HIV and Cardiovascular Disease: Responding to the Risk

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with antiretroviral treatment continuing to have a positive impact on AIDS-related morbidity and mortality rates, a great deal of attention, unfortunately, must now be paid to the potential long-term adverse effects of HIV infection and its therapies. One of the greatest concerns has been the risk of cardiovascular disease (CVD), given the high rates of metabolic and morphologic abnormalities being seen in HIV-infected individuals taking antiretroviral therapy. However, there is still much confusion as to whether the high prevalence of CVD risk factors has actually resulted in a higher incidence of acute cardiovascular events, particular myocardial infarctions and strokes.

Culling data sets from a variety of studies, many of which were completed over the past two years, Dr. Marshall Glesby—a member of the AIDS Clinical Trial Group's metabolic and cardiovascular complications subcommittees—returned to PRN in February in an effort to make heads or tails of some of the existing confusion. This extended article reviews much of the data presented by Dr. Glesby, one of the most extensive lectures on this subject PRN has ever hosted.

I. CVD Risk Factors in HIV-Infected Patients

Numerous CVD risk factors have been documented in HIV-infected patients, particularly among those receiving antiretroviral therapy. Risk factors include dyslipidemia, insulin resistance (and diabetes mellitus), endothelial dysfunction, truncal/visceral adiposity, hypercoagulability, elevated high-sensitivity C-reactive protein (hsCRP), hypertension, and elevated homocysteine. What follows is an overview of lipid abnormalities documented in HIV-positive patients, including those on and off antiretroviral treatment, along with discussions of the various other CVD risk factors that have been explored in various *in vitro*, retrospective, and prospective studies.

Lipid Abnormalities

Lipid abnormalities are not a new phenomenon among HIV-positive patients. Prior to the widespread availability and use of combination antiretroviral therapy—and among HIV-infected patients today who have not yet initiated treatment—some of the more common observations included decreased levels of HDL and LDL. Increased triglyceride levels were also frequently seen, which were likely associated with increased levels of very low-density lipoprotein (VLDL). During the years of zidovudine (Retrovir) monotherapy, treatment-induced decreases in triglycerides were a frequent observation.

Most of the protease inhibitors (PIs), with the exception of atazanavir (Reyataz), are known to cause increases in VLDL and triglycerides. Often, but not always, PIs are also associated with increases in LDL levels, with little effect on HDL levels. As for the non-nucleoside reverse transcriptase inhibitors (NNRTIs), increases in total cholesterol and LDL levels have been reported, but increases in HDL are typically seen as well. Nucleoside reverse transcriptase inhibitors (NRTIs)—most notably stavudine (Zerit)—have also been implicated as a possible cause of dyslipidemia.

While there has been no shortage of reports evaluating pre- and post-treatment lipid levels among HIV-positive patients, only recently have we seen data involving pre-HIV infection lipid levels. With these data, a much clearer trajectory of lipid changes associated with HIV infection and its treatment comes into view. With access to data from the Multicenter AIDS Cohort Study (MACS), now in its 20th year of follow up, Dr. Sharon Riddler of the University of Pittsburgh and her colleagues analyzed lipid levels of 50 participants from whom blood samples were available from each of the following points in time: before HIV infection (preseroconversion), after infection but before initiation of combination antiretroviral therapy, at two points during antiretroviral therapy between 1997 and 1999, and at two points during antiretroviral therapy between 2000 and 2002 (Riddler, 2003).

The patients' mean total cholesterol before HIV infection was 201 mg/dL, the mean LDL level was 122 mg/dL, and the mean HDL level was 51 mg/dL, all of which are considered to be within the normal range and consistent with the general population of adult men. Study participants' average age at preseroconversion was 35 years.

After HIV infection, but prior to initiation of combination antiretroviral therapy, total cholesterol decreased by 30 mg/dL, LDL by 22 mg/dL, and HDL by 12 mg/dL. Upon initiating combination antiretroviral therapy, total and LDL cholesterol levels began to rise again. After three years on therapy, the patients' mean total cholesterol was 221 mg/dL (a 20 mg/dL increase from baseline); the mean LDL was 121 mg/dL (a 1 mg/dL drop from baseline); and the mean HDL was 42 mg/dL (a 9 mg/dL drop from baseline) (see Figure 1 on page 16). Patients' average age at the end of the study period was 47 years and it is important to keep in mind that cholesterol levels tend to increase with age.

The conclusion of this analysis is that total cholesterol does increase with the use of antiretroviral therapy, but to levels that are near the preseroconversion levels. In other words, the cholesterol levels return to normal. "It's important to keep in mind that there are issues to consider in this study," Dr. Glesby commented. "The overwhelming majority of men actually changed at least one component of their regimens during the course of the study and there's really no way to factor this into the analysis. Also, these results are based on non-fasting data, so there's no information available on triglycerides. Nonetheless, I think the data are intriguing and help put things in the context of what HIV itself may do to lipid levels."

Some of the most compelling evidence indicating that protease inhibitors are, in and of themselves, a cause of increased lipid levels comes from a University of Washington study published four years ago in *AIDS* (Purnell, 2000). Twenty-one healthy, HIV-negative volunteers participated in this two-week double-blind, placebo-controlled study to

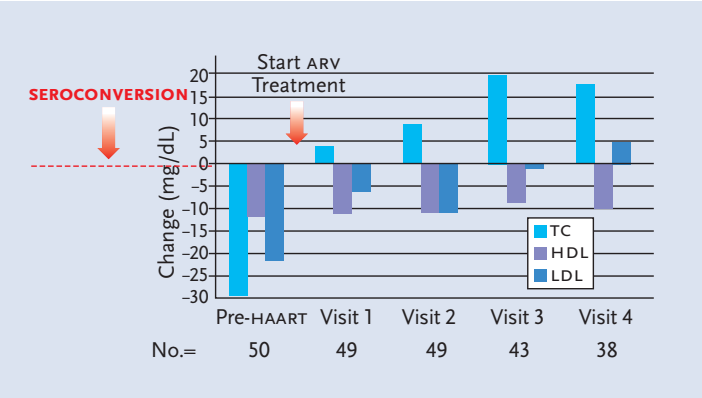

FIGURE 1. Change in Lipids Relative to Pre-seroconversion Values (MACS)

Data from the Multicenter AIDS Cohort Study (MACS) evaluating lipid levels in 50 participants from whom blood samples were available from each of the following points in time: before HIV infection (preseroconversion), after infection but before initiation of combination antiretroviral therapy, at two points during antiretroviral therapy between 1997 and 1999, and at two points during antiretroviral therapy between 2000 and 2002. The patients' mean total cholesterol before HIV infection was 201 mg/dL, the mean LDL level was 122 mg/dL, and the mean HDL level was 51 mg/dL, all of which are considered to be within the normal range and consistent with the general population of adult men. Study participants' average age at preseroconversion was 35 years. After HIV infection, but prior to initiation of combination antiretroviral therapy, total cholesterol decreased by 30 mg/dL, LDL by 22 mg/dL, and HDL by 12 mg/dL. Upon initiating combination antiretroviral therapy, total and LDL cholesterol levels began to rise again. After three years on therapy, the patients' mean total cholesterol was 221 mg/dL (a 20 mg/dL increase from baseline); the mean LDL was 121 mg/dL (a 1 mg/dL drop from baseline); and the mean HDL was 42 mg/dL (a 9 mg/dL drop from baseline).

Source: Riddler SA, Smit E, Cole SR, et al. **Impact of HIV infection and HAART on serum lipids in men.** *JAMA* 289(22):2978-82, 2003.

evaluate the effect of ritonavir (Norvir) on total lipids, apolipoproteins, and post-heparin plasma lipase activities. The eleven volunteers who received ritonavir for two weeks experienced significantly higher levels of total cholesterol (+40 mg/dL vs. –1 mg/dL respectively) and higher levels of triglycerides (+160 mg/dL vs. +40 mg/dL respectively), compared to the eight volunteers who received placebo. VLDL cholesterol, intermediate-density lipoprotein (IDL) cholesterol, and apolipoprotein B levels were also higher in the ritonavir-treated volunteers compared to the placebo recipients.

Mechanisms of PI-Induced Lipid Abnormalities

THE MECHANISMS BY WHICH PIS LEAD TO DYSLIPIDEMIA HAVE NOT BEEN definitively characterized. PI-associated dyslipidemia appears to be complex, multifactorial, and associated with multiple hepatocyte, adipocyte, and endothelial enzyme abnormalities.

As discussed by Dr. Andrew Carr and his colleagues in 1998, the catalytic region of HIV protease, to which PIs bind, has approximately 60% homology to regions within two proteins that regulate lipid metabolism: cytoplasmic retinoic-acid binding protein type 1 (CRABP-1) and low-density lipoprotein-receptor-related protein (LRP) (Carr, 1998). Dr. Carr's group hypothesized that PIs inhibit CRABP-1-modified and cytochrome P450 3A-mediated synthesis of cis-9-retinoic acid, a key activator of the retinoid X receptor. PIs may also inhibit the peroxisome proliferator activated receptor type-gamma (PPAR-γ) heterodimer, an adipocyte receptor that regulates peripheral adipocyte differentiation and apoptosis. PI binding to LRP would impair hepatic chylomicron uptake and triglyceride clearance by the endothelial LRP-lipoprotein lipase complex. While data published in 2000 confirmed that impaired adipogenesis is the basis of PI-associated lipodystrophy, it occurred via a PPAR-γ-independent mechanism (Wentworth, 2000).

Another possible mechanism, explored by a team in Toulouse-Cedex, France, involves specific polymorphisms in the apolipoprotein C-III gene. In one study, apolipoprotein C-III and apolipoprotein E genotypes of 60 HIV-infected male patients who were treated with at least one PI were evaluated (Fauvel, 2001). The specific apolipoprotein C-III polymorphisms of interest included two on an insulin-response element, –455C and –482T, and one in the 3'-region, SstI-2. Thirty-five patients carried the –455C variant and 24 carried the –482T variant. The eight patients who carried the SstI-2 variant also carried the –455C variant and all but one carried the –482T variant. The patients were distributed into four haplotype groups based on whether 0, 1, 2, or all 3 variants were present. All three apolipoprotein C-III variants were associated with a dramatic increase in triglycerides and decrease in HDL levels. Multivariate analysis revealed that the apolipoprotein C-III haplotype group accounted for about 43% of the variability in triglyceride and HDL levels. In contrast, the patients' apolipoprotein E genotype had no bearing on triglyceride or HDL levels. What's more, a synergistic effect between the apolipoprotein C-III variants and PI treatment was noted on triglyceride levels. The study team did say that patients without any such variants receiving PI treatment also experienced increases in triglycerides, but the increases were more pronounced in patients with the apolipoprotein C-III variants.

Also of interest are data published by a team at Columbia University College of Physicians and Surgeons (Liang, 2001). Using cultured human and rat hepatoma cells and primary hepatocytes from transgenic mice, the group demonstrated that PI treatment inhibits proteasomal degradation of nascent apolipoprotein B, the principal protein component of triglyceride and cholesterol-rich plasma lipoproteins. Unexpectedly, PIs also inhibited the secretion of apolipoprotein B. This was associated with inhibition of cholesteryl-ester synthesis and microsomal triglyceride transfer-protein activity. However, in the presence of oleic acid, which stimulates neutral-lipid biosynthesis, PI treatment increased secretion of apolipoprotein B-lipoproteins above controls.

The fourth potential mechanism reviewed by Dr. Glesby comes from data published by a team of researchers at the University of Cincinnati College of Medicine (Riddle, 2001). This study explored the mechanism associated with the adverse effects of ritonavir in mice. Ritonavir treatment increased triglyceride and cholesterol levels by way of increased fatty acid and cholesterol biosynthesis in adipocytes and hepatocytes. Ritonavir treatment also resulted in hepatic steatosis and hepatomegaly. These abnormalities, which were especially pronounced after feeding the mice a high-fat diet, were due to ritonavir-induced accumulation of the activated forms of sterol regulatory binding protein (SREBP)-1 and -2 in the nucleus of hepatocytes and adipocytes, resulting in elevated expression of lipid metabolism genes. Interestingly, ritonavir treatment did not alter SREBP mRNA levels in these tissues. Thus, according to this study, the adverse lipid abnormalities associated with PI therapy are caused by the constitutive induction of lipid biosynthesis in liver and adipose tissues due to the accumulation of activated SREBP in the nucleus.

The Role of Specific Antiretroviral Agents

MOST OF THE PIS CURRENTLY AVAILABLE HAVE BEEN SHOWN TO INCREASE both triglycerides and LDL cholesterol, albeit to varying degrees. According to an Infectious Disease Society of America (IDSA) and AIDS Clinical Trials Group (ACTG) review of the various studies conducted over the past six years, ritonavir (Norvir)—taken at its approved (but rarely used) dose of 600 mg twice daily—and Kaletra have the most pronounced effect on cholesterol levels and triglycerides (Dubé, 2003). Amprenavir (Agenerase) and nelfinavir (Viracept) tend to have intermediate effects, whereas indinavir (Crixivan) and saquinavir (Invirase, Fortovase) tend to have minimal effects. The most recently approved PI, atazanavir (Reyataz), appears to have little if any effect on lipid concentrations, as determined on the basis of preliminary reports.

As for the NNRTIs, nevirapine (Viramune) has been shown to increase both LDL and HDL cholesterol. However, for patients experiencing hypertriglyceridemia while taking a protease inhibitor-based regimen, switching to nevirapine has repeatedly been shown to be a saving grace. With respect to efavirenz (Sustiva), data have been decidedly mixed. Some studies have indicated that triglyceride and cholesterol levels can increase upon initiating therapy or switching to an efavirenz-based regimen, whereas other studies have not yielded any such findings.

The NRTI stavudine has also been linked to abnormal lipid levels. In a prospective, randomized study, antiretroviral-naive subjects who initiated therapy with stavudine (combined with lamivudine [Epivir] and nelfinavir) had significantly higher increases in total cholesterol, LDL, and triglyceride levels, compared with subjects receiving zidovudine (Retrovir) plus lamivudine and nelfinavir (Kumar, 2002). In another study, elevations in nonfasting triglyceride levels were more commonly seen in patients receiving stavudine plus didanosine (Videx; Videx EC) and indinavir than in patients receiving zidovudine, lamivudine, and indinavir (Eron, 2000). And in a third study, a regimen consisting of tenofovir (Viread), lamivudine, and efavirenz was significantly less likely to result in triglyceride, total cholesterol, and LDL increases than a regimen consisting of stavudine, lamivudine, and efavirenz (Staszewski, 2002).

Insulin Resistance and Diabetes

DIABETES, AND TO A LESSER EXTENT SUBCLINICAL INSULIN RESISTANCE, ARE significant risk factors for CVD. Studies in HIV-negative patients have consistently demonstrated that insulin resistance has effects on thrombosis, lipid metabolism, blood pressure regulation, and vascular function. There have also been data concluding that the risk of CVD is similar in patients with type 2 diabetes mellitus and no prior MI as it is in nondiabetic patients with a prior MI. Although it has not yet been determined whether similar risk is associated with insulin resistance in HIV-positive patients receiving antiretroviral therapy, the presence of type 2 diabetes is considered a major CVD risk factor. In turn, interventions aimed at preventing type 2 diabetes mellitus should favorably modify coronary risk factors.

Dr. Glesby reminded PRN members that insulin resistance actually has a number of potential causes, which can complicate matters considerably. "Among general populations, genetic factors, liver disease, such as hepatitis C and steatosis, obesity, and age can play a role in the development of insulin resistance," Dr. Glesby said. "In HIV-infected patients, we have additional factors to consider, including fat redistribution, protease inhibitor use, cytokine activity, and possibly HIV itself. In this way, insulin resistance is both a potential cause and an effect of disease."

Endothelial Dysfunction

ENDOTHELIAL DYSFUNCTION HAS LONG BEEN KNOWN TO BE A MAJOR factor in CVD. According to Dr. Glesby, a handful of studies have demonstrated that endothelial dysfunction has been documented in HIV-infected patients receiving PI-based regimens.

In one study reported in a 2001 issue of *Circulation*, PI-treated HIV-infected patients were more likely to have abnormal flow-mediated vasodilation (FMD) than control subjects (Stein, 2001). In another study reported at the 9th Conference on Retroviruses and Opportunistic Infections (CROI), indinavir given to HIV-uninfected study volunteers for four weeks resulted in endothelial dysfunction in the absence of dyslipidemia or blood pressure changes (Dubé, 2002). Perhaps the most intriguing study of them all was published in *QJM*, indicating that FMD was associated with the percentage of CD4+CD45RA+ ("naive") T-lymphocytes, rather than hyperilipidemia, insulin resistance, body-mass index, and smoking history in 24 HIV-infected patients receiving PI-based regimens (Nolan, 2003). "This study raised the question as to whether immune reconstitution seen in successfully treated HIV-infected patients is a factor to consider," Dr. Glesby said.

Elevated hsCRP

HIGH-SENSITIVITY C-REACTIVE PROTEIN (hsCRP), AN ESTABLISHED MARKER of chronic inflammation, has been shown to predict risk for CVD independent of other risk factors. In turn, it has been suggested that by treating HIV infection and therefore reducing chronic inflammation, hsCRP levels will decrease and potentially reduce the risk of cardiovascular problems. In an analysis conducted by the ACTG (ACTG A5056), Dr. Keith Henry and his colleagues evaluated hsCRP levels and looked for an association between hsCRP and CVD risk in a cohort of HIV-infected patients who achieved durable virologic suppression while receiving an indinavir-based regimen while participating in another ACTG clinical trial, ACTG 372A (Henry, 2004).

The A5056 analysis involved a random sample of 99 ACTG 372A study participants who had hsCRP levels measured after an average of 42 months of antiretroviral therapy. Pre-antiretroviral therapy hsCRP levels were available for 79/99 (80%) patients and an additional hsCRP value obtained after an average of 31 additional months (73 months in total) of antiretroviral therapy was available for 56/99 (57%) patients. The hsCRP values were assigned to CVD risk categories and evaluated for trends over time and associations with demographic, surrogate marker, or metabolic parameters.

Pre-antiretroviral therapy mean and median hsCRP levels were 3.83 and 2.39 mg/dL respectively. As for CVD risk category based on hsCRP levels prior to initiating indinavir-based therapy, 19% had an average risk, 14% had a slightly increased risk, 19% had a moderately increased risk, and 48% had a high risk. After 42 months of therapy, the mean and median hsCRP levels were 4.08 and 2.29 respectively. The CVD risk distribution at this time point was similar to pre-treatment rates. Twenty-two percent had an average risk, 15% had a slightly increased risk, 13% had a moderately increased risk, and 49% were at high risk. Among the 79 patients who had hsCRP levels available after 73 months of therapy, the mean and median levels were 3.11 and 1.72 respectively and the cardiovascular risk distribution was 20%, 20%, 21%, and 39% respectively at the four time points. Of the 50 patients who had pre-treatment, 42-month, and 73-month hsCRP values available, the mean and median values were: 4.55/2.75, 4.83/2.19, and 3.32/2.03 respectively. For all 99 patients, hsCRP levels at the second time point were correlated with higher fibrinogen levels, lower HDL levels, lower percentage of lympho-

cytes, higher white blood cell levels and fewer months on indinavir—all statistically significant findings.

In summarizing these data, Dr. Glesby pointed out that indinavir-based therapy was associated with stable or decreasing hsCRP levels over extended periods of exposure. In addition, CRP levels were correlated with some standard CVD or inflammatory risk factors. In essence, a high proportion of PI-treated patients maintained their hsCRP risk values despite successful treatment of HIV infection (e.g., durable suppression) and ongoing medical care. "Whether it's HIV itself, even in patients who have well-controlled disease, that is somehow contributing to elevated C-reactive protein through cytokine perturbations is still unclear at this point," he said. "But I think the data are intriguing."

Hypertension

HYPERTENSION, ANOTHER SIGNIFICANT RISK FACTOR ASSOCIATED WITH CVD, has been reported in HIV-infected patients receiving antiretroviral therapy. To further explore this issue, Dr. Glesby drew upon data reported by a State University of New York, Buffalo team of investigators who retrospectively compared the incidence of hypertension among 445 HIV-infected patients taking either indinavir (n=178) or nelfinavir (n=163) to HIV-infected patients who were naive to protease inhibitor-based therapy (n=104) (Hewitt, 2001).

Sixty-seven percent of the subjects were male, 44% were Caucasian, 41% were African-American, and 14% were Hispanic. The median age was 37 years and the median baseline blood pressure was 120/76. Using Kaplan-Meier estimates, the probability of developing hypertension (BP >140/90) for indinavir-treated patients was 32% at 200 days after starting therapy, compared to 19% of patients receiving the nelfinavir-based regimen and 18% of the PI-naive patients. At 400 days, hypertension was documented in 41% of the indinavir-treated patients, compared to 33% of the nelfinavir-treated patients and 28% of the PI-naïve patients. And after 600 days of follow-up, hypertension was documented in 54% of the indinavir-treated patients, compared to 36% and 34% of the nelfinavir-treated and PI-naive patients respectively.

Morphologic Complications: Lipodystrophy as a CVD Risk Factor

AS HAS BEEN SUGGESTED IN BOTH HIV-POSITIVE AND HIV-NEGATIVE people with increased visceral fat, there is an increased risk of insulin resistance, lipid abnormalities, and CVD risk. However, this has not been worked out definitively.

In one key study reviewed by Dr. Glesby, Dr. Colleen Hadigan and her colleagues evaluated a number of metabolic and clinical features seen in 71 HIV-infected patients with clinically defined lipodystrophy—either lipoatrophy, fat accumulation, or a combination of both—and compared them with 213 healthy control subjects, matched for age, sex, and body mass index, enrolled in the Framingham Offspring Study (Hadigan, 2001). Also included in the analysis were 30 HIV-infected patients without fat distribution changes, compared with 90 matched control subjects, also from the Framingham Offspring Study. HIV-infected patients with lipodystrophy had fasting glucose levels similar to control subjects. However, there were significant differences in the two-hour postprandial glucose levels and both the fasting and two-hour postprandial insulin levels—three telltale signs of compensated normoglycemia and insulin resistance.

"These HIV-infected patients with lipodystrophy had a much higher prevalence of diabetes, approximately 5%, compared to less than 1% in the matched controls," Dr. Glesby explained. "More striking was the prevalence of impaired glucose tolerance, with a rate of approximately 35% among HIV patients with lipodystrophy, compared to 5% among the HIV-negative controls. Dr. Hadigan's group looked at several other factors as well and found that the HIV-positive patients with lipodystrophy had higher diastolic blood pressures, higher triglyceride and total cholesterol levels, and lower HDL levels. So, clearly, this whole constellation of risk factors is concerning in terms of long-term cardiovascular risk."

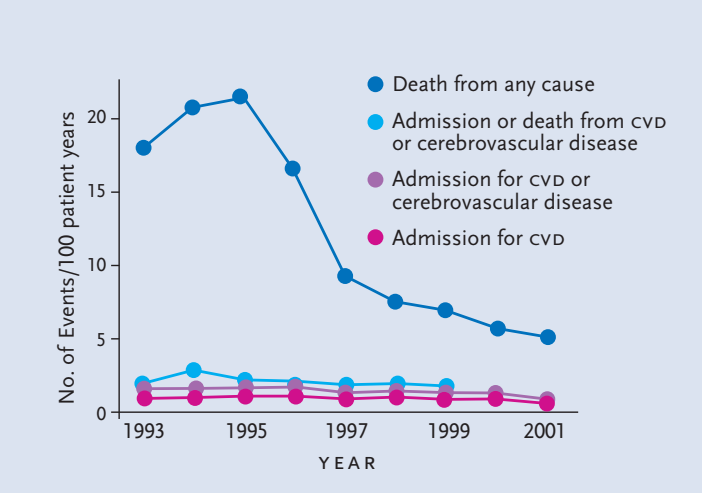

FIGURE 2. **Changing Rates of Vascular Events: The VA Study**
Risk of cardiovascular and cerebrovascular disease among the 36,766 patients receiving HIV care at Veterans Affairs facilities between January 1993 and June 2001. Of the patients followed, 70.2% patients received NRTIs, 41.6% received PIs, and 25.6% received NNRTIs for a median of 17 months, 16 months, and 9 months respectively. Approximately 1,000 patients received combination therapy with a PI for at least 48 months, and approximately 1,000 patients received combination therapy with an NNRTI for at least 24 months. Between 1995 and 2001, the rate of hospital admissions for cardiovascular or cerebrovascular disease decreased from 1.7 to 0.9 per 100 patient-years, and the rate of death from any cause decreased from 21.3 to 5.0 deaths per 100 patient-years (see Figure 2). Regression analyses indicated that there was no relation between the use of NRTIs, PIs, or NNRTIs and the risk of cardiovascular or cerebrovascular events. Instead, the use of antiretroviral drugs was associated with a decreased risk of death from any cause.

Source: Bozzette SA, Ake CF, Tam HK, et al. **Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection.** *N Engl J Med* 348(8):702-10, 2003.

Does HIV Have a Direct Role?

DR. GLESBY SPENT SOME TIME REVIEWING SOME INTERESTING DATA SUGgesting that HIV may have a direct role in causing CVD. According to one study conducted at Mt. Sinai School of Medicine, the HIV envelope protein, gp120, activates human arterial smooth muscle cells to express tissue factor, the initiator of the "coagulation cascade" (Schecter, 2001). The induction of tissue factor by gp120 appeared to be mediated by the two biologically relevant coreceptors for HIV infection, CXCR4 and CCR5, and also appeared to be dependent on the presence of functional CD4.

Also of interest are data from the Swiss HIV Cohort Study (Wolf, 2002). In this study, the effects of antiretroviral therapy on vascular activation in 41 HIV-infected patients receiving either PI-based regimen (n=21) or an NNRTI-based regimen (n=20) were evaluated. A control

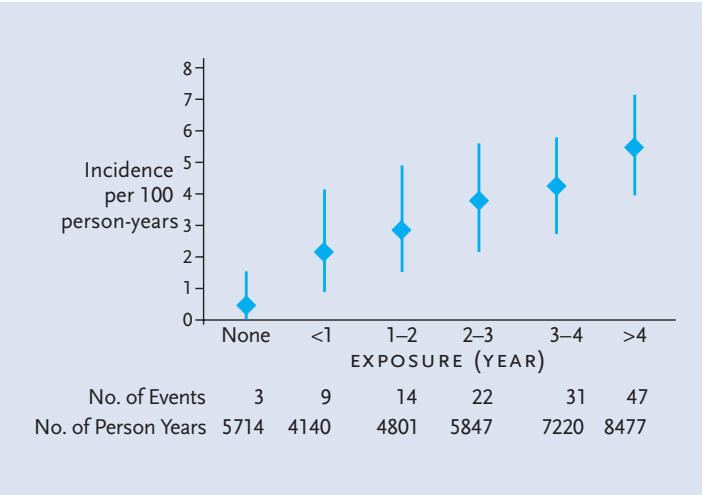

Figure 3. Incidence of MI by Duration of Exposure to Antiretroviral Therapy: DAD Study

The incidence of myocardial infarction (MI) among 23,468 HIV-positive patients enrolled in the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study. Patients were enrolled between December 1999 and April 2001 and follow-up data are available through to February 2002. Over a period of 36,199 person-years, 126 patients experienced myocardial infarctions—an incidence of 3.5 per 1000 patient-years—29% of which were fatal. Combination antiretroviral therapy was independently associated with a 26% relative increase in the rate of MI per year of antiretroviral treatment during the first four to six years of use. Other factors significantly associated with MI were older age, current or former smoking, previous CVD, and male sex, but not a family history of CVD. A higher total cholesterol level, a higher triglyceride level, and the presence of diabetes were also associated with an increased incidence of MI.

Source: Friis-Moller N, Sabin CA, Weber R, et al. **Combination antiretroviral therapy and the risk of myocardial infarction.** *N Engl J Med* 349(21):1993-2003, 2003.

group of 21 HIV-uninfected subjects was included for comparison. Levels of endothelial markers (soluble vascular cell adhesion molecule [sVCAM] 1, soluble intercellular adhesion molecule 1, and von Willebrand factor) were higher in HIV-infected patients before treatment than in control subjects and decreased significantly after five to 13 months of treatment. Based on these observations, the Swiss group concluded that the inhibition of vascular activation markers—which appear to be higher in untreated HIV and are reduced once therapy is initiated—may potentially prevent development of atherosclerosis in HIV-infected patients.

II. Epidemiology of CHD and Subclinical Atherosclerosis

A HANDFUL OF RETROSPECTIVE AND PROSPECTIVE COHORT STUDIES HAVE been conducted, looking specifically at the incidence and the relative risk of cardiovascular events among HIV-infected patients receiving antiretroviral therapy.

Dr. Glesby first reviewed a retrospective analysis conducted by Dr. Sam Bozzette and his colleagues, which set out to assess the risk of cardiovascular and cerebrovascular disease among the 36,766 patients who received HIV care at Veterans Affairs facilities between January 1993 and June 2001 (Bozzette, 2003). With respect to antiretroviral therapy usage, 70.2% patients received NRTIs, 41.6% received PIs, and 25.6% received NNRTIs for a median of 17 months, 16 months, and 9 months respectively. Approximately 1,000 patients received combination therapy with a PI for at least 48 months, and approximately 1,000 patients received combination therapy with an NNRTI for at least 24 months. It is important to note that 24% of the patients surveyed were being treated for diabetes mellitus, hypertension, dyslipidemia, or smoking prior to their first HIV-related visit; 7% were being *treated* for vascular disease prior to their first HIV-related visit.

Between 1995 and 2001, the rate of hospital admissions for cardiovascular or cerebrovascular disease decreased from 1.7 to 0.9 per 100 patient-years, and the rate of death from any cause decreased from 21.3 to 5.0 deaths per 100 patient-years (see Figure 2). Regression analyses indicated that there was no relation between the use of NRTIs, PIs, or NNRTIs and the risk of cardiovascular or cerebrovascular events. Instead, the use of antiretroviral drugs was associated with a decreased risk of death from any cause.

Dr. Glesby also spent some time reviewing data from the international Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study, the first prospective study of its kind. Data published in 2003 in the *New England Journal of Medicine* involved 23,468 patients from 11 previously established cohorts, enrolled between December 1999 and April 2001, with follow-up data collected through to February 2002 (Friis-Moller, 2003). Data were collected on infection with HIV and on risk factors for and the incidence of myocardial infarction (MI). Relative rates were calculated with Poisson regression models. Combination antiretroviral therapy was defined as any combination regimen of three or more antiretroviral drugs that included a PI or an NNRTI.

Approximately 76% of the patients followed were male and the median age, at baseline, was 39 years. Seventy-four percent of the patients followed had at least some experience taking antiretroviral agents, with a median of 1.9 years of use. Approximately 67% had been on a PI-based regimen for, on average, 1.6 years. Fifty-six percent were current or former smokers, 12% had a familial history of coronary heart disease, 7% had hypertension at baseline, 3% were diabetic, and 46% had dyslipidemia.

Over a period of 36,199 person-years, 126 patients experienced myocardial infarctions—an incidence of 3.5 per 1000 patient-years—29% of which were fatal. According to the DAD Study Group's analysis, combination antiretroviral therapy was independently associated with a 26% relative increase in the rate MI per year of antiretroviral treatment during the first four to six years of use (see Figure 3). Other factors significantly associated with MI were older age, current or former smoking, previous CVD, and male sex, but not a family history of CVD. A higher total cholesterol level, a higher triglyceride level, and the presence of diabetes were also associated with an increased incidence of MI.

Dr. Glesby also shared data from an ongoing observational study examining CVD and MI hospitalization rates among HIV-positive members of the Kaiser Permanente Medical Care Program of Northern California, before and after PI use, and before and after any antiretroviral therapy (Klein, 2002). CVD and MI hospitalization rates among HIV-infected patients are also being compared to rates among Kaiser Permanente patients not known to be infected with HIV. With a median of 4.1 years of follow-up, age-adjusted CVD and MI hospitalization rates were not significantly different among HIV-infected patients before beginning PI-based regimens, compared to rates after PI-based regimens were started (6.2 vs. 6.7 events per 1,000 person-years respectively). In fact, there were no statistically significant differences in the rates documented before and after antiretroviral therapy use in general (5.7 vs. 6.8 events per

1,000 person-years respectively). However, comparing HIV-positive and HIV-negative members, the CHD hospitalization rate was significantly higher (6.5 vs. 3.8 events per 1,000 person-years respectively), and the difference in the MI rate also was higher (4.3 vs. 2.9 events per 1,000 person years respectively). Differences between HIV-positive and -negative members in the CVD risk factors measured were mixed, and the overall clinical significance of these differences remains uncertain.

In summarizing the epidemiological data pertaining to cardiovascular events, including MIs, among HIV-infected patients taking antiretroviral therapy, Dr. Glesby reiterated what a number of experts have been saying in recent years: that the data are somewhat conflicting, but generally suggested an increased relative risk of MI in association with antiretroviral therapy. "Most of the studies that we've seen thus far have a limited duration of follow-up, a relatively small number of events, and have not adjusted for CVD risk factors or the HIV disease stage of the patients surveyed," Dr. Glesby said. "But the general feeling is that the absolute risk of myocardial infarction appears to be low in the short term, and must be considered in the context of the benefits of antiretroviral therapy."

Clinical Features of MI in HIV

STUDIES HAVE BEGUN LOOKING AT THE CLINICAL FEATURES OF ACUTE coronary events in HIV-infected individuals, in an effort to determine if the course of disease is different than is typically seen in HIV-negative individuals. In one study published by Dr. Schlomo Matetzky and his colleagues, a series of 24 consecutive HIV-infected patients admitted for acute MI between 1998 and 2000 were followed (Matetzky, 2003). During hospitalization, the patients were examined for recurrent ischemia, congestive heart failure, arrhythmia, and death. After being discharged, patients were followed up for an average of 15 months for reinfarction; recurrent angina; the need for any angioplasty, bypass surgery or target vessel revascularization for restenosis and stent thrombosis; HIV-related complications; and death. For comparison, the authors included a matched control group of 48 patients admitted to the hospital for MIs but were not HIV infected.

The HIV-infected patients hospitalized for an MI were predominantly male (88%) and, on average, 47 years of age. Twenty-two (92%) were receiving antiretroviral treatment at the time of the MI; 71% were receiving a PI-based regimen and 54% were receiving some form of lipid-lowering therapy. According to the report, MIs in HIV-infected patients were associated with a favorable in-hospital outcome, not unlike the outcome in the matched control patients. This is likely because of the young age of the patients and the absence of significant hemodynamic compromise. However, after being discharged, HIV- infected patients had a higher incidence of reinfarction (20%) and rehospitalization for revascularization (45%) than uninfected control patients (4% and 11% respectively) over the 15 months of follow-up documented. In turn, this study suggests that HIV infection is associated with an increased rate of restenosis after percutaneous coronary intervention. This association was particularly evident in patients with increased viral load, irrespective of protease inhibitor therapy.

The clinical features of acute coronary events in HIV-infected patients have also been looked at by Dr. Priscilla Hsue, a clinical research fellow in cardiology at the University of California, San Francisco (UCSF), and her colleagues (Hsue, 2004). Between 1993 and 2003, 68 HIV-infected patients were hospitalized with MIs. Dr. Hsue's group compared the clinical features and outcome of these patients with those of 68 randomly selected control MI patients without HIV infection. The HIV-positive patients were, on average, more than a decade younger than controls and more likely to be male, to be current smokers, and to have low HDL levels. They were less likely than controls to have diabetes or hyperlipidemia, and their thrombolysis in myocardial infarction (TIMI) risk scores on admission were significantly lower. Coronary angiograms revealed that the HIV-infected patients were more likely to have single-vessel disease than the HIV-negative controls. Restenosis developed in 15/29 (52%) HIV-infected patients who underwent percutaneous coronary intervention, compared with 3/21 (14%) controls, similar to the data reported by Dr. Matezky's team.

Subclinical Atherosclerosis

A FEW IMPORTANT STUDIES HAVE FOCUSED ON THE CLINICAL FEATURES OF subclinical atherosclerosis, which remains one of the most significant precursors to cardiovascular and cerebrovascular events. The first study reviewed by Dr. Glesby was A5078, an ACTG study (Currier, 2003). The second study, the SCOPE study, was recently published by Dr. Hsue and her colleagues (Hsue, 2004a).

ACTG A5078 compared carotid intima-medial thickness (IMT) in HIV-positive patients who had been receiving a PI-based regimen for at least two years to IMT in HIV-positive patients who weren't receiving a PI-based regimen, along with HIV-uninfected study volunteers. The 134 evaluable study volunteers were all matched with regard to age (within five years of each other), race, sex, blood-pressure status (either normal or hypertensive), smoking status (never, current, or former), and menopausal stage. A number of major study exclusions were also noted, including a viral load above 10,000 copies/mL in either of the HIV-positive groups, anyone with a familial history of MI involving a first-degree relative, anyone with diabetes, uncontrolled hypertension, or a history of a cardiovascular event.

As explained by Dr. Glesby, there were no significant differences in IMT among the three groups. Among the PI-treated patients, the median IMT was 0.693 mm; among the HIV-positive patients not receiving a PI, the median IMT was 0.708 mm; and among the HIV-negative study volunteers, the median IMT was 0.687 mm. "What these data tell us is that in this matched cross-sectional study, after controlling for known cardiovascular factors, PI-treated patients did not have increased IMT when compared to HIV-infected patients not receiving a protease inhibitor or HIV-negative controls," Dr. Glesby explained. Factors associated with increased IMT, across the board, included low HDL, elevated triglycerides (in the setting of low HDL), older age, and increased body mass index.

Interestingly, in the SCOPE data, Dr. Hsue and her group suggested that HIV itself, not antiretroviral treatment, is associated with subclinical atherosclerosis. Dr. Hsue's group measured IMT in 106 HIV-infected patients. The median age of the patients studied was 45 years and 88 (83%) were male. The median duration of HIV infection was 11 years and the median pre-enrollment PI treatment duration was four years.

The mean IMT was 0.90 mm, which was higher than expected when comparing the numbers to those of a larger population of similarly aged individuals. Predictors of increased IMT at baseline were age (0.12 mm per decade), LDL level (0.02 mm per 10 mg/dL), hypertension (0.15 mm), and nadir CD4+ count at or below 200 cells/mm^3 (0.16 mm). Of note, hsCRP, lipodystrophy, and duration of HIV infection were not predictive of increased baseline IMT.

IMT progression over one year was measured in a subset of 21 patients. The mean rate of progression was 0.1 mm per year, which is greatly accelerated compared to 0.01 mm/year documented in published reports involving HIV-uninfected populations. Age and duration

of PI therapy were also found to be multivariable predictors of IMT progression.

IMT was independently associated with classic coronary risk factors (age, increased LDL, and hypertension), along with low CD4+ cell counts. These data, the report concluded, suggest that both immunodeficiency and traditional risk factors contribute to atherosclerosis in HIV-infected individuals. Progression of IMT in the subset with one-year follow-up was accelerated by tenfold compared to non-HIV infected populations, and was associated with age and duration of PI use.

In summarizing his discussion of subclinical atherosclerosis in HIV, Dr. Glesby stated that additional follow-up from both studies is needed to make sense of the discrepancies in the results. "There are significant differences between the ACTG study and the SCOPE study," he said. "One major difference is that the ACTG study is carefully controlled, whereas the SCOPE study does not have a control group. Another difference is that the ACTG study is looking specifically at carotid wall thickness only, whereas the SCOPE study is looking at wall and plaque thickness together."

III. Monitoring and Management of Cardiovascular Risk Factors

WHILE THERE ARE NUMEROUS LINGERING QUESTIONS AND CONCERNS REgarding the monitoring and management of dyslipidemia in HIV-infected patients, many clinicians have taken comfort in guidelines that have been drafted—and are continuously being updated—by panels of experts with extensive knowledge of the metabolic and morphologic complications being seen in HIV. The two sets of guidelines recommended by Dr. Glesby are those authored by the Infectious Disease Society of America and the AIDS Clinical Trials Group (Dubé, 2003) and those produced by the International AIDS Society-USA (Schambelan, 2002).

As explained by Dr Glesby, both sets of guidelines recommend using the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III interactive calculator—based on data extrapolated from the Framingham Heart Study—to assess cardiovascular risk, taking into account basic factors such as age, gender, smoking status, presence of diabetes, family history, and hypertension.

But as Dr. Glesby pointed out, traditional risk stratifications—including those based on the Framingham Heart Study—may not be entirely relevant in the setting of HIV. Dr. Glesby talked about an HIV-positive, antiretroviral-treated patient of his who had a negative family history of CVD, smoked one pack of cigarettes per day for 25 years, and on examination, had a blood pressure of 136/86. Fasting labs revealed that he had a glucose level of 102 mg/dL, a total cholesterol level of 290 mg/dL, an HDL level of 36 mg/dL, a triglyceride level of 360 mg/dL, a calculated LDL level of 190 mg/dL, and a non-HDL level of 254 mg/dL. "Using traditional risk equations," Dr. Glesby pointed out, "this patient's ten-year risk of a cardiovascular event is 29%. The thing is, traditional risk equations don't take into account exposure duration. What if my patient's pre-treatment total cholesterol level was 160 mg/dL? Also missing from these equations are nontraditional risk factors. And age is of importance here, too. If my patient was 30 years old and not 45 years old, his ten-year risk would be 14%, not 29%. Would we then dismiss his lower risk?"

To look at the issue of predicted cardiovascular events, in the face of observed cardiovascular events, Dr. Glesby once again turned his attention to data from the DAD study (Law, 2004). In a recent analysis reported at the 11th CROI, held in San Francisco in February, the DAD study team compared the observed rate of MIs to those predicted by Framingham Heart Study-based risk equations.

In patients receiving antiretroviral therapy, the numbers of MIs observed during follow-up were of similar magnitude and possibly somewhat higher than the numbers predicted using the Framingham-based equation: 9 MIs were observed and 5.5 were predicted in patients treated for less than one year. Among patients treated for one to two years, 14 MIs were observed and 9.8 were predicted. Among patients treated for two to three years, 22 MIs were observed and 14.9 were predicted. Among patients treated for three to four years, 31 MIs were observed and 23.2 were predicted. And among patients treated for more than four years, 47 MIs were observed and 37 were predicted. However, predicted MI rates were within the 95% confidence interval of observed rates. "This analysis," Dr. Glesby explained, "shows us that prospectively tracking rates and risk factors indicate that the increased risk of MI is largely explained by antiretroviral therapy-induced changes in conventional risk factors."

Management of Dyslipidemia

AS THERE HAVE BEEN FEW, IF ANY, WELL-DESIGNED PROSPECTIVE CLINICAL trials evaluating the impact of dietary changes on triglyceride and cholesterol increases that occur in the setting of HIV treatment, guidelines generally recommend following NCEP dietary guidelines for all individuals with hyperlipidemia (NCEP, 2001). Specific recommendations include reducing total fat to no more than 35% of the total daily caloric intake; reducing saturated fat intake to less than 7% of the total calories consumed daily; reducing dietary cholesterol to less than 200 mg/day; increasing intake of plant sterols/stanols and soluble fiber to enhance LDL reductions; weight reduction through reduced caloric intake; and, last but not least, exercise. "Referral to a dietitian should strongly be considered for all patients with dyslipidemia," expressed Dr. Glesby.

HMG CoA reductase inhibitors ("statins") are recommended by the IDSA/ACTG and IAS-USA guidelines for the management of hypercholesterolemia. However, they should be prescribed with caution, given the documented likelihood of CYP3A4 interactions with the PIs and the NNRTIs. Simvastatin (Zocor) and lovastatin (Mevacor) are generally contraindicated in patients receiving protease inhibitors. Atorvastatin (Lipitor) is a possibility, though the starting dose should be 10 mg/day and then titrated, if necessary, to achieve the desired cholesterol-lowering effect. Pravastatin (Pravachol) is another possibility, with a starting dose of 20 to 40 mg/day. Fluvastatin (Lescol) is also considered to be safe for HIV-positive individuals being treated with a CYP3A4-inhibiting PI or NNRTI. No matter which "statin" is used, clinicians may find comfort in monitoring liver function tests levels to ensure the safety of these drugs.

In one clinical trial discussed by Dr. Glesby, 31 HIV-positive men receiving HAART who had cholesterol levels of, on average, 290 mg/dL, were randomized to receive either dietary counseling alone or dietary counseling in combination with pravastatin (Moyle, 2001). After 24 weeks, total cholesterol levels fell more than 17%—a drop of 46 mg/dL—in the pravastatin group, compared to a 4% drop among the patients who only received dietary counseling. This fall was accounted for largely by a reduction in LDL cholesterol, as HDL cholesterol increased somewhat in both groups. Weight, fasting glucose, and triglycerides did not change significantly in either group.

Statins are considered to be the appropriate lipid-lowering therapy where elevated LDL and non-HDL are the predominant abnormalities.

TABLE 1. Switching Antiretrovirals May Normalize Lipid Profiles

	Fasting Triglcyerides	Cholesterol	Insulin Resistance
Protease inhibitor switch to:			
Nevirapine (Viramune)	Reduced	↓TC, ↑HDL	Reduced
Efavirenz (Sustiva)	May increase	↑HDL	Reduced
Abacavir (Ziagen)	Reduced	↓TC	Reduced
Atazanavir (Reyataz)	Reduced	↓TC, ↓LDL	----------
Stavudine (Zerit) switch to:			
Tenofovir (Viread)	Reduced	↓TC	----------

TABLE 2. Adult AIDS Clinical Trials Group CVD Risk Factor Clinical Trials

Study No.	Title	Status
A5078	Carotid Artery Intima-Media Thickness in HIV-Infected and Uninfected Adults: A Pilot Study	Closed to accrual; accrual; 134 patients enrolled
A5152s	A Substudy of A5142: Endothelial Function in HIV-Infected Subjects Prior to and After Starting a Potent Antiretroviral Regimen	Closed to accrual; 68 patients enrolled
A5148	A Pilot Study of the Safety, Efficacy, and Tolerability of Extended-Release Niacin (Niaspan) for the Treatment of Elevated Non-HDL Cholesterol and Elevated Triglycerides in HIV-Infected Subjects	Closed to accrual; 37 patients enrolled
A5186	A Phase II Trial of the Effect of Combination Therapy with Fish Oil Supplement and Fenofibrate on Triglyceride (Tg) Levels in Subjects on Highly Active Antiretroviral Treatment (HAART) Who are Not Responding to Either Fish Oil or Fenofibrate Alone	Pending; target accrual of 100 patients
A5206	A Pilot Study to Determine the Impact on Dyslipidemia of the Addition of Tenofovir to Stable Background Antiretroviral Therapy in HIV-Infected Subjects	In development; target accrual of 54 patients
A5209	A Pilot Study of Safety, Efficacy, and Tolerability of Ezetimibe (Zetia) in Combination with Statin Therapy for the Treatment of Elevated LDL Cholesterol in HIV-Infected Subjects	In development; target accrual of 43 patients

Source: Adult AIDS Clinical Trials Group (ACTG)

Conversely, fibrates are appropriate where hypertriglyceridemia is the predominant abnormality. Choice of fibrates include gemfibrozil (Lopid), 600 mg BID taken before breakfast and dinner, or fenofibrate (Tricor), at a dose between 54 mg and 160 mg every day.

Little is known about the safety and efficacy of other lipid-lowering drugs in HIV-positive patients. Niacin, for example, has the potential to exacerbate insulin resistance and hepatotoxicity, two central concerns among HIV-infected patients receiving antiretroviral therapy. In a pilot study reported at the 10th CROI in Boston, a dose-escalation evaluation of Niaspan yielded modest decreases in triglycerides, at the expense of modestly increased insulin resistance (Gerber, 2003). The bile-acid binding resins also come with potential risks, including the possibility or poor absorption of antiretroviral drugs and worsening triglycerides. The new cholesterol absorption-blocking agent ezetimibe (Zetia) is still being studied.

Preliminary data involving omega-3 fatty acid (fish oil) supplementation were reported at the 11th CROI (Wohl, 2004). In this open-label study, HIV-infected individuals on antiretroviral therapy with fasting triglycerides between 200 and 2000 mg/dL were randomized to receive either nutritionist-administered diet/exercise counseling alone or nutritionist-administered counseling with 3 g of fish oil daily (1,150 mg DHA plus 1,750 mg EPA) for 16 weeks. Fifty-two patients were randomized and 45 completed the study (seven were lost to follow-up). As highlighted by Dr. Glesby, after four weeks there was a 7% increase in triglyceride levels among patients who received diet/exercise counseling alone, compared to a 20% decrease among patients who received diet/exercise counseling plus fish-oil supplementation. This difference was statistically significant. After 16 weeks of follow-up, decreases in triglycerides were documented in both groups, with no statistically significant differences between them.

There has been a significant amount of research indicating that switches to regimens that do not contain lipid-altering antiretrovirals are beneficial. Regimens employing nevirapine, efavirenz, or atazanavir as their therapeutic backbone are useful switch options to consider (see Table 1). A switch to a nevirapine-containing regimen has been shown to reduce triglycerides, total cholesterol, and insulin resistance, and to raise HDL cholesterol; dropping a protease inhibitor in favor of efavirenz may result in additional triglyceride increases, but with increases in HDL cholesterol and decreases in insulin resistance seen as well. There is also the possibility of switching older PIs known to have negative effects lipid and insulin levels for atazanavir, which is believed to have minimal effects on cholesterol and triglyceride levels. As for switching to an abacavir-based regimen, studies have demonstrated its ability to reduce triglycerides, total cholesterol levels, and insulin resistance among patients initially treated with PIs. However, triple-nucleoside regimens have generally fallen out of favor, given virologic control durability concerns.

As for managing non-lipid risk factors, Dr. Glesby stressed that smoking cessation is by far one of the most important. Combating insulin resistance with either the thiazolidinediones (Avandia; Actos) or metformin (Glucophage) is a possibility, but their clinical utility in patients without frank diabetes is not fully understood. As for treating truncal/visercal adiposity, studies employing thiazolidinediones and metformin have yielded conflicting results. Recombinant human growth hormone (Serostim) has been shown in phase II clinical trials to reduce truncal/visceral adiposity, but the long-term effect on cardiovascular risk has not been determined.

A number of studies, involving different approaches aimed at reducing cardiovascular risk factors, are being conducted or developed by the ACTG (see Table 2).

Conclusion

IN SUMMARIZING HIS COMPREHENSIVE LECTURE, DR. GLESBY BLEAKLY reminded PRN members in attendance that metabolic derangements associated with HIV and its treatment likely place many HIV-infected patients at an increased long-term risk of atherosclerosis and that the risk

may be higher among patients with morphologic complications. "Preliminary data on the incidence of ischemic events and the prevalence of subclinical atherosclerosis are concerning," Dr. Glesby said. "Risk assessment and reduction of modifiable risk factors are very much indicated in these patients. Fortunately, encouraging data involving management strategies continues to emerge."

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