242 Total HIV-1 DNA Levels Do Not Predict Non-AIDS-Defining Events

Colline Wong[1], Ashley McKhann[2], Carlee Moser[2], Alan L. Landay[3], Michael M. Lederman[4], Sara Gianella[5], Jonathan Z. Li[1]

[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA [2]Harvard T.H. Chan School of Public Health, Boston, MA [3]Rush University Medical Center, Chicago, IL
[4]Case Western Reserve University School of Medicine, Cleveland, OH [5]University of California San Diego, La Jolla, CA

Background

- Many individuals living with HIV continue to have elevated levels of inflammation and may be more likely to have non-AIDs-defining events.
- Higher levels of soluble inflammatory markers (IL-6, sTNFR-I, sTNFR-II, sCD14, D-dimer) predict non-AIDS-defining events.
- Individuals with HIV are nearly universally infected with CMV and EBV, which may drive clonal expansion of HIV-infected CD4 cells.
- The goal of this study was to investigate the relationship between HIV reservoir size and levels of systemic inflammation, viral co-infections, and risk of non-AIDS-defining events.

Methods

Study Design

- Case-control study of AIDS Clinical Trials Group (ACTG) participants in NWCS 411 (substudy of NWCS 329).
- Participants were ART-naïve at the time of enrollment and maintained plasma HIV-1 RNA levels <400 copies/mL within one year after ART initiation.
- Cases were defined as participants who had a non-AIDS-defining event (stroke, myocardial infarction, non-AIDS-defining serious bacterial infections, non-AIDS-defining malignancy, or death from a non-AIDS-defining event). Controls were identified and matched based on age, sex, baseline CD4+ T-cell count, and ART regimen.
- PBMCs and plasma specimens were collected at both 1 year after ART initiation and at the pre-event time point.
- Specimens were analyzed for levels of IL-6, sCD14, interferon γ (IFN-γ), inducible protein 10 (IP10), sTNFR-I, sTNFR-II, D-dimer, CMV and EBV DNA and antibody levels.
- Total HIV DNA levels in PBMCs were measured by qPCR using UltraBio's Total HIV-1 DNA Kit.

Statistical Analysis

- Conditional logistic regression analyses were performed to determine if HIV DNA levels predicted the occurrence of non-AIDS-defining events separately at each time point.
- Adjusted logistic models considered the following covariates: pre-ART HIV RNA level, CD4 cell count, chronic Hepatitis B/C status, smoking status, history of injection drug use, waist-to-hip ratio, diabetes status, hypertension status, use of antihypertensive or lipid lowering medications, and family history of MI.
- Spearman correlations were performed to determine if HIV DNA levels were associated with the biomarkers of inflammation and co-infection.

Results

At year 1 and pre-event, total HIV DNA levels did not differ between cases and controls.

- Samples from 102 cases and 201 controls at year 1 and from 65 cases and 110 controls pre-event were included.
- Unadjusted and adjusted conditional logistic regression analysis for total HIV DNA at either time point showed no significant associations with non-AIDS-defining events.

Table 1: Event Analysis for Total HIV DNA at Year 1 and Pre-Event

Event Analysis at Year 1

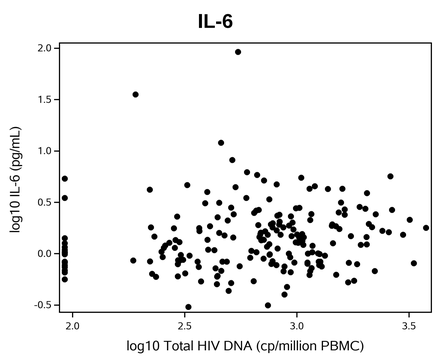
Event:	Observations:	OR (95% CL) associated with one higher level after log10 transformation		
		Per one log10	Per one IQR	P-value
Death	# cases= 16 # controls= 32	1.3 (0.2, 7.6)	1.1 (0.5, 2.6)	0.80
Malignancy	# cases= 36 # controls= 76	0.9 (0.3, 2.6)	1.0 (0.6, 1.7)	0.88
MI/stroke	# cases= 30 # controls= 61	0.7 (0.2, 2.2)	0.9 (0.5, 1.4)	0.59

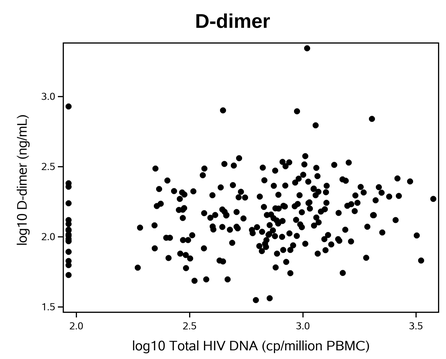
Event Analysis at Pre-Event

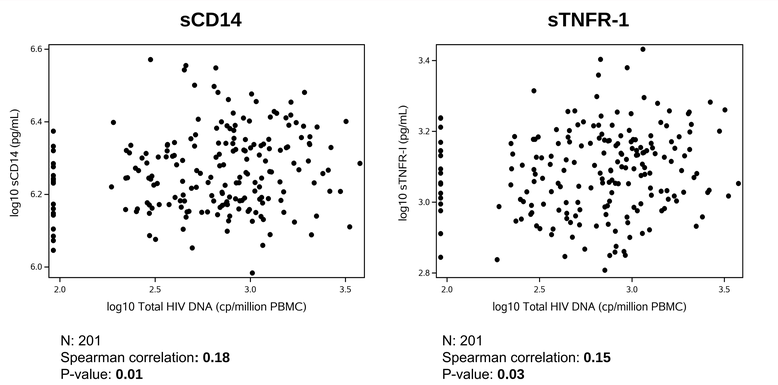
Event:	Observations:	OR (95% CL) associated with one higher level after log10 transformation		
		Per one log10	Per one IQR	P-value
Death	# cases= 10 # controls= 17	1.0 (0.1, 8.7)	1.0 (0.4, 2.7)	0.99
Malignancy	# cases= 23 # controls= 42	2.7 (0.5, 15.9)	1.7 (0.7, 4.2)	0.27
MI/stroke	# cases= 18 # controls= 32	0.3 (<0.1, 1.3)	0.4 (0.1, 1.2)	0.10

- There were no significant associations between total HIV DNA levels and death, malignancy, nor MI/Stroke at year 1 and pre-event **(Table 1)**.

Figure 1: Correlations Between HIV DNA and Biomarkers of Inflammation at Year 1

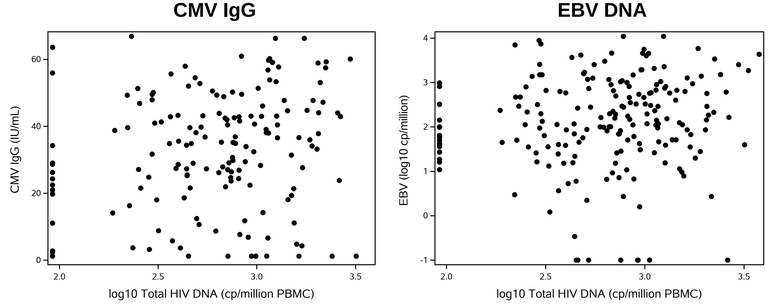






- Levels of total HIV-1 DNA are modestly associated with levels of IL-6, D-dimer, sCD14, and sTNFR-I **(Figure 1).**

Figure 2: Correlations Between HIV DNA and Biomarkers of Co-Infection at Year 1



- At year 1, HIV-1 DNA levels are modestly correlated with levels of CMV antibody, and EBV DNA levels **(Figure 2)**. HIV-1 DNA levels are not associated with EBV IgG or CMV DNA levels.

Conclusions

- **The size of the HIV reservoir, as reflected by the levels of total HIV-1 DNA, was not predictive of non-AIDs-defining events.**
- **The modest associations of HIV reservoir size with EBV DNA in PBMCs and CMV IgG levels support the potential contribution of clonally expanded populations of HIV-infected CD4+ cells to the HIV reservoir.**
- **The modest associations of HIV levels and inflammatory markers suggest potential interactions between host immune responses and HIV persistence.**

Acknowledgements

We thank the ALLRT participants and protocol team, the ACTG clinical trial sites that enrolled and followed the participants, the ACTG. The HIV DNA kits were provided by UltraBio Technologies, Inc.