Risk factors for COVID-19 death in a population cohort study from the Western Cape Province, South Africa

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Summary

In this population cohort of 3.5 million public sector patients in South Africa, increased COVID-19 mortality was associated with HIV, previous and current tuberculosis as well as older age, male sex, diabetes, hypertension and chronic kidney disease.

Abstract

Background: Risk factors for COVID-19 death in sub-Saharan Africa and the effects of HIV and tuberculosis on COVID-19 outcomes are unknown.

Methods: We conducted a population cohort study using linked data from adults attending public sector health facilities in the Western Cape, South Africa. We used Cox-proportional hazards models adjusted for age, sex, location and comorbidities to examine the association between HIV, tuberculosis and COVID-19 death from 1 March-9 June 2020 among (i) public sector "active patients" (≥1 visit in the 3 years before March 2020), (ii) laboratory-diagnosed COVID-19 cases and (iii) hospitalized COVID-19 cases. We calculated the standardized mortality ratio (SMR) for COVID-19 comparing HIV positive vs. negative adults using modelled population estimates.

Results: Among 3,460,932 patients (16% HIV positive), 22,308 were diagnosed with COVID-19, of whom 625 died. COVID-19 death was associated with male sex, increasing age, diabetes, hypertension and chronic kidney disease. HIV was associated with COVID-19 mortality (adjusted hazard ratio [aHR] 2.14; 95% confidence interval [CI] 1.70-2.70), with similar risks across strata of viral load and immunosuppression. Current and previous tuberculosis were associated with COVID-19 death (aHR [95%CI] 2.70 [1.81-4.04] and 1.51 [1.18-1.93] respectively). The SMR for COVID-19 death associated with HIV was 2.39 (95%CI 1.96-2.86); population attributable fraction 8.5% (95%CI 6.1-11.1).

Conclusion: While our findings may over-estimate HIV- and tuberculosis-associated COVID-19 mortality risks due to residual confounding, both HIV and current tuberculosis were independently associated with increased COVID-19 mortality. The associations between age, sex and other comorbidities and COVID-19 mortality were similar to other settings.

Keywords: COVID-19, HIV, tuberculosis, sub-Saharan Africa, antiretroviral

Introduction

The effects of the intersecting pandemics of HIV, tuberculosis and coronavirus disease-19 (COVID-19) in sub-Saharan Africa are unknown. Studies to date suggest no increased risk of adverse outcomes in HIV co-infected patients, but these are small studies from Europe and North America, often limited to hospitalized patients, and may not be relevant to sub-Saharan Africa where people living with HIV (PLWH) are younger with different comorbidities, frequently including tuberculosis [1-8]. PLWH may experience more severe COVID-19 disease due to HIV-related immune suppression, which may be exacerbated by transient immune deficiency from coronaviruses [9, 10]. In support of this hypothesis a large UK cohort study reported increased risk of COVID-19 death with immunosuppressive comorbidity, including PLWH [8]. Two factors may reduce risk of severe COVID-19 in PLWH, however: dysfunctional immunity may lessen a virus-induced cytokine storm [11, 12], and some antiretroviral drugs (tenofovir and some protease inhibitors) have *in vitro* activity against coronaviruses, with better outcomes reported for PLWH receiving tenofovir disoproxil fumarate (TDF) vs. other antiretrovirals [12, 13]. Tuberculosis may exacerbate COVID-19 with impaired immune responses and increased angiotensin converting enzyme 2 receptor expression in respiratory epithelial cells, while COVID-19 pneumonia may enhance tuberculosis progression [14-17].

It is important to establish if HIV and tuberculosis increase risk of COVID-19 death so that patients with these conditions can be provided with augmented prevention and potential therapeutic interventions. We used linked data from adults attending public sector health facilities in the Western Cape Province, South Africa, to identify factors associated with COVID-19 death.

Methods

Study design

We conducted a cohort study using de-identified data from the Western Cape Provincial Health Data Centre (WCPHDC) of public sector patients aged ≥20 years with documented sex and not known to have died before March 1, 2020 (before the first diagnosed COVID-19 case in South Africa, and several weeks before the first documented COVID-19 death) and included all follow up through June 9, 2020. The outcome was COVID-19 associated death. Our main analysis examined risk of COVID-19 death in the general population, so all patients were included irrespective of SARS-CoV-2 testing. The study was approved by the University of Cape Town and Stellenbosch University Health Research Ethics Committees and the Western Cape Province Department of Health. Individual informed consent requirement was waived for this secondary analysis of de-identified data.

Study population and data sources

The Western Cape has nearly 7 million inhabitants, of whom ~520,000 are PLWH with >90% of them dependent on public sector health services. The WCPHDC has been described in detail [18]. Briefly, WCPHDC consolidates administrative, laboratory, and pharmacy data from routine electronic clinical information systems used in all public sector health facilities with linkage through a unique identifier. Multiple data sources are triangulated to enumerate health conditions such as diabetes mellitus ("diabetes"), hypertension, tuberculosis and HIV, with high or moderate certainty evidence assigned for each inferred condition (Supplementary Table 1). High certainty evidence of HIV comprises a positive HIV diagnostic test and/or HIV-RNA test and/or triple antiretroviral therapy (ART) and/or registration in the HIV disease management system; moderate certainty is assigned for those with only a CD4 count measure and/or two antiretroviral drugs prescribed (previously used

for vertical HIV transmission prevention) and/or ICD-10 diagnosis code of HIV. HIV testing coverage is high, as >90% of PLWH know their HIV diagnosis [19]. High certainty evidence of tuberculosis comprised laboratory evidence of *Mycobacterium tuberculosis* infection (any anatomical site, using Xpert RIF/MTB, microscopy, culture) and/or registration on the electronic tuberculosis registers and/or combination tuberculosis treatment and/or admission to a tuberculosis hospital. Comorbidities were based on high or moderate certainty evidence but restricted to high certainty evidence in sensitivity analyses. The virologic, immunologic and ART status of PLWH on March 1, 2020 was categorized, based on most recent measures, as "confirmed virologically suppressed on ART" (HIV-RNA<1000 copies/ml in last 15 months and ART dispensed in last 6 months), "likely virologically suppressed on ART" (HIV-RNA <1000 copies/ml 15-24 months previously or HIV-RNA <1000 copies/ml >24 months previously if ART dispensed in last 6 months), "viraemic or immunosuppressed" (HIV-RNA >1000 copies/ml in last 15 months or CD4 count <200 cells/µl within 18 months before March 2020) or "unknown". Until January 2020, adult first-line ART was TDF+emtricitabine/lamivudine+efavirenz, with abacavir replacing TDF for patients with kidney disease; zidovudine+emtricitabine/lamivudine+protease inhibitor was used for second-line ART for most patients. Dolutegravir was introduced in first and second-line since January 2020. Diabetic control was categorized according to glycosylated haemoglobin (HbA1c) measurement within the last 2 years as <7% (controlled); 7-8.9% (poorly controlled), ≥9% (uncontrolled).

COVID-19 diagnosis

All COVID-19 diagnoses were based on a positive SARS-CoV-2 PCR test. Testing was available for all patients with COVID-19 symptoms until June 1, 2020; thereafter public sector laboratory testing was restricted to patients requiring admission or aged >55 years or

with comorbidities, due to temporary limited testing capacity. Hospital admissions and all deaths in SARS-CoV-2 positive cases are recorded and reviewed daily.

Statistical analysis

We used Cox-proportional hazards models adjusted for age, sex and other comorbidities to examine the association between HIV, tuberculosis and COVID-19 death among (i) all public sector patients with ≥1 health visit in the 3 years before March 1, 2020 (considered "active patients"), (ii) laboratory-diagnosed COVID-19 cases and (iii) hospitalized COVID-19 cases. We adjusted for location within Cape Town vs. rest of the province and subdistrict of residence within Cape Town to account for geographical variation in infection rates and as a proxy for socio-economic status. Patients were censored on date of death if deceased without a COVID-19 diagnosis, or on June 9, 2020, whichever was earliest. Database closure was 7 days later to allow for death reporting delays. For the analysis of COVID-19 death in laboratory-diagnosed cases we included cases diagnosed before June 1, 2020 when testing was available for all patients with COVID-19 symptoms, but included all patients diagnosed by June 9, 2020 in sensitivity analysis. The proportional-hazard assumption was assessed with Schoenfeld residuals [20]. All analyses were conducted using Stata 15.1.

We also calculated the standardized mortality ratio (SMR) of the actual number of COVID-19 deaths in PLWH vs. the number that would be expected if PLWH had the same risk of COVID-19 death as HIV-negative people of the same age and sex. We used data on the age, sex and HIV status of all COVID-19 deaths (public and private sector) and the Thembisa Western Cape HIV model to estimate the Western Cape population size and HIV prevalence, by age and sex, in 2020.[21] We calculated 95% confidence intervals (CI) for the SMR using 1000 bootstrap replications (See Supplementary Appendix 2).

Since individual socio-economic status and some comorbidities are not recorded in WCPHDC, we calculated E-values to determine the minimum strength of association that an unmeasured confounder (e.g. raised body mass index [BMI] or socio-economic status) would need to have with HIV/ tuberculosis and COVID-19 death to fully account for any association between HIV/tuberculosis and COVID-19 death [22]. We conducted quantitative bias analysis to assess the impact of potential confounding by obesity on an association between HIV and COVID-19 death.

Results

Patient characteristics

Among 3,460,932 "active patients" aged ≥20 years on March 1, 2020, 22,308 were diagnosed with COVID-19, of whom 625 (2.8%) died (Table 1). Among COVID-19 cases, 69% were diagnosed and 67% of deaths occurred before the change in testing criteria (June 1). The proportion of men was lower among COVID-19 cases vs. non-cases (31% vs. 42%), likely due to initial cases being among essential workers in retail and manufacturing sectors employing predominantly women. The proportion of women peaked (76%) in week 5 of the epidemic, declining thereafter. Diabetes and hypertension were common in all patients, with higher prevalence among COVID-19 cases than non-cases (diabetes:14% vs. 8%; hypertension: 23% vs. 16%), while proportions of other comorbidities (as listed below) were similar. COVID-19 deceased cases were older than surviving cases (median age [interquartile range] 63 years [54-71] vs. 37 [30-48]); several comorbidities were more common among deceased patients (diabetes 60% vs 14%; hypertension 58% vs. 23%; chronic kidney disease 18% vs 2%; chronic pulmonary disease/asthma 13% vs. 7%; current tuberculosis 4% vs. 1% and previous tuberculosis 14% vs. 8%).

Patients with and without HIV

Although the proportion of PLWH was similar among surviving and deceased COVID-19 cases, a greater proportion of COVID-19 deaths were in patients aged <50 years in those with vs. without HIV (39% vs 13%) (Table 2). A substantial proportion of COVID-19 deceased PLWH had diabetes (50%) and hypertension (42%), however these conditions were more common in deceased people without HIV (62% for each condition). Current and previous tuberculosis were more frequent in PLWH irrespective of COVID-19 with 14% and 37% of COVID-19 deceased cases with HIV having current and/or previous tuberculosis respectively.

COVID-19 death in all public sector patients

Among all public sector patients, the probability of COVID-19 death by 100 days since March 1, 2020 was 180/million (95% confidence interval [CI] 167-196). COVID-19 death was associated with male sex, increasing age, diabetes (with higher risk with elevated HbA1c), hypertension and chronic kidney disease (Table 3). Current tuberculosis was associated with an increased hazard of COVID-19 death (adjusted hazard ratio [aHR] 2.70; 95%CI 1.81-4.04) with a smaller increase for previous tuberculosis (aHR 1.51; 95%CI 1.18-1.93). The increased hazard of COVID-19 death associated with current tuberculosis was present for both microbiologically confirmed and unconfirmed tuberculosis and for rifampicin-sensitive and resistant disease during intensive phase treatment (Supplementary Table 3).

After adjusting for age, sex and other comorbidities, HIV was associated with increased COVID-19 mortality (aHR 2.14; 95%CI 1.70-2.70), and this association was similar irrespective of viraemia or immunosuppression prior to the COVID-19 episode. However, few patients were viraemic or immunosuppressed, as reflected in the wide CIs for the hazard

ratio in different groups. Associations with most comorbidities increased when restricting to those with high certainty comorbidity evidence (Supplementary Table 4). The associations of most comorbidities with COVID-19 death were attenuated when restricting to patients with ≥1 visit/year in the last 3 years as these patients were more likely to have comorbidities warranting regular visits, however HIV remained significantly associated with COVID-19 death (Supplementary Table 4). Among all public sector adults, 9.8% of COVID-19 deaths were attributable to HIV (95%CI 6.2-13.3), 2.6% (1.0-4.2) to current tuberculosis and 4.7% (1.5-7.8) to previous tuberculosis.

Death in COVID-19 cases and hospitalized patients

Among 15,203 COVID-19 cases diagnosed before June 1, 2020, the associations of all comorbidities with COVID-19 death were attenuated compared to the population analysis. However, HIV (aHR 1.70; 95%CI 1.32-2.18), current tuberculosis (aHR 1.62; 95%CI 1.04-2.51) and previous tuberculosis (aHR 1.55; 95%CI 1.19-2.02) remained associated with COVID-19 death (Table 4; Figure 1). Results were similar when including patients diagnosed after the change in testing criteria (Supplementary Table 5). Among COVID-19 cases in PLWH on ART, mortality was lower in patients on TDF (vs. abacavir/zidovudine) (aHR 0.41; 95%CI 0.21-0.78) with no difference for other antiretrovirals.

Among hospitalized COVID-19 cases, the associations of all mortality risk factors including HIV were attenuated, but HIV remained associated with death (aHR 1.45; 95%CI 1.14-1.84) as did previous tuberculosis (aHR 1.40; 95%CI 1.08-1.82), but not current tuberculosis. Among 601 hospitalized PLWH, 199 (33%) had CD4 measured during the COVID-19 episode, of whom 70 (35%) had CD4 <200 cells/µl, which was associated with COVID-19 death (aHR vs HIV negative 2.36; 95%CI 1.47-3.78; aHR vs HIV positive with CD4 ≥350 cells/µl 1.97; 95% CI 1.14-3.40). Among the 70 PLWH with CD4<200 cells/µl during

admission, 4 (5%) had no prior evidence of HIV in the PHDC, 47% had previous CD4<200 cells/µl, unsuppressed viral load or no recent ART, and 47% had previous CD4 ≥200 cells/µl or appeared stable on ART (VL <1000 copies/ml or ART dispensed in last year (Supplementary Figure 1).

Potential bias from unmeasured confounding

To assess whether the association between HIV or tuberculosis and COVID-19 mortality could be due to residual unmeasured confounding e.g. by socio-economic status, or unrecorded comorbidities, we calculated the E-value for an unmeasured confounder. For HIV, the E-value for the analysis among all public sector patients was 3.70 (and 2.79 for the lower bound of the CI), suggesting that only a strong association between HIV and a confounder (e.g. socio-economic status), and between the confounder and COVID-19 death would account for all of the observed association between HIV and COVID-19 death. The effect of HIV on COVID-19 death was similar when restricted to the poorest subdistrict with highest HIV prevalence in Cape Town [19]. Corresponding E-values for current and previous tuberculosis were 4.84 (3.02 for lower bound of CI) and 2.39 (1.64 for lower bound of CI), respectively. Quantitative bias analysis showed that the HIV-associated increased risk of COVID-19 death was unlikely due to confounding by raised BMI (Supplementary Appendix 4).

Standardized mortality ratio

Among all laboratory diagnosed COVID-19 cases, there were 135 deaths among an estimated ~520,000 PLWH in the province (260 deaths/million) and 786 deaths among 6.36 million people without HIV (124 deaths/million). The SMR for COVID-19 mortality in PLWH,

relative to HIV-negative people was 2.39 (95% CI 1.96-2.86) and the attributable fraction of public and private sector COVID-19 deaths due to HIV was 8.5% (95% CI 6.1-11.1).

Discussion

Among nearly 3.5 million adults (16% PLWH) in South Africa we found an approximately two-fold association of COVID-19 death with HIV, irrespective of viraemia or immunosuppression prior to the COVID-19 episode, and a similar association between COVID-19 death and current tuberculosis. Among PLWH on ART, receiving TDF was associated with lower COVID-19 mortality compared to other antiretrovirals. While the HIV- and tuberculosis-associated increased risk of COVID-19 death may be over-estimated if there is residual confounding due to socio-economic status or unrecorded comorbidities, our results, supported by sensitivity analyses, demonstrate that PLWH and persons with tuberculosis are at increased risk of severe COVID-19. Nonetheless, despite a high burden of advanced HIV in the province, the attributable fraction of all deaths ascribed to HIV was <10%.

While most case series of HIV and SARS-CoV-2 co-infection have not shown poor outcomes in PLWH, [1-3, 5-7] some cohorts of hospitalized PLWH with COVID- have reported substantial morbidity and mortality including among patients with suppressed viral load on ART [23, 24]. Comparisons by HIV status of hospitalized COVID-19 cases in New York and London have not shown differences in mortality risk [25-27], however, the absence of increased mortality risk in hospitalized patients with comorbidities may be explained by selection bias; risk factors for COVID-19 death may be attenuated by restricting to the subset of hospitalized patients already at high mortality risk [28]. It is therefore expected that in our analysis the increased risk of death associated with all comorbidities was progressively

attenuated when restricting to cases (people with sufficiently severe symptoms to be tested) and hospitalized patients.

Similar to our findings, several studies have reported a high prevalence of comorbidities among PLWH with severe COVID-19 [3, 6, 7]. The high prevalence of comorbidities in deceased PLWH suggests that the effect of HIV may at least partly be due to an increased risk of comorbidities at younger ages [2, 7], including those not recorded in WCPHDC such as cardiovascular disease. Persistent immune dysfunction may also be important in severe COVID-19 despite viral suppression; the hazard ratio point estimates for association with COVID-19 death were greater in immunosuppressed or viraemic PLWH, although the numbers of these patients with COVID-19 were small with wide CIs. Further, CD4 <200 cells/µl during admission was associated with COVID-19 death. While this may partly be due to the well-described lymphopenia in severe COVID-19 which is prognostic of poor outcomes, about half of patients with low CD4 during admission were either new HIV diagnoses or had previous immunosuppression, viraemia or no recent ART [10]. Among COVID-19 cases in PLWH on ART, receipt of TDF (vs. other therapies) was associated with reduced COVID-19 mortality. However, this association is likely to be over-estimated; in South Africa only patients on second-line ART or with poor renal function would not be on TDF, and both of these factors may themselves increase mortality. Nonetheless, the association remained when adjusting for kidney disease, viral suppression and ART duration, and concurs with results from a recently published cohort of PLWH on ART from Spain [13]. We found both current and previous tuberculosis to be associated with COVID-19 death, but since current tuberculosis itself causes death, in the absence of autopsy evidence it is difficult to disentangle the effects of COVID-19 vs tuberculosis disease on mortality *per se* [17].

In our study, the overall high prevalence of diabetes in people with and without HIV, high proportion with poor glycaemic control and very elevated risks for COVID-19 death for

diabetics compared to those reported from other countries are concerning [8]. Diabetes is often diagnosed late and/or untreated or poorly controlled in resource-limited settings, and the resulting microvascular disease even in people with good current diabetic control may increase COVID-19 mortality [29].

To our knowledge this is the largest report on SARS-CoV-2 from Africa, the largest report on HIV and tuberculosis co-infected patients and the first comparison of COVID-19 outcomes in patients with and without tuberculosis. Strengths include the study size using population-level data, laboratory confirmed SARS-CoV-2 diagnoses in all COVID-19 cases, the inclusion of hospitalized and non-hospitalized cases and deaths as well as modelling the independent associations of HIV and tuberculosis with COVID-19 death. While the population analysis approach is robust to selection bias associated with cases and hospitalized patients only, it may over-estimate associations between comorbidities and COVID-19 death if those with comorbidities live in areas with higher transmission or have closer follow-up and are more likely to be diagnosed with COVID-19. Nonetheless, the coherence of associations from population (cohort study and SMR) to diagnosed to hospitalised patients suggest that the population findings are unlikely to be solely due to different probabilities of encountering SARS-CoV2 or being diagnosed once infected. Furthermore, adjustment for subdistrict of residence should address geographic differences in transmission probability. Being an observational study, limitations include under-ascertainment of comorbidities in routine administrative data, lack of data on other potential risk factors including socio-economic status, smoking and BMI, possible under-ascertainment of all COVID-19 cases and deaths and potential misclassification of some incidental deaths in patients positive for SARS-CoV2 as COVID-19 related, although almost all deaths occurred in hospitalized patients with clinical COVID-19. Further, we were unable to systematically exclude other opportunistic infections as contributors to COVID-19 mortality as investigation for these causes varied by

facility, clinical presentation and time in hospital. Relatively large numbers of PLWH had no recent viral load or CD4 count results, limiting our ability to distinguish outcomes for different strata of these measures. In particular, patients with no recent information on disease control (e.g. HIV-RNA or HBA1c) may have less contact with health services and not reside permanently in the province, with under-ascertainment of outcomes.

Conclusion

While our findings of increased COVID-19 mortality risk with HIV or tuberculosis may over-estimate association of these conditions with COVID-19 death due to residual confounding, PLWH and/or tuberculosis should nonetheless be considered a high-risk group for COVID-19 management, especially if they have other comorbidities.

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Potential conflict of interest

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Table 1: Characteristics of (i) Western Cape "active patients" aged ≥20 years in public sector (public sector health care visit in last 3 years before March 1, 2020) according to COVID-19 outcome (ii) COVID-19 cases in "active patients" and (iii) hospitalized COVID-19 cases in "active patients".

	All public sector patients			All public-sector SARS-CoV-2 cases diagnosed before 1 June2020[a]		Hospitalized public-sector SARS-CoV-2 cases	
	No diagnosed COVID-19 n=3,438,624	COVID-19 not deceased n=21,683	COVID-19 deceased n=625	COVID-19 not deceased n=14,693	COVID-19 deceased n=510	COVID-19 not deceased n=2,428	COVID-19 deceased n=550
Sex							
female	1,983,480 (58%)	14,916 (69%)	340 (54%)	10,388 (71%)	281 (55%)	1,546 (64%)	302 (55%)
male	1,455,144 (42%)	6,767 (31%)	285 (46%)	4,305 (29%)	229 (45%)	882 (36%)	248 (49%)
Age							
20-39 years	1,913,786 (56%)	11,64 (54%)	46 (7%)	8,653 (59%)	35 (7%)	804 (33%)	45 (8%)
40-49 years	604,976 (18%)	4,515 (21%)	63 (10%)	2,991 (20%)	51 (10%)	472 (19%)	56 (10%)
50-59 years	447,739 (13%)	3,227 (15%)	162 (26%)	1,881 (13%)	137 (27%)	523 (21%)	142 (26%)
60-69 years	276,082 (8%)	1,423 (7%)	178 (28%)	739 (5%)	150 (29%)	360 (15%)	158 (29%)
≥70 years	196,035 (6%)	878 (4%)	176 (28%)	429 (3%)	137 (27%)	269 (11%)	149 (27%)
Diabetes							
none	3,177,088 (92%)	18,581 (86%)	253 (40%)	12,921 (88%)	212 (42%)	1,549 (64%)	225 (41%)
diabetes HbA1c <7%	45,054 (1%)	491 (2%)	58 (9%)	278 (2%)	43 (8%)	149 (6%)	54 (10%)
diabetes HbA1c 7 - 8.9%	47,211 (1%)	582 (3%)	94 (15%)	309 (2%)	79 (15%)	164 (7%)	85 (15%)
diabetes HbA1c ≥9%	65,639 (2%)	1,086 (5%)	158 (25%)	640 (4%)	125 (25%)	375 (15%)	136 (25%)
diabetes no HbA1c measurement	103,632 (3%)	943 (4%)	62 (10%)	545 (4%)	51 (10%)	191 (8%)	50 (9%)
Other non-communicable diseases							
hypertension	563,908 (16%)	4,910 (23%)	362 (58%)	2,972 (20%)	293 (57%)	948 (39%)	319 (58%)
chronic kidney disease	61,667 (2%)	494 (2%)	111 (18%)	250 (2%)	92 (18%)	168 (7%)	101 (18%)
chronic pulmonary disease / asthma	192,587 (6%)	1,577 (7%)	84 (13%)	949 (6%)	77 (15%)	355 (15%)	78 (14%)
Tuberculosis							
never tuberculosis	3,097,483 (90%)	19,668 (91%)	512 (82%)	13,330 (91%)	414 (81%)	2061 (85%)	448 (81%)
previous tuberculosis	286,889 (8%)	1,698 (8%)	87 (14%)	1,180 (8%)	74 (15%)	244 (10%)	77 (14%)
current tuberculosis	54252 (2%)	317 (1%)	26 (4%)	213 (1%)	22(4%)	123 (5%)	25 (5%)
HIV							
negative	2,902,050 (84%)	17,820 (82%)	510 (82%)	11,893 (81%)	415 (81%)	1,932 (80%)	445 (81%)
positive	536,574 (16%)	3,863 (18%)	115 (18%)	2,800 (19%)	95 (19%)	496 (20%)	105 (19%)
VL <1000 copies/ml (last 15 mo) & ART script (last 6 mo)	240,048 (45%)	2,332 (60%)	71 (62%)	1,726 (62%)	57 (60%)	289 (58%)	68 (65%)
VL <1000 copies/ml (2yr to 15 mo prior) OR ART script (last 6 mo) & VL <1000 copies/ml > 2yr prior	68,871 (13%)	409 (11%)	11 (10%)	283 (10%)	9 (9%)	46 (9%)	11 (10%)
VL ≥1000 copies/ml (last 15 mo) or CD4 <200 cells/µl (last 18 mo)	40,974 (8%)	209 (5%)	12 (10%)	150 (5%)	10 (11%)	58 (12%)	9 (9%)

No VL (last 15 mo); CD4 ≥200 cells/µl or unknown (last 18 mo)	186,681 (35%)	913 (24%)	21 (18%)	641 (23%)	19 (20%)	103 (21%)	17 (16%

[a]Analysis limited to cases diagnosed before 1 June 2020 when testing criteria changed with public sector tests being limited to patients >55 year of age or with comorbidities; Note: Column percentages may add up to >100% due to rounding; HbA1c glycosylated haemoglobin; VL viral load; mo months; yr years; ART antiretroviral therapy

Table 2: Characteristics of (i) Western Cape "active patients" ≥20 years of age in public sector (public sector health care visit in last 3 years) with and without HIV according to COVID-19 outcome.

	Public sector patients with HIV			**Public sector patients without HIV**		
	No diagnosed COVID-19 n=536,574	**COVID-19 not deceased** n=3,863	**COVID-19 deceased** n=115	**No diagnosed COVID-19** n=2,902,050	**COVID-19 not deceased** n=17,820	**COVID-19 deceased** n=510
Sex						
female	356,356 (66%)	3,039 (79%)	62 (54%)	1,627,124 (56%)	11,877 (67%)	278 (55%)
male	180,218 (34%)	824 (21%)	53 (46%)	1,274,926 (44%)	5,943 (34%)	232 (45%)
Age						
20-39 years	310,551 (58%)	2,187 (57%)	17 (15%)	1,603,235 (55%)	9,453 (53%)	29 (6%)
40-49 years	147,344 (27%)	1,136 (29%)	28 (24%)	457,632 (16%)	3,379 (19%)	35 (7%)
50-59 years	59,345 (11%)	418 (11%)	40 (35%)	388,394 (13%)	2,809 (16%)	122 (24%)
60-69 years	15,856 (3%)	98 (3%)	21 (18%)	260,226 (9%)	1,325 (7%)	157 (31%)
≥70 years	3,473 (1%)	24 (1%)	9 (8%)	192,562 (7%)	854 (5%)	167 (33%)
Diabetes						
none	517,609 (96%)	3,491 (90%)	57 (50%)	2,659,479 (92%)	15,090 (85%)	196 (38%)
diabetes HbA1c <7%	3,493 (1%)	65 (2%)	8 (7%)	41,561 (1%)	426 (2%)	50 (10%)
diabetes HbA1c 7 - 8.9%	2,998 (1%)	77 (2%)	16 (14%)	44,213 (2%)	505 (3%)	78 (15%)
diabetes HbA1c ≥9%	4,562 (1%)	126 (3%)	25 (22%)	61,077 (2%)	960 (5%)	133 (26%)
diabetes no HbA1c measurement	7,912 (1%)	104 (3%)	9 (8%)	95,720 (3%)	839 (5%)	53 (10%)
Other non-communicable diseases						
hypertension	62,676 (12%)	692 (18%)	48 (42%)	501,232 (18%)	4,218 (24%)	314 (62%)
chronic kidney disease	6,348 (1%)	82 (2%)	21 (18%)	55,319 (2%)	412 (2%)	90 (18%)
chronic pulmonary disease / asthma	23,501 (4%)	218 (6%)	10 (9%)	169,086 (6%)	1,359 (8%)	74 (15%)
Tuberculosis						
previous tuberculosis	129,259 (24%)	864 (22%)	42 (37%)	157,630 (5%)	834 (5%)	45 (9%)
current tuberculosis	24,357 (5%)	172 (4%)	16 (14%)	29,895 (1%)	145 (1%)	10 (2%)

Note: Column percentages may add up to >100% due to rounding; HbA1c glycosylated haemoglobin

Table 3: Univariate and multivariate hazard ratios (HRs) and 95% confidence intervals (CI) for associations with COVID-19 death from March 1 to June 9, 2020, among all public sector patients ≥20 years with a public sector health visit in the previous 3 years (n=3,460,932), using Cox-proportional hazards models

	Adjusted for location only			Adjusted for age and sex			Adjusted for all variables listed		
	HR	95% CI	p-value	Adjusted HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Sex									
female	Ref			Ref			Ref		
male	1.21	1.03; 1.41	0.02	1.26	1.07; 1.47	0.005	1.45	1.23; 1.70	<0,001
Age									
20-39 years	Ref			Ref			Ref		
40-49 years	4.46	3.05; 6.52	<0.001	4.42	3.02; 6.46	<0.001	2.83	1.92; 4.15	<0.001
50-59 years	16.23	11.70; 22.52	<0.001	16.13	11.62; 22.39	<0.001	7.78	5.51; 10.98	<0.001
60-69 years	28.82	20.83; 39.87	<0.001	28.81	20.82; 39.86	<0.001	11.54	8.11; 16.42	<0.001
≥70 years	41.37	29.87; 57.29	<0.001	41.85	30.21; 57.96	<0.001	16.79	11.69; 24.11	<0.001
Diabetes									
none	Ref			Ref			Ref		
diabetes HbA1c <7%	16.59	12.47; 22.09	<0.001	6.07	4.52; 8.16	<0.001	5.37	3.96; 7.27	<0.001
diabetes HbA1c 7 - 8.9%	25.32	19.98; 32.10	<0.001	9.26	7.23; 11.85	<0.001	8.53	6.60; 11.02	<0.001
diabetes HbA1c ≥9%	29.57	24.23; 36.10	<0.001	12.90	10.47; 15.88	<0.001	12.07	9.70; 15.02	<0.001
diabetes no HbA1c measurement	7.29	5.52; 9.62	<0.001	3.02	2.27; 4.02	<0.001	2.91	2.18; 3.89	<0.001
Other non-communicable diseases									
hypertension	6.72	5.73; 7.88	<0.001	2.20	1.85; 2.62	<0.001	1.31	1.09; 1.57	0.004
chronic kidney disease	11.43	9.30; 14.05	<0.001	3.21	2.57; 4.01	<0.001	1.86	1.49; 2.33	<0.001
chronic pulmonary disease / asthma	2.49	1.98; 3.13	<0.001	1.08	0.85; 1.36	0.538	0.93	0.73; 1.17	0.514
Tuberculosis									
never tuberculosis	Ref			Ref			Ref		
previous tuberculosis	1.79	1.42; 2.24	<0.001	1.81	1.44; 2.28	<0.001	1.51	1.18; 1.93	0.001
current tuberculosis	2.79	1.88; 4.13	<0.001	3.29	2.21; 4.88	<0.001	2.70	1.81; 4.04	<0.001
HIV									
negative	Ref			Ref			Ref		
positive	1.07	0.88; 1.32	0.494	1.97	1.59; 2.45	<0.001	2.14	1.70; 2.70	<0.001
VL <1000 copies/ml (last 15 mo) & ART script (last 6 mo)[a]							2.61	1.98; 3.43	<0.001
VL <1000 copies/ml (2yr to 15 mo prior) OR ART script (last 6 mo) & VL <1000 copies/ml >2yr prior							1.76	0.96; 3.24	0.067
VL ≥ 1000 copies/ml (last 15 mo) or CD4 <200 cells/µl (last 18 mo)							3.35	1.83; 6.12	<0.001
No VL (last 15 mo); CD4 ≥200 cells/µl or unknown (last 18 mo)							1.33	0.85; 2.07	0.217

[a]Reference category for hazard ratio is HIV negative; only included in adjusted analysis; adjusted for all other variables listed in this table in a model that included the listed categories of HIV viral load (VL), antiretroviral therapy (ART) and immunosuppression instead of the binary variable HIV positive vs negative; the effect of the other variables on mortality was similar to those presented here.
HR hazard ratio; CI confidence interval; HbA1c glycosylated haemoglobin; VL viral load; ART antiretroviral therapy; mo months; yr years.

Table 4: Multivariate hazard ratios (HRs) and 95% confidence intervals (CI) for associations with COVID-19 death from Cox-proportional hazards models among (i) all adult COVID-19 cases diagnosed before June 1, 2020 (n=15,203) and (ii) all hospitalized adult COVID-19 cases (n=2,978).

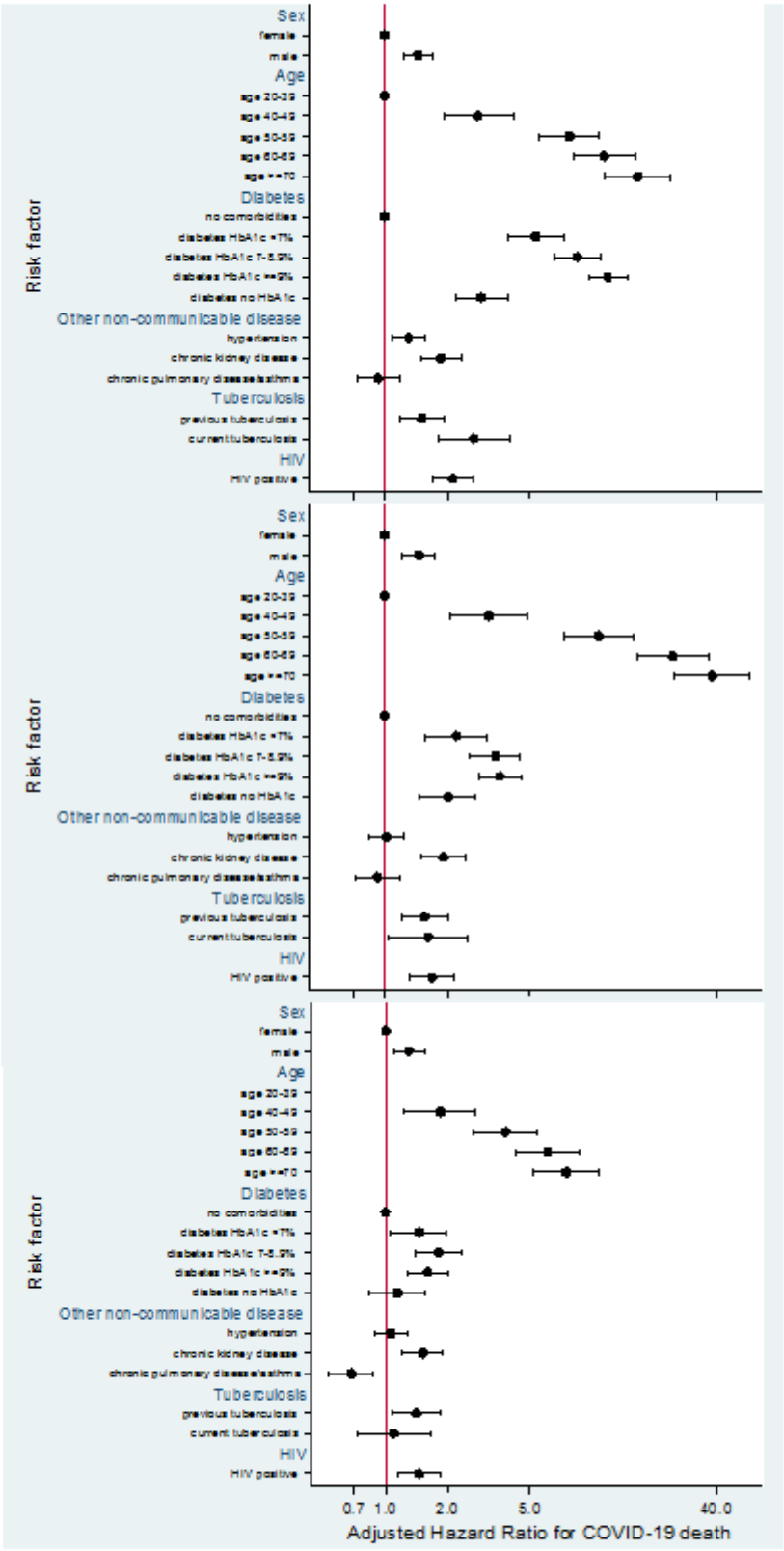
	All public-sector SARS-CoV-2 cases diagnosed before 1 June 2020[a] n=15,203			Hospitalized public-sector SARS-CoV-2 cases n=2,978		
	Adjusted HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Sex						
female	Ref			Ref		
male	1.45	1.22; 1.74	<0.001	1.29	1.09; 1.53	0.003
Age						
20-39 years	Ref			Ref		
40-49 years	3.19	2.06; 4.93	<0.001	1.83	1.23; 2.72	0.003
50-59 years	10.84	7.34; 16.01	<0.001	3.81	2.68; 5.42	<0.001
60-69 years	24.87	16.67; 37.11	<0.001	6.11	4.27; 8.75	<0.001
≥70 years	38.32	25.47; 57.64	<0.001	7.53	5.23; 10.84	<0.001
Diabetes*						
none	Ref			Ref		
diabetes HbA1c <7%	2.21	1.57; 3.12	<0.001	1.44	1.06; 1.96	0.020
diabetes HbA1c 7 - 8.9%	3.41	2.59; 4.51	<0.001	1.81	1.39; 2.35	<0.001
diabetes HbA1c ≥9%	3.62	2.85; 4.59	<0.001	1.60	1.27; 2.0	<0.001
diabetes no HbA1c measurement	2.02	1.47; 2.76	<0.001	1.13	0.83; 1.55	<0.001
Other non-communicable diseases						
hypertension	1.02	0.84; 1.24	0.843	1.05	0.88; 1.27	0.574
chronic kidney disease	1.92	1.51; 2.45	<0.001	1.51	1.20; 1.89	<0.001
chronic pulmonary disease / asthma	0.92	0.72; 1.18	0.512	0.68	0.53; 0.86	0.002
Tuberculosis						
never tuberculosis	Ref			Ref		
previous tuberculosis	1.55	1.19; 2.02	0.001	1.40	1.08; 1.82	0.011
current tuberculosis	1.62	1.04; 2.51	0.031	1.09	0.72; 1.65	0.683
HIV						
negative	Ref			Ref		
positive	1.70	1.32; 2.18	<0.001	1.45	1.14; 1.84	0.002
VL <1000 copies/ml (last 15 mo) & ART script (last 6 mo)[b]	1.60	1.19; 2.17	0.002	1.57	1.18; 2.07	0.002
VL <1000 copies/ml (2yr to 15 mo prior) OR ART script (last 6 mo) & VL <1000 copies/ml >2yr prior	1.56	0.80; 3.07	0.193	1.33	0.72; 2.46	0.357
VL ≥ 1000 copies/ml (last 15 mo) or CD4 <200 cells/µl (last 18 mo)	3.39	1.14; 3.62	<0.001	1.60	0.79; 3.25	0.190
No VL (last 15 mo); CD4 ≥200 cells/µl or unknown (last 18 mo)	1.73	1.10; 2.71	0.017	1.17	0.73; 1.87	0.506
ART in PLWH with script issued in last 12 months[c]						
abacavir or zidovudine	Ref			Ref		
Tenofovir disoproxil fumarate	0.41	0.21; 0.78	0.007	0.57	0.31; 1.04	0.067
efavirenz	Ref			Ref		
lopinavir	0.91	0.37; 2.25	0.846	0.68	0.29; 1.63	0.392
atazanavir	0.38	0.05; 2.92	0.352	1.09	0.25; 4.82	0.911
dolutegravir	0.57	0.16; 2.01	0.380	0.62	0.17; 2.22	0.461
ART duration						
<1 year	Ref			Ref		
1-2 years	0.78	0.21; 2.94	0.719	1.28	0.37; 4.42	0.701
≥2 years	0.54	0.19; 1.48	0.230	0.55	0.21; 1.42	0.213
CD4 count during COVID_19[d]						
>350 cells/µl				1.24	0.95; 1.63	0.112

200-349 cells/µl	1.65	0.94; 2.88	0.080
<200 cells/µl	2.36	1.47; 3.78	<0.001

[a]Analysis limited to cases diagnosed before 1 June 2020 when testing criteria changed with public sector tests being limited to patients >55 year of age or with comorbidities; [b]Reference category is HIV negative; adjusted for all other variables listed in this table in a model that included the listed categories of HIV viral load (VL), CD4 count and antiretroviral therapy (ART) instead of the binary variable HIV positive vs negative; the effect of the other variables on mortality was similar to those presented here; [c]Restricted to patients with documented antiretrovirals dispensed in the last 12 months, adjusted for all other variables listed in this table in a model that included the relevant antiretrovirals and ART duration; the effect of the other variables on mortality was similar to those presented here; [d]Reference category is HIV negative; restricted to HIV-negative patients and 199 of 601 PLWH with CD4 measurement at time of COVID-19 diagnosis or admission; adjusted for all other variables listed in this table in a model that included the listed categories of CD4 count instead of the binary variable HIV positive vs negative; the effect of the other variables on mortality was similar to those presented here.

HR hazard ratio; CI confidence interval; HbA1c glycosylated haemoglobin; VL viral load; ART antiretroviral therapy; mo months; yr years; PLWH people living with HIV

Figure 1: Comparison of adjusted hazard ratios (HR) and 95% confidence intervals (CI) for associations with COVID-19 death from Cox-proportional hazards models among (i) all public sector patients ≥20 years with a public sector health visit in the previous 3 years (n=3,460,932) (ii) all adult COVID-19 cases diagnosed before June 1, 2020 (n=15,203) and (iii) all hospitalized COVID-19 cases (n=2, 978).



(i) all public sector patients ≥20 years with a public sector health visit in the previous 3 years (n=3,460,932)

(ii) all COVID-19 cases ≥20 years diagnosed before June 1, 2020 (n=15,203)

(iii) all hospitalized COVID-19 cases (n=2,978)