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Associations between HIV infection and clinical spectrum of COVID-19: a population level analysis based on US National COVID Cohort Collaborative (N3C) data

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Summary

Background Evidence of whether people living with HIV are at elevated risk of adverse COVID-19 outcomes is inconclusive. We aimed to investigate this association using the population-based National COVID Cohort Collaborative (N3C) data in the USA.

Methods We included all adult (aged ≥18 years) COVID-19 cases with any health-care encounter from 54 clinical sites in the USA, with data being deposited into the N3C. The outcomes were COVID-19 disease severity, hospitalisation, and mortality. Encounters in the same health-care system beginning on or after January 1, 2018, were also included to provide information about pre-existing health conditions (eg, comorbidities). Logistic regression models were employed to estimate the association of HIV infection and HIV markers (CD4 cell count, viral load) with hospitalisation, mortality, and clinical severity of COVID-19 (multinomial). The models were initially adjusted for demographic characteristics, then subsequently adjusted for smoking, obesity, and a broad range of comorbidities. Interaction terms were added to assess moderation effects by demographic characteristics.

Findings In the harmonised N3C data release set from Jan 1, 2020, to May 8, 2021, there were 1436622 adult COVID-19 cases, of these, 13170 individuals had HIV infection. A total of 26130 COVID-19 related deaths occurred, with 445 among people with HIV. After adjusting for all the covariates, people with HIV had higher odds of COVID-19 death (adjusted odds ratio 1.29, 95% CI 1.16–1.44) and hospitalisation (1.20, 1.15–1.26), but lower odds of mild or moderate COVID-19 (0.61, 0.59–0.64) than people without HIV. Interaction terms revealed that the elevated odds were higher among older age groups, male, Black, African American, Hispanic, or Latinx adults. A lower CD4 cell count (<200 cells per μL) was associated with all the adverse COVID-19 outcomes, while viral suppression was only associated with reduced hospitalisation.

Interpretation Given the COVID-19 pandemic’s exacerbating effects on health inequities, public health and clinical communities must strengthen services and support to prevent aggrivated COVID-19 outcomes among people with HIV, particularly for those with pronounced immunodeficiency.

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Introduction

As of Oct 7, 2021, SARS-CoV-2, which causes COVID-19, has been confirmed to have infected over 236 million people and has caused more than 4.8 million deaths worldwide.1 Since the first confirmed case of COVID-19 in the USA, the countrywide COVID-19 outbreak has surged quickly, making it one of the countries hardest hit by the pandemic.2 As the pandemic surges in the USA, it is important to identify patients at elevated risk of developing severe symptoms to inform clinical management decisions. Older age and presence of comorbidities are recognised as factors that increase the severity of COVID-19.3 Patients who have malignant disease or solid-organ transplants have overall poorer outcomes of COVID-19,4 but the evidence is less clear for people with other types of immunocompromising conditions, including people living with HIV.5

Existing evidence of the association between HIV infection and COVID-19 outcomes is mixed. Throughout the COVID-19 pandemic, data have been limited and have largely consisted of case reports or case series.6 According to a systematic review, COVID-19 prevalence among people with HIV was comparable to that in the general population although there were occasional reports of atypical, but no more severe, disease course relative to people without HIV.7 Later on, emerging data from observational cohort studies showed similar findings8; however, most of these studies were restricted to hospitalised patients. By contrast, several large population-based studies have found conflicting results. Large-scale studies conducted in the UK and South
Research in context

Evidence before this study
We searched PubMed on June 3, 2021, for population-based epidemiological studies comparing risk of severe COVID-19 outcomes between people living with and without HIV. The search strategy “HIV” OR “AIDS” AND “COVID-19” OR “coronavirus” OR “SARS-CoV-2” was used, with results being filtered to articles from the past year and with abstracts available, no language restrictions were applied. We identified 140 papers for screening. One UK study that was included as the comparison of interest reported that people with HIV seemed to be at an increased risk of COVID-19 mortality than those without. Another relevant study identified on the medRxiv preprint server found a higher risk of COVID-19 mortality among people with HIV than in the general population in Western Cape, South Africa.

Added value of this study
We used the US National COVID Cohort Collaborative data from more than 6.8 million people from 54 clinical sites to compare risks of the full spectrum of COVID-19 outcomes (ie, disease severity, hospitalisation, death) between people with HIV and people without. Those with HIV were at elevated odds of COVID-19 hospitalisation and mortality compared with people without HIV, even after accounting for demographic characteristics, lifestyle factors, and comorbidities. The association was more evident among people of an older age, males, and of Black or African American ethnicity. People with HIV with more pronounced immunodeficiency (low CD4 cell counts) might have more severe clinical course than people without.

Implications of all the available evidence
People with HIV in the USA, particularly those with pronounced immunodeficiency, seem to be at elevated risk of COVID-19 hospitalisation and mortality. The exacerbated COVID-19 outcomes in Black or African American and male people with HIV suggest profound health inequities faced during the COVID-19 pandemic. The robust risk assessment of this study could inform prioritisation of prevention messaging, disease monitoring and therapies, and vaccination for people with HIV, especially those with more pronounced immunodeficiency. Given the COVID-19 pandemic’s exacerbating effects on health inequities, public health and clinical communities must strengthen services and support to prevent aggravated COVID-19 outcomes among people with HIV, particularly for those with pronounced immunodeficiency.

Figure 1: Study participant selection
*The numbers for missing race data and missing ethnicity data did not add up to 730 because some records missed both data.

Africa suggested that people with HIV had a higher risk (more than double) of COVID-19 mortality than people without HIV, although different factors were adjusted in the different studies. A prospective study of patients hospitalised with COVID-19 showed an increased 28-day mortality in people with HIV after adjusting for age. One study in New York, USA, reported a standardised in-hospital mortality ratio of 1·23 for HIV patients. Prognosis, according to HIV immune status, is also difficult to evaluate because most studies from Europe and the USA reported on individuals with overall high CD4 cell counts. In the largest published cohorts, the potentially higher risk for poorer COVID-19 outcomes were observed in people with HIV with lower CD4 cell counts. Investigating whether people with virologically controlled HIV who are clinically stable will have a greater risk for COVID-19 complications than people without HIV is of great clinical significance.

Nevertheless, the evidence linking HIV status and COVID-19 outcomes is still scarce and some knowledge gaps remain. Several studies were based on only a small number of cases; some either did not have direct comparative data for people without HIV and HIV markers, or focused only on hospitalised patients. A large, multicentre, representative clinical dataset is needed to provide timely and robust risk assessment and thereby inform prioritisation of critical therapies, vaccination, and targeted intervention. Using the US National COVID Cohort Collaborative (N3C) data, this study aims to understand the role of HIV infection and levels of immunity affecting the COVID-19 clinical outcomes (ie, disease severity, hospitalisation, and mortality).
Methods

Study design and population

The N3C Enclave, sponsored by multiple institutes of the US National Institutes of Health,\(^\text{21}\) is the largest cohort of US COVID-19 cases and representative controls to date. The N3C is a large, multicentre dataset updated on an ongoing basis that harmonises electronic health records data for all individuals with laboratory confirmed, suspected, or possible COVID-19 during any encounter after Jan 1, 2020.\(^\text{4}\) Control cases are those individuals who have tested negative for COVID-19, and are demographically matched on age group, sex, race, and ethnicity within the submitting health-care system at a case-to-control ratio of 1 to 2.\(^\text{4}\) All patients in the N3C Enclave include historical data within the same health-care system as of Jan 1, 2018, which provides information about pre-existing health conditions (eg, comorbidities) and other medical history (look back data).\(^\text{19}\) We included all adult (aged ≥18 years) COVID-19 cases from 54 clinical sites across the USA with data being deposited into the N3C and harmonised into a data release set from Jan 1, 2020, to May 8, 2021. The data ingestion and harmonisation process are described in the appendix (p 2). We excluded people with missing age, race, and ethnicity data because absence of data on these key variables probably indicated that poor data quality for these records.

The N3C data transfer to the National Center for Advancing Translational Sciences (NCATS) was done under a Johns Hopkins University Reliance Protocol (IRB00249128) or individual site agreements with the US National Institutes of Health (NIH). An institutional data use agreement was signed between the University of South Carolina and NCATS N3C Data Enclave. The N3C Data Enclave is managed under the authority of the NIH. The N3C Data Enclave is approved under the authority of the NIH Review Board. The analyses reported in this Article were approved separately by the institutional review board of University of South Carolina (Pro00107403) with data access. The NIH’s N3C data access committee approved the data use request for this project (RP-E72986).

Procedures

The N3C phenotype\(^\text{18}\) is designed to be inclusive of any diagnosis codes, procedure codes, laboratory tests, or combination thereof that might be indicative of COVID-19 (eg, Centers for Disease Control and Prevention coding guidance\(^\text{5}\)). N3C includes patients with any encounter after Jan 1, 2020, who have either one or more of a set of a priori-defined SARS-CoV-2 laboratory tests with a positive result; or one or more strong positive diagnostic codes from the International Classification of Diseases (ICD) 10 or SNOMED tables; or two or more weak positive diagnostic codes from the ICD-10 or SNOMED tables. The cohort definition is publicly available on GitHub.\(^\text{6}\)

N3C harmonises data across four clinical data models (ACT Network, PCORnet, Observational Health Data Sciences and Informatics, and TriNetX) and provides a unified analytical platform in which data are encoded by use of the Observational Medical Outcomes Partnership (OMOP) version 5.3.1.\(^\text{20}\) The concept sets in OMOP\(^\text{20,21}\) are a list of concepts from the standardised vocabulary that, taken together, describe a topic of interest for a study, were used to identify each clinical concept (eg, laboratory measure, conditions, or medication). Data domains extracted by N3C include demographics, encounter details, medications, diagnoses, procedures, vital signs, laboratory results, procedures, and social history. Specific variables included in each domain are listed in each model’s

### Table 1

| Social demographics | Overall (n=1,436,622) | People with HIV (n=13,170) | People without HIV (n=1,423,452) | p value |
|---------------------|-----------------------|-----------------------------|----------------------------------|--------|
| **Age, years**      |                       |                             |                                  |        |
| 18-49               | 47 (32-61)            | 49 (36-60)                  | 47 (32-61)                       |        |
| 50-64               | 371,489 (26.86%)      | 4533 (34.42%)               | 366,956 (25.78%)                |        |
| ≥65                 | 295,054 (20.54%)      | 1934 (14.68%)               | 293,100 (20.59%)                |        |
| **Sex**             |                       |                             |                                  |        |
| Male                | 645,956 (44.96%)      | 9641 (73.20%)               | 636,315 (44.70%)                | <0.0001|
| Female              | 789,148 (54.93%)      | 3521 (26.74%)               | 785,627 (55.19%)                |        |
| **Race**            |                       |                             |                                  |        |
| Black or African American | 202,947 (14.13%)   | 4092 (31.07%)               | 198,855 (13.97%)                | <0.0001|
| White               | 853,997 (59.44%)      | 6013 (45.66%)               | 847,984 (59.57%)                |        |
| Asian, other, or unknown | 379,678 (26.43%) | 3065 (23.27%)               | 376,613 (26.46%)                |        |
| **Ethnicity**       |                       |                             |                                  |        |
| Hispanic or Latinx  | 213,205 (14.84%)      | 2227 (16.91%)               | 210,978 (14.82%)                | <0.0001|
| Not Hispanic or Latinx | 1,001,390 (69.70%)  | 9479 (71.97%)               | 991,911 (69.68%)                |        |
| Other or unknown    | 222,027 (15.45%)      | 1464 (11.12%)               | 220,563 (14.49%)                |        |

### Comorbidities

- Diabetes
- Renal disease
- Congestive heart failure
- Chronic pulmonary disease
- Peripheral vascular disease
- Stroke
- Cancer
- Dementia
- Myocardial infarction
- Liver disease
- Rheumatological disease
- Hemiplegia or paraplegia
- Peptic ulcer disease

### Lifestyle factors

- Body-mass index, kg/m\(^2\)
- Smoking status
- Non-smoker
- Current or former smoker

See Online for appendix

For more on the management of the N3C Data Enclave see https://ncats.nih.gov/n3c/resources

See https://ncats.nih.gov/n3c/ for appendix

https://ncats.nih.gov/n3c/
documentation (ie, tables). Both concept sets and tables were used to define variables of interest.

A total of 11,170 people with HIV were identified by use of N3C concept sets and codes in the phenotype template (appendix p 2), which mapped to various domain tables, including any HIV diagnosis code (ICD-10 codes, SNOMED codes) in the condition occurrence table, HIV laboratory tests (LOINC codes) in the measurement table, and HIV drug exposure in the drug exposure table. Patients who met at least one of these inclusion criteria were counted as people with HIV in our study. Within the population of people with HIV, the most recent value of CD4 cell count and viral load before initial COVID-19 diagnosis (but during the preceding 18 months) was retrieved for analysis from laboratory tests (LOINC codes) in the measurement table. The absolute CD4 count was categorised into less than 200, 200–500, and more than 500 cells per µL. HIV viral load was classified into less than 200 copies per mL (viremically suppressed) and 200 or more copies per mL (unsuppressed).

COVID-19 hospitalisation in the current study was identified by case insensitive string matching “inpatient visit” or “inpatient critical care facility” or “emergency department” or moderate, and severe (including mortality or hospice). The binary death outcome was determined through the death table. The most severe outcome was observed, then the encounter in which the most severe outcome was observed, then the longest visit, and finally the most recent visit. Clinical severity was classified with the Clinical Progression Scale (CPS) established by WHO for COVID-19 research. On the basis of WHO criteria, N3C placed patients into strata defined by the maximum clinical severity from selected critical visits: unaffected (ie, no laboratory test, laboratory test negative, or suspected COVID-19 with laboratory tests, but identified by other diagnosis codes or procedure codes), mild (outpatient, WHO severity 1–3); mild emergency department (outpatient with emergency department visit, WHO severity 1–3); mild emergency department (outpatient with emergency department visit, WHO severity 3), moderate (hospitalised without invasive ventilation, WHO severity 4–6), severe (hospitalised with invasive ventilation or extracorporeal membrane oxygenation, WHO severity 7–9), and mortality or hospice (hospital mortality or discharge to hospice, WHO severity 10). Because of the small number in certain categories among people with HIV, we collapsed and regrouped WHO CPS categories into three categories: unaffected, mild (including mild emergency department) or moderate, and severe (including mortality or hospice). The binary death outcome was determined through the death table. The month of each patient’s COVID-19 diagnosis was also retrieved from laboratory test and clinical conditions.

We included lifestyle factors such as smoking status and obesity (indicated by body-mass index [BMI]). Smoking status was defined by a concept set, whose member comprised of “ARIScience-Smoker-1A”, “smoker_NM1”, “UVA Former Smoker”, and “UVA Current Smoker” in the observation and condition tables. BMI information was retrieved from patient severity score tables. The comorbidities were defined based on the ICD codes in the updated Charlson Comorbidity Index (CCI) scoring instrument. A series of binary variables were used to indicate the presence or absence of each comorbidity, such as myocardial infarction, chronic pulmonary disease, and chronic kidney disease. The concept code sets we used to define each comorbidity was listed in the appendix (p 2). The adapted CCI score (subtracting the score assigned to HIV diagnosis) was also calculated for the analysis.

**Statistical analysis**

Descriptive statistics were used to examine the socio-demographics of all the COVID-19 cases by HIV status. The variable distributions between COVID-19 patients with and without HIV infection were summarised and compared with the independent t test (for continuous variables) or χ2 test (for categorical variables). For all COVID-19 outcomes (ie, hospitalisation, death, and

| Table 1: Characteristics of adult COVID-19 cases by HIV status in National COVID Cohort Collaborative data, Jan 1, 2020, to May 8, 2021 |
|---|---|---|---|
| Overall (n=1,436,622) | People with HIV (n=13,170) | People without HIV (n=1,423,452) | p value |
| COVID-19 death | 26,130 (1.82%) | 445 (3.38%) | 25,685 (1.80%) | <0.0001 |
| COVID-19 hospitalisation | 262,311 (18.26%) | 3,724 (28.28%) | 258,587 (18.17%) | <0.0001 |
| COVID-19 disease severity | | | | |
| Unaffected | 476,250 (33.15%) | 6,395 (48.56%) | 469,855 (33.01%) | <0.0001 |
| Mild or moderate | 895,491 (62.33%) | 6,209 (47.15%) | 889,282 (62.47%) | - |
| Severe | 25,054 (1.74%) | 475 (3.61%) | 24,579 (1.73%) | - |
| Unknown | 39,827 (2.77%) | 91 (0.69%) | 39,736 (2.79%) | - |
| Most recent CD4 count, cells per µL | >500 | 920 (59.59%) | 920 (59.59%) | - |
| 200–500 | 445 (28.82%) | 445 (28.82%) | - |
| <200 | 179 (11.59%) | 179 (11.59%) | - |
| Most recent viral suppression, <200 copies per mL | 1265 (81.93%) | 1265 (81.93%) | - |

Data are median (IQR) or n (%). NA—not applicable. “Per National COVID Cohort Collaborative Policy, we removed the unknown category because this category included less than 20 individuals in the people living with HIV group. (Includes both the mild (outpatient, WHO severity 1–3) and mild emergency department (outpatient with emergency department visit, WHO severity >3) categories. Includes both severe (hospitalised with invasive ventilation or extracorporeal membrane oxygenation, WHO severity 7–9) and mortality or hospice (hospital mortality or discharge to hospice, WHO severity 10) categories based on WHO criterion. Defined as the most recent value in the 18 months before initial COVID-19 diagnosis.)
### Table 2: Association between HIV status and COVID-19 clinical spectrum outcomes based on hierarchical logistic regression models

**BMI=body-mass index. CCI= Charlson Comorbidity Index. OR=odds ratio.**

| Interaction models** | Unadjusted model | Adjusted for age, sex, race and ethnicities | Adjusted for BMI, comorbidities, sex and HIV status | Adjusted for BMI, comorbidities, age and HIV status | Adjusted for BMI, comorbidities, age, sex, race and HIV status |
|----------------------|------------------|------------------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|
| **Sex and HIV status** | With HIV and male vs female | 3.13 (2.89-2.88) | 1.32 (2.10-1.44) | 0.90 (0.74-0.97) | 1.24 (1.11-1.25) |
| Without HIV and male vs female | 1.54 (1.50-1.59) | 1.16 (1.15-1.17) | 1.31 (1.19-1.33) | 1.75 (1.70-1.80) |
| **Race and HIV status** | With HIV and Black or African American vs White | 3.64 (2.59-5.13) | 3.16 (2.83-3.49) | 1.10 (1.00-1.01) | 3.25 (2.44-4.41) |
| With HIV and Asian, other, or unknown vs White | 4.22 (2.88-6.46) | 2.85 (2.48-3.27) | 0.79 (0.70-0.89) | 3.63 (2.52-5.23) |
| Without HIV and Black or African American vs White | 1.16 (1.12-1.20) | 1.66 (1.64-1.68) | 0.92 (0.91-0.93) | 1.25 (1.21-1.31) |
| Without HIV and Asian, other, or unknown vs White | 1.16 (1.11-1.20) | 1.35 (1.32-1.37) | 1.01 (1.01-1.02) | 1.18 (1.13-1.22) |
| **Ethnicity and HIV status** | With HIV and Hispanic or Latinx vs not Hispanic or Latinx | 7.06 (2.52-10.37) | 3.22 (2.88-3.57) | 0.25 (0.20-0.3) | 2.33 (1.55-3.50) |
| With HIV and other or unknown vs not Hispanic or Latinx | 2.66 (2.70-5.59) | 1.70 (1.42-2.03) | 0.39 (0.34-0.45) | 1.98 (1.28-3.05) |
| Without HIV and Hispanic or Latinx vs not Hispanic or Latinx | 0.80 (1.80-9.12) | 1.26 (1.24-1.28) | 1.09 (1.08-1.10) | 1.38 (1.32-1.44) |
| Without HIV and other or unknown vs not Hispanic or Latinx | 0.87 (0.84-0.91) | 0.62 (0.61-0.63) | 0.72 (0.71-0.73) | 0.77 (0.74-0.81) |

**Stratified models, people with HIV vs people without HIV at each subgroup**

| Age, years | 18–49 (n=770,099) | 50–64 (n=371,489) | ≥65 (n=295,034) |
|-----------|------------------|------------------|-----------------|
| **Sex** | Female (n=645,956) | 1.20 (0.97-1.51) | 1.27 (1.06-1.50) |
| Male (n=789,148) | 1.24 (0.93-1.67) | 1.27 (1.17-1.34) | 0.62 (0.59-0.66) |
| Race | White (n=837,997) | 1.21 (1.11-1.34) | 1.11 (1.03-1.18) |
| Black or African American (n=202,947) | 1.26 (1.06-1.50) | 1.27 (1.18-1.36) | 0.59 (0.55-0.64) |

| Asian, or unknown (n=37,968) | 1.27 (1.02-1.57) | 1.19 (0.99-1.39) | 0.59 (0.55-0.64) |

**Results for interaction terms adjusted demographic characteristics (age, sex, race, ethnicity), smoking, BMI, and each individual comorbidities listed in the previous footnote.**

With these COVID-19 outcomes. A subsample of people with HIV (n=1544) who had data for both CD4 cell count and viral load were available for analysing the association between HIV markers and COVID-19 outcomes. In step one we first adjusted for age (18–49,
50–64, and ≥65 years), sex (male, female), race (Black or African American; White; Asian or other or unknown) and ethnicity (Hispanic or Latinx; not Hispanic or Latinx; others or unknown). In step two we subsequently adjusted for smoking (non-smoker, current, or former smoker) and obesity (BMI >30 kg/m², ≤30 kg/m², or unknown). In step three we adjusted for an array of comorbidities (hemiplegia or paraplegia, dementia, liver disease, myocardial infarction, congestive heart failure, chronic pulmonary disease, cancer, diabetes, stroke, peripheral vascular disease, rheumatological disease, renal disease, and peptic ulcer disease) or CCI score, and month of COVID-19 diagnosis. For COVID-19 severity, multinomial logistic regressions were applied with unaffected COVID-19 individuals as a reference group. Specifically, the same aforementioned factors were included in multiple multinomial regressions (mild or moderate vs unaffected, severe vs unaffected). Because information from at least one health-care encounter is required to generate index encounter and define COVID-19 severity, we first conducted multinomial regressions among the full sample in the main analysis, with those cases without health-care encounter information grouped into the first category of CPS (ie, unaffected). Then we did a sensitivity analysis to exclude those without health-care encounter information from the main analysis (ie, 1396795 [97.2%] of total sample). We did additional sensitivity analyses with people with and without HIV matched on age group, sex, and number of comorbidities using 1:2 and 1:4 ratios. Collinearity was assessed by calculating variance inflation factors for each covariate listed in the adjusted models.

To investigate whether age, sex, race, and ethnicity could be potential effect modifiers of HIV status, we fitted interaction terms between age (18–49, 50–64, and ≥65 years), sex, race (White vs Black or African American, and White vs Asian, other, or unknown), ethnicity (not Hispanic or Latinx vs Hispanic or Latinx) and HIV status in all analyses (not all the interaction analysis results are shown due to space limitation but are available from the authors upon request). We fitted stratified models with HIV infection, demographics, lifestyle, and comorbidities on each selected subgroup (ie, male; female; aged 18–49 years; aged 50–64 years; aged ≥65 years; White; Black or African American; and Asian, other, or unknown). We implemented all analyses with SQL and R (version 3.5) and created reproducible pipelines in the Code workbook on N3C Data Enclave.

Role of the funding source

The National Center for Advancing Translational Science contributed to the design, maintenance, and security of the N3C Enclave. The funders of the study had no role in the study design, data analysis, data interpretation, or writing of the report.

Results

In this population level analysis, of the 5830841 COVID-19 cases and controls harmonised into the N3C data release set from Jan 1, 2020, to May 8, 2021, a total of 1436622 adult individuals who were positive for COVID-19 were included in this study (figure 1).

Compared with people without HIV, those with HIV had a narrower age distribution overall (lower proportion aged ≥65 years) but the median age was 2 years older (49 vs 47 years); a greater proportion were males and people of Black or African American race. People with HIV had higher prevalence of all comorbidities, including diabetes, chronic pulmonary disease, and liver disease (table 1).

Among the 1436622 COVID-19 cases, 262331 (18.26%) were hospitalised and 26130 (1.82%) died. People with HIV disproportionately required more COVID-19 related hospitalisation than those without (28.28% vs 18.17% [table 1]). Crude odds ratios (ORs) of COVID-19 hospitalisation and death were both higher in people with HIV (table 2). The associations were both attenuated, but remained significant, after sequentially adjusting for demographics, lifestyle factors, comorbidities, and month of COVID-19 diagnosis hospitalisation (OR [aOR] 1.20, 95% CI 1.15–1.26; mortality 1.29, 1.16–1.44; table 2; figure 2; appendix pp 3–6).

Compared with people without HIV, those with HIV had a higher proportion of severe illness (3.61% vs 1.73%), but a lower proportion of mild or moderate illness (47.15% vs 62.47%; table 1). Using unaffected COVID-19 individuals as a reference group in multinomial regression, people with HIV had lower odds of presenting with mild or moderate illness than people without HIV even after adjusting for all the covariates (aOR 0.61, 95% CI 0.59–0.64); by contrast, the odds of severe COVID-19 were comparable after sequential adjustments for all the covariates (1.04, 0.94–1.16; table 2; figure 2; appendix pp 7–8). In the sensitivity analysis (excluding individuals without health-care encounter information), the results were similar to the findings in the models with the full sample (appendix pp 9–10). The results from additional sensitivity analyses among the subsample of 1:2 and 1:4 matched people with and people without HIV were similar to the findings in the primary analyses (appendix p 11). Among 1544 people with HIV with both CD4 cell count and viral load data, a lower CD4 cell count (<200 cells per µL) was positively associated with all the adverse COVID-19 outcomes (ie, disease severity, hospitalisation, mortality) after adjusting for all the covariates, while viral suppression was only negatively associated with hospitalisation (table 3).

The interaction effect of age and HIV status suggested that the ageing process in people with HIV exacerbated all the adverse outcomes of COVID-19. Those with HIV in the older age groups had much higher odds of death and hospitalisation than those without HIV in the same age range. As another potential modifier, male sex could...
Unadjusted
Adjusted for age + sex + race + ethnicity
Adjusted for age + sex + race + ethnicity + smoking + BMI
Adjusted for age + sex + race + ethnicity + smoking + BMI + comorbidities + month of diagnosis
Adjusted for age + sex + race + ethnicity + smoking + BMI + comorbidities + month of diagnosis + CCI

Age 18–49 years
Aged 50–64 years
Aged ≥65 years
Female
Male
White
Black or African American
Asian, other, or unknown

Odds ratio (95% CI)
also interact with HIV infection in increasing the odds of severe clinical outcomes of COVID-19, yet with a smaller magnitude. Similar results were found in the interaction of race or ethnicity and HIV status, by which Black or African American race and Hispanic or Latinx ethnicity interacted with HIV infection in developing higher odds of adverse COVID-19 outcomes. Stratified models revealed that the elevated odds were higher in the similar subgroups (eg, older age, male sex, and Black or African American race; table 2; appendix pp 12–13).

To adjust the role of cumulative burden of comorbidities in the model development, CCI was considered in all adjusted models. However, a high collinearity was detected between CCI and the other covariates (variance inflation factor=7–97). Therefore, additional models were developed to include CCI (replacing individual comorbid conditions) in the analyses. Findings from the two sets of adjusted models (adjusting individual comorbid condition vs adjusting CCI) were similar (appendix pp 14–16).

Discussion

Our population-level analysis from N3C data found that people with HIV might not be disproportionately vulnerable to SARS-CoV-2 infection but are more likely to be hospitalised and die from COVID-19, although such risk might be attenuated when other confounding factors are taken into consideration. The associations between HIV and these outcomes seem particularly pronounced among older people, males, Black or African American adults, and Hispanic or Latinx adults. Among people with HIV, we find that the risks for poor COVID-19 outcomes are much higher among those with lower CD4 cell counts (<200 cells per µL) and an association between viral suppression and the COVID-19 outcome of hospitalisation. The to the best of our knowledge, this is the largest population-level analysis to investigate the role of HIV infection in COVID-19 clinical spectrum across the USA. Our results show a smaller but consistent effect of HIV infection on COVID-19 related mortality with large population-based cohort studies from South Africa and the UK. The differences of effect size between these three studies could possibly be explained by the different sample characteristics. Results from the interaction effects illustrate that the adverse COVID-19 outcomes among people with HIV might be explained by the overlapping demographic (eg, male and African American) and co-morbidity characteristics (eg, a significant interaction effect of HIV and CCI, and data not shown but available upon request) that are highly prevalent in this population. Our study shows people with HIV require more COVID-19 hospitalisation, at a level of risk similar to a recent New York study and other USA studies using TriNetX network data, which controlled for BMI and various comorbidities.

Regarding the clinical severity of COVID-19, people with HIV are less likely to have mild illness, but more likely to have severe outcomes when only adjusting for demographics and lifestyle factors. The adjustment for comorbidities obviates the estimated risk of severe outcomes among people with HIV. This finding suggests

Table 3: Estimates for the associations between HIV status and COVID-19 clinical spectrum outcomes

| HIV factors | Death, OR (95% CI)* | Hospitalisation, OR (95% CI)* | Mild† or moderate vs unaffected, OR (95% CI)* | Severe‡ vs unaffected, OR (95% CI)* |
|-------------|----------------------|------------------------|--------------------------------------------|----------------------------------|
| Most recent CD4 count§ |                       |                        |                                            |                                  |
| >500 cells per µL | 1.00                  | 1.00                   | 1.00                                       | 1.00                             |
| 200–500 cells per µL | 1.49 (0.55–4.03)      | 1.28 (0.94–1.75)       | 1.15 (0.89–1.48)                           | 1.62 (0.59–4.44)                 |
| <200 cells per µL | 3.10 (1.06–9.13)      | 2.73 (1.80–4.14)       | 1.51 (1.04–2.12)                           | 3.91 (1.31–11.62)                |
| Most recent viral suppression, <200 copies per mL§ | 0.71 (0.27–1.83) | 0.69 (0.49–0.97) | 0.87 (0.64–1.17) | 0.62 (0.24–1.57) |
| Social demographics |                       |                        |                                            |                                  |
| Age, years |                       |                        |                                            |                                  |
| 18–49 | 1.00 | 1.00 | 1.00 | 1.00 |
| 50–64 | 1.51 (0.52–4.39) | 0.88 (0.65–1.20) | 0.60 (0.47–0.77) | 0.62 (0.23–1.69) |
| >65 | 3.39 (1.07–10.8) | 0.79 (0.50–1.25) | 0.37 (0.25–0.55) | 0.58 (0.17–1.96) |
| Male vs female |                       |                        |                                            |                                  |
| Male | 1.12 (0.42–2.94) | 0.88 (0.63–1.23) | 0.69 (0.52–0.91) | 1.29 (0.47–3.54) |
| Female | 1.00 | 1.00 | 1.00 | 1.00 |
| Race |                       |                        |                                            |                                  |
| White | 1.00 | 1.00 | 1.00 | 1.00 |
| Black or African American | 2.33 (0.82–6.67) | 1.77 (1.26–2.47) | 1.56 (1.18–2.04) | 2.08 (0.74–5.83) |
| Asian, other, or unknown | 1.12 (0.30–4.18) | 1.66 (1.09–2.54) | 1.32 (0.93–1.86) | 1.36 (0.36–5.06) |
| Ethnicity |                       |                        |                                            |                                  |
| Not Hispanic or Latinx | 1.00 | 1.00 | 1.00 | 1.00 |
| Hispanic or Latinx | 1.33 (0.33–5.35) | 0.83 (0.55–1.25) | 0.93 (0.68–1.27) | 0.89 (0.23–3.50) |
| Other or unknown | 2.67 (0.69–10.35) | 0.82 (0.45–1.50) | 0.48 (0.29–0.80) | 1.16 (0.27–5.01) |
| Lifestyle factors |                       |                        |                                            |                                  |
| Body-mass index, kg/m² |                       |                        |                                            |                                  |
| ≤30 | 1.00 | 1.00 | 1.00 | 1.00 |
| >30 | 3.30 (1.14–9.53) | 0.67 (0.47–0.96) | 0.77 (0.55–1.08) | 2.70 (1.00–7.29) |
| Unknown | 1.71 (0.58–5.04) | 0.22 (0.16–0.31) | 0.45 (0.34–0.60) | 0.52 (0.16–1.68) |
| Smoking status |                       |                        |                                            |                                  |
| Non-smoker | 1.00 | 1.00 | 1.00 | 1.00 |
| Current or former smoker | 2.57 (1.03–6.43) | 1.09 (0.80–1.47) | 0.46 (0.35–0.60) | 1.41 (0.57–3.53) |

(Table 3 continues on next page)
that people with HIV might show less symptoms at the earlier stage of SARS-CoV-2 infection. Such protection from the most serious sequelae of COVID-19 might be attributable to the possible anti-SARS-CoV-2 activity of tenofovir disoproxil fumarate plus emtricitabine, as suggested in both observational and randomised closed trials studies.\(^8\) Another hypothesis is that people with HIV with mild illness might be underrepresented (47.15% vs 62.33% in the overall group; table 1) because of higher stigma, increased fear of hospitalisation, higher social deprivation, and lower medical coverage when compared with people who do not have HIV. A consequence of such late linkage to care could be a higher risk of severe COVID-19.

As declining CD4 cell counts are associated with COVID-19 severity in general,\(^8\) people with HIV and low CD4 cell counts might have a raised risk of severe COVID-19.\(^6\) Our study supported this hypothesis and found that a lower CD4 cell count is associated with a higher risk of adverse COVID-19 outcomes, which is also in agreement with another multicentre study conducted by Dandachi and colleagues.\(^8\) No association was observed between viral suppression and COVID-19 disease severity or mortality. Although our study observed the protective effect of viral suppression in reducing disease severity or mortality. Although our study observed the protective effect of viral suppression in reducing disease severity or mortality. Therefore, these potential misclassifications might change as the phenotype template of HIV patients changes as a result of continuous data updates from different contributing sites. Additionally, the release of other available concept sets might yield different classifications as well. However, previous studies have shown acceptable sensitivity and specificity of a similar approach.\(^8\) Therefore, these potential misclassifications are likely to be non-differential through-out the cohort and unlikely to change our conclusions. Third, some key exposure variables (eg, CD4 cell count, viral load, BMI, and smoking status) are not uniformly available or measured accurately across all the study sites; for example, a large proportion of patients have missing CD4 cell count and HIV viral load data. Furthermore, the effect of obesity on COVID-19 outcomes might be underestimated because of the large proportion of unknown responses and the uneven distribution of unknown responses between the two comparison groups. Moreover, the inability to separate the former smokers from current smokers in the dataset did not allow us to examine the effect of different smoking status between people living with HIV and people without HIV in adverse COVID-19 outcomes. Fourth, the adverse COVID-19 outcomes

| Comorbidities                  | Death, OR (95% CI)* | Hospitalisation, OR (95% CI)* | Mild or moderate vs unafflicted, OR (95% CI)* | Severe† vs unafflicted, OR (95% CI)* |
|--------------------------------|---------------------|-------------------------------|----------------------------------------------|-------------------------------------|
| Hemiplegia or paraplegia       | 4.73 (0.79–28.17)   | 5.55 (2.08–14.78)             | 2.17 (0.90–5.24)                             | 4.32 (0.54–35.37)                   |
| Dementia                       | 2.85 (0.55–14.91)   | 0.90 (0.31–2.61)              | 0.85 (0.32–2.28)                             | 5.94 (1.09–32.38)                   |
| Liver disease                  | 1.46 (0.61–3.40)    | 1.15 (0.83–1.58)              | 1.12 (0.85–1.48)                             | 1.54 (0.64–3.72)                    |
| Myocardial infarction          | 0.42 (0.09–2.05)    | 2.12 (1.13–3.98)              | 0.90 (0.50–1.61)                             | 0.22 (0.02–1.49)                    |
| Congestive heart failure       | 2.37 (0.77–7.25)    | 2.45 (1.49–4.04)              | 0.88 (0.54–1.43)                             | 1.86 (0.59–5.79)                    |
| Chronic pulmonary disease      | 0.76 (0.30–1.90)    | 1.21 (0.89–1.65)              | 1.08 (0.83–1.39)                             | 1.61 (0.68–3.78)                    |
| Cancer                         | 4.52 (1.85–11.03)   | 1.46 (0.98–2.19)              | 1.07 (0.75–1.54)                             | 3.56 (1.40–9.07)                    |
| Diabetes                       | 0.93 (0.35–2.49)    | 1.41 (1.01–1.96)              | 1.20 (0.92–1.58)                             | 1.57 (0.60–4.14)                    |
| Stroke                         | 1.03 (0.30–3.53)    | 1.28 (0.76–2.14)              | 0.75 (0.46–1.21)                             | 0.42 (0.09–1.96)                    |
| Peripheral vascular disease    | 0.79 (0.24–2.64)    | 1.32 (0.81–2.16)              | 2.21 (1.41–3.48)                             | 1.57 (0.47–5.27)                    |
| Rheumatologic disease          | 0%                  | 1.16 (0.56–2.39)              | 1.53 (0.86–2.72)                             | 0.00 (0.00–2.00)                    |
| Renal disease                  | 2.58 (1.02–6.49)    | 1.55 (1.06–2.27)              | 1.06 (0.75–1.49)                             | 3.06 (1.19–7.87)                    |
| Peptic ulcer disease           | 0.67 (0.06–7.21)    | 1.26 (0.52–3.02)              | 1.06 (0.48–2.33)                             | 0.69 (0.06–7.81)                    |
| Month of COVID-19 diagnosis    | 1.00 (0.92–1.08)    | 1.00 (0.97–1.03)              | 1.04 (1.01–1.06)                             | 1.03 (0.95–1.12)                    |

*Models adjusted demographics, lifestyle factors, comorbidities, and month of COVID-19 diagnosis. **Includes both the mild (outpatient, WHO severity 1–3) and mild emergency department (outpatient with emergency department visit, WHO severity ≥4) categories. §Defined as the most recent value 18 months before initial COVID-19 diagnosis. ¶In this subgroup of HIV patients with CD4 cell count and viral load data, the number of patients who died from COVID-19 was too small to calculate an estimate and 95% CI. **Includes both the moderate (hospitalised with invasive ventilation or extracorporeal membrane oxygenation, WHO severity 7–9) and mortality or hospice (hospital mortality or discharge to hospice, WHO severity 10) categories based on WHO criterion. 3Defined as the most recent value 18 months before initial COVID-19 diagnosis. **In this subgroup of HIV patients with CD4 cell count and viral load data, the number of patients who died from COVID-19 was too small to calculate an estimate and 95% CI.

Table 3: COVID-19 outcomes among people living with HIV by HIV CD4 counts and viral load level (n=15444)
might vary when stratifying by other vulnerable statuses of people with HIV, such as transgender individuals or injection drug users. However, codes for identifying these statuses were unavailable in this dataset.

In conclusion, using data from the largest COVID-19 population level analysis with a heterogeneous population in the USA, our study could identify people with HIV with mild or asymptomatic COVID-19 and examine the different risks for SARS-CoV-2 acquisition versus progression to severe disease or death once infected. In this large study, people with HIV have an elevated risk of adverse COVID-19 outcomes. The attenuated risk after controlling for comorbidities, which are more prevalent and typically occur at a younger age among people with HIV, indicates that certain underlying medical conditions had a greater influence on COVID-19 outcomes of this population. Our observation that people with lower CD4 cell counts are at a higher risk of poor outcomes suggests that people with a history of advanced immunosuppression might warrant closer observation and monitoring. The robust risk assessment of this study could inform prioritisation of prevention messaging, disease monitoring and therapies, and vaccination for people with HIV, especially those with more pronounced immunodeficiency. Given the pandemic’s exacerbating effects on health inequities, public health and clinical communities must strengthen services and support to prevent aggravated COVID-19 outcomes among people with HIV, particularly for those with pronounced immunodeficiency.

Contributors

XY conceptualised and wrote the first draft and critically revised the manuscript. JS led efforts on National COVID Cohort Collaborative (N3C) HIV markers harmonisation, as well as critically reviewed the manuscript. JZ set up the statistical test design. SG wrote data preparation code and SQL R code for data analysis, which was reviewed and verified by JZ. XY prepared tables and figures with input from SG. SBW provided clinical input and patient severity predictor considerations and use thereof. BO, RCP, JYI, GDK, and XL reviewed and edited the manuscript. RCP, JS, ALO, and QZ built N3C HIV definition, phenotype verification, and statistical analyses. ALO performed data preparation and reviewed and edited the manuscript. MH and CC reviewed and edited the manuscript, and did the project administration. XY, JZ, and SG have accessed and verified the data. The corresponding author (and XY, JZ, JS, RCP, JYI, GDK, and XL) had full access to all the data in the study. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The National Institute of Health’s (NIH) N3C data used in this study is available upon application at https://ncats.nih.gov/n3c.

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