CHEST Online Supplement

Increased Risk of Radiographic Emphysema in HIV Is Associated With Elevated Soluble CD14 and Nadir CD4

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e-Appendix 1.

METHODS

Study design and cohort

Examinations of HIV-Associated Lung Emphysema (EXHALE) is an observational, longitudinal study, enrolling Veterans Aging Cohort Study (VACS) participants from the Atlanta, Bronx, Houston and Los Angeles Veterans Affairs (VA) Medical Centers since 2009 [Emory University Institutional Review Board #CR5_IRB00005662, Bronx VA Medical Center Institutional Review Board #BRO-08-046, Institutional Review Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals #H-25605, and VA Greater Los Angeles Healthcare System #PCC 2013-020186, respectively as well as the University of Washington Institutional Review Board #37257]. This study was conducted in accordance with the amended Declaration of Helsinki. EXHALE is a dedicated pulmonary substudy of VACS. COPD and/or asthma diagnoses were not required for participation. However, individuals with clinical diagnoses of lung disease other than COPD and/or asthma or respiratory tract infections in the 4 weeks preceding baseline measurements were excluded.

Chest computed tomography (CT) scan examinations

All participants underwent chest CT scans at enrollment. Non-contrast CT scan images were acquired using a standard acquisition protocol with moderate-dose radiation (~3.5 mSv). Images were 1-1.25 mm in thickness and were obtained at 0.5-0.625 mm intervals. Scans from the lung apices to the bases were obtained at end inspiration breath-hold in the supine position, using 16 and 64 multi-detector CT scanners

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calibrated across centers using a standardized lung phantom. The lung phantom was sent to each site for scanning and standardization per research protocol.

Statistical analysis

We also evaluated ordinal logistic regression models and multinomial regression models using a multilevel outcome of no emphysema, 1-10% emphysema and >10% emphysema. As these models demonstrated similar results for risk factors associated with >10% emphysema and power was limited in some groups, we present only results of the logistic regression models for simplicity. Pearson chi-square test statistics were used to assess model goodness-of-fit. All analyses were performed using STATA 12.0 (Stata Corp., College Station, TX).

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e-Table 1. Baseline characteristics of HIV-infected participants by nadir CD4 cell count

	Nadir CD4 <200 ***n* = 69**	**Nadir CD4 ≥200** ***n* = 45**	***p*-value**
Age, median (IQR)	55 (50 – 58)	54 (49 – 58)	0.9
Male, %	99	96	0.6
Race/ethnicity, %			
Black	75	56	0.03
White	10	29	
Hispanic/other	15	15	
Cigarette smoking history			
Never smoker, %	15	18	0.4
Former smoker, %	18	27	0.4
Pack-years, median (IQR)	22 (15 – 36)	18 (5 – 48)	0.6
Current smoker, %	67	55	0.4
Pack-years, median (IQR)	22 (11 – 42)	32 (14 – 40)	0.5
Other substance abuse, ever, %			
Marijuana (smoked)	85	84	0.9
Alcohol	25	23	0.8
Injection drug use	32	31	0.9
COPD (FEV1/FVC <LLN), %	26	11	0.06
% predicted DLCO, median (IQR)	59.0 (52.6 – 74.1)	64.7 (55.3 – 78.8)	0.2
% predicted FEV1, median (IQR)	90.5 (80.6 – 103.4)	92.1 (82.9 – 103.1)	0.5
Prior pneumonia, %			
Bacterial community-acquired	23	16	0.3
Pneumocystis jiroveci	1	0	1.0
Mycobacterium tuberculosis	10	4	0.5
Emphysema severity, %			
None/negligible (0%)	30	53	
Trace (1-10%)	29	25	
Mild (11-25%)	21	18	0.07
Moderate (26-50%)	7	2	
Severe (51-75%)	13	2	
Very severe (>75%)	0	0	
>10% emphysema	41	22	0.04
Emphysema distribution, %*			
Diffuse emphysema	32	22	0.3
Upper lung zone	70	47	0.01
Middle lung zone	49	31	0.06
Lower lung zone	33	24	0.3
Emphysema type, %*			
Centrilobular	65	44	0.03
Paraseptal	35	31	0.7
Panlobular	3	2	1.0
Bullous	23	13	0.2
Serum biomarkers, median (IQR)			
IL-6 (pg/mL)	1.72 (1.20 – 3.12)	1.90 (1.38 – 3.43)	0.6
sCD14 (ng/mL)	1631 (1392 – 2122)	1877 (1547 – 2152)	0.1
D-dimer (μg/mL)	0.28 (0.20 – 0.50)	0.23 (0.17 – 0.42)	0.3

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HIV-related variables			
CD4 cell count (cells/μL), median (IQR)	355 (223 – 504)	531 (407 – 658)	<0.001
Nadir CD4 cell count (cells/ μL), median (IQR)	70 (23 – 125)	272 (234 – 349)	<0.001
Detectable HIV RNA (≥400 copies/mL)	25	13	0.2
ART use	94	91	0.5

*Percents do not add to 100% as individuals may have emphysema in more than one lung zone and more than one type of emphysema.

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e-Table 2. Baseline characteristics of HIV-infected participants by >10% emphysema

	>10% emphysema *n* = 38	**≤10% emphysema *n* = 76**	***p*-value**
Age, median (IQR)	57 (52 – 61)	53 (47 – 58)	0.01
Male, %	97	97	1.0
Race/ethnicity, %			
Black	71	66	0.08
White	24	14	
Hispanic/other	5	20	
Cigarette smoking history			
Never smoker, %	3	22	0.02
Former smoker, %	20	22	0.02
Pack-years, median (IQR)	41 (15 – 50)	17 (9 – 26)	0.1
Current smoker, %	77	56	0.02
Pack-years, median (IQR)	36 (12 – 49)	23 (11 – 37)	0.1
Other substance abuse, ever, %			
Marijuana (smoked)	94	80	0.09
Alcohol	22	25	0.8
Injection drug use	33	31	0.8
COPD (FEV1/FVC <LLN), %	42	9	<0.001
% predicted DLCO, median (IQR)	54.6 (44.5 – 64.2)	67.8 (57.2 – 78.6)	<0.001
% predicted FEV1, median (IQR)	87.5 (75.6 – 98.6)	92.6 (82.7 – 105.1)	0.06
Prior pneumonia, %			
Bacterial community-acquired	29	16	0.1
Pneumocystis jiroveci	0	1	1.0
Mycobacterium tuberculosis	13	5	0.2
Serum biomarkers, median (IQR)			
IL-6 (pg/mL)	1.79 (1.29 – 3.07)	1.82 (1.28 – 3.54)	0.8
sCD14 (ng/mL)	1883 (1521 – 2222)	1648 (1459 – 1982)	0.05
D-dimer (μg/mL)	0.27 (0.20 – 0.60)	0.26 (0.16 – 0.43)	0.2
HIV-related variables			
CD4 cell count (cells/μL), median (IQR)	384 (304 – 591)	447 (323 – 633)	0.3
CD4 cell count <200, %	21	11	0.2
Nadir CD4 cell count <200, %	74	54	0.04
Detectable HIV RNA (≥400 copies/mL)	24	18	0.6
ART use, %	92	93	1.0

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