Trends in COVID-19 admissions and deaths among people living with HIV in South Africa: analysis of national surveillance data

Waasila Jassat PhD [a b,*], Caroline Mudara MSc [a], Lovelyn Ozougwu MSc [a b], Richard Welch BSc [a b], Tracy Arendse MPH [a b], Maureen Masha MPH [a b], Lucille Blumberg DScMed [a b], Tendesayi Kufa PhD [a], Adrian Puren PhD [a], Michelle Groome PhD [a], Nevashan Govender MSc [a], Pedro Pisa PhD [b e], Sharlene Govender MPH [b], Prof Ian Sanne FCP [b c], Heena Brahmbhatt PhD [f g], Lauren Parmley MSPH [f], Milani Wolmarans BOT [h], Petro Rousseau PhD [h], Anthony Selikow BSc [i], Melissa Burgess MSc [i], Lauren Hankel MSc [i], Arifa Parker MMed [j], Prof Cheryl Cohen PhD [a]

[a] Division of Public Health Surveillance and Response, National Institute for Communicable Diseases, National Health Laboratory Service, Johannesburg, South Africa
[b] Right to Care, Pretoria, South Africa
[c] School of Pathology (M Groome), Clinical HIV Research Unit, Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[d] School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[e] Department of Human Nutrition and Dietetics, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa
[f] United States Agency for International Development, Pretoria, South Africa
[g] Department of Population, Family and Reproductive Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
[h] National Department of Health, Pretoria, South Africa
[i] Council for Scientific and Industrial Research, Pretoria, South Africa
[j] Tygerberg Hospital and Division of Infectious Disease, University of Stellenbosch, Cape Town, South Africa
* Correspondence to: Dr Waasila Jassat, Division of Public Health Surveillance and Response, National Institute for Communicable Diseases, National Health Laboratory Service, Johannesburg 2192, South Africa.
Email: waasila.jassat@health.gov.za

Summary

Background: In 2021, the HIV prevalence among South African adults was 18% and more than 2 million people had uncontrolled HIV and, therefore, had increased risk of poor outcomes with SARS-CoV-2 infection. We investigated trends in COVID-19 admissions and factors associated with in-hospital COVID-19 mortality among people living with HIV and people without HIV.

Methods: In this analysis of national surveillance data, we linked and analysed data collected between March 5, 2020, and May 28, 2022, from the DATCOV South African national COVID-19 hospital surveillance system, the SARS-CoV-2 case line list, and the Electronic Vaccination Data System. All analyses included patients hospitalised with SARS-CoV-2 with known in-hospital outcomes (ie, who were discharged alive or had died) at the time of data extraction. We used descriptive statistics for admissions and mortality trends. Using post-imputation random-effect multivariable logistic regression models, we compared characteristics and the case fatality ratio of people with HIV and people without HIV. Using modified Poisson regression models, we compared factors associated with mortality among all people with COVID-19 admitted to hospital and factors associated with mortality among people with HIV.

Findings: Among 397 082 people with COVID-19 admitted to hospital, 301 407 (75·9%) were discharged alive, 89 565 (22·6%) died, and 6110 (1·5%) had no recorded outcome. 270 737 (68·2%) people with COVID-19 had documented HIV status (22 858 with HIV and 247 879

without). Comparing characteristics of people without HIV and people with HIV in each COVID-19 wave, people with HIV had increased odds of mortality in the D614G (adjusted odds ratio 1·19, 95% CI 1·09–1·29), beta (1·08, 1·01–1·16), delta (1·10, 1·03–1·18), omicron BA.1 and BA.2 (1·71, 1·54–1·90), and omicron BA.4 and BA.5 (1·81, 1·41–2·33) waves. Among all COVID-19 admissions, mortality was lower among people with previous SARS-CoV-2 infection (adjusted incident rate ratio 0·32, 95% CI 0·29–0·34) and with partial (0·93, 0·90–0·96), full (0·70, 0·67–0·73), or boosted (0·50, 0·41–0·62) COVID-19 vaccination. Compared with people without HIV who were unvaccinated, people without HIV who were vaccinated had lower risk of mortality (0·68, 0·65–0·71) but people with HIV who were vaccinated did not have any difference in mortality risk (1·08, 0·96–1·23). In-hospital mortality was higher for people with HIV with CD4 counts less than 200 cells per μL, irrespective of viral load and vaccination status.

Interpretation: HIV and immunosuppression might be important risk factors for mortality as COVID-19 becomes endemic.

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Introduction

WHO considers HIV a risk factor for severe COVID-19 disease. [1] South Africa has one of the highest burdens of HIV globally and has had a high burden of COVID-19. In 2022, the HIV prevalence among adults aged 15–49 years was 18% and there were 7·6 million people living with HIV, 5·7 million (75%) on antiretroviral therapy (ART), and 2·4 million (31%) with unsuppressed viral load in South Africa, posing a risk for poor COVID-19 outcomes among those co-infected.[2]

South Africa had five waves of COVID-19 by the end of 2022, recording more than 4 million cases, 546 693 admissions, and 104 648 in-hospital deaths. By April, 2022, before the fifth wave, more than 90% of the population had developed immunity to COVID-19 through a combination of natural and vaccine-induced immunity.[3] By January, 2023, 49% of adults were fully vaccinated against COVID-19. South Africa first rolled out COVID-19 vaccinations among health-care workers in February, 2021, using Ad26.COV2.S (Janssen) under the Sisonke programme. In May, 2021, vaccinations using BNT162b (BioNTech–Pfizer) or Ad26.COV2.S were introduced for the general population, beginning with individuals older than 60 years. In December, 2021, an additional dose was introduced for individuals who were immunocompromised, including people with HIV, and, in January, 2022, booster doses were introduced for all adults.

Research in context

Evidence before this study

We aimed to determine the association of HIV with COVID-19 mortality after the emergence of the omicron variant and COVID-19 vaccine roll-out. We searched PubMed and medRxiv using the terms "SARS-CoV-2", "COVID-19", "HIV", "variants", "COVID-19 vaccines", and "mortality", for articles published between Jan 1, 2020, and March 20, 2023. We did not apply language restrictions. Multicountry analyses, large cohort studies, and meta-analyses have demonstrated an increased risk of COVID-19 mortality among people living with HIV. Vaccine studies have also suggested reduced effectiveness among people with HIV. Few studies included national-level data from high HIV seroprevalence settings. We did not identify any studies post-omicron variant emergence or population-based studies evaluating the performance of COVID-19 vaccines in people with HIV.

Added value of this study

Our study included data for over 20 000 people with HIV admitted in public and private hospitals from three high-quality national databases that were linked to provide data on previous SARS-CoV-2 infection, COVID-19 admissions, and vaccination, across all five pandemic waves in South Africa. We provide robust evidence of the increased risk for COVID-19 mortality in people with HIV, particularly individuals with immunosuppression irrespective of viral load. We also report findings of COVID-19 vaccination being protective against death among individuals who have been hospitalised for people without HIV but not for people with HIV. In addition, among people with HIV, CD4 count of 200 cells per μL or more was protective against COVID-19 mortality in both individuals who had been vaccinated and individuals who were unvaccinated. Compared with people without HIV, the risk of mortality among people with HIV was more pronounced in the omicron waves.

Implications of all the available evidence

These findings suggest that as COVID-19 becomes endemic, the protection conferred against severe outcomes from COVID-19 vaccination is lower in susceptible groups, such as in people with HIV, compared with adults without HIV, and HIV and immunosuppression might become more important risk factors for severe outcomes in the era after the emergence of the omicron variant of concern.

Understanding epidemiology and outcomes of COVID-19 in people with HIV is crucially important. HIV is a recognised risk factor for severe COVID-19, particularly among people with low CD4 cell counts,[1] and increased viral evolution has been reported in people with prolonged SARS-CoV-2 infection.[4] Moreover, people with HIV with low CD4 cell counts have prolonged viral shedding, suggesting increased risk for transmission and viral evolution. Studies have reported vaccine hesitancy among people with HIV[6,7] and reduced effectiveness of the COVID-19 vaccine in those with advanced HIV disease.[8,9] Moreover, disrupted health services during COVID-19 lockdowns have affected routine HIV care and treatment services.[10]

Studies done earlier in the COVID-19 pandemic did not investigate the effect of SARS-CoV-2 variants of concern, previous SARS-CoV-2 infection, or COVID-19 vaccination among people with HIV.[11] Studies have also been inconclusive about the role of HIV treatment status, especially poor HIV control (low CD4 cell count and high viral load), on COVID-19 outcomes and the association of immunosuppression and detectable HIV RNA with severe COVID-19.[12] Using data from three large national surveillance systems, we aimed to investigate trends in hospitalisation and mortality among people with HIV and people without HIV and identify factors associated with in-hospital COVID-19 mortality in South Africa.

Methods

Study design

In this analysis of national surveillance data, we analysed all data for COVID-19 admissions nationally in the period from the first case of hospitalisation in South Africa to the end of the fifth wave (March 5, 2020, to May 28, 2022). We linked three data sources for this analysis using South African identification numbers, first names, surnames, and dates of birth. These databases were the DATCOV national COVID-19 hospital surveillance system established by the South African National Institute for Communicable Diseases (NICD), the South African national SARS-CoV-2 case line list (Notifiable Medical Conditions Surveillance System [NMC-SS]) established by the NICD, and the Electronic Vaccination Data System (EVDS) established by the South African National Department of Health.

Data on SARS-CoV-2 infection and hospitalisation are collected by the NICD for public health surveillance and, because COVID-19 is a notifiable medical condition, patient consent was not required. Data were securely stored in the South African National Department of Health Microsoft Azure cloud and data access was restricted. Ethical approval was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand for the collection of COVID-19 case data (M210752) and for the DATCOV surveillance programme (M2010108).

Procedures and outcomes

DATCOV surveillance collects data on all individuals with a positive SARS-CoV-2 RT-PCR test or antigen test, with a confirmed duration of stay in hospital of 1 full day or longer, regardless of the reason for admission. This database included patients who had COVID-19 symptoms, were admitted for isolation, acquired nosocomial COVID-19 infection, or tested positive for SARS-CoV-2 incidentally when admitted for other reasons. Incidental positive SARS-CoV-2 tests were noted mainly during the initial period when numbers of cases were rising in all five waves in South Africa.

We defined in-hospital mortality as a death related to COVID-19 that occurred during the hospital stay and excluded deaths due to other causes or after discharge from hospital. Because the main outcome of our study was in-hospital mortality, we implemented all analyses among patients hospitalised with SARS-CoV-2 with a known in-hospital outcome (ie, discharged alive or died) at the time of data extraction.

We used a weekly incidence of 30 cases per 100 000 population as the threshold for the start and end of each wave, thereby defining the distinct periods of analysis: the D614G B.1 variant (first) wave from June 7 to Aug 22, 2020; the beta B.1.351 variant (second) wave from Nov 15, 2020, to Feb 6, 2021; the delta B.1.617.2 variant (third) wave from May 9 to Sept 18, 2021; the omicron BA.1 and BA.2 variant (fourth) wave from Nov 28, 2021, to Feb 5, 2022; and the omicron BA.4 and BA.5 variant (fifth) wave from April 17 to May 28, 2022.

Data on HIV status, CD4 cell count, and viral load measured in the 12 months before hospitalisation were submitted to DATCOV by the hospital, based on information contained in the patient's written hospital record and, where missing, were obtained from laboratory records. Virological control or immunosuppression was assessed based on the last available data on viral load or CD4 cell count result within the past year and categorised as virologically

suppressed (HIV RNA <1000 copies per mL) or viraemic (HIV RNA ≥1000 copies per mL), and immune reconstituted (CD4 count ≥200 cells per μL) or immunosuppressed (CD4 cell count <200 cells per μL). CD4 cell count is no longer routinely measured at baseline in all patients and is done when indicated during care in accordance with South African HIV care guidelines.

We identified previous SARS-CoV-2 infection through linking hospitalisation data to the NMC-SS and previous infection was regarded as affirmative if an individual had a recorded positive test more than 90 days after a previous positive test. We identified vaccination status at date of admission through EVDS linkage and considered individuals to be unvaccinated if they had not received any COVID-19 vaccine dose, partially vaccinated if they received one dose of BNT162b, fully vaccinated if they received two doses of BNT162b or one dose of Ad26.COV2.S with the most recent dose at least 14 days before hospitalisation, and boosted if they received at least one additional COVID-19 vaccine dose of any kind at least 14 days before hospitalisation (in addition to being fully vaccinated).

Statistical analysis

We used descriptive statistics to show trends in numbers of cases, admissions, deaths, and in-hospital case fatality ratios (CFRs) during each wave.

We first implemented six post-imputation multivariable logistic regression models for each wave and all waves comparing people with HIV and people without HIV, with a random effect on admission facility included to account for potential differences in the service population and the quality of care at each facility. The models included HIV status as the outcome and age, gender, presence of a comorbidity, health sector, previous SARS-CoV-2 infection, COVID-19 vaccination, and hospital outcome as exposures.

We implemented post-imputation modified Poisson regression, with hospital mortality as the model outcome and admission facility accounting for the clustering effect, and we aimed to identify factors associated with in-hospital COVID-19 mortality among all people admitted to hospital with COVID-19. The model included hospital mortality as the model outcome, with age, sex, race, individual comorbidities (HIV, hypertension, diabetes, chronic cardiac disease, chronic pulmonary disease, chronic kidney disease, malignancy in the past 5 years, obesity, and past and current tuberculosis disease), type of health sector (private or public), province, wave period, recorded laboratory-confirmed previous SARS-CoV-2 infection, and COVID-19 vaccination as exposures. Additional interaction terms assessed the influence of vaccination and previous infection between people with HIV and people without HIV.

The third model comprised post-imputation random-effect (on admission facility) modified Poisson regression among people with HIV, and included hospital mortality as the model outcome, with age, sex, race, individual comorbidities, ART status, CD4 cell count and viral load, type of health sector, province, wave period, recorded laboratory-confirmed previous SARS-CoV-2 infection, and COVID-19 vaccination as exposures.

We censored data on Dec 31, 2022, 6 months after the last hospital admission that was included in the study to allow outcomes to be accumulated. We restricted multivariable analysis of mortality to patients who had already accumulated outcomes and we excluded all patients still in hospital or transferred to other hospitals without final outcomes because they remained at risk of still developing severe outcomes, including death.

To account for incomplete or missing data on selected variables, we used multivariate imputation by chained equation and generated ten complete imputed datasets that were used for subsequent analyses. We included HIV status and in-hospital outcomes in the imputation process, as we had done for conditional imputation for ART, CD4 cell count, and viral load. Variables where data were imputed included race and comorbidities, where up to a third of data were missing. Complete or near-complete variables included in the imputation process were age, sex, province, health sector, in-hospital outcome, and vaccination status.

For each multivariable model, we assessed all variables that were significant with p values of less than 0·2 in the univariate analysis (to evaluate absence of significance in the univariate analysis after adjusting for potential confounders) and excluded non-significant factors ($p \geq 0{\cdot}05$) with manual backward elimination. Pairwise interactions were assessed by inclusion of product terms for all variables remaining in the final multivariable additive model.

The statistical analysis was implemented using Stata (15). We followed STROBE guideline recommendations (appendix p 1).

Role of the funding source

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

Results

Among 397 082 people with COVID-19 admitted to hospital during five waves, 301 407 (75·9%) were discharged alive, 89 565 (22·6%) died, and 6110 (1·5%) had no recorded outcome (appendix p 3). Overall, 270 737 (68·2%) of 397 082 people with COVID-19 admitted to hospital had a documented HIV status. Comparison of demographic characteristics showed that a higher proportion of individuals who were younger (<40 years), female, or Black African or mixed race had no recorded HIV status (appendix p 4). Among patients with recorded HIV status, people with HIV accounted for 4582 (6·4%) of 71 248 in the D614G wave, 6016 (5·7%) of 105 623 in the beta wave, 6947 (4·7%) of 147 516 in the delta wave, 4484 (7·8%) of 57 510 in the omicron BA.1 and BA.2 wave, and 829 (5·5%) of 15 185 in the omicron BA.4 and BA.5 wave.

Among individuals who had recorded outcomes, in-hospital CFRs were 5445 (24·5%) of 22 222 among people with HIV versus 53 248 (21·7%) of 245 268 people without HIV overall; 1100 (24·6%) of 4465 versus 9114 (20·5%) of 44 430 in the D614G wave; 1627 (27·9%) of 5833 versus 17 760 (26·6%) of 66 649 in the beta wave; 1774 (26·3%) of 6743 versus 22 823 (24·5%) of 92 999 in the delta wave; 801 (18·3%) of 4374 versus 2893 (9·1%) of 31 673 in the omicron BA.1 and BA.2 wave; and 143 (17·7%) of 807 versus 658 (6·9%) of 9517 in the omicron BA.4 and BA.5 wave (figure , appendix p 5).

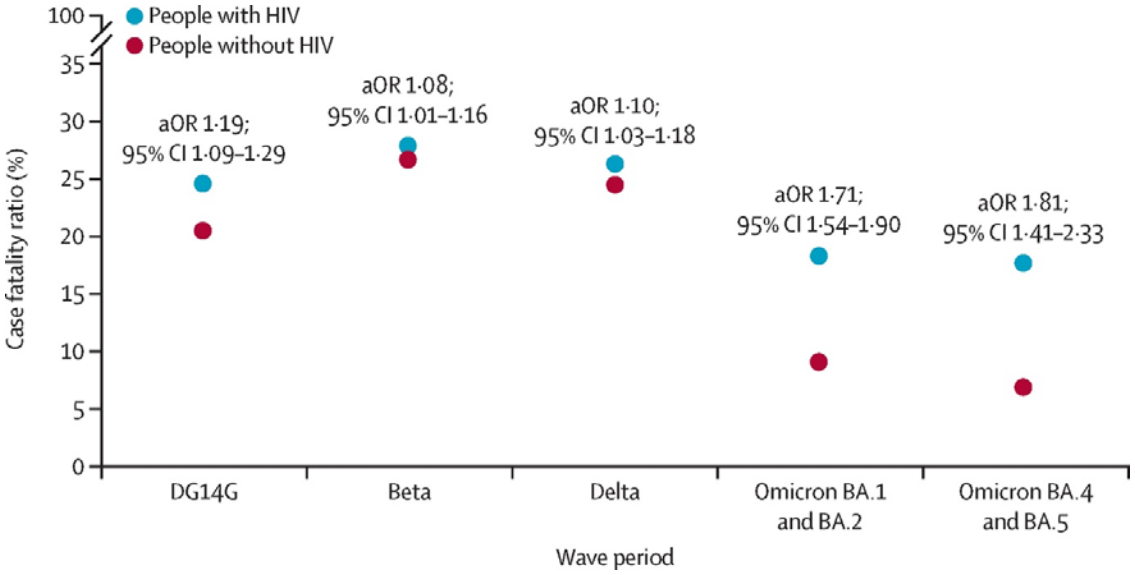

Figure . COVID-19 in-hospital CFRs and aOR comparing CFRs in South Africa, March 5, 2020 to May 28, 2022, by wave
Each model was adjusted for age, sex, comorbidity, health sector, previous SARS-CoV-2 infection, and COVID-19 vaccination. aOR=adjusted odds ratio. CFR=case fatality ratio.

The median age of people with HIV was 44 (IQR 35–54) years and the median age of people without HIV was 55 (40–67) years (p=0·0010). Among people with HIV, 12 335 (54·0%) of 22 858 were on ART, 1299 (5·7%) were not on ART, and 9224 (40·4%) had unknown ART status. 8093 (35·4%) had CD4 cell counts of 200 cells per µL or more, 5411 (23·7%) had CD4 counts of less than 200 cells per µL, and 9354 (40·9%) had an unknown CD4 cell count. 9235 (40·5%) had a viral load of less than 1000 copies per mL, 5411 (23·7%) had a viral load of 1000 copies per mL or more, and 10 739 (47·0%) had an unknown viral load.

In multivariable analysis of each wave, people with HIV were more likely to be younger than 45 years, female, have an additional comorbid condition, and be admitted in the public health sector than were people without HIV. Compared with people without HIV, those with HIV were more likely to have in-hospital mortality from COVID-19 overall and in each wave (table 1 and figure). Overall, people with HIV were more likely to be fully vaccinated than were people without HIV (table 1). Previously diagnosed SARS-CoV-2 infection was more common among people with HIV in the latter three waves (delta, omicron BA.1 and BA.2, and omicron BA.4 and BA.5) than in people without HIV.

Table 1. Multivariable analysis comparing people with HIV and people without HIV admitted to hospital with COVID-19 in South Africa, March 5, 2020, to May 28, 2022

	D614G (n=48 895)	Beta (n=72 482)	Delta (n=99 742)	Omicron BA.1 and BA.2 (n=36 047)	Omicron BA.4 and BA.5 (n=10 324)	All waves (n=267 490)
Age group						
<45 years	2·06 (1·91–2·21)	2·57 (2·41–2·75)	2·23 (2·09–2·38)	2·44 (2·24–2·66)	2·51 (2·05–3·08)	2·40 (2·32–2·49)
≥45 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Sex						
Male	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Female	1·34 (1·25–1·43)	1·32 (1·24–1·40)	1·21 (1·14–1·28)	1·09 (1·01–1·18)	1·22 (1·02–1·46)	1·22 (1·19–1·26)
Comorbidity *						
No	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Yes	1·10 (1·02–1·18)	1·05 (0·99–1·13)	1·31 (1·22–1·39)	1·82 (1·67–1·98)	1·65 (1·35–2·02)	1·30 (1·25–1·34)
Health sector						
Private sector	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Public sector	6·35 (5·90–6·85)	14·28 (13·03–15·65)	19·39 (17·71–21·23)	23·72 (20·72–27·17)	54·52 (39·50–75·26)	13·50 (12·92–14·12)
Previous infection						
No	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Yes	..	1·00 (0·82–1·21)	1·36 (1·16–1·61)	1·45 (1·19–1·78)	1·86 (1·16–3·00)	1·10 (1·00–1·20)
Complete primary COVID-19 vaccination						
No	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Yes	..	..	1·24 (1·05–1·46)	0·93 (0·84–1·03)	0·90 (0·72–1·13)	1·08 (1·00–1·16)
Outcome						
Discharged alive	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Died	1·19 (1·09–1·29)	1·08 (1·01–1·16)	1·10 (1·03–1·18)	1·71 (1·54–1·90)	1·81 (1·41–2·33)	1·14 (1·10–1·19)

Data are adjusted odds ratio (95% CI). Case fatality ratios are provided in the appendix (p 6) . We show one model each per wave period and for the full pandemic period (each model adjusted for age, sex, comorbidity, health sector, previous SARS-CoV-2 infection, and COVID-19 vaccination).

* Comorbidity included the presence of hypertension, diabetes, chronic cardiac disease, chronic kidney disease, asthma or chronic pulmonary disease, malignancy, or active and past tuberculosis infection.

In-hospital COVID-19 mortality was higher in people with HIV (table 2). Additionally, mortality was higher among individuals who were older than 20 years, male, Black, or Indian; those who had cardiovascular disease, diabetes, chronic kidney disease, malignancy, active tuberculosis disease, or obesity; those who were admitted in the public sector; and those who were admitted in the beta or delta waves compared with the D614G wave (table 2). Mortality was lower in individuals with previous SARS-CoV-2 infection and in individuals who were partially vaccinated, fully vaccinated, or boosted than in those who were unvaccinated. In-hospital mortality was also lower during the omicron BA.1 and BA.2 and omicron BA.4 and BA.5 waves (table 2).

Table 2. Risk factors for in-hospital mortality among 390 023 people admitted to hospital with COVID-19 in South Africa, March 5, 2020, to May 28, 2022

	CFR, n/N (%)	aIRR (95% CI)	p value
HIV			
No	53 248/245 268 (21·7%)	1 (ref)	..
Yes	5445/22 222 (24·5%)	1·23 (1·19–1·27)	<0·0001
Wave			
D614G	15 168/70 100 (21·6%)	1 (ref)	..
Beta	29 353/103 882 (28·3%)	1·22 (1·14–1·31)	<0·0001
Delta	37 538/144 778 (25·9%)	1·24 (1·15–1·34)	<0·0001
Omicron BA.1 and BA.2	6123/56 384 (10·9%)	0·70 (0·64–0·75)	<0·0001
Omicron BA.4 and BA.5	1212/14 879 (8·1%)	0·56 (0·51–0·62)	<0·0001
Previous diagnosed SARS-CoV-2 infection			
No	88 622/374 893 (23·6%)	1 (ref)	..
Yes	772/15 130 (5·1%)	0·32 (0·29–0·34)	<0·0001
COVID-19 vaccination			
Not vaccinated	82 193/350 098 (23·5%)	1 (ref)	..
Partially vaccinated	4381/15 295 (28·6%)	0·93 (0·90–0·96)	<0·0001
Fully vaccinated	2712/22 922 (11·8%)	0·70 (0·67–0·73)	<0·0001
Boosted	108/1708 (6·3%)	0·50 (0·41–0·62)	<0·0001
Age group			
<20 years	692/25 727 (2·7%)	1 (ref)	..
20–39 years	6394/82 423 (7·8%)	2·55 (2·26–2·89)	<0·0001
40–59 years	28 338/140 198 (20·2%)	6·08 (5·35–6·91)	<0·0001
≥60 years	53 970/141 675 (38·1%)	11·46 (9·95–13·21)	<0·0001
Sex			
Female	45 877/215 467 (21·3%)	1 (ref)	..
Male	43 485/174 330 (24·9%)	1·17 (1·16–1·19)	<0·0001
Race			
White	6830/28 844 (23·7%)	1 (ref)	..
Mixed	3945/15 688 (25·1%)	1·05 (0·98–1·13)	0·19
Black	45 039/184 341 (24·4%)	1·13 (1·08–1·18)	<0·0001
Indian	3168/13 439 (23·6%)	1·18 (1·11–1·26)	<0·0001
Other	154/727 (21·2%)	0·92 (0·74–1·15)	0·49
Cardiovascular disease			
No	56 077/258 314 (21·7%)	1 (ref)	..
Yes	2209/6091 (36·3%)	1·07 (1·01–1·12)	0·012
Diabetes			
No	40 823/210 455 (19·4%)	1 (ref)	..
Yes	22 357/65 443 (34·2%)	1·18 (1·14–1·22)	<0·0001
Chronic kidney disease			
No	54 986/256 426 (21·4%)	1 (ref)	..
Yes	2902/6497 (44·7%)	1·25 (1·22–1·29)	<0·0001
Malignancy			
No	56 974/260 888 (21·8%)	1 (ref)	..
Yes	574/1 536 (37·4%)	1·26 (1·19–1·34)	<0·0001
Active tuberculosis			
No	56 725/259 259 (21·9%)	1 (ref)	..
Yes	1145/4610 (24·8%)	1·23 (1·17–1·30)	<0·0001
Obesity			
No	15 826/66 805 (23·7%)	1 (ref)	..
Yes	2845/8132 (35·0%)	1·25 (1·19–1·32)	<0·0001
Health sector			
Private sector	35 693/190 425 (18·7%)	1 (ref)	..
Public sector	53 701/199 598 (26·9%)	1·26 (1·17–1·35)	<0·0001

aIRR=adjusted incidence rate ratio. CFR=case fatality ratio.

Compared with people without HIV who were unvaccinated, we observed a reduced risk of mortality among people without HIV who had been vaccinated (table 3) but not among people with HIV who had been vaccinated; people with HIV who were unvaccinated had increased risk of mortality. Previous SARS-CoV-2 infection was associated with lower risk of mortality in people with HIV and people without HIV. People with HIV and no previous SARS-CoV-2 infection had higher mortality.

Table 3. Risk factors for in-hospital mortality among 390 023 people with COVID-19 in South Africa, March 5, 2020, to May 28, 2022

	CFR, n/N (%)	aIRR (95% CI)	p value
HIV status and vaccination			
HIV negative, unvaccinated	51 214/226 211 (22·6%)	1 (ref)	..
HIV positive, unvaccinated	5273/21 248 (24·8)	1·22 (1·18–1·26)	<0·0001
HIV negative, vaccinated	2034/19 057 (10·7%)	0·68 (0·65–0·71)	<0·0001
HIV positive, vaccinated	172/974 (17·7%)	1·08 (0·96–1·23)	0·20
HIV status and previous SARS-CoV-2 infection			
HIV negative, no previous infection	52 747/233 537 (22·6 %)	1 (ref)	..
HIV positive, no previous infection	5376/21 608 (24·9%)	1·22 (1·18–1·26)	<0·0001
HIV negative, previous infection	501/11 731 (4·3%)	0·29 (0·27–0·32)	<0·0001
HIV positive, previous infection	69/614 (11·2%)	0·71 (0·58–0·88)	0·0017

Model adjusted for age, sex, race, comorbidities, and health sector. aIRR=adjusted incidence rate ratio. CFR=case fatality ratio.

Among people with HIV, in-hospital COVID-19 mortality was higher in those who were older than 20 year or were male, and those with diabetes, chronic kidney disease, malignancy, active tuberculosis infection, obesity, CD4 counts less than 200 cells per μL, or a viral load of 1000 copies per mL or more. Mortality was lower in individuals with previous SARS-CoV-2 infection; individuals who were fully vaccinated; or those admitted in the omicron BA.1 and BA.2 or omicron BA.4 and BA.5 waves (table 4). Compared with individuals with controlled HIV (CD4 ≥200 cells per μL and viral load <1000 copies per mL), mortality was higher among people with HIV with CD4 counts less than 200 cells per μL irrespective of viral load (table 5).

Table 4. Risk factors for in-hospital mortality in 22 222 people with HIV admitted to hospital with COVID-19 in South Africa, March 5, 2020, to May 28, 2022

	CFR, n/N (%)	aIRR (95% CI)	p value
Wave period			
D614G	1100/4465 (24·6%)	1 (ref)	..
Beta	1627/5833 (27·9%)	1·09 (0·96–1·24)	0·20
Delta	1774/6743 (26·3%)	1·04 (0·90–1·20)	0·58
Omicron BA.1 and BA.2	801/4374 (18·3%)	0·79 (0·68–0·91)	0·0012
Omicron BA.4 and BA.5	143/807 (17·7%)	0·72 (0·58–0·90)	0·0033
Previous diagnosed SARS-CoV-2 infection			
No	5376/21 608 (24·9%)	1 (ref)	..
Yes	69/614 (11·2%)	0·55 (0·43–0·69)	<0·0001
COVID-19 vaccination			
Not vaccinated	5173/20 869 (24·8%)	1 (ref)	..
Partially vaccinated	100/379 (26·4%)	0·96 (0·81–1·13)	0·62
Fully vaccinated	169/947 (17·9%)	0·85 (0·74–0·99)	0·036
Boosted	3/27 (11·1%)	0·60 (0·22–1·68)	0·33
ART			
On ART	3169/11 855 (26·7%)	1 (ref)	..
Not on ART	353/1253 (28·2%)	1·08 (0·93–1·25)	0·34
CD4 count			
≥200 cells per μL	1494/7731 (19·3%)	1 (ref)	..

<200 cells per μL	1530/5225 (29·3%)	1·55 (1·44–1·67)	<0·0001
Viral load			
<1000 copies per mL	1972/8994 (21·9%)	1 (ref)	..
≥1000 copies per mL	665/2788 (23·9%)	1·13 (1·02–1·25)	0·023
Age group			
<20 years	52/526 (9·9%)	1 (ref)	..
20–39 years	1254/8004 (15·7%)	1·57 (1·21–2·02)	0·0005
40–59 years	2776/10 502 (26·4%)	2·47 (1·92–3·17)	<0·0001
≥60 years	1363/3190 (42·7%)	3·61 (2·80–4·67)	<0·0001
Sex			
Female	3132/14 132 (22·2%)	1 (ref)	..
Male	2312/8079 (28·6%)	1·16 (1·10–1·22)	<0·0001
Race			
White	29/92 (31·5%)	1 (ref)	..
Mixed	90/383 (23·5%)	0·93 (0·66–1·31)	0·67
Black	4278/16 423 (26·0%)	1·00 (0·74–1·36)	0·99
Indian	18/67 (26·9%)	0·92 (0·56–1·50)	0·73
Other	11/36 (30·6%)	1·02 (0·54–1·92)	0·95
Diabetes			
No	2912/13 826 (21·1%)	1 (ref)	..
Yes	1156/3316 (34·9%)	1·26 (1·18–1·35)	<0·0001
Chronic kidney disease			
No	3269/14 855 (22·0%)	1 (ref)	..
Yes	297/701 (42·4%)	1·36 (1·25–1·47)	<0·0001
Malignancy			
No	3446/15 275 (22·6%)	1 (ref)	..
Yes	56/161 (34·8%)	1·22 (1·00–1·48)	0·054
Active tuberculosis			
No	3011/13 754 (21·9%)	1 (ref)	..
Yes	612/2389 (25·6%)	1·20 (1·09–1·32)	0·0003
Obesity			
No	1764/7440 (23·7%)	1 (ref)	..
Yes	256/781 (32·8%)	1·31 (1·19–1·43)	<0·0001
Health sector			
Private sector	487/2529 (19·3%)	1 (ref)	..
Public sector	4958/19 693 (25·2%)	1·36 (1·13–63)	0·0011

Model adjusted for age, sex, race, comorbidity, health sector, SARS-CoV-2 wave, vaccination status, and previous SARS-CoV-2 infection. aIRR=adjusted incidence rate ratio. ART=antiretroviral therapy. CFR=case fatality ratio.

Table 5. Risk factors for in-hospital mortality in 22 222 people with HIV in South Africa, March 5, 2020, to May 28, 2022

	CFR, n/N (%)	aIRR (95% CI)	p value
CD4 cell count, viral load			
≥200 cells per μL, <1000 copies per mL	1147/6027 (19·0%)	1 (ref)	..
≥200 cells per μL, ≥1000 per mL	123/769 (16·0%)	1·05 (0·88–1·25)	0·59
<200 cells per μL, <1000 per mL	652/2322 (28·1%)	1·48 (1·36–1·62)	<0·0001
<200 cells per μL, ≥1000 per mL	520/1917 (27·1%)	1·76 (1·56–1·99)	<0·0001
CD4 cell count, vaccination status			
<200 cells per μL, not fully vaccinated	1481/5010 (29·6%)	1 (ref)	..
≥200 cells per μL, not fully vaccinated	1461/7478 (19·5%)	0·63 (0·59–0·68)	<0·0001
<200 cells per μL, fully vaccinated	49/215 (22·8%)	0·86 (0·68–1·10)	0·23
≥200 cells per μL, fully vaccinated	33/253 (13·0%)	0·54 (0·37–0·77)	0·0007

aIRR=adjusted incidence rate ratio. CFR=case fatality ratio.

In people with HIV with CD4 counts less than 200 cells per μL, being not fully vaccinated had no statistically significant association with mortality compared with being fully vaccinated and

people with HIV with CD4 counts of 200 cells per μL or more had reduced risk of in-hospital COVID-19 mortality regardless of vaccination status (table 5).

Discussion

We found increased risk of in-hospital COVID-19 mortality among a cohort of over 20 000 people with HIV who were hospitalised in South Africa between March 5, 2020, and May 28, 2022. Increased risk of death was particularly prevalent in people with HIV with advanced disease (CD4 cell count <200 cells per μL), irrespective of viral load. Previous SARS-CoV-2 infection was protective against mortality in both people with HIV and people without HIV; however, COVID-19 vaccination was protective only for people without HIV and not for people with HIV. Among people with HIV, having CD4 counts of 200 cells per μL or more was protective in both vaccinated and unvaccinated individuals. The difference in CFRs between people with HIV and people without HIV in the omicron waves was greater than in earlier waves.

Earlier studies were inconclusive about the risk of HIV and COVID-19 mortality. A few studies showed no increased risk, but these were single-centre or small cohort studies[13,14] and early meta-analyses.[15] However, evidence has accumulated from multicountry analyses; large cohort studies in the UK,[17] the USA,[18] and South Africa;[19] and from meta-analyses[20] showing an increased risk of COVID-19 mortality among people with HIV.

Evidence is also sparse around HIV disease severity and COVID-19 outcomes. One US cohort study reported no association between viral suppression and COVID-19 disease severity or mortality.[21] Other cohort studies[22] and meta-analyses[23] reported increased mortality in people with CD4 counts less than 200 cells per μL. A study in a Spanish cohort reported that COVID-19 severity was increased in people with CD4 counts less than 200 cells per μL and detectable HIV RNA but not in those with undetectable HIV RNA.[12] Our study, which benefited from being among the largest cohorts of people with HIV and COVID-19 in a setting of high HIV prevalence, found an increased risk of mortality among those with low CD4 cell counts (irrespective of viral load).

Geographical differences in the mortality of people with HIV with COVID-19 have been reported in meta-analyses, with higher risk of mortality for people with HIV in Africa than in other regions.[24] This variability could be due to regional differences in the prevalence of HIV, undiagnosed HIV, access to health care for treatment of HIV and COVID-19, prevalence and treatment of opportunistic infections, low uptake of ART and poor HIV disease control, behaviour of people with HIV, and disruption to routine clinical care as well as various socioeconomic factors resulting in a disproportionate burden of the pandemic for people with low socioeconomic status and of colour.[25]

We reported that older age, male sex, and comorbidities (including diabetes, chronic kidney disease, malignancy, active tuberculosis infection, and obesity) were associated with COVID-19 mortality among people with HIV, as has been described in other studies.[12,16,26,27] Some studies have suggested that older age and multimorbidity were crucial factors for the increased rate of death among people with HIV[27] and that no increased risk of COVID-19 death was observed among those with no additional comorbidities.[28]

The mechanisms for increased risk among people with HIV could be related to a disrupted innate and adaptive immune response to COVID-19 infection, leading to severe disease (more

so for those who are not on ART, have detectable viral load, or have lower CD4 cell counts).[23,29] The chronic inflammatory condition in HIV might lead to cytokine storm.[30] People with HIV have increased rates of chronic comorbidities such as cancer and cardiovascular disease, which also predispose people with HIV to severe COVID-19.[30] People with HIV are more prone to co-infection with other infectious diseases, which might worsen during the course of COVID-19, and to anaemia, neutropenia, thrombocytopenia, and abnormal serum electrolytes. Increased impairment of immune responses might be related to the ageing cohort of people with HIV and the natural immune-senescence process in older people with HIV.[30] Early theories that immunodeficiency could be protective against the inflammatory response in COVID-19 and that ART might provide collateral immunity to COVID-19 have been discarded.[23]

Another factor that could have contributed to COVID-19 severity among people with HIV is the effect of disruption in HIV prevention and treatment services. Globally, routine services were interrupted by strict quarantine measures, transport lockdowns, ART shortages, and diversion of health-care workers to provide COVID-19 care. The Global Fund to Fight AIDS, Tuberculosis and Malaria reported declines in HIV prevention and treatment in 2020 from the previous year: a 22% decline in HIV testing, 5% in mothers receiving medicine to prevent transmitting HIV to their babies, and 16% in patients on ART who were HIV positive and had tuberculosis infection.[10] More restrictive national lockdowns were implemented in South Africa for 7 weeks before and during the first wave, 3 weeks at the peak of the second wave, and 3 weeks around the peak of the third wave. A South African study described how the COVID-19 pandemic and responses resulted in substantial declines in the number of HIV-infected individuals starting treatment in South Africa.[31]

Our study showed that, in people with HIV, previous SARS-CoV-2 infection (*vs* no previous infection) and full COVID-19 vaccination (*vs* unvaccinated) were protective against in-hospital mortality. However, we report the novel finding that, compared with people without HIV who were unvaccinated, people without HIV who were vaccinated had lower mortality, whereas people with HIV who were vaccinated had no significant difference in mortality compared with those who were unvaccinated. In addition, vaccination was not protective among people with HIV with immunosuppression, whereas vaccination among people with HIV with immune reconstitution was protective. These findings suggest an attenuated protective response of vaccination against COVID-19 mortality among people with HIV. This finding could indicate that immune protection is lower in vulnerable groups and that HIV and immunosuppression might become important risk factors for severe outcomes as COVID-19 becomes endemic.

Residual inflammation on ART and ongoing immune dysregulation among people with HIV might influence responsiveness to vaccination.[32] Previous studies have shown suboptimal responses in people with HIV to other vaccines, such as influenza and pneumococcal vaccines.[33] HIV could affect magnitude and durability of protection from COVID-19 vaccination, and people with HIV might require additional vaccine doses.[34] Several observational studies suggested that immune responses to COVID-19 vaccination might be reduced in people with low CD4 cell counts.[35] In one study, antibody responses were weaker and delayed among people with HIV compared with those in people without, regardless of whether they had high CD4 cell counts with effective ART.[9] In people with advanced HIV disease, an additional vaccine dose at least 4 months after the initial two-dose vaccination resulted in markedly higher levels of boosted immunity.[36] These data would support the recommendation for an additional dose in people with HIV and a further booster dose in

individuals with low CD4 cell counts, depending on their response to the second dose. UNAIDS recommends that people with HIV are given priority in COVID-19 vaccinations regardless of CD4 cell count and HIV viral load.

Although we found people with HIV to have a higher chance of being fully vaccinated, other studies have reported higher rates of COVID-19 vaccine hesitancy among recently diagnosed people with HIV[6] and among those with high viral load and low CD4 cell count,[7] who are at greater risk of severe COVID-19. The South African Government explicitly included people with HIV as a high-risk group to be prioritised for vaccination and to be offered additional booster doses. Donors and development partners supported health districts to increase uptake of COVID-19 vaccination among people with HIV through community outreach and provider-initiated vaccination in health facilities.

A strength of this analysis was that it included data for more than 20 000 people with HIV admitted to public and private hospitals from three high-quality national databases that were linked to provide data on previous SARS-CoV-2 infection, COVID-19 admissions, and vaccination, across all five pandemic waves.

This study has several limitations. First, the data submitted by health-care institutions included high levels of missing fields for race and comorbidities. Data were submitted to DATCOV by hospitals according to the information contained in the patient's written or electronic hospital record and could not be independently verified. We used multiple imputation to address missing data; however, the validity of the imputed data relies on the assumption that data were missing at random. Differences in demographic characteristics between patients with and without recorded HIV status should be considered in interpreting the findings. Second, the prevalence of HIV among COVID-19 admissions (8·4%) was lower than national HIV prevalence (18%),[2] which might be explained by gaps in reporting HIV status, people with HIV facing challenges in accessing care, and the over-representation of private sector data because of a lower threshold for COVID-19 admission to private hospitals. HIV prevalence among patients aged 20–59 years admitted to public sector hospitals was 14·0–15·2%, similar to the population HIV prevalence in these age groups (appendix p 6). Third, the DATCOV dataset uses wave period as a proxy for variants and does not contain individual-level data on infecting lineage; however, each wave correlated well with a particular SARS-CoV-2 variant. Fourth, although DATCOV can be linked with EVDS and contains full vaccination history of all COVID-19 admissions, the analysis did not consider time since last vaccine dose to account for waning immunity. Fifth, data on previous SARS-CoV-2 infections were probably incomplete because infections and reinfections are substantially under-ascertained due to the high proportion of asymptomatic infections as well as challenges or fatigue in testing. Sixth, we included all patients admitted to hospital who tested positive for SARS-CoV-2 infection as data on the reason for admission were incomplete and there might have been patients included who had been admitted to hospital or who had died from other causes. Seventh, the study population included only patients with COVID-19 who were hospitalised and, therefore, did not take into account the effect of HIV status pre-COVID-19 and did not consider biases related to decisions by health-care providers to admit patients to hospital on the basis of HIV status. Finally, small numbers in some categories of data might explain the absence of statistical associations, unrealistically large estimates, and confidence limits, suggesting sparse-data bias. It is also possible that there are other unmeasured sources of bias.

It is still important to prevent severe COVID-19 among people with HIV by preventing HIV infection, promoting screening and early diagnosis of HIV, initiating ART, and treatment of

comorbidities and opportunistic infections among people with HIV and by preventing COVID-19 through vaccination or early COVID-19 treatment. In line with global and local guidelines, people with HIV should be prioritised for additional COVID-19 booster doses. Integrated approaches will be required to prioritise COVID-19 vaccination of people with HIV, delivered within existing public health services to avoid discrimination and stigmatisation.

Contributors

WJ and LO contributed to the literature search. WJ, LB, CC, MM, LO, and CM contributed to the study design and refining methods of analysis. MB and LH contributed to the analysis of data from the Electronic Vaccination Data System, the linkage of the Electronic Vaccination Data System and DATCOV database, and verification of the output of the linkage. CM, LO, WJ, and RW contributed to data analysis and the creation of tables and figures. WJ, CC, RW, and CM contributed to data interpretation. WJ drafted the initial manuscript and all other coauthors contributed scientific inputs equally towards the interpretation of the findings and the final draft of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing

Aggregated data are available on request to the South African National Institute for Communicable Diseases. The data dictionary is available on request to the corresponding author, waasila.jassat@health.gov.za .

Declaration of interests

We declare no competing interests.

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