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Assessing the burden of Long-Covid in Persons with HIV using the RECOVER Research Index

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Assessing the burden of Long-Covid in Persons with HIV using the RECOVER Research Index

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B.S., Georgia Tech, 2019

MD, Emory University, 2025

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Abstract

Assessing the burden of Long-Covid in Persons with HIV using the RECOVER Research Index

Some individuals recovering from COVID-19 experience persistent symptoms after the initial infection, a condition commonly referred to as Long Covid (LC). Persons with HIV (PWH), because of their immune dysregulation, are speculated to have an increased risk of LC. However, existing data are sparse and conflicting due to inconsistencies in the definition of LC. In this study, we used the RECOVER Research Index (RRI)[22] to assess the burden and pattern of LC presentation in PLWH relative to persons without HIV (PWoH) who had a history of COVID-19 in the MACS/WIHS Combined Cohort Study (MWCCS).

We employed a descriptive study design, including MWCCS participants who self-reported a positive COVID-19 test between April 2020 and November 2023. Participants who completed the prospectively administered MWCCS COVID-19 survey, detailing persistent symptoms occurring between 30 and 365 days after COVID-19 infection, were included. LC was defined using the RRI, which weights 12 common LC symptoms according to strongest association with LC in the RECOVER cohort and sums the weights for a total score. Participants with total scores >=12 met criteria for LC. Among those with LC, we further characterized LC symptom-type by HIV status, sex, and COVID-19 vaccination status using chi-square tests.

Of 4,970 MWCCS participants, 1,616 (33%) reported a positive COVID test, 153 (10%) of whom met RRI criteria for LC. Among persons with LC, half were female, 63% were PWH, 37% were persons without HIV, and most (93%) had received at least 1 dose of COVID vaccine at time of study. Overall, the most common LC symptoms were post-exertional malaise (93%), chronic cough (94%), and loss of smell/taste (88%), while the least common LC symptoms were brain fog (28%), dizziness (19%), and

palpitations (13%). There was no significant difference in LC symptom-type by HIV status. Neither sex nor vaccination status had measurable impact on LC prevalence or symptom-type in the study population.

Using the highly specific yet conservative RRI to define LC, PWH were similarly as likely as PWoH to develop LC after an acute COVID-19 infection with similar symptomatology. Our study is limited by the relatively small number of individuals with LC.

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BACKGROUND

The World Health Organization (WHO) estimates that there have been over 700 million reported cases of COVID-19[1]. Research suggests that more than half of individuals who are acutely infected by SARS-CoV-2 experience lingering symptoms for weeks, months, or even years following the initial infection[7]. The most common symptoms include fatigue, headache, cognitive dysfunction, and dizziness but symptomatology varies widely[24]. This constellation of symptoms has been described as Long COVID (LC)[24]. Certain populations are presumed to be vulnerable to developing LC, and among them are immunocompromised individuals including people with HIV (PWH). Emerging evidence suggests that PWH experience more severe acute SARS-CoV-2 infections, higher prevalence of adverse social determinants of health, chronic inflammation, and mitochondrial toxicities induced by antiretroviral therapy (ART) all of which may increase risk for LC[8,18,26]. Despite the concerns for heightened risk of LC in PWH, there remains an absence of information regarding the extent of LC burden in this population. With the global number of PWH estimated at 39 million in 2022[10], it is imperative to explore the intersection of LC prevalence and HIV infection due to the significant public health implications posed by both conditions.

Numerous systematic reviews and meta-analyses have been conducted to evaluate the prevalence of LC in the general population. Current estimates of LC prevalence vary widely, ranging from 14% to 51%, with significant uncertainty about the true prevalence[2]. The variability in prevalence estimation stems largely from the lack of a universally agreed-upon definition for LC. Defining LC has been particularly challenging given its clinical heterogeneity and substantial overlap with common chronic ailments,[3,24]. To address this challenge, researchers from the NIH-funded Researching COVID to Enhance Recovery (RECOVER) Consortium have recently proposed a 12-point scoring paradigm aimed at systematically defining LC, marking a crucial initial step towards establishing a framework for characterizing this condition[22] .The RECOVER Research Index (RRI) was generated from a prospective observational cohort

of COVID-infected and uninfected participants. A rule for identifying LC was derived. Symptoms differentiating infected and uninfected participants were identified using least absolute shrinkage and selection operator (LASSO) with balancing weights[22]. Each symptom was assigned a score based on the estimated coefficients and participants were assigned a total score by summing the symptom scores for each reported symptom[22]. Using 10-fold cross-validation, an optimal score threshold of **12** for LC was selected (**Figure A2**)[22]. Participants meeting the LC score threshold were classified as LC positive; others were classified as LC unspecified. Additionally, this study leveraged data from the nation's longest-running cohort study aimed at understanding the long-term effects of HIV in a diverse population known as the MACS/WIHS Combined Cohort Study (MWCCS)[9].

In this cross-sectional study we aim to provide an accurate estimate of the prevalence of LC among PWH while employing the RRI. We hypothesize that PWH with history of an acute COVID-19 infection will have an increased burden of LC compared to their at-risk, seronegative counterparts in the MWCCS. Additionally, we anticipate that demographic and clinical characteristics including biological sex, age and pre-existing comorbidities will impact the burden and the clinical manifestations of LC in this population. Notably, this study utilizes a standardized approach for defining LC, offering novel insights into the LC burden in PWH while leveraging the extensive, longitudinal data available through the MWCCS.

METHODS

Setting

The Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS) established in 1983 and 1993 respectively, merged in 2019 as the MWCCS. The MWCCS is designed to investigate the long-term effects of HIV infection among both gay and bisexual men (MACS) and cisgendered women (WIHS) across 13 research sites in the United States. Participant characteristics are detailed in the

paper authored by D'Souza et al[8]. Participants partake in biannual visits in which health information is garnered through administered surveys, biological specimen collection, and physical examination. The MWCCS study protocol was ethically reviewed and approved by the Institutional Review Board at each local site.

Study Design

We adopted a cross-sectional study design to evaluate the prevalence of LC, our primary outcome of interest among PWH and PWoH with HIV serostatus as our primary exposure. Secondary exposures evaluated include sex, age, CD4 count, Covid-19 vaccination status, hypertension, diabetes, and dyslipidemia. We utilized data collected through surveys administered by trained interviewers completed during the visit period between October 2022 and September 2023. If multiple surveys were completed during the visit period, we selected the most recent information available. Participants who did not have data available for outcomes assessed were excluded from our analysis.

The COVID-19 survey, developed by MWCCS investigators, aims to gather comprehensive information about persistent COVID-19 symptoms, testing history, disease severity. Over 15 common LC symptoms were assessed using yes/no questions, along with associated start dates. We utilized LC symptom presence in our determination of LC status utilizing the RRI created by Thaweethai et al[22]. The surveys used in our study are publicly accessible at the MWCCS website (https://statepi.jhsph.edu/mwccs/data-collection-forms/), under the V103 tab. Our study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[23].

Statistical Analyses

Baseline participants characteristics were stratified by HIV serostatus, and continuous variable differences were assessed with Wilcoxon rank-sum tests and categorical variable differences were assessed with Chi-

squared tests if individual cell counts >5 and Fishers exact test if individual cell counts <5.

Differences in LC symptoms used in the RRI (alterations in smell/taste, post exertional malaise, chronic cough, brain fog, palpitations, chest pain, fatigue, dizziness, gastrointestinal disruptions, abnormal movements, and hair loss) were stratified by HIV serostatus, age, sex and Covid-19 vaccination status were assessed using Chi-squared tests if individual cell counts were >5 and Fisher's exact test if individual cell counts were <5.

LC prevalence was stratified by HIV serostatus, age, Covid-19 vaccination status, and sex. Using this information, crude estimates of prevalence of LC was calculated among PWH and their seronegative counterparts. To assess the relationship between demographic and clinical factors and the likelihood of experiencing LC, we constructed a multivariable logistic regression model. The outcome variable was the presence or absence of LC, defined as >12 score using the RRI. These variables were chosen according to the a priori criteria of confounding. We employed a complete case analysis approach for missing data. Statistical significance was defined using 2 tailed tests at $p<0.05$. All analyses were conducted in 2023 using SAS version 9.4 (SAS Institute)

RESULTS

Of 4,970 MWCCS participants, 1,616 (33%) reported a positive COVID test, 153 (10%) of whom met RRI criteria for LC. Among persons with LC, half were female and most (93%) had received at least 1 dose of COVID vaccine at time of study. Among PWH who reported having COVID, 97/1010 (9.6%) had LC, compared to 56/606 (9.2%) of PWoH (p=0.89) (Table 2). In our cohort, HIV was well controlled with 95% of PWH on combination ART and virally suppressed with majority having CD4 counts greater than 500 cells/mm^3 (Table 1). Overall, the most common LC symptoms were post-exertional malaise (93%), chronic cough (94%), and loss of smell/taste (88%), while the least common

LC symptoms were brain fog (28%), dizziness (19%), and palpitations (13%). There was no significant difference in LC symptom-type by HIV status. Neither gender identity, age, nor Covid-19 vaccination status had measurable impact on LC prevalence in the study population (Tables 2-5). A logistic regression analysis was conducted to examine the relationship of HIV serostatus on the probability of developing LC. HIV serostatus was not significantly associated with LC status (OR: 1.119 CI: 0.725, 1.726) when controlling for race, biological sex, comorbidities (hypertension, diabetes, dyslipidemia), Covid-19 vaccination status, and age. Dyslipidemia status was significantly associated with LC status, holding all other predictor variables constant, the odds of ruling in LC was increased by 68% if a participant has dyslipidemia which was defined as LDL cholesterol levels >130 mg/dL and HDL cholesterol levels <40 mg/dL. No other variable was significantly associated with Long Covid status.

Table 1. Baseline Demographic and Clinical Characteristics of participants in the MWCCS, by Long Covid Status between October 2022- September 2023

Participant Characteristics	Participants with **Long Covid** n=**153** **n (%) or median (Q1,Q3)**	**P**articipants without **Long Covid** n= **1463** **n (%) or median (Q1,Q3)**	**Total** Participants n= **1616** **n (%) or median (Q1, Q3)**
Age (years)	58.0 (50.0, 66.0)	56.0 (45.0, 64.0)	56.0 (46.0, 64.0)
Race			
White	72 (47.1)	605 (41.5)	677 (42.1)
Black	65 (42.5)	670 (46.0)	735 (45.7)
Other	16 (10.5)	182 (12.5)	198 (12.3)
Ethnicity			
Hispanic	14 (9.2)	269 (18.4)	283 (17.5)
Non-Hispanic	139 (90.9)	1194 (81.6)	1333 (82.5)
Sex			
Male	71 (48.3)	734 (53.7)	805 (53.2)
Female	74 (50.3)	620 (45.4)	694 (45.8)
Covid -19 Vaccination Status			
>1 Booster	68 (44.4)	623 (43.2)	691 (43.3)
1 Booster	42 (27.5)	386 (26.8)	428 (26.8)
1 Dose	5 (3.3)	40 (2.8)	45 (2.8)
2 Doses	32 (20.9)	279 (19.4)	311 (19.5)
Unvaccinated	6 (3.9)	114 (7.9)	120 (7.5)
Comorbidities			
Hypertension	83 (61.5)	656 (51.7)	739 (52.6)

Dyslipidemia	101 (78.9)	821 (68.0)	922 (69.0)
Type 2 diabetes mellitus	38 (29.2)	304 (26.3)	342 (26.7)
ART status**			
No therapy	3 (3.1)	31 (3.5)	34 (3.5)
Mono/dual ART	2 (2.1)	13 (1.5)	14 (1.4)
Combination ART	92 (95.8)	841 (95.0)	933 (95.1)
HIV Viral Load**			
Suppressed (VL <200)	65 (92.9)	649 (95.6)	714 (95.3)
VL >= 200	5 (7.1)	30 (4.4)	35 (4.7)
CD4 cell count/ cells/mm^3**			
>500	57 (81.4)	524 (76.8)	581 (77.3)
<500	13 (18.6)	158 (23.2)	171 (22.7)

** Among HIV positive only (n=1010 overall; n=913 without long covid, n=97 with long covid)
* Chi-square or Wilcoxon rank sum test unless otherwise noted
†Fisher exact test
Column percents may not total to 100% due to rounding
MWCCS – MACS (Multicenter AIDS Cohort Study)/WIHS (Women's Interagency HIV Study) Combined Cohort Study

Table 2. Crude Prevalence of Long Covid and Median Long Covid score in MWCCS participants stratified by HIV serostatus

	Prevalence of participants with LC n/N (%)	**Median LC Score (Q1, Q3)**
PWH	97/1010 (9.6%)	13 (12, 17)
PWoH	56/606 (9.2%)	14 (12, 17.5)
p-value	0.89$^{\tau}$	0.406$^{\phi}$

LC= Long Covid, PLWH= People Living with HIV, PWoH= People without HIV;
$^{\tau}$Chi-Square test used to determine statistical significance
$^{\phi}$Wilcoxon rank-sum test used to determine statistical significance
p-value <0.05 was considered statistically significant

Table 3. Crude Prevalence of Long Covid in MWCCS participants stratified by gender identity

Gender Identity	**Prevalence of participants with LC n/N (%)**	**p-value**
Female	74/694 (11%)	0.4337
Male	71/805 (8.8%)	

LC= Long Covid,
Chi-Square test used to assess statistical significance

p-value <0.05 was considered statistically significant

Table 4. Crude prevalence of Long Covid as stratified by Covid-19 Vaccination Status of participants in the MWCCS

COVID-19 Vaccination Status	Participants with LC n/N (%)	Participants without LC n/N (%)	p-value
>1 Booster	68/153 (44.4%)	623/1463 (43.2%)	0.5113
1 Booster	42/153 (27.5%)	386/1463 (26.8%)	
1 Dose	5/153 (3.3%)	40/1463 (2.8%)	
2 Doses	32/153 (20.9%)	279/1463 (19.4%)	
Unvaccinated	6/153 (3.9%)	114/1463 (7.9%)	

LC= Long Covid
Chi-Square test used to assess statistical significance
p-value <0.05 was considered statistically significant
MWCCS = MACS (Multicenter AIDS Cohort Study)/WIHS (Women's Interagency HIV Study) Combined Cohort Study

Table 5. Median age of participants in the MWCCS as stratified by Long Covid status

	Participants with LC (Median [Q1, Q3])	Participants without LC (Median [Q1, Q3])	p-value
Age, years	58.0 (50.0, 66.0)	56.0 (45.0, 64.0)	0.0734

LC= Long Covid
Wilcoxon rank sum test used to assess statistical significance
P-value <0.05 considered significant
MWCCS = MACS (Multicenter AIDS Cohort Study)/WIHS (Women's Interagency HIV Study) Combined Cohort Study

DISCUSSION

In this cross-sectional study, we assess the burden and clinical features of LC among PWH and compare these findings to those in HIV-seronegative individuals. Our analysis suggests that PWH are similarly likely to develop LC following acute SARS-CoV-2 infection, with comparable symptomology to those without HIV. This study contributes to a growing body of literature exploring the relationship between HIV and LC, a particularly important topic given concerns that PWH may be more vulnerable to LC due

to underlying factors such as chronic immune activation, vascular impairment, and social determinants of health (SDoH) that disproportionately and adversely impact PWH [17,26]. Currently, there is no consensus on whether HIV is an independent risk factor for LC. Some studies report that HIV is associated with a 2.7-fold increase in the odds of developing LC[12], while others, find no such association and instead emphasize demographic and clinical characteristics such as female sex and comorbidities as more influential[14]. In line with existing literature, our study observed a higher LC prevalence among women; however, this difference did not reach statistical significance. Additionally, logistic regression analysis revealed that dyslipidemia was significantly associated with LC status, while hypertension and diabetes were not. The overlap in risk factors for both LC and HIV, particularly in the realm of SoDH, further complicates efforts to identify HIV-specific contributions to LC risk.

Regarding LC symptomatology and HIV serostatus, current data remain limited and conflicting. In our study, we found that the symptom profile of LC among PWH closely resembled that of individuals without HIV, with the most reported symptoms including post-exertional malaise, chronic cough, and loss of smell or taste. This finding contrasts with previous studies, which noted a predominance of neurological symptoms in PWH compared to more respiratory symptoms in HIV-negative individuals[16,18]. Conversely, other studies have suggested that PWH may experience lower prevalence and reduced frequency of LC symptoms over time relative to their HIV-negative counterparts[13]. Additionally, there are reports of persistent LC symptoms in PWH, emphasizing the need for future research to explore symptom trajectories and potential differences in long-term outcomes across HIV serostatus groups.

One possible explanation for the observed similar LC prevalence rates in PWH and PWoH is that our study population includes PWH with well-controlled HIV (Table 1). In line with prior studies, we found minimal differences in LC prevalence between groups, consistent with literature suggesting that HIV viral suppression may mitigate LC risk[25]. It remains important to understand whether LC prevalence differs between those with poorly controlled HIV and those without HIV, given that people with low CD4 counts

and detectable viral loads often experience greater immune dysregulation making them potentially more susceptible to LC following a SARS-CoV-2 infection[9]. Emerging evidence points to viral persistence as a potential mechanism driving LC[7]. If this is indeed a key factor, HIV serostatus alone may not influence LC risk potentially explaining the lack of significant association observed in our analysis.

This study is notable for use of a rigorous, standardized approach to define LC through the RRI to our knowledge, the first time this tool has been applied within a large cohort of people living with HIV. The methodology employed here highlights the RRI's utility in creating a more consistent clinical definition of LC, which remains a challenge in the field. Standardizing LC criteria is critical not only for improving diagnosis and clinical care, but also for informing public health strategies. By contributing to this effort, our study supports the broader goal of improving outcomes for those affected by LC.

This study has several limitations. First, we used a novel scoring tool RRI to define LC. While rigorous, the tool has not yet been fully validated. Additionally, our primary outcome measures LC symptoms and symptom duration were self-reported, introducing potential for recall bias. Symptom mapping was also incomplete. For example, symptoms such as decreased libido and excessive thirst, included in the RRI, were not captured in the MWCCS surveys. This led to a lower possible maximum score in our analysis. While we maintained a conservative rule-in threshold (score ≥12) in line with the original RRI publication, a few participants may have been misclassified.

To the authors' knowledge this is the first study to apply the RRI within one of the longest-running longitudinal cohorts examining the natural history of HIV. Our findings offer a standardized, systematic description of LC prevalence among PWH and contribute to efforts to better understand and address LC in populations that may be at increased risk.

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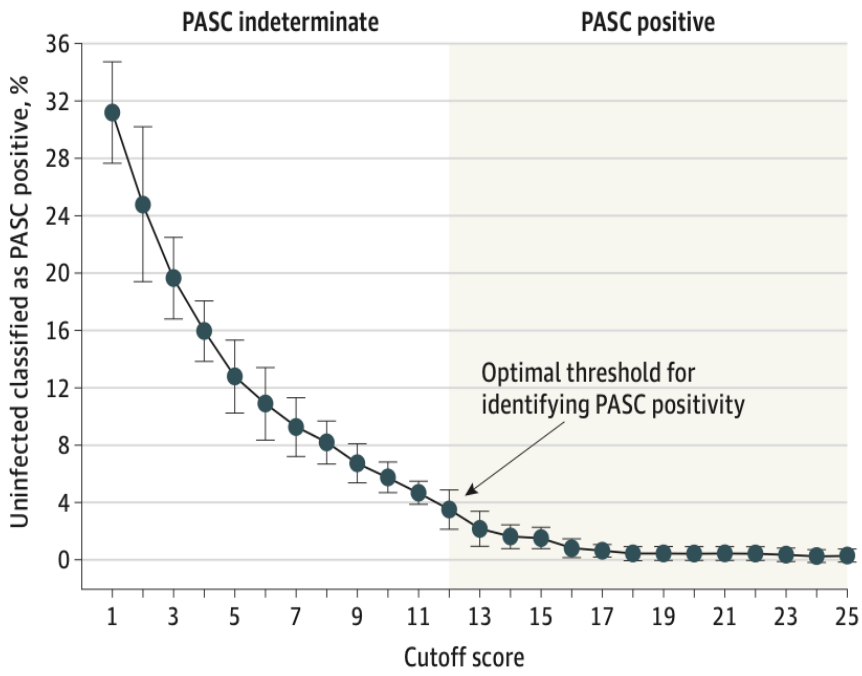
Appendix: Supplementary Figures

Figure A1. RECOVER Research Index: Model-Selected symptoms that define Long Covid and their corresponding scores[22]

Symptom	Log odds ratio	Score
Smell/taste	0.776	8
Postexertional malaise	0.674	7
Chronic cough	0.438	4
Brain fog[b]	0.325	3
Thirst	0.255	3
Palpitations	0.238	2
Chest pain[b]	0.233	2
Fatigue[b]	0.148	1
Sexual desire or capacity	0.126	1
Dizzines	0.121	1
Gastrointestinal	0.085	1
Abnormal movements	0.072	1
Hair loss	0.049	0

Least absolute shrinkage and selection operator was used to identify which symptoms were associated with Long Covid. This scoring system is the RECOVER (Researching COVID to Enhance Recovery – a National Institutes of Health research consortium tasked with understanding Long Covid) Research Index. Long Covid was operationalized using the RECOVER Research Index (2023) [11]

Figure A2. Threshold for ruling in Long Covid as determined by the RECOVER Research Index [22]



PASC (Post Acute Sequelae of SARS-CoV-2) is another name for Long COVID.
A threshold score of 12, based on cumulative symptom reporting, was used to determine Long COVID status, as illustrated in Figure A1.

Table A1. Mapping of Symptoms in the RECOVER Research Index and the MWCCS Long Covid Symptom Questionnaire

RRI Symptom	MWCCS Long Covid Symptom Questionnaire
Smell/Taste	f. Changes to any of your senses? – i. Loss of smell – ii. Loss of taste
Post-exertional malaise	d. Fatigue, lack of energy, body aches, or muscle weakness – ii. Body aches or weakness
Chronic Cough	a. Shortness of breath, chest pain or tightness, or a persistent cough – i. Cough
Brain Fog	k. Problems with your memory, concentrating on things, or finding the right word "brain fog."
Thirst*	No corresponding MWCCS question
Chest Pain	a. Shortness of breath, chest pain or tightness, or a persistent cough – ii. Chest pain or tightness
Fatigue	d. Fatigue, lack of energy, body aches, or muscle weakness – i. Fatigue or lack of energy

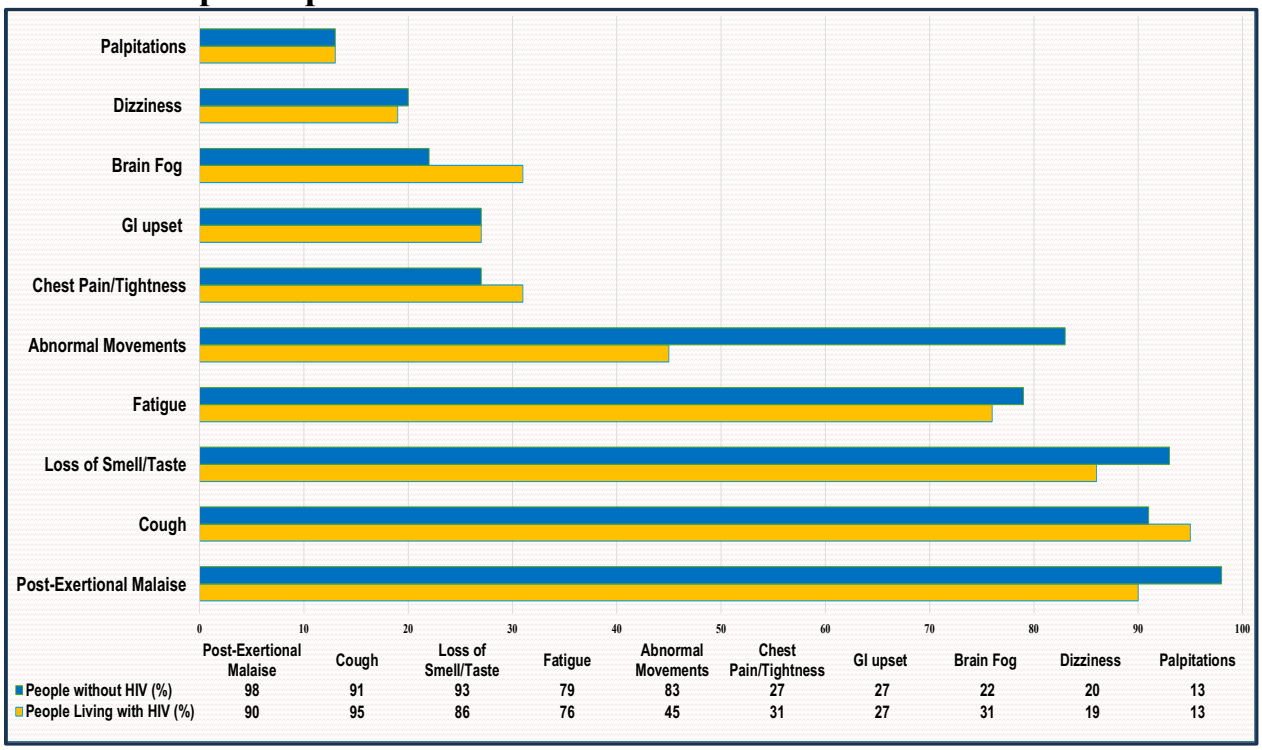
Sexual Desire/Capacity*	No corresponding MWCCS question
Dizziness	i. Loss of balance or difficulty walking, or feeling dizzy like the room is spinning – ii. Dizziness (room spinning)
Gastrointestinal	a. Abdominal Pain, Nausea or Diarrhea
Abnormal Movements	h. Numbness or tingling; tremors or involuntary muscle movements – ii. Tremors/involuntary movements (e.g., restless leg)
Hair Loss	n. Hair loss

RRI – RRI= RECOVER Research Index

MWCCS – MACS (Multicenter AIDS Cohort Study)/WIHS (Women's Interagency HIV Study) Combined Cohort Study

*Thirst with a corresponding score of 3 and Sexual Desire/Capacity with a corresponding score of 1 (Figure A1) was not captured in the MWCCS Long Covid questionnaire

Figure A3. Long Covid symptom distribution as stratified by HIV serostatus in MWCCS participants



MWCCS – MACS (Multicenter AIDS Cohort Study)/WIHS (Women's Interagency HIV Study) Combined Cohort Study

Table A2. Odd Ratio Estimates of Multivariable Logistic Regression Modeling Long Covid Status

Variable	Point Estimate	95% CI Lower	95% CI Upper
Hypertension			
Yes	1.344	0.862	2.098
No	REF	REF	REF
Dyslipidemia *			
Yes	1.685	1.038	2.736
No	REF	REF	REF
Diabetes			
Yes	0.932	0.569	1.527
No	REF	REF	REF
Covid-19 Vaccination Status			
>1 Booster	1.478	0.493	4.427
1 Booster	2.245	0.766	6.579
1 Dose	4.455	1.074	18.472
2 Doses	1.720	0.563	5.252
Unvaccinated	REF	REF	REF
Race			
Black	1.038	0.509	2.12
White	1.456	0.690	3.073
Other	REF	REF	REF
Age	1.005	0.986	1.026
Gender Identity			
Female	0.441	0.114	1.697
Male	0.383	0.103	1.431
Gender non- conforming	REF	REF	REF
HIV serostatus			
Seroprevalent	1.119	0.725	1.726
Seronegative			

REF- reference group
*significant result

Table A3. Type 3 Analysis of Effects from Multivariable Logistic Regression Modeling Long Covid Status

Effect	Degrees of Freedom	Wald Chi-Square	P-value
Hypertension	1	1.6991	0.1924
Dyslipidemia	1	4.4493	0.0349 *
Type 2 Diabetes	1	0.0784	0.7795
Covid-19 Vaccination Status	4	6.9677	0.1376
Race	2	1.713	0.4247
Age	1	0.2881	0.5914

Gender Identity	2	2.1619	0.3393
HIV Serostatus	1	0.2588	0.6109

p-value <0.05 considered statistically significant,
*significant result