Lower CD4 Count, Detectable Viral Load, & Traditional CVD Risk Factors are Associated with Increased Risk of Primary Myocardial Infarction in the CNICS cohort

DR Drozd[1], RM Nance[1], JAC Delaney[1], GA Burkholder[2], WC Mathews[3], RD Moore[4], JJ Eron[5], PW Hunt[6], MM Kitahata[1], HM Crane[1]
for the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) Cohort

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[1] University of Washington, Seattle, WA, USA; [2] University of Alabama at Birmingham, Birmingham, AL, USA; [3] University of California, San Diego, San Diego, CA, USA; [4] Johns Hopkins University, Baltimore, MD, USA; [5] University of North Carolina, Chapel Hill, NC, US; [6] University of California, San Francisco, San Francisco, CA, USA

BACKGROUND

Myocardial infarctions (MI) may be more common among persons living with HIV (PLWH) compared to those without HIV.[1-3] Controversy remains about the contribution of traditional cardiovascular disease (CVD) and HIV-specific risk factors for MIs in PLWH. In CNICS, we developed a centralized screening algorithm and validation protocol for adjudication of MIs.[4] All confirmed events were classified by their underlying pathophysiology as either due to plaque rupture/atherothrombosis (primary) or supply-demand mismatch (secondary), the latter most commonly caused by cocaine use or sepsis. No studies to date have been able to separately examine risk factors for these distinct types of events. Our previous finding that secondary MIs are much more common in PLWH[5] suggests that prior studies may have misclassified MI risk in PLWH by not separately exploring MIs by pathophysiologic type.

OBJECTIVE

To examine the importance of traditional CVD risk factors for primary and secondary MIs and the role of immunologic and virologic risk factors for primary atherothrombotic MIs in the CNICS cohort.

METHODS

CNICS is a diverse 8-site observational HIV cohort with comprehensive clinical data on >29,000 patients, including data on traditional CVD risk factors and definitive adjudicated outcomes including MIs. Among 17,626 eligible participants, we found 128 primary and 144 secondary confirmed incident MIs. All confirmed events were previously classified as either primary or secondary by consensus of multiple reviewers. We used a Cox Proportional Hazards model to separately estimate risk of MI by type using baseline traditional CVD risk factors including: total and HDL cholesterol, triglycerides, estimated glomerular filtration rate (eGFR), hypertension, age, sex, diabetes, race, smoking, body mass index (BMI), injection drug use, and adjusted for calendar period of treatment. Individuals were followed until they experienced an event or were lost to follow-up. Multiple imputations were used for missing covariates using standard techniques. We then examined the effects of most recent CD4 count and current detectable viral load on primary MIs with marginal structural models (MSM) using inverse probability of treatment weights and robust confidence intervals. Both unweighted and weighted models using known CVD risk factors were fit by CD4 strata and weighted models were then fit with CD4 strata conditional on detectable viral load (Table 3). All models were stable with max weight of 71, 38, 9.4, and 7.5 for the <100, <200, <350, and <500 models respectively.

RESULTS

Baseline patient demographic and known CVD risk factors are outlined in Table 1. Cox Proportional Hazard models (Table 2) found older age, tobacco use, diabetes, untreated hypertension, and stage 3-5 chronic kidney disease (CKD) to be associated with primary MIs.

Table 1. Baseline Characteristics of Patients with Primary, Secondary, and Without MI.

Characteristic	No MI (n=17354)	Primary MI (n=128)	Secondary MI (n=144)
Male - n (%)	13,741 (79)	107 (84)	103 (72)
Age - n (%)			
<40	9,307 (54)	18 (14)	59 (40)
40-49	5,612 (32)	52 (41)	46 (32)
50-59	2,051 (12)	29 (23)	30 (21)
≥60	384 (2)	8 (6)	10 (7)
Race - n (%)			
White	7,614 (44)	70 (55)	44 (31)
Black	7,008 (40)	48 (38)	88 (61)
Hispanic	1,957 (11)	6 (5)	6 (4)
Other	775 (4)	4 (3)	6 (4)
Calendar period - n (%)			
1996-2000	5,080 (29)	64 (50)	60 (42)
2001-2005	5,672 (33)	38 (30)	45 (31)
2006-2012	6,602 (38)	26 (20)	39 (27)
Injection drug use - n (%)	3,487 (20)	23 (18)	59 (41)
Tobacco use - n (%)	7,325 (42)	91 (71)	93 (65)
Hypertensive medication use - n (%)	1,437 (8)	21 (16)	20 (14)
eGFR (ml/min/1.73m^2) - n (%)			
≥60	16,662 (96)	110 (86)	131 (91)
30-59	456 (3)	13 (10)	6 (4)
<30	236 (1)	5 (4)	7 (5)
Other			
Diabetes - n (%)	751 (4)	15 (12)	13 (9)
Years of follow-up - mean (SD)	4.8 (4.2)	4.6 (3.5)	4.5 (3.5)
BMI (kg/m^2) - mean (SD)	25 (5)	25 (5)	25 (6)
Systolic blood pressure (mmHg) - mean (SD)	125 (17)	132 (24)	127 (18)
Lipid levels - mean (SD)			
Total cholesterol (mg/dL)	173 (47)	185 (58)	159 (55)
HDL cholesterol (mg/dL)	40 (15)	35 (11)	39 (17)
Triglycercides (mg/dL)	177 (160)	219 (166)	190 (119)

Table 2. Hazard Ratios of MI by Baseline Characteristics.

Characteristic	Primary MI	Secondary MI	Characteristic	Primary MI	Secondary MI
Male	1.11 (0.66-1.85)	0.80 (0.53-1.21)	Diabetes	2.17 (1.21-3.89)	1.71 (0.93-3.13)
Age - years			**Hypertension**		
<40	1.00	1.00	No	1.00	1.00
40-49	2.27 (1.47-3.48)	1.15 (0.77-1.71)	Treated	1.60 (0.93-2.78)	1.22 (0.72-2.08)
50-59	3.52 (2.11-5.87)	2.33 (1.45-3.74)	Untreated	1.81 (1.08-3.00)	0.93 (0.52-1.68)
≥60	5.30 (2.37-11.83)	4.87 (2.39-9.90)	**eGFR (ml/min/1.73m2)**		
Race			≥60	1.00	1.00
White	1.00	1.00	30-59	3.43 (1.88-6.26)	1.34 (0.58-3.10)
Black	0.84 (0.56-1.27)	1.98 (1.34-2.92)	<30	3.38 (1.29-8.84)	2.95 (1.33-6.51)
Hispanic	0.48 (0.20-1.11)	0.64 (0.27-1.50)	**Total Cholesterol (mg/dL)**		
Other	0.78 (0.28-2.14)	1.62 (0.69-3.81)	<200	1.00	1.00
Calendar Period			200-239	1.08 (0.66-1.76)	0.62 (0.33-1.17)
1996-2000	1.00	1.00	≥240	1.45 (0.76-2.75)	0.66 (0.25-1.74)
2001-2005	0.64 (0.42-0.99)	1.15 (0.76-1.74)	**HDL Cholesterol (mg/dL)**		
2006-2012	0.91 (0.53-1.55)	2.27 (1.38-3.75)	≥60	1.00	1.00
Injection Drug Use	0.63 (0.39-1.00)	2.20 (1.54-3.15)	40-59	2.43 (0.57-10.41)	1.12 (0.51-2.48)
Tobacco use	2.76 (1.86-4.10)	1.54 (1.07-2.20)	<40	3.91 (0.78-19.44)	1.27 (0.52-3.12)
BMI ≥30 (kg/m2)	0.76 (0.39-1.47)	1.02 (0.51-2.03)	Triglycerides ≥150 (mg/dL)	1.07 (0.56-2.03)	1.25 (0.71-2.21)

Injection drug and tobacco use, older age, black race, later calendar period, and stage 4-5 CKD were associated with secondary MIs. Marginal structural models that examined the risk of primary MI adjusted for known risk factors by various CD4 strata (Table 3) show a significantly increased risk of primary MIs when comparing individuals at CD4 count <100 to those with a CD4 ≥100. There is a trend toward decreasing risk at higher CD4 strata, but they do not reach significance. In the final models adding detectable viral load was associated with increased risk in the higher CD4 strata.

Table 3. Inverse Probability of Treatment Weighted Marginal Structural Models.[a]

Model	Primary MI
Unweighted CD4 Models	
CD4 <100	1.95 (1.13-3.36)
CD4 <200	1.69 (1.07-2.67)
CD4 <350	1.36 (0.88-2.08)
CD4 <500	1.26 (0.79-2.01)
Weighted CD4 models	
CD4 <100	2.02 (1.13-3.62)
CD4 <200	1.52 (0.94-2.44)
CD4 <350	1.23 (0.79-1.93)
CD4 <500	1.16 (0.72-1.89)
CD4 & viral load models (reference: ≥ threshold and undetectable viral load)	
CD4 <100 & undetectable viral load	1.82 (0.97-3.43)
CD4 <200 & undetectable viral load	1.39 (0.85-2.26)
CD4 <350 & undetectable viral load	1.15 (0.75-1.78)
CD4 <500 & undetectable viral load	1.12 (0.70-1.81)
CD4 ≥100 & detectable viral load	1.49 (0.69-3.22)
CD4 ≥200 & detectable viral load	1.65 (0.97-2.81)
CD4 ≥350 & detectable viral load	1.81 (1.17-2.81)
CD4 ≥500 & detectable viral load	1.61 (1.03-2.54)

[a] Adjusted for age, sex, tobacco, IDU, MSM, diabetes, statin use, treated hypertension, eGFR, ART

CONCLUSIONS

In this study, we show that traditional CVD risk factors are important predictors of primary MIs, whereas injection drug use is an important predictor of secondary MIs. These findings suggest that only by properly classifying these events by underlying mechanism can we accurately assess risk and guide clinical management. Among primary atherothrombotic events:

- Low CD4 count independently predicts primary MIs and shows a trend towards being a stronger predictor at lower CD4 counts.
- Detectable viral load is associated with risk of primary MIs at CD4 >350 and >500 suggesting that viremia and ART may differentially impact primary MI risk at higher CD4 counts.

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