Cardiovascular Risk in HIV Infection and Treatment

A Roundtable Organized by the Forum for Collaborative HIV Research

Report by Mark Mascolini

Based on presentations by David Pizzuti, Gil L'Italien, Jonathan Sterne, and others, and on roundtable discussions led by Ralph D'Agostino and Marshall Glesby

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Background and Introduction

Continuing use of highly active antiretroviral therapy (HAART) since 1996 has revealed an array of short- and long-term side effects. Among the most troubling and possibly portentous are the lipodystrophy syndrome(s), dyslipidemia, insulin resistance, and diabetes mellitus. HAART has proved highly effective in controlling HIV infection and preventing or delaying disease progression, yet it must be taken for much an infected person's life. Although there is broad consensus that the benefits of HAART far outweigh toxicity-related risks—at least for the exposure experienced to date—concern has arisen that the just-noted side effects may heighten the risk of cardiovascular disease.

Because of these concerns the Forum for Collaborative HIV Research convened a meeting of cardiologists, HIV clinicians and researchers, statisticians, industry and community members, and others to consider recent work on cardiovascular risk in people with HIV infection. Forum director Veronica Miller outlined the meeting's goals:

1. Review completed and ongoing studies addressing the meeting's topic.
2. Put data in context and identify issues related to study design, control populations, duration of follow-up, and outcomes and endpoints.
3. Evaluate the degree of consensus concerning cardiovascular risk in people with HIV infection.
4. Discuss further investigative approaches.

Miller suggested that, with a concerted effort, parties interested in this issue could take significant steps toward these goals.

The meeting had the following agenda:

- Introduction to EMEA Oversight Committee for Evaluation of the Metabolic Complications of HAART: David Pizzuti
- Review of key studies on cardiovascular risk with HIV and HIV therapy: Gil L'Italien
- Review of study designs and analysis: Jonathan Sterne
- Moderated roundtable discussion: Ralph D'Agostino and Marshall Glesby
  Selected attendees make informal presentations to spur discussion of:
    - o Issues regarding study design for clinical events studies
    - o Issues regarding study design for risk modeling studies
    - o Issues regarding study design for surrogate marker studies
    - o Issues regarding control populations
    - o Future studies
- Recommendations for ongoing or future studies
- Consideration of consensus regarding treatment of HIV infection and increased or excess cardiovascular risk

Participants

Beverly L. Alston NIH-NIAID,DAIDS	**Gerald S. Berenson** Tulane University Health Sciences Center (Written comments submitted)
Biykem Bozkurt Baylor College of Medicine	**Sam A. Bozzette** SDVA Medical Center
Umberto Campia Cardiovascular Research Institute-Washington Hospital Center	**Ben Cheng** Forum for Collaborative HIV Research
Paul Coplan Merck & Co.	**Dominique Costagliola** INSERM
Judith Currier UCLA Care Center	**Michele G. Curtis** Unites States Senate
Ralph D'Agostino, Sr. Boston University	**Sybil Eng** Pfizer
Nina Friis-Møller Copenhagen HIV Programme	**Shawn L. Fultz** VA Pittsburgh Healthcare System
Marshall Glesby Weill Medical College of Cornell University	**Carl Grunfeld** University of California-San Francisco, Veterans' Affairs Medical Center
Francois Houyez European AIDS Treatment Group	**Priscilla Hsue** University of California-San Francisco
Leo Hurley Kaiser Permanete Medical Care Program- Northern California	**Lawrence Kingsley** University of Pittsburgh

Gil L'Italien Ingenix Epidemiology	**John C. LaRosa** State University of New York Downstate Medical Center (Written comments submitted)
Edde Loeliger GlaxoSmithKline	**Jens Lundgren** Copenhagen HIV Programme
Veronica Miller Forum for Collaborative HIV Research	**Larry Mole** Veterans Health Administration, Palo Alto
Richard D. Moore John Hopkins University	**Anne Moorman** Centers for Disease Control and Prevention
Bob Munk New Mexico Aids Infonet	**Jeffrey Murray** FDA
Tim Peto John Radcliffe Hospital, Headington, Oxford	**David Pizzuti** Bristol Myers Squibb Company
Robert E. Ratner MedStar Research Institute (Written comments submitted)	**Robert Reynolds** Pfizer
Peter Sklar NIH/NIAID	**Jonathan Sterne** Department of Social Medicine, University of Bristol
Walter Straus Merck & Co.	**Erik Stroes** Academic Medical Center, Amsterdam
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EMEA Oversight Committee for Evaluation of the Metabolic Complications of HAART

The European Agency for the Evaluation of Medicinal Products (EMEA) has taken an active role in organizing research on morphologic and metabolic consequences of highly active antiretroviral therapy (HAART). David Pizzuti, a member of the Forum's Steering Committee, reviewed the EMEA's work to date on these issues.

In 1998-1999 the EMEA added text to the labeling of protease inhibitors (PIs) warning of possible body fat changes and metabolic abnormalities. Early in 1999 the agency sent a letter to PI manufacturers Abbott, Merck, and Roche (for Agouron) requesting a meeting to discuss short- and long-term complications of HAART. The letter posed numerous questions about lipodystrophy, its mechanisms, and cardiovascular risk issues and asked for cooperation in addressing those issues.

The meeting with the EMEA's Committee for Proprietary Medicinal Products (CPMP), held in March 1999, included manufacturers of licensed PIs and industry members with PIs then in the pipeline. They presented a meta-analysis of PI clinical trial data on cardiovascular risk. That analysis showed no evidence of increased cardiovascular risk in PI-treated study participants. It was noted that both sample size and duration of follow up were limited, thus the data were not sufficient to evaluate the effect of long term PI exposure on risk for cardiovascular disease. The manufacturers agreed to convene a panel of experts over the next 6 months to develop programs that would address two issues:

1. What are the most appropriate ways to address questions raised by the CPMP related to the prevalence and especially the incidence of (a) long-term treatment complications, and (2) short-term treatment effects on body composition and metabolic abnormalities?

2. What resources and infrastructure are required to accomplish these objectives, and how do we obtain them?

A steering committee met three times in 1999 and presented recommendations to the CPMP in October 1999. On the basis of these discussions, the CPMP endorsed four projects addressing metabolic abnormalities and cardiovascular risk:

- A retrospective cohort study of the risk of cardiovascular events: the Veterans Administration database analysis.
- A multicohort prospective study to evaluate cardiovascular risk: the D:A:D study ((Data Collection on Adverse Events of anti-HIV Drugs)
- A lipodystrophy case definition study
- A meta-analysis of clinical trials

Two of these studies—the VA analysis and D:A:D—were scrutinized during the Forum meeting.

In April 2003 the CPMP reached the following conclusions based on cardiovascular risk data analyzed to that point:

- "The available results from the studies clearly demonstrate that the benefit-risk balance of anti-retroviral treatment remains strongly positive."
- "The long-term cardiovascular effect of combination anti-retroviral therapy . . . has not been conclusively demonstrated and therefore concerns . . . should not lead to withholding CART [combination antiretroviral therapy] when indicated for these patients."
- "The ongoing studies of long-term cardiovascular complications . . . should be continued for an extended follow-up time, at least until January 2005. The CPMP regards this extension and any additional follow-up time that

may be necessary to provide conclusive results as part of the ongoing commitment from MAHs" [marketing authorization holders].

The Oversight Committee agreed on the following course of action concerning ongoing and future work:

- To maintain an oversight committee framework for supervision of study
- To continue funding D:A:D until January 2005
- To continue funding the VA study to capture 2 additional years of follow-up
- To complete a meta-analysis of collaborative trials and to consider a meta-analysis of more recently completed trials
- To support independent review of all cardiovascular risk studies

These proposals were also endorsed by the CPMP in February, 2003.

Review of Key Studies on Cardiovascular Risk with HIV and HIV Therapy

Gil L'Italien surveyed three groups of studies on cardiovascular risk in people with HIV infection—those involving (1) clinical manifestations of cardiovascular disease, (2) estimates or models of risk based on risk factors, and (3) surrogate markers of cardiovascular disease.

Appendix A provides an overview of these studies, and Appendix B tabulates their designs, endpoints, methods, results, conclusions, and other features.

Because these features differ markedly from study to study, results are not concordant. Briefly, six of 10 studies of clinical manifestations found evidence for increased rates of cardiovascular disease (CVD) in people treated with antiretrovirals; three found no significant increase in CVD risk; and one found an increased risk associated with HIV infection but could not attribute it to antiretroviral therapy.

The two studies discussed most during the Forum roundtable were the VA database analysis [1] and the D:A:D study [2]. The VA study compared CVD-specific hospitalization rates from 1993 through 2001, with a total of 323,489 patient-months of exposure to PIs (41.6% of the population, with a median exposure time of 17 months). All subjects were HIV-positive, and the population was primarily male. Thus the comparison was between HIV patient follow-up during the HAART and the pre-HAART era.

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). Patient-level analysis revealed no relation between the use of antiretrovirals and rate of cardiovascular or cerebrovascular events, but use of antiretroviral drugs was associated with a decreased hazard of death from any cause.

The D:A:D study (*n* = 23,468 with 36,199 patient-years) found a low but significant independent association between combination antiretroviral therapy and MI (26% increase per year exposure compared with HIV-positive patients not receiving treatment). D:A:D researchers have not broken down MI incidence by type of antiretroviral regimen. The D:A:D model included age, body mass index, race, family history of CVD, smoking, gender, HIV risk category, originating cohort, and pre-existing CVD; it did not include baseline levels of total cholesterol, triglycerides, diabetes, lipodystrophy, and hypertension.

L'Italien summarized hazard ratios for PI use and coronary heart disease (CHD) events in the VA study [1] and three other cohort studies [3-5]. (See table 1)

COHORT analyses: PI use and CHD Events Reported Hazard Ratios (the largest studies)

Table 1

Study	***HR***	***95% CI***	***# Patients***	***Median PI exposure***
Krause et al	**2.6**	**1.0-6.3**	**34,976**	**23 months**
Bozette et al	**1.2**	**0.8-1.9**	**36,766**	**16 months**
Coplan et al	**1.7**	**0.5-7.5**	**10,986**	**12 months**
Iloeje et al	**2.1**	**0.9-5.0**	**6,711**	**34 months**

He also outlined CHD events per 1000 patient-years in four cohort studies [3,4,6,7]. (See table 2)

COHORT analyses: PI use and CHD Events Reported Incidence (/1000PY)

Table 2

Study	*PI*	*Non-PI*	*# Patients*
Krause et al	**1.3**	**0.3**	**34,976**
Klein et al	**7.1**	**6.0**	**4,408**
Coplan et al	**1.8**	**1.1**	**10,986**
Holmberg et al	**1.4**	**0.5**	**5,672**

L'Italien proposed these conclusions for the clinical endpoint studies:

- CHD/CVD risk appears to be greater in the HIV-infected population than in the general population.
- HAART use, particularly with PIs, is associated with CHD/CVD to varying degrees.
- Absolute CHD/CVD risk remains low in these populations.
- Concern is expressed regarding increasing CHD/CVD risk with the aging of the HIV-infected population.

Three studies estimated the risk for CVD or coronary artery disease (CAD) based on risk calculation algorithms. Comparing a male French cohort taking PIs with the general population, Leport found a significantly higher relative CVD risk in the PI group [8]. However, the PI cohort had a significantly higher prevalence of CVD risk factors. Comparing HIV-infected treated and untreated individuals and seronegative controls, Wall found a higher 10-year CVD risk with HIV infection and particularly PI use [9]. Hadigan estimated risk in a cohort of HIV-infected people with or without lipodystrophy compared with sex-, age-, and body mass

index-matched seronegative controls from the Framingham cohort [10]. This analysis found a significantly higher 10-year risk of CVD in people with lipodystrophy than in matched HIV-negative controls. The risk for the HIV group without lipodystrophy did not differ from that of the seronegative controls.

Six surrogate markers studies evaluated carotid intima media thickness (IMT), four arterial calcification scores, two levels of C-reactive protein (CRP), and two endothelial dysfunction.

L'Italien offered the following overall conclusions: Most of these studies tend to show a relative effect of HIV or antiretroviral therapy on CVD risk, after adjusting for established risk factors. Absolute rates of CVD are low, but that may reflect the relatively young population of people infected with HIV.

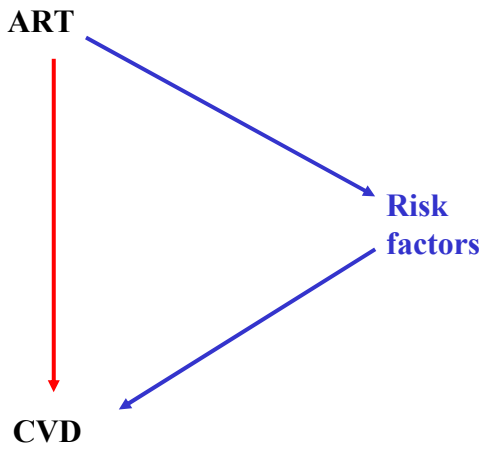
Review of Study Designs and Analysis

Jonathan Sterne analyzed direct and indirect estimates of associations with CVD, exploring methodological issues and issues in modeling cardiovascular risk from multiple cohorts. He began by asking what questions should be addressed:

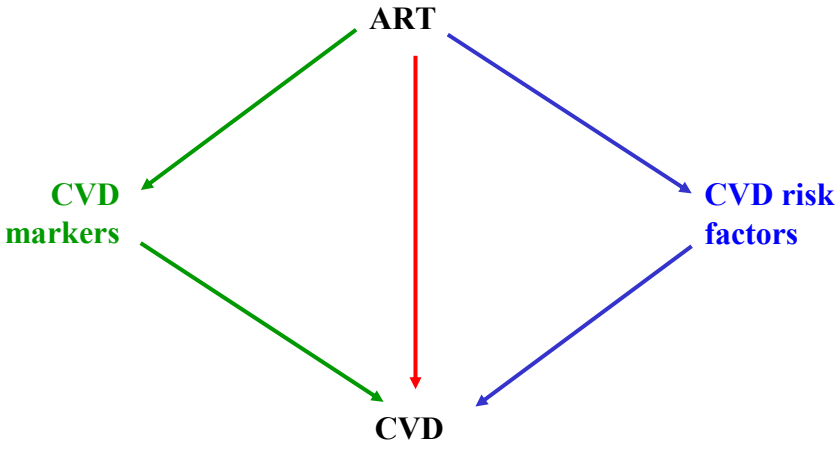
- Does HIV infection affect the risk of CVD?
- Does antiretroviral therapy, or some types of antiretroviral therapy, affect CVD risk in HIV-infected individuals?
- By how much does antiretroviral therapy, or some types of antiretroviral therapy, affect CVD risk in HIV-infected individuals?
- If there is an increase in CVD risk associated with antiretrovirals, is it sufficient to:
    - **o** Offset the beneficial effects of antiretrovirals on progression of HIV infection?
    - **o** Justify special efforts to counsel HIV-infected individuals?
    - **o** Justify (for example) automatic use of lipid-lowering drugs?
- Might an antiretroviral-associated increase in CVD risk become sufficient to justify some counseling or intervention in the future as HIV-infected individuals age and/or the effectiveness of therapy declines?

Considering studies presented to date, Sterne believes at least one conclusion is possible: "The evidence is absolutely clear: we should treat with HAART," because the benefits outweigh any reported risk. But it is clear that no single "gold-standard study" will sort out the still-unanswered questions. Therefore, he suggested it will be necessary to compare results from three lines of evidence: antiretroviral therapy (ART), CVD risk factors, and CVD.

Triangulation of direct and indirect evidence



A fourth arm, CVD risk markers, could also be added to that analysis:



Direct strategies to estimate CVD risk

Strategies to estimate the association between HAART and CVD risk could take a direct or an indirect approach. A direct approach would compare CVD rates, or markers of CVD, within or between *large* populations. Sterne listed several methodological issues with such studies:

- What comparison groups should be used, and what confounders should be anticipated?
- How should one compare the adverse effect of HAART on CVD risk with the beneficial effects of HAART on HIV disease progression?
- Are associations consistent in different patient groups, or between populations?
- If physicians are already allocating treatments on the basis of CVD risk, then randomized controlled trials may be the only way to assess the implications of a particular HAART regimen for CVD risk.

Addressing the first question, Sterne asked whether comparisons with HIV-uninfected groups are useful. Perhaps the "effect" of HAART can be examined meaningfully only in HIV-infected individuals. The effect of HAART on the risk of myocardial infarction can be outlined in the following series:

HIV infection → Wasting → Low cholesterol → HAART → CD4 count recovers → Cholesterol increases

Behaviors that increase the risk of CVD, such as smoking, might have been considered a rational response to a shortened life expectancy before HAART. If a longer life expectancy with HAART encourages a person to stop smoking, can that be counted as a beneficial effect of HAART? Such examples, Sterne noted, indicate that the choice of confounders in risk studies will require careful thought.

A further complication is confounding by indication for antiretroviral therapy, which can make observational studies of the effect of treatment uninterpretable. Sterne believes cohort studies have provided the best direct evidence of CVD risk so far, but very large studies are needed, it is difficult to decide on comparison groups, and it is difficult to measure all confounders. Case-control studies offer another approach. If such studies are nested in existing cohorts, they can be useful in measuring confounders in detail, and this can be done retrospectively.

Indirect strategies to estimate CVD risk

Indirect strategies to estimate the association between HAART and CVD risk could estimate the effect of antiretrovirals on risk factors for CVD or model the effects of changes in risk factors on the risk of CVD. Sterne listed these methodological issues with indirect strategies:

- Are there consistent effects of antiretrovirals on CVD risk factors?
- Do antiretroviral-induced differences in risk factors have the same effect as population differences?
- How should one model the effects of risk factors on CVD risk?
    - **o** Are existing models applicable to existing patient populations?
    - **o** Do we need to develop new models?

When considering indirect evidence, Sterne stressed that researchers must compare *absolute* increases in the risk of CVD with *absolute* reductions in the risk of progression to AIDS and HIV-related death. Determining relative changes—for example, that HAART doubles the risk of CVD—offers no help to patients. Thus research will have to combine:

- Estimated levels of CVD risk factors in patients treated with particular HAART combinations for particular lengths of time

- Estimated increases in CVD risk associated with the difference between these values and those expected in the absence of treatment

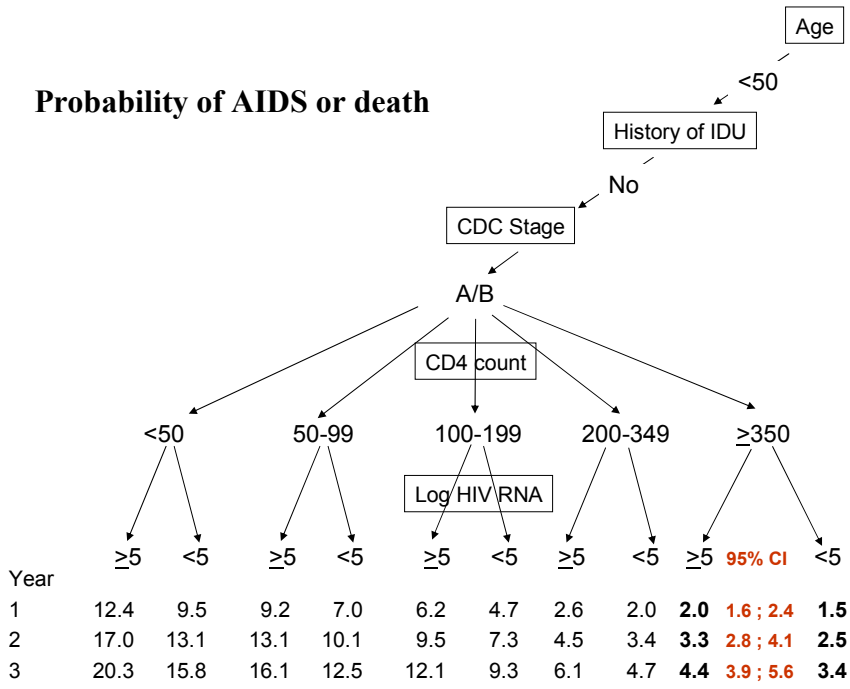
Sterne noted that existing models for the risk of CVD, particularly the Framingham equations, are known to require recalibration to estimate absolute CVD risks in different populations.

Models for the effect of HAART-associated changes in CVD risk

The ART Cohort Collaboration, which includes 13 cohorts from Europe and North America, is one attempt at modeling risks associated with HAART (http://www.art-cohort-collaboration.org). The strategy of this joint effort began by fitting candidate parametric survival models on data pooled from all but one of the 13 cohorts. Models were then tested on the omitted cohort, and that process was repeated, rotating the omitted cohort. The best-generalizing model was then chosen. The final model for the ART Cohort Collaboration is a Weibull model with stratification for CD4 count and transmission group (injecting drug users versus others).

The first publication of results from this collaboration confirmed an increasing probability of AIDS or death with lower pretreatment CD4 counts and with a baseline viral load above 100,000 copies/mL [11]. The model can predict the probability of AIDS or death based on age, history of injecting drug use, CDC stage of disease, CD4 stratum, and viral load above or below 100,000 copies/mL:

Probability of AIDS or death



Year	≥5	<5	≥5	<5	≥5	<5	≥5	<5	≥5	95% CI	<5	95% CI
1	12.4	9.5	9.2	7.0	6.2	4.7	2.6	2.0	**2.0**	1.6 ; 2.4	**1.5**	1.2 ; 1.9
2	17.0	13.1	13.1	10.1	9.5	7.3	4.5	3.4	**3.3**	2.8 ; 4.1	**2.5**	2.1 ; 3.0
3	20.3	15.8	16.1	12.5	12.1	9.3	6.1	4.7	**4.4**	3.9 ; 5.6	**3.4**	2.8 ; 4.1

Sterne and others are now developing a CVD risk model combining data from five large heart disease cohorts and pooling estimates of the effects of blood pressure, total cholesterol, HDL cholesterol, triglycerides, smoking, and diabetes.

Summary

Sterne concluded with four points:

- Questions asked by studies of CVD risk in people with HIV must be clarified. (Can we move on from, "Does HAART affect CVD risk?")
- Results from a range of study designs will contribute.
- In the short and median term, we know that HAART leads to dramatic reductions in rates of progression to AIDS and death. (This must be kept in mind when interpreting and reporting CVD risk study results.)
- Are randomized controlled trials needed?

Moderated Discussion on Study Designs, Control Populations, Duration of Follow-up, Outcomes and Endpoints

Co-moderator Ralph D'Agostino began the discussion by asking attendees to consider the quality of the existing data on CVD risk in people taking antiretrovirals. Despite inevitable shortcomings in study designs, length of follow-up, and so on, are these results telling us something useful? Or are the deficiencies of the studies too great?

If D'Agostino were advising the pharmaceutical industry on the ideal HIV/CVD study, he would propose a large, simple trial factorially randomizing participants to different antiretrovirals and other interventions. The study would need 20,000 people with 5 to 6 years of follow-up. Instead of results from such a trial, we have observational studies with inadequate matching, confounding variables, and different definitions of disease and endpoints.

D'Agostino also asked discussants to begin formulating advice on future directions of HIV/CVD research:

- What should the next steps be?
- Should current studies be continued and, if so, for how long?
- What new studies are needed?

Co-moderator Marshall Glesby suggested two background considerations that may not be obvious to the many non-HIV specialists assembled:

1. While certain antiretroviral class effects have been suggested, there is actually much heterogeneity within classes. Some PIs, for example, are more prone to elevate lipids, and some to promote insulin resistance. The new PI atazanavir seems not to raise lipids. In addition, PIs and nucleoside reverse transcriptase

inhibitors (NRTIs) appear to interact in the evolution of body fat changes, and the NRTI stavudine (d4T) may have a direct effect on lipids. Any trial analysis must consider whether a certain drug itself is having a specific effect, or whether that effect results from some interaction.

2. People starting antiretroviral therapy tend not to stay on their initial regimen for a long time. They change regimens for varying reasons, including toxicity. So a randomized study may have a limited amount of time to discern regimen-related atherosclerotic changes. Defining antiretroviral exposure in CVD risk trials will be complex.

As a cardiologist not working in the HIV field, John LaRosa "found it impressive that the evidence for an effect of drug treatment itself [on CVD risk] was not robust." In written comments he suggested that antiretrovirals may exert such an effect by increasing triglycerides or low density-lipoprotein cholesterol, by suppressing HIV infection itself, or by some direct effect on blood vessels.

Issues regarding designs of clinical event studies

D'Agostino asked attendees, beginning with statistician Tim Peto, to consider issues regarding the design of clinical event studies, particular the VA study [1] and D:A:D [2]. Peto said a key question those studies raise is why one chooses specific cardiovascular events. That choice obviously affects the event rate. Should one choose an event to make it specific for CHD, because it matters to the patient, or to avoid complications with the effects of HIV? He believes mortality is the most revealing endpoint.

Peto observed that large populations are needed to determine the long-term effects of HIV and antiretroviral therapy, and the follow-up in VA and D:A:D remains short. A related question is what are the risk factors for CVD events? Are traditional risk factors sufficient to predict clinical events in people with HIV, or do we have to define new ones?

Overall, Peto said, he found the VA and D:A:D designs good. He noted that prospectively designed studies are preferable, "but we have to work with data we have." He suggested that data already produced by the two studies could be further mined.

Gil L'Italien agreed that the designs were the best possible given the populations available for study and the questions being addressed. Both D:A:D and the VA study, he felt, took pains to identify risk factors and events correctly.

Frank van Leth suggested that a critical question about D:A:D and the VA study is "What is measured and at what point?" An important difference between D:A:D and the VA study is how they defined endpoints. The question is whether to use common or restricted endpoints. He felt that D:A:D did a good job in strictly formulating endpoints and defining antiretroviral exposure. He found the VA endpoint of hospital admission for CVD or cerebrovascular disease more problematic.

Peter Sklar thought D:A:D had a clear definition of how to count MIs through review by an outside panel. Cerebrovascular disease in the VA study raises more difficulties as an endpoint because people with HIV have comorbidities that may cause it. The VA researchers tried to account for that possibility, but admission for cerebrovascular disease may be a softer outcome and may not be worth following. He noted that hard endpoints for each of the various clinical manifestations (coronary artery disease, cerebrovascular disease, and peripheral vascular disease) will be important in the attempt to quantify and categorize the risks posed by HIV infection and its treatment. These endpoints should have commonly agreed upon definitions and first events should be distinguished from recurrent event.

The principal investigator of the VA study, Sam Bozzette, noted that CVD and cerebrovascular events were not adjudicated by an outside panel, as they were in

D:A:D. The study is an examination of an administrative database, he reminded attendees, and it should be understood as such. Determining individual patient risk was not a goal of the study. The goal was to determine whether there is a strong enough signal of MI or stroke risk over a short enough period to cancel the benefit of antiretroviral therapy. The study found that the risk of MI or stroke was not strong enough to cancel HAART's benefit. To put it another way, the VA study showed with great confidence that even if MI or stroke results in death every time, these patients were still better off taking antiretrovirals. That result, Bozzette observed, does not contradict the main findings of D:A:D.

Jens Lundgren, principal investigator of D:A:D, explained that when designing the study he did not focus on the acute public health implications of CVD in people taking antiretrovirals because he knew the population was too young for many people to die of heart disease over a few years. Rather, the D:A:D team planned the study to see if there was a *signal* of increased risk, so they designed it to detect 2-fold risk over 2 to 5 years of antiretroviral exposure. D:A:D did find a 1.26-fold higher risk of MI with each additional year of antiretroviral therapy. Now, Lundgren said, the question becomes how to quantify this increase. Are we seeing the extreme left of the risk curve, that is, people who will develop this risk early during treatment? He added that D:A:D researchers are working to collect metabolic data.

Dominique Costagliola, who helped plan the large French study of MI risk in men taking PIs [3], noted that this study and D:A:D had very different designs. Yet they both arrived at the same conclusion—an increasing risk of MI with continuing therapy.

Tim Peto proposed that groups with observational cohort data on CHD risk with antiretrovirals should pool their data to determine whether increased rates of CHD seen in individual studies are greater than would be expected by chance.

In written comments, Robert Ratner noted that "absence of standardized covariates makes comparisons of previous studies or meta-analyses difficult to impossible."

Issues regarding study designs of risk modeling studies

Gil L'Italien noted that the risk modeling studies [8-10] suggest a somewhat higher risk of CHD among people being treated for HIV infection. Even though the risk models used may not be particularly appropriate for an HIV population, the consistent finding of higher risk in treated people is a flag that the drugs are exerting some effect. But ultimately, he said, researchers should develop risk prediction models unique to the HIV-infected population.

Russell Tracy maintained that it is important to establish biologically whether progression to CVD in people with HIV differs from progression in the general population. But in the absence of evidence that there are differences, HIV clinicians should treat the disease in antiretroviral-treated people as they would in people without HIV infection. Still, he said, the burden should be on the research community to establish whether there are some differences in progression, for example, through autopsy or imaging studies.

Jonathan Sterne agreed that some technical issues in the design of modeling studies need to be addressed. For example, he said, there is no doubt that rising cholesterol levels increase the risk of CVD. The interesting question is how much it increases that risk and how much in conjunction with other risk factors in the populations studied.

Co-moderator Ralph D'Agostino concurred that the modeling approaches tried so far probably are quantifying risk, even given all the caveats about the suitability of these models to HIV-infected people taking antiretrovirals. But in his mind the critical question is, are there better approaches? More specifically, is dyslipidemia in the HIV-infected population the same as in the general population? Lipids do

rise in people taking antiretrovirals, and clinicians should react to them. But it may turn out that these increases do not have the same outcome as in HIV-negative populations.

A piece of evidence from one of the modeling studies suggests that the HIV population differs in important ways from the general population when it comes to CHD risk. The study by Colleen Hadigan found an increased CVD risk among people with *lipoatrophy* compared with the Framingham population [10]. That correlation runs counter to the expectation that central fat accumulation increases heart disease risk, as it does in the general population.

Carl Grunfeld argued that research should try to find causes of discrete elements of risk in the HIV population and not simply assume, for example, that "lipodystrophy" in people with HIV is equivalent with the metabolic syndrome in the general population. Before the HAART era Grunfeld showed that HIV itself affects lipids [12]; metabolic abnormalities do not begin with HAART, they begin with HIV. One reason D:A:D was able to pick up an early signal of increasing risk may be because of this pretreatment impact of HIV on lipids.

Grunfeld noted that underlying changes in people with HIV superficially resemble the metabolic syndrome, but some are caused by HIV, some by drugs, and some by fat changes. He believes definitions of lipodystrophy are too general in HIV/CVD risk studies. Studies that can measure fat and not simply use a clinical definition of the syndrome will yield more accurate results.

Robert Ratner made a related point in written comments about planning future studies: "Of paramount importance, standardization of covariate measures for future studies must be established. These include recognition that PI therapy is common and subsequent lipodystrophy must be appropriately defined and assessed. Furthermore, consequences of lipodystrophy such as insulin resistance, dyslipidemia, and hyperglycemia must be prospectively defined and measured."

Issues regarding study designs of surrogate marker studies

As long as the questions asked by a surrogate marker study are clear, Russell Tracy maintained, researchers can decide which markers to include. But the biology behind these markers has to be considered carefully, so CVD marker studies should measure as much as possible—not just carotid intima media thickness and lipids, for example, but also T-cell activation and macrophage activation. Researchers should not just assume that they know what factors matter. With marker studies that have already been presented, stored samples may let researchers measure some additional variables that could clarify the results.

Umberto Campia reviewed the major markers studied to date, reminding attendees that surrogates do more than flag risk, they also give clues to pathogenic mechanisms.

Carotid intima media thickness (IMT) is a marker of early atherosclerosis. Studies of IMT in people taking antiretrovirals can give an idea of the long-term effect of treatment, but only one IMT study so far has longitudinal data [13]. Campia believes studies to date have not shown with certainty that PIs affect IMT, but it seems certain that long-standing HIV infection has an effect. The longitudinal study found a 10 times higher rate of IMT progression than in the control group, a finding suggesting that both traditional risk factors and PI therapy were affecting at least this marker of atherosclerosis. All of the IMT studies show that baseline classic risk factors matter [13-17]. Aggressively treating these underlying factors should benefit an HIV population as much as it does a non-HIV population.

Coronary calcium score is not considered one of the most sensitive markers in his cardiovascular research environment, Campia said. He believes IMT is a more easily measured endpoint, but it requires skilled technicians and readers to ensure reproducibility. A good design itself is not enough; good execution is also necessary.

C-reactive protein (CRP) data reported so far have not shown a clear association between CVD and PIs or antiretrovirals in general, but they have shown a link with the underlying metabolic syndrome. CRP studies have the advantage of needing fewer patients, usually 10s to 100s. This small population size allows researchers to check the metabolic profile in much more detail than is possible in larger trials.

Endothelial-dependent vasodilation is a sensitive and early indicator of the potential to develop atherosclerosis. The changes measured are not only early, but also acute. Such studies can be done in 1 week.

Overall, Campia concluded, surrogate marker research to date does not definitely support a role of antiretroviral therapy in increasing the risk of CVD, but they raise that possibility. The studies do support a role of HIV infection in metabolic abnormalities seen in this population.

Erik Stroes believes IMT can be used to prove that CVD risk is increased in people taking antiretrovirals. A wealth of data supports its role as a reliable predictor. The best way to proceed may be to do within-group comparisons over time. For example, what will a total cardiovascular intervention program do over a period of a few years?

Priscilla Hsue, principal investigator of the longitudinal IMT study [13], added that IMT is relatively cheap, easy for skilled technicians, and very reproducible. Studies in the general population correlate IMT to the risk of heart attack or stroke. Her study correlated IMT with nadir CD4 count. That suggests a role for immune suppression in arteriovascular disease, which can be studied with other markers. Hsue believes cardiologists should also consider other approaches in studying CVD risk in people with HIV, such as exercise treadmill testing, stress echocardiograms, cardiac catheterization, quantitative coronary angiography,

coronary artery MRI, and Holter monitoring. None of those techniques have been tried so far.

Biykem Bozkurt noted that markers can do five things: diagnose and predict clinical events, evaluate progression of coronary atherosclerosis, target intervention, and evaluate biology. For diagnosing plaques, IMT is easy and noninvasive, but inter-reader variability can be great. Other imaging techniques, such as stress testing alone or with imaging, are functional studies that can estimate the significance of plaques.

If you look at the cardiovascular system as a continuous organ, Bozkurt continued, coronary artery disease could be one endpoint and clinical events another. HIV/CVD risk researchers must ask a priori what they are trying to identify. She suggested that a focus on clinical events may be more valuable because clinical events are what matter most to patients. Studies might look at intragroup rather than intergroup progression of events; intergroup comparisons become more difficult because statisticians have to correct for differences between groups.

Robert Ratner offered these opinions on surrogate markers in written comments: "Carotid IMT is currently the most meaningful and best accepted [surrogate of atherosclerosis]. It is my personal belief that endothelial dysfunction will provide little additional information beyond the basic metabolic parameters, and that calcium score and EBCT are the least useful of all."

Issues regarding control populations

When considering control groups in HIV/CVD risk studies, Dale Williams observed, a fair test designed is not a fair test conducted. Subgroup analyses can be misleading. The ideal control group would be a clone of the treatment group, and not just a genetic clone but also an environmental and a psychosocial clone. Since that's impossible, the best way to approximate that idea is with a

randomized trial. An important question to ask about control groups, Williams noted, is *when* they are comparable with the treatment group. At the beginning of the study, or at end when researchers are comparing events? No single control group is the best choice to address all questions.

In written comments, Robert Ratner made several points about control populations: "In view of the increasing observation of CVD in subjects with HIV, it does not appear to me that non-HIV-infected populations are appropriate control groups. Rather, studies of large populations of HIV-infected individuals over time will provide more data illuminating contributory factors for CVD."

Biykem Bozkurt observed that a shift in VA admission policy in the past 10 years could color interpretation of the results. Today only people with unstable angina or MI are admitted; a decade ago someone with chest pain might be admitted. As a result a non-VA control arm may have been helpful in the VA database analysis [1].

The VA study's Sam Bozzette agreed that so-called secular trends like the one described by Bozkurt could chip away at the solidity of the VA data. But he believes VA admissions policies have now stabilized, so continued follow-up should determine whether the shift in those policies affected data presented so far.

Issues regarding follow-up time for clinical event studies

Gil L'Italien noted that the VA study and D:A:D have unavoidable shortcomings: Length of follow-up for cardiovascular events and length of exposure to particular antiretrovirals are still too short. He urged that drug exposure be quantified as carefully as possible.

Frank van Leth maintained that study length is not the principal difficulty in analyzing the VA study and D:A:D. Both need longer follow-up, but that should

surprise no one. But even with only a few years of follow-up, D:A:D already showed an increasing MI rate. Extending follow-up in those studies will add the complication that physicians will begin to treat more cohort members for lipid abnormalities.

Discussion summary

Ralph D'Agostino offered the following summary of the preceding discussion.

- There is general agreement that D:A:D is a well-done study that carefully collected endpoints prospectively.
- D:A:D is not an ideal study, and some data are still missing. But D:A:D does support the idea that there is an elevated cardiovascular risk in people taking antiretrovirals.
- The VA study does not contradict the findings of D:A:D.
- Other clinical endpoint studies support the D:A:D finding of an elevated cardiovascular risk in people taking antiretrovirals.
- More work should be done to confirm this preliminary conclusion, including looking more closely at the data sets and getting more follow-up.
- The risk modeling studies do not contradict the clinical outcome studies.
- Multivariate analyses in risk modeling studies confirm the importance of classic risk factors like elevated cholesterol.
- Questions that remain about the modeling studies include whether they would have reached clearer conclusions if they had all looked explicitly at the metabolic syndrome, and whether more detail can be derived from these studies.
- The surrogate markers studies have produced data that is probably better at implicating HIV itself rather than protease inhibitors.
- The surrogate marker studies do not contradict findings of an elevated CVD risk in the clinical endpoint studies.

Moderated Roundtable Discussion on Recommendations for Future Study and Consensus on Treatment of HIV Infection and Increased Cardiovascular Risk

Co-moderator Marshall Glesby began the second part of the roundtable by offering his interpretation of the discussion so far: Studies done to date suggest an increased relative risk of cardiovascular disease (CVD) in people with HIV infection. The absolute risk is low, but it will increase over time.

Glesby listed the following key questions that should be addressed as research continues:

- What is the impact of baseline factors—duration of infection and treatment—on CVD risk?
- When is the more meaningful time to compare study subjects and control groups—at baseline or at the end of study?
- Are long-term survivors who have not started antiretrovirals different from those who have started?
- What is the effect of relatively short durations of initial regimens on results of randomized controlled trials?
- What control groups should be used?
- What is the lag time between intervention and an endpoint?

The following discussion focused on two issues—potential confounders in reported and future studies, and recommendations for future studies. Roundtable attendees then suggested statements that could be considered in working toward a consensus on CVD risk in antiretroviral-treated people.

Potential confounders

In cohort studies, Gil L'Italien said, some forethought should make it possible to distinguish between intermediate variables and confounders. Longitudinal cohort studies should allow researchers to distinguish between *true confounders and variables on the causal pathway*.

Richard Moore noted the *trend favoring treatment with NNRTIs* rather than PIs, based largely on lipid and glucose elevations with PIs. That change will affect the ability of researchers to mount long-term clinical trials evaluating the impact of PI therapy on CVD disease.

Clinicians are using *antilipid medications* more in PI-treated people with lipid elevations, Biykem Bozkurt observed. That will have an effect on lipid trends in ongoing and future studies, and possibly on endpoints. Prophylactic use of *aspirin* will also have an impact. As Carl Grunfeld added, a randomized trial cannot be done ethically with placebo statins.

Clinical endpoint trials in the current US or European HIV populations will be almost impossible because *CVD endpoints are* so *rare*, clinician Douglas Ward pointed out. And they will become rarer with more use of statins.

Another HIV clinician, Christine Wanke, noted that trials of treatment-naive people will be difficult because there are *few antiretroviral-naive people* in most practices. Because a growing number of people now have virus susceptible to only one or two antiretrovirals, many are taking five- to seven-drug regimens. Sorting out toxicities in such patients is difficult.

Lawrence Kingsley observed that other *rarely considered confounders* could have a great impact on results of current or future studies. One example is a rising incidence of type II diabetes among US adults, and another is an increasingly

sedentary lifestyle. Clinical studies of CVD risk will need adequate measures of physical activity.

Recommendations for future studies

Gil L'Italien noted that work done so far has already yielded a wealth of data, including longitudinal data. It may be worthwhile to review data from these studies using *consistent definitions of CVD endpoints*. Methodologies already exist that may help make these studies more interpretable, such as "propensity score mashing." In addition, *more markers* could be analyzed in ongoing studies.

He added that *adjudication of endpoints*, as was done in D:A:D, could be done more systematically with algorithms. Cardiologists could review algorithms to verify their validity, and algorithms could be validated against data in patients' charts.

L'Italien called for *predictive models specific to HIV*-infected populations to determine whether relative risks of variables in this population are comparable to those in general population models such as Framingham.

L'Italien also stressed the importance of *measuring person-time exposure* to antiretrovirals. That is being done as part of the SMART protocol.

Tim Peto proposed that researchers focus on the *absolute risk of coronary events* in people with HIV versus seronegative people with same risk factors.

Peto suggested that people with *prior CVD* should not be eliminated from prospective trials. Because of that history they are likely to progress more quickly to another cardiovascular endpoint.

Determining the *all-cause mortality while taking effective HAART* would be a worthwhile goal, Peto added. If clinicians are to advise patients about addressing

risks of CVD, other risks must be determined as well. For example, would a clinician prescribe statins for a person with elevated lipids if that person had a high risk of dying from liver failure?

Peto also urged researchers to *combine datasets* for further analysis. If each research group agreed to contribute results even from only eight or nine data fields, much could be learned. But clinical researcher Leo Hurley thought that merging datasets would prove problematic because of *different baseline variables* in different cohorts.

Pooling data from future studies would be easier, Carl Grunfeld argued, if those trials all adopted the *endpoint adjudication* used in D:A:D.

A study to determine *whether statin therapy will lower the risk of CVD* in people with antiretroviral-induced lipid elevations would require several thousand people followed for several years and would cost $200 million or more, according to Dale Williams. Researchers should consider those assumptions when deciding whether that question is important enough to answer.

Lawrence Kingsley echoed the opinion that an adequate trial will never be done with a control group of untreated HIV-infected people. As a result he is trying to organize a surrogate marker study, looking at *coronary calcium scores*, as part of the Multicenter AIDS Cohort Study. He believes that study would require only 400 to 500 people.

Considering the wide agreement that D:A:D establishes a heightened CVD risk in people taking antiretrovirals, Jonathan Sterne observed that a marker study is not needed for confirmation. Rather, *marker studies should aim to quantify risk*.

Another marker, endothelial dysfunction, is an early and acute measure of atherosclerosis risk, noted Biykem Bozkurt. Thus is may be a useful *marker in treatment interruption studies*.

Ralph D'Agostino proposed that the most valuable HIV/CVD risk studies will be clinical endpoint studies. Therefore the best use of surrogate marker studies may be as *endpoint trial substudies* addressing pathophysiologic questions.

In written comments John LaRosa suggested consideration of a clinical trial comparing aggressive risk factor modification—including antilipid and antihypertensive drugs—versus "usual" care of people taking antiretrovirals. Because a large number of study participants would be needed for a clinical endpoint study, he proposed using carotid intima media thickness as a marker. Such a trial could also explore potential drug interactions, such as those between statins and protease inhibitors.

LaRosa also noted the scarcity of data comparing different cardiovascular risk rates in women and men taking antiretrovirals. Because of the growing number of women with HIV infection in the US, and the already high proportions in most developing countries, he called for further observational studies to address gender issues.

Working toward consensus: suggested statements

The roundtable decided against fashioning a consensus statement on CVD risk with antiretroviral therapy based on studies reported so far. However, several attendees advanced points that might be considered in such a consensus.

- Although antiretroviral therapy probably increases the risk of vascular and cardiovascular disease, and although that risk is clinically significant in a high-risk patient, it is small in most patients, small relative to other risks faced

by this population, and negligible relative to the benefits of antiretroviral therapy.

- Risk modeling studies and surrogate marker studies of CVD risk generally support the finding in clinical endpoint studies that antiretroviral therapy raises that risk.
- HAART is a life-saving intervention for people in whom treatment is indicated. However, if certain drugs are found to increase risk more than others and clinicians have a choice of drugs, they should consider prescribing those associated with lower risk. At this point, though, there are not enough data to make solid recommendations about specific drugs or drug classes.

- All evidence to date indicates that the life-prolonging benefits of antiretroviral therapy far outweigh any cardiovascular risk. But clinicians should be aware that antiretrovirals do drive certain risk factors, and they should evaluate those risks as part of routine care.

- Cardiovascular risk in the HIV-infected population varies greatly from patient to patient. Clinicians should be urged to evaluate cardiovascular risk in each patient and to use that risk profile to inform treatment decisions.

- Further studies and follow-up are needed to elucidate direct and indirect cardiovascular effects of HIV and antiretroviral therapy.

- Data gathered so far on CVD risk in people taking antiretrovirals—particularly in D:A:D and the VA study—can be further analyzed to yield new insights.

- Results of the VA study do not contradict the results of D:A:D.

Finally, Marshall Glesby recommended that the Forum should consider planning a roundtable on managing cardiovascular risk in people with HIV infection.

References

1. Bozzette SA, Ake CF, Tam HK, et al. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. *N Engl J Med* 2003;348:702-710.

2. Friis-Møller N, Weber R, D'Arminio Monforte A, et al. Exposure to HAART is associated with increased risk of myocardial infarction: the D:A:D Study. 10th Conference on Retroviruses and Opportunistic Infections. 2003. Abstract 130.

3. Mary-Krause M, Cotte L, Partisani M, et al. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. *AIDS* 2003. In press.

4. Coplan PM, Nikas A, Japour A, et al. The incidence of myocardial infarction in randomized clinical trials of protease inhibitor-based antiretroviral therapy: an analysis of four different protease inhibitors. *AIDS Res Hum Retroviruses* 2003. In press.

5. Iloeje U, Yuan Y, Tuomari A, et al. Protease inhibitors may increase risk of cardiovascular disease in HIV-infected patients. 10th Conference on Retroviruses and Opportunistic Infections. 2003. Abstract 746.

6. 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.

7. Holmberg SD, Moorman AC, Williamson JM, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *Lancet* 2002;360:1747-1748.

8. Leport C, Saves M, Ducimetier P, et al. Coronary heart disease risk in French HIV-infected men started on a protease inhibitor-containing regimen compared to the general population. 9th Conference on Retroviruses and Opportunistic Infections. 2002. Abstract 697-T.

9. 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.

10. Hadigan C, Meigs JB, Corcoran C, et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infections and lipodystrophy. *Clin Infect Dis* 2003;32:130-139.

11. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* 2002;360:119-129.

12. Grunfeld C, Pang M, Doerrler W, et al. Lipids, lipoproteins, triglyceride clearance, and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. *J Clin Endocrinol Metab* 1992;74:1045-1052.

13. Hsue P, Lo J, Franklin A, et al. Increased atherosclerotic progression in patients with HIV: the role of traditional and immunologic risk factors. 10th Conference on Retroviruses and Opportunistic Infections. 2003. Abstract 139lb.

14. Currier J, Kendall M, Henry K, et al. Carotid intima-media thickness in HIV-infected and uninfected adults. 10th Conference on Retroviruses and Opportunistic Infections. 2003. Abstract 131.

15. Seminari E, Pan A, Voltini G, et al. Assessment of atherosclerosis using carotid ultrasonography in a cohort of HIV-positive patients treated with protease inhibitors. *Atherosclerosis* 2002;612:433-438.

16. Chironi G, Escaut L, Garepy J, et al. Carotid intima media thickness in heavily pretreated HIV-infected patients. *JAIDS* 2003;32:490-493.

17. Mercie P, Thiebaut R, Lavignolle V, et al. Evaluation of cardiovascular risk factors in HIV-infected patients using carotid intima media thickness measurement. *Ann Med* 2002;34:55-63.

Appendix A: 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/mm^3, 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 Sudy. AIDS 2003; In Press.

Friis-Møller N, WeberR, 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 exosure 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 Insight™, a combination of the CDC's HIV Outpatient Study with additional physician offices and clinics funded by Cerner, Inc™. 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 controls0, prior diabetes (15% cases, 7% controls), prior hypertension (43% cases, 17% controls) and CD4 count (mean 351 cells/mm^3 cases, 251cells/mm^3 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 Disesases 2003;In press.

9A. The SMART study recruits patients with CD4 cell count > 350 cells/mm^3 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/mm^3 and 258 cells/mm^3, 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 ≥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/mm^3. 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$\pm$0.27mm -- higher than expected from a large population study of similarly aged individuals. Predictors of increased IMT included age, LDL cholesterol, hypertension and a nadir CD4 cell count < 200 cells/mm^3. IMT progression over 1 year was measured in a subset of 21 patients, 41% of which had hypertension. The mean rate of progression was 0.1$\pm$0.1mm/yr, which was greatly accelerated compared to 0.01mm/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 139lb.

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 naive 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. The 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, wais 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-1infected 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 $\geq$ 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 o f HV 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±1.3 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±45 pre-IDV, +82±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±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 muU/mL pre-IDV, 54.4±7.5 muU/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 $\geq$ 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$\pm$ 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±4.6%), a marker of severe endothelial dysfunction, whereas endothelial function in group II was found to be normal (8.1±6.7%, *P* =0.005). The primary determinant of impaired endothelial dysfunction was found be the use of PI. In subjects receiving PI, cylomicron, 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.

Appendix B: Cardiovascular Risk in HIV Studies Summary Table

Cardiovascular Risk in HIV Studies Summary Table

Ref#	Study/ Author	Objective	Study Design	Endpoints	Analysis Methodology	Follow up (Calendar Years)	Sample Size Patient Years (PY)	M/F	Age (mean) Median (IQR)]	Ethnicity Race	Key Results [95% CI]	Author's Conclusions
1	Veteran's Administration/ Bozzette et al	Evaluate trends in rates of cardiovascular and cerebrovascular disease in patients receiving HIV care	Retrospective analysis based on patients receiving HIV care at VA facilities	Admissions for and/or death from cardiovascular and/or cerebrovascular disease, death from any cause	Calculation of rates per 100 PY; Kaplan-Meier curves; time to event modelling; patient level regression models	8.5 yrs (1993-2001)	36766 (121,936 PY)	1.9% F	71% 35-55; 17% <35	44.2% White 52.3% Black 0.3% Am Ind 0.3% Asian 2.8% other	Admissions: 1207 for cardiovascular disease, 1764 for cardio- or cerebrovascular disease, and 2006 admissions or deaths from cardio- or cerebrovascular disease	Clinical benefit of antiretroviral therapies not diminished by increase in rate of cardiovasular or cerbrovascular events or related mortality
		Evaluate the relationship between the risk of cardio/ cerbrovascular disease and use of antiretroviral therapy			Models controlled for year of first care for HIV, race or ethnicity, sex, age, risk factor for HIV, severity of illness, history of AIDS, drug abuse, previous Rx for vascular disease, diabetes, hypertension, hyperlipidemia, smoking						Admissions for cardio/ cerebrovascular disease decreased from 1.7 to 0.9 per 100 PY. All cause mortality decreased from 21.3 to 5.0 deaths per 100 PY	Longer term observations required
											Antiretroviral drug use not associated with risk for cardio/cerbrovascular events but associated with reduced all cause mortality	
											Hazard for admission higher with increasing age, more advanced HIV disease status, AIDS defining illness, Hx of Rx for cardiovascular risk factor, pre-existing vascular disease, earlier date of first care for HIV	
1A	French hospital database on HIV (FHDH)/ Krause et al	Analyze the impact of PI on the risk of MI among men	Retrospective analysis of data obtained from FHDH	Incidence of MI)IDC code 410;I21)	Incidence rate approach, compared to French general male population calculation of standard moribity rate (SMR)	4 yrs (1996-1999)	34,976 (88,029 PY)	0%	37.7 (±9.1) for non MI; 41.9 (±8.2) for MI	not provided	RH for MI in patients exposed to PI was 2.56 [1.03, 634]; age was the only other signficiant factor in the model	Duration-related effect relationship between PI and MI, with a higher MI incidence rate among men exposed to PI for 18 mths or more
					Association of risk factors using Cox analysis; models ajdusted for age, initial CD4, NRTI, NNRTI and PI treatments						Risk for MI increased with increasing exposure time, with SMR of 0.8, 1.5, and 2.9 for exposures of < 18 months, 18-29 months, and ≥30 months, respectively	

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1B	Medi-Cal study/Currier et al	Examine the relationship between ART exposure and CHD incidence	Retrospective analysis of Medi-Cal claims of HIV + patients	CHD incidence (defined by ICD codes)	Multivariate log-linear regression analysis to determine the relative risk of CHD by ART use; controlled for comorbid covariates of diabetes, hyperlipidemia, kidney disease & hypertension	5 yrs (1995-2000)	28,513	not provided	not provided	not provided	Incidence (non adjusted)of CHD/100 PY by age category: 1.08 (18-33 yrs), 1.74 (34-49 yrs), 3.13 (50-65 yrs), 4.90 (abv 66 yrs) Relative risk of CHD comparing individuals receiving ART to those not receiving ART: 2.06 (18-33 yrs) (P<0.001), 1.08 (34-49 yrs) (P>0.3), 0.79 (50-65 yrs) (P>0.05), 1.15 (abv 66 yrs) (P>0.6]	ART associated with increased risk of CHD in young (18-33) but not older individuals. Co-morbid conditions associated with CHD in general population were important predictos of CHD in the study population
2	D:A:D Study/ Friis-Møller et al	Determine incidence of MI. Assess association of combination antiretroviral treatment (CART) exposure with risk for MI	Prospective, multinational observational cohort study (11 established cohorts)	Acute MI	Incidence rate approach, with primary outcome presented as relative rates Models controlled for age, BMI, race, family Hx of CVD, smoking, sex, HIV risk group, cohort and pre-existing CVD	6 yrs (1999-2005)	23,468 (36,199 PY)	24.1% F	[39 (34-45)]	75.6% White 18.3% Black 6.1% other	Overall incidence of MI 3.5 events per 1000 PY (126 events) RR of MI increased with longer CART exposure; Adjusted RR 1.26 (1.12-1.41 p<0.0001) Other independent factors associated with increased risk: older age, smoking, CVD Hx, male sex, higher total serum cholesterol, diabetes mellitus	CART independently associated with 26% increased risk of MI per year exposure Absolute risk of MI remained low and should be balanced with benefit of CART

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3	Randomized Clinical Trials/Coplan et al	Compare the incidence of MI among participants of randomized clinical trials receiving PIs to NRTI therapy alone	Retrospective analysis based on 30 Phase II/III industry sponsored double-blind, randomized studies	Cases of MI from investigator reports	MI rate per 1000 PY; Relative Risk (RR) for MI in patients taking PI vs NRTI only	Mean months on PI: 11.4 - 14.3; mean months on NRTI only: 5.2 - 12.0 (prior to 1999)	10986 (7620 PY for randomized phase; 11651 PY for randomized plus extension phase)	8-18% F	{37-38}	not provided	10 MI in randomized phase and 19 cases in randomized plus extension phase; rates per 1000 PY for PI vs non-PI were 1.38 vs. 1.18 and 1.82 vs 1.05 for randomized and randomized plus extension	Study did not reveal a dramatic increase in MI risk during the first year of PI exposure; however upper limit of CI indicates there may be up to 2.3 additional MIs per 1000 PY
					ITT confined to double-blind, randomized, active control phase; inclusive analysis covering double-blind and open-label phases						Absolute difference in MI risk (PI to control): +0.77 (-0.71, + 2.26); combining both phases for all studies, overall stratified RR was 1.69 [0.54, 7.48]	Small number of cases and wide CI's make calculation of relative and absolute risk impossible.
4	Iloeje et al	Quantify association between PI exposure and CVD events	Retrospective cohort analysis of a prospectively collected database (HIV Insite Database)	First CVD event (MI, angina, CAD, PCA/CABG, stroke, TIA, PVD)	Cox proportional hazards models; adjusted HR	Median of 2.8 yrs (1996-2002)	6,711	13.3% F	38 [18-88]	58.6% Whites 27.8%AA 13.6% Other	93 CVD events (rate 1.6% in PI and 0.5% in non PI) and 74 CHD events (rate 1.3% in PI and 0.4% in non PI),	PI use doubles the risk of developing both CVD and CHD events. Greater risk seen in middle aged patients
					Models controlled for age, sex, race, weight, PI exposure,hyperlipidemia, CVD, DM, HTN, smoking, IV drug use, cocaine use						Adjusted HR all CVD events for PI use was 1.99 [0.95-4.14]; CHD model HR 2.13 [0.91,4.95];PI exposure > 60 days (subset analysis) HR 2.10[1.00, 4.40]	Absolute event rates remain low. Prolonged exposure may increase event rates, especially as population ages
5	HOPS/ Holmberg et al	Determine whether rate of MI, angina, cerebrovascular accident (CVA) is increased in patients taking PI's	Prospective observational cohort based on 9 clinics in the USA	Verfied MI, angina, CVA events	Incidence per 1000PY; Cox proportional hazards analysis (HR); multivariate logistic regression models (OR)	(1993-2002)	5672 (17,712.4 PY)	18% F	{42.6}	38% Non White	21 MI events; 1.42/1000 PY for PI, 0.46/1000 PY for non-PI	Use of PI may be associated with MI and perhaps angina
					Models controlled for hypertension, smoking, diabetes mellitus, age, sex and evidence of dyslipidemia						Unadjusted HR of MI for PI: 8.06 [1.14,56.8], but not significant in controlled model (p=0.065); adjusted OR 4.92 [1.3 - 32.3] 15 angina events; OR for PI 1.93 [0.63, 5.96] Most patients with events also had traditional risk factors	

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6	Kaiser Permanente/ Klein et al	Estimate the coronary heart disease (CHD) and MI rate in KPNC patients, stratified by PI and other ART use Compare rate in HIV+ populations to HIV- populations Describe prevalence of classic CHD risk factors in HIV+ and HIV- patients	Retrospective analysis of the KPNC database	Confirmed hospital admissions with primary discharge diagnosis of CHD (ICD 9 codes)	Events per PY of follow up, age adjusted event rates	HIV+:Mean 4.3, median 4.5 years (1996 - present) HIV-: mean 5.4, median 6.5 years	4,408 (18,792 PY) HIV+ patients, and 39,425 HIV- patients (211,221 PY)	0% F	not provided	not provided	in HIV+: 100 CHD events (65 MI); age adjusted event rate of CHD and MI for HIV+: 6.6 [5.0,8.1] and 3.8 [2.7, 5.0]; for HIV- controls 3.3 [3.0-3.5] and 2.6[2.4-2.8], with p values of <0.001 and 0.03 for CHD and MI respectively No clear trend for CHR or MI with increasing length of PI use Prevalence of CHD risk factors in all HIV+ patients: hypertension 38%, smoking 21%, diabetes mellitus 16% and hyperlipidemia 5%.	Increased CHD and MI hospitalization in HIV+ compared to HIV-; risk factors for CHD were frequent in patients with events Patients started on PI-containing HAART do not exhibit increased risk for CHD compared to patients not exposed to PI
7	Maryland Clinical Cohort/ Moore et al	Assess incidence of and factors associated with CHD and CVD	Nested case control, with 5 non CVD/CHD controls per case, matched on enrollment date and duration of follow up	CHD (MI or unstable angina) CVD (ischemic stroke or TIA)	Event rates per 1000 PY; Mantel-Haenszel chi-square and conditional regression analysis	(post 1996)	Total 2671 (7.330 PY); 78 cases and 336 controls	42% and 32%F	46 and 41 yrs	76% and 80% AA	43 CHD and 37 CVD events; CHD/CVD risk associated with older age, higher cholesterol, prior diabetes, prior hypertension, higher CD4, PI use and d4T use Multivariate analysis: age, hypertension, total cholesterol and d4T use independently associated with CHD/CVD risk Race, IVDU, and HIV-1 RNA levels were not associated with risk	Incidence of MI and CVD are 2-3 times higher the expected national age, sex, race based rates

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8	HERS/ Gardner et al	Examine renal, CVD, diabetic and hepatic-specific hospitalization rates in HIV+ women	Prospective multicenter cohort study	Diagnosis specific hospitalization: non-acute renal, cardiovascular, diabetes mellitus, hepatic and AIDS-defining	Hospitalization rates per 100 PY; rate ratios (RR) using Poisson regression with repeated measures and GEE estimation method	mean 4.5 yrs (1994-2000)	885 HIV+ ; 425 high risk HIV-neg	100% F	not provided	61% AA 17%Hispanic	360 CDV specific hospitalizations,; overall empirical event rate of 9.5.	Hospitalization rates for CVD doubled (hepatic conditions increased 10-fold)
											In HIV+ women, compared to 1994, the adjusted RR for CVD hospitalization in 1997 was 1.8 (p=0.02), in 1998 2.1 (p<0.01) and in 1999/2000 2.0 (p=0.02)	Close monitoring of non-AIDS risk factors for morbidity is warranted
9	APROCO/ Leport et al; Saves et al	Estimation of risk for CVD morbidity in HIV+ patients receiving PI compared to a sample of general population	Prospective follow up within French APROCO cohort (every 4 M); cross-sectional analysis of risk at M12 or M20; controls derived from MONICA study; age & sex stratified	Risk for CVD estimated using predictive models (PRIME model and Anderson model from Framingham)	Relative Risk	mean ART 26 M and mean PI 13M; (May 97 - June 98)	274 HIV+; 1038 controls	18.6% F in HIV+; 49.2% F in control	Restricted to 35-44	not provided	BMI . Hypertension and HDL were lower in HIV+ men compared to MONICA sample but prevalence of smoking, W/H, triglyceridemia were higher; similar trends observed for women; similar trends shown for populations aged 45-54	HIV+ patients have aa particular therogenic profile, rsulting in moderate but significant increased CH risk
					Risk factors: BMI, smoking, blood pressure, W/H, cholesterol (total, HDL, LDL), triglycerimia, fasting blood glucose						5 yr RR for CHR was 1.2 for men and a.159 wor women; or 1.39 and 2.17 in women, depending on model, p<10[6;]	
											Risk attributable to smoking was 65% and 29% for men and women	

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9A	SMART study/El-Sadr et al	Comparison of CHD risk factors among HIV+ men and women on HAART enrolled in the SMART study	Crossectional estimation of CHD risk factors among patients enrolled in the SMART study; baseline characteristics, lab assays and EKGs evaluated; 10 yr risk of CHD calculated using Framingham equation Baseline data presented here; study will assess effect of treatment/type of treatment	Framingham Scores and other CHD risk factors	% men and women at risk (baseline data presented;) Blood pressure therapy used as indicative of stage I hypertension; conditions for metabolic syndrome assessed Risk factors: BMI, MI/stroke history, EKG abnormalities, TGL, LDL, HDL, BP therapy, diabetes, smoking, metabolic syndrome, Framingham scores		649 HIV+ cases	24.9% F	{44.8} yrs	38% African Americans, 16.2% Latino, 45.8% White	97.4% HAART experiencedI; median baseline and nadir CD4 cell counts were 598 cells/mm^3& 258 cells/mm^3; 69% had viral load <400 copies; 28% had prior AIDS diagnosis 7.8% of men and 0.6% of women had Framingham high/very high 10 yr risk for CHD; 26.1 % men and 31.5% of women had MI/strie, major EKG, metabolic syndrome, or high/very high risk	Significant number of men and women in SMART are at a high risk of CHD based on Framingham risk, history of MI and stroke, prevalance of metabolic syndrome and major EKG abnormalities
10	Wall et al	Estimate risk of ischemic CHD in HIV+ patients on different ART regimen, based on ATP3 Framingham score	Prospective evaluation of a convenience sample of HIV+ patients and uninfected controls; cross-sectional analysis	Estimation of CVD risk using the Framingham Point Scoring System	Comparison of HIV+ patients on PI to non-PI,; risk factor assessment Risk factors included: smoking, hypertension, low HDL cholesterol, family Hx of premature CVD, older age,		111/125 HIV+; 25/49 controls were evaluated	10% F in HIV+; 53% F in HIV-neg	41 in HIV+; 36 in HIV-neg	In HIV+: 65% White 35% AA In HIV-neg: 76% White 14% AA	4% median risk for CVD progression in HIV+ cohort vs 1% in controls; 6% for PI using HIV+ vs 3% in non-PI using individuals	Significant prevalence of risk for progression of CVD in HIV infection Longitudinal studies needed to assess changes in risk over time

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10A	Hadigan et al	Estimate the 10-year risk of CHD in HIV+ patients with fat redistribution compared to risk estimate in matched non-HIV subjects from Framingham	Comparison of risk between HIV+ with fat redistribution (HIV+ LD+) and matched controls; HIV+ without fat redistribution (HIV+ LD-) and matched controls	Estimation of CHD risk using the Framingham Point Scoring System	Consecutive patients (age 18-60)enrolled; exclusion criteria: change in ART, Hx diabetes mellitus, previous Rx with antidiabetic, use of hormones, steroids, active alcohol/substance abuse	(HIV+1: 998-1999; controls 1991-1995))	HIV+ LD+: 91; controls 273; HIV+LD-: 30, controls 90)	29% F(LD+) 40%F (LD-)	{44.6} and {45.07} for men; {39.5 and 40.6} for women	not provided	Estimated 10-year risk significantly higher in HIV+LD+ (7.4 ±0.6 vs 5.3±0.3); for men only, 9.0±0.7 vs 6.5±0.3; ns for women only; percentage of subjects with >10% risk significantly higher in total HIV+LD+ populations and men only; risk not higher than controls for HIV+LD-;	CHD risk is increased in patients with fat redistribution
			HIV+ LD+ were matched for sex, age and BMI wifh subjects from Framingham; substudy matched for sex, age, BMI and W/H		10-year risk estimates (sex specific) incl age, total and HDL C, S/DBP, diabetes, smoking						When also matched for W/H, no difference in 10yr risk between HIV+LD+ and controls (7.6±0.6 vs 7.6±0.4)	Patterns of fat redistribution and sex may be important components of risk determination
			HIV+ without fat redistribution (HIV+ LD-) were matched for age and BMI		CHD events: angina pectoris, MI and death due to CHD						Risk significantly higher in patients with lipoatrophy compared to lipohypertrophy, or mixed LD	
					Analysis on total patient population as well as stratified by sex						No association with current PI use	
10B	Study A1424-008/Grover et al	Estimation of the impact of nelfinavir and atazanavir on CVD risk and life expectancy (LE) after adjustment for HIV related mortality	Used data from a randomized controlled trial, that compared nelfinavir and atazanavir effects on CVD, and adjusted for HIV related mortality	CVD risk, LE	CVD risk estimated through Cardiovascular Life Expectancy Model; validation of the forecasted LE based on the 3rd National Health and Nutrition Examination Survey Study and results compared to US Life Tables	32 weeks	269 (178 atazanvir; 91 nelfinavir)	not provided	not provided	not provided	Changes in total and LDL cholesterol (+24% and +28%) observed among 91 nelfinavir patients were significantly greater (p<0.05) than those among 178 atazanavir patients (+4%,+1%); predicted LE reasonably well approximated LE from US life tables	Estimated CVD risk and LE models indicated a lower risk and higher LE for atazanavir compoared to nelfinavir
					Assumption of 2.9% HIV related annual mortality rate						CVD risk 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% CI, 0.05 TO 0.29); presence of additional risk factors increased potential advantage of atazanavir vs nelfinavir to an increased LE from 0.22 to 1.18 years (95% CI, 0.20 TO 1.53)	

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11	David et al	Identify factors associated with proven ischemic CVD in HIV+ persons	Retrospective; matched case control; based on medical records of all patients seen	Documented CVD (angiography, echocardiography, exercise stress testing or MI)	All patients with events included as cases, sex and age matched controls (2:1) Impact of specific variables assessed using conditional logistic regression analysis Variables included in model: nadir CD4, duration of PI exposure, duration of NRTI exposure, smoking, hypertension, hyperlipidemia, HIV-RNA, family history, race, and recent CD4	(1999-2000)	16 cases; 32 controls	19% F in each group	43 [42-66] and 45[37-65]	50% White 50% Black among ICVD patients 47% White and 53%Black in Control	Hypertension, smoking, elevated cholesterol, family history and CD4 count <200 were significant predictors for CD in univariate models Use of PI or other ART was not a risk factor	Ischemic CVD occurs in HIV+ patients and is associated with traditional risk factors
12	ACTG 5078/ Currier et al	Compare differences in baseline IMT between HIV+ on PI and not on PI Compare differences in baseline IMT between HIV+ and HIV- individuals Examine predictors for IMT	Prospective, longitudinal; matched cohort Triads (HIV+ PI > 2 yrs; HIV+ no PI; HIV negative) were matched for age, race, sex, blood pressure, smoking and menopause Baseline, week 24, 48, 72 and 96 week evaluations planned	Subclinical atherosclerosis determined by carotid IMT	IMT of far wall obtained in duplicate Median IMT differences between groups Cross sectional analysis for baseline	Baseline reported here	134 in 45 triads	40 M and 4 F triads	not provided	76% White 3% Black 16%Hispanic 4%API	HIV+ PI group had higher levels of total cholesterol and triglycerides Median IMT in the three groups were 0.693, 0.711 and 0.687, the median differences between any two groups non significant Independent predictors for increased IMT: cholesterol (total, LDL), triglycerides, age, BMI and current smoking	No clinically relevant differences were demonstrated at baseline Longitudinal follow-up is ongoing

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13	Hsue et al	Identify predictors for carotid IMT in HIV infection	Prospective, longitudinal study	Mean maximal IMT of 12 preselected segments	B-mode ultrasound for carotid IMT; IMT progression measured in 21 patients	1 year	106	17% F	{45 +/- 8}	not provided	Mean baseline IMT was 0.90 +/- 0.27 mm	IMT associated with classic coronary risk factors and nadir CD4 <200
					Multi-variable linear regression to identify predictors						Mutlivariable predictors of baseline IMT increase: age, LDL cholesterol, hypertension, and nadir CD4<200	Both traditional and immunodeficiency contribute to atherosclerosis in HIV
		Follow IMT progression over 1 year									Mean rate of IMT progression was 0.1 =/- 0.1 mm/yr; age and duration of PI therapy predictors	10-fold acceleration in progression of IMT over 1 year follow up, associated with age and PI use
14	Seminari et al	Evaluate the extent of IMT in PI treated HIV+ patients compared to PI-naïve and HIV negative subjects	Multicenter cross-sectional study	IMT	Hematological and carotid ultrasound		59	34% F	{33-37}	not provided	PI-using patients had significantly higher triglyceride, HDL and apo B levels	IMT more pronounced in PI using patients
											IMT increased in PI-using patients compared to naïve and HIV-negative	
15	Chironi et al	Assess IMT in pretreated HIV+ patients prone to atherosclerosis and 2 groups of HIV negative controls (without or with metabolic profiles similar to patients)	Matched case control study	IMT	IMT measurement in plaque free far wall segment of right CCA, calculated as average of 100 measurements		36/group	17% F	{44-45}	not provided	IMT greater in cases than control group 1 (without similar metabolic profile); significant after adjustment for age, sex, BMI, waist, SBP, smoking and prior CVD; not significant after adjustment for glucose, triglyceride, total:HDL cholesterol ratio	Study was not designed to detect association of IMT with duration of infection or type/duration of antiretroviral treatment
					General linear model for adjusted comparison						IMT not different between cases and control group 2 (similar metabolic profile)	Lipid disturbances may be involved in the early atherosclerotic process in HIV+ patients
											Multivariate analysis: IMT associated with age (case and control 1), waist (case only) and total HDL (case only)	

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16	Mercie et al	Assess IMT in HIV+ patients in relation to treatment, lipodystrophy and conventional risk factors	Cross sectional analysis within a multicenter, prospective cohort	IMT	B-mode ultrasonography Variables: lipodystrophy, age, gender, BMI, smoking, alcohol, SBP, HIV risk group, AIDS stage, type and duration of HAART, CD4, HIV-RNA, glucose, insulin, total cholesterol and homocysteine		424	?	?	?	Mean IMT was 0.54 mm (0.5-0.6). IMT significantly higher in older age, male sex, higher BMI, higher W:H ratio, increased SBP, total cholesterol, glucose disorders and homocysteine, regular smoking, alcohol consumption, lipodystrophy and HAART HAART and lipodystrophy lost significance in multivariate model	Only conventional risk factors are indpendently associated with increased IMT in HIV infected patients
17	Depairon et al	Determine association between PI use and prevalence of atherosclerosis	Cross sectional analysis within a prospective cohort study	Carotid and femoral IMT	B-mode ultrasound imaging of carodi and femoral arteries performed by same (blinded) investigator Univariate and multivariate logistic regression analysis		168 HIV+, 68 HIV-	HIV+: 28.6% F; HIV-: 20.5%F	HIV+: restricted to age 30-50	Caucasian only	HIV+ patients were younger, had lower BMI, higher total cholesterol, triglycerides, and total:HDL cholesterol ratio, higher prevalence of smokers and higher prevalence of plaques; Presence of plaques associated with male sex, older age, and higher LDL cholesterol but not HIV infection nor PI treatment	Atherosclerotic plaques were associated with traditional (modifiable) risk factors
18	Acevedo et al	Estimate the coronary atherosclerotic burden in HAART treated HIV+ patients (severe dyslipidemic, or not) compared to HIV- controls	Matched pilot study, cross sectional including HIV+ and HIV- patients HIV+ pts on HAART min 6 M	CT derived calcium scores	Coronary artery imaging using multi-detector scanner and Imatron electron beam tomography scanner. Coronary calcium quantified using Agatston method HIV+ patients were those referred to a preventive cardiology unit or from same referring clinic; 1:4 matched controls		17 referred, 63 non referred and 68 matched HIV- controls	not provided	42 [37-49]	not provided	Framingham 10yr risk score nearly 10% in referred group; 75% had detectable coronory calcium, with mean scores of 2.93 ± 2.3 vs. 1.97 ± 2.45 in matched controls	High prevalence of detectable coronary calcium and traditional risk factors in severely dyslipidemic HIV+ patients

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19	Nutrition for Healthy Living/ Wanke et al	Evaluate cardiovascular risk factors (lipids and calcification scores) in HIV+ patients	Substudy of the Nutrition for Healthy Living Cohort Study	CT derived coronary calcification scores (CCS)	Comparison of iipid profiles by HAART, PI use, for men & women; comparison of CCS >100 to <100	(post 1995)	119	23.5% F	45.7	38%Minority	Men on HAART had higher TG, TC, Apo A1, Apo B, Apo E, RLPC and BMI; women on HAART higher TC, HDL, LDL and lower BMI	Correlates of coronary calcification in HIV infected adults are not distinct to HIV nor necessarily related to HIV therapy
			Cross sectional analysis; 66% of patients were on HAART								Men on PI had higher TC, Apo E, RLPC and lower glucose; women on PI had higher homocysteine, glucose and insulin	Impact of abnormal lipids associated with HAART on CHD remains to be defined
											>100 CCS group (222.7) were older, had higher SBP and higher W/H	
20	Meng et al	Assess the effect of PI on subclinical atherosclerosis in black HIV+ adults	Black patients from MD enrolled into a longitudinal study of atherosclerosis and cocaine use; 73% recruited from ALIVE cohort	Coronary artery calcification (CAC)	CAC determined by scanning, average 12 scans /patient; score by Agatston method	(2000-2001)	98 (55 PI, 43 non PI)	27% F and 33% F	{39.3} and {37.8}	100% Black	PI group had significantly higher cholesterol, LDL cholesterol, MCV,	Use of PI associated with coronary artery calcification, atherogenic lipid changes and increased MCV
		Characterize lipoprotein, erythrocyte abnormalities; alterations of CRP and CAC associated with PI use	Cross sectional analysis								CAC scores 11.0±28.6 in PI and 1.7±5.8 in non PI, p=0.043; CAC scores associated with duration of PI Rx,	
21	ACTG 5056s/ Henry et al	Assess CRP levels and association with CAD risk and HIV surrogate marker status in patients who achieved virologic suppression	Cross sectional analysis of a random sample of 99 ACTG372A patients on an indinavir containing regimen	CRP	CRP measured using ultrasensitive immunonephelometric assay		99	13% F	40.5	67% Cauc	Median CRP was 2.29 mg/L; a significant proportion of patients had high CRP risk levels, and higher risk associated with increased age, WBC, fibrinogen, TG, insulin, HOMA, Framingham heart scores, and lower HDL-C	In virologically suppressed patients, elevated CRP levels were observed and clustered with some features of metabolic syndrome and CAD
											CRP levels not associated with baseline HIV-1 RNA or CD4 cell counts	All patients received indinavir, thus data may not be generalizable

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21A	Sklar et al	Analysis of the effectiveness of CRP as a biomarker for determining CV risk in HIV patients	Prospective, longitudnal cohorts of HIV$^+$ patients on ART	CRP	CRP measured using high sensitivity assay (0.1 mg/L;Immulite) on plasma from 4 cohorts of HIV$^+$ patients	1 year	cohort I: 17, cohort II: 18, cohort III: 24 cohort IV: 8	not provided	not provided	not provided	No significant change (median 0.1 mg/L, p=0.85) in CRP levels after 1 yr of cont. ART; no significant change in CRP levels after 1 yr of long (med -0.1,p=0.33), or short cycle (med -0.1, p=0.07) SIT.	Reduction of viral replication or reduced exposure to ART do not influence CRP levels
			Cohort I: on I yr of continuous ART; cohort II &, III: on structured intermittent therapy (SIT) with randomized and continuous long cycle interruptions; cohort IV: on short cycle SIT								Median CRP for all patients at the time of optimum viral suppression was 1.8 mg/L. 18% classified as low, 21% mild, 28% moderate, 16% high and 16% highest risk on quantiles established for healthy individuals	Variability in CRP values among individuals with well controlled HIV disease could be due to associations between CRP and traditional CV risk factors
											CRP values inversely correlated with HDL-C (p=0.03) and directly associated with TC (p=0.04). CRP values approached significant for age (p=0.08) but not other traditional risk factors.	CRP may be an important biomarker for determining CV risk in HIV patients
22	Dube et al	Assess effect of indinavir monotherpay on endothelial function in HIV negative men	Examination of 6 HIV negative men before and after administering 800 mg tid of indinavir	Leg Blood Flow (LBF)	Leg blood flow measures in basal conditions and during intra-arterial infusion of vasoactive compounds (methacholine and nitroprusside)	4 weeks	6	0% F	{41 yrs}	not provided	Increase in LBF during femoral artery infusion of maximal doses of methacholine was markedly impaired between baseline and 4 weeks of IDV treatment (227±45 to 82±18).; response to nitroprusside did not change; the expected effect of NO antagonist -LNMMA was abolished by indinavir; HOMA-IR increased significantly (1.15 ± 0.23 to 1.52 ± 0.34)	IDV induces endothelial dysfunction when administered as monotherapy to healthy HIV negative subjects
											Steady state insulin concentrations during hyperglycemia increased during treatment (43.3±9.3 to 54.4± muU/ml); mean blood pressure, cholesterol, and triglycerides did not change	

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23	Stein et al	Analyse the lipid/lipoprotein abnormalities associated with use of PI in HIV patients	Crossectional study with HIV+ patients divided in 2 groups : using PI and not using PI	Lipid/lipoprotein levels	Enzymatic analysis and nuclear magnetic resonance spectroscopic analysis		37 (22 PI, 15 non-PI)	22% F	{42.2-49.8}	not provided	PI-using patients had significantly higher total cholesterol and triglyceride levels	Metabolic changes associated with PI are atherogenic and cause endothelial dysfunction
		Assess the effect of lipid/lipoprotein changes on endothelial dysfunction		Flow mediated vasodilation (FMD) of brachial artery (BA)	High resolution ultrasound						PI-using patients had markedly impaired FMD compared to non-PI patients (2.6±4.6% vs 8.1±6.7%); use of PI was the primary determinant for impaired endothelial cell function; in addition, chylomicron, VLDL, IDL, and HDL-C levels predicted FMD	Patients receiving PI should be screened for hyperlipidemia