Comorbidity in context: Part 1. Medical considerations around HIV and tuberculosis during the COVID-19 pandemic in South Africa.

MEDICINE AND THE LAW

Comorbidity in context: Part 1. Medical considerations around HIV and tuberculosis during the COVID-19 pandemic in South Africa

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Infectious diseases pandemics have devastating health, social and economic consequences, especially in developing countries such as South Africa. Scarce medical resources must often be rationed effectively to contain the disease outbreak. In the case of COVID-19, even the best-resourced countries will have inadequate intensive care facilities for the large number of patients needing admission and ventilation. The scarcity of medical resources creates the need for national governments to establish admission criteria that are evidence-based and fair. Questions have been raised whether infection with HIV or tuberculosis (TB) may amplify the risk of adverse COVID-19 outcomes and therefore whether these conditions should be factored in when deciding on the rationing of intensive care facilities. In light of these questions, clinical evidence regarding inclusion of these infections as comorbidities relevant to intensive care unit admission triage criteria is investigated in the first of a two-part series of articles. There is currently no evidence to indicate that HIV or TB infection on their own predispose to an increased risk of infection with SARS-CoV-2 or worse outcomes for COVID-19. It is recommended that, as for other medical conditions, validated scoring systems for poor prognostic factors should be applied. A subsequent article examines the ethicolegal implications of limiting intensive care access of persons living with HIV or TB.

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Rationing of scarce medical resources is inevitable during a pandemic. Even the best-resourced countries will have inadequate intensive care facilities for the large numbers of patients needing admission and ventilation due to SARS-CoV-2 infection. Scarcity of resources creates the need for national governments to establish admission criteria that are evidence-based and fair.[1] In South Africa (SA), where the number of patients with COVID-19 is steadily increasing, this conversation is just beginning. There has been widespread speculation in the lay and medical media about whether infection with HIV or tuberculosis (TB) may amplify the risk of adverse COVID-19 outcomes.[2] Conversely, some have proposed that HIV-infected patients may be protected against infection with SARS-CoV-2 by the antiviral effect of antiretroviral therapy (ART),[3] especially the protease inhibitor, ritonavir-boosted lopinavir (LPV/r). Unfortunately, as demonstrated by a recent systematic review, such optimism is likely to be unfounded.[4] The review included two randomised trials and 21 observational studies that reported on the use of LPV/r for the treatment of COVID-19, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) and concluded that there was no evidence that LPV/r prevented infection or improved clinical outcomes. In addition, many are sceptical about the potency of LPV/r against coronavirus proteases.[5] Since the body of evidence is limited, several randomised trials are ongoing to assess the safety and efficacy of ART for the treatment of COVID-19.

In these uncertain times, it is important not to lose sight of clinical evidence. Given the large number of people living with HIV (PLWH) and TB in SA, the inclusion of these diseases as comorbidities relevant to intensive care unit (ICU) admission triage criteria should be carefully examined. In this article, we briefly discuss the risk factors and proposed immunopathological mechanisms of adverse outcomes of COVID-19 and how these may be affected by HIV and TB. We further describe the clinical profiles of patients with HIV and TB with regard to COVID-19 risk factors and conclude by reviewing the outcome of cases of HIV/SARS-CoV-2 co-infected patients reported in the medical literature.

This is the first in a series of two articles. The present article serves in part to provide the scientific and medical basis for a subsequent article outlining the ethicolegal implications of limiting ICU access.

Predictors of adverse outcomes

South Africa is (in)famous for social and economic inequality, and this inequality is strongly reflected in healthcare provision. The country has, in effect, a two-tier system – a well-resourced and minimally burdened private, fee-paying system, and an under-resourced, overburdened public system that is essentially free at

the point of care. These inequalities in our healthcare system may affect the outcomes of patients with COVID-19. Regardless of the healthcare system, critical care is expensive, labour-intensive and specialised. As a scarce resource, it has to be rationed, with access determined by evidence-based clinical criteria and ethicolegal considerations. Internationally, it is recommended that access be informed by a holistic assessment of the patient using the Clinical Frailty Scale as appropriate, together with considerations of the severity of the acute illness, comorbidities and underlying health conditions, and how these will impact on the desired outcome.[6] The comorbidities most commonly associated with an adverse outcome during the COVID-19 pandemic are hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), malignancy[7] and coronary heart disease.[8] Multiple comorbidities, advanced age and smoking have also been identified as risk factors for poor outcome.[9]

Advanced age is the clinical variable with the strongest associated risk for hospitalisation, ICU admission and mortality from COVID-19.[9] The pathophysiological mechanisms underlying this risk are under intense investigation. A popular working hypothesis is that ageing is associated with thymic involution, leading to a significant, continuous decrease in precursor CD4+ and CD8+ T-cells, which are vital for antiviral responses.[10] This effect of ageing is more pronounced in men than women.[10] Consequently, older people, and men in particular, are at risk for worse outcomes following infection with a variety of viruses – including West Nile virus, HIV, influenza and SARS.[11-13] In addition, ageing is characterised by a senescence-associated secretory phenotype, with increased levels of proinflammatory mediators and matrix-degrading molecules contributing to a state of chronic, systemic, low-grade inflammation called 'inflammaging'.[14] Older age has been shown to be a major risk factor for developing acute respiratory distress syndrome,[15] the most common cause of death in patients with COVID-19,[16] possibly secondary to high levels of underlying inflammation.

Clinical profile of HIV-infected patients

The effects of HIV infection on the immune system are in many ways similar to those observed during ageing. In the context of prolonged, untreated HIV infection, naive CD4+ T-cell populations decrease. In addition, a preponderance of T-cells exhibit an exhausted and activated profile,[17] eventually leading to immunosenescence and inflammaging.[18] Therefore, both ageing and untreated HIV infection lead to significant T-cell dysfunction and inflammation, increasing the risk of adverse outcomes following viral infection. Initiation of ART and suppression of HIV replication increase the proportion of circulating naive T-cells[17] and significantly improve, but do not normalise, the risk of infection with a wide range of pathogens.[19]

In 2018 there were ~7.7 million PLWH (~14% of the total population) in SA, with an estimated 4.8 million (or 62%) on ART, and 54% of PLWH were virally suppressed.[20] SA has a relatively young population, with a median age of 27 years; this is also reflected in the age of people starting ART, which was 38 years in 2017.[21] However, in 2015, 14% of patients in HIV care were aged ≥50 years, and this figure is likely to have increased since then.[22] Keeping in mind that comorbidities are often under-reported,[23] non-communicable diseases are common in PLWH, with hypertension being the most prevalent.[24] In addition, smoking is common in males with HIV (34% in one cross-sectional survey), and less so in females.[25]

Untreated HIV and low CD4+ counts have been suggested as possible risk factors for COVID-19.[26] Approximately 37% of PLWH in SA initiate ART at a CD4+ count <200 cells/μL, and they have a higher mortality,[21] especially from infection with influenza and unspecified severe respiratory tract infections,[27] than individuals with a higher CD4+ count. Mortality in the first year after ART initiation is highest in those with a CD4+ count <50 cells/μL (19.54/100 person-years), and decreases significantly above this level (CD4 >200 cells/μL = 4.01/100 person-years).[28] After 48 months of ART, irrespective of the starting CD4+ count, mortality rates approximate those of HIV-negative people.[28]

Despite the widespread availability of ART, up to 75% of HIV-related admissions to hospitals in SA are of patients with advanced disease and low CD4+ counts (CD4+ T-cell counts <200 cells/μL).[29] The primary reason for an ICU admission in PLWH is a respiratory illness. In-hospital mortality is high in PLWH who are admitted to intensive care with a World Health Organization (WHO) stage IV-defining illness, lower CD4+ counts (<100 cells/μL) and higher APACHE II scores, and in those who need inotropic support or renal replacement therapy.[30] The following clinical six-point scoring system has been proposed to predict mortality in PLWH admitted to intensive care, with one point allocated to each of the following: (1) an AIDS-defining illness; (2) CD4+ <50 cells/μL; (3) extrapulmonary TB; (4) *Pneumocystis jirovecii* pneumonia (PCP); (5) septic shock; and (6) renal dysfunction.[31] In a retrospective validation study, >80% of patients with a score of 3 died, and no patient with a score of 4 survived.[31]

Clinical profile of TB-infected patients

SA is one of eight countries accounting for two-thirds of the global TB burden.[32] It has the highest burden of HIV co-infected cases globally: ~59% of TB patients with known HIV status are HIV-positive.[32] Men are more prone to infection (as demonstrated by a female-to-male ratio of 0.72), particularly between the ages of 25 and 54 years, with 33 - 44-year-olds having the highest incidence.[33] TB and COVID-19 share many of the same symptoms, which could complicate timely diagnosis. They also share risk factors for severe disease, most notably smoking and diabetes mellitus, estimated to contribute ~7.6% and 3.1% to global TB cases.[32]

TB is reported to be a cause of non-HIV-associated CD4+ lymphopenia, with a recent meta-analysis demonstrating a low CD4:CD8 ratio in peripheral blood of TB patients.[34] On the other hand, increased levels of inflammation have been described in diabetic patients with TB, presumably secondary to hyperactive T-cell responses,[35] leading to lung damage, cavitation and enhanced transmission.[36] Whether these factors could predispose patients to SARS-CoV-2 infection is unknown. What is widely believed, however, is that people who have post-TB chronic lung disease may be at increased risk of more severe COVID-19.[37]

The mortality rate of HIV/TB co-infected patients is nearly double that of TB monoinfected patients (73 v. 37/100 000).[32] Approximately 3% of confirmed TB cases in SA are drug resistant, which is associated with a high mortality risk – 39% in one large retrospective cohort study.[38,39] Mortality of multidrug-resistant (MDR) TB has decreased dramatically since the introduction of injectable-free regimens containing bedaquiline,[40] although untreated HIV co-infection remains a significant risk factor for mortality in MDR TB.[38] The role of HIV co-infection is also clear in the scoring system proposed for predicting mortality in people admitted to intensive care with TB. The six factors are: (*i*) HIV co-infection with a CD4+ count <200 cells/μL; (*ii*) a raised creatinine level; (*iii*) diffuse parenchymal infiltrates/miliary pattern on chest radiograph; (*iv*) absence of TB

treatment on admission; (*v*) septic shock; and (*vi*) a low arterial partial pressure of oxygen/fractional inspired oxygen ratio.[41] People admitted to intensive care with PCP are at a dramatically increased risk of mortality if they are co-infected with TB (TB co-infected PCP admission relative to PCP only for 90-day mortality outcomes = adjusted odds ratio of 82).[42]

International experience

There is scant evidence to help clinicians understand the risks of COVID-19 in PLWH. The European AIDS Clinical Society and the British HIV Association have issued a joint statement affirming that there is currently no evidence to suggest that HIV infection alone predisposes to an increased risk of infection with SARS-CoV-2, or worse outcomes for COVID-19.[43] Looking at past coronavirus epidemics, there is a case report of an HIV-positive man infected with MERS coronavirus who had successful resolution of multilobar pneumonia following antiviral therapy with interferon and ribavirin.[44] Of note, this patient had a critically low CD4+ count of 58 cells/μL and was receiving prednisone when admitted for MERS, after recovering from a recent admission for PCP.[44] A current case report showed that a person who was HIV/HCV co-infected produced a weak SARS-CoV-2 antibody response in the context of persistent negative diagnostic polymerase chain reactions following hospital admission for fever and pneumonia.[45] Furthermore, a community survey of 1 178 PLWH in Wuhan, China, confirmed that their COVID-19 incidence was similar to the general population. In the 8/1 178 confirmed cases, age (and not CD4+ count, HIV viral load or ART) was associated with severe disease.[46] These data suggest that age and comorbidity are likely to be more important factors to consider than HIV *per se*.

A recent COVID-19 case series reported that 5/543 (0.92%; 95% confidence interval 0.39 - 2.14) patients admitted to a hospital in Spain were HIV-infected. Of these 5 patients, 4 were virologically suppressed, with CD4+ counts >400 cells/μL, and 1 patient, a late presenter, had a CD4+ count of 13 cells/μL with an HIV viral load of 45 500 copies/mL. Two patients had upper respiratory tract infections, and 3 had viral pneumonia. Of the latter, 2 required ventilatory support; one was a 31-year-old with advanced AIDS and the other was a 49-year-old with hypothyroidism as his only additional comorbidity. None of the patients died, although the 49-year-old was still in the ICU at the time of writing. The authors highlight the need to exclude other pathogens that could present in a similar way to SARS-CoV-2 in late presenters.[47]

There is even less information available on the impact of TB on COVID-19. The WHO has issued a statement that co-infected patients may be more susceptible to infection, with the presence of communal risk factors, namely diabetes mellitus and COPD, playing a major role.[37] A recent observational case-control study of 36 confirmed COVID-19 cases from China, available as a preprint, reported that TB appears to increase susceptibility to, and severity of, COVID-19. While these data still need to be peer reviewed and validated in larger studies, they underscore the need to routinely verify the TB infection status of COVID-19 patients.[48] Interestingly, during the SARS pandemic, two SARS-infected patients who recovered were reported to have developed active TB after recovering from the viral infection,[49] raising the question of whether SARS-CoV-2 infection will trigger TB reactivation in latent carriers. Epidemiological data from SA indicate that annual influenza epidemics are followed by a peak in incidence for pulmonary TB and invasive pneumococcal disease.[50] We may have to prepare for an increase in the incidence of TB or pneumococcal disease after COVID-19 has receded.

Conclusions

At this early stage of the pandemic, there is no evidence suggesting that HIV or TB infection on their own predispose to an increased risk of infection with SARS-CoV-2 or worse outcomes for COVID-19. However, both conditions have well-known poor prognostic indicators, and these should be considered when patients are assessed for eligibility for ICU admission. Persons at the highest risk of dying from COVID-19 in SA are expected to be those aged >60 years with multiple comorbidities. HIV-positive patients are likely to be most at risk when they are not yet on ART and have CD4+ counts <50 cells/μL. Co-infections with *Cryptococcus neoformans, P. jirovecii* or *Mycobacterium tuberculosis* would also be strong predictors of in-hospital mortality in severe COVID-19. Considering the current evidence and in light of the probable future demand on ICU care, we recommend that protocols for determining eligibility to ICU do not include the presence of HIV and TB *per se* as exclusion criteria, but rather make use of validated disease-specific scoring systems. As the pandemic unfolds in SA, it is important to stay updated with the emerging evidence and review this recommendation if the balance of evidence changes.

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1. Singh JA, Moodley K. Critical care triaging in the shadow of COVID-19: Ethics considerations. S Afr Med J 2020;110(5):355-359. https://doi.org/10.7196/SAMJ.2020.v110i5.14778
2. Boffa J, Mhlaba T, Sulis G, et al. COVID-19 and tuberculosis in South Africa: A dangerous combination. S Afr Med J 2020;110(5):341-342. https://doi.org/10.7196/SAMJ.2020.v110i5.14747
3. Chen XP, Li GH, Tang XP, Xiong Y, Chen XJ, Cao Y. Lack of severe acute respiratory syndrome in 19 AIDS patients hospitalized together. J Acquir Immune Defic Syndr 2003;34(2):242-243. https://doi.org/10.1097/00126334-200310010-00016
4. Ford N, Vitoria M, Rangaraj A, et al. Systematic review of the efficacy and safety of antiretroviral drugs against SARS, MERS or COVID-19: Initial assessment. J Int AIDS Soc 2020;23:e25489. https://doi.org/10.1002/jia2.25489/full
5. Dorward J, Gbinigie K; on behalf of the Oxford COVID-19 Evidence Service Team. Lopinavir/ritonavir: A rapid review of effectiveness in COVID-19. Centre for Evidence-Based Medicine, University of Oxford, 14 April 2020. https://www.cebm.net/covid-19/lopinavir-ritonavir-a-rapid-review-of-the-evidence-for-effectiveness-in-treating-covid/ (accessed 21 April 2020).
6. NICE (National Institute for Health and Care Excellence). COVID-19 rapid guideline: Critical care in adults. NICE guideline [NG159], 20 March 2020. www.nice.org.uk/guidance/ng159 (accessed 15 April 2020).
7. Wei-jie G, Wen-hua L, Yi Z, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A nationwide analysis. Eur Respir J 2020;55:2000547. https://doi.org/10.1183/13993003.00547-2020
8. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020;395(10229):1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3
9. Xu L, Yaqian M, Chen G. Risk factors for severe corona virus disease 2019 (COVID-19) patients : A systematic review and meta analysis. MedRxiv 2020 (epub 1 April 2020). https://doi.org/10.1101/2020.03.30.20047415
10. Márquez EJ, Chung C, Marches R, et al. Sexual-dimorphism in human immune system aging. Nat Commun 2020;11:751. https://doi.org/10.1038/s41467-020-14396-9
11. Montgomery RR, Murray KO. Risk factors for West Nile virus infection and disease in populations and individuals. Expert Rev Anti Infect Ther 2015;13(3):317-325. https://doi.org/10.1586/14787210.2015.1007043
12. Dawood H, Hassan-Moosa R, Zuma NY, Naidoo K. Mortality and treatment response amongst HIV-infected patients 50 years and older accessing antiretroviral services in South Africa. BMC Infect Dis 2018;18:168. https://doi.org/10.1186/s12879-018-3083-z
13. Martínez A, Soldevila N, Romero-Tamarit A, et al. Risk factors associated with severe outcomes in adult hospitalized patients according to influenza type and subtype. PLoS ONE 2019;14(1):e0210353. https://doi.org/10.1371/journal.pone.0210353
14. Balistreri CR, Candore G, Accardi G, Colonna-Romano G, Lio D. NF-κB pathway activators as potential ageing biomarkers: Targets for new therapeutic strategies. Immun Ageing 2013;10(1):24. https://doi.org/10.1186/1742-4933-10-24
15. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020 (epub 13 March 2020). https://doi.org/10.1001/jamainternmed.2020.0994
16. Guan WJ, Ni ZY, Hu Y, et al.; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-1720. https://doi.org/10.1056/NEJMoa2002032

17. Di Mascio M, Sereti I, Matthews LT, et al. Naive T-cell dynamics in human immunodeficiency virus type 1 infection: Effects of highly active antiretroviral therapy provide insights into the mechanisms of naive T-cell depletion. J Virol 2006;80(6):2665-2674. https://doi.org/10.1128/jvi.80.6.2665-2674.2006
18. Sokoya T, Steel HC, Nieuwoudt M, Rossouw TM. HIV as a cause of immune activation and immunosenescence. Mediators Inflamm 2017;2017:6825493. https://doi.org/10.1155/2017/6825493
19. Benito N, Moreno A, Miro JM, Torres A. Pulmonary infections in HIV-infected patients: An update in the 21st century. Eur Respir J 2012;39:730-745 https://doi.org/10.1183/09031936.00200210
20. Joint United Nations Programme on HIV/AIDS (UNAIDS). South Africa country profile. https://www.unaids.org/en/regionscountries/countries/southafrica (accessed 14 April 2020).
21. Lilian RR, Rees K, Mabitsi M, McIntyre JA, Struthers HE, Peters RPH. Baseline CD4 and mortality trends in the South African human immunodeficiency virus programme: Analysis of routine data. South Afr J HIV Med 2019;20(1):a963. https://doi.org/10.4102/sajhivmed.v20i1.963
22. Cornell M, Johnson LF, Schomaker M, et al. Age in antiretroviral therapy programmes in South Africa: A retrospective, multicentre, observational cohort study. Lancet HIV 2015;2:e368-e675. https://doi.org/10.1016/S2352-3018(15)00113-7
23. George S, McGrath N, Oni T. The association between a detectable HIV viral load and non-communicable diseases comorbidity in HIV positive adults on antiretroviral therapy in Western Cape, South Africa. BMC Infect Dis 2019;19:348. https://doi.org/10.1186/s12879-019-3956-9
24. Van Heerden A, Barnabas RV, Norris SA, Micklesfield LK, van Rooyen H, Celum C. High prevalence of HIV and non-communicable disease (NCD) risk factors in rural KwaZulu-Natal, South Africa. J Int AIDS Soc 2017;20(2):e25012. https://doi.org/10.1002/jia2.25012
25. Elf JL, Variava E, Chon S, et al. Prevalence and correlates of smoking among people living with HIV in South Africa. Nicotine Tob Res 2018;20(9):1124-1131. https://doi.org/10.1093/ntr/ntx145
26. Centers for Disease Control and Prevention. COVID-19: People who are at higher risk for severe illness. https://www.cdc.gov/coronavirus/2019-ncov/specific-groups/people-at-higher-risk.html (accessed 22 March 2020).
27. Cohen C, Walaza S, Moyes J, et al. Epidemiology of severe acute respiratory illness (SARI) among adults and children aged ≥5 years in a high HIV-prevalence setting, 2009 - 2012. PLoS ONE 2015;10(2):e011776. https://doi.org/10.1371/journal.pone.0117716
28. Cornell M, Johnson LF, Wood R, et al. Twelve-year mortality in adults initiating antiretroviral therapy in South Africa. J Int AIDS Soc 2017;20(1):21902. https://doi.org/10.7448/IAS.20.1.21902
29. Long LC, Fox MP, Sauls C, Evans D, Sanne I, Rosen SB. The high cost of HIV-positive inpatient care at an urban hospital in Johannesburg, South Africa. PLoS ONE 2016;11(2):e0148546. https://doi.org/10.1371/journal.pone.0148546
30. Mkoko P, Raine RI. HIV-positive patients in the intensive care unit: A retrospective audit. S Afr Med J 2017;107(10):877-881. https://doi.org/10.7196/SAMJ.2017.v107i10.12298
31. Koegelenberg CFN, Bulaya T, Balkema CA, Taljaard JJ, Irusen EM. Validation of a severity-of-illness score in HIV-positive patients requiring intensive care unit admission for mechanical ventilation. Q J Med 2016;109(6):434-435. https://doi.org/10.1093/qjmed/hcw061
32. World Health Organization. Global Tuberculosis Report 2019. Geneva: WHO, 2019. https://tbsouthafrica.org.za/sites/default/files/WHO%20Global%20Tuberculosis%20Report%202019.pdf (accessed 16 April 2020).
33. South African Community Rights and Gender Assessment. Exploring the impact of gender, key population membership and the legal environment on TB vulnerability, treatment access and quality of care. http://www.stoptb.org/assets/documents/communities/CRG/TB%20CRG%20Assessment%20South%20Africa.pdf (accessed 16 April 2020).
34. Yin Y, Qin J, Dai Y, Zeng F, Pei H, Wang J. The CD4+/CD8+ ratio in pulmonary tuberculosis: Systematic and meta-analysis article. Iran J Public Health 2015;44(2):185-193.
35. Bastos HN, Osório NS, Gagneux S, Comas I, Saraiva M. The troika host-pathogen-extrinsic factors in tuberculosis: Modulating inflammation and clinical outcomes. Front Immunol 2018;8:1948. https://doi.org/10.3389/fimmu.2017.01948
36. Sia JK, Rengarajan J. Immunology of *Mycobacterium tuberculosis* infections. Microbiol Spectr 2019;7(4). https://doi.org/10.1128/microbiolspec.GPP3-0022-2018
37. World Health Organization. Information Note: Tuberculosis and COVID-19. 11 May 2020. https://www.who.int/docs/default-source/documents/tuberculosis/infonote-tb-covid-19.pdf (accessed 30 May 2020).
38. Chingonzoh R, Manesen MR, Madlavu MJ, et al. Risk factors for mortality among adults registered on the routine drug resistant tuberculosis reporting database in the Eastern Cape Province, South Africa, 2011 to 2013. PLoS ONE 2018;13(8):e0202469. https://doi.org/10.1371/journal.pone.0202469
39. Ismail N, Ismail F, Omar SV, et al. Drug resistant tuberculosis in Africa: Current status, gaps and opportunities. Afr J Lab Med 2018;7(2):781. https://doi.org/10.4102/ajlm.v7i2.781
40. Schnippel K, Ndjeka N, Maartens G, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: A retrospective cohort study. Lancet Respir Med 2018;6(9):699-706. https://doi.org/10.1016/S2213-2600(18)30235-2
41. Koegelenberg CFN, Balkema CA, Jooste Y, Taljaard JJ, Irusen EM. Validation of a severity-of-illness score in patients with tuberculosis requiring intensive care unit admission. S Afr Med J 2015;105(5):389-392. https://doi.org/10.7196/SAMJ.9148
42. Chiliza N, du Toit M, Wasserman S. Outcomes of HIV-associated pneumocystis pneumonia at a South African referral hospital. PLoS ONE 2018;13(8):e0201733. https://doi.org/10.1371/journal.pone.0201733
43. British HIV Association. Coronavirus (COVID-19) and HIV – responses to common questions from the British HIV Association (BHIVA). 19 March 2020. https://www.bhiva.org/coronavirus-and-HIV-responses-to-common-questions-from-BHIVA (accessed 10 April 2020).
44. Shalhoub S, AlZahrani A, Simhairi R, Mushtaq A. Successful recovery of MERS CoV pneumonia in a patient with acquired immunodeficiency syndrome: A case report. J Clin Virol 2015;62:69-71. https://doi.org/10.1016/j.jcv.2014.11.030
45. Zhao J, Liao X, Wang H, et al. Early virus clearance and delayed antibody response in a case of COVID-19 with a history of co-infection with HIV-1 and HCV. Clin Infect Dis 2020;ciaa408. https://doi.org/10.1093/cid/ciaa408
46. Guo W, Ming F, Dong Y, et al. A survey for COVID-19 among HIV/AIDS patients in two districts of Wuhan, China. Available at SSRN (epub 13 March 2020). https://doi.org/10.2139/ssrn.3550029
47. Blanco JL, Ambrosioni J, Garcia F, et al.; on behalf of the COVID-19 in HIV Investigators. COVID-19 in patients with HIV: Clinical case series. Lancet HIV 2020;7:e314-e316. https://doi.org/10.1016/S2352-3018(20)30111-9
48. Liu Y, Bi L, Chen Y, et al. Active or latent tuberculosis increases susceptibility to COVID-19 and disease severity. medRxiv 2020 (epub 16 March 2020). https://doi.org/10.1101/2020.03.10.20033795
49. Liu W, Fontanet A, Zhang PH, et al. Pulmonary tuberculosis and SARS, China. Emerg Infect Dis 2006;12(4):707-709. https://doi.org/10.3201/eid1204.050264
50. Dangor Z, Izu A, Moore DP, et al. Temporal association in hospitalizations for tuberculosis, invasive pneumococcal disease and influenza virus illness in South African children. PLoS ONE 2014;9(3):e91464. https://doi.org/10.1371/journal.pone.0091464

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