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Authors

Durstenfeld, Matthew S

Peluso, Michael J

Spinelli, Matthew A

et al.

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ORIGINAL RESEARCH

Association of SARS-CoV-2 Infection and Cardiopulmonary Long COVID With Exercise Capacity and Chronotropic Incompetence Among People With HIV

Matthew S. Durstenfeld, MD, MAS; Michael J. Peluso, MD, MPhil, MHS, DTM&H; Matthew A. Spinelli, MD, MAS; Danny Li, PA-C; Rebecca Hoh, MS; Ahmed Chenna, PhD; Brandon Yee, BS; John Winslow, PhD; Christos Petropoulos, PhD; Monica Gandhi, MD, MPH; Timothy J. Henrich, MD, PhD; Mandar A. Aras, MD, PhD; Carlin S. Long, MD; Steven G. Deeks, MD; Priscilla Y. Hsue, MD

BACKGROUND: Postacute sequelae of COVID-19 (PASC) and HIV are both associated with reduced exercise capacity, but whether SARS-CoV-2 or PASC are associated with exercise capacity among people with HIV (PWH) is unknown. We hypothesized that PWH with PASC would have reduced exercise capacity from chronotropic incompetence.

METHODS AND RESULTS: We conducted cross-sectional cardiopulmonary exercise testing within a COVID recovery cohort that included PWH with and without prior SARS-CoV-2 infection and people without HIV with prior SARS-CoV-2 infection (controls). We evaluated associations of HIV, SARS-CoV-2, and PASC with exercise capacity (peak oxygen consumption) and chronotropy (adjusted heart rate reserve). We included 83 participants (median age, 54 years; 35% women; 37 PWH): 23 out of 37 (62%) PWH and all 46 controls had prior SARS-CoV-2 infection, and 11 out of 23 (48%) PWH and 28 out of 46 (61%) without HIV had PASC. Peak oxygen consumption was reduced among PWH versus controls (80% predicted versus 99%, P=0.005), a difference of 5.5 mL/kg per minute (95% CI, 2.7–8.2; P<0.001). Chronotropic incompetence was more prevalent among PWH (38% versus 11%, P=0.002), with lower adjusted heart rate reserve (60% versus 83%, P<0.0001) versus controls. Among PWH, SARS-CoV-2 coinfection and PASC were not associated with exercise capacity. Chronotropic incompetence was more common among PWH with PASC: 7 out of 11 (64%) with PASC versus 7 out of 26 (27%) without PASC (P=0.04).

CONCLUSIONS: Exercise capacity and chronotropy are lower among PWH compared with individuals with SARS-CoV-2 infection without HIV. Among PWH, SARS-CoV-2 infection and PASC were not strongly associated with reduced exercise capacity. Chronotropic incompetence may be a common underrecognized mechanism of exercise intolerance among PWH, especially those with cardiopulmonary PASC.

Key Words: cardiopulmonary exercise testing ■ cardiorespiratory fitness ■ chronotropic incompetence ■ exercise ■ HIV ■ long COVID ■ postacute sequelae of SARS-CoV-2

Cardiorespiratory fitness is a modifiable factor for living a longer, healthier life.[1,2] Multiple studies have demonstrated that people with HIV (PWH) have reduced exercise capacity compared with individuals uninfected with HIV.[3–9] Reduced fitness may contribute to the excess burden of cardiovascular

Correspondence to: Matthew S. Durstenfeld, MD, MAS, Division of Cardiology, UCSF at Zuckerberg San Francisco General Hospital, 1001 Potrero Avenue, 5G8, San Francisco, CA 94110. Email: matthew.durstenfeld@ucsf.edu

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RESEARCH PERSPECTIVE

What New Question Does This Study Raise?

- This study confirms that chronotropic incompetence is prevalent among people with HIV, which raises the question of what causes chronotropic incompetence in HIV and whether there are HIV-specific mechanisms possibly related to direct effects of HIV or the HIV reservoir, exposure to antiretroviral therapy, underlying immune activation and chronic inflammation, coinfections, and HIV-associated comorbidities.

What Question Should Be Addressed Next?

- The second major question this study raises is whether chronotropic incompetence in HIV is a marker of underlying subclinical cardiovascular disease or is associated with development of incident cardiovascular disease as has been shown in the general population.
- Especially relevant for clinicians is the question of what to do about chronotropic incompetence among people with HIV and whether it is modifiable through exercise training or other interventions.

Nonstandard Abbreviations and Acronyms

AHRR	adjusted heart rate reserve
CPET	cardiopulmonary exercise testing
LIINC	Long-Term Impact of Infection With Novel Coronavirus
PASC	postacute sequelae of COVID-19
PWH	people with HIV

disease among PWH.[10] Mechanisms of exercise limitations among PWH are unknown but may include cardiac limitations,[11,12] pulmonary limitations,[13,14] muscular limitations,[15] or other causes. A prior study that evaluated exertional dyspnea in HIV did not identify differences in cardiac contractile reserve or exercise-induced pulmonary hypertension, 2 previously hypothesized mechanisms.[16]

Beyond the effects of HIV discussed above, our prior work and that of others suggest that cardiopulmonary phenotype postacute sequelae of COVID-19 (PASC) consistent with current long COVID definitions is associated with reduced exercise capacity on cardiopulmonary exercise testing (CPET).[17,18] Beyond deconditioning, mechanisms of reduced exercise capacity after SARS-CoV-2 infection, especially among those with PASC, are uncertain but may include chronotropic incompetence.[17] Chronotropic incompetence is defined as an inadequate increase in heart rate during exercise without an alternative reason for exercise limitation.[19] We have demonstrated that HIV is associated with PASC,[20,21] and, in an exploratory analysis, that HIV is associated with chronotropic incompetence in the setting of PASC.[18]

Therefore, within a COVID recovery cohort, we sought to compare exercise capacity and chronotropy by (1) HIV and (2) among PWH by SARS-CoV-2 coinfection and prevalent cardiopulmonary symptoms consistent with PASC. We hypothesized that exercise capacity and chronotropy would be reduced among people with HIV, and that among PWH, exposure to SARS-CoV-2 infection and PASC would be associated with worse exercise capacity and chronotropy compared with vaccinated, PWH uninfected with SARS-CoV-2 (Figure 1).

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

This was a cross-sectional substudy embedded within a San Francisco, California–based COVID recovery cohort (LIINC [Long-Term Impact of Infection With Novel Coronavirus], NCT04362150) that included people with and without HIV with a history of SARS-CoV-2 infection and PWH who had received SARS-CoV-2 vaccination without history of SARS-CoV-2 infection.[22]

Participants

We included adult participants >18 years of age with and without HIV who had previously participated in an echocardiogram study visit and were able to participate in cycle ergometry >1 year after SARS-CoV-2 infection. LIINC includes individuals with and without HIV recruited from the community and acute COVID studies as well as a vaccine cohort that only included individuals with HIV recruited predominantly from SCOPE (Observational Study of the Consequences of the Protease Inhibitor Era ([NCT00187512]) and from Ward 86, a public HIV clinic based at Zuckerberg San Francisco General Hospital. We excluded those with known cardiac disease, including history of myocardial infarction, heart failure, atrial fibrillation, pulmonary hypertension, congenital heart disease, valvular heart disease, and those with severe pulmonary disease, including those requiring home oxygen or with prior lung

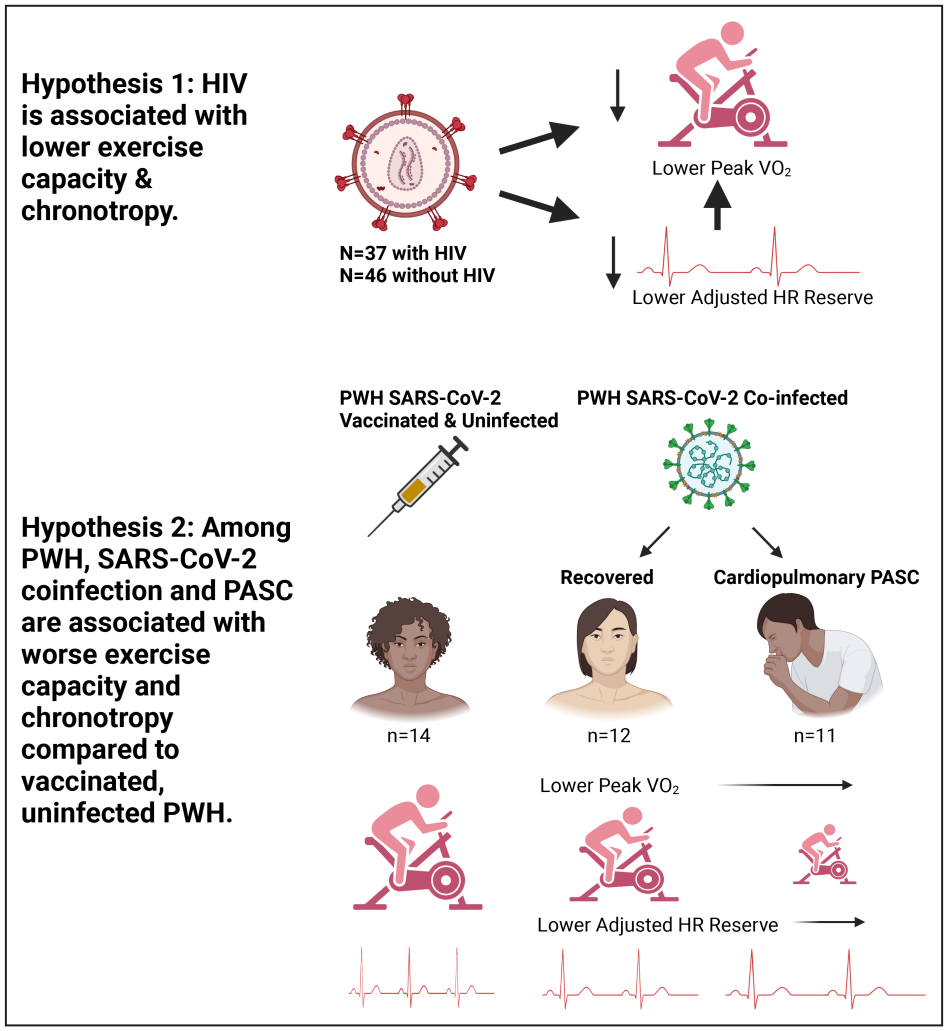

Figure 1. Hypotheses: HIV, SARS-CoV-2 coinfection, and postacute sequelae of COVID-19 (PASC) are associated with lower exercise capacity and chronotropy.
We hypothesized the following. Hypothesis 1a: Exercise capacity (peak VO_2) is lower among PWH compared to people without HIV. Hypothesis 1b: Chronotropy (adjusted heart rate reserve) is lower among PWH compared to people without HIV. Hypothesis 2a: Among PWH, exposure to SARS-CoV-2 is associated with reduced exercise capacity and chronotropy compared to PWH who are SARS-CoV-2 vaccinated and uninfected. Hypothesis 2b: Among PWH, prevalent cardiopulmonary PASC is associated with lower exercise capacity and chronotropy compared to PWH without PASC. Figure made with biorender.com. HR indicates heart rate; PASC, postacute sequelae of COVID-19; and PWH, people with HIV.

surgery. Finally, we excluded those with orthopedic, musculoskeletal, or neurologic issues that precluded participation in cycle ergometry.

Exposures

The 2 primary exposures we studied were HIV infection, and among those with HIV, SARS-CoV-2 coinfection stratified by presence of cardiopulmonary symptoms consistent with PASC/long COVID at the time of CPET. Participants were classified as having never had SARS-CoV-2 infection if they reported no history consistent with symptomatic SARS-CoV-2 infection and no history of a positive SARS-CoV-2 test (including home testing) at the time of CPET. Participants were classified as having cardiopulmonary PASC if they had a confirmed SARS-CoV-2 infection and reported ≥1 new or worse symptom, including chest pain, shortness of breath, palpitations, fatigue, or reduced exercise capacity, that persisted at least 90 days after onset of infection without an alternative diagnosis in accordance with the World Health Organization consensus definition of long COVID.[23]

Cardiopulmonary Exercise Testing

We performed cardiopulmonary exercise testing using a cycle ergometer (Lode Corival CPET) with

continuous metabolic cart measurements of gas exchange (Medical Graphics Corporation; Ultima CardiO$_2$), 12-lead ECG monitoring, blood pressure, and pulse oximetry measurement in accordance with guidelines.[24,25] After a 2-minute rest phase and 2-minute no-resistance warm up, work was increased at a set rate per minute (5–25 W/min rounded to nearest 5) to target a 10-minute test estimated from each participant's measured maximum voluntary ventilation and self-reported habitual exercise.[18] Participants were encouraged to maintain a cadence of 50 to 60 cycles per minute and exercise to their maximum ability unless stopped prematurely for safety. We classified the reasons for exercise limitations as we have previously reported.[18]

Outcomes

The primary outcome was exercise capacity (peak VO$_2$) on maximal cardiopulmonary exercise testing. Because of the demographic differences between those with and without HIV, for the primary comparison between people with and without HIV we used the percent of predicted exercise capacity achieved using the Wasserman equations for prediction.[26] Secondary outcomes included classification of patterns among those with reduced exercise capacity <85% predicted, relative peak VO$_2$ in mL/kg per minute, absolute peak VO$_2$ in L/min, heart rate response at peak exercise using the continuous adjusted heart rate reserve (AHRR) calculated as ([HR$_{peak}$-HR$_{rest}$]/[220-age-HR$_{rest}$]) and chronotropic incompetence defined as adequate effort measured using a respiratory exchange ratio >1.05, peak VO$_2$ <85% predicted, AHRR <80%, and no alternative explanation for exercise limitation.[19]

Correlative Data

We used previously assessed HIV characteristics, including duration of HIV infection, nadir CD (cluster of differentiation) 4 count (self-reported and verified from medical records if possible), current CD4 count, CD8 count, and CD4/CD8 ratio. Additionally, most participants had high-sensitivity troponin I, NT-proBNP (N-terminal pro-B-type natriuretic peptide), and hsCRP (high-sensitivity C-reactive protein) previously measured, which we included as exploratory measures.[27] We additionally measured IL-6 (interleukin 6), IL-1β (interleukin 1β), and VEGF (vascular endothelial growth factor) from samples collected by the LIINC study at the closest study date to the CPET. Samples were assayed by Monogram Biosciences (South San Francisco, CA) using the Quanterix Simoa platform with Simoa Assay Kits from Quanterix Corporation (Billerica, MA) blinded with respect to patient and clinical information, and assay performance was consistent with manufacturers' specifications.

Statistical Analysis

First, we described participant demographics and medical history by HIV status using number and proportion for categorical variables and median and interquartile range (IQR) for continuous variables. For unadjusted analyses, Fisher exact test was used for categorical variables, Wilcoxon rank sum test for non-normally distributed continuous variables, *t* tests for normally distributed continuous variables, and for correlation between continuous measures Pearson correlation coefficients and *P* values were reported. We used logistic regression to estimate adjusted odds ratios for categorical outcomes (reduced exercise capacity and chronotropic incompetence) and then used the adjrr package to estimate adjusted relative risks by taking the ratio of the predicted probabilities from logistic models by group, with 95% CIs estimated on the log scale and then exponentiated.[28] We used linear regression models to estimate the mean differences in peak VO$_2$ and AHRR between those with and without HIV and adjusted for possible confounders, including age, sex, and body mass index. We checked for interactions between age, sex, body mass index, and biomarkers and HIV on peak VO$_2$ and AHRR by incorporating interaction terms into the models (ie, age*HIV); for those with potential interactions, we reported the stratified subgroups by HIV status. To check whether our findings were robust to our decision to exclude medical history, sensitivity analyses were performed, including medical history. Primary consideration was given to the effect estimates and confidence intervals, but *P* values <0.05 were considered statistically significant for the primary outcomes. Interaction terms were considered potentially meaningful if *P*<0.10. Sample size was not determined a priori. Our key variables had no missing data. Analyses were performed using Stata 17.1.

Approval

The University of California San Francisco institutional review board approved this study (IRB 20–33000), and all participants provided written informed consent before participation. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.

RESULTS

Participant Characteristics

We included 83 participants, including 37 PWH and 46 without HIV. The median age was 54 years, and 29 (35%) were women, with PWH predominantly older and men (Table 1). All 46 without HIV had prior

Table 1. Demographics, Medical History, SARS-CoV-2, and HIV Characteristics

Characteristic	People with HIV (N=37)	People without HIV (N=46)	*P* value
Age, y, median (IQR)	57 (53–62)	49 (40–57)	0.03*
Female sex	5 (14%)	24 (52%)	<0.001†
Hispanic or Latinx	11 (32%)	8 (18%)	0.002‡
Black	7 (21%)	1 (2%)	
Asian or Pacific Islander	0	6 (13%)	
White	16 (47%)	30 (67%)	
Hypertension	16 (43%)	6 (13%)	0.002†
Diabetes	6 (17%)	3 (7%)	0.17‡
Asthma/COPD	2 (11%)	10 (23%)	0.32‡
Ever smoker	7 (47%)	9 (24%)	0.11‡
Body mass index, kg/m^2	28.7±5.2	30.1±7.8	0.36§
Hospitalized for COVID-19	1/23 (4%)	7/46 (15%)	0.42‡
Vaccinated at time of CPET	35 (95%)	44 (96%)	1.00‡
SARS-CoV-2 infected	23/37 (62%)	46/46 (100%)	<0.001‡
Long COVID symptoms at CPET	12/23 (52%)	28/43 (65%)	0.31†
Time since SARS-CoV-2 infection, mo	16.0 (14.5–17.2)	18.0 (16.3–20.0)	0.02*
Time since HIV diagnosis, y (IQR)	21 (15–28)		
Nadir CD4 count, self-reported	228 (50–408)		
Current CD4 count (IQR)	608 (270–736)		
Current CD8 count (IQR)	707 (559–904)		
Current CD4/CD8 ratio (IQR)	0.92 (0.56–1.27)		
Current ART regimen			
INSTI based	29 (78%)		
NRTI based	2 (5%)		
NNRTI based	1 (3%)		
PI based	2 (5%)		

Participant characteristics by HIV status. Current ART regimen was missing for 3 participants. ART indicates antiretriviral therapy; CD, cluster of differentiation; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; INSTI, integrase strand inhibitor-based; IQR, interquartile range; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor-based; NNRTI, nonnucleoside reverse transcriptase inhibitor; and PI, protease inhibitor.

*Wilcoxon rank sum test.

†Pearson χ^2 test.

‡Fisher exact test.

§Two-sample *t* test.

SARS-CoV-2 infection, of whom 7 (16%) were hospitalized; they completed CPET at a median 18 months after infection (IQR, 16–20), and 28 (61%) reported cardiopulmonary PASC symptoms at the time of CPET. Overall, 95% of participants with and without HIV received at least 1 SARS-CoV-2 vaccine before CPET, with 90% in both groups having received their last dose >3 months earlier.

Of the 37 PWH who completed CPET, 23 (62%) had a history of SARS-CoV-2 infection at a median 15 months prior (IQR, 15–17), and 11 (48% of SARS-CoV-2 infected) reported cardiopulmonary PASC symptoms at the time of CPET consistent with long COVID. Among PWH, the median duration of diagnosed HIV infection was 21 years (IQR, 15–28); all were virally suppressed on antiretroviral therapy at the time of CPET; median CD4 count was 608 (IQR, 370–736), and median CD4/CD8 ratio 0.92 (IQR, 0.56–1.27).

Worse Exercise Capacity Among PWH Compared With People Without HIV

PWH had lower exercise capacity compared with individuals without HIV, with an average achieved exercise capacity only 80% predicted compared with 99% predicted among those without HIV (Figure 1), a difference in peak VO_2 of 23.6% predicted (95% CI, 11.8–35.5; *P*<0.001) or 5.5 mL/kg per minute (95% CI, 2.7–8.2; *P*<0.001) after adjustment for age, sex, and body mass index (Table 2). Results were similar when including diabetes, hypertension, and asthma/chronic obstructive pulmonary disease (15.9% [95% CI, 1.7–30.1]; *P*=0.03).

Among those with adequate effort (respiratory exchange ratio >1.05), exercise capacity was <85% predicted among 64% of PWH compared with 29% without HIV (adjusted relative risk [RR], 2.80 [95% CI, 1.63–4.83]; *P*<0.001). HIV was associated with greater

Table 2. Key Cardiopulmonary Exercise Findings by HIV

Outcome	People with HIV (N=37)	People without HIV (N=46)	Unadjusted *P* value	Adjusted effect size (95% CI; *P* value)
Maximal tests	33/37 (89%)	45/46 (98%)		
Respiratory exchange ratio, median (IQR)	1.16 (1.11–1.23)	1.20 (1.15–1.26)	0.16	
Exercise capacity <85% predicted	21/33 (63%)	13/45 (29%)	0.002	OR, 10 (2.7–39; 0.001)
Peak VO_2, % predicted	80±20	99±25	0.0004	−24% predicted (12–36; <0.001)
Peak VO_2, mL/kg per min	22.4±6.8	25.2±9.3	0.14	−5.5 mL/kg per min (2.7–8.2; <0.001)
Adjusted heart rate reserve (%)	63±23	83±20	<0.0001	−28% (18–38; <0.001)
Chronotropic incompetence	14/33 (42%)	6/45 (13%)	0.01	OR, 5.7 (1.5–22.0; 0.01)

Exercise capacity and chronotropy were lower among people with HIV compared with people without HIV. IQR indicates interquartile range; OR, odds ratio; and VO_2, exercise capacity.

RR of reduced exercise capacity among those without PASC (RR, 10.0 [95% CI, 1.5–67.8]; *P*=0.02) compared with those with PASC (RR, 2.1 [95% CI, 1.16–3.71]; *P*=0.01).

Exercise Capacity Is Reduced Among PWH Independent of SARS-CoV-2 Infection and PASC

Among participants with HIV, 45% without SARS-CoV-2 coinfection had reduced exercise capacity compared with 73% with prior SARS-CoV-2 infection (unadjusted *P*=0.25; adjusted RR, 1.0 [95% CI, 0.56–1.81]; *P*=0.98). Among those with HIV and SARS-CoV-2 coinfection, the proportion with reduced exercise capacity did not vary by the presence of PASC (75% versus 67%; unadjusted *P*=1.00; adjusted RR, 1.5 [95% CI, 0.73–2.97]; *P*=0.28). The overall proportion with reduced exercise capacity among PWH (63%) was higher than among people with PASC without HIV (41%) and much higher than the SARS-CoV-2 recovered group without HIV (11%).

Compared with people without HIV who had recovered from prior SARS-CoV-2 infection without PASC, PWH without SARS-CoV-2 coinfection achieved an exercise capacity 33% lower on the percent-predicted scale (95% CI, −15 to −51; *P*=0.001; Figure 2), PWH with SARS-CoV-2 coinfection without PASC 26% lower (95% CI, −8 to −45; *P*=0.006), and PWH with PASC also 26% lower (95% CI, −8 to −45; *P*=0.005; Figure 1). In other words, the magnitude of the reduction in exercise capacity was to a similar degree among PWH regardless of SARS-CoV-2 coinfection or PASC, comparable to people without HIV with PASC.

Chronotropic Incompetence Is More Common Among PWH and Possibly Especially After PASC

Chronotropic incompetence was present in 14 out of 37 (38%) of PWH versus 6 out of 45 (13%) without HIV (unadjusted *P*=0.02; adjusted RR, 4.5 [95% CI, 1.7–12.2]; *P*=0.003). AHRR (normal >80%) was lower among PWH versus people without HIV (60% versus 83%, *P*<0.0001; Figure 2). AHRR was 26% lower among PWH compared with people without HIV when controlling for age, sex, and body mass index (95% CI, 15.8–35.3; *P*<0.001; Figure 1). Compared with PWH without SARS-CoV-2 coinfection, PWH with recovered SARS-CoV-2 infection and PASC both had reduced chronotropy (−18% [95% CI, −39 to 3]; *P*=0.09, and −23% [95% CI, −41 to −4]; *P*=0.02, respectively). Among PWH, the proportion with chronotropic incompetence varied by PASC: namely, 3 out of 14 (21%) without SARS-CoV-2 coinfection, 4 out of 12 (25%) with recovered SARS-CoV-2 coinfection, and 7 out of 11 (64%) with PASC had chronotropic incompetence (*P*=0.04 PASC versus no PASC). Chronotropic incompetence as a binary variable is associated with a 21% reduction in peak VO_2 on the percent predicted scale accounting for age, sex, BMI, and HIV (95% CI, 9–33; *P*=0.001) or 4.6 mL/kg/min difference per 10% difference in AHRR (95% CI, 2–7; *P*<0.0001).

Other patterns of reduced exercise capacity among PWH included cardiac limitations (ie, ECG diagnostic for ischemia) in 3 participants, deconditioning/obesity in 2 participants, and ventilatory, pulmonary vascular, and hypertensive limitations in 1 each, respectively.

Correlates of Reduced Exercise Capacity and Chronotropic Incompetence

Diabetes was associated with lower exercise capacity only on the relative scale (−3.9 mL/kg per minute [95% CI, −8.8 to −0.1]; *P*=0.04), whereas hypertension was associated with lower exercise capacity only on the percent predicted scale (−14% [95% CI, −26 to −0.9]; *P*=0.04), and history of asthma/chronic obstructive pulmonary disease was not on either scale (*P*=0.34 and *P*=0.53). Body mass index was inversely associated with exercise capacity on both scales, with a possible interaction by HIV (Table 3). IL-6 was also inversely associated with exercise capacity (−2.7 mL/kg per minute per doubling [95% CI, −4.0 to 1.3]; *P*<0.001), without evidence of an interaction by HIV. Higher hsCRP was

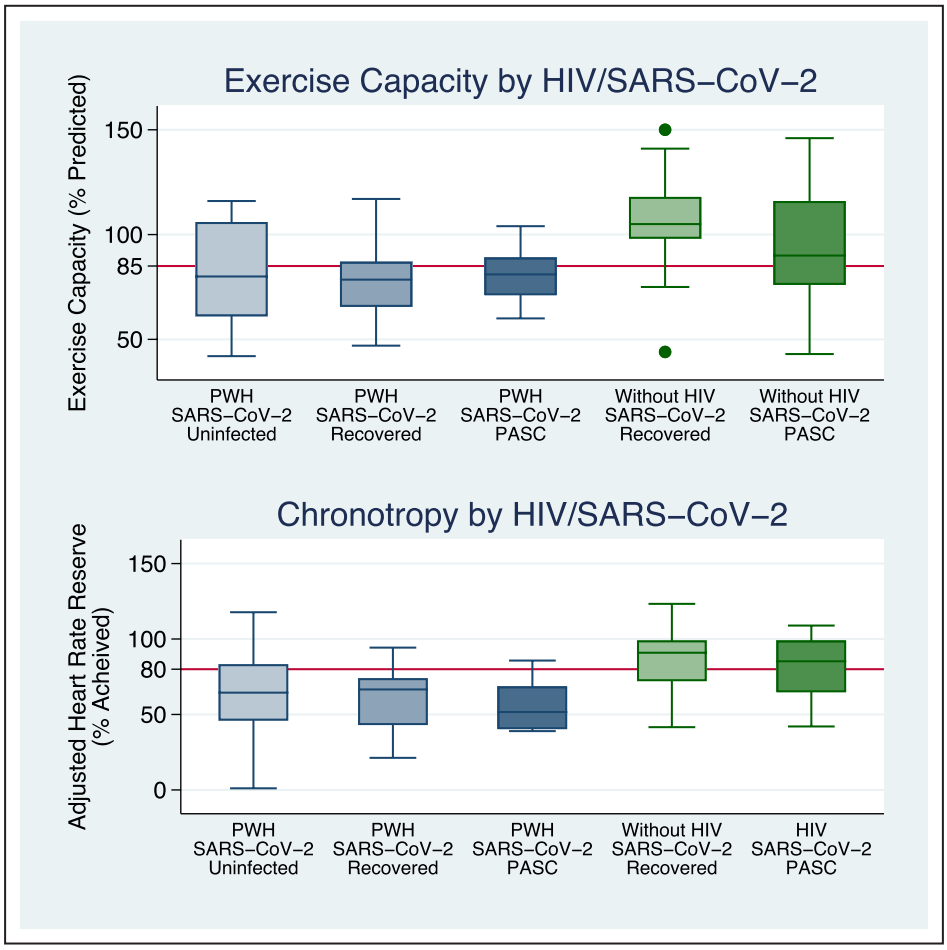

Figure 2. Exercise capacity and chronotropic response by HIV and SARS-CoV-2 infection. Boxplots of exercise capacity on the percent predicted scale (top, red line indicates 85% which was our threshold for classifying as reduced) and adjusted heart rate reserve (bottom, normal >80%) are plotted by HIV and SARS-CoV-2 infection status. Exercise capacity is lower among PWH compared to individuals without HIV regardless of SARS-CoV-2 infection status. Adjusted heart rate reserve was lower among PWH, especially among those with cardiopulmonary PASC symptoms consistent with Long COVID. PASC indicates postacute sequelae of COVID-19; and PWH, people with HIV.

associated with lower peak VO_2 (–1.0 per doubling [95% CI, –1.9 to –0.1]; P=0.03), with a possible interaction by HIV. Other biomarkers (hs-troponin I, NT-proBNP, IL-1β, and VEGF) were not associated with peak VO_2.

In terms of chronotropy, older age was not associated with lower AHRR (–0.1% per year [95% CI, –0.47 to 0.28]; P=0.63), and there was no multiplicative interaction with HIV ($P_{interaction}$=0.28; Figure 3). Higher body

Table 3. Correlates of Reduced Exercise Capacity Stratified by HIV Status

Factor	Scale	$P_{interaction}$ value	Difference among PWH, (95% CI; P value)	Difference among people without HIV, (95% CI; P value)
Body mass index, per 1 kg/m^2	Peak VO_2, mL/kg per min	0.07	–0.50 (–0.15 to –0.85; 0.006)	–0.87 (–0.67 to –1.08; <0.001)
	Peak VO_2, % predicted	0.14	0.2% (–1.3 to 1.7; 0.81)	–1.1% (–0.2 to 2.0; 0.01)
IL-6, per doubling	Peak VO_2, mL/kg per min	0.82	–2.5 (–4.3 to –0.7; 0.008)	–2.8 (–4.5 to –1.0; 0.002)
	Peak VO_2, % predicted	0.15	–9% (–16 to –2; 0.02)	–16% (–23 to –9; <0.001)
hsCRP, per doubling	Peak VO_2, mL/kg per min	0.38	–0.7 (–1.9 to 0.5; 0.27)	–1.3 (–2.4 to –0.2; 0.02)
	Peak VO_2, % predicted	0.06	–1.2% (–6.2 to 3.8; 0.62)	–7.0% (–3.4 to –16.9; 0.004)

Change in exercise capacity in terms of mL/kg per min and percent predicted stratified by HIV status per change in body mass index, IL-6, and hsCRP. hsCRP indicates high-sensitivity C-reactive protein; IL, interleukin; PWH, people with HIV; and VO_2, exercise capacity.

mass index was associated with lower AHRR (–1.4% per kg/m^2 [95% CI, –2.1 to –0.8]; P<0.001), without significant interaction by HIV (Figure 3). Although IL-6 is inversely associated with AHRR (–12% [95% CI, –19 to –5]; P=0.001) in a model adjusted for age, sex, and body mass index, this is attenuated when accounting for HIV (–4% [95% CI, –9 to 1]; P=0.11; $P_{interaction}$=0.91). This is partially explained by higher IL-6 levels among PWH (median 1.70 versus 0.96; P=0.004). Other biomarkers (hcCRP, hs-troponin I, NT-proBNP, IL-1β, and VEGF) were not associated with chronotropy.

In exploratory analyses among PWH, HIV disease-specific characteristics including nadir CD4 count, current CD4 count, current CD8 count, and current CD4/CD8 ratio were not strongly correlated with AHRR (Figure 4).

DISCUSSION

Reduced exercise capacity has been reported among people with HIV for 30 years,[3,29] but few studies have explored the mechanisms of reduced exercise capacity. We found that exercise capacity was significantly reduced by nearly 25% among PWH compared both with their predicted exercise capacity and compared with people without HIV with prior SARS-CoV-2 infection. PWH had more than twice the relative risk of having an exercise capacity <85% of predicted. The average reduction in exercise capacity is of similar magnitude to the reduction among people without HIV with PASC/long COVID and was present regardless of prior SARS-CoV-2 infection status, which is a finding limited by our sample size. Chronotropic incompetence was the most common pattern of exercise limitation we identified, explaining the observed exercise limitations among about half of PWH with reduced exercise capacity and with a relative risk 7 times higher among PWH. Chronotropic incompetence was more common among those with HIV and SARS-CoV-2 coinfection experiencing cardiopulmonary symptoms compared with HIV-uninfected individuals with cardiopulmonary symptoms and PWH without symptoms.

Consistent Findings Compared With Other Studies of Exercise Capacity in HIV

Our finding of reduced exercise capacity among PWH is similar to prior reports. Although our comparison with the participants with SARS-CoV-2 infection without HIV is subject to confounding given differences in baseline characteristics, we also demonstrated a much lower exercise capacity than predicted by standard equations. Prior studies have consistently identified that PWH have reduced exercise capacity compared with peers who do not have HIV,[4] even among newly diagnosed individuals as well as children and

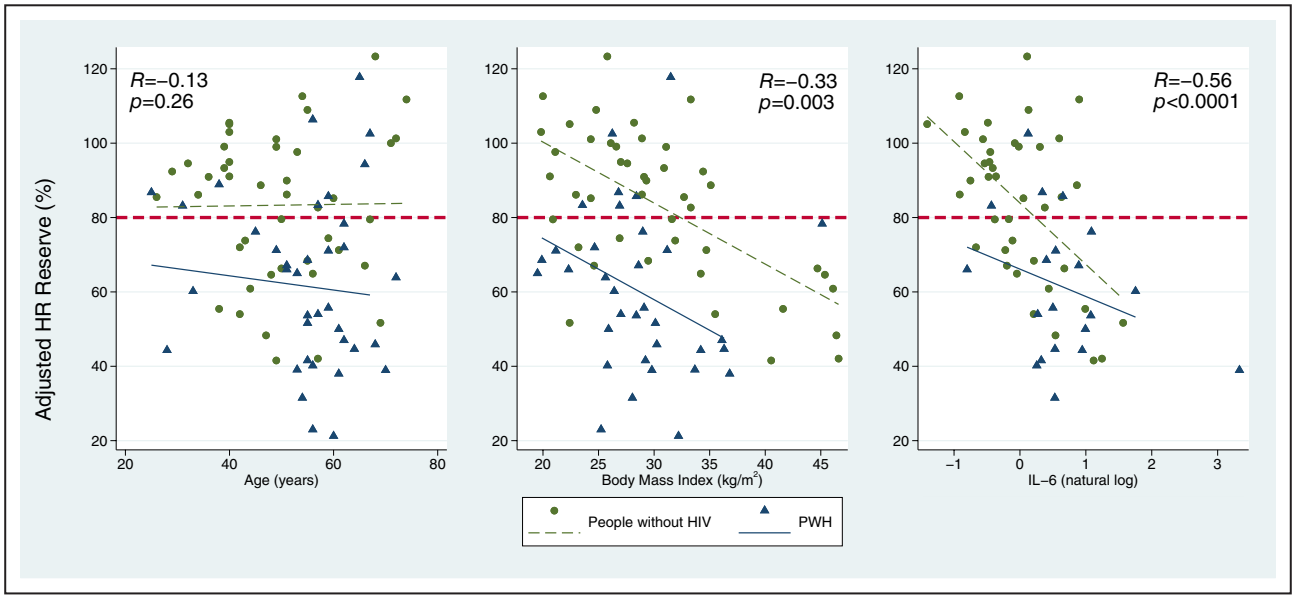

Figure 3. Chronotropy by age, body mass index, and IL (interleukin)-6 among people with and without HIV.
Scatterplots with linear fit lines for adjusted heart rate reserve (AHRR, *y*-axis) by age (left), body mass index (center), and natural log transformed Il-6 (right) stratified by HIV status (blue triangles/solid lines PWH, green circles/dashed lines People without HIV). Pearson correlation coefficients and *P*-values are for the unadjusted correlations for the total sample including those with and without HIV. The first panel demonstrates that AHRR is about 20% lower among PWH across the entire age spectrum compared to people without HIV. The second panel demonstrates that adjusted heart rate reserve decreases with increasing BMI with a stronger association among those without HIV, perhaps because PWH with low BMI start out with a lower AHRR compared to people without HIV. The third panel shows that IL-6 is inversely associated with chronotropy, with higher IL-6 levels and lower AHRR among PWH; results were robust to exclusion of the outlier with very high IL-6. AHRR indicates adjusted heart rate reserve; BMI, body mass index; IL-6, interleukin 6; and PWH, people with HIV.

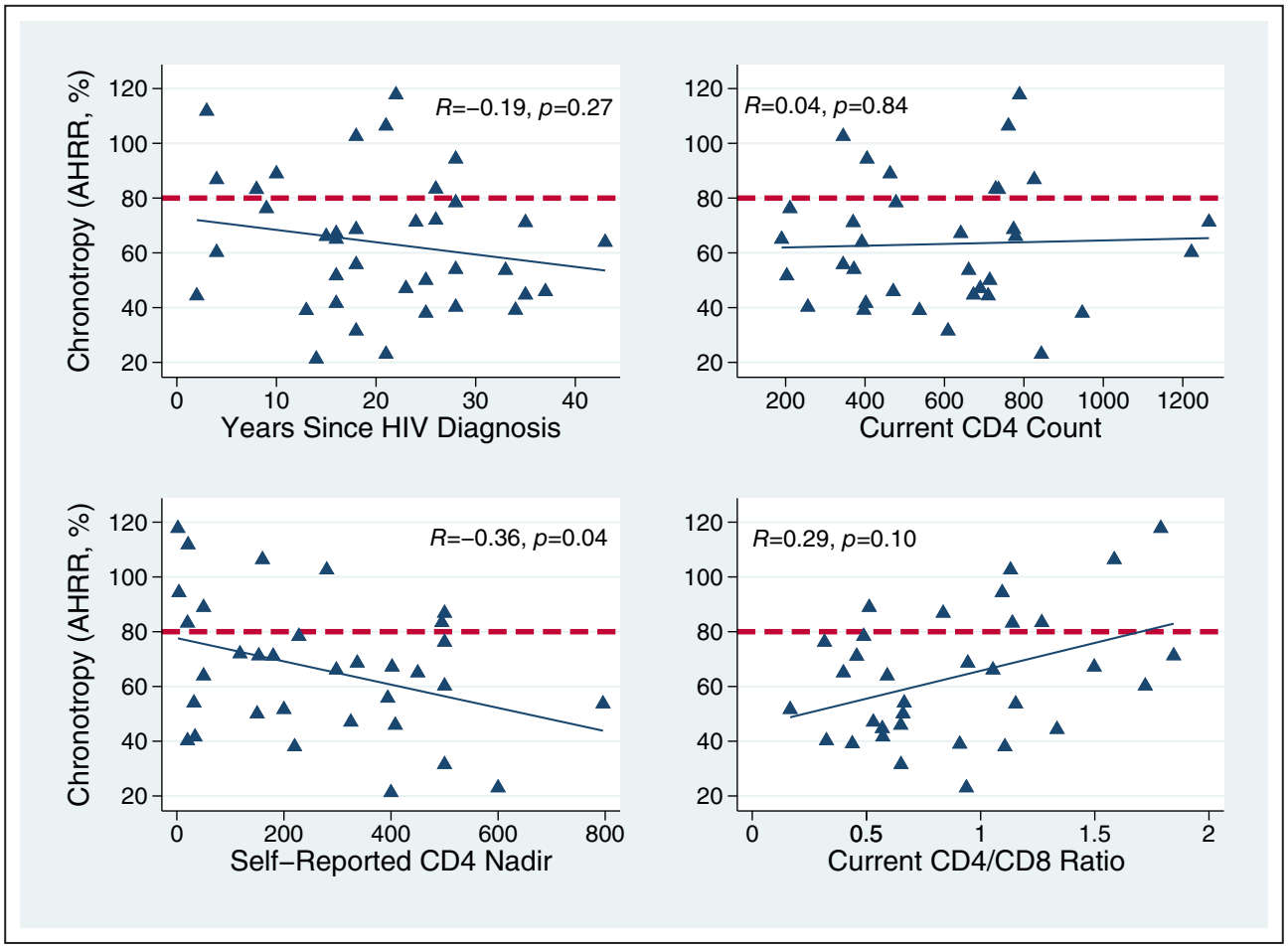

Figure 4. Chronotropy by HIV characteristics.
Adjusted heart rate reserve was not strongly correlated with years since HIV diagnosis, self-reported nadir CD4 count, current CD4 count, or current CD4/CD8 ratio, although there were trends of borderline statistical significance for self-reported CD4 nadir in the opposite direction we hypothesized and for current CD4/CD8 ratio. These exploratory analyses will need to be validated in larger studies. Red dashed line represents the lower limit of normal for chronotropy (AHRR <80%); navy lines represent linear trends among PWH. AHRR indicates adjusted heart rate reserve; CD, cluster of differentiation; and PWH, people with HIV.

adolescents.[30,31] Yet only a few studies have leveraged cardiopulmonary exercise testing to identify reasons for exercise limitations or exertional dyspnea. One earlier study found differences in peak arteriovenous oxygen differences suggestive of peripheral oxygen extraction or use limits.[32] Higher body mass index, lipodystrophy, and sarcopenia may also contribute.[6,15,33]

Contribution of SARS-CoV-2 Infection and PASC

Our study makes several novel contributions. To our knowledge, the effect of SARS-CoV-2 infection and self-reported PASC symptoms per World Health Organization criteria on exercise capacity has not been well characterized, and our findings on chronotropic incompetence are novel. The proportion of PWH we identified with chronotropic incompetence is similar to a prior study that found that 35% of PWH without known cardiovascular disease had chronotropic incompetence using treadmill stress tests rather than CPET.[34] Similar to our exploratory findings, they did not identify HIV-specific risk factors for chronotropic incompetence, including duration of HIV, nadir CD4 count, or exposure to protease inhibitors.

Potential Mechanisms of Chronotropic Incompetence in HIV

The mechanisms of chronotropic incompetence in HIV, and specifically why the prevalence of chronotropic incompetence (and reduced exercise capacity more broadly) is so high among PWH remains unknown. One possible mechanism is that chronic inflammation from immune activation related to the underlying HIV viral reservoir may cause chronic adrenergic overactivation.

Interestingly, a hyperadrenergic state is associated with elevated inflammatory markers, including IL-6, in HIV,[35] and IL-6 is strongly associated with peak VO_2 and with adjusted heart rate reserve in our study. This, in turn, may result in reduced β-receptor responsiveness, a common feature of chronotropic incompetence among people without structural heart disease.[36] With decreased responsiveness to adrenergic signals, the natural response may be to generate higher levels of catecholamines in response to stress, which may activate inflammatory and hypercoagulable pathways that can accelerate atherosclerosis and cause cardiovascular events.

A second potential explanation for chronotropic incompetence in HIV may be interstitial myocardial fibrosis. Our group previously reported higher rates of myocardial interstitial fibrosis on autopsy among PWH[37] compared with people without HIV who experienced presumed sudden cardiac death. HIV is also associated with higher rates of heart failure with a preserved ejection fraction[38] and atrial fibrillation.[39] Chronic inflammation due to immune activation is common in HIV and a likely contributor to heart failure with a preserved ejection fraction among PWH.[11,40,41] Myocardial interstitial fibrosis in heart failure with a preserved ejection fraction may be increased by chronic inflammation.[42,43] Chronotropic incompetence is highly prevalent in heart failure with a preserved ejection fraction and a major contributor to exercise intolerance.[44–46] Myocardial interstitial fibrosis is a hypothesized connection between chronotropic incompetence and atrial fibrillation.[47] Thus, it is plausible that myocardial fibrosis in the setting of chronic HIV infection underlies chronotropic incompetence and may contribute to heart failure and arrhythmias in HIV.

Clinical Significance of Chronotropic Incompetence

In the general population without HIV, chronotropic incompetence is a mechanism of reduced cardiopulmonary fitness associated with a particularly adverse prognosis. Data from multiple cohorts have demonstrated that chronotropic incompetence on stress testing among individuals without known cardiovascular disease or cardiopulmonary symptoms is associated with subsequent incident cardiovascular events, including myocardial infarction and stroke, cardiovascular mortality, and all-cause mortality.[1,48–51] Whether chronotropic incompetence has a causal role or is simply a marker of either poor cardiorespiratory fitness or underlying subclinical cardiovascular disease is uncertain among people without cardiovascular disease. To our knowledge, there are no data to inform whether chronotropic incompetence is associated with a similarly poor prognosis among PWH. Furthermore, therapeutic interventions for chronotropic incompetence that might include implantable cardiac pacemakers or exercise training have not been evaluated in the setting of HIV at this time.

There are limited data to inform treatment of chronotropic incompetence in HIV. In a randomized clinical trial of exercise training for patients with chronotropic incompetence in the setting of heart failure, peak exertional heart rate improved with exercise training but not in the control arm.[52] Interventional trials for chronotropic incompetence in heart failure have largely focused on pacemakers, but implanting pacemakers to increase heart rate during exercise does not improve exercise capacity, because the increase in heart rate is offset by a decrease in stroke volume.[53] Yet, among those with pacemakers, improved chronotropy is associated with better quality of life.[54] Interventions for chronotropic incompetence among patients without heart failure or pacemakers have not been studied. Exercise training is beneficial for sedentary PWH unselected for chronotropic incompetence,[55] and post hoc analysis suggests that the observed benefit on exercise capacity may be partially attributable to improvement in chronotropy (unpublished).

Limitations

There are several limitations of this study. First, this is an observational study with a small sample size. In San Francisco, the prevalence of HIV is much higher among men than women, and many of our active research participants are older White men, limiting the diversity of our sample and possibly external generalizability. There were notable differences in baseline characteristics between those with and without HIV, including factors that may be associated with chronotropic incompetence, which is why we used the percent predicted exercise capacity rather than the absolute peak VO_2 or relative peak VO_2 as our primary measures for comparison between those with and without HIV. Although we conducted sensitivity analyses, there are still important confounders we could not adjust for, including smoking status (given few current smokers among those without HIV) and unmeasured confounders such as pre-COVID-19 fitness. PASC symptoms are based on self-report, which is the current gold standard for long COVID. In terms of measurement, we did not perform invasive CPET to assess for differences in arteriovenous oxygen delivery or use, or measure cardiac output, exercise diastolic function, or pulmonary hypertension with exertion, but we excluded those with evident structural heart disease on transthoracic echocardiography. We did not confirm that participants uninfected with SARS-CoV-2 were uninfected by nucleocapsid antibody testing, so it is possible that some had previously had asymptomatic SARS-CoV-2 infection.

CONCLUSIONS

Exercise capacity is reduced among PWH, with no large differences by SARS-CoV-2 infection or PASC, although our small sample size limits our ability to draw definitive conclusions. In contrast, we found that chronotropic incompetence may be a common and underrecognized mechanism of exercise intolerance among PWH, especially among PWH following SARS-CoV-2 infection with ongoing cardiopulmonary symptoms consistent with long COVD, similar to our findings among people without HIV. These preliminary findings will need to be validated in other populations to ensure external generalizability.

ARTICLE INFORMATION

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Affiliations

Department of Medicine, University of California, San Francisco, CA (M.S.D., M.J.P., M.A.S., M.G., M.A.A., C.S.L., S.G.D., P.Y.H.); Division of Cardiology, Zuckerberg San Francisco General, San Francisco, CA (M.S.D., D.L., P.Y.H.); Division of HIV, Infectious Diseases, and Global Medicine, Zuckerberg San Francisco General Hospital, University of California, San Francisco, CA (M.J.P., M.A.S., R.H., M.G., S.G.D.); Monogram Biosciences, LabCorp, South San Francisco, CA (A.C., B.Y., J.W., C.P.); Department of Experimental Medicine, University of California, San Francisco, CA (T.J.H.); and Division of Cardiology, UCSF Health, San Francisco, CA (M.A.A., C.S.L.).

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