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REGION

HIV IS INDEPENDENTLY ASSOCIATED WITH HIGHER ALPHA-1 ANTITRYPSIN

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BACKGROUND

Alpha-1 antitrypsin (AAT) is the most abundant circulating serine protease inhibitor and its main function is to protect the lung against proteolytic damage[1]. Little is known about AAT in people living with HIV (PLWH), but in theory:

i) AAT may be associated with lower pulmonary function.
ii) as an inducer of HIV inhibition *in vitro,* AAT may be associated with immune status[2].
iii) as an acute phase reactant, AAT may be a novel biomarker for non-AIDS events[3].

We measured AAT in PLWH and in uninfected controls and studied associations with pulmonary function and CD4+ T-cell counts.

	PLWH (n=1011)	Controls (n=11962)
Characteristics		
Age, mean (SD)	50.7 (11.3)	52.7 (11.1)
Sex (male), n (%)	857 (84.8)	9745 (81.7)
Ancestry		
• Scandinavia, n (%)	722 (72.6)	10567 (89.3)
• Other European, n (%)	119 (12.0)	805 (6.8)
• Middle East, n (%)	18 (1.8)	369 (3.1)
• Other, n (%)	136 (13.7)	88 (0.7)
Smoking status		
• Current, n (%)	294 (29.1)	1526 (12.8)
• Former, n (%)	345 (34.1)	4562 (38.1)
• Never, n (%)	339 (33.5)	5688 (47.6)
Pulmonary function		
FEV_1-predicted, n (%)		
• FEV_1 ≥80 %	783 (78.5)	10566 (89.9)
• FEV_1 50-79 %	196 (19.6)	1080 (9.2)
• FEV_1 30-49 %	16 (1.6)	76 (0.6)
• < 30 %	3 (0.3)	37 (0.3)
FEV_1/FVC < LLN, n (%)		
• Normal	889 (89.3)	10487 (89.4)
• Obstructive	106 (10.7)	1246 (10.6)
FEV_1/FVC < 0.7 with FEV_1-predicted < 80 %, n (%)		
• Normal	903 (90.2)	11075 (94.2)
• Obstructive	98 (9.8)	678 (5.8)
HIV variables		
Current CD4 per µL, n (%)		
• >500	780 (77.8)	NA
• 350-500	144 (14.4)	NA
• 200-349	58 (5.8)	NA
• <200	20 (2.0)	NA
CD4 nadir <200 per µL, n (%)	405 (41.0)	NA
Current cART use, n (%)	994 (98.6)	NA
HIV RNA <50 copies/ml, n (%)	955 (95.1)	NA

Table 1: Clinical characteristics, pulmonary function and HIV related variables in people living with HIV and uninfected controls. NA, not applicable.

METHODS

Study population: Using data from the Copenhagen Comorbidity in HIV Infection (COCOMO) study[4] we assessed AAT concentrations in PLWH and age- and sex-matched uninfected controls. Low AAT was defined as below 1.0 g/L.
Pulmonary function analysis: Airflow limitation was assessed by spirometry and defined by forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) below the lower limit of normal (LLN) and by FEV_1/FVC<0.70 with FEV_1-predicted<80% (fixed).
Statistics: We assessed whether AAT to a greater extend contribute to low FEV_1-predicted in PLWH than in uninfected controls by studying the interaction between HIV status and AAT in a linear regression model adjusting for age, sex, ethnicity and cumulative smoking. Controlling for the same variables, we assessed whether AAT was associated with current CD4+ T-cell count or CD4+ nadir. Finally, we assessed whether HIV was independently associated with AAT controlling for the same variables and high-sensitivity CRP (hsCRP).

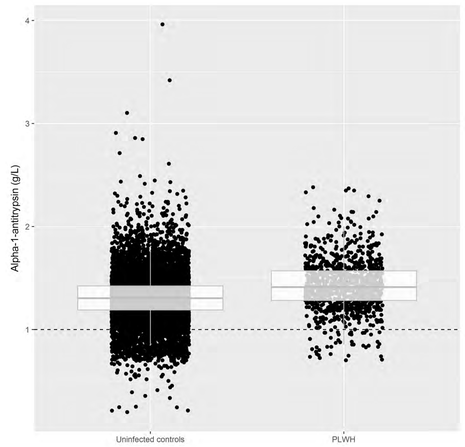


Figure 1: Alpha-1-antitrypsin concentrations in people living with HIV and in uninfected controls. Stipulated line indicating low alpha-1-antitrypsin concentration (<1.0 g/L).

	Crude β [95% CI]	p-value	Model A* β [95% CI]	p-value	Model A+ log(hsCRP) β [95% CI]	p-value
HIV (yes vs. no),	0.12 [0.10; 0.13]	<0.0001	0.11 [0.10; 0.13]	<0.001	0.10 [0.08; 0.11]	<0.001
Age, per decade	0.01 [0.01;0.01]	<0.0001	0.01 [0.00; 0.01]	<0.001	-0.00 [-0.01; 0.00]	0.106
Sex (male vs female)	-0.06[-0.07; -0.05]	<0.0001	-0.08 [-0.09;-0.07]	<0.001	-0.08 [-0.09;-0.07]	<0.0001
Cumulative smoking, per 10 pack years	0.03[0.02; 0.03]	<0.0001	0.03 [0.02; 0.03]	<0.001	0.02 [0.01; 0.02]	<0.0001

Table 2: Effect of HIV status on AAT concentration. *Model A: Adjusted for HIV, age, sex, ethnicity and cumulative smoking.

RESULTS

- AAT was measured in 1.011 PLWH and 11.962 uninfected controls with mean (SD) age of 52.7 (11.5) and predominantly males (81.7%) (Table 1). PLWH had a higher median (interquartile range) AAT: 1.4 [95%CI: 1.3-1.6] vs. 1.3 [1.2-1-4], (p<0.0001) (Figure 1).
- A total of 4.2% [3.1-5.6] PLWH and 6.6% [6.2-7.1] uninfected controls had low levels of AAT (p<0.01).
- Low AAT were not more common in PLWH with airflow limitation assessed by LLN (p=0.57) or the fixed criterion (p=0.80) (Table 3). The effect of AAT on FEV_1-predicted was similar in PLWH and uninfected controls (p-interaction=0.66).
- AAT concentrations (per 1 g/L) did not affect current CD4+ T-cell count (adjusted β=12.2 [-86.2-61.5], p=0.74) or CD4+ nadir (adjusted β= 6.7 [-38.9-52.2], p=0.77).
- HIV status was independently associated with higher AAT concentration adjusted β (0.10 [0.08; 0.11], p<0.001]) (Table 2).

	PLWH (n=1011)	Controls (n=11962)	p-value
Overall			
ATT concentration (g/L), median (IQR)	1.4 [1.3 – 1.6]	1.3 [1.2 – 1.4]	<0.0001*
Low AAT (<1.0 (g/L)), n (%)	42 (4.2)	792 (6.6)	<0.01*
Prevalence of low AAT according to airflow limitation			
• FEV_1/FVC < LLN, n (%)	3 (2.8)	56 (4.5)	0.58*
• FEV_1/FVC < 0.7 with FEV_1-predicted<80%, n (%)	5 (5.1)	42 (6.2)	0.80*
Prevalence of low AAT according to CD4 T-cell counts			
Current CD4+ cells per µL, n (%)			
• >500	37 (3.7)	NA	0.80†
• 350-500	1 (0.1)	NA	
• 200-349	4 (0.4)	NA	
• <200	0 (0)	NA	
CD4+ nadir			
• >200 cells per µL, n (%)	20 (2.0)	NA	0.23†
• <200 per µL, n (%)	21 (2.1)	NA	

Table 3: AAT concentration and prevalence of low AAT (<1.0 g/L) according to pulmonary function and CD4+ T-cell count in PLWH and uninfected controls. *Comparing PLWH with uninfected controls. † Comparing different groups of CD4+ T-cell counts in PLWH.

CONCLUSION

- AAT did not explain the excess pulmonary morbidity previously observed in PLWH.
- AAT was not associated with immunological status.
- HIV was independendtly associated with higher concentratoin of AAT and may be an interesting biomarker for non-AIDS events.

References: 1. Green CM et al. Nature Rev Dis Prim, 2016; 2. Münch et al. Cell, 2007; 3. Gabay C et al. NEJM, 1999. 4. Ronit A et al. Thorax, 2018.

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