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 1 436 622 adult COVID-19 cases, of these, 13 170 individuals had HIV infection. A total of 26 130 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 aggravated 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.[1] 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.[2] Patients who have malignant disease or solid-organ transplants have overall poorer outcomes of COVID-19,[3] but the evidence is less clear for people with other types of immunocompromising conditions, including people living with HIV.[4]

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.[5] 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.[5] Later on, emerging data from observational cohort studies showed similar findings;[6–10] 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

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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 5·8 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.

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.[11,12] A prospective study of patients hospitalised with COVID-19 showed an increased 28-day mortality in people with HIV after adjusting for age.[13] One study in New York, USA, reported a standardised in-hospital mortality ratio of 1·23 for HIV patients.[14] 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.[15] 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.[8,16] 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,[5] or focused only on hospitalised patients.[7–9] 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).

See Online for appendix

Methods

Study design and population

The N3C Enclave, sponsored by multiple institutes of the US National Institutes of Health,[17] 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.[18] 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 same submitting health-care system at a case to control ratio of 1 to 2.[18] 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).[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[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[20]). 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.[18]

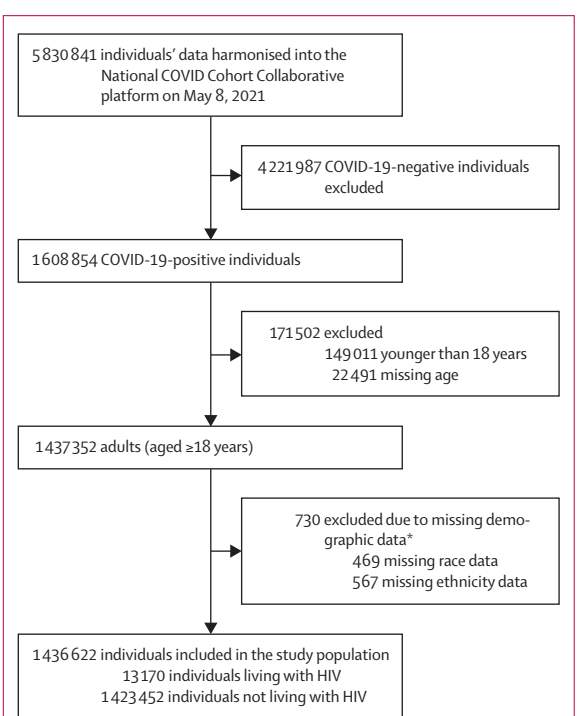


Figure 1: **Study participant selection**
*The numbers for missing race data and missing ethnicity data did not add up to 730 because some records missed both data.

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.[21] The concept sets in OMOP[22,23] 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

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

	Overall (n=1 436 622)	People with HIV (n=13 170)	People without HIV (n=1 423 452)	p value
Social demographics				
Age, years	47 (32–61)	49 (36–60)	47 (32–61)	..
18–49	770 099 (53·60%)	6703 (50·90%)	763 396 (53·63%)	<0·0001
50–64	371 489 (25·86%)	4533 (34·42%)	366 956 (25·78%)	..
≥65	295 034 (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 (15·49%)	..
Comorbidities				
Diabetes	233 838 (16·28%)	3066 (23·28%)	230 772 (16·21%)	<0·0001
Renal disease	86 803 (6·04%)	1758 (13·35%)	85 045 (5·97%)	<0·0001
Congestive heart failure	75 461 (5·25%)	1026 (7·79%)	74 435 (5·23%)	<0·0001
Chronic pulmonary disease	200 998 (13·99%)	2974 (22·58%)	198 024 (13·91%)	<0·0001
Peripheral vascular disease	72 808 (5·07%)	979 (7·43%)	71 829 (5·05%)	<0·0001
Stroke	68 171 (4·75%)	878 (6·67%)	67 293 (4·73%)	<0·0001
Cancer	78 909 (5·49%)	1205 (9·15%)	77 704 (5·46%)	<0·0001
Dementia	24 622 (1·71%)	251 (1·91%)	24 371 (1·71%)	0·095
Myocardial infarction	42 165 (2·94%)	693 (5·26%)	41 472 (2·91%)	<0·0001
Liver disease	72 701 (5·06%)	2152 (16·34%)	70 549 (4·96%)	<0·0001
Rheumatological disease	46 861 (3·26%)	501 (3·80%)	46 360 (3·26%)	0·0005
Hemiplegia or paraplegia	11 656 (0·81%)	222 (1·69%)	11 434 (0·80%)	<0·0001
Peptic ulcer disease	14 237 (0·99%)	230 (1·75%)	14 007 (0·98%)	<0·0001
Lifestyle factors				
Body-mass index, kg/m²				
>30	218 159 (15·19%)	2469 (18·75%)	215 690 (15·15%)	<0·0001
≤30	295 370 (20·56%)	4560 (34·62%)	290 810 (20·43%)	..
Unknown	923 093 (64·25%)	6141 (46·63%)	916 952 (64·42%)	..
Smoking status				
Non-smoker	1 194 746 (83·16%)	9318 (70·75%)	1 185 428 (83·28%)	<0·0001
Current or former smoker	241 876 (16·84%)	3852 (29·25%)	238 024 (16·72%)	..

(Table 1 continues on next page)

	Overall (n=1 436 622)	People with HIV (n=13 170)	People without HIV (n=1 423 452)	p value
(Continued from previous page)				
Clinical spectrum outcomes				
COVID-19 death	26 130 (1·82%)	445 (3·38%)	25 685 (1·80%)	<0·0001
COVID-19 hospitalisation	262 331 (18·26%)	3724 (28·28%)	258 607 (18·17%)	<0·0001
COVID-19 disease severity				
Unaffected	476 250 (33·15%)	6395 (48·56%)	469 855 (33·01%)	<0·0001
Mild† or moderate	895 491 (62·33%)	6209 (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%)	..
HIV factors (n=1544)				
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 1: **Characteristics of adult COVID-19 cases by HIV status in National COVID Cohort Collaborative data, Jan 1, 2020, to May 8, 2021**

included in each domain are listed in each model's documentation (ie, tables). Both concept sets and tables were used to define variables of interest.

A total of 13 170 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 (virally 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 room and inpatient visit" in the Selected Critical Visit table. The Selected Critical Visit table was created by the N3C Consortium to document a COVID-19 related medical encounter. Specifically, N3C defined a single index encounter for each laboratory-confirmed COVID-19 positive patient by selecting encounters that start up to 30 days before or 7 days after the positive test result, or a positive test result during the visit.[19] When multiple encounters met these criteria, the N3C Consortium broke ties by preferentially selecting the encounter in which the most severe outcome was observed, then the longest visit, and finally the most recent visit.[19]

Clinical severity was classified with the Clinical Progression Scale (CPS) established by WHO for COVID-19 clinical research.[24] On the basis of WHO criteria, N3C placed patients into strata defined by the maximum clinical severity from selected critical visits:[19] 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 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).[19] 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-JA", "smoker_NMH", "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.[25] 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.[25]

Statistical analysis

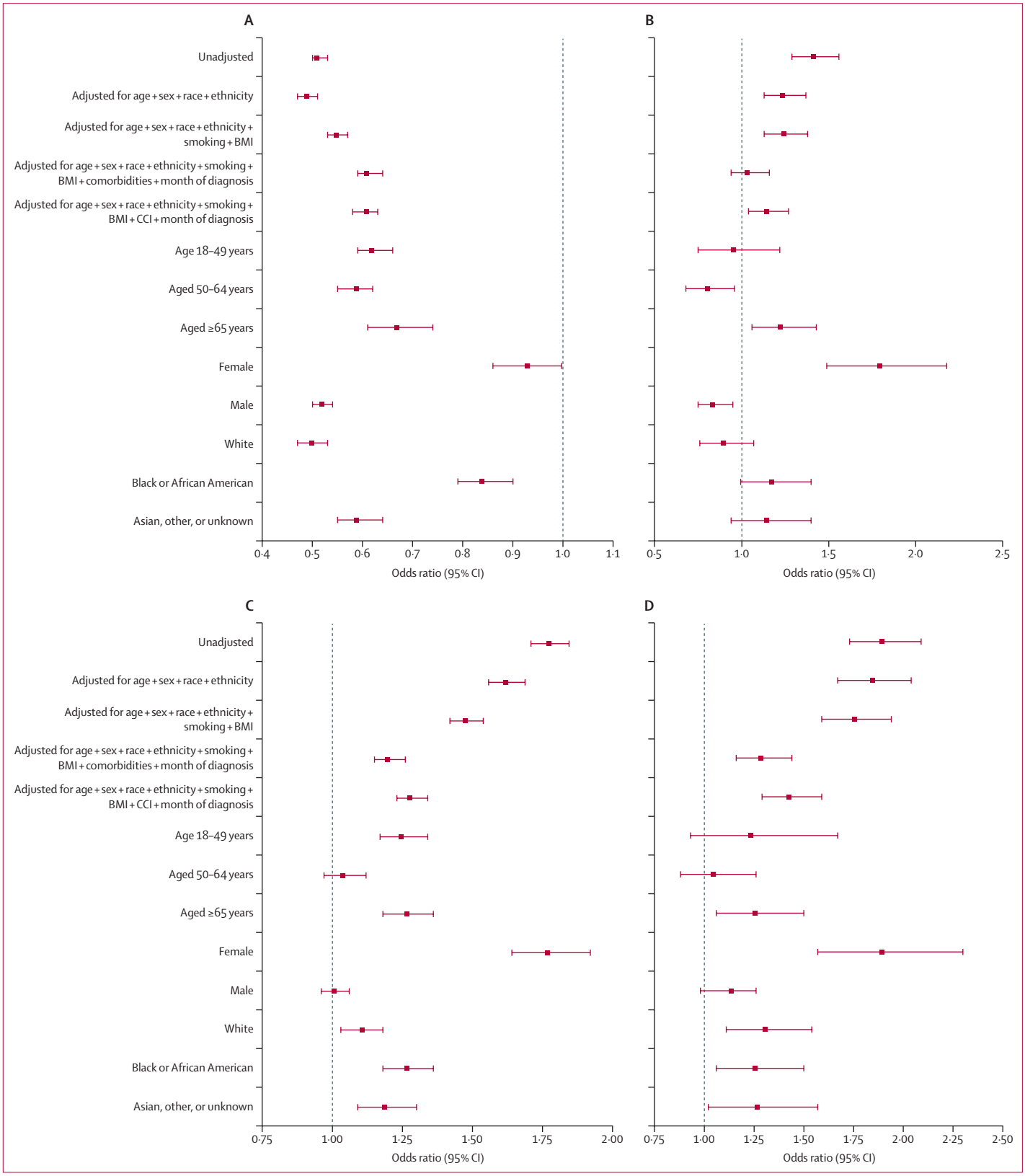
Descriptive statistics were used to examine the sociodemographics of all the COVID-19 cases by HIV status. The variable distributions between COVID-19 patients with and without HIV infection were summarised and compared with the independent *t* test (for continuous variables) or χ^2 test (for categorical variables). For all

	Death, OR (95% CI)*	Hospitalisation, OR* (95% CI)	Mild† or moderate COVID-19 *vs* unaffected‡, OR (95% CI)§	Severe¶ COVID-19 *vs* unaffected‡, OR (95% CI)§
Unadjusted model	1·90 (1·73–2·09)	1·78 (1·71–1·84)	0·55 (0·53–0·57)	1·52 (1·38–1·67)
Adjusted models				
Adjusted for age + sex + race + ethnicity	1·85 (1·67–2·04)	1·62 (1·56–1·69)	0·53 (0·51–0·55)	1·34 (1·21–1·48)
Adjusted for age + sex + race + ethnicity + smoking + BMI	1·76 (1·59–1·94)	1·48 (1·42–1·54)	0·59(0·57–0·61)	1·34 (1·21–1·47)
Adjusted for age + sex + race + ethnicity + smoking + BMI + comorbidities|| + month of diagnosis	1·29 (1·16–1·44)	1·20 (1·15–1·26)	0·61 (0·59–0·64)	1·04 (0·94–1·16)
Adjusted for age + sex + race + ethnicity + smoking + BMI + CCI + month of diagnosis	1·43 (1·29– 1·59)	1·28 (1·23–1·34)	0·61 (0·58–0·63)	1·15 (1·04–1·27)
Interaction models**				
Age and HIV status				
With HIV and aged 50–64 years *vs* aged 18–49 years	7·86 (5·86–10·53)	2·17 (1·93–2·44)	0·48 (0·49–0·61)	3·08 (2·30–4·13)
With HIV and aged ≥65 years *vs* aged 18–49 years	22·20 (16·91–29·12)	3·42 (2·98–3·93)	0·57 (0·50–0·64)	7·57 (5·73–9·99)
Without HIV and aged 50–64 years *vs* aged 18–49 years	4·23 (4·00–4·48)	1·43 (1·41–1·45)	0·81 (0·81–0·82)	2·32 (2·21–2·43)
Without HIV and aged ≥65 years *vs* aged 18–49 years	12·46 (11·82–13·13)	2·39 (2·36–2·42)	0·71 (0·7–0·72)	4·66 (4·45–4·87)
Sex and HIV status				
With HIV and male *vs* female	3·13 (2·29–4·28)	1·32 (1·20–1·44)	0·50 (0·47–0·53)	1·89 (1·44–2·48)
Without HIV and male *vs* female	1·54 (1·50–1·59)	1·16 (1·15–1·17)	1·13 (1·12–1·14)	1·75 (1·70–1·8)
Race and HIV status				
With HIV and Black or African American *vs* White	3·64 (2·59–5·11)	3·16 (2·85–3·49)	1·10 (1·001–1·2)	3·25 (2·4–4·41)
With HIV and Asian, other, or unknown *vs* White	4·32 (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 (1·21–1·3)
Without HIV and Asian, other, or unknown *vs* White	1·16 (1·11–1·20)	1·35 (1·33–1·37)	1·01 (1–1·02)	1·18 (1·13–1·22)
Ethnicity and HIV status				
With HIV and Hispanic or Latinx *vs* not Hispanic or Latinx	3·48 (2·25–5·37)	1·88 (1·62–2·19)	0·86 (0·76–0·97)	2·33 (1·55–3·50)
With HIV and other or unknown *vs* not Hispanic or Latinx	3·50 (2·20–5·59)	1·70 (1·42–2·03)	0·49 (0·42–0·57)	1·98 (1·28–3·05)
Without HIV and Hispanic or Latino *vs* not Hispanic or Latinx	1·07 (1·02–1·12)	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)	1·24 (0·93–1·67)	1·25 (1·17–1·34)	0·62 (0·59–0·66)	0·96 (0·75–1·22)
50–64 (n=371 489)	1·05 (0·88–1·26)	1·04 (0·97–1·12)	0·59 (0·55–0·62)	0·81 (0·68–0·96)
≥65 (n=295 034)	1·26 (1·06–1·50)	1·27 (1·18–1·36)	0·67 (0·61–0·74)	1·23 (1·06–1·43)
Sex				
Female (n=645 956)	1·90 (1·57–2·30)	1·77 (1·64–1·92)	0·93 (0·86–0·997)	1·80 (1·49–2·18)
Male (n=789 148)	1·14 (0·98–1·26)	1·01 (0·96–1·06)	0·52 (0·50–0·54)	0·84 (0·75–0·95)
Race				
White (n=853 997)	1·31 (1·11–1·54)	1·11 (1·03–1·18)	0·50 (0·47–0·53)	0·90 (0·76–1·07)
Black or African American (n=202 947)	1·26 (1·06–1·50)	1·27 (1·18–1·36)	0·84 (0·79–0·90)	1·18 (0·995–1·40)
Asian, other, or unknown (n=379 678)	1·27 (1·02–1·57)	1·19 (1·09–1·30)	0·59 (0·55–0·64)	1·15 (0·94–1·40)

BMI=body-mass index. CCI= Charlson Comorbidity Index. OR=odds ratio. *Results from hierarchical logistic regression. †Includes both the mild (outpatient, WHO severity 1–3) and mild emergency department (outpatient with emergency department visit, WHO severity ~3) categories. ‡Unaffected refers to the individuals with no laboratory test, a negative laboratory test, or suspected COVID-19 with laboratory tests, but identified by other diagnosis codes or procedure codes. §Results from multinomial regression with log-transformation. ¶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. ||The model adjusted simultaneously for the following comorbidities: hemiplegia or paraplegia, dementia, liver disease, myocardial infarction, congestive heart failure, chronic pulmonary disease, cancer, diabetes, stroke, peripheral vascular disease, rheumatologic disease, renal disease, and peptic ulcer disease. **Results for interaction terms adjusted demographic characteristics (age, sex, race, ethnicity), smoking, BMI, and each individual comorbidities listed in the previous footnote.

Table 2: **Association between HIV status and COVID-19 clinical spectrum outcomes based on hierarchical logistic regression models**

COVID-19 outcomes (ie, hospitalisation, death, and disease severity), we used hierarchical logistic regression analyses to estimate the association of HIV infection and HIV markers (CD4 cell count, viral load) 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


A
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 + CCI + month of diagnosis
Age 18–49 years
Aged 50–64 years
Aged ≥65 years
Female
Male
White
Black or African American
Asian, other, or unknown
0·4
0·5
0·6
0·7
0·8
0·9
1·0
1·1
Odds ratio (95% CI)
B
0·5
1·0
1·5
2·0
2·5
Odds ratio (95% CI)
C
0·75
1·00
1·25
1·50
1·75
2·00
Odds ratio (95% CI)
D
0·75
1·00
1·25
1·50
1·75
2·00
2·25
2·50
Odds ratio (95% CI)

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 multinominal 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 multinominal 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 in the multinomial analysis (ie, 1 396 795 [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 checked 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.

Figure 2: **Estimates for the associations between HIV status and COVID-19 clinical spectrum outcomes**

(A) Mild or moderate disease. (B) Severe disease. (C) Hospitalisation. (D) Death. All stratified models (by age, sex, and race) were adjusted for age, sex, race, ethnicity, smoking, BMI, and comorbidities, including hemiplegia or paraplegia, dementia, liver disease, myocardial infarction, congestive heart failure, chronic pulmonary disease, cancer, diabetes, stroke, peripheral vascular disease, rheumatologic disease, renal disease, and peptic ulcer disease. Mild COVID-19 includes both the mild (outpatient, WHO severity 1–3) and mild emergency department (outpatient with emergency department visit, WHO severity ~3) categories. Moderate COVID-19 includes patients who were hospitalised but without invasive ventilation (WHO severity 4–6). Severe COVID-19 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. BMI=body-mass index.

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Results

In this population level analysis, of the 5 830 841 COVID-19 cases and controls harmonised into the N3C data release set from Jan 1, 2020, to May 8, 2021, a total of 1 436 622 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 1 436 622 COVID-19 cases, 262 331 (18·26%) were hospitalised and 26 130 (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 adjusted 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 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).

	Death, OR (95% CI)*	Hospitalisation, OR (95% CI)*	Mild† or moderate *vs* unaffected, OR (95% CI)*	Severe‡ *vs* unaffected, OR (95% CI)*
HIV factors				
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 (1·04–2·21)	3·91 (1·31–11·62)
Most recent viral suppression, <200 copies per mL§	0·71 (0·27–1·89)	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	1·12 (0·42–2·94)	0·88 (0·63–1·23)	0·69 (0·52–0·91)	1·29 (0·47–3·54)
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)

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.

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[11] and the UK.[12] 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[14] and other USA studies using TriNETX network data, which controlled for BMI and various comorbidities.[6,26]

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 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.[27,28] 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,[29] people with HIV and low CD4 cell counts might have a raised risk of severe COVID-19.[30] 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.[16] 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 hospitalisation, the multicentre study did not.[16] Our larger sample size was possibly the reason for detecting such a difference, because the multicentre study had a smaller sample and most of the study participants were receiving antiretroviral therapy.[16]

In this study, the age, sex, and race or ethnicity disparities in COVID-19 severe outcomes are pronounced among people with HIV. The study sample characteristics mirror the demographics of this population in the USA, with higher proportions of males, Hispanic or Latinx adults, and Black or African Americans adults. Hispanic or Latinx individuals, as well as those of an older age, have higher mortality and hospitalisation rates among people with HIV than in people without HIV, which were not reported in the UK study.[12] However, both our study and the UK study showed similar findings of the larger association between HIV and adverse COVID-19 outcomes among Black or African American adults. Understanding the reasons for the disproportionately large association between HIV and adverse COVID-19 outcomes in these subgroups will be a priority if effective policies are to be developed to mitigate any increased risks among these groups.

Our study had several limitations. First, although we included around 6 million individuals from the N3C dataset, the majority are based in the southeast, mid-Atlantic, and mid-west, and therefore might not be representative of the entire COVID-19 population or HIV population in the USA. Second, the algorithm for HIV case identification is not validated. Potential misclassification of HIV status might occur because of data availability and missing data on the N3C concept sets (HIV condition codes, antiretroviral therapy exposure, and laboratory results) that were available to the investigation team at the time of this study. Such identifications 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.[31] Therefore, these potential misclassifications are likely to be non-differential throughout 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 on adverse COVID-19 outcomes. Fourth, the adverse COVID-19 outcomes might vary when stratifying by other vulnerable statuses

	Death, OR (95% CI)*	Hospitalisation, OR (95% CI)*	Mild† or moderate *vs* unaffected, OR (95% CI)*	Severe‡ *vs* unaffected, OR (95% CI)*
(Continued from previous page)				
Comorbidities				
Hemiplegia or paraplegia	4·73 (0·79–28·17)	5·55 (2·08–14·78)	2·17 (0·90–5·24)	4·37 (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 (0·61–3·49)	1·15 (0·83–1·59)	1·12 (0·85–1·48)	1·54 (0·64–3·71)
Myocardial infarction	0·42 (0·09–2·05)	2·12 (1·13–3·98)	0·90 (0·50–1·61)	0·22 (0·03–1·49)
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 (0·24–2·61)	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 (0·00–0·00)
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 ~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 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 rheumatological disease is 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=1544)**

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 of 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 CGC 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, JS, RCP, JZ, SG, QZ, and ALO) 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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References

1 Coronavirus Resource Center. COVID-19 Dashboard by the Center for Systems Science and Engineering at Johns Hopkins University. 2021. https://coronavirus.jhu.edu/map.html (accessed Sept 9, 2021).

2 Center for Disease Prevention and Control. Underlying Medical Conditions Associated with High Risk for Severe COVID-19: Information for Healthcare Providers. 2021. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html (accessed Sept 9, 2021).

3 Waters LJ, Pozniak AL. COVID-19 death in people with HIV: interpret cautiously. *Lancet HIV* 2021; **8:** e2–3.

4 Fung M, Babik JM. COVID-19 in immunocompromised hosts: what we know so far. *Clin Infect Dis* 2021; **72:** 340–50.

5 Baluku JB, Olum R, Agolor C, et al. Prevalence, clinical characteristics and treatment outcomes of HIV and SARS-CoV-2 co-infection: a systematic review and meta-analysis. *medRxiv* 2020; published online June 3. https://doi.org/10.1101/2020.05.31.20118497 (preprint).

6 Hadi YB, Naqvi SFZ, Kupec JT, Sarwari AR. Characteristics and outcomes of COVID-19 in patients with HIV: a multicentre research network study. *AIDS* 2020; **34:** F3–8.

7 Karmen-Tuohy S, Carlucci PM, Zervou FN, et al. Outcomes among HIV-positive patients hospitalized with COVID-19. *J Acquir Immune Defic Syndr* 2020; **85:** 6–10.

8 Sigel K, Swartz T, Golden E, et al. coronavirus 2019 and people living with human immunodeficiency virus: outcomes for hospitalized patients in New York city. *Clin Infect Dis* 2020; **71:** 2933–38.

9 Stoeckle K, Johnston CD, Jannat-Khah DP, et al. COVID-19 in hospitalized adults with HIV. *Open Forum Infect Dis* 2020; **7:** ofaa327.

10 Mascolini M. COVID-19 rate no higher with HIV in largest US HIV+/HIV- cohort. AIDS 2020: 23rd International AIDS Conference; online; July 6–10, 2020.

11 Boulle A, Davies M-A, Hussey H, et al. Risk factors for COVID-19 death in a population cohort study from the Western Cape Province, South Africa. *Clin Infect Dis* 2020; published online Aug 29. https://doi.org/10.1093/cid/ciaa1198.

12 Bhaskaran K, Rentsch CT, MacKenna B, et al. HIV infection and COVID-19 death: a population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform. *Lancet HIV* 2021; **8:** e24–32.

13 Geretti AM, Stockdale AJ, Kelly SH, et al. Outcomes of coronavirus disease 2019 (COVID-19) related hospitalization among people with human immunodeficiency virus (HIV) in the ISARIC World Health Organization (WHO) clinical characterization protocol (UK): a prospective observational study. *Clin Infect Dis* 2020; published online Oct 23. https://doi.org/10.1093/cid/ciaa1605.

14 Tesoriero JM, Swain CE, Pierce JL, et al. COVID-19 Outcomes among persons living with or without diagnosed HIV infection in New York state. *JAMA Netw Open* 2021; **4:** e2037069.

15 Ambrosioni J, Blanco JL, Reyes-Urueña JM, et al. Overview of SARS-CoV-2 infection in adults living with HIV. *Lancet HIV* 2021; **8:** e294–305.

16 Dandachi D, Geiger G, Montgomery MW, et al. Characteristics, comorbidities, and outcomes in a multicenter registry of patients with human immunodeficiency virus and coronavirus disease 2019. *Clin Infect Dis* 2020; published online Sept 9. https://doi.org/10.1093/cid/ciaa1339.

17 Haendel MA, Chute CG, Bennett TD. The National COVID Cohort Collaborative (N3C): rationale, design, infrastructure, and deployment. *J Am Med Inform Assoc* 2020; **28:** 427–443.

18 National COVID Cohort Collaborative. Phenotype Data Acquisition. 2020. https://github.com/National-COVID-Cohort-Collaborative/Phenotype_Data_Acquisition (accessed Sept 9, 2021).

19 Bennett TD, Moffitt RA, Hajagos JG, et al. Clinical characterization and early severity prediction. *JAMA Netw Open* 2021; **4:** e2116901.

20 Centers for Disease Control and Prevention. ICD-10-CM Official Coding and Reporting Guidelines April 1, 2020 through September 30, 2020. 2020. https://www.cdc.gov/nchs/data/icd/COVID-19-guidelines-final.pdf (accessed Sept 9, 2021).

21 Voss EA, Makadia R, Matcho A, et al. Feasibility and utility of applications of the common data model to multiple, disparate observational health databases. *J Am Med Inform Assoc* 2015; **22:** 553–64.

22 ARIScience. OMOP/N3C Templates and Codes. 2020. https://www.ariscience.org/y1_omop_n3c.html (accessed Sept 9, 2021).

23 ATLAS. Atlas OHDSI concept sets. 2020. http://atlas-covid19.ohdsi.org/#/home (accessed Sept 9, 2021).

24 WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis* 2020; **20:** e192–97.

25 Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011; **173:** 676–82.

26 Yendewa GA, Perez JA, Schlick K, Tribout H, McComsey GA. Clinical features and outcomes of COVID-19 among people living with HIV in the United States: a multicenter study from a large global health research network (TriNetX). *Open Forum Infect Dis* 2021; **8:** ofab272.

27 Del Amo J, Polo R, Moreno S, et al. Incidence and severity of COVID-19 in HIV-positive persons receiving antiretroviral therapy: a cohort study. *Ann Intern Med* 2020; **173:** 536–41.

28 Parienti JJ, Prazuck T, Peyro-Saint-Paul L, et al. Effect of tenofovir disoproxil fumarate and emtricitabine on nasopharyngeal SARS-CoV-2 viral load burden amongst outpatients with COVID-19: a pilot, randomized, open-label phase 2 trial. *EClinicalMedicine* 2021; **38:** 100993.

29 Zhang H, Wu T. CD4+T, CD8+T counts and severe COVID-19: a meta-analysis. *J Infect* 2020; **81:** e82–84.

30 Ho HE, Peluso MJ, Margus C, et al. Clinical outcomes and immunologic characteristics of coronavirus disease 2019 in people with human immunodeficiency virus. *J Infect Dis* 2021; **223:** 403–08.

31 Paul DW, Neely NB, Clement M, et al. Development and validation of an electronic medical record (EMR)-based computed phenotype of HIV-1 infection. *J Am Med Inform Assoc* 2018; **25:** 150–57.