

Is there a difference in the frequency or severity of acute respiratory illness between HIV positive and negative individuals?

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Background: A growing prevalence of chronic non-communicable respiratory illness is recognised among people living with HIV (PLWH).¹ Mechanisms underlying this are unclear: one possible cause could be a greater incidence and/or severity of acute respiratory illness despite antiretroviral therapy. We therefore sought to evaluate whether the frequency or severity of acute respiratory illness differed by HIV status now that most PLWH are using antiretroviral therapy (ART).

Methods: In this prospective observational cohort study, PLWH and age, gender and tobacco smoking matched HIV negative participants were followed for 12 months with weekly documentation of any acute respiratory illness using standardised illness definitions.

We assessed severity of illness using a self-reported scale asking about 9 different symptoms and impacts, each scored out of 6 points, where a higher score corresponded to more severe symptoms. Participants recorded daily diaries during acute illnesses detailing symptoms and treatment.

To assess the relationship between participant baseline characteristics and severity of symptoms during acute respiratory illness, participant symptom scores were log-transformed and analysed using linear regression models.

Results:

Recruitment and participant characteristics

In total, 136 HIV positive and 73 HIV negative participants provided longitudinal data (**Table 1**). Mean (SD) ages were 50 (11) and 52 (8) years; and 78% and 75% were male. The median (IQR) CD4 count for PLWH was 686 (456-848) cells/ μ L – all used ART during the study (87% had a baseline HIV plasma load <40 copies/ml). When free from acute respiratory illness, respiratory symptoms were more prevalent in HIV positive than negative participants, with median (IQR) St George's Respiratory Questionnaire (SGRQ) Total scores of 13 (6-29) and 6 (2-9) respectively ($p < 0.001$).

Incidence of acute respiratory illness

The frequency of acute respiratory illness did not differ with HIV status: incidence rate ratio (IRR) 0.87, (95% CI 0.70-1.08), $p = 0.22$.

Severity of symptoms

When acute respiratory illnesses occurred, PLWH reported more severe symptoms (fold-change in symptom score 1.61 (1.28-2.02), $p < 0.001$) (**Figure 1**). Higher baseline SGRQ scores were associated with greater symptom scores during acute respiratory illness; however, after adjustment in a multivariable model, PLWH still had higher symptom scores (**Table 2**)

Treatment and healthcare utilisation

HIV positive participants were more likely to seek advice from a healthcare professional during acute respiratory illness (42% vs 14%, $p = 0.003$) and more likely to seek hospital outpatient assessment (for instance in an HIV ambulatory care service) 32% vs 9%, odds ratio 4.73 (1.91-11.69), $p = 0.001$. There was no significant difference in the proportion of illnesses for which participants took non-prescription medications (59% vs 54%); HIV positive participants took antibiotics during a numerically greater proportion of illnesses (22% vs 11.5%), but this difference was not statistically significant (OR (95% CI) 2.11 (0.75-5.94), $p = 0.16$).

	HIV Positive N=136	HIV Negative N=73	p value
Gender			0.67*
Male	30 (22%)	18 (25%)	
Female	106 (78%)	55 (75%)	
Age, years, mean (SD)	50 (11)	52 (8)	0.11**
Immunisations (self-report)			
Influenza (last 12 months)	90 (66%)	21 (29%)	<0.01*
Pneumococcal (ever)	50 (37%)	9 (12%)	<0.01*
Comorbid conditions (self-report)			
Asthma	22 (16%)	7 (10%)	0.21 ^Δ
COPD	3 (2%)	1 (1%)	0.56 ^Δ
Heart disease	5 (4%)	2 (3%)	1 ^Δ
Previous history of respiratory opportunistic infection (HIV positive participants only)	9 (7%) ^{##}	---	---
Use of inhaled medications			
Any inhaled medication	25 (19%)	5 (7%)	0.07 ^Δ
Inhaled corticosteroids	13 (10%)	1 (1%)	0.04 ^Δ
Tobacco smoking			
Current smoker, n (%)	39 (29%)	12 (16%)	0.08*
Ex-smoker, n (%)	46 (34%)	34 (47%)	
Never smoker, n (%)	41 (37%)	27 (37%)	
Baseline St George's Respiratory Questionnaire scores			
Symptoms, median (IQR)	30 (8-45)	11 (0-28)	<0.001 [†]
Activity, median (IQR)	18 (6-36)	6 (0-12)	<0.001 [†]
Impacts, median (IQR)	4 (0-16)	0 (0-2)	<0.001 [†]
Total score, median (IQR)	13 (6-29)	6 (2-9)	<0.001 [†]
Spirometry*			
FEV1, L, mean (SD)	3.22 (0.78)	3.53 (0.73)	0.01-
FEV1 % predicted, mean (SD)	91% (14%)	97% (11%)	0.005-
FVC, L, % predicted, mean (SD)	4.16 (1.01)	4.55 (0.98)	0.02-
FVC % predicted, mean (SD)	93 (14%)	99% (12%)	0.02-
Spirometry interpretation			
Airflow obstruction, n%	13 (13%)	5 (8%)	0.004 ^Δ
Restriction, n%	18 (19%)	2 (3%)	
Normal spirometry n%	65 (68%)	54 (88%)	

* Chi squared test, ** t-test # Mann Whitney Test, ^Δ Fisher's exact test [†] calculated for smokers and ex-smokers only * 96 HIV positive and 61 HIV negative participants had spirometry results meeting ATS/ERS quality criteria ## consisting of Pneumocystis jirovecii pneumonia (7 cases) tuberculosis (1 case) non-tuberculous mycobacterial infection (1 case)

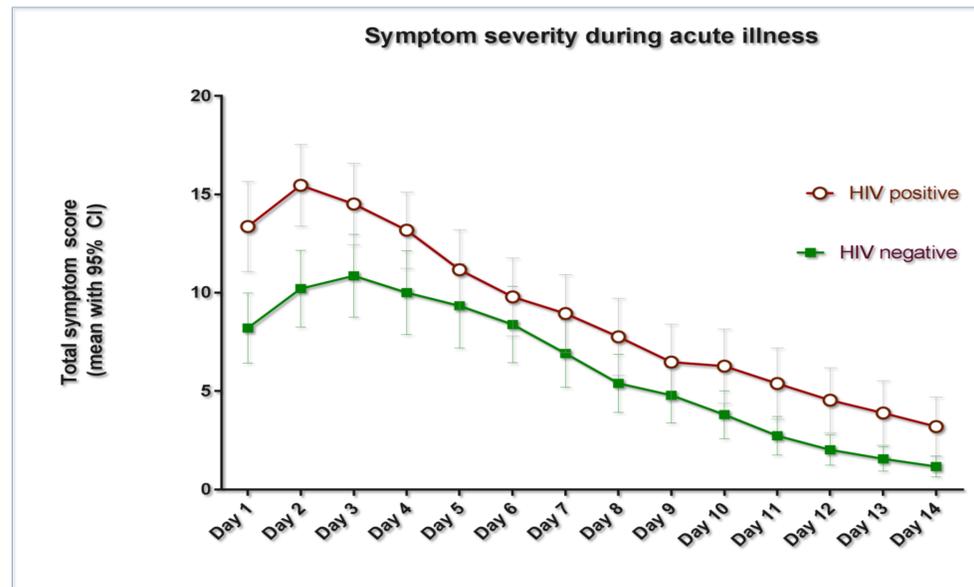


Table 2: Relationship between participant baseline characteristics and symptom severity at time of reporting acute respiratory illness, log-scale linear regression analyses

Characteristic	Median (IQR) symptom score [#]	Univariable analysis		Multivariable analysis	
		Fold-change in total symptom score*	P value [#]	Fold-change in total symptom score	P value**
HIV Status					
HIV Positive	14 (8-23)	1.61 (1.28-2.02)	<0.001	1.50 (1.14-1.97)	0.004
HIV Negative	9 (5-14)	1		1	
Gender					
Female	13 (7-22)	1.08 (0.77-1.66)	0.65	1.30 (0.92-1.83)	0.13
Male	11 (6-20)	1		1	
Spirometry					
Restrictive	12 (6-23)	1.00 (0.66-1.51)	0.99	0.96 (0.69-1.35)	0.82
Obstructive	20 (10-23)	1.51 (1.10-2.07)	0.01	1.16 (0.80-1.67)	0.51
Normal	11 (6-19)	1		1	
Recreational drugs, past 3 months					
Yes	15 (8-21)	1.34 (1.07-1.67)	0.01	1.27 (0.95-1.72)	0.11
No	11 (6-20)	1		1	
Baseline St Georges Respiratory Questionnaire score					
>20	14 (9-23)	1.68 (1.30-2.18)	<0.001	1.42 (1.11-1.83)	0.01
10-20	14 (8-21)	1.48 (1.14-1.93)	0.004	1.43 (1.05-1.96)	0.02
<10	9 (4-18)	1		1	
Tobacco smoking					
Current smoker	11 (1-21)	1.12 (0.83-1.51)	0.47	0.91 (0.63-1.33)	0.63
Ex-smoker	11 (5-20)	0.92 (0.70-1.02)	0.54	1.06 (0.81-1.38)	0.68
Never smoker	12 (6-19)	1		1	

#Univariable log-scale linear regression analysis ** multivariable log-scale linear regression including all factors with data in this column

Conclusions: Although HIV suppression reduces the frequency of acute respiratory illness to background levels, when these illnesses occur they are associated with more severe symptoms and greater healthcare utilisation. This is seen most often in PLWH with chronic respiratory symptoms – providing an opportunity to target interventions such as immunisations and smoking cessation that may improve patient outcome.

References

1. Drummond MB, Kirk GD. HIV-associated obstructive lung diseases: insights and implications for the clinician. *Lancet Respir Med.* 2014 Jul;2(7):583-92.

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