

The Graying of an Epidemic:

Clinical Considerations of HIV and Aging

II/III

The second of three newsletters addressing the special needs of the aging HIV-positive patient

FOCUS ON INCREASED RISK OF CVD

Cardiovascular disease (CVD) is the leading cause of death in the United States (US) and worldwide.^{1,2} Increased longevity of patients with the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) has made it more urgent to treat diseases normally associated with older age in the general population, including CVD. HIV itself is a risk factor for CVD and some types of antiretroviral therapy (ART) have been associated with increased CVD risks in patients infected with HIV as well. Appropriate medical management can reduce the risk of CVD in patients with HIV, and CVD risk management has become an important part of routine management strategies practiced by health care providers caring for patients with HIV.

Traditional Risk Factors for CVD

According to the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III), the major independent risk factors for coronary heart disease (CHD) include high levels of low-density lipoprotein cholesterol (LDL-C), cigarette smoking, hypertension, low levels of high-density lipoprotein cholesterol (HDL-C), family history of premature CHD or CHD risk equivalents (see below), and older age (Table 1).³ Smoking, elevated serum cholesterol, and hypertension combine synergistically to increase CHD risk. When any one factor is present, CHD risk approximately doubles; with two factors, the risk increases fourfold; and with all three risk factors, CHD risk increases eightfold.⁴ In addition, the American Heart Association includes male gender among the major risk factors for CHD and heart attack.⁵ Even in view of recent data associating ART with increased risk for CVD, these traditional risk factors remain the most important predictors of cardiovascular events in patients with HIV disease.

Forms of atherosclerosis including peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease carry a risk for major coronary events equal to that of established CHD, as does diabetes.³ Other factors influencing CHD risk include what the ATP III refers to as life-habit risk factors (obesity, physical inactivity, and atherogenic diet) and emerging risk factors (lipoprotein, homocysteine, prothrombotic and proinflammatory factors, impaired fasting glucose, and evidence of subclinical atherosclerotic disease).³

Many patients suffer from a condition called *metabolic syndrome*, a constellation of major CHD risk factors, life-habit risk factors, and emerging risk factors including abdominal obesity, atherogenic dyslipidemia (elevated triglycerides, small LDL

Table 1. Major Risk Factors for CVD

- LDL cholesterol ≥ 160 mg/dL
- Cigarette smoking
- Hypertension (blood pressure $\geq 140/90$ mm Hg or on antihypertensive medication)
- Low HDL cholesterol (< 40 mg/dL)^a
- Family history of premature CHD (CHD in male first-degree relative < 55 years; CHD in female first-degree relative < 65 years)
- Age (men ≥ 45 years; women ≥ 55 years)

^a HDL cholesterol > 60 mg/dL counts as a "negative" risk factor; its presence removes 1 risk factor from the total count.

CVD, cardiovascular disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CHD, coronary heart disease.

Source: NCEP. *Circulation*. 2002;106(25):3143-3421.

particles, and low HDL-C), hypertension, insulin resistance, and prothrombotic and proinflammatory states.³ For more information about metabolic syndrome, CVD, and HIV, see the third newsletter in this series, *Non-AIDS-Defining Illnesses in the Mature Patient*.

HIV INCREASES TRADITIONAL RISK FACTORS FOR CVD

Patients with HIV are at increased risk of CVD due to a greater prevalence of traditional CVD risk factors such as smoking, insulin resistance, and lipid abnormalities, found among HIV-positive individuals. A number of studies have demonstrated higher rates of metabolic abnormalities among patients with HIV compared to the uninfected general population. The Community Programs for Clinical Research on AIDS (CPCRA) Flexible Initial Retrovirus Suppressive Therapies (FIRST) study found that lower CD4 cell counts and higher HIV RNA levels were associated with lower HDL-C levels. In addition, higher viral loads were associated with lower levels of LDL-C and higher levels of very-low-density lipoprotein cholesterol (VLDL-C) and triglycerides. Moreover, a history of AIDS-defining events was associated with higher total cholesterol (TC), VLDL-C, and triglyceride concentrations.⁶ Data from the ongoing Multicenter AIDS Cohort Study (MACS) showed that metabolic syndrome was more common in HIV-positive men compared with HIV-negative controls.⁷ An analysis of data from the Medi-Cal database suggested an increased incidence of diabetes in HIV-infected individuals compared to noninfected individuals.⁸ In the SIMONE study of CVD risk factors in HIV-positive patients, the greatest single predictor of increased cardiovascular risk was smoking (60% of whole sample).⁹ By contrast, an estimated 20.8% of all adults in the US were smokers in 2006.¹⁰

 INDIANA UNIVERSITY
SCHOOL OF MEDICINE

 healthmatterscme
A CONTRIBUTING MEDICAL EDUCATION COMPANY

This activity is jointly sponsored by Indiana University School of Medicine and HealthmattersCME.

 ANAC
ASSOCIATION OF
NURSES IN AIDS CARE

The Association of Nurses in AIDS Care is an approved provider of continuing education by the Virginia Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

 GILEAD
Advancing Therapeutics.
Improving Lives.

This activity is supported by an independent educational grant from Gilead Sciences Medical Affairs.

CME/CE INFORMATION

Editor

Trevor Hawkins, MD

Medical Director
Southwest CARE Center
Associate Clinical Professor
University of New Mexico
Albuquerque, NM

Program Description:

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) continues to be associated with significant morbidity and mortality in the United States, with an increasing number of adults aged 50 and older living with HIV. Older adults account for 15% of all new HIV/AIDS cases and 24% of persons living with HIV/AIDS, an increase from 17% in 2001. Projections indicate that by 2015, older adults will constitute over 50% of the overall population living with HIV/AIDS. As the HIV population ages, health care professionals who treat patients with HIV need to be informed about special considerations in managing HIV in older patients, including comorbidities such as cardiovascular disease (CVD), metabolic disorders, liver and renal problems, and non-AIDS-defining malignancies. These comorbidities may be attributed to increasing age, as well as to HIV infection itself and antiretroviral therapy (ART). This program will provide an opportunity for HIV health care providers to increase their knowledge about a variety of these internal medicine topics that play important roles in the whole health care of the older patient with HIV.

Educational Objectives:

At the conclusion of this activity participants should be able to:

- Articulate the issues associated with treating older, treatment-naïve, and treatment-experienced HIV patients, including reduced immunologic recovery, increased ART toxicity, and drug-drug interactions
- Define the most important health care issues related to the aging HIV patient, including CVD, metabolic abnormalities, diabetes, renal disease, and increased risk of non-AIDS-defining malignancies
- Design and implement strategies for managing aging- and HIV-related comorbidities in older adults

CME Information

Release Date: December 14, 2009

Valid for Credit: December 14, 2010

Estimated time to complete this activity: 1.5 hours

Accreditation Statement



INDIANA UNIVERSITY
SCHOOL OF MEDICINE

This activity has been planned and implemented in accordance with the Essential

Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME), through the joint sponsorship of Indiana University School of Medicine and HealthmattersCME. Indiana University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Designation Statement

Indiana University School of Medicine designates this educational activity for a maximum of *1.5 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Faculty Disclosure Statement

In accordance with the Accreditation Council for Continuing Medical Education (ACCME) Standards for Commercial Support, educa-

tional programs sponsored by Indiana University School of Medicine (IUSM) must demonstrate balance, independence, objectivity, and scientific rigor. All faculty, authors, editors, and planning committee members participating in an IUSM-sponsored activity are required to disclose any relevant financial interest or other relationship with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services that are discussed in an educational activity.

Editor's Disclosure of Relevant Financial Relationships

Trevor Hawkins, MD, disclosed that he is a paid advisory board member of Gilead Sciences, Pfizer, Inc, and Tibotec Therapeutics. In addition, he disclosed that he has received speaker honoraria from Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Tibotec Therapeutics, Pfizer, Inc, and Virco.

Note

While it offers CME credits, this activity is not intended to provide extensive training or certification in the field.

How to Obtain CME/CE Credit

To receive CME/CE credit, participants must read this newsletter and then complete the evaluation and posttest online at <http://cme.medicine.iu.edu/forms/HIVandAgingVol2.aspx>. Certificate will be mailed to participants upon request.

CE Information

ANAC
ASSOCIATION OF
NURSES IN AIDS CARE
This program is approved for 1.5 contact hours by the Association of Nurses in AIDS Care (ANAC). The Association of Nurses in AIDS Care (ANAC) is an approved provider of continuing education by the Virginia Nurses Association Continuing Education Approval Committee, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.



Commercial Support

Indiana University School of Medicine and HealthmattersCME gratefully acknowledge the unrestricted educational grant provided by Gilead Sciences Medical Affairs.



Trevor Hawkins, MD
 Medical Director
 Southwest CARE Center
 Associate Clinical Professor
 University of New Mexico
 Albuquerque, NM

LETTER FROM THE EDITOR

Dear Health Care Professional:

Recent years have seen an increase in the number of people aged 50 years and older living with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). This increase has resulted both from the availability of effective antiretroviral therapy (ART), which has very significantly reduced AIDS-related mortality, and from more newly diagnosed infections in older adults. Individuals 50 years of age and older accounted for approximately 10% of all new HIV infections in the United States (US) in 2006. As a consequence of these trends, approximately one quarter of HIV-infected adults in the US in 2007 were at least 50 years old.

Older adults with long-term or new HIV infection experience complex interactions among HIV, ART, age-related changes to the body, and often, treatment for illnesses associated with aging. These interactions affect the health care needs and quality of life of older adults. It is essential that health care providers understand the medical implications of aging with HIV and continue to develop more sophisticated treatment approaches so that these older adults can live longer, healthier lives. In this issue of *The Graying of an Epidemic: Clinical Considerations of HIV and Aging* newsletter series, we review important data on the associations among HIV infection, ART, and cardiovascular disease (CVD) risk, particularly as they relate to older patients with HIV.

Traditional risk factors for CVD, such as smoking and diabetes, are present in a greater percentage of HIV-positive patients compared to HIV-negative patients. In addition, HIV infection has been shown to be an independent risk factor for CVD and the use of ART is associated with the development or worsening of some traditional cardiovascular risk factors, including dyslipidemia and insulin resistance. Recent data suggest that endothelial dysfunction, impaired fibrinolysis, and excess inflammation may contribute to increased cardiovascular risk in the HIV-positive population. Recent studies of large numbers of HIV-positive subjects have also documented increased cardiovascular risk using myocardial infarction rates as end points. This newsletter will consider the pathogenesis of various cardiovascular risk factors in the HIV-positive population and strategies to reduce risk in these patients.

This CME/CE activity will benefit patients with HIV by helping clinicians make informed decisions regarding treatment choices that will reduce HIV patients' risk for CVD. I hope that you will find this newsletter and accompanying slides to be a useful part of your own continuing education about this multifaceted and ever-changing epidemic.

Sincerely,

Trevor Hawkins, MD

HIV INFECTION MAY INCREASE MICROVASCULAR RISK FACTORS FOR CVD

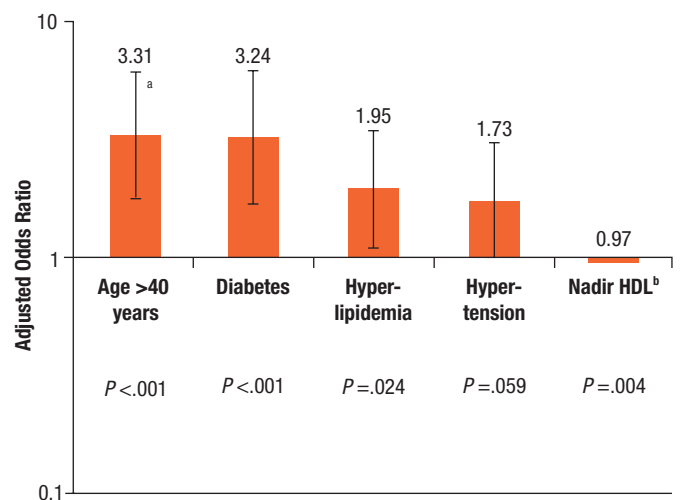
HIV infection may contribute to CVD risk by promoting dyslipidemia, endothelial dysfunction, and elevation of proinflammatory markers. A 2005 study found that a higher viral load was associated with endothelial dysfunction, a microvascular indicator of CVD risk.¹¹ Several recent studies have shown that median carotid intima-media thickness (CIMT), a validated measure of atherosclerosis, is higher among HIV-infected patients than among HIV-negative controls.¹²⁻¹⁶ To quantify the additional CVD risk attributable to HIV infection, Grunfeld et al assessed preclinical atherosclerosis by CIMT measurements in HIV-infected participants and uninfected controls. Even after adjusting for traditional CVD risk factors, HIV infection was associated with extensive atherosclerosis. The association of HIV infection with CIMT was found to be similar to that of traditional CVD risk factors such as smoking or diabetes.¹⁵ In addition, several studies have found that patients with HIV have increased levels of proinflammatory markers that have been linked to increased CVD risk—including high sensitivity C-reactive protein (hs-CRP), tissue plasminogen activator inhibitor-1, soluble intercellular adhesion molecule-1, dimerized plasmin fragment D (D-dimer), and interleukin-6 (IL-6).¹⁶⁻¹⁹

OLDER AGE INCREASES RISK OF CVD IN PATIENTS WITH HIV

Older age has been associated with increased risk of CVD among HIV-infected patients in a number of major studies. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study found that among 23,468 patients receiving combination ART, the incidence of myocardial infarction (MI) increased with greater exposure to ART (adjusted relative rate [RR] per year of exposure: 1.26; 95% confidence interval [CI]: 1.12-1.41; $P < .001$). At the same time, increased cardiovascular risk was also associated with established risk factors, including older age among the patients included in this study. The adjusted RR per 5-year increase in age in HIV-positive individuals was 1.38; 95% CI: 1.26-1.50; $P < .001$.²⁰

In a recent analysis of data from the HIV Outpatient Study (HOPS) cohort, age older than 40 years was associated with increased CVD risk (adjusted odds ratio [OR] 3.31; $P < .001$). Other significant independent

Figure 1. Multivariate Logistic Regression Analysis of Risk Factors for CVD in the HOPS Cohort (n=1807, CVD cases = 57).



^aVertical bars = 95% confidence intervals.

^bContinuous variable.

CVD, cardiovascular disease; HOPS, HIV Outpatient Study; HDL, high-density lipoprotein.

Age older than 40 years was associated with increased CVD risk.

Source: Lichtenstein KA, et al. 13th CROI, February 5-8, 2006. Denver, CO. Poster 735.

risk factors for CVD were diabetes, hyperlipidemia, and nadir HDL-C (see Figure 1).²¹

The Strategies for Management of Anti-Retroviral Therapy (SMART) study was a prospective trial (N=5472) comparing outcomes in persons with CD4-guided interruption versus persons on uninterrupted highly active antiretroviral therapy (HAART) that was stopped early owing to an increased rate of death or disease progression in the treatment interruption arm.^{22,23} In this study, age older than 60 years was an independent predictor of ischemic heart disease (OR 2.3; 95% CI: 1.4-3.6 for patients aged >60 vs <40 years; $P < .005$). Current antihypertensive therapy was also predictive of ischemic heart disease (OR 1.5; 95% CI: 1.1-2.0; $P = .01$).²⁴ None of the other parameters were statistically significant, including total HAART exposure, nonnucleoside analogue exposure, or duration of exposure to protease inhibitors (PIs).²⁴

ART AND CVD RISK IN PATIENTS WITH HIV: POTENTIAL BENEFICIAL AND NEGATIVE EFFECTS

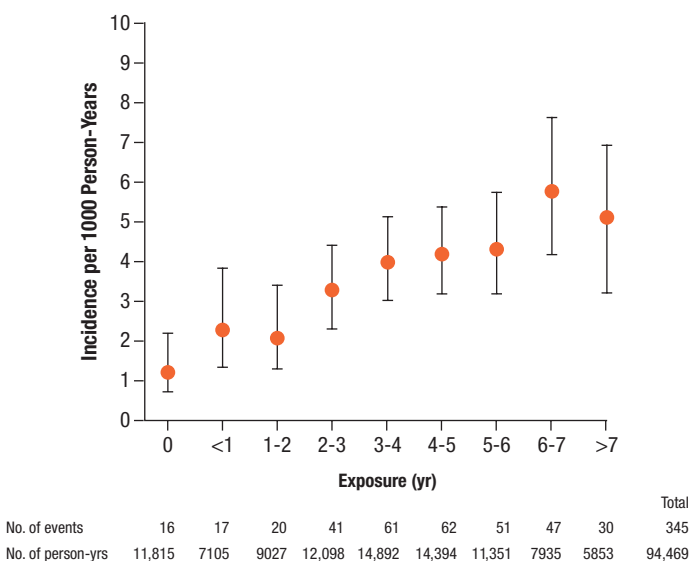
There are a range of possible effects that ART can have on the risk of CVD in patients with HIV. Numerous studies have demonstrated the beneficial effects of ART on CVD risk in HIV-infected patients. Some studies have shown a reduction in CVD risk with ART; others have shown that interruption of ART may exacerbate CVD risk. There is also evidence that long-term ART may increase CVD risk in some patients with HIV (Figure 2).²⁵ The data supporting these statements are summarized below.

Potential Beneficial Effects of ART on Risk of CVD

Studies on CVD risk in HIV-infected patients have demonstrated reduced CVD risk with ART, as well as increased risk when ART is interrupted.

Two recent studies have shown that ART may reduce the risk of CVD in HIV patients. The AIDS Clinical Trials Group (ACTG) study 5152s (a substudy of ACTG 5142) showed that ART improves endothelial function in treatment-naïve HIV patients as measured by brachial artery flow-mediated dilation, a measure of atherosclerosis and a surrogate

Figure 2. Incidence of MI According to the Duration of Exposure to Combination ART in the D:A:D Study.

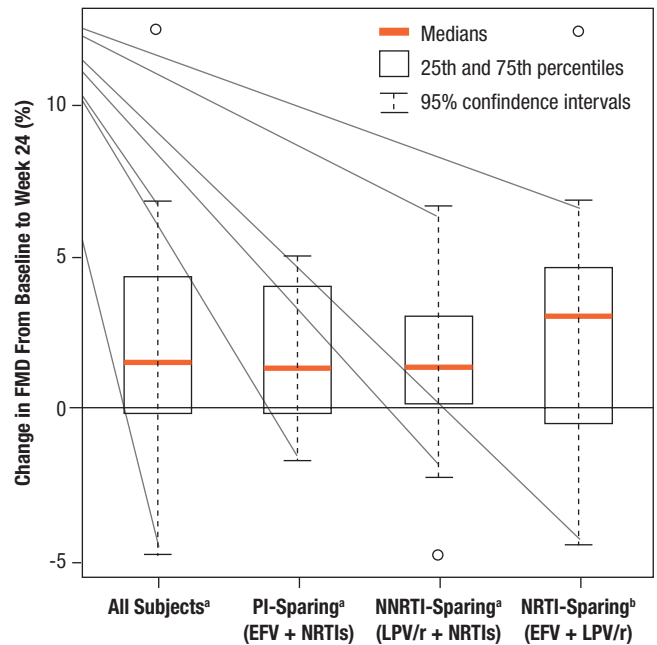


MI, myocardial infarction; ART, antiretroviral therapy; D:A:D, Data Collection on Adverse Events of Anti-HIV Drugs.

The D:A:D Study found that the incidence of MI increased with greater exposure to ART.

Source: DAD. *N Engl J Med.* 2007;356(7):1723-1735. Copyright ©2007 Massachusetts Medical Society. All rights reserved.

Figure 3. Changes in Brachial Artery Flow-Mediated Vasodilation from Baseline to Week 24 in ACTG 5152.



^a $P < .005$.

^b $P = .015$ within arm, compared to baseline (between groups $P = .828$).

ACTG, AIDS Clinical Trials Group; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; EFV, efavirenz; LPV/r, lopinavir/ritonavir.

ART improves endothelial function in treatment-naïve HIV patients as measured by brachial artery flow-mediated dilation (FMD).

Source: Torriani FJ, et al. *J Am Coll Cardiol.* 2008;52(7):569-576. Copyright ©2008 Elsevier Inc. All rights reserved. Reprinted with permission.

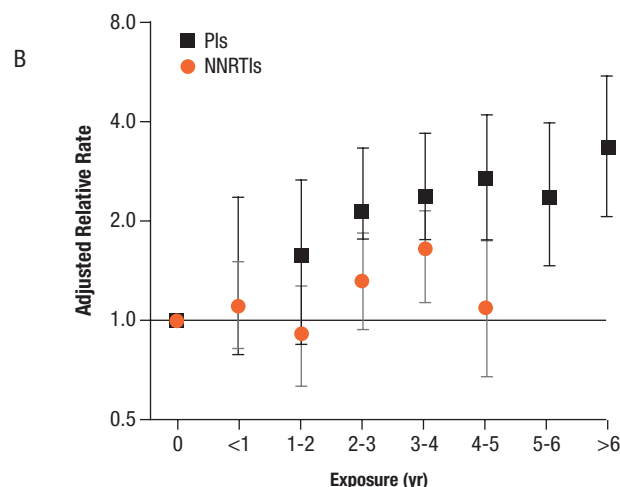
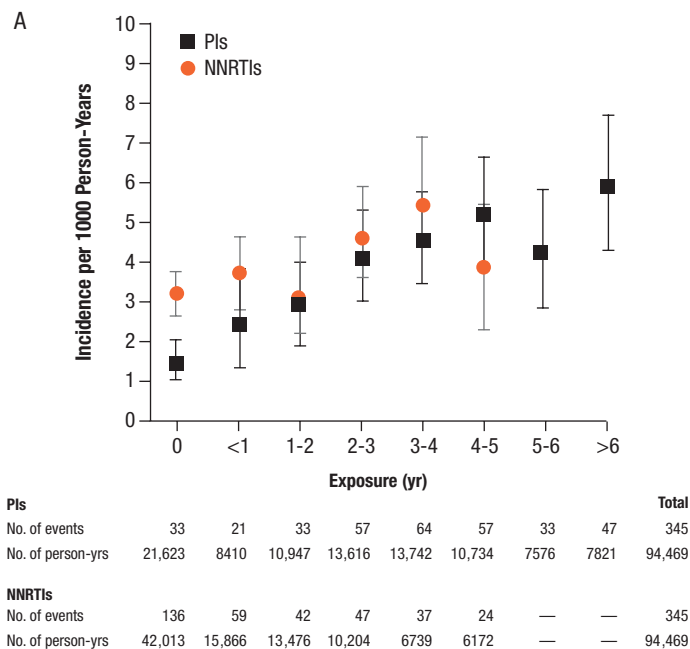
marker of CVD risk (see Figure 3).²⁶ Data from MACS demonstrated that long-term ART use reduced coronary artery calcification, an indicator of subclinical atherosclerosis and a surrogate marker for CVD risk.²⁷

Other data from SMART have shown that interruption of ART may exacerbate CVD risk. The study found that intermittent ART guided by CD4 cell count was associated with evidence of cardiac abnormalities such as Q wave, resting heart rate, and repolarization abnormalities.²⁸ An analysis of data from the SMART study population showed that intermittent ART was associated with increases in the inflammatory markers IL-6 and D-dimer.¹⁹ In addition, an analysis of data from STAC-CATO, a CD4-guided treatment interruption compared to continuous treatment trial similar to SMART, showed that patients who interrupted ART had increased inflammatory markers compared with patients who remained on therapy, including soluble vascular cell adhesion molecule-1 (sVCAM-1), adiponectin, monocyte chemoattractant protein-1, and interleukin-10.²⁹

Potential Negative Effects of ART on Risk of CVD

There is also evidence that long-term ART use may increase CVD risk in some HIV patients. A 2003 report by the D:A:D study group found that ART was associated with a 26% increased risk of CVD/MI.²⁰ A 2007 D:A:D report found that use of PIs but not NNRTIs was associated with an increased risk of CVD/MI (see Figure 4).²⁵ Some components of ART regimens may exacerbate existing traditional CVD risks by causing metabolic abnormalities. Some studies have found associations between ART and dyslipidemias, including increased TC, LDL-C, and triglycerides.³⁰⁻³² The results of these studies partly explain the increased CVD/MI risk seen with PI use in the D:A:D study.²⁵ Other studies have found increased insulin resistance/diabetes in patients on ART.³³ A number of studies have associated ART with body fat redistribu-

Figure 4. Risk of MI According to Exposure to PIs and NNRTIs.



MI, myocardial infarction; PIs, protease inhibitors; NNRTIs, nonnucleoside reverse transcriptase inhibitors; CVD, cardiovascular disease.

A 2007 D:A:D report found that use of PIs (A) but not NNRTIs (B) was associated with an increased risk of CVD/MI.

Source: DAD Study Group. *N Engl J Med.* 2007;356(17):1723-1735. Copyright ©2007 Massachusetts Medical Society. All rights reserved.

tion. In particular, substantial evidence has accumulated implicating thymidine analogue nucleoside reverse transcriptase inhibitors (NRTIs) in lipotrophy.³⁴ Recent data also provide evidence of increased risk of CHD in patients with body fat redistribution.³⁵

A number of recent studies have shed new light on the relationship between ART and CVD risk in patients with HIV, although results are not entirely consistent. Data from the HOPS cohort suggested that ART does not influence CVD risk. The investigators found a risk of CVD associated with traditional risk factors (age, preexisting dyslipidemias, diabetes, low HDL) but not pre-ART CD4 counts, initial ART choice, or switches in ART regimen. In addition, the risk of CVD was reduced with use of lipid-lowering agents in this study.²¹

Abacavir, Didanosine, and Risk of MI

Beginning with a finding in a study report issued by the D:A:D Study Group, a number of studies have found evidence for an increased risk

of MI with the use of the NRTIs abacavir (ABC) and didanosine (ddl). In attempting to reproduce these initial findings, other studies have failed to confirm the association with one or both drugs. In addition, several studies evaluating biomarkers related to CVD risk have failed to support the hypothesis of a role for ABC in the pathophysiology of the increased MI risk observed in some cohort studies. A summary of these studies follows.

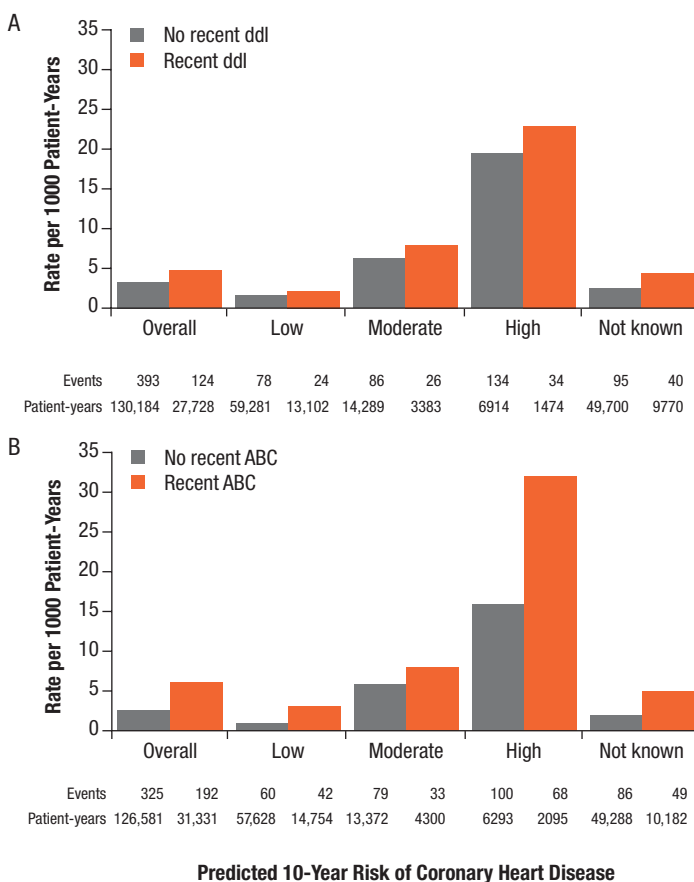
Studies Associating ABC With Increased MI Risk

The following studies found evidence for an increased risk of MI with the use of specific antiretroviral drugs, including but not limited to ABC.

D:A:D Study Group. A 2008 report from the D:A:D Study Group found an increased risk of MI in patients exposed to ABC and ddl within the preceding 6 months (see Figure 5). This excess risk did not appear to be accounted for by underlying CVD risk factors and was no longer observed beyond 6 months after the patient stopped taking the drug.³⁶ In 2009, based on additional follow-up, the D:A:D Study Group reported increased risk of MI with use of the PIs indinavir and lopinavir/ritonavir (LPV/r) as well as the NRTIs ddl and ABC.³⁷

STEAL Study. In the Simplification with Fixed-Dose Tenofovir-Etricitabine or Abacavir-Lamivudine in Adults with Suppressed HIV Replication (STEAL) study, use of the fixed-dose combination ABC 600 mg/lamivudine 300 mg was associated with increased risk of CVD and lipid end points.³⁸

Figure 5. Rates of MI, Stratified by Predicted 10-year Risk of CHD, and Recent Use of Either ddl (A) or ABC (B), in the D:A:D Study.



MI, myocardial infarction; CHD, coronary heart disease; ddl, didanosine; ABC, abacavir.

A series of reports from the D:A:D study found that use of the NRTIs ABC and ddl was associated with increased risk of MI.

Source: D:A:D. *Lancet.* 2008;371(9622):1417-1426. Copyright ©2008 Elsevier Inc. All rights reserved. Reprinted with permission.

SMART Study. A post hoc analysis of data from the Strategies for Management of Anti-Retroviral Therapy (SMART) study confirmed an association between ABC use and increased CVD/MI events, but not between ddl and CVD/MI events.³⁹

Quebec Cohort Study. In the Quebec Cohort Study, use of the NRTIs ABC, ddl, stavudine, and zalcitabine and the PIs LPV and ritonavir was associated with increased MI risk. The study, however, did not control for chronic kidney disease, although the investigators attempted to control for traditional risk factors by looking at the concomitant use of antihypertensive, antidiabetic, lipid-lowering, or antiplatelet medications.⁴⁰

Studies Failing to Detect Association of ABC With Increased MI Risk

The following studies failed to detect an association between increased MI risk and the use of ABC or had ambiguous results.

GSK Analysis. Clinical investigators at GlaxoSmithKline, the manufacturer of ABC, summarized data from the company's HIV data repository, including 54 company-sponsored clinical trials of ABC-containing regimens. They assessed data from 9639 patients who received ABC and 5044 patients who did not. They found that the incidence of coronary/myocardial events was similar between the groups.⁴¹

ALLRT (ACTG A5001). The AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT) study did not find a significant association between recent ABC use and either MI or severe CVD risk for ART-naïve patients randomized to an initial ABC-containing regimen. The investigators concluded that the association observed in other studies between recent ABC use and increased MI risk may be a marker for factors not revealed in those studies.⁴²

VA Cohort Study. An analysis of data from the Veterans Administration (VA) Clinical Case Registry found that the effect of ABC on CVD risk was not statistically significant, and that any association observed was further attenuated by controlling for traditional CVD risk factors, including renal disease.⁴³

FHDH ANRS CO4. The French National Agency for AIDS Research (ANRS) French Hospital Database on HIV (FHDH) Study CO4 (referred to as FHDH ANRS CO4) found that the risk of MI was increased by cumulative exposure to LPV/r and to amprenavir or fosamprenavir. The data on ABC were ambiguous; the study found that initiating treatment with ABC was associated with an increased risk of MI, but longer exposure to ABC was not.⁴⁴

Surrogate Markers of CVD Risk Not Associated With ABC Use

The following studies evaluated biomarkers of CVD risk to determine whether evidence could be found of a role for ABC in the increased MI risk observed with recent ABC use in some cohort studies.

ACTG 5095. In AIDS Clinical Trial Group (ACTG) Study 5095, the investigators found no difference in serum hs-CRP levels, a surrogate marker for CVD risk, between ABC- and non-ABC-containing regimens.⁴⁵

HEAT Study. An analysis of data from the Head-to-head Epcicom and Truvada (HEAT) study population found that both ABC/3TC- and tenofovir (TDF)/emtricitabine (FTC)-containing regimens similarly decreased inflammatory markers associated with CVD risk in treatment-naïve patients. The investigators concluded that the decreases in hs-CRP, IL-6, and sVCAM-1 concentrations observed in HEAT do not support the hypothesis of an ABC-induced inflammatory response leading to increased cardiovascular risk.⁴⁶

BICOMBO Study. The open-label Spanish BICOMBO trial compared TDF/FTC with ABC/3TC in patients who had already achieved virologic suppression on HAART.⁴⁷ A BICOMBO substudy found treatment with ABC/3TC did not lead to significant changes after 48 weeks in markers of inflammation, endothelial dysfunction, insulin resistance, or hypercoagulability as compared with TDF/FTC, arguing against the involvement of ABC in the pathophysiology of the increased MI risk associated with recent ABC use in some cohort studies.⁴⁸

STRATEGIES TO REDUCE RISK OF CVD IN PATIENTS WITH HIV

Aggressive management of traditional risk factors and comorbidities is the cornerstone for reducing risk of CVD in patients with HIV. Also, the benefit of treating HIV with ART and reducing viral load to <50 copies/mL greatly outweighs the risks of CVD associated with some antiretroviral agents. Nevertheless, as we fine tune therapy, avoiding adding risk, especially in patients already at risk, becomes an important part of modern treatment strategies.

Switching ART in At-Risk Patients

The November 2008 update to the Department of Health and Human Services guidelines suggests switching ART regimens to simplify treatment and reduce toxicity, particularly if the patient's current regimen is no longer recommended as preferred or alternative treatment.⁴⁹ Recommendations include switching from thymidine analogues (zidovudine, stavudine) within the NRTI class. Lesser consensus exists around the idea of switching from ABC in patients with traditional CVD risks and switching to a more lipid-friendly PI. Out-of-class substitutions such as switching to raltegravir are controversial because of lack of long-term safety data on new treatments. ART switching should be done with caution, taking into account possible drug resistance and virologic failure, as well as any drug-drug interactions that may occur with other medications that the patient may be taking.

Lifestyle Changes

Some CVD risk factors cannot be changed; these include age, gender, race, and family history. Risk of CVD increases for men over 45 and women over 55, and men have a greater CVD risk than women, as well as having MIs earlier in life. A higher prevalence of hypertension among African Americans compared with Caucasians correlates with a greater risk of CVD. Those whose parents or siblings have a history of premature CHD (<55 years of age) are more likely to develop it themselves.⁵⁰ Fortunately, some CVD risk factors can be modified, including smoking, hyperlipidemia, hypertension, obesity, inactivity, diabetes, and use of alcohol or cocaine.⁵⁰

Smoking Cessation. Patients with HIV who smoke cigarettes, cigars, or pipes should stop. Quitting smoking decreases CVD risk over time, even among patients who have smoked for many years.⁵⁰

Lipid Reduction. To reduce lipidemia, patients should maintain a diet low in fat, saturated fat, and cholesterol. Statins should be used as needed but with caution in patients on PI- or efavirenz-containing ART, as drug-drug interactions may alter statin concentrations in serum. Simvastatin and lovastatin are contraindicated with PIs. Treatment with atorvastatin or rosuvastatin should be initiated at low doses. Pravastatin is less effective and may interact with darunavir. Fibrates and fish oil may be effective for hypertriglyceridemia.⁵¹

Hypertension. Health care providers who care for patients with HIV should counsel them to follow standard guidelines on diet and exercise to control high blood pressure. If lifestyle changes fail, antihypertensive therapy should be initiated.

Obesity. Health care providers should counsel their overweight patients to use diet, exercise, and other behavioral changes to lose weight and maintain weight loss.⁵⁰

Inactivity. Health care providers should ask patients about their level of physical activity and counsel sedentary patients to engage in regular moderate-to-vigorous exercise. Adequate exercise can help control cholesterol, diabetes, obesity, and in some cases, hypertension. Patients should be encouraged to develop a regimen that includes appropriate levels of both aerobic and weight-bearing exercise.⁵⁰

Diabetes. For patients with insulin resistance or type 2 diabetes, health care providers should combine diet, exercise, and appropriate pharmacologic interventions.⁵⁰

Alcohol/Cocaine Use. Excessive alcohol consumption can increase blood pressure and contribute to risk of heart failure and stroke.⁵⁰ Cocaine use is also associated with increased rates of MI.⁵⁰ Health care providers should ask patients about their alcohol and cocaine use and make appropriate recommendations for moderate alcohol consumption or substance abuse treatment.

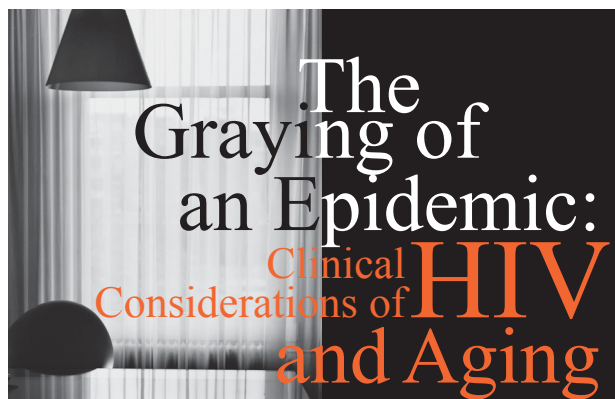
KEY LEARNINGS ON HIV AND RISK OF CVD

- Improved longevity of HIV patients and increasing diagnosis in people over 50 years old has increased focus on management of diseases common in the general population, including CVD
- Although traditional CVD risk factors continue to play a major role in CVD etiology in HIV patients, substantial evidence points to a relationship among HIV infection, ART, and increased cardiovascular risk
- Physicians should be aware of the increased risk of CVD in patients infected with HIV when initiating or altering treatment regimens
- Appropriate medical management may reduce risk of CVD in patients with HIV already receiving ART

REFERENCES

- Centers for Disease Control and Prevention. Leading causes of death. *Fast-Stats*. May 15, 2009. Available at <http://www.cdc.gov/nchs/FASTATS/lcod.htm>. Accessed on September 14, 2009.
- World Health Organization. The top ten causes of death. Fact sheet no. 310. November 2008. Available at http://www.who.int/mediacentre/factsheets/fs310_2008.pdf. Accessed on September 14, 2009.
- National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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) final report. *Circulation*. 2002;106(25):3143-3421.
- Centers for Disease Control and Prevention. Perspectives in disease prevention and health promotion smoking and cardiovascular disease. *MMWR*. 1984;32(52):677-679.
- American Heart Association. Risk Factors and Coronary Heart Disease. Available at http://www.americanheart.org/print_presenter.jhtml?identifier=4726. Accessed on September 14, 2009.
- El-Sadr WM, Mullin CM, Carr A, et al. Effects of HIV disease on lipid, glucose and insulin levels: results from a large antiretroviral-naïve cohort. *HIV Med*. 2005;6(2):114-121.
- Palella F, Wang Z, Chu H, et al. Correlates and prevalence of the metabolic syndrome over time in the Multicenter AIDS Cohort Study (MACS). 3rd International AIDS Society Conference on HIV Pathogenesis and Treatment. July 24-27, 2005. Rio de Janeiro. Abstract TuPe2.2B18.
- Currier, JS, Boyd F, Kawabata H, et al. Incidence, prevalence, and pathogenic correlates of insulin resistance and lipodystrophy syndrome. 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002. Seattle, WA. Poster 677-T.
- De Socio GV, Parruti G, Quirino T, et al. Identifying HIV patients with an unfavorable risk profile in the clinical practice: Results from the SIMONE study. *J Infect*. 2008;57(1):33-40.
- Centers for Disease Control and Prevention. Cigarette smoking among adults—United States, 2006. *MMWR*. 2007;56(44):1157-1161.
- Blum A, Hadas V, Burke M, et al. Viral load of the human immunodeficiency virus could be an independent risk factor for endothelial dysfunction. *Clin Cardiol*. 2005;28(3):149-153.
- Hsue PY, Hunt PW, Schnell A, et al. Role of viral replication, antiretroviral therapy, and immunodeficiency in HIV-associated atherosclerosis. *AIDS*. 2009;23(9):1059-1067.
- Hsue PY, Hunt PW, Sinclair E, et al. Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses. *AIDS*. 2006;20(18):2275-2283.
- Hsue PY, Lo JC, Franklin A, et al. Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. *Circulation*. 2004;109(13):1603-1608.
- Grunfeld C, Delaney JA, Wanke C, et al. Preclinical atherosclerosis due to HIV infection: carotid intima-medial thickness measurements from the FRAM study. *AIDS*. 2009;23(14):1841-1849.
- Ross AC, Rizk N, O'Riordan MA, et al. Relationship between inflammatory markers, endothelial activation markers, and carotid intima-media thickness in HIV-infected patients receiving antiretroviral therapy. *Clin Infect Dis*. 2009;49(7):1119-1127.
- Lau B, Sharrett AR, Kingsley LA, et al. C-reactive protein is a marker for human immunodeficiency virus disease progression. *Arch Intern Med*. 2006;166(1):64-70.
- Kristoffersen US, Kofoed K, Kronborg G, et al. A Longitudinal study of changes in circulating markers of endothelial function in HIV patients starting combination antiretroviral therapy. 15th Conference on Retroviruses and Opportunistic Infections. February 3-6, 2008. Boston, MA. Poster 953.
- Kuller L, and SMART Study Group. Elevated levels of Interleukin-6 and D-dimer are associated with an increased risk of death in patients with HIV. 15th Conference on Retroviruses and Opportunistic Infections. February 3-6, 2008. Boston, MA. Abstract 139.
- DAD Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med*. 2003;349(21):1993-2003.
- Lichtenstein KA, Armon C, Buchacz K, et al. Analysis of cardiovascular risk factors in the HIV Outpatient Study (HOPS) cohort. Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006. Denver, CO. Poster 735.
- Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355(22):2283-2296.
- National Institute of Allergy and Infectious Disease. International HIV/AIDS Trial Finds Continuous Antiretroviral Therapy Superior to Episodic Therapy. Press Release. January 18, 2006.
- Carr A, Grund B, Neuhaus J, et al. ART and asymptomatic ischemic heart disease in HIV-infected adults: a cross-sectional analysis of patients enrolling in the SMART trial. Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections. February 5-8, 2006. Denver, CO. Abstract 736.
- DAD Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007;356(17):1723-1735.
- Torriani FJ, Komarow L, Parker RA, et al. Endothelial function in HIV-infected antiretroviral naïve subjects before and after starting potent antiretroviral therapy: AIDS Clinical Trials Group Study 5152s. *J Am Coll Cardiol*. 2008; 52(7): 569-576.

27. Kingsley LA, Cuervo-Rojas J, Muñoz A, et al. Subclinical coronary atherosclerosis, HIV infection and antiretroviral therapy: Multicenter AIDS Cohort Study. *AIDS*. 2008;22(13):1589-1599.
28. Prineas R, Roediger M, Carr A, et al. Effect of alternate treatment protocols on the incidence of electrocardiographic abnormalities among HIV infected adults in the SMART trial. 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention. July 22-25, 2007. Sydney, Australia. Abstract WEPEB077.
29. Calmy A, Nguyen A, Montecucco F, et al. HIV activates markers of cardiovascular risk in a randomized treatment interruption trial: STACCATO. 15th Conference on Retroviruses and Opportunistic Infections. February 3-6, 2008. Boston, MA. Abstract 140.
30. Haubrich RH, Riddler SA, DiRienzo AG, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. *AIDS*. 2009;23(9):1109-1118.
31. Stein JH, Komarow L, Cotter BR, et al. Lipoprotein changes in HIV-infected antiretroviral-naïve individuals after starting antiretroviral therapy: ACTG Study A5152s. *J Clin Lipidol*. 2008;2(6):464-471.
32. Thiébaud R, Dabis F, Malvy D, et al. Serum triglycerides, HIV infection, and highly active antiretroviral therapy, Aquitaine Cohort, France, 1996 to 1998. Groupe d'Epidémiologie Clinique du Sida en Aquitaine (GECSA). *J Acquir Immune Defic Syndr*. 2000;23(3):261-265.
33. Calza L, Manfredi R, Chiodo F. Insulin resistance and diabetes mellitus in HIV-infected patients receiving antiretroviral therapy. *Metab Syndr Relat Disord*. 2004;2(4):241-250.
34. Phillips DR, Hay P. Current perspectives on the management and prevention of antiretroviral-associated lipodystrophy. *J Antimicrob Chemother*. 2008;62(5):866-871.
35. Hadigan C, Meigs JB, Wilson PW, et al. Prediction of coronary heart disease risk in HIV-infected patients with fat redistribution. *Clin Infect Dis*. 2003;36(7):909-916.
36. D:A:D Study Group. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet*. 2008;371(9622):1417-1426.
37. Lundgren J, Reiss P, Worm S, et al. Risk of myocardial infarction with exposure to specific ARB from the PI, NNRTI, and NRTI drug classes: the D:A:D study. 16th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2009. Montréal, Canada. Abstract 44LB.
38. Cooper DA, Bloch M, Humphries A, et al. Simplification with fixed-dose tenofovir/emtricitabine or abacavir/lamivudine in adults with suppressed HIV replication (the STEAL study): a randomized, open-label, 96 week, non-inferiority trial. 16th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2009. Montréal, Canada. Poster 576.
39. Strategies for Management of Anti-Retroviral Therapy/INSIGHT; DAD Study Groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS*. 2008;22:F17-F24.
40. Durand M, Sheehy O, Baril JG, Leloir J, Tremblay C. Relation between use of nucleoside reverse transcriptase inhibitors (NRTI) and risk of myocardial infarction (MI): a nested case control study using Quebec's public health insurance database (QPHID). Program and abstracts of the 5th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention. July 19-22, 2009. Cape Town, South Africa. Abstract TUPEB175 and poster.
41. Cutrell A, Brothers C, Yeo J, et al. Abacavir and the potential risk of myocardial infarction. *Lancet*. 2008;371(9622):1413.
42. Benson C, Ribaud H, Zheng E, et al. No association of abacavir use with risk of myocardial infarction or severe cardiovascular disease events: results from ACTG A5001. 16th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2009. Montréal, Canada. Abstract 721.
43. Bedimo R, Westfall A, Drechsler H, et al. Abacavir use and risk of acute myocardial infarction and cerebrovascular disease in the HAART era. 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention. July 19-22, 2009. Cape Town, South Africa. Abstract MOAB202.
44. Lang S, Mary-Krause M, Cotte L, et al. Impact of specific NRTI and PI exposure on the risk of myocardial infarction: a case-control study nested within FHDH ANRS CO4. 16th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2009. Montréal, Canada. Abstract 43LB.
45. Shikuma CM, Ribaud HS, Zheng E. 96 week effects of suppressive efavirenz-containing antiretroviral therapy, abacavir, and sex on hs-CRP in ACTG A5095. 16th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2009. Montréal, Canada. Poster 736.
46. McComsey GA, Smith KY, Pate P, et al. Similar reductions in markers of inflammation and endothelial activation after initiation of abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC) in the HEAT study. 16th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2009. Montréal, Canada. Poster 732.
47. Martínez E, Arranz JA, Podzamczar D, et al. A simplification trial switching from nucleoside reverse transcriptase inhibitors to once-daily fixed-dose abacavir/lamivudine or tenofovir/emtricitabine in HIV-1-infected patients with virological suppression. *J Acquir Immune Defic Syndr*. 2009;51(3):290-297.
48. Martínez E, Larrousse M, Perez I, et al. No evidence for recent abacavir/lamivudine use in promoting inflammation, endothelial dysfunction, hypercoagulability, or insulin resistance in virologically suppressed HIV-infected patients: a substudy of the BICOMBO randomized clinical trial (ISRCTN6189). 5th International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention. July 19-22, 2009. Cape Town, South Africa. Abstract MOAB203.
49. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. November 3, 2008; 1-139. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed September 25, 2009.
50. Kressy J, Wanke C, Gerrior J. Cardiovascular disease risk. *HIV Nutrition & Health*. Available at http://www.tufts.edu/med/nutrition-infection/hiv/health_cvd.html. Accessed on September 14, 2009.
51. Oh RC, Lanier JB. Management of hypertriglyceridemia. *Am Fam Physician*. 2007;75(9):1365-1371.



A series of three newsletters addressing the special needs of the aging HIV-positive patient:

- I. Managing HIV Infection in the Mature Patient
- II. Cardiovascular Disease in the Mature Patient
- III. Non-AIDS-Defining Illnesses in the Mature Patient