Clinical course, management and outcomes of COVID-19 in HIV-infected renal transplant recipients: A case series

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Background. HIV-infected kidney transplant recipients with COVID-19 are at increased risk of acute illness and death owing to their underlying comorbidities and chronic immunosuppression.
Objectives. To describe the incidence, clinical presentation and course of COVID-19, vaccination status, and SARS-CoV-2 antibody positivity rate among HIV-infected-to-HIV-infected kidney transplant recipients in South Africa (SA).
Methods. This retrospective study reports on rates of SARS-CoV-2 infection, COVID-19 and mortality among SA HIV-infected kidney transplant recipients who received organs from HIV-infected donors (HIV positive to HIV positive), before and after vaccination. Patient demographics, clinical presentation, course, management and disease outcomes were analysed. Antibody serology tests were performed between May and September 2022.
Results. Among 39 HIV-positive-to-HIV-positive transplant recipients, 11 cases of COVID-19 were diagnosed from March 2020 to September 2022. Six patients (55%) required hospitalisation, of whom 3 were admitted to a high-care unit or intensive care unit. Two patients required mechanical ventilation, and 2 received acute dialysis. One patient was declined access to intensive care. Four patients (10%) died of COVID-19 pneumonia. All the COVID-19-positive patients had at least one comorbidity. Vaccination data were available for 24 patients, of whom 5 had refused SARS-CoV-2 vaccination. SARS-CoV-2 antibody data were available for 20 patients; 4 vaccinated patients had a negative nucleocapsid protein antibody test and a positive spike protein antibody test, suggesting vaccination-acquired immunity. The remaining 16 patients demonstrated immunity that was probably due to COVID infection, and of these, 14 were also vaccinated. Of the 11 COVID-19 cases, only 1 was observed after vaccination.
Conclusion. In our case series, ~10% of the HIV-positive-to-HIV-positive transplant recipients died of COVID-19 pneumonia. This mortality rate appears higher than figures reported in other transplant cohorts. However, it is likely that the actual number of cases of SARS-CoV-2 infection was much higher, as the study only included polymerase chain reaction-confirmed cases. It remains unclear whether HIV infection, transplant or the combination of the two drives poorer outcomes, and larger studies adjusting for important demographic and biological factors may isolate these effects.

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Kidney transplant recipients living with HIV have been reported to be at particularly high risk of acquiring COVID-19. Furthermore, the combined impact of impaired T-cell immunity and the use of immunosuppressive agents increases the risk of severe disease.[1] A multicentre series of 482 solid-organ transplant (SOT) recipients infected with SARS-CoV-2 reported mortality of 20.5% among hospitalised recipients.[2] In addition, a multicentre series of 11 291 kidney and liver transplant recipients living with HIV reported 36% mortality (n=4/11) in those hospitalised with COVID-19.[3]

HIV-positive individuals have an increased burden of comorbidities, and the effect of overlapping risk factors for COVID-19 is not completely understood. Studies on COVID-19 in people living with HIV have presented conflicting findings on the incidence of COVID-19 that ranged from lower than to equivalent to and higher than the general population.[4,5] However, small sample sizes and a lack of adjustment for confounders have limited this interpretation.[4] Most studies that have focused on the interplay between HIV and COVID-19 have therefore argued that a patient who is virally suppressed on antiretroviral therapy (ART) would have an increased risk relative to the number of comorbidities rather than underlying HIV disease.[4] However, a systematic review demonstrated that people living with HIV had an increased risk of acquiring SARS-CoV-2 infection and death.[6]

In South Africa (SA), ART coverage and certain HIV healthcare support services (testing and initiation of ART) declined during the pandemic lockdowns, but ART adherence appeared to have been reasonably maintained in patients on established regimens.[7] The COVID-19 pandemic led to a significant reduction in transplant activity in SA, partly motivated by concerns of disproportionately more severe disease among SOT recipients.[8] Furthermore, there was a reduction in all services as healthcare systems prepared for admissions and management of patients during the successive waves of COVID-19 infection.[7]

Nucleocapsid protein (N-prt) and spike protein (S-prt) antibodies can be used to measure the response to natural and vaccinated immunity, respectively.[9] The presence of N-prt antibodies, regardless of S-prt antibody status, indicates exposure to SARS-CoV-2 with

unknown vaccination response. The presence of S-prt antibodies with no N-prt antibodies suggests a vaccine response, but viral infection cannot be fully ruled out in this case either. In the absence of longitudinal data, it is difficult to determine the exact SARS-CoV-2 exposure risk, but use of antibody testing can estimate vaccination status as well as exposure. A large systematic review showed that vaccine antibodies can wane over time, particularly in SOT patients,[10] while another study showed that early humoral immune response was delayed and lower in people living with HIV compared with their uninfected counterparts.[11]

Methods

Patients and data collection

Demographic and clinical transplant data were extracted from the HIV-infected kidney transplant database, which collects data from recipients who received kidneys from HIV-infected deceased donors. Additional details on the study design and methods can be found in Muller *et al.*[12] At the start of the COVID-19 pandemic in SA in March 2020, there were 32 patients alive with a functioning graft who were at risk of COVID-19 infection (pre-pandemic transplant cohort). Another 7 patients received transplants during the pandemic, until June 2022 (peri-pandemic transplant cohort). Antibody serology tests were performed between May and September 2022.

Inclusion and exclusion criteria

To be included in the SARS-CoV-2 case review, patients had to have a positive SARS-CoV-2 polymerase chain reaction (PCR) test from a nasal swab between 5 March 2020 and 30 April 2022. Patients who died or had graft rejection prior to March 2020 were excluded from the case review, and those who died or had graft rejection during the pandemic before May 2022 were excluded from the vaccination and COVID-19 antibody analysis. Positive PCR tests were correlated with COVID-19 waves in SA.[13]

Descriptive statistics were used to present demographic and clinical variables, patient mortality and graft loss data. A case-series design was used to outline the clinical course and outcomes of the positive SARS-CoV-2 cases.

Ethical considerations

The University of Cape Town Human Research Ethics Committee granted permission for this study (ref. no. 947/2014), and all the participants provided written informed consent.

Results

The demographics and clinical characteristics of the 39 HIV-infected kidney transplant recipients, 32 transplanted pre-pandemic and 7 transplanted during the pandemic (peri-pandemic), are shown in Table 1.

The median (interquartile range) age of the pre- and peri-pandemic cohorts was 48 (40 - 53) years and 32 (30 - 36) years, respectively. The majority were black Africans, and the sex distribution in the two cohorts was similar. All the patients were virally suppressed and received antithymocyte globulin at the time of the transplant. Most patients had underlying hypertension, and most had HIV-associated nephropathy and hypertension as the cause of end-stage renal failure. During the pandemic, 2 patients experienced graft loss and 1 patient died of causes unrelated to COVID-19. From March 2020, 11 patients (28%) had a positive SARS-CoV-2 PCR test from a nasal swab (Table 2), and of these, 4 (36%) died. All 4 deaths were in the pre-pandemic transplant cohort.

Table 2 outlines the characteristics, clinical course and outcomes of the 11 COVID-19 cases, presented by chronological wave of infection. Additional details on the case series are provided in Supplementary Table 1 (available online at https://www.samedical.org/file/2169). There were five distinct waves of SARS-CoV-2 infection in SA. Of the 3 HIV-positive transplant recipients who tested positive for COVID-19 during the first wave, 1 was admitted, and subsequently died. During the second wave, both patients who tested positive were admitted, and died. Of 4 patients who tested positive in the third wave, 2 were admitted, and 1 died. During the fourth wave there were 2 patients who had COVID-19, and 1 was admitted. No patient died during this wave of infections.

Six of the 11 patients (55%) tested SARS-CoV-2 positive before vaccination roll-out. Of these patients, 3 died after being admitted to hospital. After vaccinations became available in SA, 4 patients (36%) had not been not vaccinated when they tested positive for SARS-CoV-2, and 1 of these patients died. Only 1 patient tested positive after vaccination.

All 11 patients with COVID-19 had underlying hypertension. Those who died of COVID-19 pneumonia (n=4; 36%) were older (median 52 v. 40 years of age), had higher BMIs (median 36 v. 27 kg/m^2), and had a greater median change in creatinine between the baseline pre-pandemic measure and COVID-19 diagnosis (345 mmol/L) compared with patients who survived (39 mmol/L).

There was a large variation in time between the transplant and acquiring COVID-19. Two patients acquired COVID-19 only 3 months after their transplant, with 1 of these patients diagnosed concurrently with TB, and 1 patient 6 months after the transplant. Three patients acquired COVID-19 ~2.5 years after the transplant, 3 patients ~4 years after the transplant, and 2 patients ~7 years after the transplant.

Of the 6 patients (55%) who were hospitalised, 3 were admitted to an ICU or high-care facility. The 2 patients in the ICU were ventilated, and 1 also received dialysis. The patient in the high-care facility received oxygen via a face mask, and the decision was made not to ventilate the patient. In total, 2 patients were assessed not to be ICU candidates according to the locally implemented public sector policy during the COVID pandemic,[14] and subsequently died. The remaining 2 patients were admitted to a general COVID-19 ward and were subsequently discharged. The average length of stay for the 6 admitted patients was 5.2 days, and the time between diagnosis and death ranged from 1 to 14 days.

Vaccination data were available for 24 patients. Of these patients, 19 (79%) were vaccinated, and the remaining 5 (21%) declined vaccination. Of the vaccinated patients, 16 (67%) received two doses of the Pfizer vaccine, and 3 (13%) received a single-dose Johnson & Johnson vaccine.

SARS-CoV-2 antibody data were available for 20 patients, 18 of whom were vaccinated and 2 unvaccinated (Table 3). Sixteen patients (80%) were positive for N-prt and S-prt antibodies, indicating either exposure to SARS-CoV-2 or vaccination, and 4 vaccinated patients (20%) were negative for N-prt antibodies with positive S-prt antibodies, indicating exposure to the vaccine.

Discussion

To date, this is the largest case series reporting on the clinical course of COVID-19 infection, vaccination and antibody status in kidney transplant recipients living with HIV. Our cohort includes patients with virally suppressed HIV infection on significant immunosuppressive therapy, which allows insight into the interaction between these and response to SARS-CoV-2 infection and vaccination.

From the start of the SA pandemic, 11 cases of COVID-19 were diagnosed in our cohort of 39 kidney transplant recipients (28%). In the HOPE in Action cohort,[3] which included 291 HIV-infected

Table 1. Demographic and clinical characteristics of kidney transplant recipients at risk of COVID-19

Characteristics†	Pre-pandemic transplant cohort (March 2020) (*n*=32), *n* (%)*	Peri-pandemic transplant cohort (April 2020 - May 2022) (*n*=7), *n* (%)*
Age (years), median (IQR)	48 (40 - 53)	32 (30 - 36)
Male sex	16 (50)	3 (43)
Race		
Black African	28 (88)	7 (100)
Mixed ancestry	4 (12)	
ART		
NRTI and NNRTI-based ART	20 (63)	6 (86)
Protease-based ART	12 (37)	1 (14)
CD4 count (cells/μL), median (IQR)	414 (303 - 577)	498 (303 - 548)
HIV VL suppressed	32 (100)	7 (100)
Creatinine, pre-pandemic (mmol/L), median (IQR) (*n*=32)	127 (93 - 162)	-
Primary cause of ESKD		
HIVAN + HPT	14 (44)	4 (57)
HIVAN only	11 (34)	1 (14)
HPT	4 (12)	1 (14)
Glomerulonephritis	1 (3)	
HPT + glomerulonephritis	1 (3)	
ADPKD	1 (3)	
Severe IFTA		1 (14)
Comorbidities in recipients‡		
HPT	29 (91)	6 (86)
DM	2 (6)	0
Obesity	12 (37)	0
Hepatitis B positive	3 (9)	0
Prior TB	8 (25)	3 (43)
Retransplanted	0	1 (14)
Outcomes		
Confirmed COVID-19	8 (25)	3 (43)
Graft failure	1 (3)	1 (14)
Died of COVID-19 pneumonia	4 (12)	0

IQR = interquartile range; ART = antiretroviral therapy; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; VL = viral load; ESRD = end-stage renal failure; HIVAN: HIV-associated nephropathy; HPT = hypertension; ADPKD = autosomal dominant polycystic kidney disease; IFTA = interstitial fibrosis and tubular atrophy; DM = diabetes mellitus; TB = tuberculosis.
*Except where otherwise indicated.
†Age, CD4 count and HIV VL were captured at the start of the pandemic in the pre-pandemic transplant cohort (those alive with a functioning graft at the start of the pandemic, *n*=32) and at the time of transplant in the peri-pandemic transplant cohort (those transplanted during the pandemic, *n*=7).
‡Some patients had more than one comorbidity.

kidney and liver recipients from multiple sites, the reported incidence was considerably lower at 4%. However, the HOPE in Action cohort received organs from HIV-positive and negative donors.

Earlier in the pandemic, recipients in our cohort presented with predominantly typical symptoms of COVID-19, in contrast to the patients presenting later in the pandemic, who were mainly asymptomatic. This pattern follows that in the general population,[15] and is probably due to natural immunity and vaccination. Among our 11 cases, 4 patients with severe symptoms died of COVID-19 pneumonia (36%), which is comparable to the mortality reported in the HOPE in Action cohort.[3] However, our mortality rate in hospitalised patients appears higher than figures reported in other transplant cohorts.[1,16] Our mortality rate is considered to be an overestimation, as the actual number of cases of SARS-CoV-2 infection was probably much higher in this cohort, which may have included asymptomatic patients or those with mild disease who would have not sought testing and/or medical care.

Underlying non-communicable diseases have been significantly associated with poorer outcomes in patients with COVID-19.[17] Despite underlying HIV infection and immunosuppression, the deaths in our cohort appear likely to be associated with the presence of comorbidities. All the patients were virologically suppressed on antiretroviral therapy at the time of infection, and those who died all had a background of hypertension and underlying comorbidities such as obesity (*n*=3), cancer (*n*=1) and diabetes mellitus (*n*=1). None of the COVID-19 patients who received transplants during the pandemic required high-care or intensive care hospitalisation, which could be due to their younger age, a lower number of underlying comorbidities and a lower number of accumulated clinical insults.

Clinical outcomes in SARS-CoV-2 infection in non-transplanted HIV-infected patients have been shown to be similar to those in the general population in local and international studies.[18] However, a higher risk of infection and mortality was reported in a systematic review of 22 studies (*n*=20 982 498 patients).[6] Furthermore, the mortality rate in kidney transplant recipients who were hospitalised with COVID-19 was considerably higher than that in the general population.[1] This mortality rate in kidney transplant recipients hospitalised with COVID-19 was found to be 24 - 32%, while a mortality rate of 8 - 14% was observed in New York, Italy and Spain in the general population during the same period.[1]

Table 2. Summary of polymerase chain reaction-confirmed COVID-19 cases in HIV-positive transplant recipients

Case	1	2	3	4	5	6	7	8	9	10	11
COVID wave	1	1	1	2	2	3	3	3	3	4	4
Dominant COVID-19 vector	Alpha	Alpha	Alpha	Alpha	Alpha	Delta	Delta	Delta	Delta	Delta	Omicron
Vaccination status	Pre-vaccination roll-out	Pre-vaccination roll-out	Pre-vaccination roll-out	Pre-vaccination roll-out	Pre-vaccination roll-out	Pre-vaccination roll-out	Unvaccinated	Unvaccinated	Unvaccinated	Vaccinated	Unvaccinated
Characteristics											
Age (years) at diagnosis, sex	41, male	39, female	49, female	54, male	54, female	38, female	53, male	40, female	36, male	53, male	41, female
Comorbidities	HPT Obese	HPT Obese	HPT Overweight	HPT Cancer	HPT Obese	HPT	HPT Obese DM	HPT Obese	HPT Overweight	HPT	HPT TB
Clinical course											
Time since transplant	4 yr, 11 mo	2 yr, 7 mo	2 yr, 7 mo	4 yr, 4 mo	7 yr, 9 mo	3 mo	4 yr, 8 mo	2 yr, 10 mo	6 mo	6 yr, 9 mo	3 mo
Days of symptoms pre-Dx	7	3	Nil	7	6	7	7	Unknown	14	7	Nil
GFR (mL/min/1.73 m^2) baseline	33	63	43	47	49	28	40	68	49	42	23
GFR (mL/min/1.73 m^2) at COVID-19 Dx	Not done	10	42	12	38	18	10	69	25	49	13
Admitted	No	Yes	No	Yes	Yes	No	Yes	No	Yes	No	Yes
ICU/high care	No	Yes	No	Yes	Yes	No	No	No	No	No	No
O_2 requirement	No	FMO^2	No	HFO2 Ventilated	CPAP Ventilated	No	HFO2	No	No	No	No
Died (COVID)	No	Yes	No	Yes	Yes	No	Yes	No	No	No	No

HPT = hypertension; DM = diabetes mellitus; TB = tuberculosis; Dx = diagnosis; GFR = glomerular filtration rate; ICU = intensive care unit; O_2 = oxygen; FMO_2 = face-mask oxygen; HFO_2 = high-flow oxygen, CPAP: continuous positive airway pressure.

Eighty percent of the patients who had their antibodies measured had positive N-protein and S-protein antibodies, implying previous infection. The timing of this infection is unknown and would indicate an episode of asymptomatic COVID-19 infection. Of the 4 patients who did not have N-prt antibody positivity, 1 had had a PCR-confirmed COVID-19 infection 10 months before the antibody measurement, confirming the difficulty of interpreting antibody status. The SARS-CoV-2 antibody titre was reported as a quantitative measurement of total nucleocapsid and total spike antibodies. Nucleocapsid antibodies may be undetectable during the very early phase of COVID-19 infection, and some individuals may not develop detectable antibodies after infection.[19] A meta-analysis looking at the differences in COVID-19 vaccine efficacy between immunocompetent and immunocompromised people showed that patients with an organ transplant were 16 times less likely to seroconvert after a single dose of a vaccine, and only a third of patients seroconverted after a second dose of a vaccine.[10] Detectable N-prt antibodies are indicative of a recent infection, vaccination or past exposure to SARS-CoV-2. False-positive results may occur, and these are due to cross-reactivity to other coronaviruses.[20] It is difficult to determine the time of infection, or how long an individual may be protected against COVID-19 infection, based on the presence of antibodies; however, immunoglobulin G S-prt antibodies have been shown to be positive a year after infection.[20,21]

The present case series also highlights the challenge of managing immunosuppressed HIV-positive transplant patients during the COVID-19 pandemic. COVID-19-directed therapies (antiviral or convalescent plasma) were not available to our cohort of patients, and supportive strategies may have differed between centres or may not have been applied universally. We observed a high prevalence of non-communicable diseases such as hypertension and obesity that are known to be strongly associated with increased morbidity and mortality in COVID-19.

Our main limitation was the small sample size of HIV-infected kidney transplant recipients and the number of confirmed cases, which limited our analysis and interpretation. Absolute lymphocyte and CD4 counts and HIV viral loads at COVID-19 diagnosis were not routinely performed, so we could not correlate these parameters with outcome.[22] Future studies of COVID-19 and HIV that include longitudinal CD4 data may determine whether a low CD4 count is a risk factor for severe disease or merely a marker of severe illness, which could provide a distinction and improve targeted prevention strategies.

Table 3. N-prt antibodies and S-prt antibodies by vaccination status (*N*=20)

	Antibody status		
Vaccination status	N-prt antibodies negative S-prt antibodies negative	N-prt antibodies negative S-prt antibodies positive	N-prt antibodies positive S-prt antibodies positive
Pre-vaccination/refused vaccination	0	0	2
Vaccinated	0	4	14

N-prt = nucleocapsid protein; S-prt = spike protein.

Conclusion

In our case series, ~10% of the HIV-infected transplant recipients died of COVID-19 pneumonia. It is likely that the actual incidence of SARS-CoV-2 infection was much higher, as this study only included PCR-confirmed cases. It remains unclear whether HIV, SOT and subsequent immunosuppression, or the combination of the two, drives poorer outcomes, and larger studies adjusting for important demographic and biological factors may isolate these effects. Our patients had the combined synergistic risk of underlying HIV, immunosuppression and underlying comorbidities.

Declaration. None.

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Conflicts of interest. None.

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