

Implications of COVID-19 in high burden HIV/TB countries: A systematic review of evidence

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Abstract

Background

The triple burden of COVID-19, tuberculosis and human immunodeficiency virus is one of the major global health challenges of the 21st century and in the future. In high burden HIV/TB countries, the spread of COVID-19 among people living with HIV is a well-founded concern. A thorough understanding of HIV/TB and COVID-19 pandemics is important as the three diseases interact. This may clarify HIV/TB/COVID-19 as a newly related field and play an important role in the present and future management of the co-infections. However, several gaps are remaining in the knowledge of the burden of COVID-19 on patients with TB and HIV, the diagnosis, and management of these patients. The study was conducted to review different studies on SARS-CoV, MERS-CoV or COVID-19 associated with HIV/TB co-infection or only TB and to understand the interactions between HIV, TB and COVID-19 and its implications on the burden of the COVID-19 among HIV/TB co-infected or TB patients, screening algorithm and clinical management.

Methods

We conducted electronic search of potential eligible studies published in English in the Cochrane Controlled Register of Trials, PubMed, Medrxiv, Google scholar and Clinical Trials Registry databases. We included case studies, case series and observational studies published between January, 2002 and March, 2020 in which SARS-CoV, MERS-CoV and COVID-19 co-infected to HIV/TB or TB were managed in adult patients. We screened titles, abstracts and full articles for eligibility. As we anticipated heterogeneity in the literature, results were reported narratively.

Results

After removing 69 duplicates, 24 out of 246 articles were assessed for eligibility, of which 9 studies were included for qualitative analysis. Among them, we included two case reports, four case series, one case-control and two retrospective observational studies. The studies have shown that TB may occur during or after SARS-CoV. In terms of severity, the proportion of severe/critical SARS, MERS and COVID cases with TB co-infection was higher than in patients with mild/moderate stages ($P = 0.0008$).

Conclusion

SARS/MERS-CoV/COVID-19 associated to HIV/TB or TB subjects had a higher risk of developing severe/critical than mild/moderate SARS/MERS-CoV/COVID-19. Diagnostic algorithms and clinical management were suggested for efficiently improving COVID-19/HIV/TB co-infections outcomes.

1. Background

The triple burden of COVID-19, tuberculosis (TB) and human immunodeficiency virus (HIV) is one of the major global health challenges of the 21st century and beyond. In the last two decades, three major coronavirus epidemics have been reported worldwide. Those epidemics are caused by different agents: severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 and the current of SARS-CoV-2 outbreak, known as COVID-19 [1]. In 2002, SARS-CoV originated in Guangdong province, China, which spread to 37 countries, and the subsequent global epidemic was associated with 8,096 cases and 774 deaths [2]. Ten years later, the MERS-CoV spread to 27 countries, causing 2,494 infected cases and 858 deaths worldwide [2–3]. The novel coronavirus currently known as (2019-nCoV) was identified and is the third highly pathogenic CoV detected, with a fatality rate varying across countries and ranges of age. In addition, the 2019-nCoV transmissibility is higher, the 2019-nCoV mean R_0 (R_0 is used to measure virus transmissibility) ranged from 3.3 to 5.5, and it appeared higher than that of SARS-CoV (2–5) and MERS-CoV (2.7–3.9) [2, 4, 5–6]. An estimated 6,416,828 people have been infected and 382,867 have died from December 2019 to 04 June 2020, yielding a fatality rate of 5.96% worldwide [7].

HIV, TB and newly Emerging Infectious Diseases such as Coronavirus epidemics are expected to overlap in high HIV and TB burden countries. The intersecting coronavirus, HIV and TB epidemics in countries with a high disease burden of both infections pose several public health challenges. In fact, TB is the leading immune-suppressing infection and the most common cause of death among HIV-infected patients [8]. Worldwide, there were 37.9 million [32.7 million–44.0 million] people living with HIV and 1.7 million [1.4 million–2.3 million] people became newly infected with HIV at the end of 2018 [9]. WHO reports that people living with HIV are 20 times more likely to develop TB than their counterparts [10]. It is estimated that 1,1 million people worldwide live with TB and HIV, 80% of whom live in sub-Saharan Africa [11]. The growing incidence of TB in Africa since HIV is the most significant factor of people living with HIV/AIDS over the last ten years [12]. In post-mortem, the overall prevalence of TB in adults and children was huge and accounted for almost 40% of HIV-related facility-based deaths in adults in resource-limited countries [13]. This is greater than the WHO/UNAIDS estimate that overall TB accounts for approximately 25% of HIV/AIDS related deaths worldwide [13]. How COVID-19 will manifest itself in persons co-infected with HIV/TB is still uncertain [14]. Populations infected with HIV and TB, those with undiagnosed pulmonary TB (PTB), drug-resistant tuberculosis or complex presentations such as disseminated types and those who have only started PTB treatment may be at elevated risk for severe responses if they are infected with COVID-19 [14]. In the future, lung lesions associated with COVID-19 may increase the risk of PTB, which induces a true vicious circle between HIV-TB-COVID-19. TB incidence is also anticipated to increase in high burden HIV/TB countries including sub-Saharan countries with high COVID-19 burden. While COVID-19 continues to spread across the world, many areas face the risk of infection with SARS-CoV-2 and the obstacles and challenges to sustaining the continuum of HIV and TB treatment in high-burden HIV/TB countries are increasing [14]. Co-infection SARS-CoV/HIV/TB was previously scared because

SARS-CoV and MERS-CoV pandemics did not occur in high burden countries of HIV/TB. Since December 2019, COVID-19 is spreading very fast, with the high HIV/TB burden countries not spared from the pandemic and the number of new COVID-19 cases expected to rise in the next few months. The intersecting coronavirus, TB and HIV epidemics in sub-Saharan African countries where HIV and TB have the highest prevalence and incidence respectively, pose many challenges from the point of view of COVID-19/TB diagnostics, COVID-19/HIV/TB clinical management and post COVID-19 epidemic TB incidence.

In fact, the pathogenicity of COVID-19 could be accelerated in people living with HIV with compromised immunity [1]. Recent evidence has indicated a substantial association between coronavirus-related Lower Respiratory Tract Infections (LRTIs) and increased risk of death in immune-compromised individuals [15–16]. At the same time, the depletion of CD4 T cells in HIV and latent TB-infection disrupts the integrity and architecture of TB granulomas in the lung, thus facilitating progression to active TB [17, 18–19]. Similarly, TB promotes a microenvironment which facilitates the replication of HIV-1 via various mediators [20]. In fact, irreversible improvements in the lung architecture after SARS-CoV and/or TB play a significant role in both SARS-CoV and TB pathogenesis. Nonetheless, severe SARS-CoV can induce the development of rapid pulmonary fibrosis compared with mild courses of SARS-CoV disease usually advanced to organize phase diffuse alveolar damage (DAD) and eventual long-term deposition of fibrous tissue [21]. On the whole, SARS-CoV, HIV and TB co-infection may have deleterious consequences in all stages of SARS, HIV and TB because the triple pandemics are related in the immuno-pathological phase, constituting a vicious circle. A thorough understanding of the interactions between the three deadly pandemics is crucial. Reviewing the statistics in relation to high burden HIV/TB countries and recent World Health Organization data on COVID-19 in Sub-Saharan Africa; the following countries may expect an increased number of TB during or post COVID-19: South Africa, Nigeria, Cameroon, Kenya, Tanzania, Mozambique, Zambia, Zimbabwe and Uganda. The distribution of estimated new HIV cases (2018), new TB cases and relapses (2018) and COVID-19 cases (04 June 2020) are respectively 240,000; 227,999; 37,525 (South Africa), 130,000; 103,921; 11,166 (Nigeria), 23,000; 23,403; 6,752 (Cameroon), 46,000; 94,534; 2,216 (Kenya), 72,000; 74,692; 509 (Tanzania), 150,000; 92,381; 316 (Mozambique), 48,000; 35,071; 1,089 (Zambia), 38,000; 25,204; 222 (Zimbabwe) and 53,000; 55,835; 636 (Uganda) [7, 9–22]. The map was drawn to illustrate the distribution of COVID-19, HIV and TB in the nine high burden countries in Sub-Saharan African (Fig. 1). The aim of this study was to review different studies on SARS-CoV or MERS-CoV associated with HIV/TB co-infection or only TB and understanding the interactions between HIV, TB and COVID-19 and its implications on the burden of the COVID-19 among TB/HIV patients, screening algorithm and management.

2. Methods

The protocol was accepted by the international prospective register of systematic reviews (PROSPERO) (identification number: CRD42020181457). We conducted a systematic review of the literature to examine SARS-CoV or MERS-CoV associated with HIV/TB or TB co-infection. The justification to conduct a systematic review rather than a meta-analysis was the anticipated heterogeneity in the literature. We utilized formal methods of literature search, selection of articles for inclusion, abstraction of data and quality assessment, and synthesis of results to review the literature on to examine SARS-CoV or MERS-CoV associated with HIV/TB or TB co-infection. Furthermore, we computed the test of two proportions with STATA version 14 to compare SARS, MERS or COVID-19 disease severity compared to TB and/or HIV.

Inclusion Criteria

The inclusion criteria were studies published in English, from January 2020 until May 2020 that established co-occurrence of SARS-CoV, MERS-CoV, COVID-19 HIV and TB. Study designs included case reports, case series and observational studies (case-control, prospective and retrospective cohorts). Studies reporting COVID-19/HIV co-infection without screening PTB, those reporting other outcomes, letters to the editor, theoretical and incomplete studies were excluded. The outcomes include TB occurrence (before, during or after SARS, MERS or COVID-19), SARS, MERS or COVID-19 severity (mild, moderate, severe and critical stages) in case of HIV/TB or TB co-infections, the mean time of COVID-19 severe/critical stages occurrence and the fatality rate.

Search Strategy

We searched eligible studies from 01 January 2002 to 21 May 2020 through Medline (PubMed), Google Scholar, Medrxiv and the Cochrane Library without any study design, published in English. Additionally, the WHO COVID-19 database [23] and Clinicaltrials.gov were also used to search for ongoing and completed studies related to co-infection COVID-19/HIV/TB. The following terms were used "SARS-CoV", "MERS-CoV", "COVID-19", "SARS-CoV-2" AND "pulmonary tuberculosis", "PTB", "lung TB", "TB" AND "HIV/TB co-infection" AND "TB/SARS co-infection" AND "TB/MERS co-infection" "TB/Covid-19 co-infection" AND "HIV/SARS co-infection" AND "HIV/MERS co-infection" AND "HIV/COVID-19 co-infection". Relevant articles published in English that resulted from the searches, and references cited therein, were reviewed and duplicate studies were removed. After removing duplicates, we checked the title and abstract, and reviewed full-text, inclusions and exclusions were recorded following PRISMA guidelines presented in the form of a PRISMA flow diagram and detailed reasons recorded for exclusion. Critical appraisal checklists appropriate to each study design were applied and checked by a second team member.

3. Results

Electronic search identified 315 articles. Inclusions and exclusions are reported following PRISMA guidelines presented in the form of a PRISMA flow diagram (Fig. 2) with reasons for exclusion recorded (Table 1) as follows: 59 duplicates were removed; after reading the titles of 246 articles, 207 articles were removed. Among 39 records screened, 24 full text studies were assessed for eligibility. Fifteen articles were excluded for other reasons, including incomplete and irrelevant articles. Nine studies were included for qualitative analysis, of which two were case reports, four case series, one case-control

and two retrospective observational studies (Table 2). Each article that met selection criteria was fundamentally assessed for Author/Country, Population/Study design, Exposures, Comparators, Treatments, TB occurrence and SARS/MERS/COVID-19 severity and Fatality rate.

Table 1
Description of studies excluded in review

Author/Country	Population/Study design	Reasons for exclusion
Shalhoub 2015 Saudi Arabia	A patient with MERS-CoV/HIV co-infection/case study	TB status was not reported
Bogorodckaya 2020 Russia	three TB patients co-infected with COVID-19/ case study	Cases were incompletely reported.
Wang 2020 China	A patient with COVID-19/HIV co-infection/case report	TB status was not reported
Zhu 2020 China	A patient with COVID-19/HIV co-infection/case report	TB status was not reported
Zhao 2020 China	A patient with COVID-19/HIV/HCV co-infection/ case report	TB status was not reported
Baluku 2020 Uganda	A patient with COVID-19/HIV co-infection /case report	TB status was not reported
Blanco 2020 Spain	Five cases of COVID-19/HIV co-infection/ clinical case series	None reported TB status
Riva 2020 Italy	Three cases with COVID-19/HIV co-infection / case series	None reported TB status
Aydin 2020 Turkey	Three patients with COVID-19/HIV co-infection /case series	Outcomes of interest were not reported
Benkovic 2020 USA	Four patients with COVID-19/HIV Co-infection/Case series	Outcomes of interest were not reported
Haddad 2020 USA	A case with COVID-19/HIV co-infection/Case report	TB screening was not reported
Gervasoni 2020 Italy	47 COVID-19/HIV co-infected patients Retrospective study	Outcomes of interest were not reported
Wang 2020 China	A patient with COVID-19/HIV Co-infection/Case report	TB status was not reported
Härter 2020 Germany	33 COVID-19/HIV co-infected patients Retrospective study	Outcomes of interest were not reported
Wu 2020 China	Two patients with COVID-19/HIV co-infection/Case series	TB screening was not reported

Table 2
Description of studies included in review

Author/Country	Population/Study design	Exposures	Comparators	Treatments	TB occurrence	SARS/MERS/COVID-19 progression/time	Fatality rate
Liu 2006 China	-Three males of 48(case 1), 18 (case 2) and 20 years (case 3) old with confirmed SARS-CoV -case series	Pulmonary TB SARS-CoV	N/A	Corticosteroids mechanical ventilation Anti TB drugs	PTB diagnosed while case 1 was in the hospital. Case 2 and 3 were known TB on treatment.	Two patients developed mild SARS-CoV and one developed severe stage.	N/A
Low 2004 Singapore	-Two males of 54 and 39 years old with confirmed SARS-CoV -Case series	Latent TB SARS-CoV	N/A	intravenous immunoglobulin short course of high-dose corticosteroids Anti TB drugs	PTB developed after four and two months prior to SARS-CoV.	Both of them developed severe SARS-CoV	N/A
Wong 2004 Hong Kong	-30 years old male with confirmed SARS-CoV and HIV on ART -Case report	HIV Latent TB SARS-CoV	N/A	Abacavir 300 mg Efavirenz 600 mg Kaletra Tenofovir 300 mg Ribavirin 1200 mg prednisolone 25 mg	Diagnosed with PTB during hospitalization	Mild course SARS	N/A
Alfaraj 2017 Kingdom of Saudi Arabia	-13-year-old girl and A 30-year-old female with confirmed MERS-CoV -Case series	TB contact MERS-CoV	N/A	intensive care admission Anti TB drugs	Both patients initially had TB before MERS-CoV	The 13 years old had severe MERS-CoV. However, the disease severity was moderate with the 30 years old.	N/A
Singh 2020 India	76-year-old female with confirmed COVID-19 Case study	Latent TB COVID-19	N/A	hydroxychloroquine 400 mg twice daily in addition to antibiotics. Anti TB drugs	Diagnosed with TB during admission	Mild to moderate COVID-19	N/A
He 2020 China	All three patients were males with 26, 67 and 76 years -Case series	Previous TB status Latent TB COVID-19	N/A	Lopinavir + Ritonavir Arbidol Methyl prednisolone Antibiotics Traditional Chinese medicine Intravenous immunoglobulin Ventilatory support Antituberculosis	Past medical history of TB years ago for all the three patients	All of them had severe type of COVID-19 10 days after onset for the first case	N/A
Liu 2020 China	-36 confirmed COVID-19 cases Among which 13 were IGRA + ve to TB, mean age: 47 years -case-control study	Previous TB status Latent TB COVID-19	Case series study of 115 bacterial and 62 other viral pneumonia. Controls selected in the same setting.	N/A	3 had active TB (1 MDR-TB), and 5 were recovered TB. 3 with Old TB calcifications, previous TB, and 2 with latent TB.	-10 patients with COVID-19/TB co-infection developed severe/critical stages and 3 were from mild to moderate COVID-19 -severe/critical COVID-19: 3.4 days after initial symptom development.	N/A

Author/Country	Population/Study design	Exposures	Comparators	Treatments	TB occurrence	SARS/MERS/COVID-19 progression/time	Fatality rate
Zhang 2020 China	-140 confirmed COVID-19 cases, 2 of whom had secondary PTB -Retrospective study	N/A	Non-severe COVID-19	N/A	N/A	All the two patients developed severe COVID-19	N/A
Motta 2020 Italy, Belgium, Brazil, France, Russia, Singapore, Spain, Switzerland	- 20 confirmed TB and COVID-19 cases, median age 70 years Retrospective cohort study	Previous TB status Latent TB COVID-19 One patient with HIV	49 confirmed COVID-19 cases Retrospective cohort study(Cohort B)	Hydroxychloroquine Lopinavir/ ritonavir Azythromycin Empiric antibiotic Enoxaparine 4000 IU Dexamethasone Oxygen through non-rebreather, 15lt/min Anti TB drugs	-3 with previous TB diagnosed -8 (simultaneous diagnosis of COVID-10 and TB -11 had COVID-19 diagnosed between 7 and 75 days) after the TB diagnosis	-5 patients had severe COVID-19 -8 patients developed critical COVID-19 -Critical COVID-19: median of 9 (range 6–14) days after COVID-19 diagnosis	8 deaths: 7 patients had TB before COVID 1 patient had almost simultaneous COVID-19 and TB

3.1. Case reports

The twelve cases included six patients reported in China, two in Singapore and one patient in Hong Kong; two patients were reported in the Kingdom of Saudi Arabia and one patient was reported in India. The first case was 48 years (male), the second 18 years (male), the third 20 years (male) [24], the fourth 54 years (male), the fifth 39 years [25], the sixth 30 years (male) [26], the seventh 13 years (female), the eighth 30 years (female) [27], the ninth 76 years old (female) [28], the tenth 26 years (male), the eleventh 67 years (male) and the twelfth 76 years (male) [29]. Table 2 describes all cases. For further clarifications, cases were grouped as follows:

Previous PTB diagnosed with SARS-CoV or MERS-CoV

The second, third, seventh, eighth, tenth, the eleventh and twelfth cases were known to have a history of PTB (sputum smear–negative for acid-fast bacilli) and became infected with SARS-CoV (first, second cases, tenth, the eleventh and twelfth) or MERS-CoV(seventh and eighth cases). PTB diagnosis was made based on previous exposure to TB, relevant symptoms of typical PTB, chest radiographs suggestive of active disease. SARS-CoV or MERS-CoV was confirmed based on amplification of SARS-CoV/MERS-CoV RNA by reverse transcriptase–polymerase chain reaction (RT-PCR) from sputum. Both the second and third cases were managed with corticosteroids and anti TB drugs. Clinical management was not specified to the seventh and eighth cases; however anti TB drugs were administered. Lopinavir/r, Arbidol, methyl prednisolone, empirical antibiotics, traditional Chinese medicine and antituberculosis treatment were indicated to the tenth, eleventh and twelfth cases. Five out of seven had severe/critical COVID-19 and had a long recovery process.

Newly PTB diagnosed with SARS-CoV

The first, sixth and ninth cases were diagnosed with PTB (positive acid-fast bacilli smear on sputum samples) while they were admitted for SARS-CoV in the hospital and RT-PCR was used to confirm SARS-CoV. Only one case had severe COVID-19. The first case was managed with mechanical ventilation corticosteroids and anti TB drugs, the sixth with abacavir/efavirenz/kaletra/tenofovir/ribavirin, prednisolone and anti TB drugs and the ninth with hydroxychloroquine, empiric antibiotics and anti TB drugs. The first case developed severe SARS-CoV, however, the sixth and the ninth had mild to moderate SARS.

Previous SARS-CoV with newly PTB diagnosed

The fourth and the fifth cases were diagnosed with PTB with positive bacilli smear respectively four and two months after SARS-CoV. At day 80 of disease on convalescence, the fourth patient was positive for coronavirus IgG serum antibody and the fifth patient was positive for SARS coronavirus by PCR of an endotracheal tube test, as well as coronavirus IgM and IgG antibodies in the blood. Both of them had severe COVID-19 before developing PTB. Intravenous immunoglobulin and short course of high-dose corticosteroids were indicated during SARS course and anti TB drugs were administered during TB course. They remained well at follow-up.

3.2. Observational studies

We included three observational studies (a case control and two retrospective studies). The case control and the first retrospective studies were conducted in China [30–31] and the last retrospective cohort was undertaken in eight countries (Italy, Belgium, Brazil, France, Russia, Singapore, Spain, Switzerland) [32] (see Table 2). The case control included 36 cases of COVID-19, of which 13 (36.11%) had positive IGRA (Interferon Gamma Release Assay), three of which had active TB (1 MDR-TB) and 5 were retrieved from TB [30]. Old calcifications of TB were detected in 3 patients who had not previously been

diagnosed with TB on chest scans, and 2 patients had latent TB [30]. TB infection rates among COVID-19 patients were substantially higher than among patients with bacterial pneumonia (36.11% vs. 20%; P-value = 0.047) and patients with viral pneumonia (36.11% vs. 16.13%; p = 0.024), indicating that TB infection status is a particular risk factor for SARS-CoV-2 infection rather than for general pneumonia and TB co-infection associated with disease severity (severe/critical 78% vs mild/moderate cases 22%; P-value = 0.0049) [30]. Ten patients with COVID-19/TB co-infection developed severe/critical stages and three were from mild to moderate COVID-19 in this study, and the time of developing disease severity was 3.4 days after initial symptom development.

The first retrospective study involved 140 patients diagnosed with COVID-19, two (1.4%) of whom had PTB and both experienced severe/critical COVID-19 with a P-value of 0.17 relative to the mild/moderate COVID-19 group [31]. The last retrospective cohort included 69 patients infected with COVID-19, among whom 20 were co-infected with COVID / TB [32]. COVID-19 was confirmed by RT-PCR, and microscopy as well as medical imaging diagnosed TB. COVID-19 therapy was based on antivirals, steroids, anticoagulants, empiric antibiotics, maximum oxygen flow and ventilation. Among twenty COVID-19/TB co-infected patients, three had previous TB diagnosed; eight with simultaneous diagnosis of COVID-19 and TB, and eleven had COVID-19 diagnosed between 7 and 75 days after the TB diagnosis [31]. Eight patients with COVID-19/TB co-infection developed critical COVID-19 stage of them seven had TB before COVID-19 and had COVID-19 and TB almost simultaneously [32]. All eight died, including a 70-year-old co-infected with COVID-19 / HIV / TB. Critical COVID-19 median time after COVID-19 diagnosis was estimated from 6 to 14 days (median 9 days) [32].

This review identified a total of 46 SARS-CoV / MERS-CoV associated with people living with TB or HIV / TB (Table 2). They were stratified with PTB diagnosed with SARS-CoV or MERS-CoV, newly diagnosed PTB with SARS-CoV and previously diagnosed with newly diagnosed PTB with 63.64%, 31.81% and 4.55% respectively.

The proportion of severe/critical SARS, MERS and COVID-19 cases with HIV/TB or TB co-infection was higher than that in the mild/moderate stages (P = 0.0008). The onset of COVID-19 severe/critical stages the mean of 3.4 days [30] and the median of 9 days [32] for two observational studies and 10 days for a case study [29]. Only one observational study reported the fatality rate, meaning COVID-19/TB co-infection case fatality rate was 40% in this study.

4. Discussion

Reviewing the above case reports grouped in three, the interactions between SARS-CoV, HIV and TB have illustrated PTB may occur during SARS-CoV or after SARS. It is highly likely that both cases 4 and 5 acquired active pulmonary tuberculosis after contracting SARS, as both had laboratory-confirmed clinical syndromes associated with SARS, and both recovered well without anti-TB treatment, with initial biochemical and radiological improvement [24]. The analysis of cases found that SARS-CoV could induce a transient suppression of cellular immunity that further predisposed patients to exacerbated reactivation or new TB infection, as is the case with HIV. SARS-CoV and HIV may decrease conjunctly CD4 count and lymphocytes, adding high corticosteroids [24] as treatment for SARS-CoV in cases 4 and 5 may be TB precipitant factors. Following this, SARS-CoV patients may be more susceptible to active and latent TB during SARS-CoV infection as evidenced by the first, sixth and ninth cases or after SARS-CoV infection as in cases 4 and 5. It is important to realize that lung lesions due to SARS and/or TB may increase significantly the likelihood of SARS-CoV and TB.

The overall review included 46 cases among whom 31(67.4%) had severe/critical SARS, MERS or COVID-19, 15(32.6%) had mild to moderate. We computed two proportions between severe/critical and mild/moderate with STATA 14. The percentage of severe/critical SARS, MERS and COVID associated with TB was higher than those with mild/moderate stages (P= 0.0008). Among severe/critical stages, 60.86% had TB past medical history. These findings are a cautionary reminder to clinicians that TB infection status should be considered when treating COVID-19 patients in order to prevent rapid deterioration in patient health [30]. The onset of COVID-19 severe/critical stages varied between studies with the mean of 3.4 days [30] and the median of 9 days [32], this illustrated that the progression of COVID-19 disease may be faster and more severe [30]. The fatality rate of 40% among COVID-19/TB or HIV/TB co-infected patients should be considered with caution because only one study reported the fatality rate, with a poor study design and small sample size. However, COVID-19/TB or HIV/TB co-infections fatality seems to be higher than fatality rate of 5.96% worldwide [7]. Particular emphasis is placed on two cases with SARS-CoV/HIV and TB co-infection; given his immune-compromised condition, the first patient SARS-CoV/HIV and TB co-infection went on a relatively mild course and the second developed COVID-19 critical stage and died. The first SARS-CoV/HIV/TB case had mild SARS-CoV because of two possible reasons. Firstly, during the viraemic process, the antiretroviral therapy (ART) regime may have protective antiviral effects [26]. Kaletra was found to have some in-vitro anti-coronavirus activities [26]. Even though ART regimen was not given for the second case of SARS-CoV/HIV/TB, this case had multiple comorbidities including hepatitis B, metastatic prostate cancer and liver cirrhosis [32].

As shown above, SARS-CoV/HIV/TB co-infection is a new medical field that needs further attention and research in high burden HIV/TB countries more specifically in sub-Saharan Africa as the co-existence of those three pandemics may imply vulnerability to SARS-CoV infections and increase TB occurrence. Clear diagnostic algorithms, exploration of drug–drug interactions and clinical management should be addressed to improve SARS/HIV/TB outcomes.

5. Review Implications

TB, HIV and COVID-19 diagnostics and clinical management

Even though data are scarce, the analysis indicated that COVID-19/HIV/TB or COVID-19/TB co-infections may have poor treatment outcomes. This may be worsened in case TB is not diagnosed and treated early. Furthermore, COVID-19 can shadow TB in HIV-infected people or vice versa. For this reason, we suggest screening for both COVID-19 and TB in HIV-infected people with COVID-19 / TB symptoms during the COVID-19 pandemic in countries with high HIV / TB burden. HIV / COVID-19 co-infection requires a simple algorithm and management to boost TB outcomes.

5.1. TB diagnostic in COVID-19/HIV co-infection

Suspected cases of COVID-19 and TB show similar fever and/or respiratory symptoms (difficult respiration, coughing, chest pain, etc.). COVID-19 RT-PCR should be done in real-time for differential diagnosis of cases with unknown respiratory syndromes such as PTB [33]. Due to poor outcomes among COVID-19/HIV/TB or COVID-19/TB co-infections, we recommend COVID-19 real-time RT-PCR should be coupled with Xpert MTB/RIF assay. In suspected HIV/TB co-infected patients, Xpert MTB/RIF should be used first rather than traditional microscopy, culture and drug susceptibility testing (DST) [33]. Instead of collecting upper respiratory tract specimens, lower respiratory tract specimens, such as sputum, bronchoalveolar lavage, and tracheal aspirates should be collected in suspected COVID-19/HIV/TB or COVID-19/TB co-infected patients. COVID-19 real-time RT-PCR may last at least 24 hours. At the same time, the Xpert MTB / RIF assay detects *M. tuberculosis* and rifampicin resistance within less than two hours [34]. Xpert MTB/RIF is also a major advance in the diagnosis of TB, particularly for multidrug-resistant (MDR) TB and HIV-associated TB [34]. The Xpert MTB/RIF assay simultaneously detects *M. tuberculosis* and rifampicin resistance in less than two hours [34]. Furthermore, Xpert MTB/RIF is a major advance for TB diagnostic; especially for MDR-TB and HIV/TB co-infection [34]. The Xpert MTB / RIF assay's sensitivity to detect TB is superior to that of microscopy and comparable to that of solid culture, along with high specificity [35].

This is important to emphasize that possible causes of false negative COVID-19 real-time RT-PCR results in COVID-19/HIV co-infection may be identified in patients on protease inhibitors (PIs) based regimens. We also recommend systematic TB screening in COVID-19/HIV co-infection. The adapted algorithms to diagnose TB in confirmed COVID-19/HIV co-infected adults in high burden HIV/TB countries are described below:

Option 1: This algorithm includes an interrogatory about cough of any duration, fever, short breathing, sore throat, loss of weight, loss of appetite, nausea, hemoptysis and night sweat. Past medical history includes previously confirmed TB, previous TB contact, TB preventive therapies, HIV viral load and CD4 count. Xpert MTB/RIF assay should be indicated. If Xpert MTB/RIF assay is positive, start anti TB drugs.

Option 2: This algorithm includes symptoms and medical history of COVID-19, HIV and TB as described in option 1. Xpert MTB/RIF assay should be indicated. If Xpert MTB/RIF assay is negative, the culture associated with the chest X-ray should be requested. If abnormal chest X-ray suggestive of TB, start anti-TB drugs, in the meantime while waiting for culture results.

Option 3: This algorithm includes symptoms and medical history of COVID-19, HIV and TB as described in option 1. If Xpert MTB/RIF assay is negative and the X-ray is not suggestive of TB, the culture associated with an approved interferon-gamma release assays (IGRAs) should be performed. Current evidence indicates that IGRAs perform similarly to the tuberculin skin test (TST) at identifying HIV-infected individuals with TB [36]. However, the decision to use either test should be based on country guidelines and resource and logistical considerations. If IGRAs is positive, start anti TB drugs, in the meantime while waiting for culture results.

Option 4: This algorithm includes a history of previous COVID-19, previous contact or active TB, HIV positive, HIV viral load and CD4 count. All people with cough of any duration, fever, short breathing, sore throat, weight loss, hemoptysis, night sweat, arthralgia or myalgia should be investigated for TB. Xpert MTB/RIF assay coupled with COVID-19 IgG/IgM should be indicated. A recent study has found that the specificities of serum IgM and IgG to diagnose COVID-19 were both more than 90% when compared to molecular detection [37]. If the Xpert MTB/RIF assay is negative, see options 2 and 3.

5.2. Clinical management

5.2.1. Drug-drug interactions and clinical considerations

In the case of concurrent HIV and tuberculosis infection plus SARS-CoV-2 infection, additional drug might cause interaction complicating the integrated therapy. In fact, some pharmaceutical interventions found for COVID-19 treatment including Protease inhibitors (PIs) (atazanavir, lopinavir, ritonavir, duranavir, raltegravir, cobicistat), remdesivir, chloroquine, hydroxychloroquine, methylprednisolone, anticoagulants and carrimycin may interfere and interact to TB and/or HIV treatments in multiple ways. Although protease inhibitors (PIs) were developed to be selective inhibitors of HIV-1 replication, they have shown inhibitory activity against a wide variety of pathogens [38], including SARS-CoV. Lopinavir / ritonavir (LPV/r) has a moderate anti-SARS-CoV-2 antiviral activity which works against the 3CL protease virus [39-40]. A recent systematic review concluded that it is unclear whether LPV/r and other ART enhance clinical outcomes in severe symptomatic disease or prevent infection in patients at high- risk of COVID-19 based on the evidence available [41], as most of the studies included were case studies and also observational studies were low of power. Drug-drug interactions between PIs and rifampicin are known in HIV/TB co-infection. Studies have demonstrated that co-administration of PIs with rifampicin reduces PIs systemic concentration to less than 75% (cytochrome P 450 induction) [42-43]. This may compromise COVID-19 treatment. Remdesivir should also not associate to rifampicin in COVID-19/TB co-infection because of strong induction [44]. A recent review has reported that Chloroquine phosphate and Hydroxychloroquine showed favorable outcomes in the recovery of COVID-19 patients [45,46,47,48-49]. Both chloroquine and hydroxychloroquine are metabolized by hepatic cytochrome P450 enzyme 2D6 (CYP2D6) [50]. The most frequently involved in drug interactions are CYP3A4 and CYP2D6 [50]. The reduction in the efficacy of chloroquine when administered in conjunction with rifampicin may be due to the inducing effect of rifampicin on multidrug resistance associated protein (MRP) and development of CYP450 [51]. Additionally, high-dose chloroquine is more toxic than lower dose [44]. This is why; studies should clarify chloroquine and hydroxychloroquine dose adjustment in COVID-19/TB co-infection. Based on the above, dose adjustments should be taken into consideration in case PIs, chloroquine, hydroxychloroquine and remdesivir are administered with rifampicin. Another option is to shift rifampicin to rifabutin or adapted TB regimens without rifampicin. In contrast, clofazimine used in MDR-TB is a strong inhibitor of PIs, known substrates [52]. Then, caution should be taken when administered with PIs. Another TB drug with in vitro effect used in COVID-19 is carrimycin. Its use in COVID-19 may mitigate active TB and biases the TB diagnostic.

A study showed an association between corticosteroid use and lower mortality in COVID-19 patients [49]. Using a glucocorticoid in the early stages of the prognosis for a brief period of time could minimize the inflammation, but longer-term use could result in the risk of HIV and/or TB activation and even lack of treatment with TB. Careful use of corticosteroids with low-to-moderate doses in short courses is advised [49]. Besides, fibrosis and extensive pulmonary pathology secondary to TB and COVID-19, as defined in the introduction, can reduce drug penetration at the lung sites. It is a significant risk factor for bad TB outcomes in the event of potential infection or reactivation of TB [53]. This may also induce MDR-TB or extensively drug-resistant tuberculosis (XDR-TB) or recurrent pneumonia. Then, special considerations should be taken into account in the clinical management of COVID-19/TB lung fibrosis. Some RCTs are currently underway evaluating the safety and effectiveness of antifibrotic therapies on COVID-19 lung fibrosis [54].

Besides, liver and kidneys toxicities related to severe and critical COVID-19 need a tailored therapeutic approaches in HIV/TB co-morbidities due to some hepatotoxicity and nephrotoxicity of some HIV/TB drugs such as streptomycin, isoniazid, rifampicin, pyrazinamide, tenofovir disoproxil, atazanavir/ritonavir, lopinavir/ritonavir as well as HIV induced nephropathy and hepatitis associated to HIV.

5.2.1. Clinical management approach

Mild to Moderate COVID-19 associated with HIV/TB co-infection: Hospitalized in a special unit named COVID-19/TB units as risk patients. Start COVID-19 antiviral drugs, start or continue anti TB drugs according to the national guidelines and continue ART. Preferred COVID-19 antivirals are oseltamivir, chloroquine or hydroxychloroquine associated to LV/r or darunavir/cobicistat and Azithromycin may be indicated [49]. Chloroquine: 1 gm PO once on Day 1, then 500 mg PO once daily for 4–7 days, Hydroxychloroquine: 800 mg PO once on Day 1, then 400 mg PO once daily for 4–7 days [44] or lopinavir 400 mg/ritonavir 100 mg PO twice [44]. All of them should be associated with Azithromycin [44]. Drugs interactions should be reviewed as described above. Initial evaluation includes a chest x-ray, complete blood count (CBC), liver transaminases, renal function, inflammatory markers such as C-reactive protein (CRP), D-dimer, and ferritin, while not part of standard care, may have prognostic value.

Severe COVID-19 associated to HIV/TB co-infection: Hospitalized in COVID-19/TB unit as high-risk patients. Drug therapy and ventilator support are milestones. Clinicians can refer to COVID-19 antiviral therapy and immune-based therapy [44]. Start COVID-19 antiviral drugs as described in mild to moderate COVID-19, add immune-based therapy, initiate or continue anti TB drugs according to national guidelines and ART should be discontinued based on drug interactions and clinical considerations as described above. Remdesivir is recommended in severe/critical COVID-19 however this cannot be administered with rifampicin [44]. Short period low-dose corticosteroid therapy is preferred over no corticosteroid therapy in HIV/TB co-infection and also the patients are in the intensive care unit [44]. Anticoagulant therapy mainly with low molecular weight heparin should be initiated early as this appears to be associated with better prognosis in severe COVID-19 patients [55]. Ventilator support, oxygen through a face mask and symptomatic therapy should be indicated. Initial evaluation includes chest x-ray/CT-scan and CBC should be indicated. Liver transaminases and renal function should be monitored regularly in consideration of COVID-19/HIV/TB drug-drug interactions and clinical considerations. Measurements of inflammatory markers, D-dimer, and ferritin are part of the management.

Critical COVID-19 associated to HIV/TB co-infection: Hospitalized in COVID-19/TB unit with ICU as high-risk patients. Infection control and testing, ventilator support, hemodynamic, and drug therapy are milestones [44]. Apply COVID-19, TB and HIV management as described in severe COVID-19. Short period low-dose corticosteroid therapy, anticoagulant therapy and norepinephrine as the first-choice vasopressor are recommended [44]. Anticoagulant therapy mainly with low molecular weight heparin appears to be associated with better prognosis in severe/critical COVID-19 patients with markedly elevated D-dimer [55]. There is strong evidence against the use of hydroxyethyl starches for the acute reanimation of adults with COVID-19 in shock [56]. In adults with COVID-19 in shock, if the peripheral oxygen saturation (SpO₂) is < 92%, the review suggested starting supplemental oxygen if SpO₂ is < 90% [56]. Initial evaluation includes chest x-ray/CT-scan and CBC should be indicated. Liver transaminases and renal function should be monitored regularly in consideration of COVID-19-HIV and TB drug-drug interactions and clinical considerations. Inflammatory markers, D-dimer, cardiac enzymes and ferritin monitoring should be part of the management.

Previous history of COVID-19 in HIV/TB co-infection: This group of cases should be treated as HIV/TB co-infection as described in different national guidelines. Therefore, emphasis should be put on the risk of severe lung fibrosis that may induce MDR-TB or XDR-TB. Ongoing trials are evaluating the safety and effectiveness of antifibrotic therapy in COVID-19 severe and critical patients [54]. This could be beneficial in COVID-19-HIV and TB co-infected cases due to their synergic roles in inducing pulmonary fibrosis.

6. Conclusion

This is the first systematic review of the burden of COVID-19-HIV and TB co-infection in high burden HIV/TB countries. This review highlighted special considerations that should be taken in high burden HIV and TB countries at present and in the future. The review showed that PTB may occur concomitantly with COVID-19 or thereafter. Pulmonary TB was linked with SARS/MERS-CoV/COVID-19 severity. Furthermore, the pulmonary TB levels among COVID-19 patients were significantly higher than among patients with bacterial pneumonia and patients with viral pneumonia [28].

At present, COVID-19, TB and HIV could result in poorer treatment outcomes, especially if TB treatment is interrupted or TB diagnostic is delayed because COVID-19/TB co-infected people are in high risk of developing severe/critical COVID-19. In addition, factors related to co-infection with PTB and TB-HIV may complicate clinical suspicion for either COVID-19 or PTB and require clinical vigilance [57].

This review addressed the diagnostic algorithms, drug-drug interactions and clinical management of COVID-19/HIV/TB co-infections. The diagnostic algorithm suggests systematic screening and fast-tracking TB tests in COVID-19/HIV co-infection. Treatment specialists should review the dosages for patients with COVID-19/HIV/TB such as hydroxychloroquine, chloroquine, remdesivir and PIs. Adjusting the dosage of COVID-19 antiviral drugs is required in

association with rifampicin-based regimens. Further, nephrotoxic and hepatotoxic anti-TB drugs should be avoided in COVID-19 severe/critical stages. Moreover, ART should be discontinued in severe/critical COVID-19 stages.

Knowing that COVID-19 and TB may induce the development of severe lung disease leading to pulmonary fibrosis in the future, further studies are needed with cohorts of HIV/COVID-19 co-infected individuals. More research is needed to explore the effect of lung fibrosis related to COVID-19 in high burden HIV/TB countries. This pressing priority will shed light on the utility of prophylaxis treatments in preventing post-COVID-19 related LRTIs in high burden HIV/TB countries.

7. Abbreviations

COVID-19: Coronavirus Disease 19; DAD: Diffuse Alveolar Damage; IGRA: Interferon Gamma Release Assay; HIV: Human Immunodeficiency Virus; LRTIs: Lower Respiratory Tract Infections; MERS-CoV: Middle East respiratory syndrome coronavirus; MDR-TB: Multidrug-resistant TB; NIH: National Institute of Health; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PTB: Pulmonary TB; RIF: rifampicin; RT-PCR: Real-time polymerase chain reaction; SARS-CoV: severe acute respiratory syndrome coronavirus; TB: tuberculosis; UNAIDS: The joint United Nations Programme on HIV/AIDS; USAID: U.S. Agency for International Development; WHO: World Health Organization; XDR-TB: extensively drug-resistant tuberculosis

8. Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

All data and material are presented in this review.

Competing interests

Authors do not have any competing interests to declare.

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Authors' contributions

JLT and PSN conceived and designed the review. JLT and ATB played a full role in identifying eligible studies, assessing studies quality, assisting with data extraction, analysis and interpretation. JLT drafted the manuscript with input from all authors. PSN, ATB, SCS, AO, JU, THZ and JI assisted in editing and reviewing the manuscript. All authors review and approved the final version of the manuscript to be submitted for publication.

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Figures

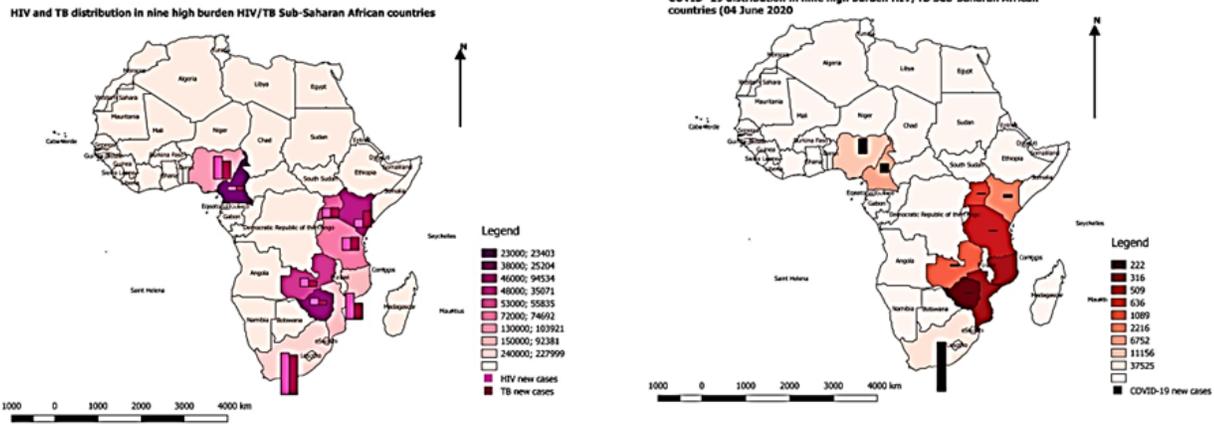


Figure 1

Distribution of COVID-19, HIV and TB in the nine high burden countries in Sub-Saharan African

Flow Diagram

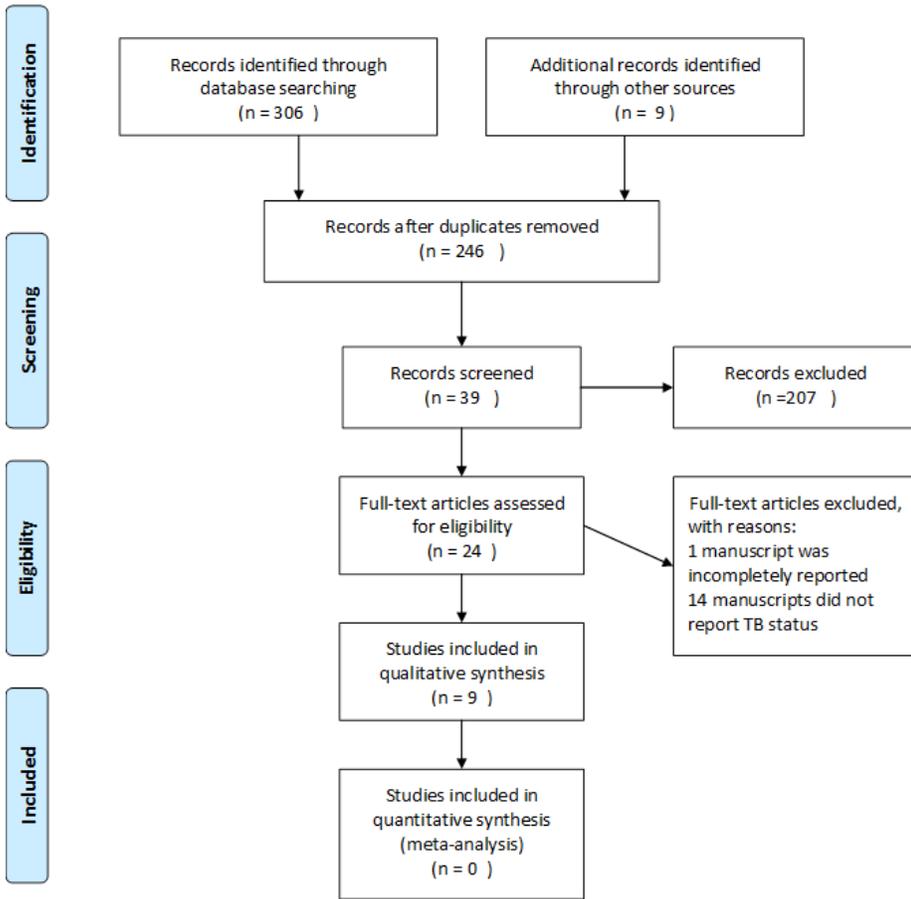


Figure 2

Study Flow Chart