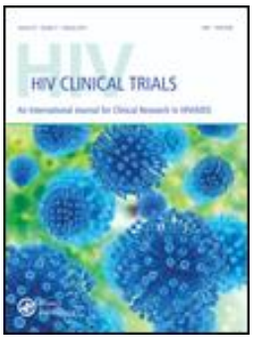

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Coronary Heart Disease Risk, Dyslipidemia, and Management in HIV-Infected Persons

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Dyslipidemia and coronary heart disease (CHD) are of increasing concern in persons with human immunodeficiency virus (HIV) infection who are living longer because of the benefits of highly active antiretroviral therapy (HAART). All classes of drugs used in HAART have been associated with atherogenic changes in lipid profiles. The management of HIV-infected persons with dyslipidemia and/or CHD currently emphasizes the importance of monitoring and optimizing lipid levels through lifestyle changes, switching antiretrovirals (ARVs), and lipid-lowering treatments utilizing guidelines developed for persons without HIV infection. In HIV-infected persons, the use of lipid-lowering drugs may result in pharmacokinetic interactions with ARVs, complicating the management of patients. Recent advances in our understanding of the differential effects of specific ARVs on lipids is beginning to alter the clinical approach to management. In the absence of randomized clinical trials, clinicians should aggressively treat atherogenic dyslipidemia by primarily utilizing or switching to ARVs with the lowest potential to induce CHD or, when this is not possible or is ineffective, secondarily by the addition of lipid-lowering therapy. The current optimal management of HIV infection requires careful selection of ARVs with consideration given to the potential development of CHD and an understanding of how to manage dyslipidemia. **Key words:** *coronary heart disease, CHD management, HAART, HIV*

The use of highly active antiretroviral therapy (HAART) has substantially reduced the mortality associated with human immunodeficiency virus (HIV) infection and the incidence of many associated opportunistic diseases.[1,2] As a result of this achievement, many HIV-infected persons are living longer and enjoying significantly improved quality of life. With the advent of HAART, and the corresponding decline in acquired immune deficiency syndrome (AIDS)-related mortality, it is now possible to better focus on other HIV- or HAART-related clinical events that can result in increased mortality.[1] Several recent reports strongly suggest that antiretroviral therapy (ART) increases the risk of developing symptomatic coronary heart disease (CHD).[3,4] As a result, there is growing concern that the number of myocardial infarctions and strokes will increase over time in this population. Therefore, it is important for clinicians to become familiar with the effects of antiretroviral therapy and the management of dyslipidemia and CHD.

The issue of increased CHD risk in HIV-infected persons is a complex one. Several CHD risk factors that are not related to HIV infection, such as age, family history of CHD, and lifestyle, can confound analysis of overall CHD risk. HIV infection itself can induce unfavorable inflammatory states and atherogenic lipid changes.[5,6] Dyslipidemia may also result from both an underlying familial disorder and from HAART-induced changes. HIV-infected patients typically must maintain ART for prolonged periods of time to control viral replication and sustain the benefits of reduced morbidity and mortality from AIDS. However, not all pa-

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tients develop dyslipidemia when exposed to specific antiretrovirals (ARVs). Further, there may be differential effects of various classes of ARVs with resulting increase in CHD risk occurring for multiple reasons.

Shortly after the introduction of protease inhibitors (PIs), cases of ART-associated atherogenic lipid changes were reported.[7] Several cases of CHD associated with dyslipidemia, characterized by increases in total cholesterol (TC) and triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C), were reported.[8–12] Mounting evidence suggests that HAART-related metabolic changes are associated with increased CHD risk. Elevated levels of LDL-C and TG, reduced levels of high-density lipoprotein cholesterol (HDL-C), and reduced sensitivity to insulin, all of which have been reported in persons taking HAART, are associated with increased risk for coronary disease in the general population.[13–16]

Several current guidelines are available for CHD risk prevention in HIV-infected patients and for managing issues such as dyslipidemia, atherosclerosis, and insulin resistance. These include the combined HIV Medicine Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group, the International AIDS Society–USA (IAS-USA), and the Department of Health and Human Services (DHHS) Panel on Clinical Practices for Treatment of HIV Infection from the USA.[17–19] These guidelines align closely with recommendations for CHD risk and management for non–HIV-infected patients[15] and provide a basis for monitoring and managing CHD-associated factors in HIV-infected patients. These guidelines highlight the fact that the management of HIV is becoming increasingly complex because of several juxtaposed problems: the need to continue ART to maintain viral suppression despite the presence of metabolic disturbances; the unique and poorly understood mechanisms of ARV-induced dyslipidemia and the incomplete response to lipid-lowering therapy; the complex drug interactions between lipid-lowering agents and ARVs; and the uncertainty of the long-term consequences of ARV-associated metabolic derangements. Thus, there is a need to increase the awareness of clinicians of these problems and to encourage them to treat patients with ARVs that have a less profound affect on lipids, particularly those persons at higher risk for CHD prior to the initiation of HAART. This article will discuss CHD risk factors in HIV-infected patients and the issues that need to be addressed when ARV regimens that can minimize these risks are being selected.

RISK FACTORS ASSOCIATED WITH CHD: LIPID MANAGEMENT GUIDELINES

The majority of guidelines for the management of CHD risk in persons with HIV infection are derived from the extensive published literature in the HIV seronegative population. Chief among these risk factors are the plasma lipid profile (including TC, TG, LDL-C, and HDL-C). Since the first publication of the National Cholesterol Education Project (NCEP) guidelines in 1988, it has been recognized that CHD risk is associated with changes in subgroups of plasma lipid levels.[20] In 2001, the third update of the NCEP guidelines (ATP III) was released; it defined the levels of various categories of lipids associated with marked increases in CHD risk and provided guidelines for further lowering risk and managing patients (**Table 1**).[15] The Framingham CHD risk-scoring system, another tool commonly used to predict risk in individuals with more than one risk factor, is based on age, gender, smoking habits, blood pressure, and hypertension.[21] It provides an indication of the 10-year risk for myocardial infarction (MI) and death due to coronary events. What remains unclear in the HIV-infected population is whether atherogenic dyslipidemia due to HIV and ARVs has the same long-term impact on the development of clinically significant atherosclerosis.

Current guidelines for CHD risk management emphasize the treatment of elevated LDL-C modified by specific risk factors including cigarette smoking, blood pressure, HDL-C levels, family history of CHD, and older age.[15] Within each risk category defined by the NCEP guidelines, therapeutic lifestyle changes are recommended for all individuals whose LDL-C levels exceed ATP III goals. Recommended lifestyle changes include diet, increasing soluble fiber, reducing the intake of saturated fats and cholesterol, reducing weight, and increasing physical activity. Lipid-lowering therapy is recommended when the above measures fail to reach the NCEP targets (**Table 1**).

While LDL-C is still the main target for managing risk associated with lipid levels, other epidemiologic studies have highlighted the potential

Table 1. LDL-C goals for drug therapy according to risk category

Risk category	LDL-C goal (mg/dL)[a]	LDL-C level indicative of drug therapy (mg/dL)
CHD or CHD risk equivalent (10-year risk >20%)	<100	≥130
≥2 Risk factors (10-year risk ≤20%)	<130	10-year risk: <10%: ≥160 10%–20%: ≥130
≤1 Risk factor	<160	≥190

Note: LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease.

[a]Initiate therapeutic lifestyle changes if at or above this level. LDL-lowering drug optional if below this level.

Adapted, with permission, from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.

limitations of using LDL-C alone to estimate CHD risk.[22] In particular, low HDL-C levels and high TG levels have been shown to be CHD risk factors that are independent of LDL-C.[15] Analysis of 10-year follow-up data from the Prospective Cardiovascular Münster (PROCAM) study indicated that even though the rates of MI were associated with LDL-C, the rates also rose independently according to increasing TG levels.[23] Similarly, data from the Framingham Study indicated that for any given level of LDL-C, the risk of developing CHD increases with decrements of HDL-C level.[21] These and other data have influenced the current ATP III guidelines, with non-HDL cholesterol now being a secondary target for intervention. This is of particular importance because hypertriglyceridemia with lowered HDL-C levels is a common problem in persons with HIV infection who are taking HAART.

Non–HDL-C levels, determined by measuring HDL-C, TC:HDL-C or LDL-C:HDL-C ratios, may provide refined risk assessments by simultaneously taking into account both atherogenic and cardioprotective lipid fractions. These measures may be particularly useful in resource-poor settings, where expensive and more labor-intensive measures of LDL-C may not be widely available. This is particularly germane to the discussion of persons with HIV infection because >95% of those with this disease reside in resource-poor settings. Other potential markers of CHD risk assessment are apolipoprotein levels, particularly apolipoprotein B-100, the sole apolipoprotein in LDL, and apolipoprotein A-I, the major constituent protein in HDL, which may add additional predictive power.[24] Thus, the CHD risk, lipid ratios, and novel CHD risk markers are particularly important considerations for individuals with HIV infection, because unfavorable lipid and glucose metabolism alterations resulting from HIV disease and ART can affect these factors and presumably increase overall risk.

IMPACT OF HIV INFECTION ON CHD RISK FACTORS

Lipid Abnormalities Associated with HIV Infection

Early studies of patients with advanced untreated HIV infection typically demonstrated reduced TC and LDL-C levels and moderately elevated TG levels, mainly in the form of very low-density lipoprotein (VLDL).[25,26] Similarly, a recently published comparison of preseroconversion and post-HIV infection lipid values in 50 patients showed a substantial decrease in TC, HDL-C, and LDL-C.[27] These studies provide us with a general baseline from which to determine the effects of ARV regimens on CHD independent of the effects of HIV infection.[28,29] Unfortunately, currently there are no adequate in vitro or in vivo models of HIV infection to study the independent effects of HIV and ARV on lipid metabolism and CHD risk. Thus,

it is sometimes difficult to tease out effects of ARVs from those of HIV infection itself.

Physical Cardiac Abnormalities Associated with HIV Infection

There is a paucity of data regarding the direct effects of HIV infection on physical cardiac abnormalities. Several studies of cardiovascular abnormalities in persons with HIV infection suggest that coronary lesions, coronary calcium levels, cardiovascular intima media thickness, and markers of cardiovascular inflammation such as C-reactive protein are important in the progression of clinically significant atherosclerosis.[30–33] Histologically, cardiac lesions in HIV patients were found to be similar to the lesions in the non-HIV population.[34] In pilot studies on the presence of coronary calcium, an indicator of atherosclerotic burden, HIV-infected patients showed a trend toward higher coronary artery calcium scores than those in matched uninfected controls.[35] One early study of coronary artery lesions in HIV-infected persons undergoing autopsy suggested that endothelial proliferation may be associated with HIV disease.[36] Most studies of CHD risk and physical lesions are confounded by the use of ARVs in the presence of HIV infection. Thus, there is currently insufficient data on whether atherosclerotic plaques, endothelial disease, or other physical abnormalities are associated with presence of HIV infection.

Cardiac Inflammation Associated with HIV Infection

Other physical changes in the cardiac endothelium due to inflammation from HIV infection and interaction with the immune system also may contribute to CHD risk. In a study of symptomatic and asymptomatic HIV-infected persons, the extent of HDL-C decrease and TG increase was greater in patients with more profound immunosuppression (lower CD4 counts).[37] A similar association of low CD4 counts and high TG levels has been reported by two other groups.[38,39] With new data linking atherosclerosis and inflammation, markers such as elevated C-reactive protein levels are being considered for improved CHD risk monitoring in combination with traditional plasma lipid levels.[40] Henry and colleagues[41] have demonstrated that elevated C-reactive protein in persons with HIV infection is associated with other risk factors for CHD. Overall, there remains insufficient data on the relationship between atherosclerosis, HIV, and cardiac inflammatory markers of disease.

CHD Associated with HIV Infection

Due to the high rate of AIDS-related mortality in the pre-HAART era, it was difficult to determine relative rates of CHD in this population. As a result, many studies that examined CHD risk in HIV-infected persons involved patients who were receiving some type of HIV therapy at the time of assessment, even if it was suboptimal monotherapy. However, data on CHD in HIV-infected persons suggest that there may be an independent association between CHD and HIV infection.[42] In the pre-PI era, eight cases of coronary artery disease were reported in persons with advanced HIV infection who died suddenly. At autopsy, these individuals had typical eccentric coronary artery lesions.[36] Several reports suggest that ischemic CHD in HIV-infected persons appears to be most closely associated with traditional risk factors such as hypertension and hypercholesterolemia.[39] However, Hsue and colleagues[43] suggest that the clinical features of acute coronary syndromes may differ in that HIV-infected persons are generally younger, have lower thrombolysis in myocardial infarction (TIMI) scores, and have a higher rate of restenosis. Similarly, Varriale and colleagues[44] reported that 17 of 22 persons younger than 55 years of age presenting with an acute myocardial infarction and HIV infection had no more than one coronary risk factor. Thus, HIV infection and/or its treatment may alter the development and presentation of CHD. With our understanding limited by the inability to study this issue easily, it remains to be confirmed if known coronary risk factors are associated with CHD risk in HIV-infected persons.

IMPACT OF ART ON CHD RISK FACTORS

The benefits of ART in advanced HIV infection are clear and outweigh the increase in CHD risk that might result from therapy. The current relatively small incidence of CHD leading to mortality should not cause physicians or patients to consider discontinuing ART or not initiating it at all for fear of developing CHD. Nevertheless, substantial evi-

Table 2. The DAD study: relationship between exposure to HAART and the incidence and relative risk (RR) of myocardial infarction[13]

HAART exposure (years)	Incidence/1000 person years	Adjusted RR
None	0.8	0.32
< 1	2.2	1
1 to <2	3.3	1.52
2 to <3	3.6	1.64
3 to <4	4.4	2.01
4 to <5	5.4	2.45
5 to <6	5.5	2.51
6	6.4	2.93

Note: HAART = highly active antiretroviral therapy.

dence obtained via large cohort studies has shown that ART may increase CHD risk factors that have been identified in the general population.[4,13,45] Indeed, the complications of ART, including dyslipidemia and CHD, are currently driving recommendations to hold off on initiating HAART until persons develop more advanced immunologic suppression due to HIV infection (i.e., a CD4+ lymphocyte count <350 cells/mm^3).

The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study is a large, prospective observational cohort designed to examine whether ART was associated with an increase in MI over 2 years. This study showed that the relative risk of MI increased with exposure to HAART (**Table 2**).[45] By multivariate analyses, significant associations were found between ART and increased CHD risk. Out of 23,490 patients, 129 developed MI during 36,479 person-years of follow-up.[46] In addition, an independent association was found between older age, previous CHD history, male gender, and other factors such as cigarette smoking, hypertension, and diabetes.

Further analysis of DAD data by conventional risk equations showed that the 3-year risk for MI was more than 3-fold higher in patients receiving ARV when compared with ARV-naive patients and 1.07% for patients receiving ARVs from all three classes, whereas the risk of AIDS or death was significantly lower with ARV use and higher if ARVs were discontinued.[46] This rate of MI was similar or somewhat higher than the risk predicted by the Framingham Study and was likely due to ART-related changes in the conventional CHD risk factors.[47] In a second study, which examined the incidence of CHD risk factors and ART use, analysis of 28,513 HIV-infected individuals from California Medicaid concluded that the incidence of CHD was higher in HIV-infected persons than in non–HIV-infected individuals and was significantly higher in younger men up to age 34 years and in women up to age 44 years. The relative risk for CHD development in patients on ART versus those not taking ART was 2.06-fold ($p < .001$).[14]

Data from the HIV Outpatient Study (1993 to 2001), a period of increasing use of HAART, showed a statistically significant association between PI therapy and MI (odds ratio [OR] = 7.1, 95% CI 1.6-44.3) when compared with patients not taking PIs.[45] Similarly, in the Frankfurt cohort study, the incidence of MI in the pre-PI interval (1983–1986) was significantly lower than in the post-PI period (1995–1998) (0.86 vs. 3.41, $p = .002$).[48] In a separate report of the French Hospital Database on HIV (19,795 men exposed to PIs), MI was diagnosed in 49 patients with 39,023 person-years of PI use, and MI events increased with increasing duration of PI use (<18 months to >30 months).[4] Finally, in a report from HIV-Insight database of 7,542 HIV-infected persons, the authors concluded that PI regimens increased CHD risk.[49]

However, there are data that do not support the association between PI use, duration of PI use, and CHD risk. A retrospective study of 36,766 HIV-positive patients treated at Veterans Affairs hospitals demonstrated no association between increased ART use and increased cardiovascular or cerebrovascular events (41.6% of patients were on PIs; median duration of use, 16 months).[50] The relatively short duration of PI use, use of lipid-lowering drugs, age of the population, and retrospective collection of data may explain the disparate results of this study compared to others. Similarly, a smaller study of the Kaiser Permanente Medical Care Program of Northern California database showed a greater increase in CHD-related hospitalization of HIV-positive patients than of HIV-negative participants. Pre- and post-PI (mean exposure 2.6 years) MI rates did not differ significantly.[42] A follow-up study indicated that although PI regimens appeared to have higher associated CHD and MI rates, the authors concluded that a longer follow-up would be needed to make definitive con-

clusions.[51] Finally, in a small study of 16 HIV-infected persons diagnosed with CHD, CHD was associated with common risk factors (e.g., cigarette smoking, hypertension, etc.), HIV infection, low CD4+ counts, and previous long exposure to nucleoside reverse transcriptase inhibitors (NRTIs) but not duration of PI use.[39]

SURROGATE MARKERS AND CHD RISK

Carotid intima thickness (IMT) is a proxy measure for progression of atherosclerosis in the general population.[52] Currier and colleagues[53] conducted a prospective matched case-control study of 135 HIV-infected patients at low risk for CAD. Each PI-treated patient was matched with one PI-naive HIV-infected individual and an HIV-negative control, with each triad matched by cardiovascular risk factors: age within 5 years, race, gender, blood pressure status (either normal or hypertensive), smoking status (never, current, or former), and menopausal status. Patients were excluded if they had a family history of MI, diabetes mellitus, prior CAD, or uncontrolled hypertension. There were no differences in the median carotid IMT levels at baseline among the groups (PI group = 0.693 mm; no-PI group = 0.708 mm; and HIV negatives = 0.687 mm). Factors associated with increased IMT in multivariate analysis included low HDL-C, elevated triglyceride levels (when HDL was low), older age, and increased body mass index. In contrast, Hsue and colleagues[54] found higher baseline mean carotid IMT values (0.9 mm) and found that progression was 0.1 mm/year with age and duration of PI use as predictive factors.

Several groups have measured quantitative calcium scores in coronary arteries (coronary artery calcium [CAC] scores) by electron beam computed tomography. Meng and colleagues[55] reported no significant differences in CAC scores in PI-treated patients compared with PI-naive patients (11.0 vs. 1.7; p = .43). Talwani[56] and Acevedo[35] also each reported no difference in CAC scores in persons with HIV infection compared with matched seronegative controls.

There are many limitations to the prior endpoint and surrogate marker studies. Most studies were retrospective and did not collect all data on known risk factors for CHD. Many studies did not have uniform collection of data or definitions of endpoints. Few studies have examined individuals prior to the use of ARVs and followed them longitudinally for a sufficient period of time to draw any conclusions. Regardless of some conflicting results and limitations in existing data, the preponderance of evidence suggests that CHD risk and events are increased in persons taking ART. Given that atherosclerosis is a process that takes decades to manifest clinically, studies that have delineated the risk of lipid changes due to specific classes of ARVs should raise concern. These changes have been strongly associated with increased CHD risk, strongly suggesting that ART would be associated with an increased risk of CHD.[15,21,23]

IMPACT OF ART ON LIPIDS IN ART-NAIVE PATIENTS

The DAD study showed that in addition to the increase in CHD associated with treatment, atherogenic lipid profiles were observed in patients who were on regimens including PIs and NNRTIs alone or in combination. An increase in the prevalence of elevated TG levels was seen in all classes, whereas NRTI and PI (but not NNRTI) regimens were associated with low HDL-C levels, which were also correlated with low CD4+ counts and high viral loads.[13] This is perhaps the strongest support to date for the hypothesis of a direct association between ART and an increased risk of CHD; however, other studies have produced similar results.[57] The effect of age and gender on the outcome of ARV therapy was evident in the results reported by Levy et al.,[58] who concluded that in ARV-naive men and women (N = 1,781) who started triple ART, there was an increase in TG in all age groups, with a maximum increase in men <25 years old, and a modest increase in TC in all groups.

Protease Inhibitors

Lipid Alterations Associated with PIs

Among the three classes of ARVs, PIs have been associated most consistently with an atherogenic effect on lipids. Significant atherogenic lipid changes that can involve TC, TG, LDL-C, and surrogate marker lipoprotein-a (LP-a) have been observed in HIV-infected persons receiving PIs.[59,60] Evidence that PIs could cause these significant changes was reported as early as 1995 with phase I/II studies of ritonavir as a single agent in HIV-

positive patients. Danner et al.[59] found that over a 32-week study period ($N = 84$), TC increased 30% to 40% and TG increased 200% to 300%. A subsequent report established that ritonavir caused dyslipidemia in normal participants, in whom significant elevations in VLDL cholesterol and TG were accompanied by a reduction in HDL-C after 2 weeks of therapy.[60]

An analysis of mean lipid levels in patients enrolled in the Swiss HIV Cohort Study further revealed that all of the PIs then in use (ritonavir, nelfinavir, and indinavir) caused elevations in TC and LDL-C, with the largest effect on TG.[61] Increases in TC and TG were also observed with lopinavir and low-dose ritonavir and amprenavir-based triple therapy.[62,63]

In a randomized, comparative trial of stavudine plus lamivudine plus nelfinavir ($n = 327$) or lopinavir/ritonavir ($n = 326$), elevations in TG >750 mg/dL were more common in the lopinavir/ritonavir group than in the nelfinavir group (9.3% vs. 1.3%, $p < .05$).[64] This study was limited by a lack of uniform collection of fasting lipid levels. Elevated LDL-C levels can also potentiate the atherogenic effects of elevated LP-a levels.[65] Koppel et al.[66] also observed that very high levels (>700 mg/L) of LP-a were more common in HAART-treated patients and correlated with levels of LDL-C. Stein and colleagues[67] reported that elevated large VLDLs, intermediate-density lipoproteins (IDLs), and small dense LDL-C particles were more common among persons taking PI-based HAART compared to those on non–PI-containing ART. A randomized open-label NEFA study that compared lipid profiles from three regimens concluded that overall lipid profiles improved when patients were switched from PI-based to PI-sparing therapy.[68] Taken together, these studies suggest that some PIs can induce atherogenic lipid changes independent of other risk factors such as HIV infection.

Not all PIs induce changes in lipid profiles. Initial data on the recently approved PI atazanavir suggest that it may not be associated with an unfavorable lipid profile, as in the case of older PIs.[69,70] In a randomized, comparative trial of stavudine plus lamivudine plus nelfinavir 750 mg thrice daily or atazanavir 400 mg daily, the change in fasting LDL-C and TG was -7.1% and 1.5% in the atazanavir-treated group, whereas increases of 31.1% and 42.2% occurred in the nelfinavir arm.[71]

Alterations in Carbohydrate Metabolism Associated with PIs

In addition to its effects on lipids, some PI use has been associated with impaired glucose tolerance and insulin in HIV-positive patients.[72–75] Both factors have been independently linked with an increased risk of CHD in the general population.[76] In one study of HIV-seronegative individuals, treatment with indinavir for 4 weeks caused insulin resistance.[77] In contrast, lack of early increase in insulin resistance was reported in antiretroviral-naive patients on nelfinavir (ACTG 384 study)[78] and seronegative participants who received atazanavir.[77,79] However, in studies of HIV seropositives taking amprenavir, insulin resistance developed relatively late in treatment, with insulin sensitivity remaining normal at 24 weeks but was decreased by 48 weeks.[63]

NRTIs

It has been suggested that as an ARV class overall, nucleoside reverse transcriptase inhibitors (NRTIs) increase CHD risk by causing mitochondrial dysfunction in many cells including cardiac endothelial cells, smooth muscle cells, and adipocytes, although this effect appears to have less of an impact than that seen with PIs, particularly if included in regimens with nonnucleoside reverse transcriptase inhibitors (NNRTIs), which appear to be less atherogenic (**Table 3**).[80–82] This has been highlighted by the introduction of a nucleotide reverse transcriptase inhibitor, tenofovir disoproxil fumarate, which does not appear to have the same effects on mitochondrial as other NRTIs. Among patients treated with either tenofovir or the NRTI stavudine, both with a backbone of efavirenz, there were fewer atherogenic changes in the tenofovir arm with respect to 96-week changes in TC, LDL-C, and HDL-C.[83] There are also differential effects among other NRTIs. For example, TC and TG increased more in patients who were taking a backbone of nelfinavir plus lamivudine with stavudine than with zidovudine plus nelfinavir and lamivudine. In addition, smaller increases in lipids occurred in patients taking only zidovudine plus lamivudine and abacavir, indicating that the NRTI contribution, although different within the class of ARVs, was less than

that of the PI nelfinavir.[84] In summary, the major side effect associated with NRTI-class compounds is mitochondrial toxicity. Data suggest that in some patients the NRTIs may be atherogenic, albeit to a lesser extent than the PIs.

Effect of NNRTIs on Lipids

As a class, NNRTIs have been shown to induce less atherogenic alterations in lipid profiles compared with PIs in treatment-naive HIV-infected persons. Data from the DAD study support this observation (**Table 3**). In this analysis, naive patients or those receiving a first-line therapy with PI-, nevirapine-, or efavirenz-containing regimens were evaluated for risk of dyslipidemia. This study concluded that, compared with PIs, patients on first-line NRTI plus NNRTI therapy had a lower TC:HDL-C ratio and a reduced likelihood of dyslipidemia.[46] A separate study (17,852 patients) that included 9 out of 11 cohorts of the DAD study found that HIV-infected persons on NNRTIs had a lower risk of low HDL than those on PIs.[85]

The ATLANTIC study, a randomized trial of first-line combination therapy that compared regimens of indinavir, lamivudine, and nevirapine on a backbone of stavudine and didanosine in naive patients, supports the findings of the DAD study. There was an increase in HDL-C of 49% with a reduction in TC:HDL-C ratio by 14% in those treated with nevirapine.[86] This trend continued at 96 weeks, and, in contrast, significant increases in mean LDL-C and TG levels were observed in the indinavir group.[87] Nevirapine was associated with the most favorable lipid profile, with a 40% increase in HDL-C, thereby reducing the TC:HDL ratio.

The lipid changes induced by efavirenz were compared with those from nelfinavir and indinavir (lamivudine and zidovudine backbone) in two separate studies. After 16 weeks of efavirenz- or nelfinavir-based HAART, TG rose 38.2% in the efavirenz arm and 26.5% in the nelfinavir arm; LDL-C increased 17% and 45%, respectively.[88] In a large, randomized study, TC significantly increased in patients receiving zidovudine/lamivudine/efavirenz (mean change +23 mg/dL, $n = 199$), zidovudine/lamivudine/indinavir (mean change +34 mg/dL, $n = 218$), or efavirenz/indinavir (mean change +58 mg/dL, $n = 218$) after 48 weeks.[89]

Table 3. Association of current antiretroviral therapy (ART) with dyslipidemia at entry into DAD study[13]

	Treatment-naive	No current ART		NRTI only		NNRTI		PI		NNRTI and PI	
	OR	OR	*p*	OR	*p*	OR	*p*	OR	*p*	OR	*p*
TC ≥240 mg/dL	1.0[a]	1.19	.25	0.73	.02	1.79	.0001	2.35	.0001	5.48	.0001
HDL ≤C ″35 mg/dL	1.0[b]	1.26	.06	1.35	.02	0.90	.37	1.46	.0001	0.93	.59
TG ≥200 mg/dL	1.0[a]	1.51	.0002	1.48	.0001	2.06	.0001	2.90	.0001	4.66	.0001

Note: HDL-C = high-density lipoprotein cholesterol; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-NRTI; OR = odds ratio relative to naive patients; TC = total cholesterol; TG = triglycerides.

[a]Multivariate analysis adjusted for variables associated with increased coronary heart disease risk for that variable: age, gender, smoking, family history of coronary heart disease, previous coronary heart disease, body mass index, transmission mode, CD4 cell count, HIV RNA, previous AIDS, cohort.

[b]Multivariate analysis adjusted for variables associated with increased coronary heart disease risk for that variable: age, gender, smoking, body mass index, transmission mode, CD4 cell count, HIV RNA, previous AIDS, cohort.

Table 4. 48-week lipid changes in the 2NN study (mmol/L)[90]

	Nevirapine once daily (*n* = 142)	*p*	Nevirapine twice daily (*n* = 275)	*p*	Efavirenz (*n* = 289)	*p*	Nevirapine + efavirenz (*n* = 127)	*p*
TG	+0.20	>.05	+0.05	>.1	+0.37	<.05	+0.45	<.05
TC	+1.01	<.05	+0.95	<.05	+1.11	<.05	+1.41	<.05
LDL-C	+0.56	<.05	+0.54	<.05	+0.70	<.05	+0.80	<.05
HDL-C	+0.35	<.05	+0.37	<.05	+0.25	<.05	+0.41	<.05
TC:HDL-C ratio	–0.32	<.05	–0.41	<.05	+0.05	>.1	–0.20	>.05

Note: HDL-C = high-density cholesterol lipoprotein; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides.

There appear to be differences in lipid effects between the two most commonly used NNRTIs, efavirenz and nevirapine.[17] In a direct comparison, the 2NN study examined patients treated with nevirapine once or twice daily, efavirenz once daily, and efavirenz plus nevirapine on a lamivudine plus stavudine backbone (**Table 4**). These data showed that while virological efficacy in the nevirapine and efavirenz arms was similar at 48 weeks,[90] compared with efavirenz, nevirapine treatment showed a greater increase in HDL-C ($p < .001$), a smaller increase in TG ($p = .010$), and a greater decrease in TC:HDL ratio ($p < .001$).[91] In a comparison of lipid and glucose profiles of HIV-infected patients on PI and NNRTI regimens, nevirapine was associated with lower levels of TG and TC than efavirenz[85] and lower levels of glucose than PI or efavirenz.[92]

In summary, lipid profile changes caused by HIV infection and associated inflammatory processes can be further complicated by ARV regimens. Utilizing ARVs with a more favorable effect on lipid profiles provides a platform for reducing the risk of CHD and possibly preventing or reducing the incidence of CHD in HIV-infected persons. An important unanswered question is whether the dyslipidemia induced by ARVs will lead to future coronary disease events at the same rate as those observed in persons without HIV infection. Long-term studies using less atherogenic regimens of ARVs, thereby reducing the CHD risks while maintaining HIV suppression, are needed.

MANAGING DYSLIPIDEMIA IN HIV-INFECTED PATIENTS

ART Switch

Dyslipidemia in HIV-infected persons is a complex problem that often requires multiple interventions. Viral suppression is the first goal of treatment, and this suppression, along with regeneration of CD4+ cells, must be maintained. Quality of life is an important consideration that influences the choice of ART; factors that should be considered include pill burden, convenience of the regimen, and adverse effects of treatment. Last, complications of ART, like metabolic disturbances, motivate initial and subsequent choices of ARVs.

Individuals with adequate viral suppression and dyslipidemia or other metabolic disturbances often consider switching to a regimen that is less likely to induce these effects. The strategic approach to switching ARVs relies upon the tolerability and potency of a new regimen, absence of underlying archived resistance to the new ARVs, and the likelihood of improvement in the metabolic derangements. Switching to a triple NRTI or NNRTI-based regimen has been shown to improve lipid profiles in patients who have developed dyslipidemia while on PI-based regimens. The likelihood of virologic failure has ranged from 10%–15% in most published trials of switch studies.[93] This annual rate of failure is probably

too high to consider this approach completely successful, because the morbidity and mortality from inadequately treated AIDS is substantial. Metabolic complications occurring in persons not on PI therapy have prompted trials comparing switching to non–NRTI-containing regimens versus standard of care. For example, the National Institute of Allergy and Infectious Diseases Adult AIDS Clinical Trials Group (ACTG) study A5116 compares switching from a PI-based regimen to an NNRTI-NRTI regimen versus switching to a non–NRTI-containing regimen (efavirenz/lopinavir/ritonavir).

Improvements in lipids and glucose metabolism have been reported for patients who switched from PI therapy to NNRTIs. Significant improvements or trends in improvements were observed in five different studies of nevirapine substitution.[93] For example, in a controlled trial of 34 patients switched from a PI- to a nevirapine-based regimen, there were significant reductions in LDL-C particles and an increase in HDL-C fraction by NMR spectroscopy.[94] Gil[95] reported a significant decline in TG and TC in 68 patients prospectively changed from a PI-based regimen to nevirapine after 3 years when compared with baseline. In the majority of studies where PI therapy was switched to an efavirenz-containing regimen, there were no dramatic improvements in dyslipidemia.[93]

There are few published randomized comparative switch studies for NNRTIs. In the Lip-NEFA study, a substudy of NEFA at 12 months, 460 PI-treated patients were randomized to abacavir, nevirapine, or efavirenz regimens. Abacavir resulted in the greatest decrease in TC ($p < .001$ vs. NNRTI groups) with no significant decrease in TG in any group.[96,97] Whereas NNRTI regimens, particularly nevirapine, resulted in improved (higher) HDL-C ($p \leq .05$).[97] A 24-month follow-up showed that switching to NNRTI regimen resulted in a marked improvement with a decrease in LDL (17% for nevirapine and 10% for efavirenz) and an increase in HDL-C (50% for nevirapine and 12% for efavirenz).[68] Analysis of virological efficacy at 18 months in the on-treatment group showed that 93%, 91%, and 80% of patients in the nevirapine, efavirenz, and abacavir groups, respectively, had viral loads of <200 copies/ mL.[98] This indicated that better virological suppression was obtained in the NNRTI group, particularly in patients with a suboptimal response to past therapy. The overall incidence of adverse events at 12 months was significantly lower in the abacavir arm than in either other arm.[96]

In summary, switch studies demonstrate somewhat conflicting results. The greatest improvements in lipids have been observed when patients switch from a PI-based regimen to abacavir (an NRTI), some improvements have been observed in patients switching to nevirapine (an NNRTI), and few changes in lipid levels have been observed in patients switching to efavirenz (an NNRTI). In persons at higher risk for CHD, particularly those with ART-associated dyslipidemia and/or insulin resistance, one of the first considerations should be a switch to a less atherogenic ART regimen. Clinicians must consider the history of ARV use, the resistance profile of HIV, and other quality-of-life issues in determining the benefits of switching therapy. Although no study has compared the strategy of switching therapy for dyslipidemia versus treatment with lipid-lowering agents, it seems generally preferable to switch therapy if possible to avoid adding to the burden of pills ingested daily, the added costs of additional therapy, and the potential for adverse drug–drug interactions. If patients can use NNRTI-based regimens, this is certainly indicated. Patients who require a PI-based regimen may want to use atazanavir preferentially because of its lesser effects on lipid or glucose metabolism. Studies comparing a switch to an NNRTI regimen versus atazanavir would be helpful. Switching from a PI-based regimen to a triple NRTI regimen or one containing abacavir is limited by higher rates of virologic failure.

Lifestyle Management

Although there are limited data in the HIV-infected population, the therapeutic lifestyle changes recommended in the NCEP guidelines should be initiated for patients at risk of CHD.[18,99] Based upon data generated in the HIV seronegative population, lifestyle changes have been recommended for HIV-infected persons at high risk of CHD.[17] These include regular monitoring of cholesterol and other lipid factors, cessation of smoking, appropriate management of hypertension and diabetes, and diet and exercise to improve lipid levels. In one small randomized trial of HIV-infected patients involving dietary counseling, diet alone resulted in a reduction in TC by 0.34 mmol/L after 24 weeks with no change in LDL-C, TG, or HDL-C.[100]

Lipid-Lowering Drugs

Epidemiologic studies demonstrate that lipid-lowering therapy is being increasingly used in the HIV-infected population. As reported in a cross-sectional study of patients on Medicaid in California (MEDI-CAL), the prevalence of lipid-lowering therapy in HIV-infected patients was greater than in the general population and increased by 6-fold between 1996 and 2000.[101] Based on multivariate models, increased use of lipid-lowering therapy ($p \leq .001$) was associated with higher age (OR = 2.3) and PI use (OR = 2.08).

Statins

In HIV-positive patients, the current indications for intervening to improve lipid profiles and reduce the risk of CHD are similar to those for HIV-negative individuals.[18,19] The HMG CoA reductase inhibitors, or statins, are generally the first-choice therapy for elevated LDL-C.[102] Improvement in TC and HDL-C makes this class of drugs useful for the spectrum of lipid disorders commonly found in patients receiving PIs.[18] However, since most statins are metabolized by the cytochrome P450 (CYP450) pathway, concomitant treatment with PIs and statins causes elevations in levels of some statins. Such unfavorable drug interactions between ART and lipid-lowering drugs are a concern in persons with HIV infection.[103]

In a pharmacokinetic study of HIV seronegative persons, a decline of 50% in the estimated area under the curve (AUC) of pravastatin occurred in the presence of 400 mg each of saquinavir and ritonavir twice daily. The AUC of simvastatin increased by 3059% and that of total active atorvastatin levels by 79%.[103] Similar pharmacokinetic interactions have also been described for the AUC of statins in the presence of nelfinavir and lopinavir/ritonavir.[104] Based upon these studies, simvastatin and lovastatin, which is metabolized similarly to simvastatin, are not recommended in patients taking PIs.[19,103] The newer statin, rosuvastatin, is not primarily metabolized by CYP450 enzymes similar to pravastatin, but there are currently no data assessing its potential interactions with ARVs.[105]

Due to recognized interactions, most authorities recommend initiation of atorvastatin and pravastatin at low doses (atorvastatin, 10 mg daily; pravastatin, 20 mg daily) if used in patients taking PIs, with careful monitoring for adverse events.[17,106] If no adverse events have occurred or if lipid levels have not improved after 6 to 8 weeks, the dose may be increased.[18,99] Pravastatin levels decrease significantly in the presence of most PIs, and doses may need to be increased to improve efficacy. Statin use in patients taking efavirenz or nevirapine is generally likely to be safe, although there are limited data on long-term concomitant use. A recent pharmacokinetic study demonstrated that simvastatin, atorvastatin, and pravastatin levels are decreased in the presence of efavirenz.[107] This study suggests that the lipid-lowering benefits of statins will be diminished in the presence of NNRTIs that induce the metabolism of CYP3A4. One additional concern over the use of statins in HIV-infected persons was raised by a recent study that showed a decrease in T-cell response when PI-based HAART and atorvastatin or pravastatin treatment were used in combination.[108] This observation requires confirmation in additional studies.

A number of small studies of statins in persons with HIV have demonstrated similar lipid-lowering properties as observed in the seronegative population (**Table 5**).[100,109-112] Aberg and colleagues[109] have demonstrated limited efficacy of pravastatin in treating combined hyperlipidemia in persons with HIV. Combination therapy with statins and fibrates may be more effective than either agent alone for the dyslipidemia associated with HIV infection, although further studies are needed.

Fibrates

Fibrates, a second class of lipid-lowering drugs, are useful for the treatment of elevated TG. Fibrates are less likely to interact with PIs, because they are not metabolized by the CYP450 system. Theoretically, they can be combined with statins to have an additional TG-lowering effect. It appears that they may be appropriate in patients with hypertriglyceridemia and can reduce TG levels to normal (success observed in 64% patients on PIs).[17,99,110,113,114] Aberg and colleagues[109] have demonstrated that fenofibrate lowers TG by more than 50% and, when used in sequential combination with pravastatin, can help persons with combined hyperlipidemia reach NCEP ATP III goals (16% on combination therapy reached all targets) in a ran-

Table 5. Lipid-lowering therapy in HIV-infected persons

	TC	TG	HDL	LDL
Pravastatin[100] (*n* = 15)	–1.23	–0.31	0.06	–1.2
Pravastatin[109] (*n* = 86)	–41 mg/dL	–27 mg/dL	No Δ	–30 mg/dL
Atorvastatin[111] (*n* = 10)	–19%	–21%		
Gemfibrozil[111] (*n* = 25)	–32%	–57%		
Gemfibrozil[113] (*n* = 8)	No Δ	–83%		
Fibrates[112] (*n* = 66)	–22%	–41%		
Statins[112] (*n* = 37)	–25%	–35%		
Prav+Feno[109] (*n* = 130)	–16%	–38%	16%	–10%
Atorv+Gem[111] (*n* = 19)	–30%	–60%		
Fenofibrate[114] (*n* = 13)	–6.6%	–45.7%		
Fenofibrate[109] (*n* = 88)	–15 mg/dL	–118 mg/dL	4 mg/dL	13 mg/dL

Note: TC = total cholesterol; TG = triglycerides; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Atorv = Atorvastatin; Prav = Pravastatin; Feno = Fenofibrate; Gem = Gemfibrozil.

domized controlled trial of 174 patients with HIV infection. The safety of fibrates in HIV-infected persons appears generally favorable, although studies in HIV seronegatives have suggested that a combination of statins and fibrates can increase the risk of hepatic and muscle toxicity.[17]

Other lipid-lowering agents, such as niacin, are not currently indicated for HIV-infected persons, because they can increase the risk of insulin resistance, a risk factor for CHD.[17,115] Cholesterol-binding resins such as cholestyramine are generally contraindicated in HIV because of their tendency to bind ARVs and reduce their bioavailability. There are no published data on the use of the cholesterol absorption blocker ezitimibe in persons with HIV.

Selection of ART

Taking into consideration the multiple factors that can affect the outcome of CHD in HIV-infected persons, it is essential to individualize therapy using general guidelines for CHD risk management. The initiation of ART should be based upon virologic and immunologic factors. The choice of ARVs should include viral potency and lower risk of metabolic disturbances. Treatment guidelines for initiation of ART recommend either a PI or NNRTI in combination with two NRTIs. Most authorities recommend the use of two NRTIs and an NNRTI as first-line therapy for persons with less severe immune deficiency. NNRTIs appear to have more favorable effects on lipids than do PIs when used as initial therapy, with the exception of atazanavir.[89,90] In persons at high risk of CHD, consideration should be given for utilizing ARVs with less potential to induce dyslipidemia. Of note, NRTIs are increasingly being scrutinized for the relationship with metabolic disturbances. Studies are currently in progress comparing non–NRTI-containing regimens versus standard recommended treatments for initial therapy. One such trial currently underway in the ACTG is study A5142 that compares two NRTIs plus efavirenz or lopinavir/ritonavir versus efavirenz/lopinavir/ritonavir.

In patients who have failed other ARVs, use of

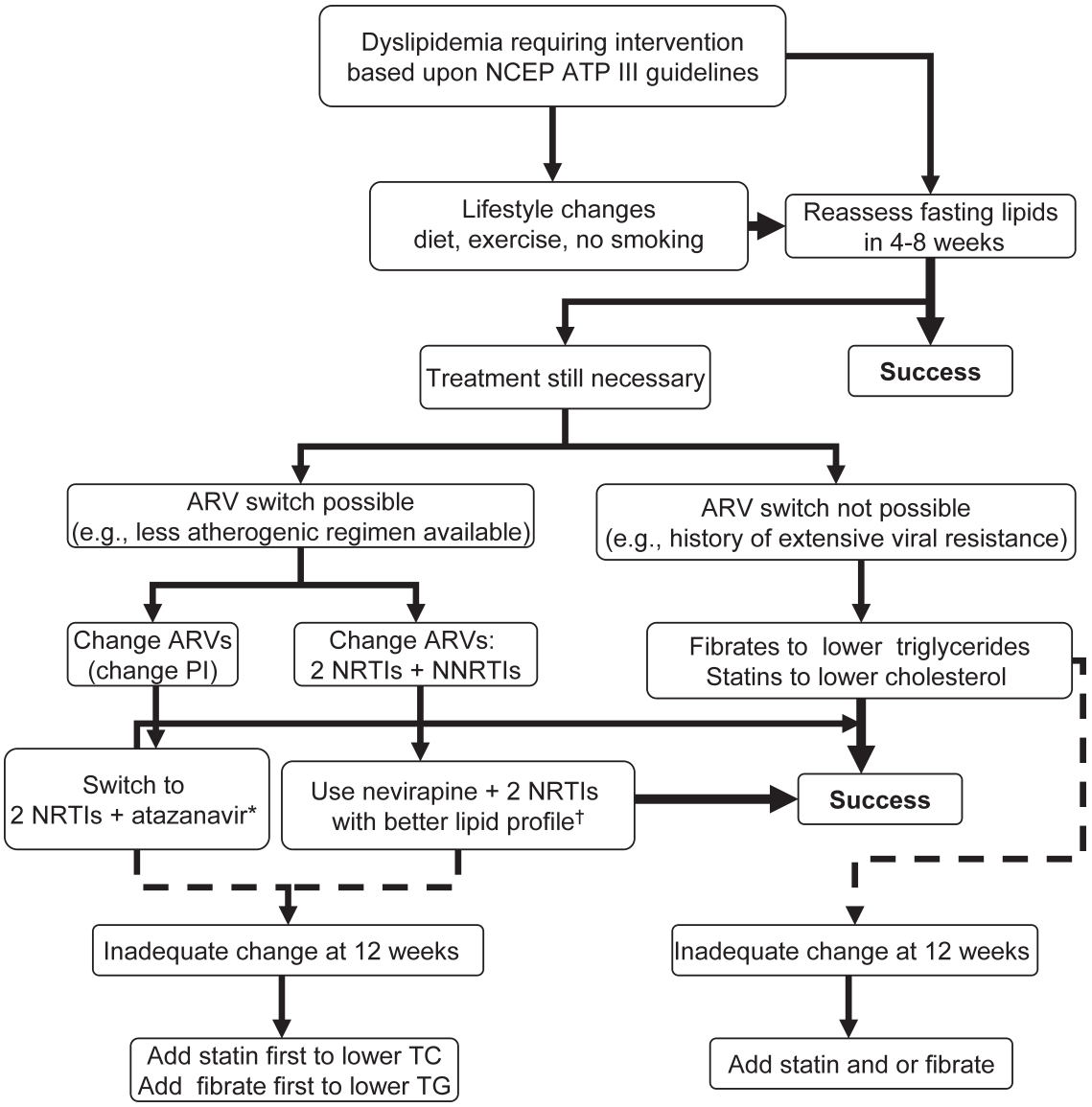

Figure 1. Algorithm for managing dyslipidemia in HIV-infected persons. ARV = antiretrovirals; NCEP ATP III = National Cholesterol Education Project, Adult Treatment Project III; NRTIs = nucleoside reverse transcriptase inhibitors; NNRTIs = nonnucleoside reverse transcriptase inhibitors; PI = protease inhibitor; TC = total cholesterol; TG = triglycerides. *Atazanavir is a PI without known effects on lipids. If a PI is required, this may be a useful choice to switch. †Improvements in lipids have been observed with a switch from a protease inhibitor–based regimen to a NNRTI-based regimen. Some NRTIs have a greater tendency to induce dyslipidemia (e.g., d4T or stavudine), and switch from these may also improve dyslipidemia associated with ARV.

ART that will cause a minimum increase in CHD risk should be implemented. The primary goal of salvage therapy is control of HIV replication. It may be that strategies of initially controlling HIV infection for 6–12 months may be followed by switching to regimens with less dyslipidemia-producing effects, although this strategy requires testing. A fasting lipid panel (TC, LDL-C, TG, and HDL-C) should be obtained prior to initiating or changing ARVs and should be repeated within 3 to 6 months and at least annually thereafter.[18]

In summary, with current advances in the devel-

opment of ARVs, the options for therapy selection include administering NNRTIs and newer PIs with better lipid profiles. Thus, clinicians should generally utilize an ARV regimen that will control HIV infection while minimizing the risk for development of CHD.

SUMMARY

CHD risk and management in HIV-infected persons is a complex issue and is of great concern to HIV-infected persons and physicians. Both HIV infection and ART can cause changes in lipid profiles and can increase the risk of CHD. Within the ARV drug classes, PIs appear to have the most detrimental effects on lipids and are implicated in coronary artery calcification and endothelial dysfunction, possibly accelerating atherosclerosis and leading to increased risk of coronary events.

For CHD risk and management in treatment-naive and experienced HIV-infected persons, the NCEP recommendations (lifestyle changes and improving the lipid profile by pharmacologic intervention) should be followed. The initiation of ART should account for the potential risk of CHD disease. Management of dyslipidemia should generally follow the recommendations of NCEP ATP III guidelines. Clinicians should be familiar with potential drug interactions between lipid-lowering therapy and ART therapy. Control of viral replication should be the primary focus of ART, with the selection of agents that minimize toxicity and dyslipidemia. An algorithm is provided to aid clinicians in thinking through the treatment options in the absence of randomized trials to prove which strategy will be safest and most effective (**Figure 1**). Long-term studies will be needed to improve our understanding of the chronic effects of ART on cardiac events.

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REFERENCES

1. Bonnet F, Morlat P, Chêne G, et al., for the Groupe d'Epidémiologie Clinique du SIDA en Aquitaine (GESCA). Causes of death among HIV-infected patients in the era of highly active antiretroviral therapy, Bordeaux, France, 1998-1999. *HIV Med*. 2002;3:195–199.
2. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med*. 1998;338:853–860.
3. Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med*. 2003;349:1993–2003.
4. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D, and the Clinical Epidemiology Group from the French Hospital Database. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. *AIDS*. 2003;17:2479–2486.
5. Chi D, Henry J, Kelley J, Thorpe R, Smith JK, Krishnaswamy G. The effects of HIV infection on endothelial function. *Endothelium*. 2000;7:223–242.
6. Mauss S. HIV-associated and antiretroviral-induced hyperlipidaemia: an update. *J HIV Ther*. 2003;8:29–31.
7. Sullivan AK, Nelson MR. Marked hyperlipidaemia on ritonavir therapy. *AIDS*. 1997;11:938–939.
8. Henry K, Melroe H, Huebusch J, et al. Severe premature coronary artery disease with protease inhibitors [letter]. *Lancet*. 1998;351:1328.
9. Vittecoq D, Escaut L, Monsuez JJ. Vascular complications associated with use of HIV protease inhibitors. *Lancet*. 1998;351:1959.
10. Perry RC, Cushing HE, Deeg MA, Prince MJ. Ritonavir, triglycerides, and pancreatitis [letter]. *Clin Infect Dis*. 1999;28:161–162.
11. Jütte A, Schwenk A, Franzen C, et al. Increasing morbidity from myocardial infarction during HIV protease inhibitor treatment. [letter] *AIDS*. 1999;13:1796–1797.
12. Gallet B, Pulik M, Genet P, Chedin P, Hiltgen M. Vascular complications associated with use of HIV protease inhibitors [letter]. *Lancet*. 1998;351:1958–1959.
13. Friis-Møller N, Weber R, Reiss P, et al, for the DAD Study Group. Cardiovascular disease risk factors in HIV-infected persons—association with antiretroviral therapy. Results from the DAD study. *AIDS*. 2003;17:1179–1193.
14. Currier JS, Taylor A, Boyd F, et al. Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr*. 2003;33:506–512.
15. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
16. Hariawala MD, Deshmukh VV, Sellke FW. Insulin resistance: a common factor in the triad of dyslipidemia, hypertension, and coronary artery disease? *Am J Med Sci*. 1997;313:104–106.
17. Dubé MP, Stein JH, Aberg JA, et al, for the Adult AIDS Clinical Trials Group Cardiovascular Subcommittee. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)–infected adults receiving antiretroviral therapy: recommendations of the HIV Medicine Association of the Infectious

Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis*. 2003;37:613–627
18. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society–USA Panel. *J Acquir Immune Defic Syndr*. 2002;31:257–275.
19. Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS). *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.* July 14, 2003. Available at: http://AIDSinfo.nih.gov. Accessed August 23, 2003.
20. Hulley SB. The US National Cholesterol Education Program. Adult treatment guidelines. *Drugs*. 1988;36(suppl 3):100–104.
21. Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. *JAMA*. 1986;256:2835–2838.
22. Assmann G. Pro and con: high-density lipoprotein, triglycerides, and other lipid subfractions are the future of lipid management. *Am J Cardiol*. 2001;87(suppl 5A):2B–7B.
23. Assmann G, Schulte H. Role of triglycerides in coronary artery disease: lessons from the Prospective Cardiovascular Munster Study. *Am J Cardiol*. 1992;70:10H–13H.
24. Simons LA, Simons J, Friedlander Y, McCallum J. Cholesterol and other lipids predict coronary heart disease and ischaemic stroke in the elderly, but only in those below 70 years. *Atherosclerosis*. 2001;159:201–208.
25. Feingold KR, Krauss RM, Pang M, Doerrler W, Jensen P, Grunfeld C. The hypertriglyceridemia of acquired immunodeficiency syndrome is associated with an increased prevalence of low density lipoprotein subclass pattern B. *J Clin Endocrinol Metab*. 1993;76:1423–1427.
26. Shor-Posner G, Basit A, Lu Y, et al. Hypercholesterolemia is associated with immune dysfunction in early human immunodeficiency virus-1 infection. *Am J Med*. 1993; 94:515–519.
27. Riddler SA, Smit E, Cole SR, et al. Impact of HIV infection and HAART on serum lipids in men. *JAMA*. 2003;289: 2978–2982.
28. Barbarini G, Barbaro G. Incidence of the involvement of the cardiovascular system in HIV infection. *AIDS*. 2003;17(suppl 1):S46–50.
29. Barbaro G. Pathogenesis of HIV-associated heart disease. *AIDS*. 2003;17(suppl 1):S12–20.
30. Chan SY, Mancini GB, Kuramoto L, Schulzer M, Frohlich J, Ignaszewski A. The prognostic importance of endothelial dysfunction and carotid atheroma burden in patients with coronary artery disease. *J Am Coll Cardiol*. 2003;42:1037–1043.
31. Wang TJ, Nam BH, D'Agostino RB, et al. Carotid intima-media thickness is associated with premature parental coronary heart disease: the Framingham Heart Study. *Circulation*. 2003;108:572–576.
32. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med*. 2002;347:1557–1565.
33. Ridker PM. High-sensitivity C-reactive protein and cardiovascular risk: rationale for screening and primary prevention. *Am J Cardiol*. 2003;92:17K–22K.
34. Tabib A, Leroux C, Mornex JF, Loire R. Accelerated coronary atherosclerosis and arteriosclerosis in young human-immunodeficiency-virus-positive patients. *Coronary Artery Dis*. 2000;11:41–46.
35. Acevedo M, Sprecher DL, Calabrese L, et al. Pilot study of coronary atherosclerotic risk and plaque burden in HIV-infected persons: "a call for cardiovascular prevention." *Atherosclerosis*. 2002;163:349–354.
36. Paton P, Tabib A, Loire R, Tete R. Coronary artery lesions and human immunodeficiency virus infection. *Res Virol*. 1993;144:225–231.
37. Zangerle R, Sarcletti M, Gallati H, Reibnegger G, Wachter H, Fuchs D. Decreased plasma concentrations of HDL cholesterol in HIV-infected individuals are associated with immune activation. *J Acquir Immune Defic Syndr*. 1994;7:1149–1156.
38. Constans J, Pellegrin JL, Peuchant E, et al. Plasma lipids in HIV-infected patients: a prospective study in 95 patients. *Eur J Clin Invest*. 1994;24:416–420.
39. David MH, Hornung R, Fichtenbaum CJ. Ischemic cardiovascular disease in persons with human immunodeficiency virus infection. *Clin Infect Dis*. 2002;34:98–102.
40. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med*. 1999;340:115–126.
41. Henry K, Zackin R, Dube M, Hammer S, Sprecher D, Currier J, for the ACTG 50561372A Team. ACTG 5056: C-reactive protein (CRP) levels and cardiovascular risk status for a cohort of HIV-1 infected persons durably suppressed on an indinavir (IDV)-containing regimen. In: Program and abstracts of the Ninth Conference on Retroviruses and Opportunistic Infections; February 24–28, 2002; Seattle, Washington. Abstract 694-T.
42. Klein D, Hurley LB, Quesenberry CP Jr, Sidney S. Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? *J Acquir Immune Defic Syndr*. 2002;30:471–477.
43. Hsue PY, Kamini G, Erickson S, et al. Clinical features of acute coronary syndromes in patients with human immunodeficiency virus infection. *Circulation*. 2004;109:316–319.
44. Varriale P, Saravi G, Hernandez E, Carbon F. Acute myocardial infarction in patients with human immunodeficiency virus. *Am Heart J*. 2004;147:55–59.
45. Holmberg SD, Moorman AC, Williamson JM, et al, HIV Outpatient Study (HOPS) Investigators. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *Lancet*. 2002;360:1747–1748.
46. Law M, Friis-Møller N, Weber R, et al, for the DAD Study Group. Modelling the 3-year risk of myocardial infarction among participants in the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study. *HIV Med*. 2003;4:1–10.
47. Law M, D'Arminio Monforte A, Friis-Moller N, et al. Cardio- and cerebrovascular events (CVE) and predicted rates of myocardial infarction (MI) in the DAD study. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; 2004; San Francisco, California. Poster 737.

48. Rickerts V, Brodt H-R, Staszewski S, Stille W. Incidence of myocardial infarctions in HIV-infected patients between 1983 and 1998: the Frankfurt HIV-Cohort Study. *Eur J Med Res*. 2000;5:329–333.
49. Iloeje U, Yuan Y, L'Italien G et al. Protease inhibitor (PIs) exposure time and risk of cardiovascular disease (CHD) in human immunodeficiency virus (HIV) infected patients. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; 2004; San Francisco, California. Poster 736.
50. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. *N Engl J Med*. 2003;348:702–710.
51. Klein D, Hurley L, Queensbury C, et al. Hospitalization for coronary heart disease and myocardial infarction among men with HIV-1 infection: follow-up through 12/31/03. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; 2004; San Francisco, California. Poster 739.
52. Jacoby DS, Mohler III ER, Rader DJ. Noninvasive atherosclerosis imaging for predicting cardiovascular events and assessing therapeutic interventions. *Curr Atheroscler Rep*. 2004;6:20–26.
53. Currier J, Kendall M, Henry K, et al. Carotid intima-media thickness in HIV-infected and uninfected adults: ACTG 5078. In: Program and abstracts of the 10th Conference on Retroviruses and Opportunistic Infections; February 10–14, 2003; Boston, Massachusetts. Abstract 131.
54. Hsue P, Lo J, Franklin A, Bolger AF, Deeks SG, Waters DD. Increased atherosclerotic progression in patients with HIV: the role of traditional and immunological risk factors. In: Program and abstracts of the 10th Conference on Retroviruses and Opportunistic Infections; February 10–14, 2003; Boston, Massachusetts. Abstract 139lb.
55. Meng Q, Lima JAC, Lai H, et al. 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. *Am Heart J*. 2002;144:642–648.
56. Talwani R, Falusi OM, Mendes de Leon CF, et al. Electron beam computed tomography for assessment of coronary artery disease in HIV-infected men receiving antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2002;30:191–195.
57. Torre D, Pugliese A, Orofino G. Effect of highly active antiretroviral therapy on ischemic cardiovascular disease in patients with HIV-1 infection. *Clin Infect Dis*. 2002;35:631–632.
58. Levy AR, Iloeje U, Hogg RS, et al. Increases in blood cholesterol and triglycerides among persons with HIV/AIDS on highly active antiretroviral therapy compared with population norms. *Antivir Ther*. 2003;8:L48. Abstract 66.
59. Danner SA, Carr A, Leonard JM, et al, for the European-Australian Collaborative Ritonavir Study Group. A short-term study of the safety, pharmacokinetics, and efficacy of ritonavir, an inhibitor of HIV-1 protease. *N Engl J Med*. 1995;333:1528–1533.
60. Purnell JQ, Zambon A, Knopp RH, et al. Effect of ritonavir on lipids and post-heparin lipase activities in normal subjects. *AIDS*. 2000;14:51–57.
61. Periard D, Telenti A, Sudre P, et al. Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors. *Circulation*. 1999;100:700–705.
62. Murphy RL, Brun S, Hicks C, et al. ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naive adults with HIV-1 infection: 48-week results. *AIDS*. 2001;15:1–9.
63. Dubé MP, Qian D, Edmondson-Melançon H, et al. Prospective, intensive study of metabolic changes associated with 48 weeks of amprenavir-based antiretroviral therapy. *Clin Infect Dis*. 2002;35:475–481.
64. Walmsley S, Bernstein B, King M, et al, for the M98-863 Study Team. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med*. 2002;346:2039–2046.
65. Maher VM, Brown BG, Marcovina SM, Hillger LA, Zhao XQ, Albers JJ. Effects of lowering elevated LDL cholesterol on the cardiovascular risk of lipoprotein(a). *JAMA*. 1995;274:1771–1774.
66. Koppel K, Bratt G, Eriksson M, Sandström E. Serum lipid levels associated with increased risk for cardiovascular disease is associated with highly active antiretroviral therapy (HAART) in HIV-1 infection. *Int J STD AIDS*. 2000;11:451–455.
67. Stein JH, Klein MA, Bellehumeur JL, et al. Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. *Circulation*. 2001;104:257–262.
68. Fisac C, Fumero E, Crespo M, et al. Metabolic changes in patients switching from a protease inhibitor-containing regimen to abacavir, efavirenz or nevirapine: 24 month results of a randomized study. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; 2004; San Francisco, California. Abstract 78.
69. Markowitz M, Simon V, Vasan S, et al. 48-week results of an atazanavir-based QD regimen in patients switching from BID-based HAART. *Antivir Ther*. 2003;8(suppl 1):S329. Abstract 543.
70. 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. In: Program and abstracts of the 10th Conference on Retroviruses and Opportunistic Infections; February 10–14, 2003; Boston, Massachusetts. Abstract 555.
71. Sanne I, Piliero P, Squires K, Thiry A, Schnittman S, for the AI424-007 Clinical Trial Group. Results of a phase 2 clinical trial at 48 weeks (AI424-007): a dose-ranging, safety, and efficacy comparative trial of atazanavir at three doses in combination with didanosine and stavudine in antiretroviral-naive subjects. *J Acquir Immune Defic Syndr*. 2003;32:18–29.
72. Mulligan K, Grunfeld C, Tal VW, et al. Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. *J Acquir Immune Defic Syndr*. 2000;23:35–43.
73. Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated li-

podystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet*. 1999;353:2093–2099.
74. Bruno R, Gazzaruso C, Sacchi P, et al. High prevalence of metabolic syndrome among HIV-infected patients: link with the cardiovascular risk [letter]. *J Acquir Immune Defic Syndr*. 2002;31:363–365.
75. Walli R, Herfort O, Michl GM, et al. Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1-infected patients. *AIDS*. 1998;12:F167–F173.
76. Haffner SM. Pre-diabetes, insulin resistance, inflammation and CHD risk. *Diabetes Res Clin Pract.* 2003;61(suppl 1):S9–S18.
77. Noor MA, Lo JC, Mulligan K, et al. Metabolic effects of indinavir in healthy HIV-seronegative men. *AIDS*. 2001;15:11–18.
78. Dube M, Zackin R, Parker R, et al, Prospective study of glucose and lipid metabolism in antiretroviral naïve subjects randomized to receive nelfinavir, efavirenz or both combined with zidovudine + lamivudine (ZDV+3TC) or didanosine + stavudine: A5005s, a substudy of ACTG 384. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; 2004; San Francisco, California. Abstract 74.
79. Sension M, Thiry A, Giordano M, for the AI424-034 International Study Team. Absence of insulin resistance through week 24 with atazanavir once-daily and efavirenz once-daily each with fixed-dose zidovudine plus lamivudine. *Antivir Ther*. 2002;7:L26. Abstract 36
80. Mascolini M. On the trail of fugitive fat: the chase turns to NRTIs. *J Int Assoc Physicians AIDS Care* 1999;5:24–43.
81. Vigouroux C, Gharakhanian S, Salhi Y, et al. Adverse metabolic disorders during highly active antiretroviral treatments (HAART) of HIV disease. *Diabetes Metab*. 1999;25:383–392.
82. Lewis W. Mitochondrial DNA replication, nucleoside reverse-transcriptase inhibitors, and AIDS cardiomyopathy. *Prog Cardiovasc Dis*. 2003;45:305–318.
83. Staszewski S, Gallant JE, Pozniak AL, et al, for the 903 Study Team. Efficacy and safety of tenofovir DF vs stavudine when used in combination with lamivudine and efavirenz in antiretroviral naïve patients: 96-week preliminary interim results. In: Program and abstracts of the 10th Conference on Retroviruses and Opportunistic Infections; February 10–14, 2003; Boston, Massachusetts. Poster 564b.
84. Kumar P, Rodriguez-French A, Thompson M, et al. Prospective study of hyperlipidemia in ART-naïve subjects taking combivir/abacavir (COM/ABC), COM/nelfinavir (NFV), or stavudine (d4T)/lamivudine (3TC)/NFV (ESS40002). In: Program and abstracts of the Ninth Conference on Retroviruses and Opportunistic Infections; February 24–28, 2002; Seattle, Washington. Abstract 33.
85. Fontas E, Van Leth F, Sabin CA, et al. Lipid profiles in HIV-infected patients receiving combination therapy: Are different antiretroviral drugs associated with different lipid profiles? *J Infect Dis*. 2004;189:1056–1074.
86. van der Valk M, Kastelein JJP, Murphy RL, et al, for the Atlantic Study Team. Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an antiatherogenic lipid profile. *AIDS*. 2001;15:2407–2414.
87. van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS*. 2003;17:987–999.
88. Simon GL, Liappis AP, Granger SL, et al. Antiretroviral therapy-induced changes in lipoprotein subclass phenotype: comparison of protease inhibitor and non-nucleoside reverse transcriptase inhibitor regimens. *Antivir Ther*. 2002;7:L9. Abstract 14.
89. Tashima KT, Bausserman L, Alt EN, Aznar E, Flanigan TP. Lipid changes in patients initiating efavirenz- and indinavir-based antiretroviral regimens. *HIV Clin Trials*. 2003;4:29–36.
90. van Leth F, Hassink E, Phanuphak P, et al, for the 2NN Study Group. Results of the 2NN study: a randomized comparative trial of first-line antiretroviral therapy with regimens containing either nevirapine alone, efavirenz alone or both drugs combined, with stavudine and lamivudine. In: Program and abstracts of the 10th Conference on Retroviruses and Opportunistic Infections; February 10–14, 2003; Boston, Massachusetts. Abstract 176.
91. van Leth F, Phanuphak P, Gazzard B, et al, for the 2NN Study Group. Lipid changes in a randomized comparative trial of first-line antiretroviral therapy with regimens containing either nevirapine alone, efavirenz alone or both drugs combined, together with stavudine and lamivudine (2NN study). In: Program and abstracts of the 10th Conference on Retroviruses and Opportunistic Infections; February 10–14, 2003; Boston, Massachusetts. Abstract 752.
92. Shahmahesh M, das S, Stolinski M, et al. Insulin resistance and apolipoprotein B kinetics: a comparison of protease inhibitor, efavirenz, or nevirapine-containing antiretroviral regimens. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; 2004; San Francisco, California. Poster 704.
93. Drechsler H, Powderly WG. Switching effective antiretroviral therapy: a review. *Clin Infect Dis*. 2002;35:1219–1230.
94. Negredo E, Ribalta J, Paredes R, et al. Reversal of atherogenic lipoprotein profile in HIV-1 infected patients with lipodystrophy after replacing protease inhibitors by nevirapine. *AIDS*. 2002;16:1383–1389.
95. Gil P, Górgolas M, Estrada V, et al. Efficacy and safety of protease inhibitor switching to nevirapine in HIV-infected persons with undetectable viral load: results after 3 years. In: Program and abstracts of the Second International AIDS Society Conference on HIV Pathogenesis and Treatment; July 13–16, 2003; Paris, France. Abstract 590.
96. Martinez E, Arnaiz JA, Podzamczer D, et al, for the Nevirapine, Efavirenz, and Abacavir (NEFA) Study Team. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. *N Engl J Med*. 2003;349:1036–1046.
97. Fisac C, Fumero E, Crespo M, et al. Metabolic and body composition changes in patients switching from a PI-containing regimen to Abacavir, Efavirenz or Nevirapine. 12 month results of a randomized study (LIPNEFA). In: Program and abstracts of the XIV International AIDS Conference; July 7–12, 2002; Barcelona, Spain. Abstract ThPE7354.

98. Martinez E, Podzamczer E, Ribera P, et al. Switching protease inhibitors to nevirapine, efavirenz or abacavir: a randomized, multicenter, open-label, simplification trial. In: Program and abstracts of the XIV International AIDS Conference; July 7–12, 2002; Barcelona, Spain. Abstract WeOrB1262.
99. Fichtenbaum CJ. The evaluation and management of dyslipidemia in HIV-infected patients. *AIDS Clin Care*. 2001;13:113–117, 120.
100. Moyle GJ, Lloyd M, Reynolds B, Baldwin C, Mandalia S, Gazzard BG. Dietary advice with or without pravastatin for the management of hypercholesterolemia associated with protease inhibitor therapy. *AIDS*. 2001;15:1503–1508.
101. Stein JH, Wu Y, Kawabata H, Iloeje UH. Increased use of lipid-lowering therapy in patients receiving human immunodeficiency virus protease inhibitors. *Am J Cardiol*. 2003;92:270–274.
102. Stein EA The power of statins: aggressive lipid lowering. *Clin Cardiol*. 2003;26(4 suppl 3):III25–III31.
103. Fichtenbaum CJ, Gerber JG, Rosenkranz SL, et al., NIAID AIDS Clinical Trials Group. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG study A5047. *AIDS*. 2002;16:569–577.
104. Hsyu PH, Lewis RH, Schultz MD, Lillibridge JH, Kerr BM. Pharmacokinetic interactions between nelfinavir and two HMG-CoA reductase inhibitors simvastatin and atorvastatin. In: Program and abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 2000; Toronto, Ontario, Canada. Abstract 425.
105. Schuster H. Rosuvastatin—a highly effective new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor: review of clinical trial data at 10-40 mg doses in dyslipidemic patients. *Cardiology*. 2003;99:126–139.
106. Carr RA, Andre AK, Bertz RJ, Hsu A, Lam W, Chang M. Concomitant administration of ABT-378/ritonavir (ABT-378/r) results in a clinically important pharmacokinetic (PK) interaction with atorvastatin (ATO) but not pravastatin. In: Program and abstracts of the 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 2000; Toronto, Ontario, Canada. Abstract 1644.
107. Gerber JG, Fichtenbaum CJ, Rosenkranz S, et al. Efavirenz (EFV) is a significant inducer of simvastatin (SIM) and atorvastatin (ATR) metabolism: results of ACTG A5108 study. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; February 8–11, 2004; San Francisco, California. Abstract L-3.
108. Narayan S, Hawley N, Giguère P, Badley AD. Attenuated T-lymphocyte response to HIV therapy in individuals receiving HMG-CoA reductase inhibitors. *HIV Clin Trials*. 2003;4:164–169.
109. Aberg JA, Zackin RA, Evans SR, et al., and ACTG 5087 Team. A prospective, multicenter, randomized trial comparing the efficacy and safety of fenofibrate (F) versus pravastatin (P) in HIV-infected subjects with lipid abnormalities: final results of ACTG 5087. In: Program and abstracts of the 11th Conference on Retroviruses and Opportunistic Infections; February 8–11, 2004; San Francisco, California. Abstract N-53.
110. Calza L, Manfredi R, Chiodo F. Dyslipidemia associated with antiretroviral therapy in HIV-infected patients. *J Antimicrobial Chemother*. 2004;53:10–14.
111. Henry K, Melroe H, Huebesch J, Hermundson J, Simpson J. Atorvastatin and gemfibrozil for protease-inhibitor-related lipid abnormalities. *Lancet*. 1998;352:1031–1032.
112. Manfredi R, Calza L, Chiodo F. Statins and fibrates for the treatment of hyperlipidemia in HIV-infected patients receiving HAART. *AIDS*. 2003:17:851–859.
113. Hewitt RG, Shelton MJ, Esch LD. Gemfibrozil effectively lowers protease inhibitor-associated hypertriglyceridemia in HIV-1-positive patients. *AIDS*. 1999;13:868–869.
114. Caramelli B, de Bernoche CY, Sartori AM, et al. Hyperlipidemia related to the use of HIV-protease inhibitors: natural history and results of treatment with fenofibrate. *Braz J Infect Dis*. 2001;5:332–338.
115. Kahn SE, Beard JC, Schwartz MW, et al. Increased beta-cell secretory capacity as mechanism for islet adaptation to nicotinic acid-induced insulin resistance. *Diabetes*. 1989;38:562–568.