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Cardiovascular Risk Among HIV-Positive Patients on Antiretroviral Therapy

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Cardiovascular risk among HIV-positive patients on antiretroviral therapy

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Introduction

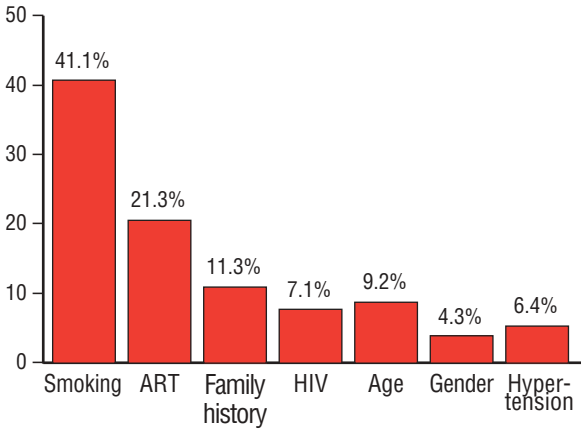
Highly active antiretroviral therapy (HAART) has been the standard of care for patients with HIV-1 infection in industrialized countries since 1996. Such treatment usually includes two nucleoside reverse transcriptase inhibitors (NRTIs), plus one protease inhibitor (PI) or one non-nucleoside reverse transcriptase inhibitor (NNRTI). The use of HAART has led to a dramatic decrease in morbidity and mortality among patients who are HIV-positive. However, this development has been coupled with an increase in the incidence of diseases associated with normal life expectancies, and of a few other diseases that are particular to the HIV-positive population.

A series of case reports of HAART-treated HIV-positive patients who developed unexplained cardiovascular events raised concern among the medical community that the survival benefits associated with HAART may be slightly offset by an increased risk of metabolic syndrome, leading eventually to heart disease.[1-4] However, only indirect evidence of an association has been garnered to date, and no prospective study has provided definitive proof of the association or its etiology.[5] Furthermore, only by conducting studies of 10- or even 20-year duration—following the Framingham study—can the medical community confidently discuss the causes and effects of cardiovascular disease among HIV-positive patients.

This situation has led to significant confusion among clinicians, as reflected in the results of two surveys conducted in August 2003 by the International Association of Physicians in AIDS Care (IAPAC). One survey involved 143 US HIV-treating physicians; the other survey involved 431 HIV-positive patients from across the United States. While 76.9 percent of the physicians surveyed perceive an increased cardiovascular risk among HIV-positive patients on antiretroviral therapy (ART), 41.1 percent attribute the increased risk to smoking, 21.3 percent attribute it to ART, and 11.3 percent point to a family history of coronary heart disease (CHD) as the cause. (Figure 1)

The physicians' responses were similarly very mixed when they were questioned by IAPAC about the antiretroviral drugs they perceive as causing an increased cardiovascular risk. (Figure 2) While 80.5 percent indicated 61 to 90 percent of their HIV-positive

Figure 1. IAPAC Physician Survey: What contributes to increased cardiovascular risk in HIV-positive patients on ART?



n = 143

patients are on some form of ART, 41.3 percent cited stavudine (d4T) as the NRTI responsible for increased cardiovascular risk, 44.8 percent pointed to efavirenz (EFV) as the NNRTI responsible, and the PIs most cited as responsible for increased cardiovascular risk were ritonavir (RTV) (94.4 percent), lopinavir (LPV) (81.1 percent), indinavir (IDV) (79.7 percent), nelfinavir (NFV) (67.1 percent), amprenavir (APV) (59.4 percent), and saquinavir (SQV) (58.7 percent).

Equally interesting, IAPAC surveyed physicians about which antiretroviral drugs, by class, caused cholesterol elevations and/or presented the most favorable lipid profile. Physicians most cited PIs as responsible for cholesterol elevations in their HIV-positive patients on ART (90.3 percent) versus 33.6 percent who cited NRTIs and 29.4 percent who cited NNRTIs. (Figure 3) Antiretroviral drugs classified as having a beneficial lipid profile included atazanavir (ATV) (53.8 percent), nevirapine (NVP) (34.3 percent), and enfuvirtide (T-20) (29.4 percent).

Encouragingly, 87.2 percent of patients surveyed by IAPAC reported having had their cholesterol levels tested. However, while 32.3 percent of patients said they have high cholesterol, only 19.7 percent are taking a medication to counter elevated cholesterol levels, 52 percent smoke, and 41.1

Figure 2. IAPAC Physician Survey: Which PIs are responsible for increased cardiovascular risk in HIV-positive patients on ART?

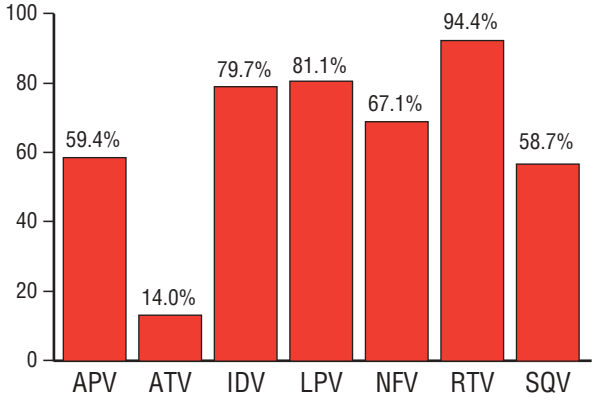


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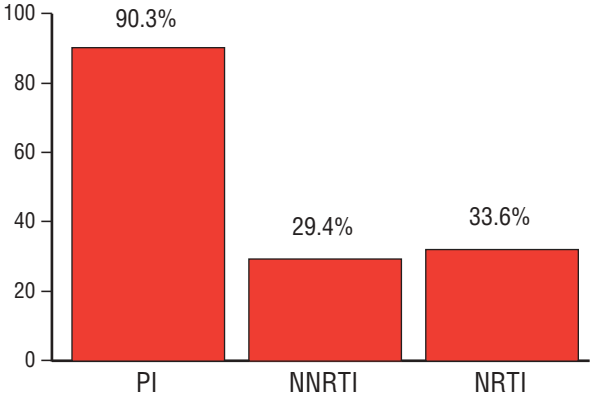
Figure 3. IAPAC Physician Survey: What class of antiretroviral drugs is responsible for cholesterol elevations in HIV-positive patients on ART?



n = 143

percent stated they do not know which, if any, of the antiretroviral drugs cause cholesterol-level elevations.

The rapidly shifting sands in this arena make it imperative that physicians remain cognizant of and fully educated about potential cardiovascular complications and their effects on the long-term treatment of HIV-positive patients. As with every other aspect of HIV medicine, the fast-evolving nature of the collective knowledge base represents a daily challenge for those men and women charged with the medical care of people living with HIV/AIDS. Nonetheless, given the potential implications of a parallel epidemic of cardiovascular disease, there is little choice but to remain vigilant while making clinical management decisions based on what is known rather than what is hypothesized.

Pathogenesis

It is well established that cardiac risk factors exist in both HIV-positive and -negative individuals. These risk factors range from hypercholesterolemia and hypertriglyceridemia to a family history of heart disease.[6] Individuals with the cluster of symptoms defined by the US National Cholesterol Education Panel (NCEP) as "metabolic syndrome" are at particularly high risk of developing heart disease. The syndrome involves abdominal obesity (defined as a waist circumference of >102 cm in men and >88 cm in women), elevated triglycerides (TG) and depressed high-density lipoprotein (HDL) cholesterol levels, as well as hypertension, insulin resistance with or without glucose intolerance, and prothrombotic states.[6]

Patients with advanced HIV disease who develop dyslipidemia tend to have a particular cluster of conditions that may include metabolic syndrome, hypercholesterolemia, type 2 diabetes mellitus, lactic academia, and elevated hepatic transaminases.[7] A recent survey of 143 HIV-treating physicians in the United States conducted by IAPAC indicates that:

- 51 percent stated that from 26 to 50 percent of their HIV-positive patients on ART experience lipodystrophy
- 33.6 percent indicated that from 26 to 50 percent of their HIV-positive patients have hypertension
- 72.1 percent said that from 26 to 75 percent of their HIV-positive patients on ART have experienced significant elevations in TG levels; 68.6 percent said that from 26 to 75 percent of their HIV-positive patients on ART have elevations in cholesterol
- 17.5 percent and 16.8 percent also noted that from 26 to 75 percent of their ART-naive HIV-positive patients have elevated cholesterol and/or TG levels, respectively
- 45.5 percent said they believe that from 26 to 50 percent of their HIV-positive patients on ART are at increased risk for cardiovascular disease; and 11.9 percent believe that from 51 to 75 percent of their HIV-positive patients on ART are at increased risk

A simultaneous IAPAC survey of 431 HIV-positive patients in the United States indicates that 48.7 percent believe they are at risk for heart disease.

HIV-positive patients have been found to possess higher titers of circulating adhesion molecules than normal subjects,[8] and to have a 7 percent absolute risk for developing heart disease within a decade.[9] In addition, some indirect evidence from retrospective cohort analyses and non-invasive imaging of peripheral arteries indicates that HIV-positive individuals are at higher risk for atherosclerosis than HIV-negative individuals.

It should be noted that Mauss *et al* recently have discovered a subgroup of HIV-positive patients on ART with hypercholesterolemia who may have lower cardiovascular risk than expected.[10] The investigators found a large, TG-rich, very low density lipoprotein (VLDL) cholesterol particle in this subgroup that resembles those found in patients with familial hypertriglyceridemia. In the latter patients, the large VLDL particles are associated with low coronary risk. Further studies, including studies utilizing nuclear magnetic resonance spectroscopy, could assist in identifying lipid subgroup particle size and determine whether lipid abnormalities are those associated with atherogenesis.

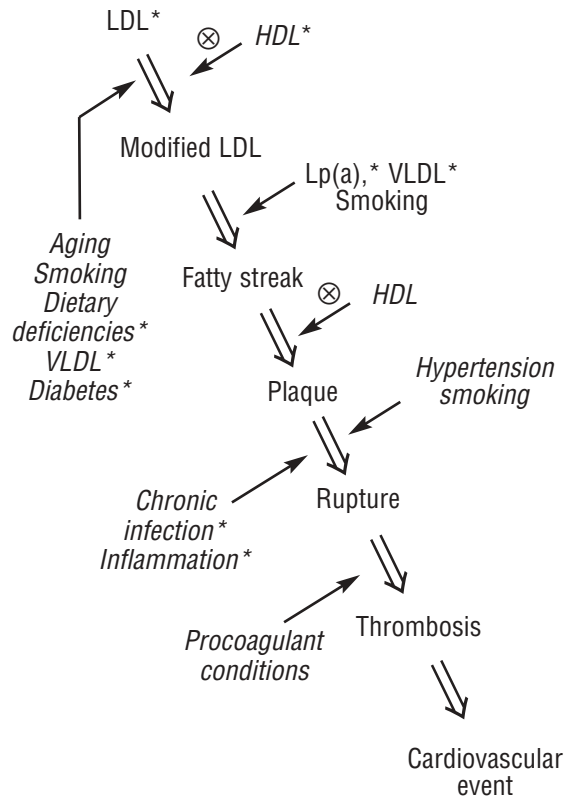
There are several places in the atherosclerotic process at which contributions could be made by HAART. (Figure 4) Low-density lipoprotein particles are trapped within the walls of blood vessels, where they undergo oxidation and subsequently attract monocytes. The monocytes engulf the LDL particles and become macrophages. Macrophages help form fatty streaks, which gradually become atherosclerotic plaques. Impairment of reverse cholesterol transport leads to further accumulation of lipids within the vessel walls. Unstable plaques may rupture and cause intravascular thrombosis and obstruction of blood perfusion.

Current knowledge regarding the etiology of altered lipid metabolism in HIV-positive patients does not afford a clear picture of whether HIV disease itself *or* ART is largely to blame—there are proponents on each side of the debate. The principal confounding factor is the sheer number of potential contributors to dylipidemia in HIV-positive patients. These patients are susceptible to traditional cardiac risk factors, as well as the following HIV-specific factors:

- disease-drug interactions
- effects of the medications' metabolites on lipid metabolism
- HIV disease-related inflammation
- fat redistribution
- creation of insulin resistance by antiretroviral drugs
- altering of lipoprotein metabolism
- HIV infection of the heart tissue
- accelerated replication of the virus
- opportunistic infections
- viral infections
- autoimmune response to viral infection
- drug-related cardiotoxicity
- nutritional deficiencies
- prolonged immunosuppression

Isolating and examining each of these factors independently is an inherently very difficult task.

Figure 4. Cascade of events, and modulators (italicized), that lead to the development of atherosclerosis and its clinical consequences



⊗=inhibitory effects
* Factors related to HIV infection and HAART

Source: Mooser V. Atherosclerosis and HIV in the highly active antiretroviral therapy era: Towards an epidemic of cardiovascular disease? *AIDS* 2003;17(Suppl 1):S65-S69.

Some current evidence indicates the elevated risk is not attributable to HAART. For example, results from the Multicenter AIDS Cohort Study (MACS) suggest that much of the increase in total cholesterol (TC) and LDL cholesterol experienced by patients on HAART reflects a return to pre-infection baseline levels and normal increases with aging.[11] (Figure 5)

Other research has shown that although lipodystrophy is more common among patients taking PIs longer than 18 months, it has also been reported in HIV-positive patients who are PI-naive and taking PI-sparing regimens.[12,13] However, other findings point to ART rather than HIV as the cause of lipodystrophy. A number of *in vitro* studies have demonstrated inhibition of lipogenesis by PIs,[14] as well as other phenomena such as mitochondrial toxicity with NRTIs, and inhibition of adipogenesis and promotion of lipolysis by NRTIs.[7] And, lipodystrophy is almost exclusive to patients receiving ART; it has not been reported in antiretroviral-naive HIV-positive patients.[7]

Figure 5. Change in lipids relative to pre-conversion values: MACS

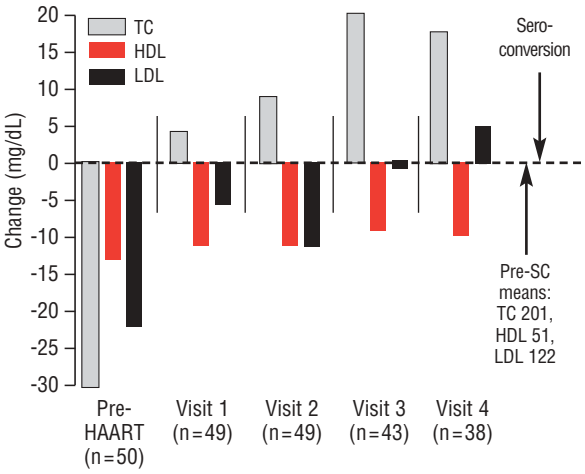
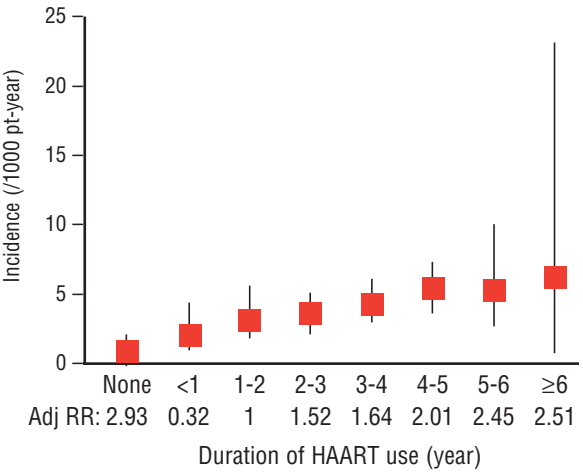


Figure 6. Incidence of MI: D:A:D study



Source: Friis-Moller N, Weber R, D'Arminio Montforte A, *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 Infections. February 10-14, 2003. Boston, MA. (Abstract 130).

Evidence for prevalence

There has neither been consistent, unequivocal evidence of a direct link between administration of HAART and an increase in risk for cardiovascular events, nor has the risk been consistently quantified.

Nonetheless, the circumstantial evidence appears to be strong. For example, two prospective studies of previously antiretroviral-naive adult patients also point to an elevated prevalence of HIV lipodystrophy with PI-containing therapy. One of the studies was a German trial involving patients treated for a median of 101 weeks with d4T or zidovudine (ZDV) as the NRTI backbone.[15] It revealed that use of HAART for more than two years is associated with an odds ratio of 4.4 for lipoatrophy. The overall prevalence of lipodystrophy was 48.7 percent with an odds ratio of 3.8 for PI use but did not differ according to NRTI backbone. The other study, conducted in Barcelona, showed 17 percent of the 494 patients developed some type of lipodystrophy after a median of 18 months.[16] The study also revealed an increased risk of 1.56 is associated with every additional six months of ART, but not with any individual antiretroviral drug.

Several large observational or database studies also point to a link. For example, an examination of the 19,795-person French Hospital Database on HIV yielded a steadily increasing incidence of myocardial infarction (MI) with increasing length of PI use.[17] The results, presented at the 8th Conference on Retroviruses and Opportunistic Infections (CROI), indicated the rate reached 34.7 MIs per 10,000 person-years among subjects who had taken PIs for at least 30 months; the investigators reported the expected MI incidence in men of the same age is 10.8 per 10,000 person-years.

Results from the D:A:D (Data on Collection of Adverse Events of Anti-HIV Drugs) observational study of 23,490 patients—presented at the 10th CROI—indicate the risk of MI increases significantly relative to non-HAART users with the duration of HAART use.[18] Subjects were enrolled from July 1999 to April 2001, with final data collection/analysis completed in August 2002. Although the subjects were followed prospectively starting in July 1999, the investigators entered data based on years since the subjects were started on HAART (PI- or NNRTI-containing). This varied from none to more than six years. It is unclear whether the investigators had source documentation for all subjects' date of first HAART initiation, or whether they derived this information from the subjects' charts. Data on HIV disease, risk factors for MI, and incident MI were also examined. The median age of this cohort was 39 years, 24 percent were female, 60 percent were smokers, and 30 percent had elevated TG levels.

During the total of 36,479 person-years covered in the study, 126 subjects had an MI. This subgroup was comprised of 90 percent men and had a median age of 48 years. Thirty-six (25 percent) of the subjects had a fatal MI. Traditional risk factors such as age, male sex, previous history of CHD, and smoking remained independent predictors of developing a MI. Other important risks included diabetes and hypertension. The relative risk per year of exposure to HAART was 1.26. (Figure 6) Interestingly, lipodystrophy was a protective risk (relative risk [RR] = 0.6). However, this term was defined by subjective measures and needs to be further studied before any conclusions can be drawn. The investigators concluded that HAART use is associated with a 26 percent relative increase in the rate of MI per year of exposure over the first seven years.

As the D:A:D study's lead investigator noted at the 10th CROI, however, the risk of MI among HIV-positive patients is low, and the obvious benefits of HAART outweigh concerns over potential CHD. Nevertheless, it remains important to consider all aspects of healthcare for HIV-positive patients. These include modification of traditional CHD risk factors whenever possible, as well as treating the complications of HAART as they arise (see page S33, "Treatment Recommendations for Dyslipidemia in HIV-Positive Patients").

Results from another very large ongoing observational study, this one using the Johns Hopkins University database, also were presented at the 10th CROI.[19] The nested case-control study was designed to assess factors associated with CHD and cerebrovascular disease (CVD). Subjects without CHD and CVD risks were randomly selected as controls. Five controls per case were identified and matched on cohort enrollment date and duration of follow-up.

Of 2,671 patients followed for 7,330 person-years after January 1, 1996, there were 43 CHD and 37 CVD events. This yielded an incidence rate of 5.9 CHD events/1,000 person-years and 5.0 CVD events/1,000 person-years, respectively. The investigators noted these rates are significantly higher than one would have expected for the same age-sex-race population: the National Health and Nutrition Examination Surveys (NHANES) reported rates of 2/1,000 person-years for CHD and 3/1,000 person-years for CVD.

The researchers also determined that factors significantly associated with having a CHD or CVD event included age (mean 46 years for cases, 41 years for controls), cholesterol (mean 186 mg/dL for cases, 156 mg/dL for controls), prior diabetes (15 percent cases, 7 percent controls), prior hypertension (43 percent cases, 17 percent controls) and CD4 counts (mean 351 cells/mm^3 cases, 251 cells/mm^3 controls). They did not detect differences between cases and controls with respect to race, injection drug use, or HIV-1 RNA levels. However, the investigators determined cases were significantly more likely than controls to have received a PI (59 percent versus 43 percent) and d4T/lamivudine (3TC) (63 percent cases, 43 percent controls). However, no differences were found for patients on other NRTIs, NNRTIs, or any individual PI. The risk factors were similar for CHD and CVD when assessed separately. The investigators did not adjust for smoking or lipodystrophy. Also, due to the limitations of this database, they could not account for nadir CD4 count or duration of HIV infection.

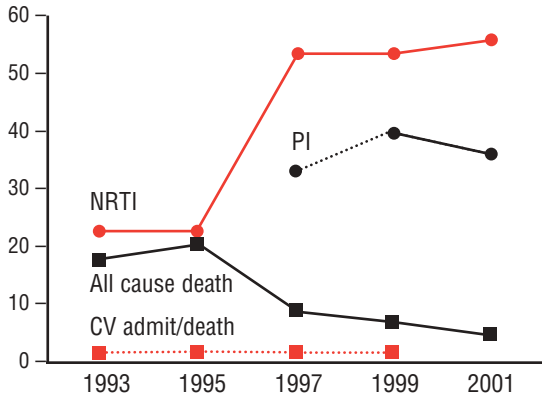
A study of carotid artery intima-media thickness (IMT)—a predictor of clinical cardiac events in individuals with or without cardiac symptoms—was presented at the 10th CROI.[20] The San Francisco General Hospital (SFGH) investigators sought to determine the predictors of carotid IMT in subjects infected with HIV and to follow IMT progression over time. The mean age of the 106 subjects was 45 years, and 88 (83 percent) were male. The average duration of their HIV infection was 11 years, their median CD4 count was 354 cells/mm^3, and their median duration of PI use prior to enrollment was four years.

The investigators found that, compared to historic controls, the baseline mean carotid IMT was 0.90 ± 0.27 mm thicker than expected. They also determined that multivariate predictors of increased IMT at baseline were age, LDL, hypertension, and nadir CD4 count <200 cells/mm^3. They found that C-reactive protein, fibrinogen, HDL, TG, lipodystrophy, and duration of HIV were not predictive of increased baseline carotid IMT. The investigators followed the first 22 subjects for a year and found their mean rate of carotid IMT progression was 0.1 ± 0.1 mm/yr. They reported this rate is 10 times higher than that reported in previous published studies of the general population. They also found that in this subgroup, age and duration of PI use were associated with carotid IMT progression. Interestingly, 41 percent of the 22 subjects had hypertension.

Results from several other studies point to a different picture. For example, a study published in 2002 from an ongoing observational study of HIV-positive patients in the Kaiser Permanente Medical Care Program of Northern California indicates that CHD and MI hospitalization rates are 1.7 and 1.5 times higher, respectively, among HIV-positive subjects relative to those who were HIV-negative.[21] However, they also indicate the elevation is not caused by the administration of a PI or any other type of antiretroviral drug.

A study published in 2003 in *The New England Journal of Medicine* also did not uncover a relationship between the use of PIs or other antiretroviral drugs and hospital admissions or deaths from heart disease.[22] In this study, Bozzette *et al* retrospectively examined the risk of CHD and CVD among 36,766 HIV-positive patients in Veterans Affairs (VA) facilities across the United States between January 1993 and June 2001. They found the rate of admissions for CHD or CVD disease decreased from 1.7 to 0.9 per 100 patient-years between 1995 and 2001, and that the rate of death from any cause dropped from 21.3 to 5.0 deaths per 100 patient-years in the same period. Regression analyses also revealed no association between the use of NRTIs, PIs, or NNRTIs and the risk of cardiovascular or cerebrovascular events—in fact, the use of antiretroviral drugs was associated with a reduced risk of death from any cause. (Figure 7)

Figure 7. Trends in exposure to ARVs and events



Furthermore, two studies of carotid IMT and another of the presence of plaque in HIV-positive patients showed no association between PI use and development of these indicators of atherosclerosis.

One of the IMT studies was published last year in *The Annals of Medicine*.[23] The prospective cohort investigation involved 423 HIV-positive patients being treated with HAART at French hospitals. The subjects' median carotid IMT measurement was 0.54 mm, and 38.1 percent (161) had lipodystrophy. The investigators also found in univariate linear regression analyses that IMT was significantly higher in subjects who were older, male, smoked regularly, drank alcohol regularly, had a higher body mass index, higher waist-to-hip ratio, increased systolic blood pressure, increased TC, increased homocysteine, glucose disorders, lipodystrophy, and HAART use. However, after the researchers performed multivariate regression analyses, lipodystrophy and HAART dropped off this list.

A more recent IMT study, ACTG 5078, which was conducted at sites across the United States, involved triads of patients consisting of one HIV-positive patient who had been on a PI for at least two years, one HIV-positive patient not on a PI, and one HIV-seronegative control.[24] All three subjects in each triad were matched for age within five years, race/ethnicity, sex, blood pressure, smoking status (using the American Cancer Society guidelines), and, for women, menopausal status. The HIV groups were also matched according to CD4 counts and HIV viral loads. Subjects were excluded if they had significant CHD risk factors such as diabetes, uncontrolled hypertension, and personal or first-degree-relative history of CHD.

Forty-five triads were enrolled; one subject in the PI group of one triad discontinued prematurely. The median duration of PI use was 216 weeks. All subjects were normotensive, and the cohort also was predominantly male (90 percent) and white (76 percent). The subjects' median age was 42 years and 56 percent were non-smokers.

The median CD4 count was 530 cells/mm^3 in the PI group, while it was 482 cells/mm^3 in the no-PI group. The nadir CD4 count was unavailable, as was duration of HIV seropositivity. The median values of LDL- and HDL-cholesterol were similar between the groups. However, TG were slightly higher in the PI group than in the no-PI and HIV-negative groups, at 219, 142, and 107 mg/dL, respectively. The TC levels were also higher, at 192 mg/dL, compared to 179 and 187 mg/dL, respectively, in the other two groups. There was also an increased waist-to-hip ratio among the PI group compared with the other two groups; however there were no differences with respect to the body mass index or waist circumference.

The ACTG 5078 team interim results revealed that when they controlled for known CHD risk factors, the PI group did not have larger carotid IMT measurements than the two other groups at baseline. They also performed regression analyses that revealed factors associated with an increased carotid IMT were low HDL, elevated TG—which became more pronounced at low HDL levels—older age and increased body mass index. The association with low HDL is of particular note, since low HDL levels are associated with HIV itself and was among the first lipid abnormalities described prior to the introduction of HAART.

However, CHD may take decades to develop and it will be critical to follow this extremely well-matched cohort for years in order to arrive at a definitive result—in fact for significantly longer than the team had initially planned.

The other study, involving 68 HIV-negative and 168 HIV-positive patients, revealed that while more HIV-positive subjects had one or more plaques, use of PI therapy was not associated with the presence of plaques.[25]

Critical examination of studies

Clearly clinicians who treat HIV-positive patients with ART are aware of the various studies on the potential for cardiovascular risk among such patients—but because of the contradicting results, they are far from uniform in their interpretation of the available data. For example, 23.4 percent of physicians who responded to a recent IAPAC survey say currently available information influences their timing of ART initiation, 69.5 percent say it impacts their choice of initial antiretroviral regimen, 66.7 percent responded that it influences their decision to switch antiretroviral drugs or antiretroviral regimens, 32 percent say it influences their choices of salvage therapy, and 23.4 percent

noted the perceived implications of cardiovascular risk in HIV-positive patients on ART influences their consideration of structured treatment interruptions.

It is, therefore, vitally important that such clinicians read all papers critically, in order to make the optimal decision for each of their patients. They should particularly be aware that some of the studies described in the previous section have serious methodological flaws. Nevertheless, these studies are crucial as they attempt to identify what the problems are so that more definitive studies may be designed. For example, the D:A:D study suffers from many of the same limitations of other, similar studies that collect information retrospectively and then follow subjects prospectively. Furthermore, the presentation of the design and results did not include complete data on the duration of HIV infection among the subjects. This is a critical omission because long-term HIV infection may be a risk factor for CHD. Thus duration of ART actually may be a surrogate marker for duration of HIV infection.

The same criticism applies to the Johns Hopkins study, which compares historic controls to the current database, which is a less-than-sound methodological approach. Also, this cohort was matched by entry into database rather than any HIV disease characteristics. Moreover, HIV replication rate may be a confounding factor in both studies, as an accelerated rate can increase the level of immunosuppression. HIV-negative controls are also absent in both of these studies.

The small number of events reported in D:A:D is also insufficient for an accurate creation of patient risk profiles based on use of various antiretroviral drugs. As the investigators follow this cohort over time—particularly the many subjects who were antiretroviral-naive or on their original antiretroviral regimens at enrollment—we perhaps can begin to sort out which factors make up the lion's share of the contribution to CHD. The investigators are to be commended for developing such a large cohort and collecting data from a number of international centers.

It is also important to note that prospective studies designed to determine the incidence of antiretroviral-induced CHD (if it exists) have an inherent limitation: as patients develop lipid abnormalities and/or glucose intolerance, these conditions are treated by the patients' physicians and thus the cardiac risk decreases.

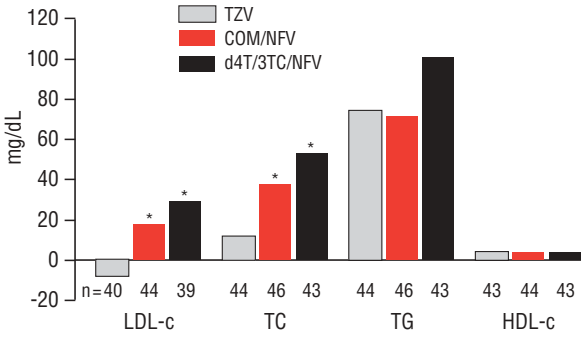
The carotid IMT studies also merit close, critical examination, as there was a remarkable difference in results between the SFGH and ACTG 5078 studies. The SFGH carotid study, which demonstrated a significantly greater increase in IMT among HIV-positive patients compared to non-HIV-infected individuals, suffered from a small number of subjects and from inclusion of patients at significant risk of CHD progression. On the other hand, the ACTG 5078 team attempted to reduce as many traditional confounding factors resulting in a very low risk poulation. Depending on the true risk, if any, attributed to ART, it may take years before such risk is identified.

The ACTG 5078 team chose to measure the carotid IMT at a specific site on the far wall of the internal carotid artery at which there is laminar flow. This has been reported to be a very precise and reproducible measurement. The SFGH group chose to measure six sites near the bifurcation on each internal carotid artery twice, for a total of 12 measurements. They then calculated the average IMT from these measurements. However to accurately determine the carotid IMT measurements in each study group, the same method should be used in each one.

Another difficulty in interpreting the SFGH results is the lack of an HIV-seronegative control group. The investigators compared the patients' results to historic controls—who may not be representative of the current population. Within the last year, for example, there have been headlines in the national news media stating that more than 20 percent of Americans now meet the definition for the metabolic syndrome—compared to less than 10 percent a decade ago. Even more disturbing is that more than 6 percent of 20-year-olds meet the criteria for the metabolic syndrome. Given the marked improvement of technology and the changing demographics, it is imperative that these trials have HIV-seronegative matched controls. The investigators at SFGH are therefore encouraged to increase their sample size and enroll controls as they continue their research.

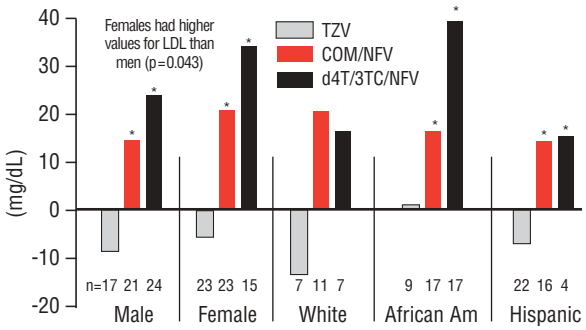
In summary, the data on the incidence of CHD in HIV-positive patients and the risk associated with PI use are still conflicting. Furthermore, they are compromised by the retrospective nature of most of the available studies, the short duration of prospective trials, lack of reliable ascertainment from many of the subjects about important factors such as duration of smoking, presence of metabolic syndrome, HIV duration, and time of CD4 nadir. Most of the studies have also been conducted with patients who are under 50 years of age—who have a relatively low prevalence of CHD compared to older patients—and thus rarely furnish statistically significant numbers of patients who have developed CHD and/or stigmata of the disease such as stroke or MI. As a result, it remains unclear whether HIV and/or anti-HIV therapies are independent risks for the development of CHD.

Figure 8. Fasting lipid values: Change from baseline at 96 weeks



*$P \leq 0.001$ compared to TZV

Figure 9. Subgroup LDL values: Change from baseline at 96 weeks



*$p \leq 0.03$ compared to TZV

In fact the February 20, 2003, issue of *The New England Journal of Medicine* contained a co-authored editorial on the study by Bozzette *et al* in which Daniel Kuritzkes (Harvard Medical School) and Judith Currier (University of California, Los Angeles) debated the issue.[26] The editorialists' conclusion—that longer follow-up of the VA and other cohorts is needed to ascertain cardiac risk among HIV-positive patients—is well-founded.

Effects of specific HAART medications on lipid levels

The studies most relevant to the daily clinical practice of physicians who treat HIV-positive patients are those that examine the effects of specific antiretroviral drugs. The recent IAPAC survey of physicians uncovered the direct effects of such studies on clinicians' knowledge. For example, the survey found 29.4 percent of physicians surveyed attribute elevated cholesterol levels to NNRTIs, while 25.2 percent attribute elevated TG levels to this class of antiretroviral drug. Furthermore, 33.6 percent and 28.7 percent attribute elevated cholesterol and TG levels, respectively, to NRTIs, and 90.3 percent and 86.8 attribute elevated cholesterol and TG levels, respectively, to PIs. In addition, 34.3 percent of respondents stated NVP is the NNRTI with the most favorable lipid profile, while 53.8 percent believe ATV is the PI with the most favorable lipid profile. And, 29.4 percent noted T-20 has a favorable lipid profile. Not surprisingly, these physician responses represent a divergence of opinion reflected in patients' beliefs, with 23 percent of 431 patients surveyed by IAPAC indicating that they believe PIs elevate cholesterol levels and 10.2 percent indicating cholesterol elevations are attributable to a combination of antiretroviral drug classes.

ESS40002 is among the studies that nicely demonstrate the contributions to lipid abnormalities within a class of NRTIs when combined with a PI.[27-29] The study was initiated in November 1999 and prospectively examined hyperlipidemia in 258 ART-naive patients from 34 sites in the United States, Panama, the Dominican Republic, Guatemala, and Puerto Rico. Sixty (23.2 percent) of the subjects are from the Latin American sites, and 48 (18.6 percent) had high viral loads, of 100,000 to 200,000 copies/mL at baseline; none of the subjects had >200,000 copies/mL and none had <1,000 copies/mL. All of the subjects also had CD4 counts >50 cells/mm^3. The participants were randomized in equal numbers to receive either Trizivir (TZV), Combivir (COM)/NFV, or d4T/3TC/NFV for 96 weeks.

There were no differences between treatment groups in change in HDL cholesterol between baseline and the end of the study. However patients taking COM/NFV or d4T/3TC/NFV experienced significant increases in LDL cholesterol, TC, and TG between the beginning and end of the study. Those on TZV experienced increases in TC and TG, but had reduced LDL levels, at week 96. The investigators also observed an additive effect of d4T that had a larger impact on TG, TC, and LDL but not on HDL. (Figure 8)

Interestingly, the investigators observed a race effect at week 24, with blacks having a higher TC level than whites or Hispanics. By week 96, Hispanics' TG and TC levels had outpaced those of both blacks and whites among those taking d4T/3TC/NFV.[28] The researchers also observed a gender effect at week 48, with female patients on the NFV-containing arms having a smaller increase in LDL than males, and with female patients in all three treatment groups having lower levels of TG than men. These particular gender effects disappeared by week 96, only to be replaced by women taking d4T/3TC/NFV having higher LDL levels than men.[29] (Figure 9) Women and Hispanic individuals taking d4T also had elevated lactate. Further analyses revealed that women tended to have more muted virologic responses than men, while response rate with

TZV was consistently higher in Hispanics. These results point to the possibility that there may be inter-individual genetic differences with respect to metabolic pathways for antiretroviral drugs and host lipoproteins.

A retrospective study presented at the Infectious Diseases Society of America (IDSA) 2001 Annual Meeting by the present author showed approximately half of the patients on a regimen containing lopinavir/ritonavir (LPV/r) developed increased TC and TG levels.[30] The investigators sought—in light of previous clinical studies showing, in non-fasting analyses, that up to 30 percent of LPV/r patients developed dyslipidemia—to define in a clinical setting the percentage of HIV-positive patients on LPV/r having fasting elevated LDL, TC, and TG as defined by NCEP Adult Treatment Panel (ATP) III guidelines.

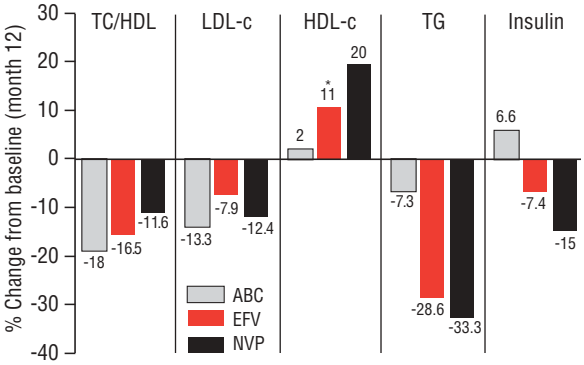
The researchers conducted a retrospective chart review of 67 patients taking LPV/r in a university clinic and private office that treated a total of approximately 1,500 HIV-positive patients. Sixty-three (94 percent) of the LPV/r users were men and the subjects' mean age was 41 years. Thirteen percent had no cardiac risk factors, while 55 percent smoked, 27 percent were ≥45 years old, 20 percent had HDL cholesterol of <40 mg/dL, 11 percent had hypertension, 5 percent had diabetes, and 5 percent had a family history of CHD. Ten patients were excluded—seven because follow-up fasting lipid profiles were not available, and three because their pre-LPV/r fasting lipid profiles were not available.

Prior to starting LPV/r, 27 percent (16 of 60) of the patients met NCEP III guidelines for initiating lifestyle changes/therapy. After LPV/r treatment, that proportion rose to 83 percent (50 of 60). Of 47 patients with TG <200 mg/dL pre-LPV/r, 27 experienced increases in TG to 200 to 399 mg/dL, three had increases in TG to 400 to 749 mg/dL, and two had increases to 750 to 1200 mg/dL. Moreover, TC levels fell in only two of 60 patients (3 percent), while 26 (43 percent) had unchanged TC levels and 32 (53 percent) experienced increased TC levels. There were non-statistically-significant increases in the subjects' LDL levels, although in the subgroup of patients whose LDL increased, 33 percent experienced an increase of ≥30 mg/dL.

Furthermore, six of 39 patients with HDL <40 mg/dL at baseline experienced increases in HDL levels to 40 to 59 mg/dL. However eight of 17 patients with HDL levels of 40 to 59 mg/dL pre-LPV/r experienced decreases, to HDL <40 mg/dL, after LPV/r administration.

The investigators calculated the subjects' mean increase in Framingham Scores to be 6 percent. They concluded

Figure 10. Metabolic changes following switch from PI to ABC, EFV, or NVP



*$P<0.05$

Source: Fisac C, Fumero E, Crespo M, *et al*. Metabolic and body composition changes in patients switching from a protease inhibitor-containing regimen to abacavir (ABC), efavirenz (EFV) or nevirapine (NVP). Twelve-month results of a randomized study (LIPNEFA). XIV International AIDS Conference. July 7-12, 2002. (Abstract ThPEB7354).

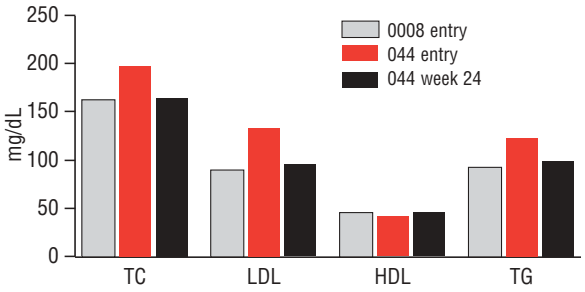
that patients on LPV/r might be at risk of developing CHD, particularly those with concomitant risk factors such as diabetes, hypertension, and smoking. It is also important to note that not all patients developed hyperlipidemia on LPV/r, suggesting that there is an underlying mechanism yet to be defined. It remains unclear why some individuals do develop metabolic abnormalities while on ART and others do not.

An ongoing prospective study comparing three different PI-sparing regimens—ABC, EFV, and NVP—has shown that all subjects experienced a significantly decreased TC-to-HDL-cholesterol ratio.[31] Patients on EFV and NVP obtained a significant elevation of HDL cholesterol, while ABC and NVP patients experienced reduced LDL cholesterol levels. Both EFV and NVP decreased TG significantly compared to ABC and, perhaps most interesting, they both decreased insulin levels whereas ABC was associated with increased insulin levels. (Figure 10)

Similarly, 48-week results from the 2NN study presented at the 10th CROI indicate that patients receiving NVP develop higher HDL cholesterol levels together with a lower TC-to-HDL cholesterol ratio, but that patients taking EFV do not accrue as much benefit.[32]

These and other research results pointing to increased serum lipid levels with certain types of antiretroviral drugs have led many physicians to switch patients from the potentially problematic drug to another medication. This switching strategy has the potential to avoid further pharmacological interventions for dyslipidemia. It should be noted, however, that a simple switch might not always

Figure 11. Changes in lipids: NFV to ATV



Source: Murphy R, Pokrovsky V, Rozenbaum W, *et al.* Long-term efficacy and safety of atazanavir with stavudine and lamivudine in patients previously treated with nelfinavir or ATV: 108-week results of BMS Study 008/044. 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2003. Boston, MA. (Abstract 555).

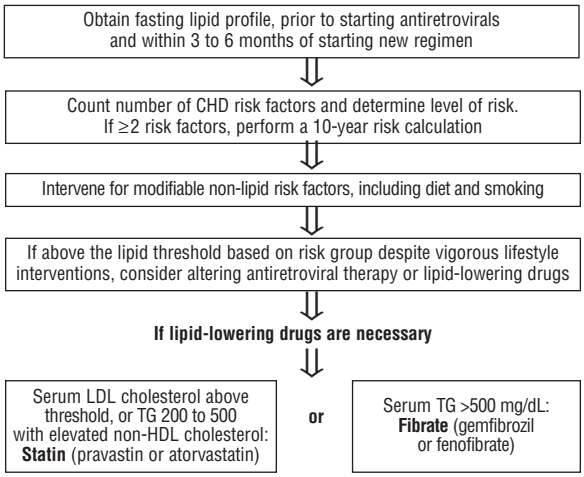
alleviate the dyslipidemia: studies in which a PI was eliminated in favor of ABC, EFV, and NVP have shown mixed results.[33]

One of the building blocks upon which clinicians can now base switching strategies is the 108-week results of BMS Study 008/044.[34] The Phase II trial was designed to assess the long-term efficacy and safety of ATV beyond 72 weeks and to assess the efficacy and safety of switching patients from NFV to ATV. The subjects had completed the Phase II trial BMS AI424-008, and those who had received NFV were switched to ATV 400 mg. Patients on ATV were continued on either ATV 400 mg or ATV 600 mg. A total of 346 patients were enrolled in the trial, and their median cumulative time on therapy was approximately 108 weeks.

The results indicated that extended ATV treatment causes sustained virologic suppression and continued CD4 cell increases without clinically relevant increases in TC, fasting LDL cholesterol, or fasting TG. (Figure 11) After a switch from NFV, 24 weeks of ATV treatment resulted in maintenance or improved virologic suppression, and in significant decreases toward pre-antiretroviral treatment levels in TC, fasting LDL cholesterol, and fasting TG. Discontinuations due to adverse events were infrequent and comparable across cohorts (ATV 400 mg, 1 percent; ATV 600 mg, 2 percent; NFV to ATV, 3 percent). Furthermore, no new safety issues were identified after approximately 108 weeks of cumulative ATV treatment in AI424-008/044. Asymptomatic elevation in indirect bilirubin (without hepatic transaminase elevation) was the most frequent laboratory abnormality.

Other research also indicates that patients experience improvement in lipid levels after switching to ATV from other HAART regimens: in a study of 10 patients who

Figure 12. General approach to lipid disorders and cardiovascular risk in HIV-positive patients on ART



Source: Guidelines for the Evaluation and Management of Dyslipidemia in HIV-Infected Adults Receiving Antiretroviral Therapy: Recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis* 2003:37;613-27.

were switched to an ATV-containing regimen after regimen failure or development of dyslipidemia, three (30 percent) were able to discontinue lipid-lowering drugs after an average of 16 weeks.[35] Switching from a PI to NVP or ABC usually improves TC and TG levels, while switching to EFV does not.[36]

However, studies of switching from d4T to ABC have also yielded inconclusive results. Patients with a favorable treatment history—that is, never previously receiving an NRTI-based regimen that was less than fully suppressive, and no history of virologic rebound occurring while on treatment—switching from a potentially lipid-raising PI to NVP or ABC may be preferable to a pharmacologic intervention with a lipid-lowering drug.

When considering such switches, clinicians must weigh the risks of new treatment-related toxicities and the possibility of virologic relapse to the risks of other difficulties arising from the use of lipid-lowering agents, such as potential drug-drug interactions and new treatment-related toxicities.

Treatment recommendations for dyslipidemia in HIV-positive patients

It is likely that lipid-lowering therapies will benefit HIV-positive patients. However during the initial phases of treatment of the HIV infection, therapy for the primary disease must take precedence over other conditions such as dyslipidemia. Conversely, HIV-positive patients need not be treated more aggressively for lipid

abnormalities when they are addressed than should the general population.[36] The recommended treatment algorithm for lipid disorders and cardiovascular risk in HIV-positive patients on HAART is shown in Figure 12.

Interestingly, while the respondents to the recent IAPAC physician survey are very experienced in treating HIV disease—62.9 percent see more than 20 patients a week and 49.7 percent have been treating HIV-positive patients for more than 15 years—their responses indicate they are reluctant to follow the recommended treatment path for patients with increased risk of CHD. For example, 26.6 percent of physicians surveyed would, as the first course of action, prescribe a lipid-lowering agent for an HIV-positive patient in which they perceive increased cardiovascular risk, while only 43.4 percent would recommend a lifestyle change. Their level of screening of patients for dyslipidemia is somewhat more in line with recommendations, with 40.6 percent of physicians indicating they screen their patients' cholesterol levels every six months and fully 37.8 percent stating they perform such screening three months. Moreover, 37.8 percent say they screen their patients' TG levels every six months and 38.5 percent screen every three months.

Clinicians should follow the NCEP ATP III guidelines when initially evaluating HIV-positive patients who have dyslipidemia and/or other risk factors for CHD.[6] This assessment incorporates serum lipid levels, which should be measured after the patient has fasted for at least eight and preferably 12 hours, and before the patient has begun taking ART. The standard screening lipid profile includes TC, HDL cholesterol, and TG. LDL cholesterol and non-HDL cholesterol levels can be calculated from these values. These measurements should be repeated within six months of the patient initiating HAART, and yearly thereafter unless abnormalities are detected or therapeutic interventions are initiated. However, for individuals with pre-existing lipid abnormalities or other known cardiac risk factors, it may be preferable to repeat lipid screening one or two months after initiation of HAART.

Clinicians also must offer patients interventions for other modifiable cardiovascular risk factors such as smoking, hypertension, physical inactivity, obesity, and diabetes mellitus at the initial counseling session. For example, smoking cessation is a far more powerful tool in reducing cardiovascular risk among smokers than is lipid-lowering medication. The physician should also check for potential exacerbating conditions such as excessive alcohol use, hypothyroidism, renal disease, liver disease, and hypogonadism. As part of the determination of appropriate therapy they must also consider the effects of particular agents—namely glucocorticoids, ß-blockers, thiazide diuretics, thyroid preparations and hormonal agents such as androgens, progestins, and estrogens—on both cholesterol and TG levels.

Table 1: Absolute five-year coronary risk and NNT_H* — Framingham equation

	Absolute five-year coronary risk—no lipodystrophy (%)	*Absolute five-year coronary risk—lipodystrophy (%)*	*NNT_H*
	Men		
Nonsmoker			
30 years old	0.5	1.9	71
50 years old	3.6	9.1	18
Smoker			
30 years old	1.1	3.6	40
50 years old	6.3	14.0	13
	Women		
Nonsmoker			
30 years old	0.04	0.5	217
50 years old	2.2	8.8	15
Smoker			
30 years old	0.1	1.1	100
50 years old	4.1	13.7	10

*Number of patients treated to harm one patient.

Source: Egger M. HAART and the heart: Lipodystrophy and cardiovascular risk. *The PRN Notebook* 2001;6(1):15-18.

In assessing a patient's cariovascular risk and corresponding treatment plan, the clinician should count the number of CHD risk factors that modify lipid goals. They should then use a risk-assessment tool based on the Framingham Heart Study to estimate the 10-year risk of MI or cardiac death of patients who have two or more risk factors for CHD.[37]

Table 1 was created by Egger to illustrate the use of the NCEP ATP III guidelines in calculating patients' risk of developing CHD.[38] Egger concluded, in his presentation of these results at the 40th International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), that while it is obvious that the benefits of HAART outweigh the risks of CHD for many patients, there are some patients—such as those who are older and who smoke cigarettes—for whom the reverse may be true.

The clinician may use this information to identify the patient's LDL cholesterol target levels. Patients with

Table 2. National Cholesterol Education Program treatment decisions based on LDL cholesterol level

		LDL cholesterol level, mg/dL	
Risk category	*Goal*	*Initiate therapeutic lifestyle change*	*Consider drug therapy*
CHD or risk equivalent	<100	≥100	≥130*
<2 risk factors and 10-year risk of ≤20%			
10-year risk of 10%-20%	<130	≥130	≥130
10-year risk of <10%	<130	≥130	≥160
0-1 risk factors	<160	≥160	≥190†

Note: Therapeutic lifestyle changes include dietary and exercise intervention. Reduction of the LDL cholesterol level is a primary goal of therapy. Reduction in the non-HDL cholesterol level is a secondary goal of therapy when the TG level is >200 mg/dL. Non-HDL cholesterol goals are 30 mg/dL higher than LDL cholesterol goals.
*For an LDL cholesterol level of 100-129 mg/dL, drug therapy is optional; consider treating HDL cholesterol and TG disorders.
† For an LDL cholesterol level of 160-189 mg/dL, drug therapy is optional.

Source: Guidelines for the Evaluation and Management of Dyslipidemia in HIV-Infected Adults Receiving Antiretroviral Therapy: Recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis* 2003;37:613-627.

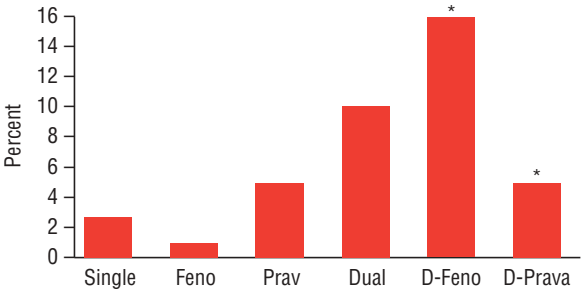
Table 3. Recommendations for choice of initial drug therapy for dyslipidemia in HIV-positive patients on ART

	Therapy		
Lipid abnormality	*First choice (rating)*	*Alternative(s) (rating)*	*Comments (rating)*
Elevated LDL-C level or elevated non-HDL-C level with TG level of 200-500 mg/dL	statin (B-I)	fibrate (C-I) or niacin (C-III)	Start with low doses of statins and titrate upward; with CYP3A4 inhibitors (PIs or DLV), pravastatin 20-40 mg QD (AI), or atorvastatin 10 mg QD (B-II) initial dose is recommended; fluvastatin 20-40 mg QD is an alternative (B-II); fibrate may elevate the LDL-C level when the TG level is elevated; niacin may worsen insulin resistance; combining fibrate and statin increases the risk of rhabdomyolosis (use with caution and monitor for clinical evidence of myopathy)
TG level >500 mg/dL	fibrate (B-I)	niacin (C-III) or fish oils (C-III)	Reduction of TG level becomes a primary target in these patients; drug interactions with fibrates are unlikely; Gemfibrozil dosage is 600 mg BID, and fenofibrate dosage is 54-160 mg QD; niacin may worsen insulin resistance

Source: Guidelines for the Evaluation and Management of Dyslipidemia in HIV-Infected Adults Receiving Antiretroviral Therapy: Recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis* 2003;37:613-627.

established CHD should be treated to achieve an LDL cholesterol target of <100 mg/dL. Moreover, patients without established CHD but with a similar 10-year risk estimate (ie, ≥20 percent) should be treated equally aggressively. Individuals with severe hypertriglyceridemia (>500 mg/dL) are not uncommon in the HIV-positive population. Thus reduction of TG levels is a primary goal among these patients. For those with

Figure 13. NCEP III Response (LDL/HDL/TG)



* P=0.04 for dual arm comparison

moderate triglyceridemia, non-HDL cholesterol becomes a secondary target for therapy after LDL cholesterol goals have been achieved. The non-HDL cholesterol target for each risk category is 30 mg/dL higher than the corresponding LDL cholesterol target. (Table 2)

Patients with metabolic syndrome should be encouraged to lose weight using dietary modification and increased exercise. Those who also have moderate to severe lipoatrophy should be encouraged to increase physical activity, but not to an extreme degree as excessive weight loss can exacerbate lipoatrophy.

For treatment of hypercholesterolemia, dietary and exercise interventions should usually be initiated first and given a thorough trial before instituting drug therapies. Studies have proven the efficacy of such non-drug approaches: one study indicated diet and exercise resulted in an 11 percent decrease in cholesterol levels in HIV-positive patients,[39] and another produced an 18 percent reduction in TC and a 25 percent reduction in TG in subjects with fat wasting who were given dietary intervention plus supervised cycling and resistance training thrice weekly.[40] Dietary intervention should include reduction of fat intake, as well as avoidance of simple sugars, and a decrease or complete elimination of alcohol. Fish oils or omega-3 fatty acid supplements may be helpful, as they have been shown to decrease TG synthesis in some patients.[41] Moreover, niacin can effectively reduce high TG and TC levels, although it also appears to increase insulin resistance.[42]

Exceptions to preemptive initiation of non-drug therapy are patients with symptomatic CHD or CHD risk equivalent, or with LDL cholesterol of >220 mg/dL. These patients require urgent intervention. Consultation with a dietitian is desirable when initiating the non-drug therapies, or after initial attempts at dietary intervention fail.

After a minimum six-month trial of non-drug therapy, clinicians must reassess the patients' lipid levels. If the levels have not decreased to target levels, the patient and clinician should discuss the alternatives of either making a switch or switches in the ART or using lipid-lowering drugs.

For patients who have serum LDL cholesterol above the target level or TG at 200 to 500 mg/dL combined with elevated non-HDL cholesterol, use of a statin should be seriously considered. The optimum first-line statin choices are either pravastatin, initiated at 20 to 40 mg/day, or atorvastatin, initiated at 5 to 10 mg/day. (Table 3)

Clinicians should also be cognizant, in making prescribing decisions, of the results of pharmacokinetic interaction studies. The investigators for ACTG 5047 found that in the presence of the combination of RTV and SQV, atorvastatin acid levels increase by 347 percent, total active atorvastatin levels increase by 79 percent, simvastatin levels increase by 3,059 percent, and pravastatin levels decrease by 47 percent.[43] Data from Agouron's drug interaction studies between NFV and atorvastatin performed with healthy volunteers showed that NFV increased total active atorvastatin levels by 74 percent, and simvastatin by 505 percent.[44] In addition, Carr noted a significant interaction between atorvastatin and LPV/r but not with pravastatin.[45] The results of a study presented at the 2nd IAS Conference on HIV Pathogenesis and Treatment indicate that, in HIV-negative patients, NFV and pravastatin co-administration results in a 47 percent decline in pravastatin serum level, while co-administration of EFV decreases the serum concentration of pravastatin by 40 percent.[46]

Overall, it appears that atorvastatin likely can be used at low initial doses in patients taking PIs, although because extensive safety data are lacking this should be done with caution. Pravastatin appears to be safe for use with PIs; however higher doses may be necessary in the presence of RTV or other agents that induce enzymes responsible for the metabolism of pravastatin.

The use of fluvastatin 30 to 40 mg/day is a reasonable alternative in patients taking PIs. This recommendation is based upon fluvastatin's known metabolism and its lack of significant interaction with other substances that inhibit CYP3A4 and CYP2C9.[47] All patients prescribed a statin should have careful monitoring for myopathy, increased CK, and myoglobin. Patients taking PIs should not concurrently take lovastatin or simvastatin. It is likely safe for patients to take any of the statins concurrently with EFV or NVP, although more data are needed to make this a solid conclusion.

The use of simvastatin and lovastatin is not recommended at this time, at least in part because of severe potential drug-drug interactions with PIs or delavirdine (DLV).[36] Drug-drug interactions are unlikely with other classes of antiretroviral drugs and lipid-lowering agents, although there is the potential for diminished efficacy of RTV and NFV if they are taken concurrently with fibrates.

Fibrates are a sound alternative when statins are not appropriate. While they are less efficacious than statins for hypercholesterolemia, fibrates can achieve modest LDL cholesterol reductions in patients with normal TG levels. Such patients can be administered micronised fenofibrate 54 to 160 mg QD or gemfibrozil 600 mg BID.[48]

Monotherapy with either pravastatin or fenofibrate appears safe—but it also seems this combination is unlikely to allow patients to achieve the composite NCEP goal for correction of dyslipidemia.[49] The ACTG 5087 investigators came to this conclusion after randomizing 86 HIV-positive patients to receive pravastatin, and 88 to receive fenofibrate. One hundred and seventy of the 174 subjects had lipid data available at 12 weeks. Four subjects (5 percent) on pravastatin achieved the NCEP composite goal, and one (1 percent) on fenofibrate achieved the goal. Thirty of the pravastatin recipients (36 percent) met the NCEP LDL goals, while eight of the fenofibrate subjects (9 percent) did so ($P<0.001$). Furthermore, 41 (49 percent) of subjects on pravastatin met the NCEP HDL goals, whereas 57 (66 percent) of those on fenofibrate did so ($P<0.05$). Fifteen (18 percent) of those on pravastatin also met the TG goal, whereas 42 (48 percent) met the TG goal ($P<0.001$). Median changes in LDL/HDL/TG were -30/0/-27 and +13/+4/-118 mg/dL in subjects receiving pravastatin and fenofibrate, respectively (P-values for treatment difference were all significant).

One hundred and thirty-six subjects subsequently went on to dual therapy, while four—three on fenofibrate and one on pravastatin—discontinued therapy due to protocol-defined toxicities. The LDL/HDL/TG response was greatest in the dual fenofibrate arm. (Figure 13) There were no reports of rhabdomyolysis.

Fibrates should be used as first-line agents in patients with TG >500 mg/dL. Such patients can be given fenofibrate 54 to 160 mg BID or gemfibrozil 600 mg BID, 30 minutes prior to breakfast and supper. Fish oils and niacin are alternative agents.

Patients who are refractory to these initial treatments are candidates for alternative treatments, including the switching of medications within the antiretroviral regimen.

Summary

Dyslipidemia is now recognized as a significant potential adverse event in HIV-positive patients who are on ART. The tide of evidence continues to flow between the shore of HIV being the primary factor behind increased cardiovascular risk in HIV-positive patients, and the ocean of HAART being the primary cause. However, there clearly is an association between long-term infection with HIV and metabolic abnormalities.

HIV-infected adults should undergo evaluation and treatment based on the NCEP ATP III guidelines. The NCEP recommends non-pharmacologic interventions be given a thorough trial prior to consideration of drug therapy. The recommendations also stipulate that intensive therapy with lipid-lowering medications should be used in individuals with metabolic syndrome. This includes aggressive treatment of hypertension, diabetes, and dyslipidemia. The NCEP also emphasizes the importance of smoking cessation, weight reduction, increased physical activity, and a salubrious diet.

The fundamental message still is that physicians must treat HIV infection *first*. The choice of ART depends on many patient-specific factors, of which cardiovascular risk is only one. ■

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