Outcomes of COVID-19 related hospitalization among people with HIV in the ISARIC WHO Clinical Characterization Protocol (UK)

Outcomes of COVID-19 related hospitalization among people with HIV in the ISARIC WHO Clinical Characterization Protocol (UK): a prospective observational study

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Summary: HIV-positive people hospitalized with COVID-19 had an age-adjusted 47% higher risk of day-28 mortality compared with a large population of HIV-negative people within the same dataset. The effect persisted after adjusting for sex, ethnicity, and major comorbidities.

Abstract

Background Evidence is conflicting about how HIV modulates COVID-19. We compared the presentation characteristics and outcomes of adults with and without HIV who were hospitalized with COVID-19 at 207 centers across the United Kingdom and whose data were prospectively captured by the ISARIC WHO CCP study.

Methods We used Kaplan-Meier methods and Cox regression to describe the association between HIV status and day-28 mortality, after separate adjustment for sex, ethnicity, age, hospital acquisition of COVID-19 (definite hospital acquisition excluded), presentation date, ten individual comorbidities, and disease severity at presentation (as defined by hypoxia or oxygen therapy).

Results Among 47,592 patients, 122 (0.26%) had confirmed HIV infection and 112/122 (91.8%) had a record of antiretroviral therapy. At presentation, HIV-positive people were younger (median 56 versus 74 years; p<0.001) and had fewer comorbidities, more systemic symptoms and higher lymphocyte counts and C-reactive protein levels. The cumulative day-28 mortality was similar in the HIV-positive vs. HIV-negative groups (26.7% vs. 32.1%; p=0.16), but in those under 60 years of age HIV-positive status was associated with increased mortality (21.3% vs. 9.6%; p<0.001 [log-rank test]). Mortality was higher among people with HIV after adjusting for age (adjusted hazard ratio [aHR] 1.47, 95% confidence interval [CI] 1.01-2.14; p=0.05), and the association persisted after adjusting for the other variables (aHR 1.69; 95% CI 1.15-2.48;

p=0.008) and when restricting the analysis to people aged <60 years (aHR 2.87; 95% CI 1.70-4.84; p<0.001).

Conclusions HIV-positive status was associated with an increased risk of day-28 mortality among patients hospitalized for COVID-19.

Key words: COVID-19, SARS-CoV-2, HIV, mortality

Introduction

Older age and presence of comorbidities including immunosuppression are recognized to increase the severity of COVID-19 [1-5]. However, existing evidence for an association between HIV infection and COVID-19 related outcomes is mixed. Despite effective antiretroviral therapy (ART), people with HIV (PWH) may continue to experience persistent immunodysfunction [6, 7] which might promote COVID-19 severity, or conversely, attenuate its pathological immune responses [8]. Although some antiretroviral drugs have been proposed to protect against COVID-19, the data remain uncertain [9,10]. Importantly, the common occurrence of co-factors such as diabetes and chronic renal and pulmonary disease [11], alongside disadvantageous socioeconomic variables [12], may increase the risk of adverse outcomes among PWH who acquire SARS-CoV-2.

Several case series and observational cohort studies have described the outcomes of COVID-19 in PWH across Europe [9,13-19], Asia [18,19], and the United States [8,18-22]. These studies have often been limited by small sample sizes, lack of direct comparative data from people without HIV, or inability to adjust for comorbidities. Some reports indicated that PWH did not experience higher rates of COVID-19 related hospitalization or mortality than people without HIV [14,21], whereas others suggested increased disease severity [9,20]. Importantly, preliminary data from South Africa indicated that despite effective ART, HIV infection more than doubled the risk of COVID-19 related mortality [23].

To characterize the presenting characteristics and outcomes of COVID-19 related hospitalization in PWH relative to those without HIV in the United Kingdom (UK), we analyzed data collected

within the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) WHO Clinical Characterization Protocol (CCP), the largest prospective observational study of patients admitted to hospital with COVID-19 worldwide [24].

Methods

Setting and participants

The ISARIC WHO CCP-UK is an ongoing prospective cohort study in hospitals in England, Scotland, and Wales [24]. The study was activated on 17th January 2020. The protocol, case report form (CRF) and other study materials, and details of the Independent Data and Material Access Committee are available online [24]. Eligible patients were people aged ≥18 years who were admitted to participating hospitals (207 at the time of analysis) with either laboratory-confirmed or highly likely (based on clinical, laboratory and radiological findings) SARS CoV-2 infection. PCR-based virus detection was the only test available during the study and the decision to test was at the discretion of the attending clinical team, who also decided upon hospital admission, transfer into critical care and use of ventilation.

Data collection

Baseline was defined as the date of hospital admission or symptom onset (for those with symptom onset after hospitalization, *see below*). We included individuals with a baseline date that was on or before 4th June 2020 for whom ≥14 days had elapsed at data extraction on 18th June. Individuals with missing admission date were excluded. Where the date of symptom onset was missing, we assumed that symptoms began on the date of the first SARS-CoV-2 PCR test.

Based on the date of symptom onset relative to the date of admission, the infection was classed as community-acquired (symptom onset <3 days), indeterminate (3-7 days), probable hospital-acquired (8-14 days) and definite hospital-acquired (>14 days). Using the CRF version 9.2 [24], demographics, comorbidities and concomitant medications were recorded on admission; measures of disease severity and laboratory test results were recorded on day 1 (baseline), day 3, day 6, day 9 and on the day of admission to critical care if applicable. CRF-reported HIV-positive status was confirmed via recorded ART, *Pneumocystis jirovecii* prophylaxis in the absence of non-HIV indications (n=2), or directly with a site investigator. Individuals with missing HIV status and those with unconfirmed HIV-positive status were excluded.

Statistical analysis

Presenting characteristics were compared between HIV-positive and HIV-negative people and between PWH who died and those who survived at 28 days using Wilcoxon rank sum tests (for continuous variables) and Pearson's chi-squared or Fisher's exact test (for categorical variables). For all individuals, follow-up ended on the date of death. Patients discharged for home palliative care were considered to have died three days afterwards. Follow-up was right-censored at day 28 for those remaining alive as an inpatient, or for those who were discharged (excepting palliative discharge) prior to day 28. No deaths were recorded among PWH after day 28. Follow-up was censored for patients transferred to another facility at date of transfer; among those with unknown outcome, it was censored on the last recorded date of follow-up where they were known to be alive. For patients who died, were transferred or discharged on the date of admission or who had no further follow-up recorded beyond the first day, we recorded 0.5 days of follow-up. The primary analysis used a Kaplan-Meier approach to display the cumulative

mortality over this period and in strata defined by sex and age. Cox proportional hazards regression with the Efron method for ties was then used to describe the association of mortality with HIV status, before and after adjustment for the following potential confounders: sex, ethnicity, age (in quadratic form), indeterminate/probable hospital acquisition of COVID-19 (as defined above), and ten separate comorbidities at admission (a series of binary variables to indicate the presence or absence of each of chronic cardiac disease, chronic pulmonary disease, chronic renal disease, diabetes, obesity, chronic neurological disorder, dementia, liver disease [mild, moderate or severe], malignancy, and chronic hematological disease). These variables were selected a priori. We also included adjustment for the baseline date to account for changes in mortality over time. For partially missing comorbidity data, we assumed missing comorbidities were absent. Participants with completely missing comorbidity data were excluded from these adjusted analyses. We fitted a further model adjusting for disease severity a at presentation, defined as oxygen saturation <94% on air or receiving oxygen therapy, in order to assess whether risk of mortality in PWH could be explained by a different stage of disease advancement at hospitalization. Finally, we repeated the same analysis among individuals aged ≤70 year. A series of sensitivity analyses were performed: i) we repeated the analyses after censoring follow-up on the day of discharge; ii) we included those with definite hospital-acquired COVID-19; iii) we used symptom onset date as the baseline date for all; iv) we excluded PWH lacking a record of ART; v) we excluded those without a recorded positive SARS-CoV-2 PCR result; vi) we calculated propensity scores for HIV-positive status using a logistic regression model based on sex, ethnicity, age (in quadratic form), indeterminate/probable hospital acquisition of COVID-19, smoking status, baseline date, and ten comorbidities, and included the propensity score in a univariate Cox regression model for death at 28 days; vii) we considered a binary endpoint of 14-day mortality and performed logistic regression (with the

same confounder adjustment as described above); and viii) we used a competing risks regression model with discharge as a competing risk for mortality. In PWH, we used a Cox proportional hazard model to investigate associations with day-28 mortality. Analyses were conducted in Stata v16.1 (Statacorp, TX, USA).

Ethical considerations

Approval was granted by the following Ethics Committees: South Central-Oxford (Ref 13/SC/0149), Scotland (Ref 20/SS/0028), and WHO (RPC571, RPC572). Data collection did not require consent. The study was carried out in accordance with the Helsinki Declaration.

Results

Participants

ISARIC CCP-UK recorded 53,993 people with COVID-19 between 17th January and 18th June 2020. After excluding non-eligible participants (**Figure 1**), we included 47,592 patients, of whom 122 (0.26%) had confirmed HIV infection. A positive SARS-CoV-2 RNA PCR test was recorded for 43,062/47,592 (90.5%) individuals. Patients excluded from the analysis did not differ by sex, ethnicity or age; in particular, the characteristics of those excluded due to missing HIV status closely resembled those reported to be HIV-negative (**Supplementary Table 1**). Among PWH, one person was diagnosed with HIV during the admission and 112 (91.8%) had an ART record. The regional distribution of study participants was similar to the UK population of PWH receiving care (**Supplementary Table 2)**.

Characteristics at presentation

PWH were younger than HIV-negative people (median 56 vs. 74 years, p<0.001) (**Table 1, Figure 2**) and comprised a greater proportion of males and people of black ethnicity. PWH had fewer comorbidities overall, and a lower prevalence of cardiac, pulmonary and rheumatological disease, dementia, and malignancy, but higher rates of moderate/severe liver disease; proportions with chronic renal disease, diabetes and hematological disease were similar. The duration of symptoms was longer in PWH (median 5 vs. 3 days, p=0.002) (**Table 2).** PWH were more likely to present with fever, headache, myalgia and tachycardia, and to have cough and chest pain. Respiratory rate, occurrence of tachypnoea and hypoxia, and radiological evidence of chest infiltrates did not differ significantly between the two groups. PWH presented with lower total white blood cell and platelet count, but higher lymphocyte count and C-reactive protein (CRP) (**Table 3**).

COVID-19 outcomes

After adjustment for sex, ethnicity, age, baseline date, indeterminate/probable hospital acquisition of COVID-19, and ten comorbidities, the odds of admission to critical care were similar regardless of HIV status (odds ratio 1.22; 95% confidence interval [CI] 0.80-1.87; p=0.35) (**Supplementary Table 3**). By day 28 (**Supplementary Table 4**), 30 (24.6%) PWH were known to have died compared with 13,969 (29.4%) of the HIV-negative group; the cumulative incidence of day-28 mortality was 26.7% vs. 32.1%, respectively (p=0.16 **Figure 3 A**). Whilst findings were similar in men and women (**Figure 3 B, C**), univariate stratification for age revealed higher mortality among PWH in the younger age group (**Figure 3 D-F**). Among participants under 60

years of age, mortality was 21.3% in HIV-positive patients versus 9.6% in HIV-negative patients (p<0.001).

In the unadjusted analysis (**Table 4**), the cumulative hazard of day-28 mortality was lower in PWH (HR 0.77, 95% CI 0.54-1.11; p=0.17). Results did not change after adjusting for sex or ethnicity. In contrast, adjustment for age resulted in a change in the direction of the association (adjusted HR 1.47, 95% CI 1.01-2.14; p=0.05). Results were similar after adjustment for sex, ethnicity, age, baseline date, indeterminate/probable hospital acquisition of COVID-19 and ten comorbidities and following additional adjustment for disease severity at presentation. When restricted to people <60 years, the analysis yielded an adjusted HR of 2.87 (95% CI 1.70-4.86; p<0.001). Sensitivity analyses showed consistent results (**Supplementary Table 5**). In particular, censoring follow-up on the day of discharge, including definite hospital-acquired COVID-19, using symptom onset as baseline and excluding PWH lacking an ART record did not significantly alter the model. A separate logistic regression model with a binary variable of day-14 mortality and a competing risk regression model with discharge as a competing risk for mortality also showed increased odds of mortality in the HIV-positive group.

Among PWH, relative to patients who survived by day 28, patients who died were older and had a higher prevalence of diabetes and obesity and were less likely to have a record of ART (**Table 5 and Supplementary Tables 6 and 7**).

Discussion

Principal findings

This study found evidence suggesting an age-adjusted 47% increased risk of day-28 mortality among PWH hospitalized with COVID-19 compared to HIV-negative individuals in the same dataset. Among people aged <60 years, HIV-positive status more than doubled the risk of mortality after adjusting for sex, ethnicity, age, baseline date, ten separate comorbidities, and disease severity at presentation (as indicated by a record of hypoxia or receiving oxygen therapy). The latter adjustment considered that doctors may be more likely to admit HIV-positive adults with COVID-19 despite less severe symptoms.

The influence of age, sex and ethnicity on COVID-19 outcomes is currently debated [1,2,25]. PWH in our study were significantly younger than the HIV-negative group and adjusting for age changed the direction of the association between HIV status and day-28 mortality, indicating that age was a significant confounder in our analyses. Men were more prevalent in the HIV-positive group, which is consistent with the epidemiology of HIV infection in the UK, where men represent just over two thirds of the whole population with HIV [26]. People of black ethnicity comprised 42% of the HIV-positive group in this analysis relative to ~26% among PWH in the UK population [26]. Adjustment for sex or ethnicity alone did not impact our relative hazard estimates.

Whilst there is a recognized interplay between HIV and comorbidities, neither omitting the adjustment for comorbidities nor adjusting for separate comorbidities modified the association.

PWH had fewer comorbidities, notably lower prevalence of chronic pulmonary disease and malignancies, and this is largely a function of their younger age. HIV-positive people who died were older and were more likely to suffer from obesity and diabetes with complications than those who survived to discharge. Similar trends have been seen in the general population [1,25]. While these observations highlight the importance of obesity and diabetes as cofactors, the increased risk of COVID-19 related mortality in PWH was not merely due to the presence of promoting comorbidities. It should be highlighted that we did not take into consideration differences in the control of comorbidities between the two groups.

Comparison with other studies

Evidence about the interplay between HIV and COVID-19 is not entirely consistent [8,9,13-23]. A case-control study from New York compared 88 PWH, all of whom were receiving ART, and 405 HIV-negative controls matched by age, gender, ethnicity, and calendar week of infection [21]. The study found no difference in the outcomes of COVID-19 related hospitalization after adjusting for demographics, chronic obstructive pulmonary disease, smoking, and baseline ferritin and white blood cell count. There are important differences in the two study populations. Participants in the New York study had a median age of 61 years (IQR 54-67), whereas we found excess mortality in HIV-positive people aged <60 years. Whereas malignancies were recorded less commonly in our cohort (3% vs. 10%), prevalence of obesity was higher (17% vs. 11%). It is also noteworthy that mortality in the overall ISARIC CCP-UK population was higher than that reported in the New York study [21] and other countries [1]. Consistent with our findings, there are preliminary data that HIV-positive status was associated with increased hazard of mortality (adjusted HR 2.75) in South Africa [23]. Although the analysis

did not account for history of tuberculosis, obesity and socioeconomic status, it is noteworthy that HIV suppression on ART did not alter the mortality risk.

Strengths and limitations of this study

A key strength of this study was the ability to perform a direct comparison of people with and without HIV in the same dataset, and to account for age, gender, ethnicity and key comorbidities.

The data for this study were collected during the first peak of the UK COVID-19 epidemic and there are missing data, including 2,742 patients with missing HIV status, who were excluded from the analysis. We also excluded 10 people initially recorded as having HIV but whose HIV status could not be confirmed; this group was similar to the HIV-negative group, with a median age of 81, suggesting that their initial HIV record was incorrect. Thus, these missing data are unlikely to affect the results.

Our focus was on the effect of HIV-positive status on day-28 mortality among people hospitalized with COVID-19. We did not address risk factors for a COVID-19 diagnosis or hospitalization among PWH, or the suggested modulating role of certain antiretroviral agents [9,10]. We also lacked data to adjust for deprivation or socioeconomic status. Our analysis cannot provide evidence of the role of HIV-related parameters on outcomes of COVID-19 related hospitalization, as we did not have details of the ART history, plasma HIV-1 RNA load, CD4 cell count, and history of HIV-related disease. HIV-positive people who died were less likely to have ART recorded than those who survived at day 28. This raises the possibility that some of

the patients who died were not receiving ART, although this cannot be stated with certainty. In the UK, 93% of the 103,000 people estimated to have HIV infection have been diagnosed; of these, 97% receive ART with excellent virological suppression and only a small subset (~3%) is either not engaged with care or experiences problems with virological control despite ART [26]. Only a few PWH in our cohort had *Pneumocystis jirovecii* prophylaxis recorded in their admission medications, suggesting that the likelihood of PWH in our study being severely immunosuppressed was overall low.

Despite effective ART and normalized CD4 cell counts, a subset of PWH continue to experience immune activation, inflammation and a pro-coagulatory state [7] which may modulate the risk of COVID-19 related morbidity and mortality [28,29]. Persistent immune dysfunction may be the consequence of advanced immunocompromise prior to the start of ART, as defined by a low nadir CD4 cell count and inverted CD4:CD8 ratio. In the UK, 43% of people newly diagnosed with HIV in 2018 had a CD4 count <350 cells/mm^3, a threshold indicative of significant immunosuppression [26,30]. Furthermore, current guidelines about starting ART at the time to diagnosis were implemented relatively recently, whereas in the past ART initiation in the UK was deferred until the CD4 count had declined below thresholds of initially 200, then 350 and subsequently 500 cells/mm^3 [6,30]. Thus, many older PWH in the UK (and worldwide) will have experienced years of uncontrolled HIV replication prior to commencing treatment and may also have received earlier regimens of suboptimal efficacy, with potentially lasting effects on immune function [30,31]. Immunological studies will be required to confirm these hypotheses.

Conclusions

Our data are limited by the relatively small number of people with HIV included in the study and the findings should be interpreted with caution. Nonetheless, after careful considerations, our analysis of the outcomes of patients hospitalized with COVID-19 in the UK shows an increased risk of day-28 mortality due to HIV-positive status. As the pandemic continues to spread, including in areas of increased HIV prevalence, it is important to record the HIV status of people hospitalized with COVID-19 and gather further data to corroborate our findings and confirm the population-specific determinants of outcomes. Meanwhile, emphasis for PWH should be placed on early HIV diagnosis, prompt ART initiation, and optimized screening for and control of comorbidities including obesity and diabetes.

NOTES

Author contributions

AMG - designed the study concept, reviewed all aspects of the data analysis and interpretation (of which she is the guarantor), contributed to the writing of the manuscript, and performed the final review of the manuscript.

AJS - performed the data analysis and contributed to the data interpretation and the writing of the manuscript.

SHK - performed the initial literature search and contributed to the conceptualization, data analysis and interpretation and the writing of the manuscript.

MC, LW, SC - contributed to conceptualization and review of the manuscript

GV - contributed to data analysis and interpretation and the writing of the manuscript

AD, EMH, LT - contributed to the ISARIC CCP-UK study design and data collection and reviewed the manuscript

PJMO - ISARIC CCP-UK Co-Lead investigator, sourced funding, contributed to the ISARIC CCP-UK study design and data collection and reviewed the manuscript

JKB - ISARIC CCP-UK Consortium lead investigator, sourced funding, contributed to the ISARIC CCP-UK study design and data collection and reviewed the manuscript

CAS - advised on all aspects of the conceptualization and data analysis and interpretation, and contributed to the writing and final review of the manuscript

MGS - ISARIC CCP-UK Protocol Chief Investigator and guarantor of the data, sourced permissions and funding, contributed to the ISARIC CCP-UK study design and data collection and reviewed the manuscript.

AMG and MGS accept full responsibility for the conduct of the study, had full access to the data and controlled the decision to publish. AMG attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data availability

The CO-CIN data were collated by ISARIC4C Investigators. ISARIC4C welcomes applications for data and material access through our Independent Data and Material Access Committee (https://isaric4c.net). ISARIC4C has a public facing website and twitter account @CCPUKstudy. We are engaging with print and internet press, television, radio, news, and documentary makers. These findings have been distributed through community groups including UK-CAB, HIV i-Base and via the British HIV Association.

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Competing interests

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Table 1. Summary of participant characteristics, stratified by HIV status

Characteristic		HIV-positive n=122		HIV-negative n=47 470		P-value
Age, median years (IQR)		56	(49, 62)	74	(60, 84)	<0.001
Age group, n (%)	<40	7/120	(5.8)	2576/46 926	(5.5)	<0.001
	40-49	26/120	(21.7)	3245/46 926	(6.9)	
	50-59	48/120	(40.0)	5945/46 926	(12.7)	
	60-69	26/120	(21.7)	7272/46 926	(15.5)	
	≥70	13/120	(10.8)	27 888/46 926	(59.4)	
Female, n (%)		41/121	(33.9)	20 302/47 303	(42.9)	0.05
Ethnicity, n (%)	White	51/112	(45.5)	35 539/42 208	(84.2)	<0.001
	Black	48/112	(42.9)	1475/42 208	(3.5)	
	Asian	1/112	(0.9)	2249/42 208	(5.3)	
	Other	12/112	(10.7)	2945/42 208	(7.0)	
Smoking, n (%)	Never	65/94	(69.2)	17 396/30 379	(57.3)	0.004
	Former	18/94	(19.2)	10 634/30 379	(35.0)	
	Current	11/94	(11.7)	2340/30 379	(7.7)	
Comorbidities, median number (IQR)		1	(1, 2)	2	(1, 3)	<0.001
Comorbidities, n (%)	None	31/122	(25.4)	9679/46 742	(20.7)	<0.001
	1	50/122	(41.0)	13 544/46 742	(29.0)	
	2	28/122	(23.0)	11 529/46 742	(24.7)	

	≥3	13/122	(10.7)	11 990/46 742	(25.7)	
Type of comorbidities, n (%)	Chronic cardiac disease	20/117	(17.1)	14 620/45 054	(32.5)	<0.001
	Chronic pulmonary disease[a]	13/120	(10.8)	8055/44 918	(17.9)	0.04
	Asthma	12/116	(10.3)	6239/44 758	(13.9)	0.26
	Chronic renal disease	21/116	(18.1)	7874/44 728	(17.6)	0.89
	Diabetes, no complications	16/117	(13.7)	7783/43 862	(17.7)	0.25
	Diabetes, with complications	9/117	(7.7)	3308/43 587	(7.6)	0.97
	Obesity	19/112	(17.0)	4597/40 458	(11.4)	0.06
	Chronic neurological disorder	8/116	(6.9)	5588/44 478	(12.6)	0.07
	Dementia	3/118	(2.5)	7464/44 554	(16.8)	<0.001
	Mild liver disease	3/118	(2.5)	632/44 228	(1.4)	0.24
	Moderate/severe liver disease	6/118	(5.1)	861/44 281	(1.9)	0.01
	Malignancy	4/118	(3.4)	4598/44 359	(10.4)	0.009
	Chronic hematological disease	4/118	(3.4)	1931/44 311	(4.4)	0.82
	Rheumatological disease	6/118	(5.1)	4874/44 183	(11.0)	0.04
	Malnutrition	5/112	(4.5)	1133/41 853	(2.7)	0.23

[a]Excludes asthma. Abbreviations: IQR, Interquartile range.

Table 2. Presenting symptoms and observations, stratified by HIV status

Symptoms and Observations		HIV-positive n=122		HIV-negative n=47 470		P-value
Presenting symptoms, n (%)	Fever	99/120	(82.5)	30 650/47 085	(65.1)	<0.001
	Myalgia	28/104	(26.9)	6351/34 839	(18.2)	0.02
	Headache	18/96	(18.8)	3661/34 790	(10.5)	0.009
	Cough	96/121	(79.3)	31 028/47 077	(65.9)	0.002
	Dyspnea	88/121	(72.7)	32 141/47 043	(68.3)	0.30
	Chest pain	25/109	(22.9)	5227/38 302	(13.7)	0.005
	Sore throat	14/100	(14.0)	2806/34 294	(8.2)	0.03
	Wheeze	6/102	(5.9)	3293/36 241	(9.1)	0.26
	Rhinorrhea	3/97	(3.1)	831/33 562	(2.5)	0.52
	Diarrhea	28/108	(25.9)	7277/39 340	(18.5)	0.05
	Nausea or vomiting	23/105	(21.9)	7650/39 560	(19.3)	0.51
	Abdominal pain	13/104	(12.5)	4033/38 136	(10.6)	0.52
	Fatigue	43/98	(43.9)	16 111/37 202	(43.3)	0.91
	Asymptomatic	0/122	(0)	888/47 470	(1.9)	0.18
Symptom group[a], n (%)	Systemic	108/121	(89.3)	32 267/47 119	(68.5)	<0.001
	Respiratory	108/121	(88.5)	38 736/47 158	(82.1)	0.04
	Gastrointestinal	45/111	(40.5)	13 444/41 311	(32.5)	0.07

Symptom duration, median days (IQR)		5	(1, 9)	3	(0, 7)	0.002
Symptom onset[b], n (%)	<3 days	114/122	(93.4)	41 285/47 101	(87.7)	0.20
	3-7 days	1/122	(0.8)	1488/47 101	(3.2)	
	8-14 days	4/122	(3.3)	1603/47 101	(3.4)	
	>14 days	3/122	(2.5)	2725/47 101	(5.8)	
Presenting signs	Temperature, median °C (IQR)	37.8	(36.9, 38.6)	37.3	(36.6, 38.1)	0.004
	Fever ≥37.8 °C, n (%)	60/117	(51.3)	16 447/45 458	(36.2)	0.001
	HR, median beats/min (IQR)	96	(81, 110)	90	(78, 105)	0.004
	Tachycardia[c], n (%)	52/117	(44.4)	15 076/45 432	(33.2)	0.01
	RR, median breaths/min (IQR)	20	(18, 27)	21	(18, 26)	0.97
	Tachypnea[d], n (%)	55/114	(48.3)	23 306/45 209	(51.6)	0.48
	Hypoxia[e]/on oxygen, n (%)	56/115	(48.7)	23 971/45 242	(53.0)	036
	Infiltrates visible on CXR, n (%)	49/74	(66.2)	19 065/30 566	(62.4)	0.50
	Systolic BP, median mmHg (IQR)	130	(118, 145)	130	(114, 147)	0.78
	Diastolic BP, median mmHg (IQR)	80	(68, 86)	74	(65, 84)	0.007

[a]Systemic symptoms: ≥1 of fever, myalgia or headache; Respiratory symptoms: ≥1 of cough, dyspnea, chest pain, sore throat, wheeze; Gastrointestinal symptoms: ≥1 of: Diarrhea, nausea, vomiting or abdominal pain. [b]Based on the onset of symptoms relative to the date of admission, COVID-19 acquisition was classed as community (<3 days), indeterminate (3-7 days), probable hospital (8-14 days), and definite hospital (>14 days). [c]Defined as HR >100 beats/min. [d]Defined as RR >20 breaths/min. [e]Defined as SpO2 <94% on air. Abbreviations: IQR, Interquartile range; HR, Heart rate; RR, Respiratory rate; CXR, Chest X-ray; BP, Blood pressure.

Table 3. Presenting laboratory parameters, stratified by HIV status

Laboratory parameter		HIV positive n=122		HIV-negative n=47,470		P-value
Hemoglobin, median g/L (IQR)		130	(117, 145)	129	(113, 143)	0.56
Anemia[a], n (%)		39/107	(36.5)	15 570/40 092	(38.8)	0.61
WBC, median count x10^9/L (IQR)		6.6	(4.8, 9.1)	7.4	(5.4, 10.4)	0.01
Lymphocytes, median count x10^9/L (IQR)		1.0	(0.8, 1.5)	0.9	(0.6, 1.3)	<0.001
Lymphopenia[b], n (%)		51/108	(47.2)	23 014/39 759	(57.9)	0.03
Platelets, median count x10^6/L (IQR)		197	(150, 258)	217	(164, 286)	0.01
Thrombocytopenia[c], n (%)		26/105	(24.8)	7440/39 739	(18.7)	0.11
Prothrombin time, median sec (IQR)		13.6	(11.0, 15.0)	13.2	(11.8, 15.0)	0.58
Creatinine, median µmol/L (IQR)		89	(72, 134)	86	(67, 121)	0.26
eGFR[d], median ml/min/1.73m^2 (IQR)		75	(52, 101)	73	(48, 97)	0.37
eGFR ml/min/1.73m^2, n (%)	≥60	68/100	(68.0)	24 783/38 821	(63.8)	0.15
	30-59	21/100	(21.0)	9786/38 821	(25.2)	
	15-29	4/100	(4.0)	2846/38 821	(7.3)	
	<15	7/100	(7.0)	1406/38 821	(3.6)	
ALT, median U/L (IQR)		28	(19, 46)	26	(17, 43)	0.16

ALT >40 U/L, n (%)	28/89	(31.5)	8458/30 478	(27.8)	0.44
Glucose, median mmol/L IQR)	6.8	(5.8, 10.3)	6.8	(5.8, 8.9)	0.44
Hyperglycemia[e], n (%)	11/54	(20.4)	2903/19 541	(14.9)	0.26
C-reactive protein, median mg/L (IQR)	107	(51, 200)	83	(36, 157)	0.02

[a]Defined as hemoglobin <130 g/L in males and <115 g/L in females. [b]Defined as lymphocyte count <1.0 x10^9/L. [c]Defined as platelet count <150 x10^6/L. [d]Based on the Modification of Diet in Renal Disease (MDRD) formula where eGFR (mL/min/1.73 m²) = 175 × (Scr/88.4)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if Black ethnicity). [e]Defined as glucose >11 mmol/L. Abbreviations: IQR, Interquartile range; Abbreviations: IQR, Interquartile range; WBC, White blood cells; eGFR, estimated glomerular filtration rate; ALT, alanine transaminase.

Table 4. Cox proportional hazards model of the association between HIV status and day-28 mortality

HIV-positive versus HIV-negative	Hazard ratio	95% CI	P value
Unadjusted	0.77	0.54 to 1.11	0.17
Adjusted for sex	0.76	0.53 to 1.10	0.15
Adjusted for ethnicity	0.88	0.60 to 1.29	0.52
Adjusted for age	1.47	1.01 to 2.14	0.05
Adjusted for age and sex	1.45	1.00 to 2.12	0.05
Adjusted for sex, ethnicity, age, baseline date, and indeterminate/probable hospital acquisition of COVID-19	1.49	1.01 to 2.20	0.04
Adjusted for sex, ethnicity, age, baseline date, indeterminate/probable hospital acquisition of COVID-19, and 10 comorbidities[a]	1.50	1.02 to 2.22	0.04
Adjusted for sex, ethnicity, age, baseline date, indeterminate/probable hospital acquisition of COVID-19, 10 comorbidities[a], and hypoxia/receiving oxygen at presentation[b]	1.69	1.15 to 2.48	0.008
Adjusted for sex, ethnicity, age, baseline date, indeterminate/probable hospital acquisition of COVID-19, 10 comorbidities[a] and hypoxia/receiving oxygen at presentation[b] among individuals aged <60 years	2.87	1.70 to 4.86	<0.001

[a]The model adjusted separately for the following comorbidities: chronic cardiac disease, chronic pulmonary disease, chronic renal disease, diabetes, obesity, chronic neurological disorder, dementia. liver disease, malignancy, and chronic hematological disease. [b]Hypoxia was defined as SpO2 <94% on air; a record of hypoxia or receiving oxygen at presentation was used as an indicator of disease severity.

Table 5. Characteristics of patients with HIV, stratified by outcome at day 28, selected variables[a]

Characteristic		Died n=30		Alive n=92		P-value
Age, median years (IQR)		58	(55, 70)	55	(49, 61)	0.01
Age group, n (%)	<40	1/28	(3.6)	6/92	(6.5)	0.12
	40-49	4/28	(13.8)	22/92	(23.9)	
	50-59	10/28	(37.9)	38/92	(41.3)	
	60-69	6/28	(20.7)	20/92	(21.7)	
	≥70	7/28	(24.1)	6/92	(6.5)	
ART recorded, n (%)		25/30	(80.7)	87/92	(94.6)	0.07
Type of comorbidities, n (%)	Chronic pulmonary disease[b]	1/29	(3.5)	12/91	(13.2)	0.19
	Diabetes, with complications	5/30	(16.7)	4/87	(4.6)	0.03
	Obesity	8/28	(28.6)	11/84	(13.1)	0.06
Presenting symptoms, n (%)	Cough	26/29	(89.7)	70/92	(76.1)	0.19
	Diarrhea	8/26	(30.8)	20/82	(24.4)	0.52
Symptom group, n (%)	Respiratory[c]	28/29	(96.6)	80/92	(87.0)	0.19
Presenting signs	HR, median beats/min (IQR)	106	(95, 121)	92	(80, 108)	0.003
	Tachycardia[d], n (%)	16/27	(59.3)	36/90	(40.0)	0.08
	RR, median breaths/min (IQR)	26	(20, 30)	20	(18, 24)	0.006
	Tachypnea[e], n (%)	18/27	(66.7)	37/87	(42.5)	0.03
	Hypoxia[f]/on oxygen, n (%)	22/28	(78.6)	34/87	(39.1)	<0.001
Laboratory parameters	WBC, median count $x10^9$/L (IQR)	8.0	(5.4, 11.8)	5.6	(4.6, 8.7)	0.02
	eGFR[g], median ml/min/1.73m^2 (IQR)	67	(50, 88)	77	(55, 107)	0.13

	Glucose, median mmol/L (IQR)	10.4	(6.4, 13.2)	6.4	(5.8, 8.3)	0.02
	Hyperglycemia[h], n (%)	6/15	(40.0)	5/39	(12.8)	0.05
	C-reactive protein, median mg/L (IQR)	187	(97, 252)	92	(40, 157)	0.001
Interventions, n (%)	Oxygen therapy during admission	22/30	(73.3)	54/87	(62.1)	0.27
	Critical care admission	20/30	(66.7)	19/92	(20.7)	<0.001
	Non-invasive ventilation	12/27	(44.4)	16/87	(18.4)	0.006
	Invasive ventilation	13/29	(44.8)	6/87	(6.9)	<0.001

[a]A full list of demographic and clinical characteristics is shown in Supplementary Table 6. [b]Excludes asthma. [c]Respiratory symptoms: ≥1 of cough, dyspnea, chest pain, sore throat, wheeze. [d]Defined as HR >100 beats/minute. [e]Defined as RR >20 breaths/min. [f]Defined as SpO2 <94% on air. [g]Based on the Modification of Diet in Renal Disease (MDRD) formula where eGFR (mL/min/1.73 m^2) = 175 × (Scr/88.4)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if Black ethnicity). [h]Defined as glucose >11 mmol/L. Abbreviations: IQR, Interquartile range; ART, Antiretroviral therapy; HR, Heart rate; RR, Respiratory rate; BP, Blood pressure; WBC, White blood cells; eGFR, estimated glomerular filtration rate.

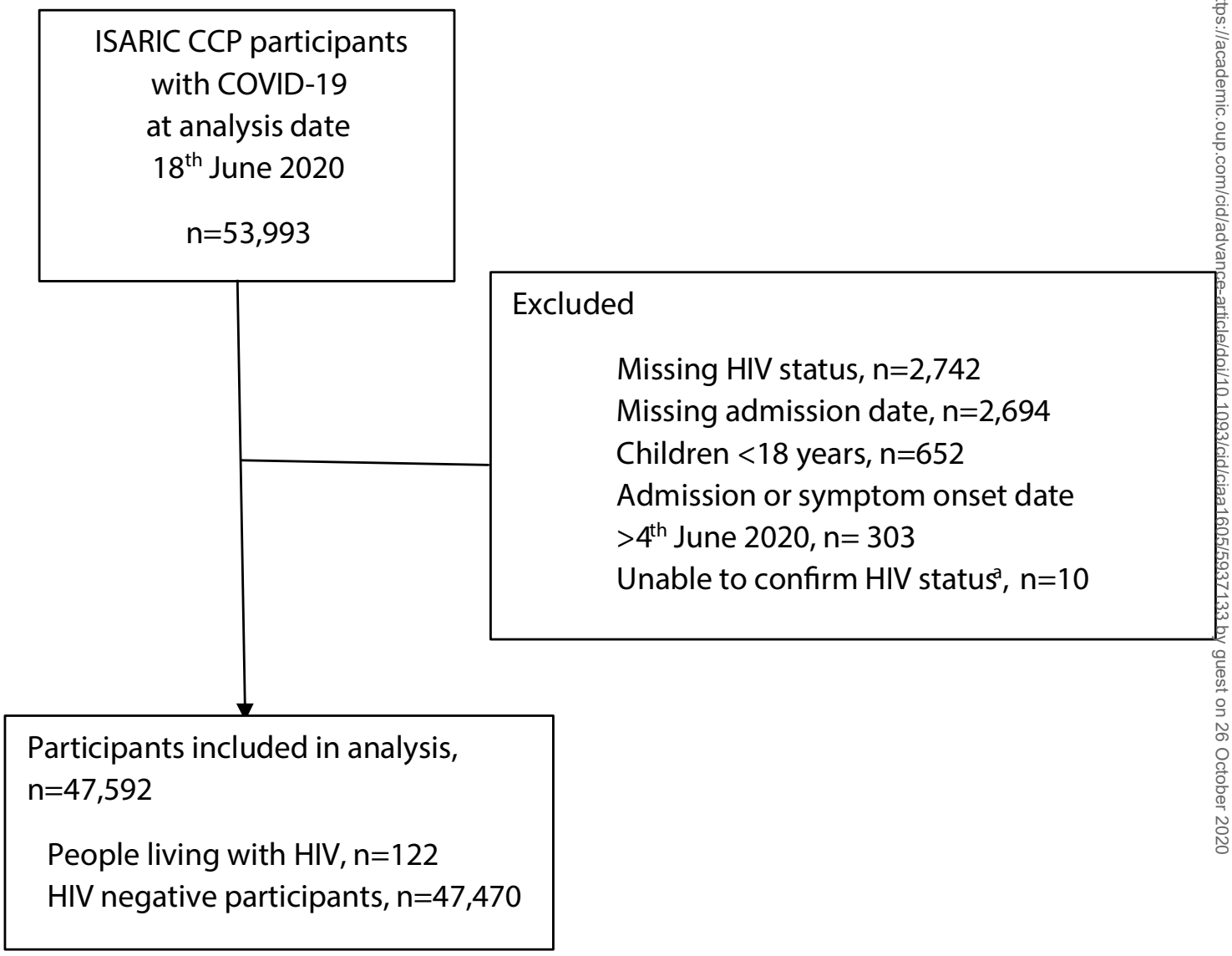
LEGENDS TO FIGURES

Figure 1. Flowchart of study participants**.**

Figure 2. Kernel density plot of age distribution of study participants stratified by HIV status.

Figure 3. Kaplan Meier survival plots stratified by HIV status. A: All, B: Female, C: Male D: <50 years, E: 50 to 59 years, F: >60 years. P values are log-rank tests.

Figure 1: Flowchart of study participants



[a]HIV status was confirmed if participants were recorded as receiving antiretroviral therapy or prophylaxis against Pneumocystis jirovecii, or if local site investigators were able to confirm HIV status.