Description of clonal hematopoiesis in a hospital-based cohort of people living with HIV

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BACKGROUND

- In the antiretroviral therapy era, people living with HIV (PLWH) are aging leading to increased mortality from chronic diseases and non-AIDS defining cancers.
- Clonal hematopoiesis (CH), the phenomenon of subpopulations in the myeloid lineage with distinct driver mutations, is infrequent in patients under 50.
- CH is associated with malignancy and cardiovascular disease risk in the non-HIV population.
- Studies have been mixed in demonstrating that PLWH have a higher risk of CH than people without HIV.
- Some prior data show that low CD4 count may be associated with increased odds of CHIP.
- **We aimed to describe CH in a cohort of PLWH as the initial phase of an ongoing analysis to determine the prognostic implications of CH in PLWH.**

METHODS

Data Source: Phenotype and whole exome sequencing data from patients recruited to the Mount Sinai BioMe Biobank

Cohort: 487 patients in the cohort who met validated criteria for HIV

Outcome: CH was called by excluding any patient with a myeloid malignancy and by filtering for predefined myeloid CH mutations with variant allele frequency (VAF) ≥ 2%.

Other variables: Viral load and CD4 count at baseline were identified by selecting the closest value within one year of entry into the cohort (see "Exposures" below).

Analysis: Logistic regression models were then fit to investigate the association between demographic and HIV-specific factors with presence of CH in the cohort of patients with HIV.

Inclusion criteria	Exclusion criteria
- Recruited into BioMe BioBank - Genotyping data available - HIV positive by ICD-10 code and prior viral load measurement	- Age <18 - Myeloid malignancy diagnosis

Predictors of CH in Persons Living with HIV

Logistic regression

Exposures: baseline CD4 count, baseline viral load (detectable/undetectable[1]), age at cohort entry, African or Hispanic ancestry, smoking (current/former), alcohol (yes/no), sex

Outcome: Presence of CH

1. Detectable threshold defined as >200 copies/ml

Age was the only predictor significantly associated with presence of CH in our cohort. Viral load, CD4 count, and smoking were not significantly associated with presence of CH.

RESULTS

- Out of 487 participants we identified 29 patients with HIV with 30 CH mutations.
- CH patients were older than non-CH, 24% of PLWH with CH were below the age of 50.
- In multivariable model age was significantly associated with presence of CH in the HIV population (p=0.006) while ancestry, smoking, alcohol, sex, viral load, and CD4 count were not.
- The most common CH mutations were *DNMT3A* (8/30) and *TET2* (4/30).
- None of the patients had mutations in *ASXL1*.
- Median VAF was 8.4% (IQR 6.6 – 11.7%).

Table 1: Cohort Demographic and Clinical Characteristics by CH

	Total (n=487)	No CH (n=458)	CH (n=29)
	N/median (%/IQR)		
Age at Baseline	50.3 (42.0, 56.4)	49.8 (41.7,56.0)	57.8 (51.0, 62.2)
Sex			
Male	382 (78%)	361 (79%)	21 (72%)
Female	105 (22%)	97 (21%)	8 (28%)
Year of Entry into Cohort	2010 (2011, 2012)	2012 (2011, 2012)	2011 (2010, 2012)
Death During Follow-Up	44 (9%)	24 (5%)	5 (17%)
Age of Death[1]	61.3 (47.6, 72.3)	61.0 (54.1, 79.2)	71.2 (58.1, 71.3)
Genetic Ancestry			
African	186 (38%)	175 (38%)	11 (38%)
European	187 (38%)	174 (38%)	13 (45%)
Other or Unknown	114 (29%)	109 (24%)	5 (17%)
Alcohol Use at Any Point			
Yes	207 (43%)	194 (42%)	13 (45%)
No	239 (49%)	225 (49%)	14 (48%)
Unknown	41 (8%)	39 (9%)	2 (7%)
Smoking at Any Point			
Ever	284 (58%)	268 (59%)	16 (55%)
Never	193 (40%)	180 (39%)	13 (45%)
Unknown	11 (2%)	10 (2%)	1 (3%)
CD4 at Baseline (n=282)	541 (342, 776)	529 (342, 778)	659 (365, 716)
Undetectable Viral Load at Baseline (n=213)	151 (70.9%)	12 (75%)	139 (71%)

Table 2: CH Gene Mutations

Gene	N (%)
DNMT3A	8 (28%)
TET2	4 (14%)
TP53	2 (7%)
BCOR/BCORL1	2 (7%)
SETD2	2 (7%)
EZH2	2 (7%)
RUNX1	2 (7%)
PHIP	2 (3%)
SETD2	2 (3%)
IKZF1	1 (3%)
CREBBP	1 (3%)
EP300	1 (3%)
RAD21	1 (3%)
SRSF2	1 (3%)
PRPF408	1 (3%)

Table 3: Predictors of CH Among PLWH

Covariate	Odds ratio (95% confidence interval)	p value
Age	1.07 (1.02, 1.14)	0.012
Sex	0.54 (0.14, 2.10)	0.375
Genetic ancestry		
African	1.0 (0.30, 3.32)	0.99
Hispanic	0.26 (0.03, 2.66)	0.26
Other	1.29 (0.11, 15.36)	0.84
Smoking		
Current	0.35 (0.04, 3.15)	0.35
Former	0.94 (0.31, 2.87)	0.92
Alcohol (any)	1.48 (0.49, 4.49)	0.49
Undetectable viral load	1.30 (0.39, 4.36)	0.67
CD4 count	1.00 (1.00, 1.00)	0.45

CONCLUSIONS

- Our findings show a seemingly young age distribution of patients with CH in our cohort of PLWH, though we have not yet compared our cohort to a non-HIV population.
- Distinct from previously reported findings that *ASXL1* was the most commonly mutated gene, we did not identify any mutations in *ASXL1* in our cohort. Instead, other common CH genes such as *DNMT3A* and *TET2* represented the majority of mutations.
- Smoking, a commonly implicated risk factor for CH, was not significantly associated with presence of CH in our cohort.
- CD4 count, which has also been associated with presence of CH, was not significantly associated with CH in our cohort, nor was undetectable viral load at baseline.
- Multivariable analyses are ongoing with plans to investigate CH in patients with HIV as a predictor of cardiovascular disease, malignancy, and death.

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