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Clonal Hematopoiesis in HIV and Atherosclerosis, Arterial Inflammation, and Hematopoietic Activity

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BACKGROUND

- Clonal hematopoiesis of indeterminate potential (CHIP) is associated with cardiovascular disease (CVD) including among people with HIV (PWH).
- HIV is associated with a prevalence of CHIP twice that of age-matched controls, but whether and how CHIP contributes to CVD PWH is unknown.
- We hypothesized that CHIP is associated with atherosclerosis, arterial inflammation, and hematopoietic activity among PWH.

METHODS

Design: Observational Study

Inclusion/Exclusion: PWH ages 35-70 years old who were treated, virally-suppressed with ≥1 CVD risk factor.

Exposure: CHIP measured in stored peripheral blood mononuclear cells with a validated targeted sequencing assay, defined as a variant allele fraction >2%.

Outcomes: Carotid intima-media thickness on carotid ultrasound at two time points and aortic inflammation (TBR) and hematopoietic metabolic activity (SUV) using ^{18}F-FDG-PET at one time point.

Correlative data: Biomarkers (CRP, IL-6, TNF, sCD14, sCD163, MCP1, or D-Dimer) were measured with a multiplex electrochemiluminescence assay and markers of HIV reservoir from cellular DNA and RNA were measured in the subset with IMT.

Statistical Approach: Non-parametric Wiilcoxon Rank Sum tests were used for unadjusted comparisons between groups. Linear regression with adjustment for age, sex, nadir CD4 count, smoking, hypertension, diabetes, and hyperlipidemia was used to adjust for potential confounders.

RESULTS

We included 231 people with HIV, of whom 32 (14%) had CHIP.

Median variant allele fraction was 3.1%. Common mutations were in DNM3TA (n=21) and TET2 (n=6). Age was associated with CHIP (OR 2.3 per decade older, 95%CI 1.2-3.9; p=0.003) and current smoking was associated with lower prevalence.

	Total (n=231)	CHIP (n=32)	No CHIP (n=199)	p value
Age	**52±8.7**	**57±8.2**	**51±8.7**	**0.002**
Female	16 (7%)	1 (3%)	15 (8%)	0.41
White	163 (71%)	25 (78%)	138 (69%)	0.42
Black	36 (16%)	2 (6%)	34 (17%)	
Hispanic/Latino	22 (10%)	1 (3%)	9 (5%)	
Hypertension	73 (37%)	12 (43%)	61 (37%)	0.52
Diabetes	18 (9%)	4 (14%)	14 (8%)	0.32
Current Smoker	**68 (30%)**	**3 (9%)**	**65 (33%)**	**0.007**
Baseline LDL-Cholesterol, mg/dl	88±46	93±47	88±46	0.50
Baseline Systolic Blood Pressure, mm Hg	124±14	120±10	124±15	0.17
Baseline CD4 Count	554±216	539±216	556±281	0.74
Baseline C-Reactive Protein	1.8 (0.7, 4.4)	1.4 (0.8, 7.2)	1.8 (0.7, 4.3)	0.68
Estimated 10-year ASCVD Risk by Pooled Cohort Equations	5.2 (3.1, 9.6)	6.2 (2.9, 11.3)	5.1 (3.1, 9.1)	0.45

In HIV, *CHIP* is associated with increased *lymph node metabolic activity*, but not carotid atherosclerosis or aortic inflammation.

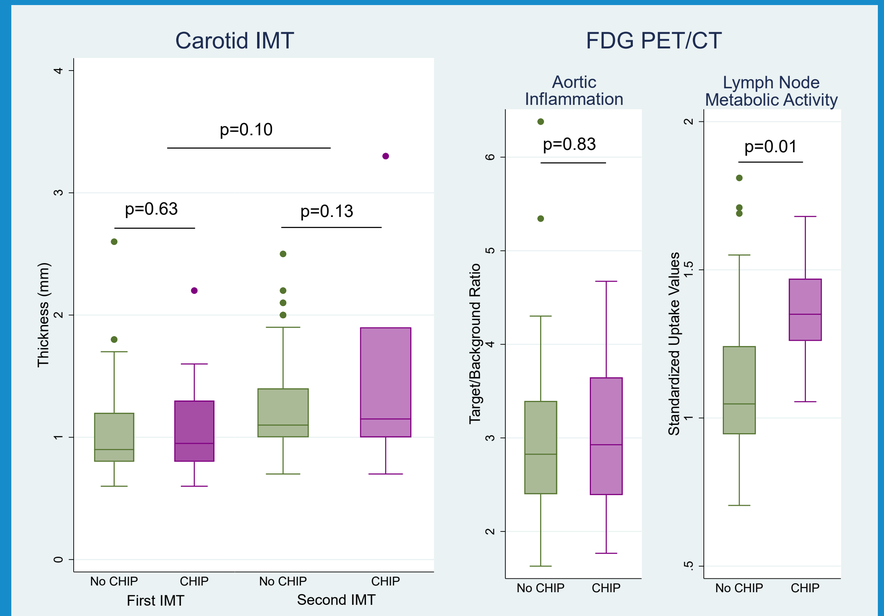


Figure 1 Legend: CHIP was not associated with **c**arotid IMT (mean baseline IMT 1.0 mm with and without CHIP) or aortic inflammation, but there was increased lymph node metabolic activity among those with CHIP.

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Other Carotid Ultrasound Results (n=165, 22 with CHIP)

- Over 3.2 years, IMT progression was faster among those with CHIP (0.033 mm/year; 95% CI -0.006 to 0.054; p=0.10), attenuated (0.022 mm/year; 95% CI -0.017 to 0.061; p=0.27) after adjustment for age, sex, nadir CD4 count, smoking, hypertension, diabetes, and hyperlipidemia.
- No association with baseline prevalent plaque (59% CHIP vs 55% no CHIP, p=0.73).
- No association with incident plaque among those without prevalent plaque (44% CHIP vs 33% no CHIP, p=0.49).

Other FDG-PET Results (n=80, 12 with CHIP)

	CHIP (n=12)	No CHIP (n=68)	Unadjusted Nonparametric P-value
Aortic Inflammation, TBR_{max}	3.0±0.9	3.1±0.9	0.83
Lymph Node Metabolic Activity, SUV_{max}	1.4±0.2	1.1±0.3	0.01
Spleen Metabolic Activity, SUV_{max}	5.0±4.6	2.5±1.1	0.10
Bone Marrow Metabolic Activity, SUV_{max}	3.5±2.6	2.9±1.3	0.68

Selected Biomarkers

	CHIP	No CHIP	Unadjusted Nonparametric P-value
D-Dimer	0.43±0.35	0.39±0.29	0.65
Fibrinogen	345±70	390±121	0.35
IL-6	1.3±0.8	1.8±2.3	0.89
TNF	4.9±1.9	6.1±11	0.48
sCD163	629±431	577±417	0.51
sCD14	1.8±0.4	1.9±0.6	0.79

CONCLUSIONS

Conclusions: Among PWH, CHIP mutations were not associated with subclinical atherosclerosis or arterial inflammation, proposed mechanisms of how CHIP could cause CVD. The mechanism by which HIV promotes CHIP could include viral persistence which may be reflected by higher levels of lymph node activity as demonstrated in our preliminary findings. Clinical outcomes studies are needed to ascertain the impact of CHIP on CVD in HIV.