Cardiovascular Diseases in HIV and Aging

Aroonsiri Sangarlangkarn, MD, MPH, Jonathan S. Appelbaum, MD, FACP

**Educational Objectives**

By the end of the session, learners will be able to:

1. Describe two risk factors for cardiovascular diseases in HIV-infected patients.
2. Outline an evaluation of cardiovascular diseases in HIV-infected patients.
3. Explain how to modify two cardiovascular risk factors in HIV-infected patients.

**Suggested reading:**


**CASE ONE:**

Mr. Heart is a 70-year-old man who comes to your office to establish care. He has a history of HIV. His last CD4 was 500 cells/mm³ with an undetectable viral load. He takes atazanavir, ritonavir, emtricitabine and tenofovir. Otherwise, he has a history of hypertension, hyperlipidemia, and diabetes. His other medications include lisinopril 20mg daily, simvastatin 20mg daily, and metformin 1000mg daily.

Mr. Heart mentions that one of his best friends just had a heart attack, which scared him. He wants to do everything he can to prevent heart disease.

**Questions:**

1. **How does the prevalence rate of cardiovascular disease in HIV-infected patients differ from that in the uninfected?**
   - *Multiple studies have shown increased incidence of cardiovascular disease in HIV-infected patients compared to their uninfected counterparts.*
   - *When stratified by age, it seems that the increased incidence in overall cardiovascular disease is found within the younger population. Based on a large study (1) evaluating California state-sponsored health insurance claims data, the incidence was 19 per 1000 person-years in uninfected patients vs 29 per 1000 person-year in the HIV-infected, although this estimate did not factor in traditional risk factors such as family history or cigarette smoking.*
Once stratified by age, higher incidence of cardiovascular disease in HIV patients was only found up until age 44 – over 45 years of age, the incidence of cardiovascular diseases is higher in the uninfected than HIV-infected patients. Specifically, the higher incidence in HIV-infected patients was found in men age 18-24 (relative risk (RR) 6.76 [3.36-13.58]), 25-34 (RR 2.16 [1.81-2.58]), and women age 18-24 (RR 2.47 [1.23-4.95]) 25-34 (RR 1.53 [1.10-2.13]) and 35-44 (RR 1.67 [1.41-1.97]).

- When using acute myocardial infarction (AMI) as the primary outcome, the Veterans Aging Cohort (VACS) Study (2) found that the mean AMI events per 1000 person-years was significantly higher in HIV-infected patients across all age groups (age 40-49 years: 2.0 (1.6-2.4) vs 1.5 (1.3-1.7); age 50 to 59 years, 3.9 (3.3-4.5) vs 2.2 (1.9-2.5); age 60 to 69 years, 5.0 (3.8-6.7) vs 3.3 (2.6-4.2)). Once adjusted for Framingham risk factors, comorbidities, and substance use, HIV-infected patients had increased risk of AMI compared to the uninfected (hazard ratio 1.48 [1.27-1.72]). The applicability of this study is limited by the fact that only veterans were included, and the main outcome was AMI, not overall cardiovascular disease.

2. What are the risk factors for cardiovascular disease in HIV patients? What are the traditional risk factors (ones also found in the uninfected)? What are risk factors related to HIV or its treatments?

- **Traditional risk factors:** A few traditional cardiovascular risk factors are more common among HIV-infected patients.
  - **Lipid profile:** Compared to the uninfected, HIV-infected patients seem to have less favorable lipid profile. Based on a study by Saves et al (3), HIV-infected patients are more likely to have low HDL (average 0.44 g/L infected vs 0.50 g/L uninfected in men, 0.54 g/L infected vs 0.62 g/L uninfected in women), and elevated triglycerides (average 1.90g/L infected vs 1.08 g/L uninfected in men, 1.71 g/L infected vs 0.83 g/L uninfected in women). It was purported that impaired cholesterol efflux of macrophages in HIV infection may cause a shift in lipid profile resulting in low HDL and high triglycerides (4).
  - **Insulin resistance and diabetes:** Prior research studies reported increased incidence of diabetes with HIV-infected patients on ART compared to the uninfected, but it is unclear whether the increased incidence is caused by ART, chronic HIV infection or underlying lifestyle habits specific to HIV-infected patients. There was also much variability regarding the definition of diabetes, regimens of ART used, the underlying prevalence of obesity and other confounding factors. Other studies found insulin resistance with older protease inhibitors or nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), but it is unclear whether the association exists with newer medications and whether it is clinically significant.
  - **Hypertension:** There is a higher prevalence of hypertension among HIV-infected patients compared to the uninfected (21.2% vs 15.9%) (5). Seaberg et al (6) suggested that the higher prevalence of
hypertension might be secondary to ART exposure. They found that HIV-infected men not on ART are less likely to have systolic hypertension (>140mmHg) than HIV-infected men on mono/combination therapy (odds ratio 0.69 [0.59-0.80]). Moreover, they found that after 2 years of ART, the prevalence of systolic hypertension increased significantly from similar to that in HIV-uninfected men to an odds ratio of 1.51 [1.25-1.82]. The analysis controlled for age, race, body mass index (BMI) and smoking.

- Smoking: HIV-infected patients are more likely to smoke. Saves et al (3) found a higher incidence of smoking among HIV-infected patients (56.6% infected vs 32.7% uninfected in men, 58% infected vs 28.1% uninfected in women). A study by Helleberg et al (7) found that among HIV-infected patients, smoking increases cardiovascular mortality (RR 4.3 [1.4-13.1]) and all-cause mortality (RR 4.4 [3.0-6.7]). The number of life-years lost in association with smoking is 12.3 [8.1-16.4], more than double the 5.1 life-years lost attributable to HIV infection alone.

- Substance use: Cocaine use has been implicated in coronary calcification. The incidence of significant stenosis (>50%) is about 15% in African-American HIV-infected patients (8).

- Effect of ART: Currently, evidence is inconclusive whether and how ART affects cardiovascular disease in HIV-infected patients. Studies seem to suggest that exposure to older protease inhibitors may contribute to the risk of cardiac events, but the beneficial effect of ART on higher CD4 counts and lower HIV RNA is associated with lower myocardial infarction risks.

- ART overall: The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study (9) showed increased incidence of myocardial infarction (MI) with increased cumulative exposure to ART (RR 1.26 [1.12-1.41]), although the absolute risk is low and may not be clinically significant.

- Protease inhibitors: A subsequent analysis on the D:A:D study group (10) found increased risk of MI associated with increased exposure to certain protease inhibitors (relative rate of MI/year of 1.16 [1.10-1.23]). The effect is reduced when adjusted for serum lipid levels (1.10 [1.04-1.18]). Another study by Durand et al (11) reported incidence ratio of acute MI by ART agent: lopinavir (1.98 [1.24-3.16]) and ritonavir (2.29 [1.48-3.54]). However, the data on smoking or HIV clinical status was not available for the analysis and confounding effects from these 2 risk factors were not accounted for. Atazanavir-ritonavir and darunavir-ritonavir have a more favorable lipid profile than lopinavir-ritonavir, although protease inhibitors are not as lipid-neutral as raltegravir (12).

- Abacavir: According to Durand et al (11), the incidence ratio of acute MI for abacavir was 1.79 [1.16-2.76]. Multiple other studies including one large meta-analysis of randomized controlled trials by Ding et al (13) found no association between abacavir and MI risk.
Non-nucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs): Of all NNRTIs, efavirenz seems to have the least favorable lipid profile. According to Durand et al, the incidence ratio of acute MI for efavirenz was 1.83 [1.21-2.76]. Another large prospective trial (14) showed that compared to efavirenz, nevirapine results in a higher increase of HDL level (43% vs 34% for efavirenz) and a smaller increase in total cholesterol level (27% vs 31% for efavirenz).

Effect of ART interruption: Episodic ART guided by CD4 counts has been shown to increase cardiovascular risks, as well as all-cause mortality and opportunistic diseases.

The SMART study (15) evaluated the effect of episodic therapy defined as deferral of therapy until CD4 count is less than 250 per cubic millimeter and the use of therapy until CD4 count increases to more than 350 per cubic millimeter. After 3700 person years of follow-up (median 16 months), the episodic group had 1.3 MI per 100 person years compared to 0.8 in the continuous therapy group.

Uncontrolled viremia: Many studies have shown associations between high viral load and low CD4 counts with increased risk of MI and cardiovascular diseases.

A study by Lang et al (16) showed an increased risk of MI with HIV RNA level>50copies/mL (odds ratio (OR) 1.51 [1.09-2.10]), low CD4 nadir (OR 0.90 [0.83-0.97]) and high current CD8 cell counts (OR 1.48 [1.01-2.18]), regardless of cardiovascular risk factors and ART.

Lipodystrophy syndrome: Although HIV-infected patients with fat redistribution have a higher risk of coronary heart disease (CHD), the increased risk might be related to the pattern of fat distribution and not necessarily chronic HIV infection. According to Hadigan et al, compared with uninfected controls, HIV-infected patients with fat redistribution have higher 10-year CHD risk (7.4% vs 5.3%) (17). However, when controlled for waist-to-hip ratio, the risk estimate did not significantly differ. HIV-infected patients without fat redistribution did not have a greater CHD risk than did control subjects.

Hepatitis C virus coinfection: Based on current evidence, hepatitis C virus (HCV) coinfection does not seem to increase CHD risk compared to HIV-monoinfected patients when controlled for risk factors such as hypertension, diabetes, and other confounders (18).

3. What other questions would you ask Mr. Heart?

Possible questions include:

- Smoking history
- Diet history
- Alcohol use
- Substance use history
- Level of exercise activity
- Family history of coronary artery or vascular disease, hypertension or diabetes mellitus
Level of medication adherence

CASE ONE CONTINUED:

Mr. Heart states he is adherent with all of his medications, although he has not seen a doctor in about a year. His father died of a heart attack at age 50, while his mother died at age 70 from a stroke. She had hypertension and diabetes.

He used to snort cocaine but quit 15 years ago, after which he picked up tobacco smoking. He now smokes 1 pack per day. He drinks a glass of wine with dinner everyday.

Mr. Heart rarely cooks. He usually eats take-out hamburgers or pasta. He tires easily because of his weight and rarely exercises.

On exam, his pulse is 78, BP 160/95, oxygen saturation 99% on room air. His BMI is 40 kg/m². There are no abnormal findings on exam. His point-of-care fasting glucose was 85 mg/dl.

4. What cardiovascular risk factors does Mr. Heart have? How would you estimate cardiovascular risk for Mr. Heart based on his risk factor profile?
   - Mr. Heart has multiple cardiovascular risk factors, including uncontrolled hypertension, hyperlipidemia, diabetes, positive family history, smoking history, prior substance abuse, alcohol use, poor diet, low level of exercise, and obesity.
   - Currently, there is no validated cardiac risk model created based on data in HIV-infected patients. Various cardiac risk models for the general population exist, but data on their applicability to HIV-infected patients is limited. For example, the American College of Cardiology/American Heart Association (ACC/AHA) guideline on the assessment of cardiovascular risk has not been extensively studied in the HIV-infected population. On the other hand, the Framingham risk score (calculator available at http://cvdrisk.nhlbi.nih.gov/) has been shown to underestimate the risk of cardiovascular disease in HIV-infected patients. Freiberg et al (19) found that for the same Framingham risk score, HIV-infected patients have a higher incidence of acute myocardial infection than uninfected controls (adjusted hazard ratio 1.48 [1.27-1.72]). As a result, the practical approach at this time may be to use existing cardiac risk models for the general population, understanding that the risk assessment will likely be underestimated.

5. How would you modify Mr. Heart’s risk factors?
   - The optimal approach to cardiovascular risk reduction in HIV-infected patients is not currently defined, but it is widely accepted that the same techniques used in HIV-uninfected patients should apply.
- **Diet modification:** Research has shown benefits of dietary intervention on cardiovascular outcomes among HIV-infected patients. A randomized controlled trial by Lazzaretti et al (20) found that nutritional guidance from a registered dietitian based on the Phase II diet of the NCEP ATP guidelines results in the reduction of fat intake (31% to 21% of calories vs no change in controls), and plasma triglycerides (135 to 101 mg/dl vs 134 to 160 mg/dl in controls). Control groups were also found to have increased LDL (85 to 106 mg/dl vs no change in the diet group). After 1 year follow-up, diet group had a lower incidence of dyslipidemia compared to controls (21% vs 68%).

- **Exercise training:** Current data is limited to small studies, and further investigation is warranted to determine the specific regimens of exercise training that may be beneficial in HIV-infected patients. A study by Yarasheski et al (21) found that 16 weeks of weight-lifting exercise consisting of 3 upper and 4 lower body exercises done for 1-1.5 hours/day, 4 days/week for 64 sessions reduced fasting serum triglycerides from 281 to 204 mg/dl, increased whole body lean mass by 1.4 kg and increased muscle strength by 23-38% among 18 HIV-infected men. However, due to small sample size, the applicability of these results to the larger HIV-infected population, especially women, is controversial.

- **Smoking cessation:** Currently, there is limited research on the effect of smoking cessation on cardiovascular outcomes among HIV-infected patients, but the benefits of smoking cessation among the general population are well-established. Clinicians should be aware that bupropion, commonly used as a smoking cessation agent, is metabolized by the cytochrome P450 enzyme system, and may cause interactions with antiretroviral drugs.

- **Moderate alcohol consumption:** Mr. Heart should be counseled to continue to consume 1-2 drinks of alcohol daily, since multiple studies have shown decreased incidence of CHD and cardiovascular mortality compared to binge drinkers or nondrinkers.

- **Management of comorbid conditions:** Diabetes and hypertension are well-known risk factors for cardiovascular disease. Both should be managed in a similar manner to that among HIV-uninfected patients.
  - **Hypertension:** In hypertensive patients with diabetes, their goal blood pressure should be less than 140/90. For Mr. Heart, his lisinopril can likely be increased to 40 mg daily if his electrolytes and renal function are within normal limits.
  - **Diabetes:** Although Mr. Heart’s fasting glucose was well-controlled, his hemoglobin A1C should be checked to provide a long-term estimate of his glucose over 3 months. His diabetic regimen can then be adjusted accordingly.

- **Aspirin use:** Mr. Heart should be started on aspirin 81 mg daily to help reduce the risk of myocardial infarctions, potentially up until the age of 79. The decision should be revisited if there is a change in goals of care or should the risk of gastrointestinal bleeding arise.

6. What workup would you order and how often would you order them?
- **Lipid and glucose levels:** Per the Infectious Disease Society of America (22), fasting lipid levels and hemoglobin A1C (HbA1C) or fasting glucose should be checked prior to and 1-3 months after initiation of ART since ART has been associated with changes in lipid levels and glucose control. Per the US Department of Health and Human Services (23), during ART use, fasting lipid levels should be checked every 6-12 months and glucose levels every 3-6 months.

- **Baseline liver function tests and creatinine phosphokinase:** Although these parameters may be measured at baseline as it may be helpful to have if there is subsequent concern for side effects of statin use, there is generally no indication for routine monitoring of these parameters in the absence of suggestive symptoms.

**CASE ONE CONTINUED:**

On labs, his HbA1C is 6.5%. His total cholesterol is 195, HDL 53, LDL 110, triglycerides 162.

His BMP is normal and you increase lisinopril from 20mg daily to 40mg daily.

7. **Is lipid-lowering treatment indicated for Mr. Heart? If yes, would you continue the current regimen of simvastatin 20mg daily?**

- The indication for the use of lipid lowering therapy in HIV-infected patients is the same as that in the uninfected. Since statin therapy reduces the relative cardiovascular risks by approximately 20-30%, lipid lowering therapy is indicated in patients with higher cardiovascular risk in which the 20-30% risk reduction may be worth the cost, burdens and potential side effects of statin therapy. The decision should be made jointly with patients based on their preferences and goals of care.

- Based on the Framingham risk score, Mr. Heart’s 10-year cardiovascular risk is 22%. A 20-30% risk reduction seems reasonable, and lipid-lowering therapy should be initiated, especially since this is also in line with his care goals of preventing cardiovascular disease.

- Statin selection should take into account potential interactions with protease inhibitors or cobicistat, both of which down-regulate the activity of CYP3A4, resulting in increased serum concentration of statin and the potential for rhabdomyolysis. In contrast, multiple studies have shown decreased levels of pravastatin, simvastatin and atorvastatin with NNRTIs such as efavirenz (24) or etravirine (25):
  - For patients on ritonavir-boosted protease inhibitor regimen: pitavastatin is the agent of choice due to minimal interactions, efficacy and favorable side effect profile. A starting dose of 2mg daily may be appropriate. However, if pitavastatin is not available due to cost, atorvastatin with a starting dose of 10mg daily can be substituted.
o For patients not on ritonavir-boosted protease inhibitor regimen: atorvastatin is the agent of choice based on its potent efficacy and greater clinical experience in HIV-infected patients. A starting dose of 10mg daily may be appropriate.

o Rosuvastatin does not have substantial interactions with antiretroviral agents and is efficacious in improving lipid profile. However, due to its potential for exacerbation of insulin resistance, pitavastatin or atorvastatin may be a better choice. A starting dose of 10mg daily may be appropriate, with routine monitoring for diabetes.

o Pravastatin is not metabolized by the CYP3A4 system and may be an acceptable alternative. However, because it is not as efficacious as the above statins, it is not considered to be first line treatment. A starting dose of 20mg daily may be appropriate.

o Fluvastatin is not metabolized by the CYP3A4 system, but there are few clinical data concerning the concurrent use of fluvastatin with protease inhibitors. As a result, it is not recommended as first line agents in the treatment of hyperlipidemia in HIV-infected patients.

o Ezetimibe: Currently, there is no convincing evidence that ezetimibe can improve clinical outcomes beyond treatment with a statin alone. In HIV-infected patients, ezetimibe may have a role among patients who cannot tolerate statins or to avoid drug interactions, since ezetimibe does not have any P450 interactions. A multi-center, double-blind, placebo-controlled crossover trial in 44 HIV-infected patients already on statin for hyperlipidemia found that ezetimibe decreases LDL level (-20.8% vs -0.7%), and lower absolute LDL level (by -32 mg/dl). There was no significant difference in HDL, triglyceride of C-reactive protein (26).

- Since Mr. Heart is on a ritonavir-boosted protease inhibitor regimen, he should be switched to Pitavastatin, with the dose equivalent to simvastatin 40mg daily (since simvastatin 20mg daily was inadequate). This comes out to be Pitavastatin 4mg daily.

8. Does Mr. Heart have hypertriglyceridemia? How would you manage it? What if his triglyceride level is more than 500mg/dl?

- Hypertriglyceridemia is associated with increased risks of cardiovascular disease as well as pancreatitis. The management of hypertriglyceridemia in HIV-infected patients is the same as that in the general population.

- With diabetes, goal triglyceride should be less than 150mg/dl, which might be achieved by switching to an appropriate statin regimen and dosing as outlined above.

- Of note, HIV-infected patients with triglyceride levels >500mg/dl should be treated with triglyceride-lowering agents, which include:
  - Fibrates: Gemfibrozil (600mg twice daily given 30 minutes before morning and evening meals) or fenofibrate (54 to 160mg daily) can both be used in HIV-infected patients. These agents are metabolized by CYP4a and are unlikely to have drug interactions with antiretroviral
medications. However, gemfibrozil can enhance the myopathic effect of atorvastatin and their combination should be avoided.

- **Niacin**: Niacin can decrease LDL and triglycerides, as well as increase HDL in HIV-uninfected patients. However, in HIV-infected patients, data is limited to small studies with questionable applicability. The use of niacin has also recently been discouraged due to potential side effects, including cutaneous flushing.

- **Fish oils**: Dosed at 4g per day in a single or divided dose, fish oils have been shown to decrease mean triglyceride levels in HIV-infected patients (461 to 306 mg/dL after 4 weeks) (27). Because fish oils have antiplatelet effects, it should be closely monitored when used with other antiplatelet agents.

- **Bile-sequestering resins**: Resins are not recommended in HIV-infected individuals due to concerns of possible effects on absorption of antiretroviral agents.

9. **What would you do with Mr. Heart’s ART regimen? What regimen would you pick if he were treatment-naïve considering he has hyperlipidemia?**

- Currently, there is no conclusive evidence on the optimal strategies for ART switch with the goals of improving lipid profiles and cardiovascular outcomes. Despite better lipid effects with certain strategies, loss of virologic control and new adverse effects/intolerance were also documented (28). Since Mr. Heart achieved virologic control with the current regimen, it may be sensible to keep the same regimen and treat his hyperlipidemia with strategies mentioned above.

- If Mr. Heart were treatment-naïve, it might be sensible to start him on an integrase inhibitor regimen since this is lipid-neutral compared to protease inhibitors or NNRTIs such as efavirenz. Despite multiple studies and meta-analyses showing no association between MI risk and abacavir, tenofovir/emtricitabine may be superior to abacavir/lamivudine until more research can be conducted to evaluate the link between MI risk and abacavir.
Additional reference:


