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SARS-CoV-2 seroprevalence, and IgG concentration and pseudovirus neutralising antibody titres after infection, compared by HIV status: a matched case-control observational study

Matthew A Spinelli, Kara L Lynch, Cassandra Yun, David V Glidden, Michael J Peluso, Timothy J Henrich, Monica Gandhi, Lillian B Brown

Summary

Background Most cohorts show similar or lower COVID-19 incidence among people living with HIV compared with the general population. However, incidence might be affected by lower testing rates among vulnerable populations. We aimed to compare SARS-CoV-2 IgG seroprevalence, disease severity, and neutralising antibody activity after infection among people with and without HIV receiving care in a county hospital system over a 3-month period.

Methods In this matched case-control observational study, remnant serum samples were collected between Aug 1 and Oct 31, 2020, from all people living with HIV who underwent routine outpatient laboratory testing in a municipal health-care system (San Francisco General Hospital, CA, USA). Samples from people living with HIV were date of collection-matched (same day) and age-matched (±5 years) to samples from randomly selected adults (aged 18 years or older) without HIV receiving care for chronic conditions at the same hospital. We compared seroprevalence by HIV status via mixed-effects logistic regression models, accounting for the matched structure of the data (random effects for the matched group), adjusting for age, sex, race or ethnicity, and clinical factors (ie, history of cardiovascular or pulmonary disease, and type 2 diabetes). Severe COVID-19 was assessed in participants with past SARS-CoV-2 (IgG or PCR) infection by chart review and compared with multivariable mixed-effects logistic regression, adjusting for age and sex. SARS-CoV-2 IgG, neutralising antibody titres, and antibody avidity were measured in serum of participants with previous positive PCR tests and compared with multivariable mixed-effects models, adjusting for age, sex, and time since PCR-confirmed SARS-CoV-2 infection.

Findings 1138 samples from 955 people living with HIV and 1118 samples from 1062 people without HIV were tested. SARS-CoV-2 IgG seroprevalence was 3.7% (95% CI 2.4 to 5.0) among people with HIV compared with 7.4% (5.7 to 9.2) among people without HIV (adjusted odds ratio 0.50, 95% CI 0.30 to 0.83). Among 31 people with HIV and 70 people without HIV who had evidence of past infection, the odds of severe COVID-19 were 5.52 (95% CI 1.01 to 64.48) times higher among people living with HIV. Adjusting for time since PCR-confirmed infection, SARS-CoV-2 IgG concentrations were lower (percentage change −53%, 95% CI −4 to −76), pseudovirus neutralising antibody titres were lower (−67%, −25 to −86), and avidity was similar (7%, −73 to 87) among people living with HIV compared with those without HIV.

Interpretation Although fewer infections were detected by SARS-CoV-2 IgG testing among people living with HIV than among those without HIV, people with HIV had more cases of severe COVID-19. Among people living with HIV with past SARS-CoV-2 infection, lower IgG concentrations and pseudovirus neutralising antibody titres might reflect a diminished serological response to infection, and the similar avidity could be driven by similar time since infection.

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Introduction

An understanding of whether susceptibility to SARS-CoV-2 infection or propensity to develop severe disease is increased in the population of people living with HIV is crucial for both these individuals and their health-care providers. Although marginal housing can limit the ability of some people with HIV to shelter in place, studies so far have found either similar or lower incidence of COVID-19 among people living with HIV compared with the general population, providing reassurance that HIV is unlikely to be a risk factor for SARS-CoV-2 acquisition. People living with HIV might take greater caution due to higher perceived susceptibility, as well as experience of the HIV epidemic, leading to less exposure to SARS-CoV-2. Conversely, persistent inflammation or lower CD4-to-CD8 cell ratios among people living with HIV than among those without HIV could increase susceptibility to viral infection.

Defining the precise incidence of COVID-19 among people living with HIV has been challenging, given...
Research in context

Evidence before this study
We searched PubMed for original research published in English between Jan 1, 2020, and Feb 21, 2021, with the search terms “HIV” AND “SARS-CoV-2” OR “COVID-19”. Previous large population-based studies found similar or lower SARS-CoV-2 incidence among people living with HIV compared with the general population, although this difference could be biased by differential testing rates among groups. One small previous seroprevalence study of a convenience sample included 270 people living with HIV in Umbria, Italy. No other systematic seroprevalence study for SARS-CoV-2 comparing people living with HIV to the general population had been published.

Added value of this study
In this matched case-control observational study, we tested for SARS-CoV-2 IgG using remnant samples among all people receiving outpatient laboratory testing in an HIV clinic from August to October, 2020. This group of people living with HIV was compared with an age-matched and date of collection-matched randomly selected sample of people without HIV from the same health-care system. We found approximately 50% lower odds of past SARS-CoV-2 infection among people living with HIV than among those without HIV. However, more cases of severe COVID-19 occurred among people living with HIV than among those without HIV, and, among those with a previous positive PCR test, IgG concentrations were 53% lower and neutralising antibody titres were 67% lower among people living with HIV than among those without HIV.

Implications of all the available evidence
Our results support previous findings that people living with HIV do not seem to be at higher risk of SARS-CoV-2 infection than are those without HIV. However, evidence is growing that the risk of severe COVID-19 might be higher among people living with HIV who are exposed to SARS-CoV-2 than among the general population. Our results also raise concern that the serological immune response to natural infection could be blunted among people living with HIV, given lower neutralising antibody titres and IgG concentrations in this group. Future studies will need to follow up people living with HIV after natural infection to measure humoral and T-cell immune responses and ensure sufficient protection.

limitations in population-based data. In light of the high proportion of asymptomatic infections with SARS-CoV-2, incidence estimates could be biased by differential testing rates among populations. Three of the largest population-based studies of COVID-19 incidence among people living with HIV (in Madrid [Spain], Barcelona [Spain], Wuhan [China], and New York State [USA]) showed similar or lower COVID-19 incidence among people living with HIV compared with those without HIV, although these studies did not report testing rates or test positivity. However, three US studies raised some concern for differential testing rates among groups. One small previous seroprevalence study of a convenience sample included 270 people living with HIV in Umbria, Italy. No other systematic seroprevalence study for SARS-CoV-2 comparing people living with HIV to the general population had been published.

Given the potential for a high degree of underascertainment of SARS-CoV-2 infection using PCR-based testing, population-based seroprevalence studies are needed to accurately determine attack rates. However, given the much smaller population of people living with HIV compared with the general population, and the challenge of doing clinical research during the ongoing pandemic, systematic seroprevalence studies comparing SARS-CoV-2 infection rates by HIV status have not yet been done, except a small seroprevalence study in Umbria (Italy). We aimed to estimate SARS-CoV-2 seroprevalence among people with HIV compared with those without HIV. Given that IgG antibodies and neutralising antibody titres naturally decline following infection, we aimed to examine differences by HIV status in quantitative SARS-CoV-2 IgG concentrations, neutralising antibody titres, and antibody avidity among those with evidence of past infection, controlling for time since infection in the substratum with past PCR-confirmed infection.

Methods
Study design
In this matched case-control observational study, remnant serum samples from metabolic panels were collected between Aug 1 and Oct 31, 2020, from all people living with HIV who underwent routine outpatient laboratory testing at San Francisco General Hospital, which houses a large HIV clinic and supports a municipal healthcare system. Each sample from people living with HIV was matched 1:1 by date of collection (same day) and age (±5 years) to samples from randomly selected adults (aged 18 years or older) from internal medicine and
family medicine clinics receiving outpatient metabolic panel laboratory testing in the same hospital, although 40 samples from people living with HIV were matched 2:1 when only a single suitable sample was available (figure 1). Because only remnant samples were used, and measures were taken to protect participant confidentiality, the University of California, San Francisco institutional review board did not require informed consent for study participation.

SARS-CoV-2 anti-RBD IgG measurement

SARS-CoV-2 antibody concentrations were quantified in serum with the Pylon COVID-19 IgG assay (ET HealthCare, Palo Alto, CA, USA), which targets the receptor-binding domain (RBD) of the spike protein. We used estimates for sensitivity of the IgG assay for past infection from an internal validation study with 79 outpatients and inpatients in the same health system (San Francisco General Hospital), with serum samples collected at least 3 weeks after PCR-confirmed infection. The RBD IgG assay showed 89% sensitivity for past infection among those with PCR-confirmed infection, which we used to estimate the adjusted seroprevalence in our study.11 As sensitivity of the IgG assay is not well established among individuals with a greater proportion of asymptomatic infection, we did a sensitivity analysis assuming 70% test sensitivity. Finally, the specificity of the RBD IgG assay was 100% using 80 blood donor specimens collected before June, 2018, so no adjustments were made for specificity in our analysis.11 In individuals with evidence of past infection, continuous IgG concentrations were measured and expressed in relative fluorescent units.

Pseudovirus neutralisation and antibody avidity

Pseudovirus neutralisation was measured with a label-free surrogate neutralisation assay (developed at a San Francisco General Hospital laboratory) that uses a thin-film interferometry immunoassay analyser.14 The label-free surrogate neutralisation assay measures the binding ability of the SARS-CoV-2 RBD to the angiotensin converting enzyme 2 receptor after neutralising the RBD with antibodies in the serum. The neutralisation index is calculated as the ratio of binding ability of the RBD to the receptor after neutralisation to the full binding ability without neutralisation. The neutralising antibody titre is defined as the reciprocal of the dilution resulting in a 50% neutralisation index. Antibody avidity, a measure of the functional affinity of antibodies to the SARS-CoV-2 spike RBD, was assayed with previously described methods.15 Antibody avidity is calculated as the ratio of RBD-IgG-anti-IgG complexes measured after use of the dissociation agent (urea) to the reference (running buffer), presented as a percentage. IgG avidity typically increases with greater time since infection, although patients with COVID-19 requiring intensive care unit admission have higher avidity than those who do not.15

Clinical data

Medical conditions including type 2 diabetes, cardiovascular disease (including hypertension, cerebrovascular disease, coronary artery disease, and heart failure), chronic pulmonary disease (including chronic obstructive pulmonary disease, asthma, pulmonary hypertension, interstitial lung disease), and HIV were assessed using International Classification of Diseases (revision 10) codes downloaded from the medical record within the previous 6 months. Severe COVID-19, assessed via chart review, was defined as oxygen saturation of less than 94% on room air, respiratory rate of more than 30 breaths per min, or arterial partial pressure of oxygen/fractional concentration of oxygen in inspired air of more than 300 mm Hg. Experience of homelessness was assessed through clinic records and was available only for people living with HIV.

Statistical analysis

We adjusted absolute seroprevalence and 95% CIs for test sensitivity.16 We compared seroprevalence by HIV status via multivariable mixed-effects logistic regression models, accounting for the matched structure of the data (random effects for the matched group), adjusting for age (by 10 year age groups), sex, race or ethnicity, and clinical factors (ie, history of cardiovascular or pulmonary disease, and type 2 diabetes). In the HIV-specific model, HIV-specific factors were included: CD4 count (dichotomised at 200 cells per µL), suppressed versus unsuppressed viral load (dichotomised at 200 copies per µL), and experience of homelessness. Severe COVID-19 among participants with evidence of past infection (IgG or PCR) was compared by HIV status with multivariable mixed-effects logistic regression, adjusting for age and sex, although profile likelihood CIs were used given very few outcomes. For participants with reactive SARS-CoV-2 IgG, we compared IgG concentrations (measured in relative fluorescent units) by HIV status with natural log-transformed mixed-effects linear models, adjusted for age and sex; the same process was repeated additionally adjusting for time since PCR-confirmed infection in participants with a previous positive PCR test. To
compare neutralising antibody titres among participants with past infection by HIV status, we used natural-log-transformed mixed-effects interval regression, adjusting for the same factors. To compare antibody avidity percentage by HIV status, we used a mixed-effects generalised linear model from the binomial distribution, adjusting for the same factors. The correlations among natural log-transformed IgG concentration, natural log-transformed pseudovirus neutralising antibody titres, and antibody percentage avidity were examined using Spearman’s rank correlation. Statistical analyses were done with Stata SE (version 15.1) and graphs were made in R (version 4.0.5).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

1138 samples from 955 people living with HIV and 1118 samples from 1062 people without HIV were tested (figure 1; table 1). 103 samples from 101 individuals showed evidence of a positive SARS-CoV-2 IgG test, with 33 samples available from 31 people living with HIV versus 70 samples from 70 people without HIV. 24 (77%) of 32 samples from people living with HIV were male sex at birth compared with 34 (49%) of 70 without HIV; median age was 50 years (IQR 40–56) and 51 years (43–58), respectively. 48 (48%) of 101 participants (18 with HIV and 30 without) with serology consistent with past SARS-CoV-2 infection had a previous positive PCR test documented within the health system (median 66 days [IQR 41–111] with serology consistent with past SARS-CoV-2 infection 48 (48%) of 101 participants (18 with HIV and 30 without) with serology consistent with past SARS-CoV-2 infection had a previous positive PCR test documented within the health system (median 66 days [IQR 41–111] previously among people living with HIV vs 56 days [28–94] previously among people without HIV, p=0.48).

Among people living with HIV, the adjusted seroprevalence for SARS-CoV-2 IgG was 3.7% (95% CI 2.4–5.9) compared with 7.4% (5.7–9.2) in people without HIV (adjusted odds ratio [OR] 0.50, 95% CI 0.30–0.83). In the sensitivity analysis, if the test sensitivity were decreased to 70%, the seroprevalence would increase to 4.7% (95% CI 2.9–6.4) among people living with HIV versus 7.4% (5.7–9.2) in people without HIV. 4.7% (95% CI 2.9–6.4) among people living with HIV (adjusted OR 0.50, 95% CI 0.30–0.83).

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Among people living with HIV with severe COVID-19, three of five individuals had a CD4 cell count of less than 200 cells per μL, reflecting greater than 25 times odds of severe disease with low CD4 cell counts, although the CI was very wide given very few outcomes (OR 25·49, 95% CI 1·41–1805·02).

In people with evidence of SARS-CoV-2 seropositivity, adjusting for age and sex, SARS-CoV-2 IgG concentration was lower (percentage change –42%, 95% CI –16 to –59) among people with HIV than among those without HIV (figure 2). The following factors were not associated with a percentage change in IgG concentrations: age (7%, 95% CI –6 to 22, per 10 years); sex (–3%, –32 to 37); cardiovascular disease (–4%, –32 to 37); type 2 diabetes (29%, –10 to 83); and pulmonary disease (4%, –57 to 152). IgG concentrations were lower among people with CD4 counts of less than 200 cells per μL than among those with counts of 200 cells or more per μL, although the 95% CI was wide (percentage change –50%, 95% CI –81 to 29); unsuppressed viral load was not associated with IgG concentrations (10%, –56 to 280). For IgG pseudovirus neutralising antibodies, people living with HIV had lower titres than those without HIV (percentage change –53%, 95% CI –1 to –78; figure 3). Antibody avidity was similar between people living with HIV and those without HIV (percentage change 10%, 95% CI –28 to 48; figure 4).

In the individuals who had a previous PCR test confirming infection, analyses were additionally adjusted for time since the PCR test. Following this adjustment, IgG concentrations were lower among people living with HIV compared with those without HIV (percentage change –53%, 95% CI –4 to –76). For pseudovirus neutralising antibodies, titres were also lower among people with HIV than among those without HIV (percentage change –67%, 95% CI –25 to –86). Antibody avidity was similar among people with HIV compared with those without HIV (percentage change 7%, 95% CI –73 to 87).

Natural log-transformed IgG concentrations and natural log-transformed pseudovirus neutralising antibody titres were correlated ($\rho=0⋅6; p<0⋅0001$); neutralising antibody titres and antibody avidity were negatively correlated ($p=0⋅0060$); and IgG concentrations were not correlated with antibody avidity ($p=0⋅40$).

**Discussion**

In this study among outpatients in a municipal health-care system during the COVID-19 epidemic, seroprevalence of SARS-CoV-2 was about two times lower among people with HIV than those without HIV (adjusted for age and sex: –53%, 95% CI –1 to –78). Lower concentrations of IgG and pseudovirus neutralising antibodies were observed among people living with HIV compared with those without HIV (adjusted for age and sex: –53%, 95% CI –4 to –76; –67%, 95% CI –25 to –86). Antibody avidity was similar between people living with HIV and those without HIV (percentage change 7%, 95% CI –73 to 87).
People living with HIV probably had fewer SARS-CoV-2 infections as a result of greater caution and sheltering in place, which in turn was probably attributable to higher perceived susceptibility, experience of the HIV epidemic, or both. Given that people with chronic medical conditions associated with severe COVID-19 other than HIV did not have reduced exposure to SARS-CoV-2, it is also possible that the additional services available to people living with HIV through the Ryan White Care Program (a US payor of last resort for those without insurance coverage) and other services (ie, food, housing, and psychosocial support) might have facilitated the ability of people living with HIV to shelter in place. Given the ongoing risk of COVID-19, these programmes should be continued or intensified. In addition, we observed a strong association between Latinx ethnicity and past SARS-CoV-2 infection, reflecting the known dynamics of the local (and national) epidemic. To avoid worsening disparities in the COVID-19 pandemic, SARS-CoV-2 vaccination should be targeted to the communities disproportionately affected.

Although there were only seven cases of severe COVID-19 in this cohort (hence this analysis should be considered exploratory), there were a greater number of severe cases of COVID-19 among people living with HIV despite fewer infections overall, compared with the sample of people without HIV. Three of the five cases of severe disease among people living with HIV occurred among individuals with low CD4 cell counts, similar to previous findings. The risk of severe disease among people living with HIV should be studied in larger population-based studies that account for possible differential testing and asymptomatic infection through systematic seroprevalence analysis.

The lower IgG concentrations and lower pseudovirus neutralising antibody titres among people living with HIV than among those without HIV in this study suggest a diminished response to natural SARS-CoV-2 infection, mirroring what is known about the serological response of people living with HIV to vaccines for other viral pathogens. Our findings contrast with Alrubayyi and colleagues’ abstract, which did not find differences in IgG concentrations or pseudovirus neutralising titres by HIV status (n=82), and Pallikkuth and colleagues’ abstract, which did not find a difference in IgG concentrations by HIV status (n=36). Differences in the source population (virally suppressed people living with HIV on antiretroviral therapy for at least 2 years in Alrubayyi and colleagues’ abstract and all virally suppressed people living with HIV with a mean CD4 cell count of 859 cells per µL in Pallikkuth and colleagues’ abstract) or our study design, which adjusted for potential confounders (age, sex, and time since infection), might explain the differences in our findings. People living with HIV show more rapidly waning neutralising antibody titres in response to yellow fever vaccination, and respond less well to hepatitis B vaccination, and, depending on CD4 cells, do not mount equivalent immune responses to other vaccines. This lack of durable neutralising antibody responses is thought to be mediated by lower CD4-to-CD8 cell ratios, a chronic inflammatory state that can persist despite antiretroviral therapy, and altered germinal centre architecture. The acute effects of SARS-CoV-2 infection include perturbations in immune function, most notably lymphopenia. People living with HIV might be particularly vulnerable to such effects, especially when total lymphocytes or CD4 lymphocytes are abnormal at baseline. Furthermore, lymphopenia can predict disease severity of COVID-19. Finally, investigators from the Novavax COVID-19 vaccine South African sites reported that vaccine efficacy rose from 49% (95% CI 6–73) to 60% (20–80) when people living with HIV were excluded.

The similar antibody avidity among people living with HIV compared with people without HIV could represent similar time from infection in this date of collection-matched outpatient cohort. Avidity responses might be less affected by disease severity in cohorts with a greater
proportion of asymptomatic infection.\textsuperscript{15} Future studies that seek to examine the immune response to infection should attempt to control for time since infection, as we did in this study.

This study has several limitations. The SARS-CoV-2 IgG used in this study showed excellent specificity with good durability, but lower sensitivity.\textsuperscript{13} Sensitivity might be lower used in this study showed excellent specificity with good specificity. Moreover, a dual antibody approach, combining a higher sensitivity test as a screening test, could be considered. Given the relatively low seroprevalence in this study, test sensitivity probably played a smaller part than it would in higher prevalence settings, as shown by our sensitivity analysis. Systematic testing of remnant samples might not accurately represent the underlying population of people living with HIV or of people without HIV, and bias could result if subpopulations avoided presenting for outpatient laboratory testing differentially. Furthermore, participants who died as a result of COVID-19 would not be captured in our analysis, as they would not be able to present for follow-up testing. Our results should be considered reflective of the population engaged in outpatient care and using laboratory services in a municipal hospital. As the primary study goals were the comparison of people living with HIV versus those without HIV, rather than the absolute seroprevalence, potential bias is unlikely to have qualitatively affected our results. Overall, there were very few cases of severe disease and individuals with low CD4 counts with severe disease in this cohort, and these analyses should be considered exploratory. Last, we were unable to measure antibody temporal dynamics or anti-SARS-CoV-2 T-cell activity in our study, and had few individuals with previously PCR-confirmed infection. Future studies should characterise antibody temporal dynamics and the T-cell response among people living with HIV compared with people without HIV, including after vaccination.

In conclusion, people living with HIV had approximately two times lower seroprevalence of SARS-CoV-2 than people without HIV in an urban health-care system. Previous analyses might have inaccurately accounted for the ratio of infections to severe disease due to differential testing, although analyses should be repeated in larger population-based studies. Among people with confirmed infection, absolute IgG concentrations and pseudovirus neutralising antibody titres were lower among people living with HIV. People living with HIV should be followed up after vaccination, with antibody and T-cell activity measured when possible, to ensure they mount a sufficient immune response to prevent cases of severe COVID-19.

Contributors

MAS drafted the initial manuscript. MAS, MG, LBB, and MJP did the initial literature search. KLL and CY did the laboratory testing and method development. MAS and DVG analysed, had access to, and verified all the data. MAS, KLL, CY, DVG, MJF, TJH, MG, and LBB reviewed and edited the manuscript, and provided substantial comments. MAS, MG, and LBB made the decision to submit for publication.

Declaration of interests

MAS, DVG, TJH, MG, and LBB report funding from the US National Institutes of Health during conduct of the study. DVG reports personal fees from Gilead Sciences outside the submitted work. All other authors declare no competing interests.

Data sharing

Data are not available for sharing.

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