**HIV, Lipid Disorders and Cardiovascular Disease**

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**Learning Objectives**

1. Understand lipid disorders in newly infected HIV patients
2. Understand dyslipidemia in HIV infected patients on ART
3. Review and understand CVD in HIV infected patients

**Case:**

Mr. Aiden is a 52 year old man Caucasian, with a PMHx significant for newly diagnosed HIV 4 weeks ago, not currently on anti-retroviral therapy (ART), HTN on amlodipine, active smoker (1ppd for 20 yrs), poor medical follow up with last visit 7 years ago. Pt communicates that he is ready to start ART now and is seen in clinic to initiate staging and get medications. HIV VL 96,000 at diagnosis CD4 count 352. On exam he is overweight gentleman, BMI 32, HR 96, RR12, BP 147/88, with RRR, CTAB, large abdomen but soft and non tender, no LE edema, and pleasant on interview.

1. **What changes in Lipid do you expect in newly diagnosed HIV patients? What other risk factors regarding CVD should be evaluated with this patient?**

* Newly Diagnosed HIV Lipid Profile Changes
  + The MACS trial newly HIV infected men had lipid profiles measured at new infection time and after starting ARVS. At the time of new onset of HIV infection changes in lipid profiles were noted to have reductions in total cholesterol, LDL-cholesterol, HDL-cholesterol with new HIV infection1.
* CVD Risk Factors
  + Family Hx of CAD, MI, Stroke, DM
  + Tobacco Use
  + Substance Use (Cocaine)
  + Hx of MI, DM, Stroke, PVD, Metabolic Syndrome, HTN
  + HIV infection
  + Age, Race, Sex

Labs and staging are completed with the following. Lipid panel Chol 160, HDL 34, LDL98, TG 111, UA + microalbuminuria, Gonorrhea/Chlamydia screening negative, Hemoglobin A1c 7.0, HLA B5701 negative, CD4 322, VL 112,000 genotype Wild Type, Hep A IgG +, Hep B immune, C serology negative, TB non-reactive, VDRL negative.

1. **Based on his laboratory testing and Hx what is his ASCVD risk score and overall CVD risk considering his HIV status?**

* ASCVD 10 year risk of 28.6% given HTN, smoking, diabetes, and current lipid profile
* CVD Risk also likely higher given uncontrolled HIV infection and higher incidence of risk behaviors (smoking, substance abuse) although no calculators or algorithm to quantify level of risk\*\*\*

1. **What is the mechanism of increased MI and CVD due to HIV infection?**

* Exact mechanisms currently unknown but several theories are investigated
  + **Decreased efflux of cholesterol via HDL**: Expression of HIV Nef gene decreases or degrades ABCA1 receptor which is used to transport intracellular cholesterol out of a cell into HDL for systemic circulation. This leads to intracellular cholesterol accumulation and development of atherosclerosis.
  + **Proinflamatory state:** Higher levels of the proinflammatory cytokines IL-6 and D-dimer in HIV patients compared to non HIV infected patients.[[75]](javascript:newshowcontent('active','references');)Increased inflammation leads to increased endothelial dysfunction from increased recruitment and adhesion of leukocytes at atheroma initiation sites.
  + **Altered Coagulation**: In vitro and vivo, abacavir was shown to increase the adhesion of leukocytes to endothelial cells, through leucocyte activation[[92]](javascript:newshowcontent('active','references');) and also increased platelet reactivity through inhibition of soluble guanylyl cyclase.

1. **What ART therapy would you consider initiating? Is there any classes or specific medications you would preferentially use? Are there any you would avoid?**

* Protease Inhibitors: In general PI drug class have been shown to have adverse effect on lipid profile with increases in TG, total cholesterol, and LDL. However, several studies have shown that dyslipidemia can be attributed to certain PI more so than others.
  + Ritonavir and indinavir (1st generation PI): Changes in lipid profiles as elevations in total cholesterol, LDL, and triglycerides. In HIV-negative volunteers, a low 'boosting' dose of ritonavir raised total cholesterol by 10.2%, LDL by 16.2% and triglycerides by 26.5%,[[49]](javascript:newshowcontent('active','references');) with the addition of lopinavir to ritonavir (LPVr) further increasing triglycerides
  + Atazanavir and saquinavir: smaller increases in total cholesterol and non-HDL-cholesterol, and triglycerides, compared with LPVr.
* NNRTI: Treatment with NNRTI class or ART has shown increases in total cholesterol and LDL-cholesterol, but no increases in triglycerides, and increases in the HDL.
  + Nevirapine has a more favorable effect on lipid profile over Efavirenz
* NRTI:
  + Zidovudine and Stavudine: Increases in TG, total cholesterol, LDL, and SE of lipodystrophy
  + Tenofovir (TDF): Worsens lipid profile from baseline with increases in TG, Cholesterol, LDL, but less so when compared to other NRTI drug classes. Independent association of decreased Cholesterol, TG, HDL, and LDL when switching from Zidovudine/Stavudine via yet unknown regimen.
  + Abacavir: Data Collection o­n Adverse events of Anti-HIV Drugs (D:A:D) data analysis of exposure to drugs from the nucleoside reverse transcriptase inhibitor (NRTI) class reported an unexpected association between exposure to the abacavir and MI.[[40](javascript:newshowcontent('active','references');)Regarding abacavir, the association with MI was strongest with current or recent (past 6 months) use (relative rate: 1.9; 95% CI: 1.47–2.45), an effect that persisted in subsequent, updated analyses.[[41]](javascript:newshowcontent('active','references');) ABC data and association to MI and CVD risk is **inconsistent**. Three meta-analyses of prospective clinical trials of patients exposed to ABC (with significant overlap of included studies between the analyses) have not revealed an association between exposure to ABC and incident MI.[[43–45]](javascript:newshowcontent('active','references');)
* Integrase Inhibitors: Integrase inhibitors have not been shown to induce any consistent lipid abnormalities when used in antiretroviral-naive patients.

Mr. Aiden starts on a regimen of Truvada and DTG with good viral response and control, now with an undetectable viral load, CD4 > 500, no complications or SE, and 100% adherence. Pt continues to have elevated BP 151/94 despite amlodipine 5mg daily, and lipid panel today noted to have Cholesterol 190, LDL 124, TG 144, and HDL of 39, he continues to smoke now ½ ppd for last year, and has very little physical activity. He worries that he will start to have “that look,” that people with AIDS had in the 1990’s.

6. **What changes in Lipid profile would you expect after initiating ART?**

* Increases in TG, total cholesterol, and LDL from initial baseline. Likely little to no change in HDL on current regimen

**7. Describe the difference between Metabolic Syndrome and HIV Lipodystrophy.**

* **Metabolic Syndrome:** Clinical syndrome characterized by central obesity, insulin insensitivy predisposing to DM, with complications including HTN, endothelial dysfunction, lipid abnormalities and eventual increases in CVD.
* **As defined by** National Cholesterol Education Program ATP III, 3 of any of the following 5 traits constitutes Metabolic syndrome.
  + Abdominal obesity, defined as a waist circumference in men ≥102 cm (40 in) and in women ≥88 cm (35 in)
  + Serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides
  + Serum high-density lipoprotein (HDL) cholesterol <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL cholesterol
  + Blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure
* **HIV Lipodystrophy: Lipid disorder characterized by peripheral fat loss and central fat deposition**
  + **Lipoatrophy:** loss of subcutaneous fat in the face, arms, legs, abdomen, and/or buttocks. Facial lipoatrophy is characterized by loss of the buccal and/or temporal fat pads, leading to facial skeletonization with concave cheeks, prominent nasolabial folds, periorbital hollowing, and visible facial musculature. Lipoatrophy also contributes to stigma of HIV as it was widely recognized as a visible marker of HIV/AIDS.
    - **Typically associated with NRTI exposure (Stavudine/Zidovudine)**
    - **Lower CD4 counts**
    - **High VL**
    - **Low BMI**

**8. What interventions would you recommend to reduce his ASCVD?**

* Weight Loss
* Increase Physical Activity
* Smoking Cessation
* DM management (consider Metformin)
* HTN Management (Consider ACEi)
* Reduce Alcohol intake
* ASA use (ASCVD > 10%)
* Augmenting ARV if not optimized for CVD risk management

**9.) What Medication would you select for this patient? Are there any special considerations for HIV patients regarding dyslipidemia treatment?**

* **Statin Therapy**
  + **Pravastatin DOC for HIV patients given multiple drug interactions of Atorvastatin**

**Recommended Reading**

# Jane A O'Halloran; Claudette S Satchell; Patrick WG Mallon. Dyslipidemia, Atherosclerosis and Cardiovascular Disease, An Increasingly Important Triad in an Aging Population Living With HIV. Future Virology. 2013;8(10):1021-1034. http://www.medscape.com/viewarticle/811580\_1

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# Worm SW, Sabin C, Weber R et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. J. Infect. Dis.201(3),318–330 (2010).

***Additional References/Reading***

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2. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J. Clin. Endocrinol. Metab.*92(7),2506–2512 (2007).
3. Saves M, Chene G, Ducimetiere P *et al.* Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. *Clin. Infect. Dis.*37(2),292–298 (2003).
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   ▪ Initial publication highlighting the association between antiretroviral therapy and cardiovascular disease.
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8. Freiberg MS, Chang CC, Kuller LH *et al.* HIV infection and the risk of acute myocardial infarction. *JAMA*173(8),614–622 (2013).
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11. Cutrell A, Brothers C, Yeo J, Hernandez J, Lapierre D. Abacavir and the potential risk of myocardial infarction. *Lancet*371(9622),1413 (2008).
12. Uptodate. **Epidemiology, clinical manifestations, and diagnosis of HIV-associated lipodystrophy**
13. **Epidemiology, clinical manifestations, and diagnosis of HIV-associated lipodystrophy**
14. <https://www.uptodate.com/contents/epidemiology-clinical-manifestations-and-diagnosis-of-hiv-associated-lipodystrophy?source=search_result&search=lipoatrophy%20HIV&selectedTitle=1~25>
15. **The metabolic syndrome (insulin resistance syndrome or syndrome X)**
16. **The metabolic syndrome (insulin resistance syndrome or syndrome X)**
17. Uptodate. https://www.uptodate.com/contents/the-metabolic-syndrome-insulin-resistance-syndrome-or-syndrome-x?source=search\_result&search=metabolic%20syndrome&selectedTitle=1~150