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Title
Cumulative Human Immunodeficiency Viremia, Antiretroviral Therapy, and Incident Myocardial Infarction

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Cumulative human immunodeficiency viremia, antiretroviral therapy, and incident myocardial infarction

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Running Head: Cumulative HIV viral load and myocardial infarction

Abstract

Background: People living with human immunodeficiency virus (HIV) are at risk of increased myocardial infarction (MI). Cumulative HIV viral load (VL) has been proposed as a better measure of HIV inflammation than other measures of VL, like baseline VL, but its associations with MI are not known.

Methods: The multi-site Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort includes clinical data and centrally adjudicated MI with distinction between atheroembolic MI (type 1) and MI related to supply–demand mismatch (type 2). We examined CNICS participants who were not on antiretroviral therapy (ART) at enrollment. Cumulative VL (copy-days of virus) from 6 months after enrollment was estimated with a time-weighted sum using the trapezoidal rule. We modeled associations of cumulative and baseline VL with MI by type using marginal structural Cox models. We contrasted the 75% percentile of the VL distribution with the 25% percentile.

Results: Among 11,324 participants, 218 MIs occurred between 1996 and 2016. Higher cumulative VL was associated with risk of all MI (Hazard Ratio (HR):1.72;95% Confidence Interval (CI):1.26-2.36), type 1 MI (HR 1.23;95%CI:0.78-1.96), and type 2 MI (HR 2.52;95%CI:1.74-3.66). While off ART, cumulative VL had a stronger association with type 1 MI (HR 2.13;95%CI:1.15-3.94) than type 2 MI (HR 1.25;95%CI:0.70-2.25). Baseline VL was associated with all MI (HR 1.60;95%CI: 1.28-2.01), type 1 MI (HR 1.73;95%CI:1.26-2.38), and type 2 MI (HR 1.51;95%CI:1.10-2.08).

Conclusion: Higher cumulative and baseline VL is associated with all MI, with a particularly strong association between cumulative VL and type 2 MI.

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Introduction

Compared with the general population, people living with human immunodeficiency virus (HIV) are known to be at an increased risk of cardiovascular events including type 1 (atheroembolic) myocardial infarction (MI), as defined by the Universal Definition [1-5]. While there is some challenge in precisely assigning MI type, a type 1 MI is a spontaneous cardiovascular event related to atherosclerosis, including plaque rupture. In contrast, a Type 2 MI is a consequence of supply-and-demand mismatch in coronary blood flow and may be due to causes such as sepsis or cocaine-induced vasospasm. Both types of MI are present in people living with HIV, with type 2 MI being much more common in people living with HIV than in the general population [6, 7], even after accounting for type 2 MIs related to substance use.

The extent to which various consequences of HIV infection contribute to the increased risk of MI is unclear. However, there is increasing evidence that inflammation is a key contributor to cardiovascular disease risk, both in people living with HIV [8] and in uninfected individuals [9]. One source of inflammation in people living with HIV is elevated HIV viral load. With modern HIV treatment, effective viral suppression may slow the progression of HIV infection to clinical AIDS and reduce the burden of comorbidities including cardiovascular disease. Thus, it is a priority to understand the impact of VL suppression from antiretroviral therapy (ART) on the risk of cardiovascular complications.

Other work in people living with HIV has suggested an adverse relation between an increased cumulative VL burden and key clinical outcomes. Mugavero *et al.* and Olson *et al.* have both demonstrated an association between cumulative VL and mortality

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among people living with HIV in routine clinical care [10, 11]. In terms of adverse cardiovascular events, Salinas *et al.* demonstrated that cumulative VL was associated with MI in a population of veterans living with HIV, although most of these participants were on ART at baseline and because they did not have a centralized adjudication process available, distinctions by MI type could not be assessed [12].

The goal of our study was to understand whether burden of cumulative VL leads to increased MI risk, particularly in the context of ART. We conducted this study in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort for two reasons. One, CNICS has adjudicated MI events – including type of MI. This is critical as previous work has shown that a substantial proportion, about half, of MI events in people living with HIV are type 2 MI events, and these events have different risk factors and mortality rates than type 1 MI events [6]. Two, CNICS has a sizeable proportion of participants who are naïve to ART at enrollment, allowing us to consider treated and untreated person–time separately.

Materials and Methods

Study Population

CNICS is a prospective observational cohort that integrates clinical data on >32,000 participants 18 years of age or older who have received routine clinical care at 8 sites in the United States [13]. The present analysis included participants who were ART naïve at enrollment into care at one of six CNICS sites with comprehensive access to inpatient and outpatient electronic medical records (EMR) and other data sources (Johns Hopkins University; University of Alabama at Birmingham; University of California, San Diego; University of California, San Francisco; University of North Carolina at Chapel

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Hill; and University of Washington, Seattle). Institutional review boards at each study site reviewed and approved CNICS protocols for patient protection, and provide general approval for secondary data analysis.

Participants entered the analytic cohort after their site began MI surveillance (which was in 1996 at the first site) and after they had been enrolled in CNICS for six months, to allow time to accrue information on clinical characteristics and to ensure that particiapants were not on ART prior to cohort entry. The cohort entry date is referred to hereafter as "baseline." Participants were censored at the earliest of any of the following: 1. an MI; 2. death; 3. administrative date (date through which clinical data including medications, laboratory values, and diagnosis data were available for a site; this was a site-specific date which varied slightly across sites but for most was in 2016; 4. last activity for a specific participant (the last date of either a laboratory value or visit date plus 9 months; and 5. when adjudication of MIs for their site ended (end of study follow-up). In addition, we censored people 8 years after cohort entry (based on the range of the weights in the marginal structure models described more below). For models estimating associations prior to ART treatment, initiation of ART was also a censoring criterion.

CNICS Data Repository

Each CNICS site captures comprehensive clinical data from all outpatient and inpatient encounters, including laboratory test results such as VL, CD4 count, cardiac biomarkers, medication data assessed from physician prescribing records and pharmacy system fill data, clinician diagnoses, and historical clinical information.

Outcome

We identified the first MI event among participants in routine clinical care. Potential MIs were ascertained by the presence of either a diagnosis consistent with acute MI, a coronary intervention, or an elevated cardiac biomarker. Reviewer packets of primary clinical data including in-patient and out-patient provider notes, electrocardiograms, imaging and procedure reports, and laboratory values were created. ART medications were redacted from packets prior to centralized review to reduce potential bias. We then adjucated potential events as either definite or probable MIs, classified by type of MI (using the five types of the Universal MI definition [5], with almost all events being type 1 or type 2 in this population) by a panel of at least two expert physician reviewers [6, 7]. In cases of discrepant findings, a third reviewer broke ties [7].

Exposure

Cumulative VL (copy-days of virus in a participant), was estimated using measures obtained from routine care with a median time between VL measures of 99 days. Cumulative VL during follow-up was estimated with a time-weighted sum using the trapezoidal rule, allowing multiple measures in the same six-month time period to contribute to the shape of the cumulative viremia distribution for that participant. This is the approach of both Mugavero *et al.* [8] and Cole *et al.* [14] for estimating cumulative burden of viremia. We log transformed, using a base 2 log, the resulting cumulative VL to reduce the impact of skew from extremely high outliers, as some (mostly ART untreated) participants had very high VL levels over extended periods of time. The total cumulative VL experienced by the participant was time-updated, using all VL measures

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available, at each six-month time interval, across follow-up, to account for increased cumulative viremia over follow-up.

Covariates

All models included sex, race/ethnicity, clinical site, and age at cohort entry, diabetes, treated hypertension, statin use, ever-smoker, all of which were time-updated over follow-up where appropriate. We also included lowest (nadir) CD4 cell count at time of study entry. We defined diabetes using a previously validated approach as any one of the following: hemoglobin A1c $\geq$ 6.5%, a clinical diagnosis of diabetes and prescription of a diabetes-related medication, or prescription of a diabetes-specific medication [15]. We defined treated hypertension as a clinical diagnosis of hypertension and prescription of an antihypertensive medication. Statin use was defined as prescription of an HMG-CoA reductase inhibitor. Ever-smoker was defined by the presence of a tobacco-use diagnosis or self-report of tobacco use on the CNICS clinical assessment of patient-reported outcomes and measures [16, 17], completed approximately every 6 months [18]. Pack–years was collected on a large subset by patient reported outcome measures. We considered time-updated ART as a key effect measure modifier.

Statistical Analysis

We modeled the association between cumulative VL and incident MI using marginal structural Cox models [19] to address any possible time-dependent confounding of this association. We examined type 1 and 2 MI separately, as well as combining them in an all MI category. The pooled logistic regression approach we used to estimate these associations gives an approximation of the hazard ratio [20]. We used 6-month time periods for assessing follow-up and updated cumulative VL at the beginning of each new

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time period, so follow-up time was always consistent between participants in each time period. Stabilized inverse cumulative VL weights were obtained fitting linear regression models to estimate each participant's density of viremia copy-days. Inverse probability weights were fit with logistic regression, using age, sex, site, race, smoking, diabetes, treated hypertension, statin use, and nadir CD4, and were used to adjust estimates for potential confounding. Models that included both treated and untreated participants also included ART in the inverse probability weight models.

Checking model assumptions, we noted that the distribution of the inverse probability weights was reasonable with the maximum weight observed as 96 even after 15 6-month intervals of follow-up, after which we censored the data to avoid concerns about weak violations of the positivity assumption [21]. Censoring due to large inverse probability weights in the more distant periods of follow-up excluded 56 additional MI events, 34 type 1 and 22 type 2, that occurred after more than 8 years of follow-up. Trimming or truncation of weights gave comparable results [21] and few participants were still under follow-up after 8 years.

Cumulative VL and baseline VL have unusual distributions (online supplementary material eFigure; http://links.lww.com/EDE/B416, eFigure2; http://links.lww.com/EDE/B416, and eFigure3; http://links.lww.com/EDE/B416). We examined cumulative and baseline VL as continuous variables after log transform as log (VL + 1) using the base 2 log. We also created a comparison of the 75% percentile of VL to the 25% percentile to give an estimate of relative effect size. This estimator compares the median of the top half of the distribution to the median of the bottom half.

For the cumulative VL estimates, we used the distribution of cumulative VL at 5 years (which was the mean length of follow-up in this study).

Separately, we assessed person–time exposed to ART and person–time ART-untreated. We did a sensitivity analysis adjusting for intravenous drug use, due to population differences between intravenous drug users and non-users. In a second sensitivity analysis, we used multiple imputation to account for all missing data [22], which allowed us to include smoking pack–years as a covariate. Assumptions about the causal structure of the problem are presented as a supplement (Supplementary Figure 4; http://links.lww.com/EDE/B416). All analyses were performed using Stata 13 (College Station, TX).

Results

Among 11,324 participants, 218 MIs occurred during a median of 4.8 years of follow-up (maximum 8 years), with relatively equal numbers of type 1 (n=103) and type 2 (n=115) MIs. Participants mean age was 39, 79% were male, and the majority were non-white (Table 1).

The range of cumulative VL was quite broad (Table 2). Median level of cumulative VL was much higher among participants who were untreated than among the treated (10.5 million copies/mL times days versus 1.0 million copies/mL times days), despite a longer period of time to accrue VL among the treated.

A doubling of the cumulative VL was associated with an increased risk of all MI (hazard ratio (HR) 1.07, 95% Confidence Interval (CI): 1.03-1.11) (Table 3). The association of VL with type 1 MI was attenuated (HR 1.02; 95% CI: 0.97-1.08), but higher cumulative VL was associated with type 2 MI (HR 1.11; 95% CI: 1.07-1.16). The

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HR for all MI contrasting participants in the 75th percentile versus the 25th percentile of cumulative VL (calibrated to 5 years of follow-up) was 1.72 (95% CI: 1.26-2.36). The association with cumulative viral load was weaker for Type 1 MI (HR 1.23; 95% CI: 0.78-1.96) than for Type 2 MI (HR 2.52; 95% CI: 1.74-3.66).

As VL accumulates differently among participants on versus off ART, we also looked at time periods in which participants were treated with ART and untreated with ART. Among the 3168 participantswho were off ART for at least one 6-month follow-up interval, during the person–time at risk in their unexposed period, doubling of the cumulative VL was associated with all MI (HR 1.09; 95% CI: 0.99-1.21), type 1 MI (HR 1.18; 95% CI: 1.03-1.35), and with type 2 MI (HR 1.05; 95% CI: 0.93-1.20), although some intervals were consistent with null associations (Table 3). While off ART, contrasting participants in the 75th percentile versus the 25th percentile of cumulative VL there was a stronger association with type 1 MI (HR 2.13;95%CI:1.15-3.94) than type 2 MI (HR 1.25;95%CI:0.70-2.25). Among the 9931 participants with at least 6 months of ART exposure during follow-up, we considered the person–time at risk in the exposed period. VL accounting began at the start of ART treatment (using an intention to treat definition of exposure) in this analysis, so median VL at end of follow-up was lower than in the full cohort analysis. (Table 2) In these participants, doubling of the cumulative VL was associated with all MI (HR 1.06; 95% CI: 1.02-1.10), type 1 MI (HR 1.02; 95% CI: 0.97-1.08), and type 2 MI (HR 1.10; 95% CI: 1.06-1.15).

We also considered baseline VL as an alternative measure, because it is commonly used in the HIV literature. Baseline VL was associated with an increase in all MI events using a Cox proportional hazards model of HR 1.06 (95% CI; 1.03-1.09) per

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doubling of VL (Table 4). If we look at the 75% percentile of baseline VL (as compared

to the 25% percentile of baseline VL) then the HR for all MI was 1.60 (95% CI: 1.28-

2.01), and this was driven by both type 1 MI (HR 1.73; 95% CI: 1.26-2.38) and Type 2

MI (HR 1.51; 95% CI: 1.10-2.08).

Results for the primary analysis were similar with imputation for missing data

(eTable 1; http://links.lww.com/EDE/B416). The sensitivity analysis that also adjusted

for intravenous drug use did not demonstrate any appreciable difference in estimates. We

also considered mortality rates over follow-up, so competing risk concerns could be

considered if there were large differences in mortality in the treated verus untreated

participants. There were 15.3 deaths per 1,000 person–years (95% CI 14.4 – 16.3) and

were similar for participants who were off ART (14.4 death per 1,000 person–years; 95%

CI 12.1 – 17.1) and on ART (15.4 deaths per 1,000 person–years; 95% CI: 14.4 – 16.5).

DISCUSSION

The goal of our study was to understand whether the burden of cumulative VL in

the context of ART leads to increased MI risk. Among people living with HIV in the

CNICS cohort who were not on ART at enrollment, greater cumulative VL was

associated with increased risk of all MI events. Effect sizes varied depending on ART

treatment during follow-up and type of MI, with type 2 MI generally showing larger

associations than type 1 MI. However, all participants appeared to benefit from lower

cumulative VL in terms of reduced MI risk. The differences in MI events may be one

element of the increased all-cause mortality among participants with high cumulative VL

[23], which appears to be associated with cardiovascular events regardless of treatment

status.

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These findings may help explain in small part how the burden of HIV infection has evolved over time with earlier initiation of effective treatments for HIV in clinical care for people living with HIV in the United States. The presence of untreated person–time allowed us to examine the burden of HIV infection prior to effective HIV treatment. Our results suggest that, in participants who are not treated, greater VL is associated with an increased risk of type 1 MI. Active treatment seems to attenuate the association of cumulative viremia with type 1 MI, in general, although the participants are also exposed to much lower VL levels under treatment. Baseline measures of VL showed an association with MI, but it was slightly weaker for all MI and for type 2 MI than with the cumulative viral load measures.

Our findings are in accordance with previous evidence that chronic viremia is related to atherosclerotic disease. Human cohort studies show atherosclerotic links to inflammation both in people living with HIV [24] and those not infected with HIV [25], which could well be a plausible pathway by which cumulative VL could increase cardiovascular risk.

Our study has several strengths, including adjudication of MIs and classification of MI type, a large population of ART-naïve participants, and extensive follow-up. Information on ART exposure was derived from clinical records and thus represents the actual treatment intentions of the provider. Extensive measurement of participant characteristics, including laboratory measures and patient reported outcomes, allowed for rich confounding control and an understanding of possible imbalances among cardiovascular risk factors among those with and without high burdens of viremia.

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The limitations of this study include the observational nature of the data, the lack of pre-enrollment VL measures, the predominantly male composition of CNICS, and the irregular pattern of VL measurements. We did not include sudden cardiac death in our MI outcome because it can be difficult to distinguish cardiac causes of death from other causes such as drug overdoses. The use of an ever-smoking definition was also sub-optimal, although results were similar when multiple imputation was used to account for missing smoking data among some participants.

We cannot rule out that some ART regimens may be less cardioprotective than others, relative to untreated people living with HIV, for atheroembolic MI [26, 27]. Thus, choice of ART regarding cardiovascular risk is still important, although remaining untreated would not be supported by this data as there were 4.9 MI events per 1000 person–years off ART and 3.9 MI events per 1000 person–years on ART, demonstrating that treatment is associated with protection from cardiovascular events in general. Perhaps improvements in the cardiovascular risk profile of newer ART approaches may further improve outcomes. It is also possible that single episodes of extremely high viremia may be important, but this is difficult to assess in irregular data.

Higher VL is associated with a higher risk of MI among people living with HIV. Higher cumulative VL is more strongly associated with type 2 MI, as opposed to type 1, highlighting the importance of examining MIs by type.

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Table 1. Baseline demographic and clinical characteristics of people living with HIV who were not on ART at entry from the CNICS cohort across the United States

Characteristic	Overall
N	11324
Age, years, mean (SD)	39 (10)
Nadir CD4 count (cells/mm^3) Mean (SD)	315 (245)
Baseline VL (copies/ml) Mean (SD)	37,053 (194,086)
Male, %	79
Race, %	
White	40
Black	42
Hispanic	12
Other/Unknown	6
Former Smoker, %	24
Current Smoker, %	38
Diabetes, %	4
Treated Hypertension, %	10
Treated Dyslipidemia, %	4

VL indicates viral load, SD standard deviation.

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Table 2. Cumulative VL (million copies/mL times days) at the end of follow-up for all participants, the end of the untreated period for those participants with untreated time, and the end of the treated period for those participants with treated time.

	Mean (Millions of copies/mL times days)	Median (Millions of copies/mL times days)	Standard Deviation	Range of VL	Median follow-up time for time period
All person–time	40.8	2.0	140	0.002 to 6,380	4.8 years
ART exposed person–time	36.1	1.0	140	0.002 to 6,380	4.4 years
ART unexposed person–time	37.1	10.5	84.8	0.002 to 1,550	1.8 years

ART indicates antiretroviral therapy, VL viral load.

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Table 3. Association between cumulative viral load (VL) and myocardial infarction (MI) in 11,324 people living with HIV who were not on antiretroviral therapy (ART) at cohort entry, overall and for person–time off and on ART during follow-up. Adjusted hazard ratios[a] (HR) and 95% confidence intervals (CI) are provided both for doubling the cumulative VL and for the 75th versus the 25th percentile of the cumulative VL distribution.

	All participants ART-untreated at baseline (52,952 person-years of follow-up, 218 MIs, 103 type 1, 115 type 2)				
Outcome	HR per doubling	95% Confidence Interval	HR for 75th vs 25th %ile)	95% CI	MI Rate per 1000 person years (95% CI)
all MI	1.07	1.03, 1.11	1.72	1.26,2.36	4.12 (3.61,4.70)
type 1 MI	1.02	0.97, 1.08	1.23	0.78,1.96	1.94 (1.60,2.36)
type 2 MI	1.11	1.07, 1.16	2.52	1.74,3.66	2.17 (1.81,2.61)

	Person–time off ART (8,270 person-years of follow-up, 41 MIs, 15 type 1, 26 type 2)				
Outcome	Hazard Ratio[a]	95% Confidence Interval	HR (75 vs 25)	95% CI	Rate per 1000 person years
all MI	1.09	0.99, 1.21	1.48	0.93,2.35	4.96 (3.65,6.73)
type 1 MI	1.18	1.03, 1.35	2.13	1.15,3.94	1.81 (1.09,3.01)
type 2 MI	1.05	0.93, 1.20	1.26	0.71,2.26	3.14 (2.14,4.62)

	Person–time on ART (44,674 person-years of follow-up, 177 MIs, 88 type 1, 89 type 2)				
Outcome	HR per doubling	95% Confidence Interval	HR for 75th vs	95% CI	MI Rate per 1000 person years (95%

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			25th %ile)		CI)
all MI	1.06	1.02, 1.10	1.65	1.22,2.23	3.96 (3.42,4.59)
type 1 MI	1.02	0.97, 1.08	1.22	0.78,1.91	1.97 (1.60,2.43)
type 2 MI	1.10	1.06, 1.15	2.31	1.59,3.35	1.99 (1.62,2.45)

[a] Estimates are adjusted for age, sex, race/ethnicity, clinical site, diabetes,

treated hypertension, statin use, ever-smoker, and lowest CD4 cell count. The all

MI model is also adjusted for ART.

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Table 4 – Association between baseline viral load and myocardial infarction (MI) in 11,324 people living with HIV who were not on antiretroviral therapy (ART) at cohort entry. Adjusted hazard ratios[a] (HR) and 95% confidence intervals (CI) are provided both for doubling the cumulative VL and for the 75th versus the 25th percentile of the baseline VL distribution.

Outcome	All participants ART-untreated at baseline (63,528 person-years of follow-up, 274 MIs, 137 type 1, 137 type 2)				
	HR per doubling	95% Confidence Interval	HR for 75th vs 25th %ile)	95% CI	MI Rate per 1000 person years (95% CI)
all MI	1.06	1.03, 1.09	1.60	1.28,2.01	4.3 (3.8,4.9)
type 1 MI	1.07	1.03, 1.11	1.73	1.26,2.38	2.2 (1.8,2.5)
type 2 MI	1.05	1.01, 1.09	1.51	1.10,2.08	2.2 (1.8,2.5)

[a] Estimates are adjusted for age, sex, race/ethnicity, clinical site, diabetes, treated hypertension, statin use, ever-smoker, and lowest CD4 cell count. The all MI model is also adjusted for ART.