

# Overview of Studies

HIV Infection, HIV Treatment and Risk for  
Cardiovascular Disease: An Independent  
Review of Ongoing Studies

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**I. Studies Assessing the  
Association between HIV  
disease/treatments and  
Cardiovascular /Cerebrovascular  
Outcomes**

# Bozette et al (NEJM 2003)

- 36,766 HIV+ VA Patients
- Mean follow-up period: 40 months
- Cardiovascular (CHD) and Cerebrovascular (CV) outcomes
- ART Exposures (mean of 15 months each)
  - PI: 42% for 16 months
  - NRTI: 70.2% for 17 months
  - NNRTI: 26% for 9 months

# Bozette et al (NEJM 2003)

- Following introduction of ART
  - CV/CHD disease hosp rate from 1.7/100PY in '95 to 0.9/100PY in '01
  - All cause death from 21.3/100PY in '95 to 5.0/100PY in '01
  - Use of ART associated with decrease hazard for all cause death

# Bozette et al (NEJM 2003)

- Conclusions:
  - Large benefit in terms of mortality
  - Not offset by any increase in CV or CHD in the short term
  - Longer follow-up required to fully assess CV/CHD risk

# Friis-Moller et al (CROI, 2003)

- 23,468 patients
- Prospective multinational study
- Dec 1999 – April 2001
- Exposure to CART /median 1.9(0-3.2) years
- Incidence of MI increased with exposure to CART (Risk Ratio: 1.26 [1.12-1.41])
- Exposure to CART associated with a 26% relative increase in the rate of MI per year of exposure

# Friis-Moller et al (CROI, 2003)

- Models adjusted for age, smoking, prior CVD, male gender, cholesterol, diabetes
- Conclusions:
  - Treatment associated risk must be balanced against marked effectiveness of CART
  - Absolute risk of MI remains low

# Coplan et al (Aids Research and Human Retroviruses – in Press)

- 10,986 HIV patients (post-hoc trial analysis)
- Average duration of PI therapy (7,951 patients): one year
- Relative Risk for PI versus NRTI was 1.69(0.54-7.48)
- Absolute difference in MI incidence between PI and NRTI was 0.77(-.71-2.26)/1000PY



# Coplan et al (Aids Research and Human Retroviruses – in Press)

- Conclusions:
  - No differences in MI Frequency in first year between PI and NRTI regimens
  - May be 2.3 additional cases of MI/1000PY
  - Longer duration studies are needed

# Iloeje et al (CROI 2003)

- 6,711 HIV+ patients (HIV Insight®database)
- Median follow-up: 2.8 years
- Mean age: 39 years
- 77.3% were exposed to ART
- CVD event rate was 1.64% for PI and 0.52% for non-PI respectively
- CVD Hazard ratio for PI vs non-PI was 1.99(0.95-4.2) and the CHD HR was 2.13(0.91-4.95)

# Iloje et al (CROI 2003)

- If PI exposure > 60 days CVD HR was 2.1(1.0-4.4) and in patients 45-65 years, CVD HR was 4.3(1.0-17.9)
- Models adjusted for
- Conclusions
  - PI exposure doubles the risk of developing both CHD and CVD
  - Risk is more evident in middle aged patients
  - Absolute event rate remains low
  - Prolonged PI exposure may lead to greater CVD event rates

# Holmberg et al (CROI 2002)

- 5,672 HIV+ patients
- HOPS database
- Odds Ratio for MI among PI users was 4.92(1.3-32.3)
- Hazard Ratio for MI among PI use was 6.51(0.89-47.8)
- Models adjusted for hypertension, smoking, diabetes, age, sex, prior dyslipidemia

# Holmberg et al (CROI 2002)

## ■ Conclusions

- MI is associated with PI use
- MI is still infrequent and should not compromise ART use
- Treat lifestyle risk factors to lower overall risk

# Klein et al (CROI 2002)

- 4,408 HIV+ patients (Kaiser Permanente of Northern California)
- 39,425 HIV- controls
- Median follow-up: 4.1 years
- Higher age-adjusted CHD rates in HIV+ vs HIV- (6.6[5-8.1] vs 3.3[3.0-3.5])
- No clear relationship between PI exposure and MI; however PI exposure > 1 year yielded higher MI rates

# Klein et al (CROI 2002)

## ■ Conclusions

- No significant effect of PI use on CHD or MI
- CHD rates higher in HIV+ vs HIV- men in the HAART era.
- Further follow-up is planned

# Moore et al (CROI 2003)

- 2,671 HIV+ patients
- CHD incidence rates: 5.9/1000PY
- CVD incidence rates: 5.0/1000PY
- Cases were significantly more likely than controls to use PI (59% vs 43%) and d4T (63% vs 43%)
- d4T use was associated with CHD/CVD (RR=2.51)



# Moore et al (CROI 2003)

- Model adjusted for age, cholesterol, diabetes, hypertension, CD4 count
- Conclusions:
  - CHD/CVD rates higher than expected in this population
  - Rates are associated with both traditional CV risk factors and ART.

# Gardner et al(CROI 2003)

- 885 HIV+ and 426 HIV- patients
- Mean follow-up 4.9 years
- Hospitalization rates for CVD increased from 7.0 in 1994 to 11.1 in 2000
- Adjusted rate ratio for CVD was 1.3 ( $p=0.28$ )
- Hospitalization rates for non-acute renal and diabetes were constant
- Conclusions
  - Close monitoring for non-AIDS risk factors is warranted

# Mary-Krause et al(AIDS, in press)

- 34,976 HIV+ men (French Hospital Database)
- MI incidence rate was 1.3/1000PY among PI patients vs 0.3/1000PY among non PI patients
- RR for MI among PI was 2.6(1.0-6.3)
- MI incidence increased with PI dosage
- Multivariate models adjusted for age, CD4 count, NNRTI, NRTI exposure

# Mary-Krause et al(AIDS, in press)

- Conclusion:

- Risk of MI in HIV+ men increased with duration of PI use but not with other ART

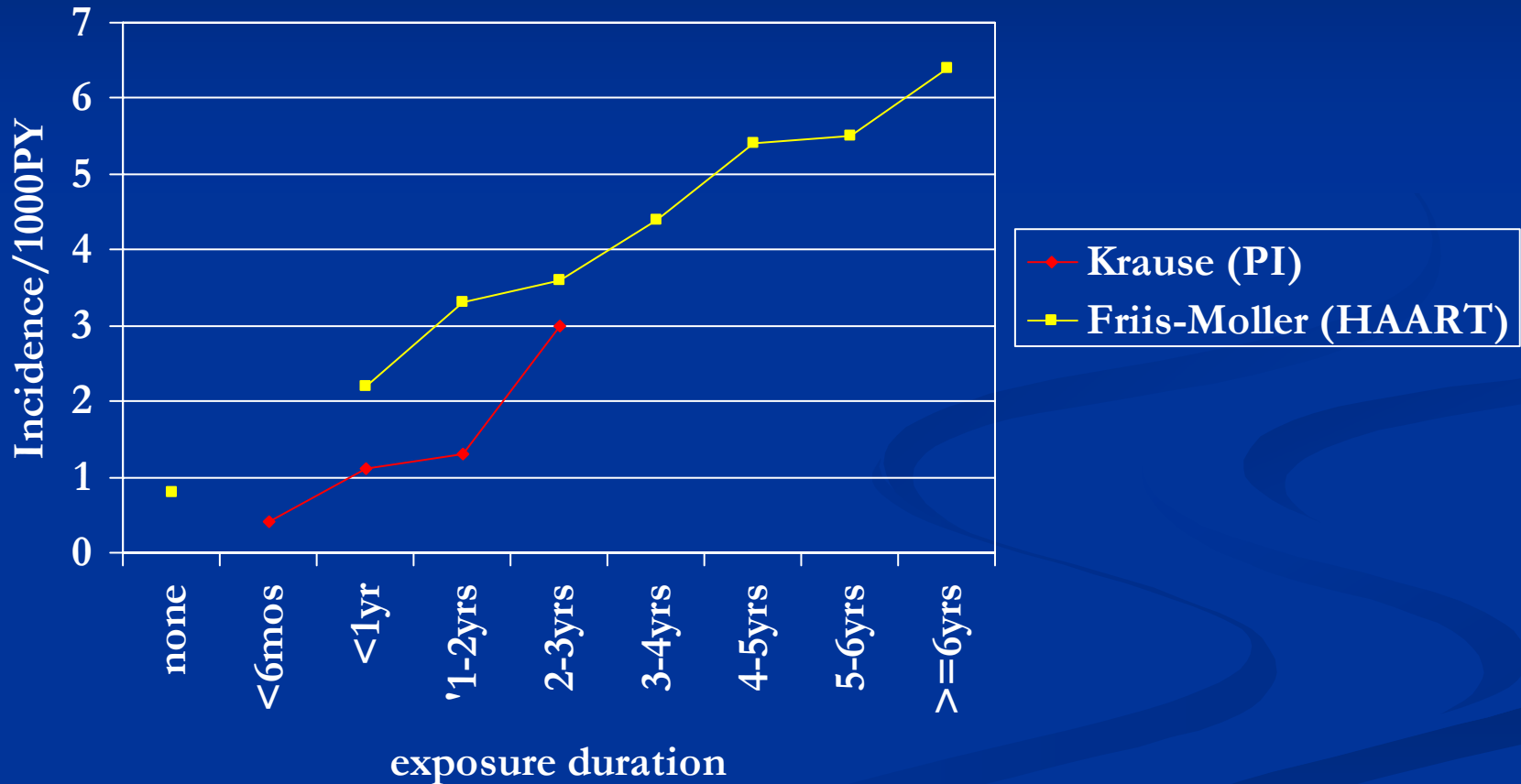
# COHORT analyses: PI use and CHD Events Reported Hazard Ratios (the largest studies)

<i>Study</i>	<i>HR</i>	<i>95% CI</i>	<i># Patients</i>	<i>Median PI exposure</i>
<b>Krause et al</b>	<b>2.6</b>	<b>1.0-6.3</b>	<b>34,976</b>	<b>23 months</b>
<b>Bozette et al</b>	<b>1.2</b>	<b>0.8-1.9</b>	<b>36,766</b>	<b>16 months</b>
<b>Coplan et al</b>	<b>1.7</b>	<b>0.5-7.5</b>	<b>10,986</b>	<b>12 months</b>
<b>Iloeje et al</b>	<b>2.1</b>	<b>0.9-5.0</b>	<b>6,711</b>	<b>34 months</b>

# COHORT analyses: PI use and CHD Events Reported Incidence (/1000PY)

<i>Study</i>	<i>PI</i>	<i>Non-PI</i>	<i># Patients</i>
Krause et al	1.3	0.3	34,976
Klein et al	7.1	6.0	4,408
Coplan et al	1.8	1.1	10,986
Holmberg et al	1.4	0.5	5,672

# Incidence of MI According to Duration of ART exposure



# Summary – endpoint studies

- CHD/CVD risk appears to be greater in HIV+ populations compared to the general population
- HAART use, particularly PI, is associated with CHD/CVD to varying degrees (no association to strong association).
- Absolute CHD/CVD risk remains low in these populations.
- Traditional risk factors for CHD/CVD similar to general populations
- Concern expressed regarding increasing CHD/CVD risk with the ageing of the HIV+ population



## II. Studies Estimating CHD/CVD Risk in HIV Patients Using Predictive Models

# Leport et al (CROI 2002)

- 223 HIV+ vs 527 HIV- men matched by age
- Estimated Relative Risk for CHD was 1.2 (Prime model) and 1.4 (Anderson model) for HIV+ men on PI versus normal population
- Conclusions
  - Elevated CHD risk for men on PI warrants long term follow-up to determine if risk increases over time.

# Wall et al (CROI 2002)

- 111/125 HIV+ vs 25/49 HIV- patients
- 10 yr Framingham CHD risk 4%(1-30%) in HIV+ and 1%(1-20%) in HIV-
- 10 yr CHD risk 6%(1-30%) in PI and 3%(<1-25%) in non-PI
- Conclusions:
  - CHD risk is greater in HIV
  - CHD risk is greater for PI users
  - Long term follow-up studies needed

# Hadigan et al (Clin Inf Dis, 2003)

- Case control study
- 10 yr Framingham CHD risk 7.4% in HIV and lipodystrophy
- 38% of HIV with lipodystrophy had CHD risk >10% vs 17% of controls
- Conclusions:
  - CHD risk is greater in HIV
  - Gender and fat distribution are determinants

# David et al (Clin Inf Dis, 2003)

- Case control study (HIV+ patients)
- Case patients (CVD events) had higher numbers of CVD events compared to matched controls (3 vs 1,  $P < .001$ )
- Conclusions:
  - CVD risk most closely associated with traditional risk factors rather than PI use

# Grover et al (AHA, 2002)

- Randomized trial comparing nelfinavir (n=91) and atazanavir (n=178) (Study AI424-008)
- Changes in total and LDL cholesterol (+24%, +28%) observed among nelfinavir patients were significantly greater ( $p < 0.05$ ) than those among atazanavir patients (+4%, +1%)
- CV risk (Cardiovascular Life Expectancy Model) 10-31% lower in atazanavir versus nelfinavir patients
- Atazanevir increased estimated life expectancy from .22 to 1.18 years among high risk patients
- Conclusions:
  - Blood lipid levels, CV risk, and life expectancy greater in nelfinavir compared to atazanavir patients

# Summary – Predictive Model Studies

- Estimated CHD/CVD risk appears to be greater in HIV+ populations versus general population
- Estimated CHD/CVD risk may be greater in ART versus HIV+
- Higher risk estimates reflects observed higher prevalence of traditional CHD/CV risk factors in HIV+ patients
- Concern that risk functions are derived from general populations and may not be applicable to HIV+ patients

## II. Studies Using CHD/CVD Diagnostic Markers



# Intimal Medial Thickness

- Currier et al (CROI, 2002):
  - Matched longitudinal cohort
  - No difference in IMT between HIV+ with 2 years PI, HIV+ not exposed to PI and HIV-
- Hsue et al (CROI, 2003)
  - Longitudinal cohort
  - Tenfold acceleration in IMT progression over 1 year follow-up associated with age and PI use
- Seminari et al (Atherosclerosis, 2002)
  - Cross sectional
  - IMT greater in HIV+ with PI than HIV+ naïve or HIV negative

# Intimal Medial Thickness

- Chironi et al (JAIDS, 2003)
  - Matched case control
  - IMT greater in treated HIV+ may be due to lipid and glucose levels
- Mercie et al (Ann Med, 2002)
  - Prospective cohort
  - No association between IMT and HIV disease

# Atherosclerosis / Coronary Calcium

- Deparion et al (AIDS 2001)
  - Cross sectional
  - Slightly higher proportion of patients with plaques among PI, but traditional risk factor implicated
- Acevedo et al (Atherosclerosis, 2002)
  - Cross sectional
  - HIV+ patients had a higher prevalence of plaques with elevated risk among HAART

# Atherosclerosis / Coronary Calcium

- Wanke et al (CROI,2003)
  - Cross sectional
  - Men on PI had higher prevalence of traditional and emergent CHD risk factors compared to non-PI
- Meng et al (Am Heart Journal, 2002)
  - Cross sectional
  - PI use associated with coronary artery calcification

# Summary – Surrogate Studies

- Higher levels of IMT and CAC/Atherosclerosis associated with levels of traditional CHD/CV risk factors in HIV+ patients
- Difficult to determine added effect of HIV disease or HAART