IL-6, sCD14 and D-dimer partially mediate the association between HIV and mortality

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ABSTRACT

Introduction: We tested the hypothesis that the relationship between HIV and mortality is mediated (explained) by altered immune function i.e. elevations in biomarkers of inflammation (interleukin-6 [IL-6]), monocyte activation (soluble CD14 [sCD14]), altered coagulation (D-dimer).

Methods: Participants were from Veterans Aging Cohort Study Biomarker Cohort (VACS BC). Biomarkers were measured in blood samples from 1498 HIV+ and 829 uninfected VACS 8 participants. Deaths were obtained from VHA vital status file, which uses inputs from the social security administration death master file, the Beneficiary Identification and Records Locator Subsystem, and the VHA Medical Statistical Analysis Systems inpatient datasetsWe used proportional odds ratio and Cox proportional hazard modeling to assess whether the relationship between HIV and death was consistent with mediation by inflammatory biomarkers.

Results: During a median of 6.9 years from baseline, 405 deaths occurred (15% of uninfected, 19% of HIV+). The proportional odds (95% CI) of being in a higher quartile of IL-6, sCD14 or D-dimer was 2-3 fold higher for HIV+ with HIV-1 RNA≥ 10000 copies/mL versus uninfected people. Mortality rates/100 person years were higher among HIV+ compared to uninfected people (incidence rate ratio (95% CI): 1.28 (1.04-1.60). Mortality rates and risk increased with increasing quartiles of IL-6, sCD14 and D-dimer independently of HIV status. Compared to uninfected people, the risk of death (Hazard ratio (95% CI)) among those with HIV-1 RNA≥10000 copies/mL was 2.09 (1.53-2.88) adjusting for demographics, prevalent comorbid disease, and substance use. Further adjustment for IL-6, sCD14 and D-dimer attenuated this risk to 1.83 (1.32-2.54).

Conclusion: Systemic inflammation, altered coagulation, and monocyte activation partially mediated the effect of HIV on mortality. These mechanisms may explain some of the excess risk of mortality among HIV+ compared to uninfected people.

STUDY DESIGN

VACS-8

- All VA Electronic medical records including text fields
- Sentinel event records (MI) requested outside VA
- DNA and tissue bank
- Annual self completed surveys (health behaviors, quality of life, symptoms, outside utilization, etc.)
- 3790 HIV+; 3962 uninfected
- Group matched: age, race/ethnicity, and site

VACS BC

- Subset of VACS-8
- IL-6, sCD14, D-dimer

vacohort.com

VACS index

VACS index (mobile)

RESULTS

Table 1: Baseline characteristics (bold indicates p<0.05 for comparison by HIV status)

	Total (% of column)		Died (% of column)	
	HIV-	HIV+	HIV-	HIV+
N	829	1498	125	280
Age	**54.1 (9.4)**	**52.3 (8.2)**	**59.0 (10.5)**	**54.7 (7.7)**
Comorbid diseases				
Prevalent CVD	**13**	**6**	**26**	**11**
Prevalent cancer	6	6	6	11
Uncontrolled hypertension	**29**	**24**	**37**	**31**
Diabetes	**32**	**20**	**43**	**22**
COPD	**7**	**5**	17	12
Current smoker	**48**	**50**	50	60
BMI>30 kg/m^2	**43**	**14**	**38**	**13**
Total cholesterol ≥200 mg/dL	**25**	**26**	17	19
Substance use				
Cocaine use in past year	**17**	**20**	17	24
At-risk or heavy episodic drinking	18	18	14	16
Alcohol abuse/dependence	**16**	**12**	17	18
VACS index				
Median (IQR) VACS Index score	**21 (12, 27)**	**28 (17, 43)**	**27 (22, 40)**	**43 (31, 62)**
HIV specific factors				
CD4 Median (IQR) (cells/mm^3)		392 (232, 583)		292 (123, 453)
HIV-1 RNA median (IQR) copies/mL		75 (75, 3339)		400 (75, 20321)
HAART (baseline)		76		71

Table 2: Association between HIV infection and biomarker level

	Proportional odds ratio (95% confidence interval)			
	HIV uninfected	HIV+ HIV-1 RNA<500 copies/mL	HIV+ HIV-1 RNA 500-9999 copies/mL	HIV+ HIV-1 RNA ≥10000 copies/mL
IL-6 quartiles	1 (ref)	1.31 (1.07-1.60)	1.32 (0.98-1.77)	2.57 (1.95-3.4)
sCD14 quartiles	1 (ref)	0.81 (0.67-0.98)	0.68 (0.51-0.91)	1.49 (1.13-1.95)
D-dimer quartiles	1 (ref)	0.58 (0.48-0.71)	1.14 (0.85-1.52)	1.78 (1.35-2.35)

Adjusted for age, race-ethnicity, cardiovascular disease, cancer, diabetes, chronic obstructive pulmonary disease, hypertension, smoking, hepatitis C, obesity, total cholesterol and cholesterol lowering medication, alcohol use, cocaine use, hemoglobin, FIB-4, eGFR

RESULTS continued

Table 3: Assessing whether addition of inflammatory biomarkers to Cox regression models attenuates the association between HIV infection (stratified by HIV-1 RNA at baseline) and mortality.

	Hazard Ratio (95% Confidence Interval)				
	Unadjusted for IL-6, sCD14 or D-dimer	Adjusted for IL-6	Adjusted for sCD14	Adjusted for D-dimer	Adjusted for IL-6, sCD14 and D-dimer
HIV uninfected	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
HIV+ HIV-1 RNA<500 copies/mL	0.99 (0.76-1.29)	0.98 (0.75-1.29)	1.00 (0.77-1.31)	1.06 (0.8-1.39)	1.04 (0.79-1.37)
HIV+ HIV-1 RNA 500-9999 copies/mL	1.33 (0.92-1.93)	1.36 (0.93-1.97)	1.39 (0.96-2.02)	1.33 (0.92-1.93)	1.40 (0.96-2.03)
HIV+ HIV-1 RNA ≥10000 copies/mL	2.09 (1.53-2.88)	1.91 (1.38-2.64)	2.06 (1.5-2.84)	1.97 (1.43-2.71)	1.83 (1.32-2.54)

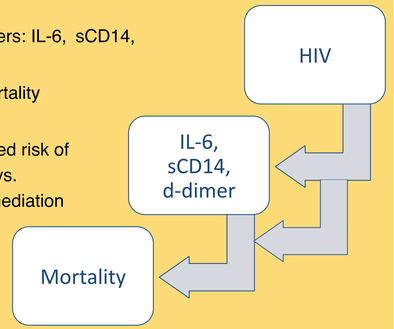
Additionally adjusted same covariates as in Table 2

LIMITATIONS

- Predominantly male cohort, limited generalizability to comen
- No longitudinal measures of IL-6, sCD14 and D-dimer
- No biomarkers of immune activation (e.g. tumor necrosis factor-α, interleukin 1β, interleukin 10).

SUMMARY

1) HIV is associated with mortality
2) HIV is associated with inflammatory biomarkers: IL-6, sCD14, D-dimer
3) IL-6, sCD14, D-dimer are associated with mortality independently of HIV status
4) Given 1-3 hold, the attenuation in the estimated risk of mortality among highly viremic HIV infected (vs. uninfected) people is consistent with partial mediation of the association between unsuppressed viral replication and mortality.



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