REPRIEVE Asymptomatic SARS-CoV-2 Infection is Extremely Common among People with HIV

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BACKGROUND

- In the general population, asymptomatic infection with SARS-CoV-2 is common, ranging from 22-85% in various studies.
- The variability of these estimates reflects local testing strategies and differentiation between persons who are pre-symptomatic (i.e. test positive before symptoms develop), and those who are truly asymptomatic and never manifest symptoms.
- A substantial proportion (25-40%) of viral transmission has been linked to persons who are pre-symptomatic or asymptomatic.
- Limited data have been published regarding the proportion of PWH who have asymptomatic SARS-CoV-2 infection.
- The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) provides a unique opportunity to characterize the spectrum of COVID-19 disease among a global HIV cohort and to evaluate asymptomatic infection among PWH.
- Here, we present data on SARS-CoV-2 infection for 2,464 participants who had samples available for COVID serology testing from May 2020-Feb 2021.
- In addition, we share data on COVID-related symptoms and comprehensive clinical, demographic, geographic, and HIV-related data to assess relationships to COVID-19 infection.

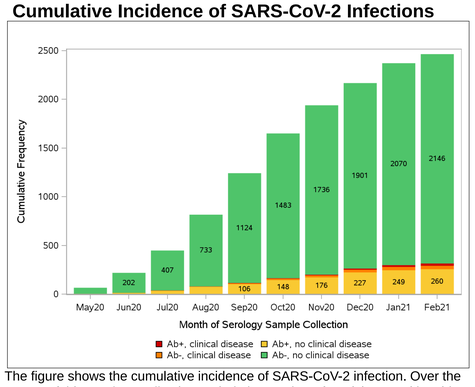
METHODS

- REPRIEVE (NCT02344290) is a randomized ASCVD prevention trial of PWH between ages 40 and 75 on stable ART.
- Beginning April 2020, targeted data on COVID-19 symptoms were collected every 4 months as part of routine trial visits.
- All participants were asked about the presence of 12 symptoms commonly associated with COVID-19 infections since their last study visit.
- All available serology samples collected at annual study visits between May 2020 and February 2021 were tested for SARS-CoV-2 antibodies (N=2,464 participants, 32% of Trial).
- We determined specimens to be antibody-positive if receptor binding domain (RBD)-specific IgG or IgA antibodies were detected above a pre-specified cutoff of five standard deviations above plate-specific negative controls on ELISA assays run by the Ragon Institute of MIT and Harvard.
- Participants were determined to have evidence of SARS-CoV-2 infection if an adverse event of COVID-19 clinical diagnosis was reported or the antibody status was positive.
- Participants were categorized as having symptomatic infection based on reporting of any COVID-19 related symptoms from May 2020 up to two weeks after the date of the serology sample collection or reporting of a grade 2 or higher COVID-19 disease.
- *Statistical analysis:* We summarize participant characteristics overall and by symptomatic infection status. We fit individual log-binomial models to estimate the relative risk (95% confidence interval) of symptomatic infection associated with each host characteristic. In adjusted log-binomial models, we control for Global Burden of Disease (GBD) Super Region and date of serology specimen collection.

Asymptomatic SARS-CoV-2 infection is very common among ART-treated PWH globally with 60% being asymptomatic among PWH in the REPRIEVE cohort.

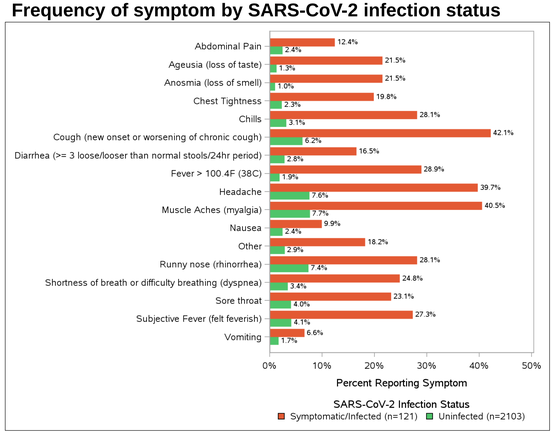
RESULTS

Cumulative Incidence of SARS-CoV-2 Infections



The figure shows the cumulative incidence of SARS-CoV-2 infection. Over the course of this serology collection period, the number of participants with evidence of SARS-CoV-2 infection (shown in red, orange, and yellow) increased from 0 to 318 (12.9%).

Frequency of symptom by SARS-CoV-2 infection status

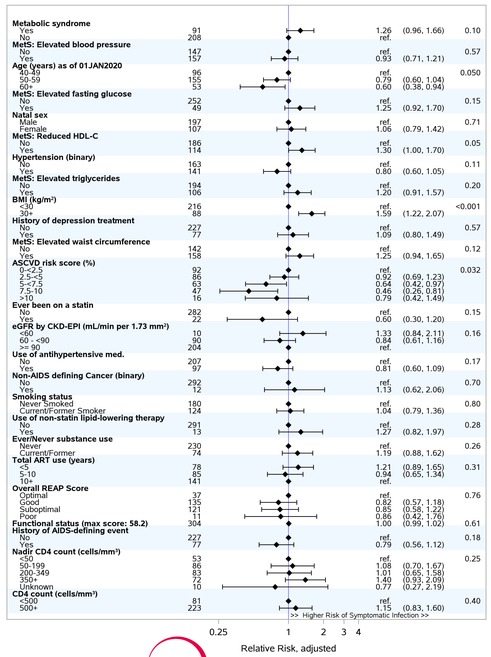


Characteristics of PWH with and without SARS-CoV-2 Infection

Characteristic*	Asymptomatic SARS-CoV-2 Infection (n=183)	Symptomatic SARS-CoV-2 Infection (n=121)	SARS-CoV-2 Uninfected (n=2146)
Age in years	53 (49,58)	52 (48, 56)	53 (48,57)
Natal female sex	67 (37%)	40 (33%)	754 (35%)
Race			
White	47 (26%)	46 (38%)	695 (32%)
Black or African American	101 (55%)	54 (45%)	988 (46%)
Asian	25(14%)	12 (10%)	337 (16%)
Hispanic Ethnicity	56 (31%)	40 (33%)	552 (26%)
GBD Super Region			
High Income	68 (37%)	70 (58%)	1,084 (51%)
Lat America/Caribbean	62 (34%)	27 (22%)	433 (20%)
Southeast/East Asia	22 (12%)	9 (7%)	305 (14%)
South Asia	2 (1%)	1 (1%)	22 (1%)
Sub-Saharan Africa	29 (16%)	14 (12%)	302 (14%)
Diabetes	2 (1%)	5 (4%)	65 (3%)
Hypertension	89 (49%)	52 (43%)	947 (44%)
Obesity (BMI ≥ 30kg/m^2)	39 (21%)	49 (40%)	511 (24%)
ASCVD Risk Score	4.7 (1.9,7.2)	3.7 (2.0,5.7)	4.1 (2.0,6.7)
eGFR (mL/min per 1.73m^2)	99 (86,111)	97 (80,108)	97 (81,109)
Current CD4 ct (c/mm^3)	583 (465,799)	693 (506,875)	652 (484, 854)
HIV VL <400 cp/mL	179 (98%)	117 (97%)	2,082 (98%)

*Continuous variables are described as Median (Q1, Q3). Other variables reported as count and percentage. Age, Diabetes, Hypertension, Obesity, CD4, and HIV viral load are time updated as of January 2020; remaining variables are as reported at study entry.

Relative Risk of Symptomatic Infection Adjusted for GBD Region and Month of Sample Collection



FINDINGS

- Among 2464 REPRIEVE participants, the cumulative incidence of SARS-CoV-2 infection increased from zero cases (0%) in May 2020 to 318 cases (12.9%) by February 2021.
- Among 304 SARS-CoV-2 Infections with symptom data, common comorbidities included BMI ≥30kg/m^2 (24%), hypertension (44%), history of treatment for depression (25%), chronic kidney disease (33%), metabolic syndrome (29%), and current/former tobacco smoking (41%).
- For 121 PWH with symptomatic infection, symptoms that were reported in >10% of participants included cough (42%), myalgias (41%), headache (40%), fever (29%), chills (28%), rhinorrhea (28%), dyspnea (25%), sore throat (23%), anosmia (22%), ageusia (22%), chest tightness (20%), diarrhea (17%), abdominal pain (12%), and nausea (10%).
- Notably, a proportion of SARS-CoV-2 uninfected participants reported these symptoms, albeit at a lower frequency than those with symptomatic infection.
- In the model adjusted for GBD Super Region and date of sample collection,
  Relative risk of symptomatic infection was greater for persons with
  - Obesity (aRR 1.59, 95% CI 1.22-2.07)
  - Metabolic syndrome (aRR 1.30, 95% CI 0.99-1.70)
  - Reduced HDL-C values (aRR 1.30, 95% CI 1.00-1.70)

  Relative risk of symptomatic infection was lower for
  - Black or African American race vs White race (aRR 0.72, 95% CI 0.52-0.98)
  - Persons age ≥60 vs persons age 40-49 years (aRR 0.79, 95% CI 0.60-1.04)
  - Persons with ASCVD risk scores from 5-<7.5 and 7.5-10 vs 0-<2.5% (aRR 0.64, 95% CI 0.42-0.97 and 0.46, 95% CI 0.26-0.81, respectively)

CONCLUSIONS

- The proportion of asymptomatic infection (60%) is higher than many previous reports of both PWH and the general population.
  - In a recent meta-analysis of 18 reports with COVID antibody testing, asymptomatic infection ranged from 22% to 85% with a median value of 41%.
- The proportion of asymptomatic infections is substantially greater than zero and must be considered as we strive to mitigate the transmission of SARS-CoV-2.
- COVID symptoms are non-specific. As noted in our data, a substantial proportion of persons without SARS-CoV-2 infection experienced symptoms commonly associated with COVID-19 disease.
- Ultimately, our data highlight the need for robust prevention and mitigation strategies to reduce the burden of the COVID-19 pandemic, including access to COVID-19 vaccines, continued adherence to facemask wearing and hand hygiene, access to COVID testing with rapid results, minimizing the size of indoor gatherings, and support of quarantine and isolation practices to limit potential outbreaks.
- HIV clinicians must remain vigilant to assure our patients have knowledge about COVID-19 disease including risks of asymptomatic disease and the appropriate mitigation strategies in place.

ADDITIONAL KEY INFORMATION

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NIH National Heart, Lung, and Blood Institute
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ACTG AIDS CLINICAL TRIALS GROUP
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