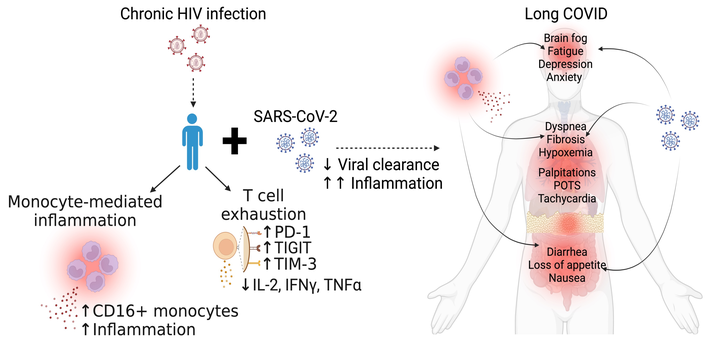
Integrated Approach to Long COVID Immune Signature Identification in People with and Without HIV

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BACKGROUND

- 10-20% of those infected with SARS-CoV-2 develop post-acute sequalae known as Long COVID
- Despite effective antiretroviral therapy (ART), people with HIV (PWH) experience persistent immune activation and inflammation, which may influence their risk for developing Long COVID



Proposed mechanism for how chronic HIV infection influences Long COVID pathogenesis

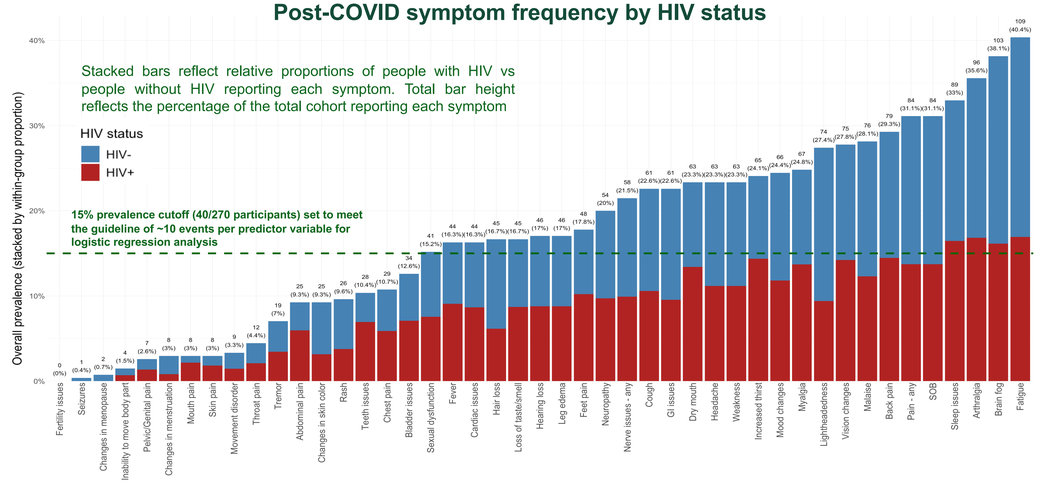
How does <u>chronic HIV</u> and <u>obesity</u> impact the <u>clinical manifestations</u> of <u>long COVID?</u>

METHODS

Surveys and blood samples were collected from PWH (n=73) and PWOH (n=197) a median of 928 days [IQR 724-1147] after initial COVID-19 infection. Of 45 reported symptoms, 28 occurring in ≥15% of participants were analyzed. Logistic regression adjusted for race, sex, and acute COVID severity was used to evaluate demographic features associated with post-COVID symptoms (false discovery rate 5%). Long COVID was defined as 1) self-reporting ≥ 1 new symptom post-COVID plus at least one of the following: A) self-reported moderate-extreme symptom interference in the last month, B) RECOVER 2023/2024 Long COVID Research Index met; or 2) self-reporting > 5 new symptoms post-COVID.

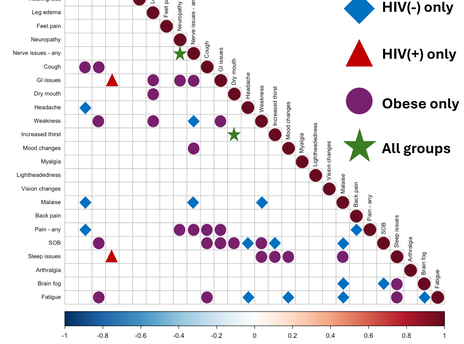
	HIV(-) (n=197)	HIV(+) (n=73)	p value
Age (median, IQR)	52 (40-61)	51 (40-60)	0.49
BMI (median, IQR)	33.24 (27.31-39.45)	31.47 (26.21-35.81)	0.12
Obese (BMI > 30)	122 (61.9%)	42 (57.5%)	0.58
Race			**0.03***
Black	89 (45.2%)	46 (63%)	
White	98 (49.7%)	24 (32.9%)	
Other	10 (5.1%)	3 (4.1%)	
Sex			**0.0001***
Male	62 (31.5%)	48 (65.8%)	
Female	135 (68.5%)	25 (34.2%)	
Tobacco use	26 (13.2%)	20 (27.4%)	**0.006***
Pre-COVID Comorbidities			
Diabetes	47 (23.9%)	16 (21.9%)	0.74
Renal disease	25 (12.7%)	13 (17.8%)	0.28
Hypertension	92 (46.7%)	47 (64.4%)	**0.01***
Pulmonary disease	38 (19.3%)	18 (24.7%)	0.33
1st COVID infection			
Vaccinated prior to first infection	105 (53.3%)	67 (91.8%)	**0.0001***
Hospitalized	94 (47.8%)	10 (13.7%)	**0.0001***
Post-COVID			
New post-COVID symptoms (median, IQR)	5 (1-13)	4 (1-12)	0.70
At least 1 new symptom post-COVID	159 (80.7%)	61 (83.6%)	0.59
ICD code for LC in chart	73 (37.1%)	7 (9.6%)	**0.0001***
Long COVID definition met	114 (57.9%)	39 (53.4%)	0.51
HIV-specific features			
Virally supressed		73 (100%)	
Years with HIV		20 (5-39)	
Prior AIDS		30 (41.1%)	
CD4 (median, IQR)			
Count		740 (554-884)	
Percent		37 (28-42)	
ART regimen			
NRTI		62 (84.9%)	
NNRTI		12 (16.4%)	
INSTI		70 (95.9%)	
PI/booster		10 (13.7%)	

Post-COVID symptom frequency by HIV status



HIV & Obesity status impact post-COVID symptom co-occurrence

Symptom pairs found to co-occur at significant frequencies that are shared between HIV and/or obesity groups



Significant symptom pair seen in:

- HIV(-) only
- HIV(+) only
- Obese only
- All groups

Symptom pairs seen in PWOH, regardless of obesity status

Brain fog	Malaise
Brain fog	SOB
Fatigue	Brain fog
Fatigue	Headache
Fatigue	Malaise
Fatigue	Mood changes
Headache	Fever
Malaise	Fever
Malaise	Nerve issues - any
Malaise	Weakness
Pain - any	Back pain
Pain - any	Fever
SOB	Headache
SOB	Increased thirst
SOB	Malaise
Weakness	Nerve issues - any

Symptom pairs seen in all individuals, regardless of HIV or obesity status

Increased thirst	Dry mouth
Nerve issues - any	Neuropathy

Symptom pairs seen in PWH, regardless of obesity status

GI issues	Hair loss
Sleep issues	Hair loss

Summary of shared symptom pairs by group

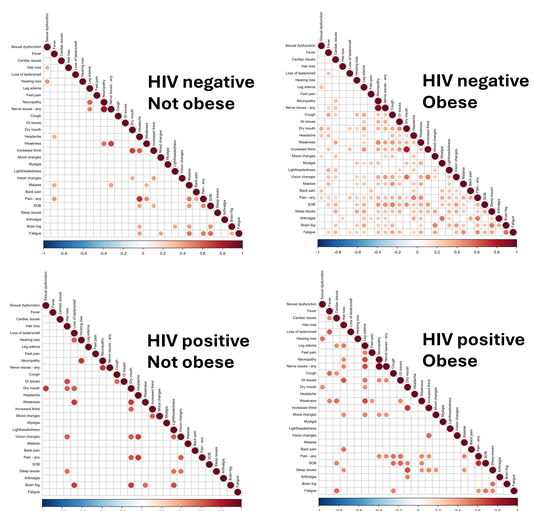
Symptom pairs seen in individuals with obesity, regardless of HIV status

Brain fog	Sleep issues
Cough	Cardiac issues
Cough	Fever
Dry mouth	Leg edema
Fatigue	Cardiac issues
Fatigue	Cough
Fatigue	Sleep issues
GI issues	Leg edema
GI issues	Nerve issues - any
GI issues	Neuropathy
Loss of taste/smell	Fever
Mood changes	Nerve issues - any
Pain - any	Cough
Pain - any	GI issues
Pain - any	Nerve issues - any
Pain - any	Neuropathy
Sleep issues	Increased thirst
Sleep issues	Malaise
Sleep issues	Mood changes
Sleep issues	Weakness
SOB	Cardiac issues
SOB	Cough
SOB	Dry mouth
SOB	GI issues
SOB	Weakness
Weakness	Cardiac issues
Weakness	GI issues
Weakness	Leg edema

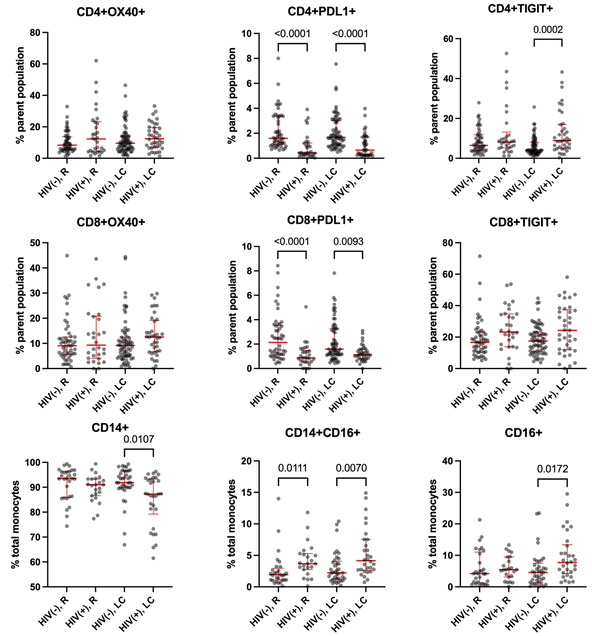
Heatmaps were generated to compare symptom co-occurrence by HIV and obesity status. **Participants with at least one new symptom post-COVID were included** in the analysis. Symptom absence/presence was recorded as a binary 0/1, meaning that correlation values approaching 1 indicate that many individuals in that group have the same co-occurring symptom pair(s). Shared significant symptom pairs are shown in the tables below. Obesity defined as a BMI ≥ 30. Correlation values only shown if p ≤ 0.05 after Benjamini-Hochberg correction for multiple comparisons.

- Regardless of HIV status…
  - Obesity was associated with a greater number of significantly correlated symptom pairs
    - PWH without obesity: 26 vs. PWH with obesity: 57; PWOH without obesity: 34 vs. PWOH with obesity: 190
  - PWH and PWOH with obesity shared 28 symptom pairs, largely defined by 1) sleep issues, 2) GI issues, 3) weakness, 4) dyspnea, and 5) cough
  - There were no shared symptom pairs between PWH and PWOH without obesity
- Regardless of obesity status…
  - PWH with and without obesity shared 2 symptom pairs, both of which included hair loss
  - PWOH with and without obesity shared 16 symptom pairs, largely defined by 1) malaise, 2) fatigue, and 3) dyspnea

Symptom co-occurrence heatmaps stratified by HIV and obesity status



Peripheral immune responses are driven by HIV status



(Top) Frequencies of CD4+ T cells expressing activation markers OX40 and PDL1 and exhaustion marker TIGIT. (Middle) Frequencies of CD8+ T cells expressing activation markers OX40 and PDL1 and exhaustion marker TIGIT. (Bottom) Frequencies of classical (CD14+), intermediate (CD14+CD16+), and nonclassical (CD16+) monocytes. R – Recovered from acute COVID-19. LC – Long COVID. HIV(-) – People without HIV. HIV(+) – people with HIV. Differences in T cell marker expression and monocyte subset frequencies were analyzed via Kruskal-Wallis with post-hoc Dunn's

Age, obesity, & immune-driven associations of post-COVID symptoms

Significant Odds Ratios Post-FDR Correction					
Odds ratio	95% CI Lower	95% CI Upper	Symptom	Feature	Adjusted p value
1.05	1.02	1.07	Arthralgia	Age	0.001
1.14	1.05	1.24	Malaise	CD16+ monocytes	0.018
0.91	0.85	0.96	Malaise	CD14+ monocytes	0.018
0.55	0.37	0.78	Malaise	CD4+PDL1+ T cells	0.018
2.83	1.55	5.39	SOB	Obesity	0.027
1.06	1.02	1.10	Leg edema	BMI	0.032

CONCLUSIONS

- Underdiagnosis of Long COVID, particularly among PWH, highlights an important gap in clinical recognition
- Symptom co-occurrence varied by HIV and obesity status, demonstrating a potential role of host metabolic and inflammatory status on Long COVID clinical presentations
- Elevated CD16+ nonclassical monocytes were associated with new onset malaise post-COVID, suggesting that host inflammatory status influences Long COVID clinical presentations
- **Future work integrating immunologic, metabolic, and clinical datasets is needed to delineate the shared and distinct mechanisms driving Long COVID in the setting of chronic inflammatory conditions**

NIH National Institute of Allergy and Infectious Diseases
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