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## Risk of COVID-19 in-hospital mortality in people living with HIV compared to general population according to age and CD4 strata: data from the ICONA network



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## ABSTRACT

**Objectives:** We aimed to study whether people living with HIV (PLWH) are at higher risk of in-hospital COVID-19 mortality compared to the general population (GenPop).

**Methods:** This was a retrospective study in 19 Italian centers (February 2020 to November 2022) including hospitalized PLWH and GenPop with SARS-CoV-2 infection. The main outcome was in-hospital mortality. Competing risk analyses by Fine-Gray regression model were used to estimate the association between in-hospital mortality and HIV status/age.

**Results:** A total of 7399 patients with COVID-19 were included, 239 (3.2%) PLWH, and 7160 (96.8%) GenPop. By day 40, in-hospital death occurred in 1283/7160 (17.9%) among GenPop and 34/239 (14.2%) among PLWH. After adjusting for potential confounders, compared to GenPop <65 years, a significantly higher risk of death was observed for GenPop ≥65 (adjusted subdistribution hazard ratio [aSHR] 1.79 [95% CI 1.39–2.31]), PLWH ≥65 (aSHR 2.16 [95% CI 1.15–4.04]), PLWH <65 with CD4 ≤200 (aSHR 9.69 [95% CI 5.50–17.07]) and PLWH <65 with CD4 201–350 (aSHR 4.37 [95% CI 1.79–10.63]), whereas no evidence for a difference for PLWH <65 with CD4 >350 (aSHR 1.11 [95% CI 0.41–2.99]).

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**Conclusions:** In PLWH aged <65 years a CD4  $\leq$ 350 rather than HIV itself seems the driver for the observed higher risk of in-hospital mortality. We cannot however rule out that HIV infection *per se* is the risk factor in those aged  $\geq$ 65 years.

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## Introduction

Since the early phase of the SARS-CoV-2 pandemic, it has been questioned which groups of subjects were at higher risk of worse COVID-19 outcomes. This would have allowed firstly to implement specific prevention interventions, allocate therapeutic resources, and in the later phases of the pandemic prioritize COVID-19 vaccination. Demographic factors shortly appeared to be the main determinants of COVID-19 outcomes, with older age, male sex, and social deprivation strongly associated with hospitalization and death [1]. Comorbidities appeared also to be associated with an increased risk of in-hospital death for COVID-19 during the first phase of the pandemic [1–4]. Initially, there was conflicting evidence regarding the risk of worse COVID-19 outcomes in subjects under immunosuppressive treatment or affected by immune system disorders [5]. Among these, people living with HIV (PLWH) were initially investigated by several case series and small cohort studies [6–11]. All these studies were limited by the absence of a comparison with the general population, an adequate study design to control for confounders, or enough power to estimate a consistent effect of HIV infection on COVID-19 major outcomes [6–11]. Taken together, these preliminary observations contributed to the speculation that HIV does not predispose to more severe disease or higher mortality rate especially in well-controlled PLWH, although several open questions remained in those with advanced HIV infection [12]. Subsequently, several large observational studies conducted in the UK [13,14] South Africa [15], the US [16] and on the World Health Organization Global Clinical Platform [17] found that PLWH appeared to be at higher risk of death when compared to the general population. Nevertheless, all these studies investigated the HIV status total effect as a main exposure of interest without trying to single out the crucial confounding and potential interaction with age and clusters of differentiation (CD)4 count in PLWH [18]. A study conducted by Dandachi et al [19] was the first to show a potential association between a low CD4 cell count ( $<200$  cell/mm<sup>3</sup>) and the risk of a composite clinical outcome of disease severity in patients with COVID-19. In addition, most of these previous studies were conducted during the first pandemic period [6–17].

With this analysis, we aimed to evaluate the risk of day-40 in-hospital mortality attributable to HIV in individuals admitted to the hospital with COVID-19, after specifically disentangling the confounding and effect modifying effects of age and CD4 count in PLWH.

## Methods

### Study design

This was a retrospective observational multicenter study conducted in 19 centers from the Italian Cohort Naïve Antiretroviral (ICONA) network [20] covering nine Italian regions.

### Study population

PLWH aged 18 years or older seen for care at one of the ICONA Network participating sites who were admitted to the hospital

between the 20<sup>th</sup> February 2020 and 30<sup>th</sup> November 2022 with a diagnosis of SARS-CoV-2 infection (documented by means of a positive real-time-polymerase chain reaction on nasopharyngeal swabs or lower respiratory tract specimens or positive SARS-CoV-2 antigenic test) and with signs and/or symptoms related to COVID-19 were included. Some participating sites also contributed a sample of the general population who were also admitted to the same hospitals over the same period with a diagnosis of SARS-CoV-2 infection (see Supplementary Table 1).

### Data collection

Data were collected by means of *ad hoc* built standardized electronic case report forms (CRF) for both PLWH and the general population groups at each of the participating sites. The collected data were the patients' demographic characteristics including biological sex, age and ethnicity; the date, site and region of admission; periods of hospital admission which were categorized in accordance to the circulating variants of concern (VOC) in Italy: wild type (WT)/Alpha/Gamma (before 15 June 2021) vs Delta (15 June 2021–19 December 2021) vs Omicron (after 20 December 2021) [21]; comorbidities (including cerebrovascular disease, chronic kidney diseases, asthma, chronic obstructive pulmonary disease [COPD], diabetes, autoimmune disorders, cancer, end and non-end-stage liver disease (ESLD), neurological disease, and obesity, defined as a body mass index of  $\geq 30$  Kg/m<sup>2</sup>); pneumonia at hospital admission; disease severity upon hospital admission (PaO<sub>2</sub>/FiO<sub>2</sub>) estimated as described by Pandharipande et al [22]; primary vaccination cycle completion before admission; the drugs used to treat COVID-19 (which included hydroxychloroquine, lopinavir/ritonavir, remdesivir, tocilizumab and other immunomodulators, heparin, steroids, molnupiravir, nirmatrelvir/ritonavir and monoclonal antibodies); laboratory parameters (including C-reactive protein); maximum level of oxygen supply required during the hospitalization (including no oxygen requirement, low flow, high flow, continuous positive airway pressure or non-invasive ventilation and mechanical ventilation) and the hospitalization outcome (death, discharge, or transfer to other facilities).

For PLWH, the following additional information was also collected: last available CD4 cell count before admission; last available HIV-RNA; antiretroviral regimen composition if they were receiving ART; previous AIDS-defining event, and the main reason of death categorized as COVID-19, AIDS, cancer, and ESLD.

### Outcome

The main outcome of interest was time from hospital admission to in-hospital death by 40 days.

### Statistical Analysis

Descriptive statistics were used to show proportions for categorical variables, and median values with their interquartile range (IQR) for continuous variables by exposure groups. The baseline demographic and clinical-epidemiological characteristics of PLWH and the general population group were compared using the  $\chi^2$  or,

when necessary, Fisher's exact test in the case of categorical variables, and Wilcoxon's rank-sum test in the case of continuous variables.

A categorical variable was constructed for the exposure of interest encompassing the following six groups: i) the general population group <65 years, ii) the general population group ≥65, iii) PLWH aged <65 and CD4 >350 cells/mm<sup>3</sup>, iv) PLWH aged <65 and CD4 201–350 cells/mm<sup>3</sup>, v) PLWH aged <65 and CD4 ≤200 cells/mm<sup>3</sup>, and finally, vi) PLWH ≥65 years.

In the survival analysis, follow-up accrued from the date of hospital admission to in-hospital death or hospital discharge. Competing risks Kaplan-Meier curves were used to estimate the cumulative probability of in-hospital mortality in hospitalized patients with COVID-19 and compare the rates across the six groups. These curves were calculated after extending the follow-up of participants who had been discharged alive before day 40 up to day 40.

Unadjusted and adjusted Fine-Gray regression models have been used to estimate the association between the six levels of exposure and COVID-19 in-hospital mortality. In this analysis, hospital discharges due to cure which occurred before day 40 were handled as a competing event.

The sources of potential confounding were controlled for in the statistical analysis by including in the model age, sex, ethnicity, comorbidities (immune disorders, cancer, cardiovascular disease, chronic kidney disease, diabetes, hypertension, liver disease, and lung disease), and region of Italy of the participating site which were sufficient to block all measured confounding pathways under the assumptions shown in the directed acyclic graph (DAG) in Supplementary Figure 1. Although calendar time of hospital admission is not a confounding factor under our assumptions was a strong predictor of death and therefore was further included to improve the efficiency of the model.

The following sensitivity analyses were also performed: i) after restricting the analysis to participants presenting at hospital admission with a documented pneumonia and/or a PaO<sub>2</sub>/FiO<sub>2</sub> <300. This would minimize the potential bias related to different thresholds in hospital admission for PLWH and the general population group, ii) after restricting the analysis to sites contributing both PLWH and the general population sample. This would minimize the potential bias introduced by the non-concurrent enrollment of exposed and unexposed subjects. For this sensitivity analysis, the model has been adjusted for participating center of enrollment instead of the region of Italy, iii) after rerunning the model under the alternative assumption that all other comorbidities already present at the time of hospital admission besides asthma and COPD are not confounding in the causal pathway to mortality. The critical assumption for this analysis is that the comorbidity was developed after having acquired HIV, iv) after restricting the analysis to the Omicron period. This would allow us to assess the potential effect of CD4 cell count in the context of a less pathogenic virus such as the period of circulation of Omicron variant of concern, v) after restricting the analysis to subjects who completed a primary COVID-19 vaccination cycle (defined as ≥2 COVID-19 vaccine shots before hospital admission). This would allow us to assess the potential effect modification of vaccination status on COVID-19 in-hospital mortality according to CD4 cell count strata.

#### Ethical statement and IRB approval

The ICONA Foundation study was approved by the individual Ethic Committees of participating centers, all involved in studies concerning clinical data of hospitalized patients with COVID-19; sensitive data from patients were seen only in aggregate form. All patients signed a consent form to participate in the single center cohorts in accordance with the ethical standards of the committee on human experimentation and the Declaration of Helsinki

(last amended in October 2013). All information, including virological and therapeutic data, was recorded and merged into a pseudo-anonymized database.

#### Role of the funding source

The present study was supported by Gilead Fellowship Program 2021. The ICONA Foundation wrote the study project, collected and analyzed the data, and finalized the drafting of the paper. The funder had no role in data collection, analysis, and interpretation, or in writing the paper.

## Results

### Characteristics of the study population at hospital entry

This analysis includes 7399 hospitalized patients with COVID-19: 239 (3.2%) PLWH and 7160 (96.8%) participants who were HIV-negative or with unknown serostatus (general population group). Characteristics of the study population are reported in Table 1. Male sex at birth was prevalent among PLWH in all the age and CD4 strata when compared to the general population group ( $P < 0.001$ ), whereas a lower proportion of Caucasian was observed among PLWH in all age and CD4 strata apart from PLWH aged ≥65 years in which the prevalence of this ethnicity appeared to be comparable with that of the general population counterpart (97.7% and 96%, respectively).

PLWH less frequently presented with pneumonia and/or PaO<sub>2</sub>/FiO<sub>2</sub> <300 at hospital admission in all age and CD4 cell strata when compared to the general population group ( $P < 0.001$ ). PLWH had a median CD4 cell count of 395 (IQR 161–620) cells/mm<sup>3</sup> with a proportion of subjects with an HIV-RNA <50 cp/mL of 76.1% (Table 2).

### Treatment and respiratory support in follow-up

When compared to the general population group, a higher proportion of PLWH did not require oxygen supply during the hospital stay in all age and CD4 strata ( $P < 0.001$ ) (Supplementary Table 2). The highest proportion of subjects requiring intensive care assistance was observed among PLWH <65 years with CD4 cell count ≤200 cell/mm<sup>3</sup> (19.4%) followed by those aged <65 years in the general population (10.5%). Regarding pharmaceutical interventions during the hospitalization, PLWH were exposed with a lower frequency to heparin in all age and CD4 strata ( $P < 0.001$ ), steroids ( $P < 0.001$ ) and hydroxychloroquine ( $P < 0.001$ ) when compared to the general population group, whereas no evidence for a difference in remdesivir use was observed ( $P = 0.639$ ), such as for monoclonal antibodies ( $P = 0.718$ ), early antiviral treatments ( $P = 0.146$ ), immunomodulant agents ( $P = 0.149$ ).

### COVID-19 in-hospital outcomes

The longest median period of hospitalization, when simply calculated as the total of days spent in hospital was observed among PLWH <65 years with CD4 cell count ≤200 cell/mm<sup>3</sup> (19 days [IQR 11–31]) followed by PLWH <65 years with CD4 cell count 200–350 cell/mm<sup>3</sup> (16 days [IQR 9–22]) and those aged ≥65 years in the general population (14 days [IQR 8–23]). Thirty-four out of 239 (14.2%) PLWH and 1283 out of 7160 (17.9%) patients of the general population group died during the hospitalization. Among PLWH, 26 (76.5%) deaths were deemed as directly related to COVID-19 whereas four (11.8%) were AIDS-related, two (5.9%) cancer-related, and two (5.9%) ESKD-related. The distribution of COVID-19-attributable death in PLWH according to age and CD4 cell count strata is reported in Supplementary Table 3. Individual causes of

**Table 1**  
 Characteristics of the study population according to age strata (< and ≥65 years) and for people living with HIV, also CD4 cell count strata (≤200, 201–350 and >350).

	Total	General Population		PLWH			P	
		<65 yrs	≥65 yrs	<65 yrs CD4 ≤200	<65 yrs CD4 201–350	<65 yrs CD4 >350		≥65 yrs
	399 (100%)	3076 (41.6%)	4084 (55.2%)	62 (0.8%)	35 (0.5%)	99 (1.3%)	43 (0.6%)	
<b>Age, median (IQR)</b>	54 (68–80)	43 (52–58)	72 (79–85)	42 (50–57)	38 (49–58)	45 (53–59)	69 (72–77)	<0.001
<b>Male sex at birth, n (%)</b>	4493 (60.7)	2013 (65.4)	2293 (56.1)	46 (74.2)	31 (88.6)	74 (74.7)	36 (83.7)	<0.001
<b>Ethnicity, n (%)</b>								<0.001
Caucasian	6360 (86.0)	2269 (73.8)	3921 (96)	34 (54.8)	20 (57.1)	74 (74.8)	42 (97.7)	
Latinix	357 (4.8)	275 (8.9)	47 (1.2)	11 (17.7)	9 (25.7)	15 (15.2)	0 (0)	
Asian	294 (4.0)	257 (8.4)	33 (0.8)	1 (1.6)	2 (5.7)	1 (1)	0 (0)	
Black	82 (1.1)	42 (1.4)	13 (0.3)	15 (24.2)	4 (11.4)	7 (7.1)	1 (2.3)	
Maghreb/Arab	277 (3.7)	217 (7.1)	57 (1.4)	1 (1.6)	0 (0)	2 (2)	0 (0)	
Missing	29 (0.4)	16 (0.5)	13 (0.3)	0 (0)	0 (0)	0 (0)	0 (0)	
<b>VOC period, n (%)</b>								<0.001
WT/Alpha/Gamma (before 15Jun21)	4962 (67.1)	2249 (73.1)	2553 (62.5)	39 (62.9)	23 (65.7)	68 (68.7)	30 (69.8)	
Delta (15Jun21–19Dec21)	915 (12.4)	414 (13.5)	480 (11.8)	3 (4.8)	4 (11.4)	11 (11.1)	3 (7)	
Omicron (after 20Dec21)	1522 (20.6)	413 (13.4)	1051 (25.7)	20 (32.3)	8 (22.9)	20 (20.2)	10 (23.3)	
<b>P/F at admission, median (IQR)</b>	310 (239–379)	328 (265–395)	299 (220–357)	324 (255–467)	362 (309–429)	376 (300–514)	304 (202–381)	<0.001
missing	725 (99.8)	309 (10)	382 (99.3)	10 (16)	2 (5.7)	14 (14.1)	8 (18.6)	
<b>P/F at admission (excluding missing) &lt;300, n (%)</b>	2938 (44)	1013 (36.6)	1858 (50.2)	21 (40.4)	8 (24.3)	21 (24.7)	17 (48.6)	<0.001
<b>With pneumonia at admission (excluding missing), n (%)</b>	5202 (85.3)	2094 (86.5)	3044 (85.3)	7 (41.2)	8 (64.5)	35 (62.5)	14 (58.3)	<0.001
missing	1300 (17.6)	655 (21.3)	516 (12.6)	45 (72.5)	22 (62.8)	43 (43.4)	19 (44.2)	
<b>With pneumonia and/or P/F &lt;300, n (%)</b>	5612 (77.2)	2247 (75.1)	3257 (80.6)	23 (399.7)	16 (45.7)	46 (46.9)	23 (53.5)	<0.001
missing	132 (1.8)	86 (2.8)	41 (1)	4 (6.5)	0 (0)	1 (1)	0 (0)	
<b>Comorbidities, n (%)</b>								
Cerebro/cardiovascular disease	1103 (14.9)	117 (3.8)	969 (23.7)	0 (0)	4 (11.4)	5 (5.1)	8 (18.6)	<0.001
CKD	528 (7.1)	100 (3.3)	410 (10)	1 (1.6)	3 (8.6)	9 (99.1)	5 (11.6)	<0.001
Asthma	144 (1.9)	53 (1.7)	79 (1.9)	7 (11.3)	2 (5.7)	0 (0)	3 (7)	<0.001
Immune disorders/Autoimmune disorders	170 (2.3)	65 (2.1)	96 (2.4)	5 (8.1)	0 (0)	0 (0)	4 (9.9)	<0.001
Cancer	393 (5.3)	40 (1.3)	346 (8.5)	1 (1.6)	0 (0)	3 (3)	3 (7)	<0.001
Diabetes	637 (8.6)	165 (5.4)	440 (10.8)	13 (21)	4 (11.4)	8 (8.1)	7 (16.3)	<0.001
Liver Diseases (non ESLD)	998 (13.5)	262 (8.5)	708 (17.3)	3 (4.8)	2 (5.7)	9 (14.1)	9 (20.9)	<0.001
ESLD	48 (0.6)	10 (0.3)	31 (0.8)	2 (3.2)	4 (11.4)	1 (1)	0 (0)	<0.001
Hypertension	1744 (27.1)	290 (11.2)	1441 (38.6)	9 (15)	3 (99.4)	13 (13.7)	18 (42.9)	<0.001
COPD	165 (2.2)	52 (1.7)	95 (2.3)	7 (11.3)	5 (14.3)	4 (4)	2 (4.7)	<0.001
Lung Diseases (Asthma+COPD+Other Lung disease)	877 (11.8)	218 (7.1)	626 (15.3)	11 (17.7)	5 (14.3)	7 (7.1)	10 (23.3)	<0.001
Neurological Diseases	109 (2.8)	17 (1)	77 (4)	5 (8.5)	4 (13.3)	3 (3.5)	3 (7.9)	<0.001
<b>Obesity, n (%)</b>								<0.001
No	3706 (50.1)	1581 (51.4)	1946 (47.7)	54 (87.1)	25 (71.4)	71 (71.7)	29 (67.4)	
Yes	1296 (17.5)	633 (20.6)	630 (15.4)	4 (6.5)	5 (14.3)	17 (17.2)	7 (16.3)	
unknown	2397 (32.4)	862 (28)	1508 (36.9)	4 (6.5)	5 (14.3)	11 (11.1)	7 (16.3)	
<b>Primary cycle COVID-19 vaccine complete, n (%)</b>	1208 (16.3)	230 (7.5)	935 (22.9)	13 (21.0)	6 (17.1)	15 (15.1)	9 (20.9)	<0.001
missing	459 (6.2)	226 (7.3)	190 (4.6)	15 (24.2)	9 (25.7)	13 (13.1)	6 (13.9)	
<b>Region, n (%)</b>								<0.001
Lombardy	6144 (83)	2525 (82.1)	3530 (86.4)	18 (29)	12 (34.3)	45 (45.5)	14 (32.6)	
Lazio	995 (13.5)	498 (16.2)	409 (10)	28 (45.2)	17 (48.6)	32 (32.3)	11 (25.6)	
Emilia Romagna	121 (1.6)	26 (0.9)	79 (1.9)	2 (3.2)	1 (2.9)	9 (99.1)	4 (99.3)	
Sardinia	100 (1.4)	27 (0.9)	66 (1.6)	2 (3.2)	2 (5.7)	1 (1)	2 (4.7)	
Liguria	19 (0.3)	0 (0)	0 (0)	2 (3.2)	0 (0)	8 (8.1)	9 (20.9)	
Campania	10 (0.1)	0 (0)	0 (0)	4 (6.5)	2 (5.7)	3 (3)	1 (2.3)	
Marche	5 (0.1)	0 (0)	0 (0)	3 (4.8)	0 (0)	1 (1)	1 (2.3)	
Apulia	3 (0)	0 (0)	0 (0)	2 (3.2)	0 (0)	0 (0)	1 (2.3)	
Sicily	2 (0)	0 (0)	0 (0)	1 (1.6)	1 (2.9)	0 (0)	0 (0)	

CKD, chronic kidney disease; CRP, C reactive protein; ESLD, end-stage liver disease; GenPop, general population; IQR, interquartile range; n, number; P/F, PaO2/FiO2; PLWH, people living with HIV; VOC, variants of concern; WT, wild type.

death were not available for the general population group. The Kaplan-Meier curves in which death and discharge have been handled as competing events are depicted in Figure 1.

In the Fine-Gray regression model main analysis, after adjusting for potential confounders (age, sex at birth, ethnicity, region of enrollment, immune disorders, cancer, cardiovascular disease,

chronic kidney disease, diabetes, hypertension, liver disease, obesity and lung disease) as well as calendar period of hospital admission, when compared to the general population group <65 years, a significantly higher risk of death was observed for the general population ≥65 years (adjusted subdistribution hazard ratio [aSHR] 1.79 [95% CI 1.39–2.31]), PLWH ≥65 years (aSHR 2.16 [95% CI 1.15–

**Table 2**  
Characteristics of people living with HIV.

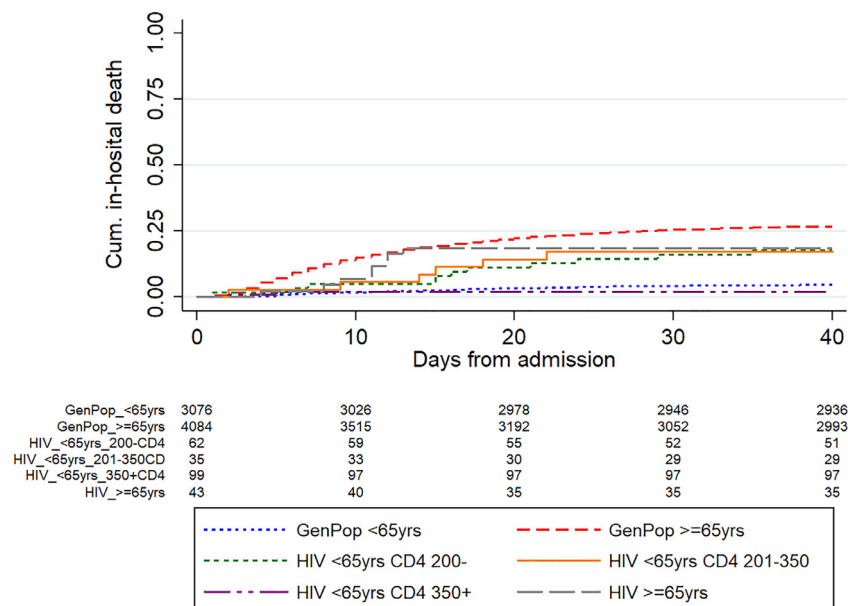
	PLWH n = 239
<b>CD4 count (cells/mm<sup>3</sup>), median (IQR)</b>	395 (161-620)
CD4 >350 (cells/mm <sup>3</sup> ), n (%)	125 (52.3)
CD4 201-350 (cells/mm <sup>3</sup> ), n (%)	44 (18.4)
CD4 ≤200 (cells/mm <sup>3</sup> ), n (%)	67 (30.2)
<b>Months from CD4 count to hospitalization, mediana (IQR)</b>	1.2 (0.0-4.1)
<b>HIV-RNA &lt;50 copies/mL, n (%)</b>	175 (76.1)
Missing	9
<b>Previous AIDS event, n (%)</b>	78 (34.8%)
Missing	16
<b>Antiretroviral Regimes, n (%)</b>	
2NRTIs+ INSTI	83 (34.7)
Dual INSTI based	30 (12.5)
2NRTIs + PI	21 (8.8)
2NRTIs + NNRTIs	31 (13)
Other regimens	42 (17.6)
missing or ART-naïve	32 (13.4)

ART, antiretroviral treatment; INSTI, integrase strand transfer inhibitors; IQR, interquartile range; n, number; NNRTI; non-nucleoside reverse transcriptase inhibitor; NRTIs, nucleoside reverse transcriptase inhibitor; PI, protease inhibitors; PLWH, people living with HIV.

**Table 3**  
Unadjusted and adjusted Fine-Gray Cox regression model of the association between the six level's exposure and in-hospital mortality.

Overall*	SHR	95% CI	aSHR	95% CI
GenPop <65 years	1	-	1	-
GenPop ≥65 years	6.83	5.75-8.11	1.79	1.39-2.31
PLWH ≥65 years	5.42	2.89-10.13	2.16	1.15-4.04
PLWH <65 years and CD4 cell count ≤200 cell/mm <sup>3</sup>	5.08	3.01-8.57	9.69	5.50-17.07
PLWH <65 years and CD4 cell count 201-350 cell/mm <sup>3</sup>	3.89	1.74-8.73	4.37	1.79-10.63
PLWH <65 years and CD4 cell count >350 cell/mm <sup>3</sup>	0.86	0.32-2.32	1.11	0.41-2.99

\* Final model adjusted for age, sex at birth, ethnicity, region of enrollment, calendar period, immune disorders, cancer, cardiovascular disease, chronic kidney disease, diabetes, hypertension, liver disease, obesity and lung disease.  
aSHR, adjusted subdistribution hazard ratio; CI, confidence interval; GenPop, general population; PLWH, people living with HIV.



**Figure 1.** Kaplan-Meier curved of in-hospital mortality stratified by HIV status, age (<65 vs >65 years) and CD4 cell count (<=200 vs >200-350 vs >350 cell/mm<sup>3</sup>).

4.04]), PLWH <65 years with CD4 ≤200 cell/mm<sup>3</sup> (aSHR 9.69 [95% CI 5.50-17.07]) and PLWH <65 years with CD4 201-350 cell/mm<sup>3</sup> (aSHR 4.37 [95% CI 1.79-10.63]), whereas no evidence for a difference for PLWH <65 with CD4 >350 cell/mm<sup>3</sup> (aSHR 1.11 [95% CI 0.41-2.99]) (Table 3). Consistent results were obtained in the i), ii), and iii) sensitivity analyses (Table 4). After restricting the anal-

yses to subjects admitted during the Omicron period (iv) and to those who completed a primary COVID-19 vaccination cycle before hospital admission (v), when compared to the general population group <65 years, a significantly higher risk of death was observed for PLWH <65 years with CD4 ≤200 cell/mm<sup>3</sup> (aSHR 9.06 [95% CI 2.87-28.65] and 15.85 [95% CI 5.03-49.93], respectively) and PLWH

**Table 4**

Unadjusted and adjusted Fine-Gray Cox regression model of the association between the six level's exposure and in-hospital mortality restricted to subjects with pneumonia and/or P/F<300 at hospital admission, restricted to centers able to provide both HIV exposed and unexposed and after rerunning the model by adjusting for comorbidities.

Restricted to subjects with pneumonia and/or P/F<300 at hospital admission <sup>a</sup>	SHR	95% CI	aSHR	95% CI
GenPop <65 years	1	-	1	-
GenPop ≥65 years	6.28	5.26-7.51	1.78	1.37-2.32
PLWH ≥65 years	7.79	4.06-14.95	2.80	1.43-5.46
PLWH <65 years and CD4 cell count ≤200 cell/mm <sup>3</sup>	7.41	3.97-13.83	9.83	4.75-20.35
PLWH <65 years and CD4 cell count 201-350 cell/mm <sup>3</sup>	5.69	2.47-13.12	4.41	1.74-11.18
PLWH <65 years and CD4 cell count >350 cell/mm <sup>3</sup>	0.86	0.32-2.32	1.23	0.38-3.95
Restricted to centers able to provide both HIV exposed an unexposed <sup>a</sup>				
GenPop <65 years	1	-	1	-
GenPop ≥65 years	6.83	5.74-8.11	1.82	1.41-2.34
PLWH ≥65 years	4.00	1.48-10.78	1.75	0.64-4.75
PLWH <65 years and CD4 cell count ≤200 cell/mm <sup>3</sup>	4.73	2.51-8.89	8.17	4.18-15.99
PLWH <65 years and CD4 cell count 201-350 cell/mm <sup>3</sup>	3.95	1.62-9.62	5.45	2.29-13.00
PLWH <65 years and CD4 cell count >350 cell/mm <sup>3</sup>	0.92	0.29-2.90	1.08	0.34-3.43
Overall <sup>b</sup>				
GenPop <65 years	1	-	1	-
GenPop ≥65 years	6.83	5.75-8.11	1.86	1.44-2.39
PLWH ≥65 years	5.42	2.89-10.13	2.18	1.18-4.06
PLWH <65 years and CD4 cell count ≤200 cell/mm <sup>3</sup>	5.08	3.01-8.57	8.65	4.91-15.22
PLWH <65 years and CD4 cell count 201-350 cell/mm <sup>3</sup>	3.89	1.74-8.73	4.25	1.76-10.29
PLWH <65 years and CD4 cell count >350 cell/mm <sup>3</sup>	0.86	0.32-2.32	1.04	0.39-2.78

<sup>a</sup> Final model adjusted for adjusted for age, sex at birth, ethnicity, region of enrollment, calendar period, immune disorders, cancer, cardiovascular disease, chronic kidney disease, diabetes, hypertension, liver disease, neurologic disease obesity and lung disease

<sup>b</sup> Final model adjusted for age, sex at birth, ethnicity, calendar period, region of enrollment and lung diseases.

aSHR, adjusted subdistribution hazard ratio; CI, confidence interval; GenPop, general population; PLWH, people living with HIV.

<65 years with CD4 201-350 cell/mm<sup>3</sup> (aSHR 24.13 [95% CI 2.70-215.83] and 11.60 [95% CI 2.08-64.78], respectively).

## Discussion

Our analysis shows that among hospitalized subjects for COVID-19, PLWH aged <65 years with a CD4 cell count <350 cells/mm<sup>3</sup> had a higher risk of in-hospital mortality when compared to the general population group of similar age, whereas there was no evidence for a difference for PLWH with a CD4 count >350 cells/mm<sup>3</sup>. Importantly, there was a clear dose-response associated with CD4 count with the risk being even higher in those with a CD4 count <200 cells/mm<sup>3</sup>. The evidence was insufficient for PLWH aged ≥65 years. Age was the strongest predictor of mortality regardless of HIV status.

The question of whether HIV status confers a higher risk of severe COVID-19 disease was highly debated during the first pandemic period. Nevertheless, the first reports and case series were undermined by the absence of an adequate sample size which guaranteed adequate power to estimate the possible effect of HIV status on the risk of mortality [6–11]. What was clear from these first reports was that, in the hospitalized setting, the demographic characteristics of PLWH were different from that of the general population with a predominance of younger men [6–11]. This difference was observed through the course of the pandemic in subsequent large observational cohort studies [13–17] and confirmed in our study.

These early studies found no association between HIV and risk of severe outcomes after hospitalization, but their results might have been confounded by age [6–11]. This pitfall was first addressed by Geretti et al [14] in a large UK dataset including 122 PLWH and 47,470 HIV unexposed subjects hospitalized with COVID-19 in which the authors found a higher risk of day-28 mortality in HIV-negative individuals in the unadjusted analysis which was reversed after controlling for age (47% higher risk in PLWH). Interestingly, age appeared to be an effect-measure modifier as

there was an almost 3-fold higher risk for PLWH when compared to the HIV-negative group when restricted to participants aged 60 or older (adjusted hazard ratio [aHR] 2.87; 95% CI 1.70-4.84) [14]. In addition, in another study conducted in South Africa, a greater proportion of COVID-19 deaths was observed in PLWH aged <50 years when compared to HIV-negative subjects (39% vs 13.1%, respectively) [23]. Other, population-level studies performed in the UK (OpenSAFELY [13]), South Africa [15,23], and the USA [24] estimated an increased risk of COVID-19 mortality for PLWH when compared to the general population (aHR 2.59 [95% CI 1.74-3.84], aHR 2.14 [95% CI 1.70-2.70] and adjusted odds ratio [aOR] 1.29 [1.16-1.44], respectively). However, even in recent years, results remained conflicting as in two other large studies conducted in the USA [25–27] and in Spain [28] in 2020-2021, conversely, the authors found no association between HIV status and COVID-19 death.

Of note, in most of these previous studies, no information was provided regarding the immunological status of PLWH and thus it was unclear if this increased risk could be attributable to low CD4 count. Our data provide a potential explanation of what has been previously observed in subjects aged <65 years. In particular, we found that, after controlling for potential confounders, PLWH aged <65 years with a CD4 cell count 201-350 cell/mm<sup>3</sup> and ≤200 cell/mm<sup>3</sup> were respectively at 4- and 9-fold higher risk of in-hospital death when compared to the general population group of similar age, whereas there was no evidence for a difference when considering PLWH with a CD4 count >350 cells/mm<sup>3</sup>. Results were confirmed in sensitivity analyses aimed to minimize the number of potential biases. In addition, we found no evidence for a difference in mortality when comparing our general population group aged <65 years with both PLWH and the general population group aged ≥65, although with large uncertainty around these estimates. There are two potential explanations for these latter secondary findings. First, it is possible that the effect of HIV on mortality is even larger in the age strata of those aged 65 or older but our study was underpowered to detect this interaction. Indeed, a pre-

vious study has shown that the effect of HIV might be exacerbated with older age [24]. Conversely, it is also possible that HIV has a smaller impact on mortality in older subjects where the course of the disease is more severe, and the outcome is mainly age-related. This second hypothesis is also consistent with the fact that in the general population the outcome of younger subjects significantly improved over time, but this was not seen in older patients with COVID-19 [29].

One key issue when analyzing data coming from the observational setting is how to minimize the effect of confounding. The set of confounders used in previous analyses typically included: sex, ethnicity, age, baseline date, a number of underlying conditions (i.e., diabetes, tuberculosis, chronic kidney diseases, pulmonary diseases, and malignancies), and COVID-19 disease severity at presentation although these were slightly different from analysis to analysis and different from those used by us in the main analysis [14,17]. This makes the comparison between results more difficult.

Nevertheless, our results are consistent with some of those already published. For instance, in a sub-group analysis of the above-mentioned population study conducted in South Africa, the authors found that PLWH with a CD4 cell count  $<200$  cell/mm<sup>3</sup> had a higher risk of death when compared to HIV-negative subjects (2.36 (95% CI 1.47–3.78)) and to PLWH with a CD4 cell count  $>350$  cell/mm<sup>3</sup> (1.97 (95% CI 1.14–3.40)) [23]. Similarly, in the analysis by Yang et al [24] after adjusting for demographics, lifestyle factors, comorbidities, and month of COVID-19 diagnosis, a CD4  $<200$  was associated with a higher odds of death (aOR 3.10 vs PLWH with CD4 count  $>500$  cell/mm<sup>3</sup> (95% CI 1.06–9.13)) [24], as well as in the analysis by Boule et al [23] where being viremic or having a CD4  $<200$  was associated with a higher hazard rate of death when compared to HIV-negative subjects (3.35 (95% CI 1.83–6.12)). With our analysis, we were able to add a piece to this puzzle by investigating the CD4 cell strata 201–350 cell/mm<sup>3</sup> and showing that also in these strata the risk of in-hospital death was significantly higher when compared to the general population counterpart of similar age. A causal relationship between immunosuppression status and risk of death in PLWH vs the general population group was further supported by the dose-response relationship with level of CD4 count with the difference in risk more than doubling when investigating the risk in the 201–350 vs  $\leq 200$  cell/mm<sup>3</sup> strata (aSHR 4.37 and 9.69, respectively). In addition, according to the sensitivity analyses restricted to the Omicron period and to vaccinated subjects, PLWH aged  $<65$  years with a CD4 cell count  $<350$  cell/mm<sup>3</sup> were confirmed to be at higher risk of in-hospital death when compared to the general population group  $<65$  years. COVID-19 vaccination and the Omicron period seem to act as effect modifiers with a potential further increased risk in a context of a less pathogenetic virus (such as Omicron variant) or in vaccinated subjects. Nevertheless, these findings should be looked at with caution considering the low number of events observed in this sensitivity analysis and the wide confidence intervals provided by the models.

### Limitations

Our study has a number of limitations.

First, a significant proportion of centers were not able to provide unexposed (HIV-negative or unknown serostatus) subjects. However, we performed a sensitivity analysis after restricting to sites that contributed both PLWH and the general population sample and the results were similar.

Second, because the outcome was all-cause mortality it is possible that some of the deaths were not COVID-19 related. However, results were similar in a sensitivity analysis which was restricted to participants with pneumonia and/or PaO<sub>2</sub>/FiO<sub>2</sub>  $<300$

mmHg at hospital admission. However, it has to be noted that PaO<sub>2</sub>/FiO<sub>2</sub> was available only for a subset of the study population so we cannot rule out potential selection bias in this sensitivity analysis. Nevertheless, we observed that most of PLWH who died in-hospital (77%) had COVID-19 reported as the leading cause of death. Moreover, the proportion of subjects who died for a reason other than COVID-19 was equally distributed among PLWH CD4 strata.

Third, the use of hospitalized individuals might not fully reflect the HIV-related risk of adverse COVID-19 outcomes. In particular, because PLWH is expected to be a high-risk population, it might be more likely that they will be admitted with a higher frequency when presenting with mild COVID-19 when compared to the general population in which only individuals with more severe symptoms are typically admitted. Nevertheless, we tried to partially address this limitation by performing a sensitivity analysis restricted only to subjects with a PaO<sub>2</sub>/FiO<sub>2</sub>  $<300$  and the results of this sensitivity analysis were consistent with the estimates provided by the main analysis.

Fourth, the significant differences between PLWH and general population observed in terms of COVID-19 treatments, in particular heparin and steroids, could be explained by the difference between the groups' severity observed at hospital admissions. As mentioned above PLWH could have been admitted with less severe forms of COVID-19 when compared to the general population but they could have been managed as a high-risk population and this could explain the similar proportion of antiviral treatments between PLWH and general population although the disease severity at admission was different. We have tried to partially address this issue by performing our sensitivity analysis restricted to those with a PaO<sub>2</sub>/FiO<sub>2</sub>  $<300$ .

Finally, our results are valid under the usual assumption of a correctly specified model and no unmeasured or residual confounding. As far as residual measured confounding is concerned, our main analysis differs from most of the others because did not control for many underlying conditions at hospital admission. Unfortunately, in absence of exact information on temporality, there is no analytic tool that will tell us whether, for example, malignancies or cerebrum/vascular disease are confounders or mediators of our association of interest and the prevalence of cerebrum/vascular disease was imbalanced between PLWH and the general population sample. Therefore, we assumed that they were confounders in the main analysis and mediators in a sensitivity analysis (which consequently was not adjusted for these factors) and the results were again similar. Calendar period (which also encapsulates the predominantly circulating VoC with variable pathogenicity) was strongly predictive of mortality and was further included in the model to increase efficiency. Vaccination is also an important predictor of mortality, but HIV is a factor potentially associated with an increased probability of vaccination. Under this assumption vaccination is a mediator in the causal pathway between HIV and risk of death and this is why has not been adjusted for in the models. Also, vaccination and natural infection were not included because we could not exclude information bias for these variables. Finally, index of deprivation, which was found to be linked to COVID-19 hard outcomes in population-level studies, is a potential unmeasured source of confounding.

Nevertheless, our study has also some important strengths. First, it covers a long period of the COVID-19 pandemic (from 2020 until the end of 2022) which extends previous findings to the era of infections with less pathogenic strains of SARS-CoV-2. In addition, because we were able to collect data on immune-virological characteristics of PLWH this allowed us to provide a deeper investigation of the possible determinants of mortality and suggest a possible explanation (i.e. specific thresholds of HIV-induced immunosuppression).

## Conclusion

In conclusion, our analysis further clarifies the impact of HIV on the risk of mortality after hospital admission for COVID-19 disease by highlighting the role of immunosuppression ( $CD4 \leq 350$  cells/ $m^3$ ) in PLWH aged <65 years. We cannot however rule out that HIV infection *per se* is the risk factor in those aged  $\geq 65$  years. Our data further support the notion that PLWH aged <65 years with  $CD4$  count  $\leq 350$  cells/ $mm^3$  and especially those with <200 cells/ $m^3$  should be prioritized for access to infection-preventing interventions and early treatments.

## Declarations of competing interest

A Giacomelli reports speakers' honoraria for ViiV Healthcare and Gilead Sciences, advisor for Janssen-Cilag and Mylan; RG reports payments to her institution from Gilead Sciences, speakers' honoraria for ViiV Healthcare, Merck Sharp and Dohme and Gilead Sciences, advisor for Thera Technologies, Janssen-Cilag and Gilead Sciences; GR reports consultancies/advisory from ViiV Healthcare, GSK, Merck Sharp and Dohme and Gilead Sciences; A Gori received speaker's honoraria and fees for attending advisory boards from ViiV Healthcare, Gilead, Janssen-Cilag, Merck Sharp & Dohme, Bristol-Myers Squibb, Pfizer and Novartis and received research grants from ViiV, Bristol-Myers Squibb, and Gilead; AM received speakers' honoraria from Gilead Sciences, and ViiV Healthcare, travel fee from ViiV Healthcare and participated in advisory boards sponsored by ViiV Healthcare; AV received an institutional grant from Gilead Sciences, speakers' honoraria/educational activities from Merck Sharp & Dohme and Janssen-Cilag, and served an advisor for Janssen-Cilag; MM received speakers' honoraria from ViiV Healthcare; LT reports consultancies/advisory from ViiV Healthcare, Gilead Sciences and Janssen-Cilag and institutional fellowship from Gilead Sciences; G Marchetti participated to advisory boards of Gilead Sciences, ViiV Healthcare, Angelini and Janssen-Cilag, and received travel grants from ViiV Healthcare and Janssen-Cilag; AdM participated in advisory board of Gilead Sciences, ViiV Healthcare, Merck Sharp and Dohme, Pfizer and GSK and reports research grant from Gilead Science, ViiV Healthcare, Merck Sharp and Dohme, GSK and Janssen-Cilag; AA received Research grants from Gilead Sciences, AstraZeneca, ViiV Healthcare and Honoraria from Gilead Science, AstraZeneca, GSK, Pfizer, Merck Sharp and Dohme, Moderna, Mylan, Janssen-Cilag, ViiV Healthcare; AT, SDB, SA, G Mancarella, FMF, ADV, VM, MA and ACL have nothing to declare.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ijid.2023.09.015](https://doi.org/10.1016/j.ijid.2023.09.015).

## References

- [1] Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;**584**:430–6. doi:10.1038/s41586-020-2521-4.
- [2] Giacomelli A, Ridolfo AL, Milazzo L, Oreni L, Bernacchia D, Siano M, et al. 30-day mortality in patients hospitalized with COVID-19 during the first wave of the Italian epidemic: a prospective cohort study. *Pharmacol Res* 2020;**158**:104931. doi:10.1016/j.phrs.2020.104931.
- [3] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020;**323**:2052–9. doi:10.1001/jama.2020.6775.
- [4] d'Arminio Monforte A, Tavelli A, Bai F, Tomasoni D, Falcinella C, Castoldi R, et al. The importance of patients' case-mix for the correct interpretation of the hospital fatality rate in COVID-19 disease. *Int J Infect Dis* 2020;**100**:67–74. doi:10.1016/j.ijid.2020.09.037.
- [5] Fung M, Babik JM. COVID-19 in immunocompromised hosts: what we know so far. *Clin Infect Dis* 2021;**72**:340–50. doi:10.1093/cid/ciaa863.



- [6] Gervasoni C, Meraviglia P, Riva A, Giacomelli A, Oreni L, Minisci D, et al. Clinical features and outcomes of patients with human immunodeficiency virus with COVID-19. *Clin Infect Dis* 2020;**71**:2276–8. doi:10.1093/cid/ciaa579.
- [7] Blanco JL, Ambrosioni J, Garcia F, Martínez E, Soriano A, Mallolas J, et al. COVID-19 in patients with HIV: clinical case series. *Lancet HIV* 2020;**7**:e314–16. doi:10.1016/S2352-3018(20)30111-9.
- [8] Vizcarra P, Pérez-Eliás MJ, Quereda C, Moreno A, Vivancos MJ, Dronda F, et al. Description of COVID-19 in HIV-infected individuals: a single-centre, prospective cohort. *Lancet HIV* 2020;**7**:e554–64. doi:10.1016/S2352-3018(20)30164-8.
- [9] Del Amo J, Polo R, Moreno S, Díaz A, Martínez E, Arribas JR, et al. The Spanish HIV/COVID-19 Collaboration. Incidence and severity of COVID-19 in HIV-positive persons receiving antiretroviral therapy: a cohort study. *Ann Intern Med* 2020;**173**:536–41. doi:10.7326/M20-3689.
- [10] Gagliardini R, Vergori A, Lorenzini P, Cicalini S, Pinnetti C, Mazzotta V, et al. Characteristics and outcomes of COVID-19-related hospitalization among PLWH. *J Clin Med* 2022;**11**:1546. doi:10.3390/jcm11061546.
- [11] Patel VV, Felsen UR, Fisher M, Fazzari MJ, Ginsberg MS, Beil R, et al. Clinical outcomes and inflammatory markers by HIV serostatus and viral suppression in a large cohort of patients hospitalized with COVID-19. *J Acquir Immune Defic Syndr* 2021;**86**:224–30. doi:10.1097/QAI.0000000000002578.
- [12] Cooper TJ, Woodward BL, Alom S, Harky A. Coronavirus disease 2019 (COVID-19) outcomes in HIV/AIDS patients: a systematic review. *HIV Med* 2020;**21**:567–77. doi:10.1111/hiv.12911.
- [13] Bhaskaran K, Rentsch CT, MacKenna B, Schultze A, Mehrkar A, Bates CJ, 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. doi:10.1016/S2352-3018(20)30305-2.
- [14] Geretti AM, Stockdale AJ, Kelly SH, Cevik M, Collins S, Waters L, 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* 2021;**73**:e2095–106. doi:10.1093/cid/ciaa1605.
- [15] Western Cape Department of Health in collaboration with the National Institute for Communicable Diseases, South Africa Risk factors for Coronavirus Disease 2019 (COVID-19) death in a population cohort study from the Western Cape Province, South Africa. *Clin Infect Dis* 2021;**73**:e2005–15. doi:10.1093/cid/ciaa1198.
- [16] Tesoriero JM, Swain CE, Pierce JL, Zamboni L, Wu M, Holtgrave DR, et al. COVID-19 outcomes among persons living with or without diagnosed HIV infection in New York State. *JAMA Netw Open* 2021;**4**:e2037069. doi:10.1001/jamanetworkopen.2020.37069.
- [17] Bertagnolio S, Thwin SS, Silva R, Nagarajan S, Jassat W, Fowler R, et al. Clinical features of, and risk factors for, severe or fatal COVID-19 among people living with HIV admitted to hospital: analysis of data from the WHO Global Clinical Platform of COVID-19. *Lancet HIV* 2022;**9**:e486–95. doi:10.1016/S2352-3018(22)00097-2.
- [18] Waters LJ, Pozniak AL. COVID-19 death in people with HIV: interpret cautiously. *Lancet HIV* 2021;**8**:e2–3. doi:10.1016/S2352-3018(20)30332-5.
- [19] Dandachi D, Geiger G, Montgomery MW, Karmen-Tuohy S, Golzy M, Antar AA, et al. Characteristics, comorbidities, and outcomes in a multicenter registry of patients with human immunodeficiency virus and coronavirus disease 2019. *Clin Infect Dis* 2021;**73**:e1964–72. doi:10.1093/cid/ciaa1339.
- [20] Fondazione Icona. ICONA cohort. [https://www.fondazioneicona.org/\\_new2/pages/publicArea/ICONAcohort/](https://www.fondazioneicona.org/_new2/pages/publicArea/ICONAcohort/); 2023 [accessed 21 March 2023].
- [21] CoVariants. Overview of variants in countries, <https://covariants.org/per-country?region=World>; 2022 [accessed 05 May 2023].
- [22] Pandharipande PP, Shintani AK, Hagerman HE, Jacques PJ, Rice TW, Sanders NW, et al. Derivation and validation of Spo2/Fio2 ratio to impute for Pao2/Fio2 ratio in the respiratory component of the Sequential Organ Failure Assessment score. *Crit Care Med* 2009;**37**:1317–21. doi:10.1097/CCM.0b013e31819cefa9.
- [23] Western Cape Department of Health in collaboration with the National Institute for Communicable Diseases, South Africa Risk factors coronavirus disease 2019 (COVID-19) death in a population cohort study from the Western Cape Province, South Africa. *Clin Infect Dis* 2021;**73**:e2005–15.
- [24] Yang X, Sun J, Patel RC, Zhang J, Guo S, Zheng Q, et al. Associations between HIV infection and clinical spectrum of COVID-19: a population level analysis based on US National COVID Cohort Collaborative (N3C) data. *Lancet HIV* 2021;**8**:e690–700. doi:10.1016/S2352-3018(21)00239-3.
- [25] Durstenfeld MS, Sun K, Ma Y, Rodriguez F, Secemsky EA, Parikh RV, et al. Association of HIV infection with outcomes among adults hospitalized with COVID-19. *AIDS* 2022;**36**:391–8. doi:10.1097/QAD.0000000000003129.
- [26] Kwapong YA, Sharma G, Shade JK, Piggott DA, Brown TT, Soleimanifard A, et al. Effect of HIV serostatus on ICU admission and mortality among hospitalized patients with coronavirus disease 2019 (COVID-19). *J Acquir Immune Defic Syndr* 2022;**90**:e13–16. doi:10.1097/QAI.0000000000003009.
- [27] Rosenthal EM, Rosenberg ES, Patterson W, Ferguson WP, Gonzalez C, DeHovitz J, et al. Factors associated with SARS-CoV-2-related hospital outcomes among and between persons living with and without diagnosed HIV infection in New York State. *PLoS One* 2022;**17**:e0268978. doi:10.1371/journal.pone.0268978.
- [28] Olalla-Sierra J, Martín-Escalante MD, García-Alegría J, Rubio-Rivas M, de Miguel-Campo B, Zurita-Etayo M, et al. Coronavirus disease 2019 hospitalization outcomes in persons with and without HIV in Spain. *AIDS* 2022;**36**:683–90. doi:10.1097/QAD.0000000000003056.
- [29] Giacomelli A, Ridolfo AL, Pezzati L, Oreni L, Carrozzo G, Beltrami M, et al. Mortality rates among COVID-19 patients hospitalised during the first three waves of the epidemic in Milan, Italy: a prospective observational study. *PLoS One* 2022;**17**:e0263548. doi:10.1371/journal.pone.0263548.