NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Dyslipidemia and HIV

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Why do we care about dyslipidemia?

HIV itself increases Cardiac risk

- Kaiser, age adjusted CHD rate 6 vs 2.9 events/ 1000 person years for HIV-infected vs. uninfected
- FRAM study found impact of HIV on Carotid Intima-Media Thickness (CIMT) to a similar degree as smoking in adjusted analyses

Dyslipidemia associated with CVD

- LDL, HDL: Framingham, Lipid Research Clinics, etc
- More recently triglyceride levels associated with CVD, even after adjusting for LDL and other lipid levels

HIV Dyslipidemia, What does it look like: distinct from general population

Studies from prior to ART

- e.g. Grunfeld *et al.* 1992 J Clin Endocrinol Metab
- Decline in TC, HDL, LDL
- Later increase in Triglycerides

After ART

- TC, LDL increase to baseline, often higher
- HDL often remains low even if it increases
- Some patients very high Triglyceride levels

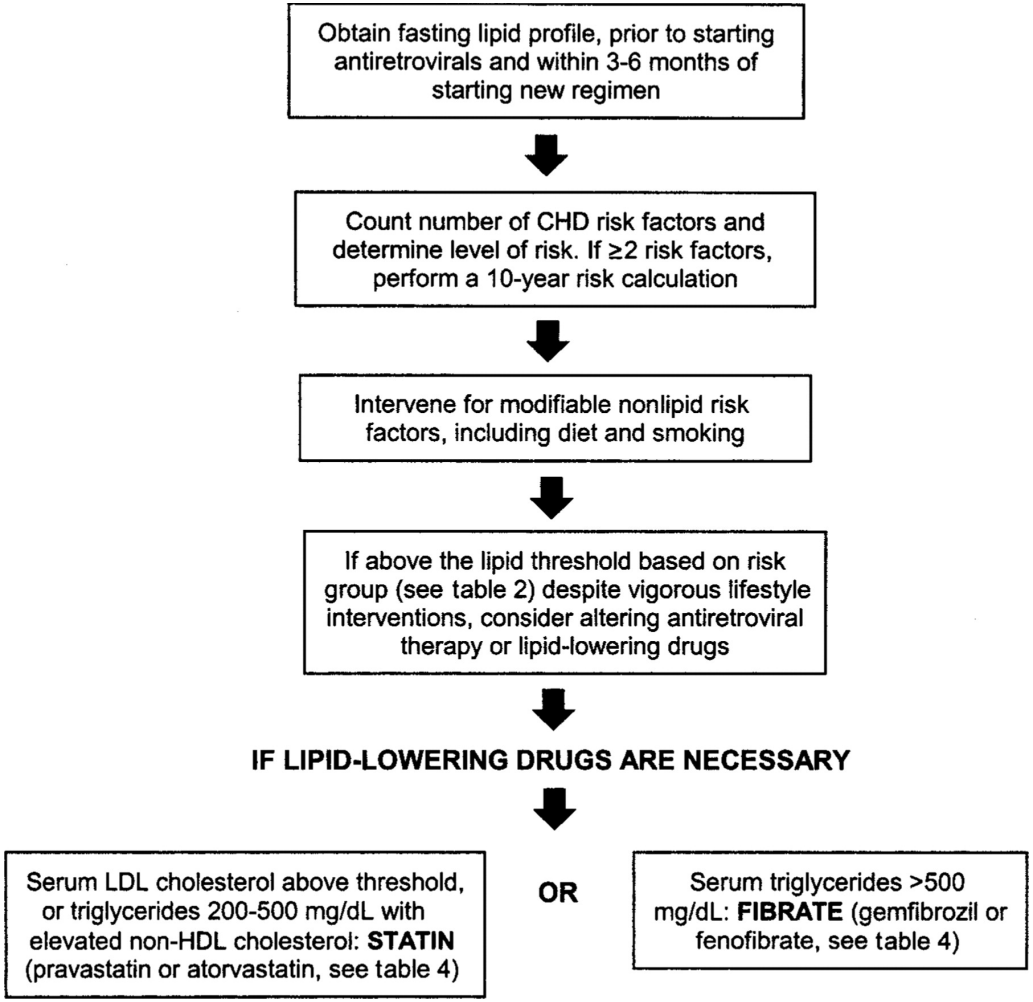
ARV's: individual agents vary in their impact

- **PIs**
  - Generally increase LDL and TRI
  - Less impact: atazanavir, darunavir
- **NNRTIs**
  - Smaller increases than PIs, small increase in HDL
- **NRTIs**
  - Stavudine: worst impact
  - Tenofovir: the least impact, slight lipid lowering effect

Screening

- HIVMA and AACTG Guidelines
  - Dube *et al,* CID, 2003
  - Follow NCEP ATP III Guidelines
  - Baseline, 3 months after starting ART
- Slight differences in guidelines, re: calculate CVD risk score on everyone vs. those with 2 or more risk factors
- Routine follow-up: check lipid panel q 6-12 months
  (Aberg *et al.,* Primary Care Guidelines for the Management of Persons Infected with Human Immunodeficiency Virus, CID, 2009)

General approach to lipid disorders and CV risk in HIV patients on ART



Dubé M P et al. Clin Infect Dis. 2003;37:613-627

National Cholesterol Education Program treatment decisions based on LDL cholesterol level

Risk category	LDL cholesterol level, mg/dL		
	Goal	Initiate therapeutic lifestyle change	Consider drug therapy
CHD or risk equivalent	<100	⩾100	⩾130[a]
>2 risk factors and 10-year risk of ⩽20%			
10-year risk of 10%–20%	<130	⩾130	⩾130
10-year risk of <10%	<130	⩾130	⩾160
0–1 risk factors	<160	⩾160	⩾190[b]

NOTE. Therapeutic lifestyle changes include dietary and exercise intervention (see the section on nondrug therapies in Hypercholesterolemia). Reduction of the LDL cholesterol level is a primary goal of therapy. Reduction in the non-high-density lipoprotein (HDL) cholesterol level is a secondary goal of therapy when the triglyceride level is >200 mg/dL. Non-HDL cholesterol goals (see text) are 30 mg/dL higher than LDL cholesterol goals. Adapted from [2]. CHD, coronary heart disease.

[a] For an LDL cholesterol level of 100–129 mg/dL, drug therapy is optional; consider treating HDL cholesterol and triglyceride disorders.

[b] For an LDL cholesterol level of 160–189 mg/dL, drug therapy is optional.

Dubé M P et al. Clin Infect Dis. 2003;37:613

Treatment

- Diet and Lifestyle modification
- Statins (HMG CoA reductase inhibitors)
- Fibrates
- Fish oil
- Niacin
- Ezetimibe
- Bile acid sequestrants (decrease absorption of ARVs?)

Treatment: Statins (HMC CoA reductase inhibitors)

- Varying effectiveness
- **Pravastain < Atorvastatin < Rosuvastatin**
  - (No **Simvastatin/Lovastatin** with PIs)
- Different drug interactions
- **Pravastatin** fewer drug interactions, also much less effective
  - (Efavirenz lowers **pravastatin** levels)
- Darunavir increases statin levels, use low dose for all
- **Atorvastatin** levels modestly increased with PIs, start low and titrate
- Certain PIs increase **rosuvastatin** blood levels (non-CYP3A4 mechanisms), cannot titrate up much (but often don't need to)
- **Pitavastatin**? Minimally metabolized by CYP3A4, data on interactions not yet available
- ~7% myalgias, CPK, other (Singh *et al*., CID)

Treatment: Ezetemibe

- Reduces cholesterol absorption in the intestinal brush border
- reduces LDL
- used among those unable to reach LDL goals with statin therapy
  - ACTG A5029 additional 21% LDL reduction on ezetimibe (and statin)
  - Disappointing results of the ENHANCE trial among those without HIV in CIMT reduction?

Treatment: hypertriglyceridemia

- Fibrate therapy: first line, **gemfibrozil** vs. **fenofibrate**
  - PIs may reduce gemfibrozil levels, less effective among patients with HIV
  - Fenofibrate: without ARV interactions, recommended fibrate (less interactions with statins)
  - Mean 54% reduction in TG level at 24 weeks (Palacios *et al,* JAIDS)
- **Fish oil**: 4 gm/ day, lack of ART interactions
  - Wohl study: 26 patients, RCT, all received dietary/exercise counseling, fish oil mean additional 25% decrease (461 to 306 mg/dL)
  - Likely less impact than fibrates
  - Keep cool if "cat fish breath"
- Extended release **niacin**
  - ACTG A5148, 70% titrated up to full dose, 38% decrease in TG
  - Less well tolerated
  - Mild increases in fasting glucose

Switching ART

- Dyslipidemia multifactorial, return to normal, etc. so do not always get the results one might expect with switching
- ATAZIP study: switch from lopinavir to atazanavir, mean 19 mg decrease in TC and 53 mg/dL in TRI
- SWITCHMRK 1 and 2: lopinavir to raltegravir RCT, TC decrease 13%, TRI 42%. However, greater virologic failures, stopped early
- Lipid lowering therapy more effective typically than switching, however Martinez *et al.* study, switching to atazanavir, almost 1/3 could stop lipid lowering medications

Additional tidbits from recent studies

- An additional benefit of rosuvastatin over pravastatin may be an increase in LDL particle size (less atherogenic phenotype of LDL)
  - AIDS. 2012 Jun 27
- Diet advice, reduced fat, actually does reduce development of dyslipidemia among patients initiating ARVs
  - J Am Coll Cardiol. 2012 Mar 13;59(11):979-88
- Rosuvastatin QOD, Q week dosing (HIV-uninfected)
- Red Yeast Rice for Hypercholesterolemia in People with Statin-Related Myalgias

Conclusions

- Dyslipidemia in HIV is multifactorial
- Must screen to treat
- Pattern of lipids different in those on/not on ART
- Treat based on specific abnormalities, not the same as traditional mixed dyslipidemia of HIV-uninfected
- Do not use bile acid resins
- **Rosuvastatin** much more effective than others (low doses in PIs)
- Switch cautiously, can help lipids but virologic failure can occur
- Stay tuned, more studies underway, **pitavastatin**? interesting findings on the roles of statins and inflammatory pathways?