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CRP, D-dimer and Oxidized LDL Predict Myocardial Infarction in Treated HIV Infection

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Background

- Despite suppressive ART, HIV+ individuals have a higher risk of myocardial infarction (MI) than the general population.
- Persistent inflammation has been proposed as a mediator, but the immunologic determinants of MI remain poorly characterized.
- Oxidized LDL levels (an inflammatory lipid) are also increased in HIV, but have yet to be linked to cardiovascular events in this setting.
- A low CD4/CD8 ratio increases disease risk in treated HIV infection, but its specific impact on MI is incompletely characterized.

Methods

- **Design:** Case-control study of HIV-infected individuals with VL<400 copies/ml on antiretroviral therapy within the CFAR Network of Integrated Clinical Systems (CNICS) network (an 8-site practice-based network in the USA).
  - **Cases with Type 1 MI**: All adjudicated and confirmed Type 1 MIs (plaque rupture/thrombosis) from 2001-2012, with plasma within 3y prior to event (median 3 months [IQR: 1-9]) and continued VL <400 between sample date and event.
  - **Controls without MI:** ≤3 matched with incidence density sampling to each case by calendar time, age, gender, race, duration VL suppression, and CD4 count.
- **Measurements:** Biomarkers were assessed by immunoassay on cryopreserved plasma from EDTA- (n=152) or ACD (n=19)-anti-coagulated blood. Measured concentrations in ACD plasma were multiplied by a factor of 1.29 to account for diluent volume.
- **Analysis**: Associations between plasma biomarkers and subsequent MI were assessed by conditional logistic regression, log-transforming predictors if necessary to satisfy model assumptions. Biomarkers associated with MI in unadjusted models (P<0.10) were assessed in adjusted models to assess independence.

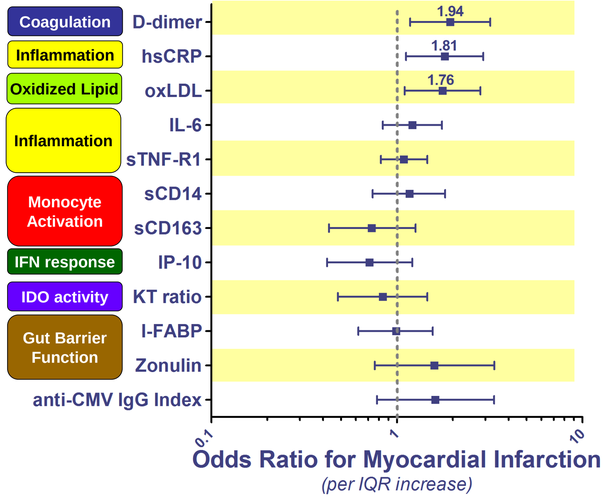
Results

Characteristics of ART-suppressed participants

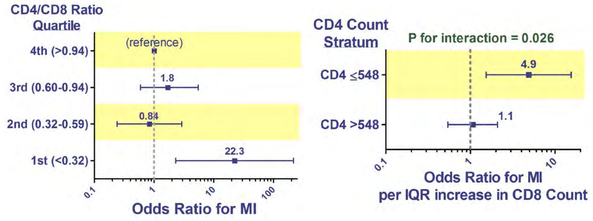
Characteristic	MI Cases Median (IQR) N=51	Controls Median (IQR) N=120	P Value
Age, years	50 (46-58)	50 (46-56)	*
Male gender, N (%)	40 (78)	93 (78)	*
Non-White Race, N (%)	29 (57)	67 (56)	*
Months VL <400 c/ml	28 (14-65)	43 (16-74)	*
CD4+ T cell count, cells/mm^3	548 (316-667)	622 (360-802)	*
Hypertension, N (%)	18 (35)	31 (26)	0.27
Type 2 Diabetes, N (%)	2 (4)	5 (4)	0.89
Current/Past Smoker (n=90†), N (%)	25 (93)	48 (76)	0.08
LDL cholesterol, mg/dl (n=120†)	**110 (85-137)**	**95 (74-116)**	**0.017**
CMV IgG Positive	46 (90)	107 (90)	0.81
Current Abacavir use, N (%)	12 (26)	21 (19)	0.30

*Cases and controls were matched on this variable.
†This variable was only available on a subset.

Immunologic Predictors of MI – Unadjusted

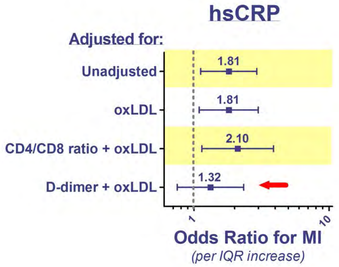


Very Low CD4/CD8 Ratio (<0.32) Strongly Predicts MI, Primarily in Those with Low CD4 Count



- *The median CD4 count in those with a CD4/CD8 ratio <0.32 was 234 cells/mm^3 (IQR: 167-365).*
- *A CD4/CD8 ratio <0.32 continued to strongly predict MI after adjustment for D-dimer, oxLDL, hsCRP, or anti-CMV IgG titer (effect size attenuation <10%).*

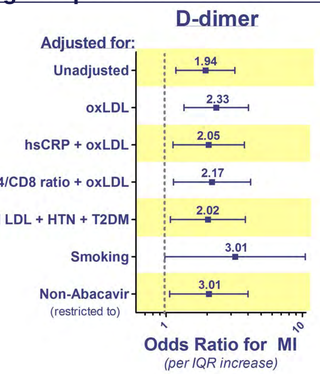
hsCRP Association with MI Explained by D-dimer



While hsCRP predicted MI independent ly of oxidized LDL and CD4/CD8 ratio, it was significantly attenuated by D-dimer adjustment.

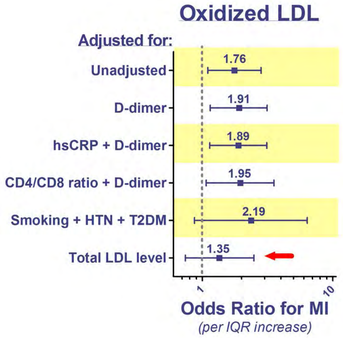
D-dimer Is a Strong Independent Predictor of MI

D-dimer remained a strong predictor of MI independent of hsCRP, oxLDL, and CD4/CD8 ratio. While abacavir users had higher D-dimer levels (P=0.03), the association between D-dimer and MI remained significant when restricted to those on abacavir-sparing regimens.



Oxidized LDL Association with MI Explained by Total LDL

While oxidized LDL levels remained independently predictive of MI after D-dimer, CRP, and CD4/CD8 ratio adjustment, its relationship with MI was largely explained by total LDL levels.



Conclusions / Implications

- While inflammation (hsCRP) predicts Type I MI in treated HIV infection, it appears to be confounded or mediated by hypercoagulability (D-dimer).
  - *Interventions targeting inflammation to reduce short-term MI risk might not be successful if they don't also decrease coagulation.*
- Oxidized LDL may contribute to MI in this setting, independently of inflammation and hypercoagulability, but it is largely reflected by total LDL level.
  - *Likely that statins may reduce MI risk in part via this mechanism.*
- A very low CD4/CD8 ratio (<0.32) and CD8+ T cell expansion strongly predict MI in this setting, primarily in those with lower CD4 counts.
  - *While the immunologic mechanisms remain unclear, this clinically available biomarker may identify a population at high risk for MI.*
- While we found little evidence that other markers of inflammation (IL-6, sTNF-R1), interferon response (IP-10), IDO activity (KT ratio), monocyte activation (sCD14, sCD163), gut barrier function (I-FABP, zonulin), and CMV-specific IgG titer predicted Type 1 MI:
  - *Modest associations cannot be excluded given the relatively small sample size*
  - *Impact on atherosclerosis and longer-term cardiovascular outcomes cannot be excluded.*

This work was supported by:
R24 AI067039
(NHLBI supplement)
R01AI110271

CNICS CFAR Network Of Integrated Clinical Systems

CFAR CENTER FOR AIDS RESEARCH University of California San Francisco Gladstone Institute of Virology and Immunology