to

continue the follow-up to further study the CHD and MI event rates in the pre- and post HAART era.

Klein D, Hurley L, Quesenberry D, Sidney S. Hospitalizations for coronary heart disease and myocardial infarction among men with HIV-1 infection: Additional Follow-up. 10th Conference on Retroviruses and Opportunistic Infections 2003; Abstract 747.

Klein D and Hurley L. Hospitalization for coronary heart disease and myocardial infarction among HIV positive patients in the HAART Era. 9th Conference on Retroviruses and Opportunistic Infections 2002; Abstract 696-T91

7. Moore and colleagues assessed the incidence of coronary heart disease (CHD -- MI or unstable angina) and cerebrovascular disease (CVD -- ischemic stroke or TIA) in a large US clinical cohort. A comprehensive database with demographic, clinical and therapeutic data collected longitudinally since 1990 was available.

The authors designed a nested case control study to assess factors associated with CVD and CHD. Non-CHD and non-CVD patients were randomly selected from the overall cohort; 5 controls per case were identified and matched on cohort enrollment date and duration of follow-up. Mantel-Haenszel chi-square and conditional logistic regression analyses were used to assess risk factors.

A total of 2,671 patients were followed for 7,330 person-years (PY). After January 1, 1996, 43 CHD and 37 CVD events were observed, for an incidence rate of 5.9 events/1000 PY and 5.0 events/1000 PY, respectively. Factors associated ($p < 0.05$) with having a CHD or CVD event included age (mean 46 in cases; 41 in controls), cholesterol mean 186g/dl cases, 156g/dl in controls, prior diabetes (15% cases, 7% controls), prior hypertension (43% cases, 17% controls) and CD4 count (mean 351 cells/mm³ cases, 251 cells/mm³ controls). Not associated with risk were: race, injecting drug use, or HIV-1 RNA levels. Cases were significantly more likely than controls to receive protease inhibitors (PI) (59% vs 43%) and d4T (63% cases, 43% controls). The risk factors were similar for CHD and CVD when assessed separately. In a multivariate model, age (RR

1.18), hypertension (RR=3.18), total cholesterol (RR=1.4) and d4T use (RR=2.51) were independently associated with CHD/CVD (these data as reported on www.natap.org).

The authors concluded that compared to national CHD and CVD rates, the incidence rates of CHD and CVD in the sample cohort were approximately 2–3 times higher than expected and are associated with traditional cardiovascular risk factors as well as with antiretroviral drug use. Based on the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, the age-sex-race population rates of CHD and CVD would be expected to be 2/1000 PY and 3/1000 PY, respectively.

Moore RD, Keruly JC, Lucas G. Increasing Incidence of Cardiovascular Disease in HIV-infected Persons in Care. 10th Conference on Retroviruses and Opportunistic Infections 2003; Abstract No. 132

8. Gardner and colleagues assessed hospitalization rates in HIV-1 positive and high risk HIV-1 negative women from the HIV Epidemiology Research Study (HERS), a prospective multicenter US cohort. 885 HIV-1 positive and 426 high risk HIV-1 negative women were followed for a mean of 4.9 years. Five condition-specific outcome variables comprised the outcome variables. The diagnoses were abstracted from inpatient medical records.

Crude hospitalization rates were calculated by dividing the number of events by total person-time of observation. Hospitalization rate ratios and p-values were calculated using Poisson regression modeling. Empirical rates for the five conditions (non-acute renal, cardiovascular, diabetes mellitus, hepatic and AIDS defining) were 4.8, 9.5, 2.9, 5.0 and 9.2, respectively. Empirical rates for CVD increased from 7.0 in 1994 to 11.1 in 2000. The Poisson regression adjusted condition-specific rate ratios for CVD, with 1994 for a reference, were 1.3 (p=0.28), 1.7 (p=0.06), 1.8 (p=0.02), 2.1 (p<0.01) and 2.0 (p=0.02) for 1995, 1996, 1997, 1998 and 1999/2000, respectively.

Hospitalization rates for CVD approximately doubled in the period between 1994 and 2000. In comparison, hospitalization for hepatic conditions increased by 10-fold.

Hospitalization for non-acute renal and diabetes conditions remained constant. The ratio of AIDS-defining to the other four conditions decreased from 1:2 in 1994 to 1:5 in 2000. The authors conclude that close monitoring for non-AIDS risk factors for morbidity is warranted.

Gardner L, Holmberg S, Tashima K, Rompalo A, Schuman P, Klein RS, Greenberg A. Recent trends in renal, cardiovascular, diabetic and hepatic condition-specific hospitalization rates in a cohort of HIV-infected women. 10th Conference on Retroviruses and Opportunistic Infections 2003; Abstract 765

9. Savès and colleagues estimated the risk for coronary heart disease (CHD) events in HIV-infected patients from the French APROCO cohort receiving protease inhibitors (PI). The distribution of CHD risk factors and estimates of CHD risk were compared to and sex and age-matched sample from the general population (WHO MONICA study). Both populations were restricted to ages 35-44 years.

The authors compared 223 HIV positive men and 51 HIV positive women on PI containing treatment to 1038 men (49.2% female) from a sample of the general population. All comparisons were adjusted for body mass index (BMI) since it was lower in the HIV-positive populations.

In HIV positive men, prevalence of hypertension was lower (5.2% vs 12.8%, $p < 0.001$), whereas the prevalence of smoking was higher (55.6 vs 32.7%, $p < 0.0001$). Mean total cholesterol and LDL-cholesterol were not significantly different in the 2 groups whereas mean HDL-cholesterol was lower (0.44 vs 0.50 g/L, $p < 0.0001$), and mean triglyceridemia was higher (1.90 vs 1.27 g/L, $p < 0.0001$). Based on the predictive French PRIME model, (including smoking status, total and HDL cholesterol and prevalence of hypertension as variables), the RR of CHD risk was 1.2 in HIV positive men on PI treatment compared to the normal population ($p < 0.0001$). Similar trends were observed in the female population, with the only exception of higher mean total cholesterol in HIV positive women. Using the Anderson model (including smoking, hypertension, total and HDL cholesterol and diabetes), the RR was 1.39 $p < 0.0001$. The risk estimation for women was 1.59 and 2.17

($p < 10^{-6}$ for both) in women, using the Prime and the Anderson models. The estimated attributable risk due to smoking was 65% and 29% for men and women, respectively.

The authors concluded that in HIV positive individuals have a moderate yet significant increased risk for CHD associated with a particular atherogenic profile. This increased risk may have significant implications. A long-term follow-up is needed to determine whether the observed CHD risk increases over time. A regular assessment of CHD risk factors should be included in the management of the HIV patients, at initiation of HAART and thereafter. Interventions to reduce potential modifiable risk factors (reduction of smoking, diet) as well as lipid lowering agents should be evaluated.

Leport C, Saves M, Ducimetier Pe, Moal GL, Amouyel P, Arveiler D, Ferrieres J, Reynes J, Duran S, Chêne G. Coronary heart disease risk (CHD) in French HIV-infected men started on a protease inhibitor (PI)-containing regimen compared to the general population. 9th Conference on Retroviruses and Opportunistic Infections 2002; Abstract 697-T.

Savès M, Chêne G, Ducimetière P, Leport C, Moal GL, Amouyel P, Arveiler D, Ruidavets JB, Reynes J, Bingham A, Raffi F, the French WHO MONICA Project, the APROCO (ANRS EP11) Study Group. Coronary Heart Disease Risk Factors in Patients treated for Human Immunodeficiency Virus infection Compared to the General Population. Clinical Infectious Diseases 2003; In press.

9A. The SMART study recruits patients with CD4 cell count > 350 cells/mm³ from U.S. and Australian centers and compares drug conservation (via episodic use of HAART) versus viral suppression strategy (via continuous use of HAART), on HIV disease progression, adverse events, and other complications. El-Sadr and colleagues assessed the CHD risk factors among 649 men and women enrolled in the SMART study. Baseline

data are currently available and were used to estimate the 10 year risk for CHD in men and women. This study will continue to follow up patients on treatment with the objective of analyzing the effect on risk profiles according to specific treatment strategies.

The investigators evaluated the baseline characteristics, laboratory assays and EKGs and calculated the ten year risk of CHD using Framingham equations based on smoking, LDL and HDL cholesterol, blood pressure (BP), and diabetes history. BP therapy was used as indicative of stage 1 hypertension and percent patients at high or very high risk (> 20%) for CHD was determined. Metabolic syndrome (condition with high CHD risk) defined as having any 3 of: triglycerides > 150 mg/d, BMI > 30, BP lowering therapy, diabetes treatment, or HDL < 40 (< 50 for women), was also evaluated.

The study population had 24.9% women and the mean age of the population was 44.8 years. There were 38% African American, 16.2% Latino, and 15.3% with history of injection drug use. Majority (97.4%) were HAART experienced with 48.2% on protease inhibitor and 36.5% on NNRTI-containing regimens. Median baseline and nadir CD4 cell counts were 598 cells/mm³ and 258 cells/mm³, 69% had viral load < 400 copies, and 28% had prior AIDS diagnosis.

The CHD risk factors were found in significant number of men and women. 42.5% men and 39.5 % women had a history of smoking; 7.2% men and 7.4% women had diabetes; 50% men and 53.6% women had HDL <40mg (<50mg in women) (p<0.43); 21.6% men and 23.5% women were on blood pressure therapy (p<0.5); triglyceride level greater than 150 mg/dl was found in 68.1% men and 54.3% women (p<0.02); 13.7% men and 36.3% women had BMI> 30 (p< 0.01); 2.5 % men and 4.9% women had a MI or stroke history (p<0.3); major EKG abnormalities were found in 8.7% men and 10.7% women (p<0.92); metabolic syndrome was evident in 17.7% men and 24.7% women (p<0.14).

The Framingham high or very high risk of CHD in 10 years was found to be in 7.8% men and 0.6% women (p< 0.01). Overall, MI/stroke, major EKG, metabolic syndrome, or

high/very high CHD 10 year risk was found to be in 26.1% men and 31.5% women (p<0.32).

The investigators concluded that a significant number of men and women in SMART are at high risk of CHD based on Framingham risk, history of MI and stroke, prevalence of metabolic syndrome, and major EKG abnormalities.

El-Sadr W, Neaton J, Neuhaus J, Gordin F. Comparison of Risk Factors for Coronary Heart Disease among Men and Women Enrolled in the SMART Study (CPCRA 065). 10th Conference on Retroviruses and Opportunistic Infections 2002; Abstract 745

10. Wall and colleagues analyzed the risk of developing ischemic cardiovascular heart disease (CHD) in HIV infected persons taking different antiretroviral regimens.

The authors evaluated a convenience sample of 111/125 HIV-positive and 25/49 HIV-negative patients (controls) attending a University based Infectious Disease Clinic in United States. Data on medical history of coronary artery disease, including family history of premature heart disease, hypertension, diabetes mellitus and cigarette smoking risk was collected, to evaluate the cardiovascular risk of these subjects. Fasting blood samples from HIV-infected persons, treatment-naïve HIV-infected persons and HIV negative controls were collected for a cross-sectional analysis. These samples were tested for cholesterol, LDL, triglycerides (TG), HDL, lipoprotein, homocysteine, and fibrinogen.

The cardiovascular risk was estimated using the Framingham Point Scoring System that provided a 10- year risk percentage. This system used age, total cholesterol, smoking status, high density lipoprotein and systolic blood pressure to calculate the cardiovascular risk percentage.

The median risk for progression of CHD in 10 years was 4% (range, 1% to 30%) in the HIV-infected cohort and 1% (range, 1 to 20%) in the HIV negative cohort. In the HIV-

infected cohort, the median risk for progression of CHD in 10 years was 6% (range, 1%-30%) in PI-treated subjects and 3% (range, <1%-25%) in those not treated with PIs. Almost 22% of the HIV positive cohort had a greater than 10% risk of progression of CHD.

The authors concluded that major risk factors for ischemic cardiovascular disease are common in persons with HIV infection. The modifiable (cigarette smoking and hypertension) should be aggressively treated. The risk for ischemic cardiovascular disease appears to be significantly higher in patients with HIV infection, particularly in those taking PI. Larger, prospective longitudinal studies are needed to determine changes in ischemic heart disease risk overtime and whether specific regimens present a greater risk.

Wall JL, David M, Fichtenbaum CJ. The Risk of Ischemic Cardiovascular Disease Is Significant in Persons with HIV Infection. 9th Conference on Retroviruses and Opportunistic Infections 2002; Abstract 695-T

10A. Hadigan and colleagues calculated to 10-year coronary heart disease (CHD) risk in 91 HIV-infected patients with self reported and confirmed lipodystrophy, compared to sex, age and body mass index (BMI) matched control subjects selected from the Framingham Offspring Study (1:3 cases:controls, n=273 for controls). In addition, they looked at 30 HIV positive subjects with no sign of lipodystrophy compared with 90 age and BMI matched controls. Patients had to be between 18 and 60 years of age. Exclusion criteria were changes in antiretroviral medication within the prior 6 weeks, history of diabetes mellitus or previous treatment with anti-diabetic agent, reported use of testosterone, estrogen or growth hormone or other steroids within the previous 6 months, and active alcohol or substance abuse. The estimated 10 year risk was calculated using the standard Framingham risk equation, which incorporates sex specific risk calculations based on age, total and HDL cholesterol, systolic and diastolic blood pressure, presence of diabetes (fasting glucose level of >140 mg/dL) and smoking status and estimates the 10-year risk for CHD events (angina pectoris, myocardial infarction, and death due to CHD). Looking at total populations, patients with HIV and lipodystrophy had a

significantly higher estimated 10-year risk (7.4 ± 0.6 vs 5.3 ± 0.3) and a significantly higher proportion of patients with a $\geq 10\%$ risk (29.1 vs 12.8, $p=.001$). In an analysis stratified by sex, the increased risk was 9.0 ± 0.7 vs 6.5 ± 0.3 ($p=0.001$) for men, and 3.4 ± 0.8 vs 2.2 ± 0.3 for women ($p=0.19$). 38.7% of men HIV positive men with lipodystrophy (compared to 17.4% of controls) had a risk $>10\%$ ($p=0.001$); for women, the percentages were 4.2 and 1.3 ($p=0.37$). The authors noted that women were substantially younger than the men in the study (mean ages of 39.5 ± 1.6 and 40.6 ± 0.8 for women compared to 44.6 ± 1.0 and 45.0 ± 0.5 for men). The investigators also looked at the effect of lipodystrophy patterns on risk estimate. Patients with lipoatrophy had a significantly higher risk (9.2 ± 1.8) than patients with lipohypertrophy (4.3 ± 0.7) or mixed phenotype (7.6 ± 0.8). There were no significant differences in risk when comparing HIV-positive subjects without lipodystrophy to matched controls. Patients had received a mean of 4.7 ± 0.3 years of antiretroviral therapy; there was no difference in estimated risk according to whether they were currently receiving protease inhibitors or not.

In a subanalysis which controlled for waist to hip ratio (WHR) in addition to sex, age and BMI, there was not difference between HIV positive and control populations.

CHD risk is increased in HIV infected individuals with lipodystrophy; however sex and pattern of fat redistribution appear to be significant components of determining risk.

Hadigan C, Meigs JB, Corcoran C, Rietschel P, Piecuch S, Basgoz N, Davis B, Sax P, Stanley T, Wilson PWF, D'Agostino RB, Grinspoon S. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infections and lipodystrophy. Clin Inf Diseases 2003;32:130-139.

10B. Grover and colleagues estimated the CVD risk and changes in life expectancy (LE) associated with changes in median blood lipid levels after 32 weeks of antiretroviral therapy. The investigators used data from a randomized trial that compared effect of nelfinavir and atazanavir on blood lipid levels.

The risk of long-term CVD events and overall LE were estimated using a validated and published Cardiovascular Life Expectancy Model. The investigators validated the forecasted LE of adults at specified ages using risk factor data from the Third National Health and Nutrition Examination Survey (NHANES III) study, and compared the results to US Life Tables. They assumed the annual rate of HIV-related mortality of 2.9% (95% C.I. 1.9% - 3.9%) from cohort data.

The results were projected for hypothetical groups of patients, low risk men and women (non-smokers with BP 120/80) and for very high risk men and women (diabetic smokers with BP 160/90).

Baseline characteristics and blood lipids were similar between atazanavir and nelfinavir groups. However the changes in total and LDL cholesterol (+24%, +28%) observed among 91 nelfinavir patients were significantly greater ($p < 0.05$) than those among 178 atazanavir patients (+4%, +1%). Predicted LE, based on the risk factors demonstrated in NHANES III, reasonably well approximated the LE from US Life Tables. The CVD risk, estimated using the Cardiovascular Life Expectancy Model, was found to be 10%-31% lower among atazanavir than among nelfinavir patients. Among low risk patients, treatment with atazanavir increased LE from 0.06 to 0.22 years (95% C.I. 0.05 to 0.29). The presence of additional risk factors (smoking, hypertension, diabetes) increased the potential advantage of atazanavir vs nelfinavir to an increased LE from 0.22 to 1.18 years (95% C.I. 0.20 to 1.53).

The investigators concluded that nelfinavir treatment was associated with a significant increase in blood lipid levels and CVD risk. The absence of similar adverse lipid changes with atazanavir could result in a substantially lower incidence of future CVD events and increased LE even after adjustment for HIV related mortality. The presence of additional CVD risk factors, common among patients receiving HAART, would further increase the potential advantage of atazanavir over nelfinavir.

Grover SA, Zowall H, Brewer C, Gilmore N, Mukherjee J. Highly active antiretroviral therapy (HAART) for HIV infections and dyslipidemia: Estimating the impact of nelfinavir and atazanavir on cardiovascular (CVD) risk and life expectancy (LE) after

adjustment for HIV related mortality. 4th Scientific Forum on Quality of Care and Outcomes Research in CVD and stroke. 2002

11. David, Hornung and Fichtenbaum investigated the factors associated with documented ischemic CVD in HIV+ patients. Sixteen proven CVD events were recorded between April 1999 and April 2000; 32 sex and age matched non CVD controls were randomly selected from the patient population. Documentation of CVD in cases included angiography, echocardiography, exercise stress testing, or myocardial infarction. Case patients had a higher number of traditional CVD risk factors than controls (3 vs 1, $p < 0.001$). Univariate analyses pointed to the following risk factors: smoking, hypertension, elevated cholesterol, family history and CD4 cell counts < 200 cells/mm³. The significance of low CD4 cell counts was upheld in multivariate models. Case patients also had a longer duration of NRTI use.

The authors concluded that CVD occurring in HIV+ patients was most closely associated with traditional risk factors rather than PI use. In addition, lower CD4 cell counts may be a marker for CVD risk.

David MH, Hornung R, Fichtenbaum JC. Ischemic cardiovascular disease in persons with Human Immunodeficiency Virus infection. Clin Inf Dis 2003;34:98-102

II Studies using diagnostic markers for CVD

12. Currier and colleagues examined carotid intima media thickness (IMT) as a measure of sub-clinical atherosclerosis among patients with HIV infection. The investigators conducted a prospective, longitudinal, matched cohort study in which individual subjects from three groups were matched by age, race, smoking status and blood pressure. At present, a total of 134 subjects in 45 triads have been enrolled. The three groups were: HIV positive subjects who had been on a protease inhibitor (PI) for more than two years, HIV positive subjects without PI use and HIV negative controls. Exclusion criteria included known coronary artery disease (CAD), diabetes mellitus, family history of CAD, uncontrolled hypertension or a body mass index > 30. Standardized IMT images were sent to a central reading site for measurement. Carotid IMT was compared within the HIV positive groups (I and II) and between the HIV positive and negative groups in a matched analysis. The study had 80% power to detect a clinically relevant difference of 0.1mm in carotid IMT.

An analysis of baseline results is available at present. Subjects in the PI treated group had higher levels of total cholesterol and triglycerides. However there were no statistically significant differences in carotid thickness between the HIV positive groups or between the HIV positive and HIV negative groups. The factors associated with increased IMT included HDL (the lower the HDL the thicker the carotid and this was further augmented in the presence of elevated triglycerides), and increased body mass index.

The authors concluded that there were no clinically relevant differences in baseline IMT between HIV-1 infected subjects with over 2 years of PI exposure, HIV-1 subjects not exposed to PI, and HIV-uninfected controls. Longitudinal follow-up of this matched cohort is ongoing to assess rates of progression in carotid IMT over time.

Currier J, Kendall M, Henry K, Torriani F, Storey S, Shikuma C, Mickelberg K, Alston B, Basar M, Zackin R, Hodis H. Carotid intima-media thickness in HIV-infected and uninfected adults. 10th Conference on Retroviruses and Opportunistic Infections 2002; Abstract 131.

13. Hsue and colleagues identified risk factors for carotid artery intima media thickness (IMT) and progression of IMT in HIV-1 infected patients on treatment. At baseline, the median duration of PI treatment was 4 years; patients were followed over 1 year after enrollment.

The investigators measured lipid and lipoprotein levels, inflammatory markers, and carotid artery IMT by B-mode ultrasound and assessed CAD risk factors, HIV disease characteristics, fat distribution, and anthropometry. The primary endpoint was the mean maximal IMT of 12 pre-selected segments in the carotid arteries. Multivariable linear regression was used to identify independent predictors of baseline IMT and IMT progression after 1 year.

A total of 106 HIV positive subjects, with duration of HIV infection of 11 +/- 5 years were studied. The mean IMT was found to be 0.90 ± 0.27 mm -- higher than expected from a large population study of similarly aged individuals. Predictors of increased IMT included age, LDL cholesterol, hypertension and a nadir CD4 cell count < 200 cells/mm³. IMT progression over 1 year was measured in a subset of 21 patients, 41% of which had hypertension. The mean rate of progression was 0.1 ± 0.1 mm/yr, which was greatly accelerated compared to 0.01 mm/yr from published reports of non-HIV infected populations. In a multivariate model, age and duration of PI use were predictors for IMT progression.

The authors concluded that among HIV-infected patients on PI treatment, carotid IMT was independently associated with classic coronary risk factors (age, LDL cholesterol, and hypertension). Both immunodeficiency and traditional risk factors contribute to atherosclerosis in HIV-infected individuals. Progression of IMT in the subset with 1 year follow-up was accelerated by tenfold compared to non-HIV infected populations, and was associated with age and duration of PI use.

Hsue P, Lo J, Franklin A, Bolger AF, Deeks SG, Waters DD. Increased atherosclerotic progression in patients with HIV: The role of traditional and immunologic risk factors. 10th Conference on Retroviruses and Opportunistic Infections 2003; Abstract 1391b.

14. Seminari and colleagues examined the relation between the use of protease inhibitors (PI) in HIV treatment and lipid disorders leading to premature atherosclerosis. The authors performed a cross-sectional analysis to evaluate the intima media thickness (IMT) of the carotid arteries as a marker of cardiovascular risk among HIV patients treated with PI containing regimens compared to PI-naïve and HIV-1 negative individuals.

A total of 59 subjects were enrolled for this study and were divided into 3 groups. HIV positive patients treated with PI combination regimen for at least 18 months (n=28) were placed in the first group. Asymptomatic HIV positive patients never exposed to antiretroviral therapy (naïve patient group) and HIV negative subjects formed the two control groups consisting of 15 and 16 patients respectively. The subjects were matched for age, risk factors for HIV infection, cigarette smoke use and CD4+ cell count.

Hematological and carotid ultrasound examinations were performed to determine the plasma lipid levels and carotid IMT in the study population.

PI-treated patients had higher triglyceride, HDL and ApoB levels than controls. Carotid IMT was significantly increased in PI-treated patients compared to naïve or HIV-negative subjects, with means reported to be 0.63, 0.45 and 0.5 mm, $p < 0.05$. A correlation between cholesterol HDL, triglyceride and ApoB levels and IMT was observed among the entire cohort.

The authors concluded that plasma lipid alterations were associated with an increased IMT and intima media thickening was more pronounced in PI-treated patients than in the two control groups. They recommended a periodical evaluation of blood lipid profile and the use of lipid lowering agents in HIV treatments involving PIs. They also emphasized the need for the physicians to address concurrent risk factors for atherosclerosis like smoking, hypertension, obesity and sedentary life style.

Seminari E, Pan A, Voltini G, Carnevale G, Maserati R, Minoli L, Meneghetti G, Tinelli C, Testa S. Assessment of atherosclerosis using carotid ultrasonography in a cohort of HIV-positive patients treated with protease inhibitors. Atherosclerosis 2002;162:433-438.

15. Chironi and colleagues compared carotid intima media thickness (IMT) in heavily pretreated patients (cases) and two control groups, without (control group 1) or with (control group 2) blood lipid and glucose profiles similar to the patients. IMT was measured in a plaque free far wall segment, calculated as the average of at least 100 measurements along the length of vessel explored. Cases (n=36) were selected consecutively from the pretreated patient population based on presence of at least one cardiovascular risk factor. The two control groups (age, sex and smoking status matched) were selected from two large pools of subjects. Patients had been HIV infected for a mean of 11 years, and treated for a mean of 73 (± 34) months. ITM was greater in cases than control group 1 ($p < 0.05$). The difference remained significant after adjusting for age, sex, BMI, waist circumference, systolic blood pressure, current smoking, prior CVD, but lost significance after adjusting for blood glucose levels, triglyceride levels or total-to-HDL cholesterol ratio. There was no significant difference between IMT of cases and control group 2. IMT was positively associated with age (cases and control 1), and with waist circumference and total-to-HDL cholesterol ratio (cases only).

Increased IMT in HIV disease can be attributed to lipid and glucose disturbances. No associations with use of antiviral treatment and HIV infection parameters were found, but the study was not designed to detect these.

Chironi G, Escaut L, Garepy J, Cogny A, Monsuez JJ, Levenson J, Simon A, Vittecoq D. Carotid intima media thickness in heavily pretreated HIV-infected patients. JAIDS 2003;32:490-493.

16. Mercie and colleagues evaluated CVD risk factors in HIV-1 infected patients using carotid intima media thickness measurements (IMT). 423 patients from a multicenter

prospective cohort study were evaluated. Information was collected on lipodystrophy clinical manifestations, age, sex, body mass index (BMI), smoking habits, alcohol intake, systolic blood pressure, HIV transmission category, AIDS stage, HAART (type and duration), CD4 cell count, plasma HIV-1 RNA levels, glucose, insulin, total cholesterol and homocysteine.

The prevalence of lipodystrophy was 38.1%. Median IMT was 0.54 (range 0.50 – 0.60). In multiple regression models, IMT was significantly higher in older age, male sex, higher BMI, and higher tobacco consumption but there was not significant association with lipodystrophy and HAART.

Only conventional risk factors appear to be associated with increased IMT in HIV-1 infected patients.

Mercie P, Thiebaut R, Lavignolle V, Pellegrin JL, Yvorra-Vives MC, Morlat P, Ragnoud JM, Dupon M, Malvy D, Bellet H, Lawson-Ayayi S, Roudaut R, Dabis F. Evaluation of cardiovascular risk factors in HIV-infected patients using carotid intima media thickness measurement. Ann Med 2002;34:55-63.

17. Depairon and colleagues investigated whether the administration of a protease inhibitor (PI) containing antiretroviral regimen to middle aged HIV-1 infected individuals is associated with increased prevalence of atherosclerosis. Subjects were recruited from patients registered in the Swiss Cohort Study; inclusion was restricted to Caucasians aged 30-50 years. 68 negative and 168 HIV-infected individuals were included; those exposed to PI (n=136), had to be treated for at least six months (mean duration of 26.8 ± 8.9 months). HIV+ patients were 39.0 ± 5.5 years; HIV-negative controls were significantly younger (37.5 ± 5.7 years). HIV-1 infected subjects also had lower body mass index (BMI), higher prevalence of smokers, higher total cholesterol, triglycerides and total cholesterol to HDL cholesterol ratio, as well as a higher prevalence of one or more carotid and/or femoral plaques. Adjusted odds ratios (OR [95% CI]) for presence of plaques (all patients) were 2.1 [1.0, 4.4] for male sex, 2.0 [0.9, 4.3] for age 36-40

compared to 30-35 years, 6.7 [2.8, 16.8] for ages 41-45, 12.0 [4.1, 35.3] for ages 46-50, 3.2 [1.4, 7.5] for LDL cholesterol > 4.0 mmol/l, and 3.4 [1.7, 6.5] for smoking. HIV infection was not associated with presence of plaques.

Comparison of the 136 PI receiving patients to non-PI treated HIV-infected individuals revealed a slightly higher proportion of patients with plaques. Factors associated independently with presence of plaque in this group were age, cigarette smoking and plasma LDL cholesterol, but not PI treatment. Because of possible colinearity between PI treatment and plasma LDL cholesterol levels, the analysis was repeated without this variable; this did not affect the result.

The authors concluded that presence of carotid and/or femoral plaques in HIV-infected individuals was associated with traditional, modifiable risk factors rather than with PI treatment.

Depairon M, Chessex S, Sudre P, Rodondi N, Doser N, Chave JP, Riesen W, Nicod P, Darioli R, Telenti A and Mooser V. Premature atherosclerosis in HIV-infected individuals – focus on protease inhibitor therapy. AIDS 2001;15:329-334.

18. Acevedo and colleagues examined the level of traditional cardiovascular risk factors and coronary atherosclerotic risk in HIV positive patients treated with HAART.

The pilot study was carried out on seventeen HIV patients treated with HAART for at least six months, referred to a preventive cardiology unit of a dyslipidemia treatment clinic and had no known coronary artery disease (CAD) (referred group). Coronary calcium scores of these patients were measured by performing computed tomography (CT) of the coronary arteries. The referred group was matched 1:4 for age, sex, and traditional risk to HIV seronegative and non-CAD subjects selected from entries of the University of Illinois Electron Beam Tomography database (matched group). A third group (non-referred) consisted of 73 HIV positive patients (non-CAD, on HAART for at least 6 months) attending the same referring clinic as the referred group. The total of 90 referred and non referred HIV positive patients had a median age of 42 years (range 37 – 49). Framingham risk scores were used to calculate the 10-year cardiovascular risk for

both the referred and non-referred groups. Calcium scores were transformed using the natural log of 1+ calcium score.

The Framingham 10 years risk score was 9.65 ± 8.15 in the referred group and 6.96 ± 5.65 in the non referred group; 50% of referred patients were smokers and 50% had hypertension. 13 of the 17 (76%) referred patients had coronary calcium detectable on CT compared with 43 of the 68 (63%) of the matched HIV-negative controls (NS). The mean log transformed calcium scores were 2.93 ± 2.3 in the referred group versus 1.97 ± 2.45 in the matched group ($p=0.09$).

A high prevalence (75% of dyslipidemic patients) of detectable coronary calcium was observed in this pilot study. The population of HIV patients on HAART also had an enhanced prevalence of traditional cardiovascular risk. The authors expressed the need for development of preventive strategies in this population.

Acevedo M, Sprecher DL, Calabrese L, Pearce GL, Coyner DL, Halliburton SS, White RD, Sykora E, Kondos GT, Hoff JA. Pilot study of coronary atherosclerotic risk and plaque burden in HIV patients: 'a call for cardiovascular prevention'. Atherosclerosis. 2002;163:349-354.

19. Wanke and colleagues evaluated cardiac risk factors (lipid profiles and coronary calcification scores [CCS]) in HIV infected patients in the “Nutrition for Healthy Living” cohort.

The authors performed a cross sectional analysis including 119 HIV positive subjects with lipid analysis and a CCS test. Their lipid profiles were compared by HAART and PI use as well as for men and women. Those with CCS equal to or greater than 100 were compared to those with CCS less than 100. Lipid levels were compared to age, sex, and BMI matched controls from the Framingham Heart Study. All comparisons used non-parametric Kruskal-Wallis test. Correlations with CCS were assessed using Spearman's correlation coefficient.

Men on HAART had a higher triglyceride (TG), total cholesterol (TC), Apo A1, Apo B, Apo E, remnant lipoprotein-C (RLPC) level and BMI than men not on HAART. Men on PI had a higher TG, Apo E, RLPC and lower glucose compared to men not on PI.

Women on HAART had a higher TC, HDL and LDL and lower BMI compared to women not on HAART and women on PI had a higher homocysteine, glucose and insulin level compared to women not on PI. Coronary calcification was found to be significantly correlated with age, waist-hip ratio, RLPC, Apo B, CRP and BP and not to duration of HIV infection. Patients with a CCS ≥ 100 were significantly older (55.3 vs. 44.4, $p < 0.001$), had higher systolic blood pressure (126 vs 117, $p = 0.03$) and had a larger waist to hip ratio (0.96 vs 0.93, $p = 0.03$) than patients with a CCS < 100 . These groups did not differ according to other variables including duration of HIV infection, viral load levels and CD4 cell counts.

The authors concluded that patients infected with HIV appeared to have multiple established and emerging risks for cardiovascular disease that appear distinct from non-HIV controls.

Wanke C, Lamon-Fava S, Tang A, Hendricks K, Gerrior J, McNamara J, Skinner S, Schaefer E. Risk Factors for CHD and coronary calcification in a cohort of HIV-infected subjects. 10th Conference on Retroviruses and Opportunistic Infections 2003. Abstract 74.

20. Meng and colleagues examined the impact of protease inhibitor (PI) therapy on subclinical atherosclerosis (coronary artery calcification [CAC], lipid profile, C reactive protein (CRP) and red blood cell morphology and black HIV infected patients from Baltimore. 73% of patients were from the ALIVE (AIDS Link to Intravenous Experience) cohort, an ongoing prospective study of the natural history of HIV infection among injection drug users in Baltimore. 98 patient (55 PI, 43 non PI) were recruited. Exclusion criteria were previously reported heart problems, recent opportunistic infection, and active use of anabolic steroids, immunomodulators, lipid-lowering agents and smoking more than 1 pack per day. Additional exclusion criteria were known respiratory, hepatic and renal abnormalities or diabetes mellitus. The groups did not differ

significantly with respect to cigarette, alcohol, cocaine, heroin and speedball consumption.

83.7% of patients completed the lipid measurement and questionnaires. Patients in the PI group had significantly higher cholesterol and LDL-C levels, as well as mean corpuscular volumes (MCV) compared to patients not taking PI. All three parameters were significantly associated with log transformed duration of PI therapy. 80.6% of patients completed spiral CT examinations and questionnaires. The CAC scores were significantly higher in the PI group (11.0 ± 28.6 vs 1.7 ± 5.8). Mean serum CRP levels were similar in both groups.

The authors concluded that PI use is associated with coronary artery calcification, atherogenic lipid changes and increased erythrocyte volume in HIV-infected individuals. *Meng Q, Lima JAC, Lai J, Vlahov D, Celentano DD, Strathdee SA, Nelson KE, Wu KC, Chen S, Tong W, Lai S. Coronary artery calcification, atherogenic lipid changes, and increased erythrocyte volume in black injection drug users infected with human immunodeficiency virus-1 treated with protease inhibitors. American Heart Journal 2002;144:642-648.*

21. Henry and colleagues examined the C-reactive protein (CRP) levels as part of a substudy in patients from the ACTG372 clinical trial. Patients had virologic suppression and were receiving indinavir.

The authors took a random sample of 99 patients on indinavir containing regimen and examined their CAD risk information along with their fasting blood samples. CRP was measured using an ultra sensitive immunonephelometric assay.

The median CRP level of the subjects was 2.29 mg/L (range=0.18-42.9). The distribution of CRP levels by CAD risk categories was: average risk (0.55mg/L in men and 1.39 mg/L in women), low risk (0.56-1.14mg/L in men and 1.4-2.85 mg/L in women), moderate risk (1.15-2.1 mg/L in men and 2.86-5.25 mg/L in women) and high risk (2.1 mg/L in men and 5.25 mg/L in women). The proportion of subjects with high-risk CRP levels was significantly greater than in the general population. High-risk CRP values

were associated with greater age, fibrinogen levels, triglyceride levels, WBC, lower HDL levels and Framingham cardiovascular disease risk scores.

The authors concluded that, elevated CRP levels were observed in the cohort of HIV-1 infected persons. The CRP levels tended to cluster with some features of the metabolic syndrome and other CAD risk factors. However, the relationship of CRP with long-term CAD risk needs to be assessed in a greater detail.

Henry K, Zackin R, Dube M, Hammer S, Sprecher D, Currier J. C-reactive protein (CRP) levels and cardiovascular risk status for a cohort of HIV-1-infected persons durably suppressed on an indinavir (IDV)-containing rRegimen. 9th Conference on Retroviruses and Opportunistic Infections 2002; Abstract 694-T

21A. Sklar and colleagues analysed the importance of C-reactive protein (CRP) as a biomarker for determining the cardiovascular (CV) risk in HIV patients.

The authors measured CRP levels using a high-sensitivity assay (0.1 mg/L; Immulite), on plasma from 4 cohorts of patients. Samples were analyzed at baseline and after 1 year of antiretroviral therapy (ART) in treatment-naïve individuals (n = 17) to explore the impact of HIV viremia on CRP. Samples from patients on structured intermittent therapy (SIT)—long cycles of 2 months on medications/1 month off (n = 18 randomized to SIT, n = 24 continuous) and short cycles of 7 days on/7 days off (n = 8)—were analyzed at multiple time points to explore the impact of exposure to ART on CRP. Data at a time of optimal viral suppression were combined from all cohorts for purposes of analysis. Non-parametric statistics (Spearman rank correlation and Kruskal-Wallis analysis of variance) were used.

No significant change (median 0.1mg/L, p = 0.85) on CRP levels was seen after 1 year of continuous ART with 15 out of 17 patients achieving HIV-1 viral load < 50. No significant change was seen after 1 year of SIT for the group on long-cycle interruptions (median -0.1, p = 0.33) or for short-cycle interruptions (median -1.0, p = 0.07) vs baseline values. The median CRP, at a time point of optimal viral suppression for all patients (n =

67) was 1.8 mg/L. Eighteen percent (18%) classify as low, 21% mild, 28% moderate, 16% high, and 16% highest risk on quintiles established for healthy individuals. CRP values were inversely correlated with HDL-C ($p = 0.03$) and directly associated with total cholesterol:HDL-C ($p = 0.04$); approached significance for age ($p = 0.08$) but not other traditional CV risk factors. There was no relationship between CD4⁺ lymphocyte count, HIV-1 RNA level, protease-inhibitor or non-PI based therapy and CRP.

The authors concluded that neither reduction of viral replication nor reduced exposure to ART influenced CRP levels, although variability in CRP values was seen even among individuals with well-controlled HIV disease. This variability may in part be due to associations between CRP and traditional CV risk factors. Accordingly, CRP may be an important biomarker for determining CV risk in HIV patients.

Sklar P, Blackwelder W, Csako G, Metcalf J, Dybul M, Polis M, Masur H, Cannon R. C-reactive protein may be an important biomarker of cardiovascular risk and does not appear to be confounded by antiretroviral use or HIV viremia. 10th Conference on Retroviruses and Opportunistic Infections 2002; Abstract 742.

22. Dubé and colleagues assessed the effect of indinavir (IDV) monotherapy on endothelial function in men without HIV infection.

The authors evaluated 6 healthy, non-obese, normotensive, HIV-seronegative men with mean age 41 years before and after 4 weeks of administering IDV 800 mg three times daily. Subjects did not change diet or exercise habits during study. Hyperglycemic clamps (plasma glucose levels ~200 mg/dL for 240 minutes) and direct, invasive measurements of leg blood-flow were performed in basal conditions and during intra-arterial infusion of vasoactive compounds.

Mean BMI was found to be $23.8 \pm 1.3 \text{ kg/m}^2$. Subjects lost a mean of 0.7 kg ($p = 0.3$) over 4 weeks. The increase in leg blood-flow (LBF) during femoral artery infusion of the endothelium-dependent vasodilator methacholine (Mch) at maximal doses (15 g/minute),

expressed as percentage of change from pre-Mch basal values, were markedly impaired after 4 weeks of IDV: $+227\pm 45$ pre-IDV, $+82\pm 18$ post-IDV, $p = 0.003$. The response to the endothelium-independent vasodilator nitroprusside, an exogenous source of nitric oxide (NO), did not change. The expected reduction in LBF after infusion of the NO synthase antagonist L-NMMA, expressed as the percentage of change from pre-LNMMA values, was abolished with IDV: -30.4 ± 8.9 pre-IDV vs $+7.2\pm 9.2$ post-IDV, $p = 0.03$. HOMA-IR increased significantly: 1.15 ± 0.23 pre-IDV, 1.52 ± 0.34 post-IDV, $p = 0.03$. During hyperglycemic clamp, steady-state plasma glucose was similar: 201 ± 1 mg/dL pre-IDV, 196 ± 3 mg/dL post-IDV, as were glucose infusion rates: 16.1 ± 1.5 pre-IDV, 15.4 ± 2.2 mg/kg/minute post-IDV. Steady-state insulin concentrations during hyperglycemia were increased during treatment: 43.3 ± 9.3 μ U/mL pre-IDV, 54.4 ± 7.5 μ U/mL post-IDV, $p = 0.06$. Mean blood pressure, cholesterol, and triglycerides did not change.

The authors concluded that IDV induces endothelial dysfunction when administered as monotherapy for 4 weeks to healthy, HIV seronegative men. This does not appear to be mediated by dyslipidemia or changes in blood pressure. Endogenous NO-mediated vasodilation appears to be impaired, although other mechanisms may also be involved. Insulin resistance, and perhaps other drug-related effects, may contribute to endothelial dysfunction from IDV.

Dubé MP, Shankar S, Vanderluitgaren JM, Leffler CM, Baron AD, Steinberg HO. Effect of indinavir (IDV) monotherapy on endothelial function in men without HIV infection. 9th Conference on Retroviruses and Opportunistic Infections 2002; Abstract LB 10.

23. Stein and colleagues analyzed the lipoprotein abnormalities associated with use of protease inhibitors (PI) in individuals with HIV infection and assessed the effect of these changes on endothelial dysfunction.

The authors conducted a cross-sectional study of 37 HIV-1 infected adults. The subjects were divided into 2 groups; group I (receiving PIs, $n=22$) took stable doses of PIs for ≥ 6

months and group II (not receiving PIs, n=15) underwent stable antiretroviral regimen that did not include a PI. Analysis for clinical, lipid/lipoprotein and brachial artery parameters were conducted on both groups. Lipids and lipoproteins were measured by enzymatic techniques and nuclear magnetic resonance spectroscopic analysis. Brachial artery reactivity studies were performed by measuring the flow-mediated vasodilation (FMD) of the brachial artery (BA) using high-resolution ultrasound.

The average age of the subjects was 42.2 ± 7.6 years. Subjects in group I tended to have a higher body mass index and waist to hip ratio, however there was no significant difference in their resting heart rate, systolic blood pressure and serum glucose levels.

Indinavir was found to be the most commonly used PI.

Group I subjects had higher total cholesterol (5.68 versus 4.42 mmol/L, $P = 0.007$) and triglyceride (4.43 versus 1.98 mmol/L, $P = 0.009$) levels, characterized by elevated levels of IDL and VLDL, compared to group II.

Resting BA diameters and blood flow rates were similar in both groups. The increase in forearm blood flow was similar in both groups, indicating a similar stimulus to FMD of the BA. However, subjects in group I had markedly impaired FMD ($2.6 \pm 4.6\%$), a marker of severe endothelial dysfunction, whereas endothelial function in group II was found to be normal ($8.1 \pm 6.7\%$, $P = 0.005$). The primary determinant of impaired endothelial dysfunction was found to be the use of PI. In subjects receiving PI, chylomicron, VLDL, IDL and HDL-C levels were found to be the predictors of FMD.

The authors concluded that metabolic changes associated with use of PIs are atherogenic and cause endothelial dysfunction. Patients receiving PIs should be screened for hyperlipidemia and treated with lipid lowering therapies that improve endothelial function and prevent adverse cardiovascular events.

Stein JH, Klein MA, Bellehumeur JL, McBride PE, Wiebe DA, Otvos JD, Sosman JM. Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. Circulation 2001;104:257-262.

