HIV infection and plasma biomarkers as independent risk factors for radiographic emphysema

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Background

- COPD is a frequent comorbidity in HIV+ persons
- HIV is associated with chronic inflammation, immune activation and altered coagulation, which are linked to comorbidities and early mortality
- The association between HIV infection and emphysema remains incompletely understood

Research Questions

- Is HIV an independent risk factor for emphysema?
- Does the severity and distribution of emphysema differ by HIV status?
- Is emphysema associated with systemic biomarkers and markers of HIV severity?
  - Interleukin-6 (IL-6)—chronic inflammation
  - Soluble CD14 (sCD14)—immune activation
  - D-dimer—altered coagulation
  - Nadir CD4+ cell count—prior HIV severity

Methods

- Subjects: 114 HIV+ and 89 HIV- participants enrolled in 2009-2012 in Examinations of HIV Associated Lung Emphysema (EXHALE), pulmonary substudy of Veterans Aging Cohort Study
  - Block-matched by HIV and current smoking status
  - Lung disease other than COPD/asthma excluded
- Outcome: >10% emphysema on research chest CT scan
  - Semi-quantitative visual inspection by radiologist
  - Defined as > median global emphysema severity score
  - Distribution based on scores in each lung zone
- Exposures: HIV infection based on laboratory data
  - Nadir CD4 reflected lowest prior VA lab CD4
  - Biomarkers (plasma) measured at enrollment
- Covariates: Demographics, pulmonary, smoking and substance use history via questionnaires; HIV-related variables from VA lab/pharmacy data; COPD based on post-bronchodilator FEV1/FVC < lower limit of normal
- Analysis: Multivariable logistic regression models to determine association of risk, severity and distribution of emphysema with 1) HIV infection, 2) HIV severity and biomarker levels among those with HIV

Results

Table 1. Select baseline characteristics of participants

Characteristic	HIV+ *(n = 114)*	HIV- *(n = 89)*	*p*-value
Age (years), median (IQR)	55 (50 – 58)	52 (48 – 57)	0.07
COPD (post-BD FEV1/FVC <LLN), %	20	12	0.1
Cigarette smoking history			
Never smoker, %	16	20	0.7
Former smoker, %	22	24	0.7
Current smoker, %	62	56	0.7
Pack-years, median (IQR)	27 (12 – 41)	22 (11 – 34)	0.3
Marijuana (smoked) ever, %	85	72	0.04
Injection drug use ever, %	32	10	<0.001
Prior pneumonia based on ICD9 codes, %			
Bacterial community-acquired	20	3	<0.001
Mycobacterium tuberculosis	8	1	0.03

Table 2. Emphysema characteristics, markers of HIV severity and biomarkers

Characteristic	HIV+ *(n = 114)*	HIV- *(n = 89)*	*p*-value
Emphysema severity score, %			
0 None/negligible (0%)	40	46	
1 Trace (1 – 10%)	27	37	
2 Mild (11 – 25%)	19	8	0.01
3 Moderate (26 – 50%)	5	8	
4 Severe (51 – 75%)	9	1	
Emphysema distribution, %†			
Diffuse emphysema (all lung zones involved)	28	16	0.04
Upper lung zone	61	53	0.3
Middle lung zone	42	30	0.09
Lower lung zone	30	18	0.05
HIV-related variables			
Nadir CD4+ cell count <200/μL, %	61	--	--
Detectable HIV RNA (≥400 copies/mL), %	20	--	--
Antiretroviral therapy (ART) use, %	93	--	--
Serum biomarkers, median (IQR)			
IL-6 (pg/mL)	1.81 (1.28 – 3.43)	1.23 (0.94 – 2.07)	<0.001
sCD14 (ng/mL)	1671 (1472 – 2128)	1386 (1171 – 1569)	<0.001
D-dimer (μg/mL)	0.26 (0.17 – 0.47)	0.28 (0.17 – 0.42)	1.0

†percents do not add to 100% as individuals may have emphysema in >1 lung zone

Results

Table 3. HIV infection, high sCD14, nadir CD4 <200 associated with increased emphysema risk

Risk factor	Unadjusted OR [95% CI]	Adjusted OR [95% CI]
HIV+ and HIV-		
HIV infection	2.47 [1.25-4.87]	1.55 [0.71-3.41]
sCD14 >75th percentile	2.63 [1.32-5.21]	2.30 [1.02-5.19]
Pack-years*	1.34 [1.13-1.59]	1.39 [1.15-1.68]
Prior pneumonia	2.85 [1.34-6.07]	--
Restricted to HIV+		
Nadir CD4 <200	2.39 [1.02-5.62]	2.98 [1.14-7.81]
sCD14 >75th percentile	3.95 [1.20-12.9]	2.55 [1.04-6.22]
Pack-years*	1.24 [1.03-1.55]	1.29 [1.05-1.59]
Prior pneumonia	2.45 [1.04-5.74]	--

*increments of 10 pack-years

Limitations

- Temporal relationships between HIV infection, pneumonia, and emphysema not known
- Dichotomous outcome for % emphysema based upon median value given limited sample size in absence of clinically defined threshold

Conclusions

- HIV is an independent risk factor for radiographic emphysema (>10% on CT), adjusting for smoking
- HIV infection significantly associated with:
  - Greater emphysema severity
  - Increased likelihood of diffuse emphysema
- Among those with HIV, nadir CD4 <200 and high sCD14 significantly associated with emphysema

Implications

- Emphysema distribution and association with biomarkers may point toward potential vascular-related mechanisms linking emphysema with HIV
- Further investigation required to elucidate mechanisms and impact of emphysema on outcomes

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