ISCHEMIC CARDIAC RISKS OF HIV INFECTION and HAART

Key Points:

1. Although a definite relationship between the development of CAD and HAART has not been proven, PI induced hyperlipidemia, insulin resistance, and lipodystrophy may play a role in accelerating CAD, especially in patients with concomitant risk factors.
2. Independent of PI use, HIV positive patients appear to have significantly higher rates of CAD than matched pts without HIV disease.

Patients with HIV infection can manifest cardiac disease in multiple ways:
1. Pericarditis (infectious, malignant, idiopathic)
2. Pulmonary hypertension
3. Cardiac tumors (KS, NHL)
4. Valvular disease (IE, marantic endocarditis, MVP)
5. Myocardial disease (myocarditis, cardiomyopathy, LV dysfunction)
6. Increased incidence of coronary artery disease

Increased incidence of CAD:

Accelerated atherosclerosis has been described in HIV positive patients. Is this due to HIV or to PI’s?

- Endothelial dysfunction, hypercoagulability, high TG, and abn coronary pathology were associated with HIV before the use of protease inhibitors.¹
- The data re: risk of coronary heart disease in HIV+ patients on protease inhibitors is conflicting, but it is postulated that PI’s may increase CAD risk via lipid derangements, insulin resistance, and fat redistribution:

Data suggesting NO increased risk of CAD associated with PI’s:

- 423 HIV infected patients:²
  - Univariate analysis: thickened arterial intima-media by ultrasound associated with: older age, male gender, high BMI, increased SBP, total cholesterol, glucose intolerance/ diabetes, smoking, alcohol, and lipodystrophy on HAART.
  - Multivariate analysis: after adjusting for traditional cardiovascular risk factors: effects of lipodystrophy with HAART not associated with increased arterial wall thickening.
- VA study of all HIV + patients 1993-2001 (42% on PI’s and 26% on NNRTIs):
  - Numbers of admissions and numbers of deaths not higher for patients on PI’s.
- Kaiser, Northern California four year study of all HIV + patients:
  - Age adjusted risk of CAD and MI the same with and without PI’s. HOWEVER: HIV positive patients vs. HIV negative patients: significantly higher CAD hospitalization and MI rate in HIV + patients (6.5 vs 3.8 per 1000 patient years).³

Data suggesting increased risk of CAD associated with Protease Inhibitors:

- 102 HIV patients-- half on PI’s and half not: 53% of those on PI’s showed thickening of coronary intima-media by ultrasound vs. 15% not taking PI’s. ⁴
- 5672 patients from outpatient HIV clinics: Odds ratio of 7.1 for MI in patients on PI’s vs those not on PI’s even after adjusting for traditional cardiac risk factors. ⁵

Metabolic abnormalities associated with PI’s theorized to confer increased risk of CAD:

1. Hypertriglyceridemia/ Hyperlipidemia:
   - 11% of pts on PI’s have TG levels > 1500; tx’d with fibrates +/- statins
   - PI’s bind to the HIV protease that has 60% homology with two proteins regulating lipid metabolism. This binding impairs hepatic chylomicon uptake and TG clearance.
   - Pts with lipodystrophy from HAART have lower levels of LDL receptor expression than pts without lipodystrophy. Lower levels of LDL receptor are a/w higher TG levels.
   - 90% of patients with normal pre-HAART lipids experience a rise in lipids during PI tx. ⁶
2. Glucose intolerance: multiple mechanisms; tx’d with usual DM meds
   - Hyper TGemia causes central adipose deposition and insulin resistance leading to DM2.
   - Beta cell destruction and therefore low insulin levels is common in HIV + patients
   - Low insulin levels or insulin resistance leads to increased lipolysis, ketosis, and increased levels of FFAs all prominent findings in patients on HAART.
3. Lipodystrophy: abnormal redistribution of fat from the periphery to the thorax and abdomen.
   - “Protease paunch”, “buffalo hump” and others; seen in 64% on PI’s after 14 months on meds vs 1% in control group of HIV patients not on PI’s.
   - One small RCT showed metformin led to decreases in weight, BP, glucose intolerance, and visceral/ abdominal fat deposition. ⁸
References: