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Minimizing the impact of the triple burden of COVID-19, tuberculosis and HIV on health services in sub-Saharan Africa

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ABSTRACT

In this perspective, we discuss the impact of COVID-19 on tuberculosis (TB)/HIV health services and approaches to mitigating the growing burden of these three colliding epidemics in sub-Saharan Africa (SSA). SSA countries bear significantly high proportions of TB and HIV cases reported worldwide, compared to countries in the West. Whilst COVID-19 epidemiology appears to vary across Africa, most countries in this region have reported relatively lower-case counts compared to the West. Nevertheless, the COVID-19 pandemic has added an additional burden to already overstretched health systems in SSA, which, among other things, have been focused on the longstanding dual epidemics of TB and HIV. As with these dual epidemics, inadequate resources and poor case identification and reporting may be contributing to underestimations of the COVID-19 case burden in SSA. Modelling studies predict that the pandemic-related disruptions in TB and HIV services will result in significant increases in associated morbidity and mortality over the next five years. Furthermore, limited empirical evidence suggests that SARS-CoV-2 coinfections with TB and HIV are associated with increased mortality risk in SSA. However, predictive models require a better evidence-base to accurately define the impact of COVID-19, not only on communicable diseases such as TB and HIV, but on non-communicable disease comorbidities. Further research is needed to assess morbidity and mortality data among both adults and children across the

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African continent, paying attention to geographic disparities, as well as the clinical and socio-economic determinants of COVID-19 in the setting of TB and/or HIV.

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Epidemiology of COVID-19, tuberculosis and HIV

As of January 09, 2021, Africa reported 3,392,117 COVID-19 cases with 83,787 deaths [2.4% case fatality rate (CFR)] in Africa, to the World Health Organization (*Coronavirus (COVID-19), n.d.-a*). The highest number, and roughly 40% of confirmed cases (1, 214, 176 cases) were from South Africa, currently the epicentre of the pandemic on the continent (*Coronavirus (COVID-19), n.d.-b*). A year into the pandemic, Africa has consistently recorded lower COVID-19 incidence and mortality compared to Europe and North America (Nachega et al., 2020a,b). Several explanations have been put forward for this unexpected finding: early and strong political commitment and implementation of public health measures, robust community engagement, and coordinated public health responses and messaging. Other postulated but yet-to-be proven factors include a less COVID-19-vulnerable younger population, and cross-immunity from parasitic diseases and/or other circulating coronaviruses (Coker et al., 2020; Massinga Loembé et al., 2020; Mehtar et al., 2020; Musa et al., 2021).

However, as it is for TB (*Global Tuberculosis Report 2020, n.d.*), inadequate case identification and reporting may be contributing to an underestimation of the COVID-19 burden in sub-Saharan Africa (SSA); mortality surveillance systems in SSA may also not be optimal. In addition, country-level data on COVID-19 epidemiology and outcomes among African children is scanty (Coker et al., 2020). Furthermore, there is little data on the prevalence, clinical manifestations, and outcomes of SARS-CoV-2 coinfection with chronic infectious diseases of public health importance such as TB and HIV, which are highly prevalent in SSA (Coker et al., 2020). While SSA reported relatively lower case counts during the first COVID-19 wave (before August 2020), the pandemic added an additional burden to already overstretched health systems addressing the longstanding dual epidemics of TB and HIV. As with TB and HIV, infrastructure, commodity and human resources for health disparities may be contributing to underestimations of the true COVID-19 case burden and mortality in SSA (Musa et al., 2021).

According to the WHO, an estimated 815,000 people living with HIV (PLHIV) worldwide fell ill with TB in 2019; these persons comprised 8.2% of all active TB cases in that year (*Global Tuberculosis Report 2020, n.d.*). Indeed, TB is the leading cause of death among PLHIV, accounting for some 270,000 people who died from HIV-associated TB in 2019, and about a third of AIDS-related deaths (*Global HIV & AIDS Statistics – 2020 Fact Sheet, n.d.*; *Global Tuberculosis Report 2020, n.d.*). In addition to TB disease, PLHIV bear a high burden of drug-resistant TB strains, thus, if diagnosis is delayed, there is increased risk of mortality from multidrug-resistant and extensively drug-resistant TB in this population (Karim and Karim, 2020). SSA countries bear high burdens of TB and HIV: in 2019, people in Africa accounted for 73% of TB/HIV coinfection cases and 81% of all TB/HIV deaths (*Global HIV & AIDS Statistics – 2020 Fact Sheet, n.d.*). At the country level, South Africa and Nigeria rank among the worst affected in SSA and globally, for both diseases. Despite comprising just 0.7% of the world's population, South Africa has the highest PLHIV population (estimated 7.5 million) and bears ~20% of the global burden of HIV (*Global Tuberculosis Report 2020, n.d.*); in 2019, it had the highest burden of TB/HIV coinfection cases (estimated 209,000), globally (*Global Tuberculosis Report 2020, n.d.*). In 2019, South Africa had an estimated 200,000 new HIV cases (11.8% of global

(Karim and Karim, 2020) and 360,000 new TB cases (3.6% of global) (*Global Tuberculosis Report 2020, n.d.*). Nigeria is Africa's most populous country; it ranks a global second with its PLHIV population of 1.8 million and has the third-highest TB/HIV coinfection case burden (estimated 46,000) globally (Karim and Karim, 2020). In 2019, Nigeria had 100,000 new HIV cases (~5.9% of global) and 440,000 new TB cases (4.4% of global) (Karim and Karim, 2020).

The effect of TB and HIV on COVID-19

Data on the biological and epidemiological interactions between COVID-19, TB, and HIV remain scarce. It is known that immunosuppressed PLHIV with low CD4+ cell count and high viral loads are at high risk for Acute Respiratory Distress Syndrome in other viral co-infections (Cortegiani et al., 2018). First data did not show immunosuppression among PLHIV as risk factor for severe COVID-19 (CDC, 2020a), although an increased frequency of some known risk factors for severe COVID-19 has been reported in this population (*Coronavirus Disease 2019, 2020*). Almost 50% of PLHIV in the US are aged ≥ 50 years (CDC, 2020b); and compared with the general population, have higher rates of cardiovascular and pulmonary disease, including chronic obstructive pulmonary disease (Fitzpatrick et al., 2018; Triant, 2013). In one of the largest HIV and COVID-19 studies, out of 77,590 Spanish PLHIV receiving antiretroviral therapy (ART), 236 were diagnosed with COVID-19 in February – April 2020, 151 were hospitalized, 15 admitted to the ICU, and 20 died (Del Amo et al., 2020). HIV did not increase susceptibility to SARS-CoV-2 infection and did not increase outcome severity of COVID-19.

In contrast, in a large population-based observational study (N = 12,987) from the Western Cape Province, South Africa, an HIV-positive status was associated with more than double the odds of death (adjusted HR: 2.14; 95% CI: 1.70–2.70); this increased risk was unchanged regardless of the level of HIV-related viral load or immune suppression (Bouille et al., 2020). Also, TB and HIV showed modest effects on COVID-19 mortality, with 2% and 12% of COVID-19 deaths associated with these two diseases, respectively, compared to 52% of COVID-19 deaths associated with diabetes mellitus. However, one limitation of this study was that PLHIV in the study setting (as in many others) generally come from significantly more socioeconomically disadvantaged backgrounds, compared to people living without HIV. Another population-based cohort analysis of UK primary care data (linked to OpenSAFELY platform) including 17,282,905 adults (27,480 PLWHIV), found that living with HIV almost triple the risk of dying with COVID-19 compared to those without HIV and that the risk increase by fourfold among people with black ethnicity compare to almost two folds in non-Black individuals (Bhaskaran et al., 2021). In addition, a multicenter cohort study in US (286 PLHIV from 36 canters) reported older age, hypertension, chronic lung diseases and lower CD4+ counts to be independently associated with poor survival (Dandachi et al., 2020). Sub-analysis of European cohorts of PLWH demonstrated that CD4+ cell count < 350 cells/mm³ associated with increased risk for severe COVID-19 (Hoffmann et al., 2020). Similar findings have been reported in other recent studies (Braunstein et al., 2020; Geretti et al., 2020; Tesoriero et al., 2020). Interestingly, in a seven-study meta-analysis by Tamuzi et al., TB was found to be a risk factor for COVID-19 in terms of both severity and mortality, irrespective of HIV status (Tamuzi et al.,

2020). Unfortunately, only one of the seven studies was conducted in an African country (South Africa); the other countries represented were China and the Philippines.

HIV drugs repurposed for treatment and/or prevention of COVID-19

Several antiretrovirals have been or are being evaluated to prevent or treat COVID-19 in the general population. Lopinavir/ritonavir (LPV/r) attracted high interest due to promising in vitro efficacy against the severe acute respiratory syndrome (SARS) virus of the early 2000s (Chu et al., 2004). An early trial initiated LPV/r a median of 13 days after symptom onset for hospitalised COVID-19 patients, but treatment was not better than standard of care

(Cao et al., 2020). However, the sample size was small, and LPV/r may have been initiated later in the disease course, where systemic hyperinflammation rather than viral pathogenicity dominates (Park et al., 2020). The UK-based RECOVERY Collaborative Group allocated 1616 patients to LPV/r for a median of 8 days after disease onset and found no clinical benefit (RECOVERY Collaborative Group, 2020). Interestingly, Spanish PLHIV receiving HIV treatment that included tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) were less likely to be hospitalized with COVID-19 than those receiving ART that did not include TDF/FTC (Fitzpatrick et al., 2018). Mortality was also lower in South African PLHIV on TDF (adjusted HR 0.41; 95% CI 0.21 – 0.78) with no difference for other antiretrovirals. However, this association should be interpreted with caution, as patients with poor renal function or on

Table 1
 Specific concerns/challenges, and approaches to minimize the impact of the triple burden of COVID-19, TB and HIV in sub-Saharan Africa.

	Areas of specific concerns/challenges	Recommended solutions and/or Research agenda
1	<p>Epidemiology, biologic interactions and socio-economic determinants of TB-HIV and COVID-19</p> <ul style="list-style-type: none"> • Measuring and containing the overlapping burden of TB/ HIV and COVID-19 in SSA • Increased risk of COVID-19 in TB/HIV co-infected patients • Little is known about biological and epidemiological interactions of COVID-19, TB and HIV 	<ul style="list-style-type: none"> - Large-cohort observational studies required to better define the epidemiology and determinants of COVID-19 alone and as co-infections with TB and HIV. - Assessing socio-economic determinants of COVID-19 in the context of HIV and TB infection - Targeted studies needed to elucidate the biological mechanisms behind the relatively low COVID-19 burden in the region, and pathophysiology and outcomes of co-infection with TB and HIV.
2	<p>Impact of COVID-19 on TB-HIV treatment services (medical visits, drug refills)</p> <ul style="list-style-type: none"> • Decreased access to services and follow-up for TB/HIV suspects or patients. • Poor adherence to TB and HIV medication due to lower access to refills • Virologic failure and emergence of drug resistance • Increase in incidence and severity of mental health disorders which may impact adherence. 	<ul style="list-style-type: none"> - Use of community based DSD models for TB/HIV care; Telephone/virtual visits whenever feasible (Barnabas et al., 2020, p.; Keene et al., 2020) - Longer (multi-monthly, e.g., 4–6 month) TB and HIV treatment refills (Fatti et al., 2020) with prioritization of the WHO shorter regimens vs injection - Home or community delivery of TB and HIV medication - Mobile clinics - Virtual care e.g., telephone counseling or use of mHealth adherence support. - Community-based TB and HIV treatment refills (Fatti et al., 2020; Fox et al., 2019) - Intensified psychosocial and mental health support (telephone hotlines)
3	<p>Impact of COVID-19 on TB-HIV Prevention Services</p> <ul style="list-style-type: none"> • Decreased uptake of PreP • Decreased BCG vaccination • Decreased TB preventive therapy. • Decreased impact of HIV treatment-as-prevention 	<ul style="list-style-type: none"> - Use and scale-up community-based DSD models of care for TB-HIV preventive services. - Strengthening community healthcare worker prevention activities
4	<p>Health System to Holistically Address COVID-19, HIV and TB</p> <ul style="list-style-type: none"> • Established community engagement and outreach for HIV, TB, and noncommunicable diseases (such as hypertension and diabetes mellitus) 	<ul style="list-style-type: none"> - Opportunity for integrating screening and testing for major communicable and non-communicable diseases in the long-term COVID-19 response - Mobile clinics - Establish a broader program of health promotion, prevention, and early detection.
5	<p>Strengthening Testing for COVID-19, HIV and TB while conserving primary resources</p> <ul style="list-style-type: none"> • Decreased TB testing following COVID-19 related stigmatization (mainly in rural settings) • Capacity for PCR testing (e.g., GeneXpert) developed for TB and HIV may be drained by increasing COVID-19 testing needs • Use of TB facility for COVID-19 testing. 	<ul style="list-style-type: none"> - Address COVID-19 related stigma - Close monitoring to identify and prevent disruptive diversion of HIV and TB testing to COVID-19. - Scale up COVID-19 testing commodities and human resources while leveraging on pre-existing testing platforms. - Sharing facilities and pairing testing for COVID-19-TB to ensure continuity of TB service
6	<p>Prioritizing pediatric data disaggregation and reporting for COVID-19, including in the context of TB/HIV</p> <ul style="list-style-type: none"> • Paucity of data on risk factors, case burden, clinical characteristics, and outcomes for COVID-19 in African children (Coker et al., 2020) • Limited data on the effects of TB and HIV co-infection in COVID-19, and on specific interventions for children (Coker et al., 2020) • Limited real-time data on impact of COVID-19 on TB and HIV service delivery for children (Coker et al., 2020) 	<ul style="list-style-type: none"> - Public health/disease surveillance authorities at country/ regional level to age-disaggregate COVID-19 reports as done for TB and HIV (Coker et al., 2020) Multi-country prospective and retrospective studies to generate data for devising solutions and for policymaking. - COVID-19 diagnostics, vaccines and other prevention/ treatment tools tailored and/or dosed for safety and efficacy in children

SSA: Sub-Saharan Africa; HIC: high-income countries; LMIC-low- and middle- income countries; TB: tuberculosis; DSD: differentiated service delivery. PreP: HIV pre-exposure prophylaxis.

second-line ART (presumably high-risk for severe COVID-19) would be excluded from receiving TDF. Nevertheless, this observation was hypothesis-generating, since TDF has been proposed to be a potential SARS-CoV-2 RNA-dependent RNA polymerase inhibitor, based on a molecular docking study (Fitzpatrick et al., 2018). The current recommendations for HIV treatment failure among PLHIV would be similar to those for COVID-19 for this population: ART should not be switched or adjusted by adding an antiretroviral to a pre-existing regimen for the specific purpose of preventing or treating SARS-CoV-2 infection (HIV, n.d.).

The impact of COVID-19 on tuberculosis and HIV health services in sub-Saharan Africa

Of 49 patients reported in the preliminary results from the Global Tuberculosis Network cohort (8 countries, 3 continents) of current or former TB patients with COVID-19, 26 had TB before COVID-19, 14 had COVID-19 first and nine had both TB–COVID-19 diagnosed within the same week. The Network stressed that the impact on the healthcare system (days of admission, intensive care unit beds, etc.) will require targeted attention and response (Tadolini et al., 2020)

In SSA, COVID-19 has disrupted TB/HIV treatment and prevention services and impacted upon patient outcomes, such as with lower drug supply and uptake; fewer patient visits and new diagnoses, and increased substance use, and depression (Buonsenso et al., 2021a; Migliori et al., 2020; Shiau et al., 2020). Modelling data has showed that COVID-19 could trigger an excess of 6 million TB deaths by 2025, stemming from decreases in diagnosis, treatment initiation, and successful treatment completion (*Stop TB Partnership|TB and COVID-19, n.d.*). In one hand, missed opportunities for diagnosis due to COVID-19 has deepened the low detection rate of TB in many African high-burden TB countries (e.g.: DRC, Nigeria, South Africa). Therefore, among priority, national TB programs should focus on actively finding millions of individuals with TB missed over 2020 (*Global Tuberculosis Report 2020, n.d.*; Shrinivasan et al., 2020). On the other hand, the WHO estimated that a 6-month disruption in ART delivery could result in up to half a million additional AIDS-related deaths, double the mother-to-child HIV transmission rates in SSA over one year, and increase AIDS-related mortality by up to 40% over the next 5 years (Hogan et al., 2020). In addition, disrupted drug supply could lead to HIV drug resistance, amplifying the costs of managing the HIV epidemic. As an example, in South Africa, it was reported that 1090 TB patients and 10,950 HIV patients in one province had not collected their medications on schedule since the start of the national lockdown (*Department Of Health - Covid 19, n.d.*). A national survey of 19,330 South Africans with chronic disease reported that 13.2% found their medication inaccessible during lockdowns (Jewell et al., 2020). Furthermore, hospital admissions for TB and HIV declined, because hospitals were reducing non-urgent admissions in preparation for a COVID-19 surge, and to reduce exposure to COVID-19 patients (*Global HIV & AIDS Statistics – 2020 Fact Sheet, n.d.*; *Global Tuberculosis Report 2020, n.d.*). Most SSA countries depend on drug, laboratory, and medical supplies from external sources, therefore the lockdowns meant supply chain disruptions that consequently led to shortages, including for TB and HIV commodities. Moreover, the existing TB facilities (GeneXpert, technicians) have been used for COVID-19 response (*Global Tuberculosis Report 2020, n.d.*).

Even as there is a general paucity of data on COVID-19, TB, and HIV in SSA, even less is known and reported about the interactions of these three epidemics in children (including adolescents) zero to 19 years of age. The well-known, prevailing challenges in TB and HIV prevention and treatment among African children have been

and will continue to be complicated by the arrival of COVID-19 (Coker et al., 2020). First, COVID-19 epidemiological reports from African countries are largely not disaggregated, thus making it difficult to ascertain the pediatric case burden and to devise and tailor prevention and control strategies specific to this population. Furthermore, the lack of robust data on COVID-19 clinical manifestations and outcomes in these children continues to limit critical knowledge on risk factors and co-infections, including TB and HIV (Coker et al., 2020). Modelling studies have predicted dire pandemic-related consequences for HIV prevention programs among children in Africa. For example, Jewell et al. predict new HIV infections spiking by 41–81% among children in four African countries with a 3-month disruption in prevention of mother-to-child transmission of HIV services (Jewell et al., 2020). Furthermore, Masresha et al. reported COVID-19 pandemic-related gaps of >10% decline in routine vaccine doses provided in six African countries, including for the TB-preventive Bacille–Calmette Guérin (BCG) vaccine (Masresha et al., 2020). A study in rural Sierra Leone reported a staggering 53% decline in at-birth BCG vaccinations in a two-month period in 2020 for children under five years of age, compared to the same period in 2019 (Buonsenso et al., 2020). Other determinants of TB, such as undernutrition, will be triggered by the loss of household income and the shutdown of school food programs during lockdowns and school closures (Buonsenso et al., 2021b; Coker et al., 2020). Clearly, the continued neglect of children in COVID-19 reporting and response planning and implementation will have dire consequences, not only for their COVID-19 outcomes, but for pre-existing epidemics such as TB and HIV. There is need to improve COVID-19 data collection and reporting for children, and to integrate this into the well-established TB and HIV surveillance systems in SSA.

In Table 1 we summarize the key challenges of TB/HIV services in the COVID-19 era and suggested solutions to minimize the impact of the pandemic. These include proactive approaches to minimize exposure and the impact of COVID-19 on PLHIV and TB patients, such as replacing non-urgent in-person visits with virtual/telephone communications and adherence counseling; longer (multi-month, e.g., 4–6 month) HIV and TB treatment refills; and home-based prevention, treatment and psychosocial service delivery (Barnabas et al., 2020; Ehrenkranz et al., 2019; Fatti et al., 2020; Fox et al., 2019; Nachega et al., 2020a,b).

Monitoring the indirect effect of COVID-19 on population health

For public health systems that deliver care to people living with TB and/or HIV, service disruptions can have profound effects on individual health outcomes and on overall population health. These disruptions comprise the pathway for the harms that the ongoing pandemic inflicts on human health and must be monitored and addressed. Indeed, in many low- and middle-income countries, health systems routinely operate with over-extended human resources, limited budgets, and limited equipment/commodities. These systems are especially vulnerable to disruption when a crisis such as COVID-19 emerges, and the effects are already being witnessed.

If disruptions to routine health systems are a major mechanism of harms to human health, then monitoring their functioning becomes an important component of disease surveillance and epidemic response programs. In other words, we need to measure, document and respond to routine program implementation failures during crises such as with the ongoing COVID-19 pandemic. For TB, such metrics could be the disposition of public awareness campaigns, availability of testing, number of TB tests conducted and contact tracing activities, and number of individuals initiated on prophylaxis and on treatment. Similar metrics for

HIV would apply, and for all populations, including children, pregnant women, and adults. In short, surveillance of routine health services during a pandemic is as urgent as directly responding to the emergency.

Conclusions

Although SSA is seemingly less-impacted by COVID-19, the pandemic's indirect effects on TB/HIV treatment and prevention services are of substantial concern. There may be increased COVID-19 mortality among people living with HIV or TB, by a factor of about two. The main effects of COVID-19 on TB and HIV, including among children, include disruptions in testing, treatment and BCG vaccine access, poorer treatment outcomes, and increased susceptibility to new infections. Rapidly generated but rigorous data are needed to address COVID-19 effects in the context of TB and HIV programming for populations of different ages and dispositions, geographical residence, and socioeconomic status. Innovative adaptations of ongoing TB and HIV programming resources are important to mount impactful responses while containing costs in resource-limited African countries. Finally, robust political and donor commitments, and provision of adequate and equitable funding for TB, HIV and COVID-19 services in addition to other major diseases of public health concern (e.g., malaria, vaccine-preventable diseases) are required to maintain population health and well-being.

Author declarations

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Declaration of interests

The authors below declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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