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REGION

Interstitial lung abnormalities in people living with HIV and uninfected controls

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BACKGROUND

Chronic respiratory conditions may be more common in people living with HIV (PLWH) compared to uninfected controls. Specifically PLWH have more gas change abnormalities (1, 2) and fidings suggestive of restrictive impairment assesed by spirometry (3, 4). The underlying mechanisms are largely unknown but interstitial lung abnormalities (ILAs), and interstitial lung diseases (ILDs) in particular, may contribute to these observations. We assessed the spectrum of ILAs in PLWH and uninfected controls and determined factors associated with these abnormalities.

METHODS

Study population and outcome definitions

We performed a cross sectional study of inspiratory chest computed tomography (CT) scans obtained and reconstructed using a high resolution technique (5) in PLWH and uninfected controls from the Copenhagen Comorbidity in HIV Infection (COCOMO) Study and the Copenhagen General Population Study (CGPS), respectively. We defined the following four outcomes of increasing severity (6):

1) Any ILA: Any of the characteristics below

2) Equivocal for the presence of ILD: Focal ground-glass opacity (GGO), focal reticulation or patchy GGO<5% of the lung

3) Suspicious for the presence of ILD: Non-dependent GGO, non-dependent reticulation (>5% of the lung), diffuse centrilobular abnormality with GGO, honeycombing, traction bronchiectasis, non-emphysematous cysts, or architectural distortion

4) Definite ILD: Bilateral fibrosis in multiple lobes associated to honeycombing and traction bronchiectasis in a sub-pleural distribution

Statistical analysis

Logistic regression analyses were used to compute crude and adjusted odds ratios (ORs) to determine risk factors associated with the three former outcomes. Models were adjusted for age, sex, ethnicity, and cumulative smoking (pack-years). We also assessed whether HIV-associated factors were each associated these outcomes.

RESULTS

Clinical charactertistics of PLWH and uninfected controls are presented in Table 1. The spectrum of ILAs in these populations are depicted in Figure 1. Only one individual (63.2 years old male living with HIV) was categorized with definite ILD. Characteristics of PLWH according to the presence of ILAs, equicoval and suspicious for the presence of ILDs are presented in Table 2.

	PLWH (n=742)	Uninfected controls (n=470)	p-value
Age, mean (SD)	54.2 (9.1)	57.4 (8.8)	<0.001
Male, n (%)	648 (85.9)	386 (82.1)	0.09
Scandinavian, n (%)	563 (75.9)	429 (92.1)	<0.001
BMI (kg/m^2), mean (SD)	25.0 (3.8)	26.7 (3.6)	<0.001
Smoking status			<0.001
- Current smokers, n (%)	195 (26.3)	46 (9.8)	
- Ex-smokers, n (%)	288 (38.8)	206 (43.8)	
- Never smokers, n (%)	245 (33.0)	217 (46.2)	
Tobacco consumption in pack-years ‡, median [IQR]	19.5 [7.4-33.0]	18.0 [7.5-32.0]	0.44
$FEV_1/FVC<LLN$, n (%)	79 (10.7)	49 (10.6)	1.00
%FEV_1 predicted	89.8 (15.7)	97.5 (14.7)	<0.0001
%FVC predicted	92.4 (13.8)	101.4 (13.3)	<0.0001
Any ILA, n (%)	82 (10.9)	36 (7.7)	0.079
Equivocal for the presence of ILD	59 (7.8)	33 (7.0)	0.684
Suspicious for the presence of ILD	22 (2.9)	4 (0.9)	0.025

Table 1. Clinical characteristics. Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in one second, FVC, forced vital capacity; ILA, interstitial lung abnormality; ILD, interstitial lung disease; IQR, interquartile range; LLN, lower limit of normal; SD, standard deviation. ‡For current and ex-smokers. Cumulative smoking is defined as (average number of cigarettes per day/20) x number of years smoked).

	Without any ILA (n=672)	Equivocal for the presence of ILD (n=59)	Suspicious for the presence of ILD (n=22)	P-value
Mode of HIV transmission, n (%)				0.09
• MSM	476 (71.7)	35 (59.3)	17 (77.3)	
• Heterosexual	143 (21.5)	18 (30.5)	3 (10.6)	
• IDU	4 (0.6)	2 (3.4)	1 (4.5)	
• Other	41 (6.2)	4 (6.8)	1 (4.5)	
Current CD4, cells/mm^3 (SD)	711.3 (285.5)	686.6 (273.5)	774.6 (369.6)	0.47
CD4 nadir <200 cells/mm^3, n (%)	309 (46.7)	29 (50.0)	11 (52.4)	0.79
Current cART use, n (%)	661 (98.5)	59 (100)	22 (100)	0.55
VL suppression, n (%)	638 (95.5)	55 (93.2)	22 (100)	0.43
Previous AIDS event, n (%)	128 (19.0)	18 (30.5)	7 (31.8)	0.04
Detectable HCV RNA, n (%)	36 (5.4)	0 (0.0)	2 (9.1)	0.14
Previous PCP, n (%)	47 (7.0)	6 (10.2)	3 (13.6)	0.36
Previous TB, n (%)	14 (2.1)	3 (5.1)	0 (0)	0.25

Table 2. HIV characteristics according to interstitial lung abnormalities. Abbreviations: AIDS, acquired immune deficiency syndrome; cART, combination anti-retroviral therapy; HCV, hepatitis C virus; IDU, injection drug use; ILA, interstitial lung abnormality; ILD, interstitial lung disease MSM, men having sex with men; PCP, *Pneumocystis* pneumonia; TB, pulmonary tuberculosis; VL, viral load.

HIV-infection was independently associated with any ILA and with a finding suspicious for the presence of ILD but not with a finding equivocal for the presence of ILD (Table 3). We found no independent associations between any of the HIV related risk factors in Table 2 and the outcomes considered.

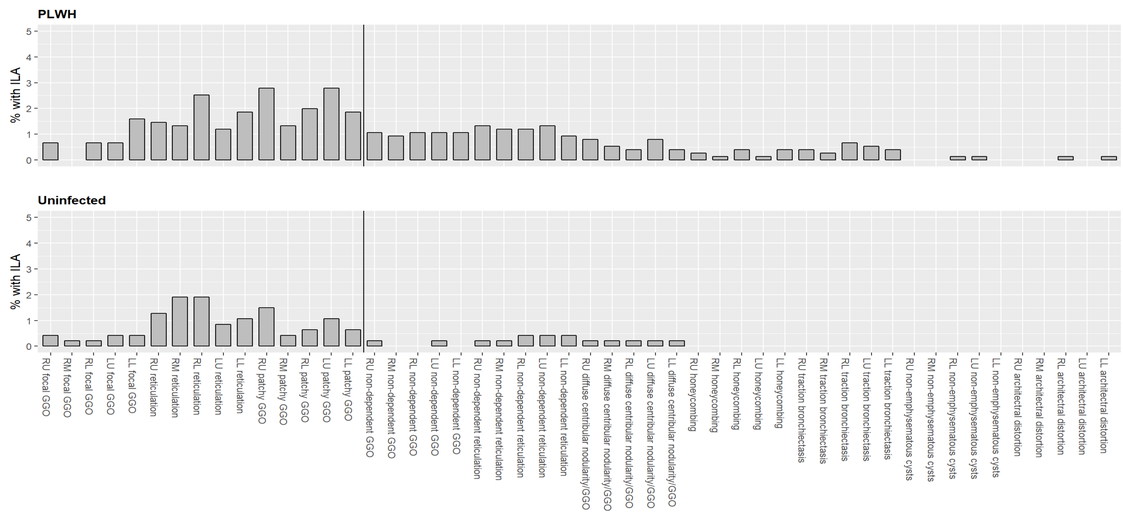

Figure 1. Spectrum of interstitial lung abnormalities in PLWH and uninfected controls.
The figure depicts the prevalence of specific interstitial lung abnormalities in PLWH and uninfected controls. The prevalence is depicted for both the left (upper, lower) and right lung lobes (upper, middle, lower). Vertical lines separate findings that were defined as equivocal (left side) and suspicious for interstitial lung disease (right side). Abbreviations: GGO, ground-glass opacity, LL, left lower lobe; LU, left upper lobe; PLWH, people living with HIV; RL, right lower lobe; RM, right middle lobe; RU, right upper lobe.

	OR (95%CI) for any ILA (n=118)	aOR‡ (95%CI) for any ILA (n=118)	P-value	OR (95%CI) for findings suspicious for ILD (n=26)	aOR‡ (95%CI) for findings suspicious for ILD (n=26)	P-value
HIV, yes vs. no	1.47 (0.98- 2.24)	1.82 (1.18-2.88)	<0.01	3.50 (1.33-12.03)	5.15 (1.72-22.2)	<0.01
Age, per decade	1.66 (1.36-2.04)	1.64 (1.32-2.05)	<0.0001	1.51 (1.00-2.27)	1.41 (0.90-2.20)	0.129
Cumulative smoking, per 10 pack-years	1.17 (1.07-1.29)	1.09 (0.99-1.20)	0.084	1.35 (1.14-1.58)	1.26 (1.06-1.48)	<0.01

Table 3. Multivariate table depicting associations between HIV status and any interstitial lung abnormality and a findings suspicious for the presence of interstitial lung disease
Abbreviations: ILA, interstitial lung abnormality; ILD, interstitial lung disease.

Mean %-forced vital capacity (FVC) was comparable in PLWH with and without any ILA (90.1% vs 92.6%, p=0.12), but %FVC in PLWH with a finding suspicious for the presence of ILD seemed to be slightly lower compared to PWH without any abnormalities (86.6% vs 92.6%, p=0.05).

Limitations

- No standardized methods for the detection of ILAs exists
- The recorded abnormalities are unspecific and may not be exclusively associated with ILD
- No concensus readings were performed and radiologist was unblinded to HIV status

CONCLUSIONS

- One tenth of PLWH have an ILA detected by chest CT
- We found a higher burden of ILAs and findings suspicious for the presence of ILD in PLWH compared to uninfected controls
- This was not explained by measures of prior immunedeficiency
- The impact of these abnormalities are uncertain but did not seem to be associated with major functional abnormalities

References: 1. Crothers K et al. J Acquir Immune Defic Syndr 2013; 64:271-8; **2.** Fitzpatrick ME et al. J Acquir Immune Defic Syndr 2013; 64:284-8; **3**. Drummond MD et al. AIDS 2015; 29: 1691-700; **4**. Verboeket SO et al. J Infect Dis 2019; 219: 1274-84; **5**. Ronit A et al. Eur Resp J 2018; 52: 1800296; **6.** Washko GR et al. Acad Radiol 2010; 17:48-53.
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