Effects of the Covid-19 Pandemic on "The Big Three": Hiv, Tuberculosis, and Malaria

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Abstract

Monumental progress against human immunodeficiency virus/acquired immune deficiency syndrome, tuberculosis, and malaria has been made over the past few decades. Numerous local, national, and international programs to detect, treat, and prevent the so-called "Big Three" infectious diseases have been established and successfully operated. The COVID-19 pandemic has posed a sudden challenge to these interventions, and threatens to reverse decades of progress both directly and indirectly. In this review, overall aspects of COVID-19 pandemic-related disruption to control programs as well as challenges specific to each of The Big Three diseases are discussed.

Keywords

COVID-19, Pandemic, HIV, AIDS, Tuberculosis, Malaria

Introduction

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) emerged in Wuhan, China, and was quickly isolated following cases of viral acute respiratory distress syndrome (ARDS). Understanding of the clinical constellation associated with SARS-CoV-2 expanded to include cardiovascular, neurological, and systemic inflammatory manifestations, and disease following infection with SARS-CoV-2 became collectively called Corona Virus Disease - 2019 (COVID-19) [1]. The mortality rate and the occurrence of long-term, post-infectious symptom logy due to COVID-19 made control and prevention of this disease a high priority.

As COVID-19 grew to pandemic proportions, local and national mitigation measures to reduce SARS-CoV-2 transmission were adopted. In the absence of effective antiviral therapies and vaccines, initiatives focused on physical measures such as restriction of movement, face masking, social distancing, and full or partial lockdowns. Postponement of non-essential medical procedures was a common tactic to both create additional hospital capacity for an influx of COVID-19 patients, and to minimize contact with potentially infected individuals with high-risk patients. Though critical for the disruption of viral transmission, an emerging consequence of these collective measures has been indirect increases in mortality and morbidities associated with other causes, including treatment and prevention programs for human immunodeficiency virus (HIV), malaria, and tuberculosis (TB). This mini-review discusses the potential syndemic impacts of the COVID-19 pandemic on these three infectious diseases.

Widespread Challenges to Disease Control Programs

The COVID-19 pandemic created several unprecedented challenges, and revealed many previously under-considered aspects of effective disease control. While the global shortage of healthcare workers (HCWs) was generally recognized, the pandemic brought it into sharp focus both for its hindrance in managing the current crisis and for the lack of capacity to maintain ongoing disease control programs when HCWs were diverted [2,3]. National stockpiles of personal protective equipment (PPE) were quickly depleted, and widespread shortages were experienced in many communities. The lack of PPE presented a challenge to other healthcare endeavors, including treatment and/or diagnostic initiatives for HIV, TB, and malaria.

The use of social/physical disease control measures to mitigate the spread of COVID-19 were met with mixed success globally. For example, the practice of quarantine is some-

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what stigmatizing in many countries (as discussed for Guinea by Kpanake, et al. and Senegal by Desclaux, et al. [4,5]. This risk of stigmacan make people reluctant to seek judgement, which is problematic for diseases whose symptoms overlap with COVID-19. For the purposes of this review, this presents a challenge for those with symptomology of TB (cough, dyspnea, fever) and malaria (fever). Contact tracing is also a key component of social disease control, but at least one report from South Korea described suboptimal compliance due to privacy concerns [6].

Finally, HIV, TB, and malaria control programs often require patients to report to certain clinics or supply dissemination locations (e.g., needle exchange sites or bed net distribution points). Limited disposable income due to stay-at-home orders or job loss can hinder travel to clinics [7]. Reduced capacity of public transit has also been widely reported in many countries which may also hinder access to care or other interventions [7].

COVID-19 Pandemic Disruptions to HIV/AIDS Treatment and Control

Preventing the progression of HIV infection to acquired immune deficiency syndrome (AIDS) requires continuous use of antiretroviral (ARV) drugs by people living with HIV (PLHIV). Compliance with antiretroviral therapy (ART) must be at or above 90% to suppress the replication of HIV, which diminishes progression to AIDS and further transmission of HIV [8]. Routine clinic visits are critical to ensure continued ARV and other prophylactic drug administration [7]. Continued access to ARVs during the COVID-19 pandemic is a critical public health priority, and for good reason. Numerous studies have demonstrated that impaired access to medication often causes patients to ration their doses, which leads to sub-therapeutic drug levels [7]. Should access to ARVs be disrupted, several adverse outcomes are likely on both individual (see Co-Infections below) and community health levels. Community health can be threatened by limited access to ARVs in two distinct ways: ARV drug resistance and HIV transmission rates. Patients using sub-therapeutic doses of ARVs experience an increase in viral load, and the HIV virions present are tolerant of low ARV levels [9,10]. These virions are highly permissive for further drug resistance to develop. The ongoing presence of non-lethal ARV levels applies selective pressure on HIV to accumulate resistance-associated mutations [11]. Compounding this problem is that the higher viral load facilitates increased HIV transmission [12]. Use of sub-therapeutic ARV doses creates a scenario wherein infected patients could become more likely to transmit HIV to other members of the community, and the transmitted strains may have an elevated level of ARV resistance. The Joint United Nations Programme on HIV/AIDS (UNAIDS) has suggested multiple strategies to ensure continuity of care and ART compliance, including multi-month ARV dispensing and local ARV distribution for PLHIV unable to physically report to clinics. Alternatively, UNAIDS suggested field distribution of ARVs. However, many programs in low and middle income countries (LMIC) could potentially face budgetary challenges having to procure PPE for field workers who distribute ARVs [13].

At least two additional logistic aspects of the COVID-19 pandemic are likely to accelerate HIV transmission in currently uninfected persons: disruption of needle exchange programs (NEPs) and pre-exposure prophylaxis (PrEP) distribution clinics. Pandemic-related lockdowns and other movement restrictions in several countries led to closures of some medical services deemed non-essential, including both NEPs and PrEP clinics. Other NEPs AND PrEP clinics closed due to redirecting of resources including HCW staff and PPE for use in combating COVID-19 [14-16]. Movement restrictions still impacted NEP sites that remained operational in the United Kingdom, where site visits declined by roughly one third across several weeks [17]. The lower availability of NEPs and PrEP clinics combined with at least one report of substantially reduced usage in those that remained operational create the alarming potential for a spike in new HIV infections during the COVID-19 pandemic.

COVID-19 Pandemic Disruptions to Tuberculosis Treatment and Control

Maintaining TB control programs has become an important priority for the World Health Organization (WHO). Several factors have emerged as potential threats to these programs, and each require distinct, coordinated strategies to mitigate. Reports of patients missing scheduled TB clinic visits have emerged, due in at least some instances to national or regional lockdowns restricting movement [18,19]. Stigmatization likely also played a significant role in these absences, wherein patients avoid travelling for TB treatments due to fear of violence in response to their respiratory symptoms, which could be mistaken for COVID-19 [13,20]. Disruption of TB control programs resulting from COVID-19 fears has been reported on the HCW side as well. At least one report documents fear of COVID-19 exposure leading to avoidance of processing diagnostic specimens for TB due to a lack of PPE available to HCWs in Nigeria [13].

In order to address missed TB clinic visits, program directors have explored giving additional doses of antimycobacterial drugs to patients in order to reduce the frequency; however, inadequate drug stores coupled with supply chain disruptions have made this practice challenging. Disruption of supply chains to countries with high TB burdens have occurred due to flight cancellations, border closures, and additional logistical challenges [13,21]. Incomplete treatment courses due to drug shortages have potential to drive further antimicrobial resistance (AMR) among *Mycobacterium tuberculosis* strains, which would fuel and expand the catastrophic problem of multi (M), extensively (X), or totally (T) drug-resistant (DR) TB [22]. Notably, the case-fatality rate (CFR) in TB patients is almost triple in patients with MDR strains [23]. To compound the crisis of un- or under-medicated TB patients, many are co-infected with HIV and at high risk for aggressive reactivation of disease if treatment is prematurely stopped [13].

COVID-19 Pandemic Disruptions to Malaria Treatment and Control

Malaria is a mosquito borne disease, and it therefore

tempting to assume that most aspects of malaria control would be unaffected by COVID-19. While some vector control programs remain ongoing, much of the reduction in malaria deaths over the past twenty years are the result of face-to-face interactions with patients or people in endemic areas at risk for infection [7]. Massive campaigns to distribute insecticide-treated bed nets were halted in many locations to prevent the spread of COVID-19, though some have now resumed with volunteers distributing nets door-to-door rather than at a single, central point [24]. Areas with suspended distribution campaigns can be predicted to have increased malaria disease burden [25]. Even a temporary uptick in malaria cases can have long-term consequences beyond the COVID-19 pandemic. With the exception of *Plasmodium knowlesii*, *Plasmodium* species that cause the majority of malaria cases do not have sylvatic cycles. This indicates that controlling the disease burden in humans by early, aggressive ant malarial therapy is a key strategy for reducing further infection throughout the population. Administration of treatment requires clinic access wherein physical exams and diagnosis by blood smear can be performed [26,27]. Pandemic-related lockdowns and movement restrictions have also hindered patient access to malaria treatment. As described for patients with TB, fear of stigmatization may be discouraging patients from seeking treatment because their fevers could be mistaken for COVID-19. Screening and treatment of pregnant women for falciparum malaria has been a critical intervention resulting in improvements in maternal-child health on the African continent, and these restrictions threaten to disrupt the practice [7,26].

Finally, as with HIV and TB, malaria treatment and control is impacted by the diversion of resources and supply chain disruptions. The most critical resources that have been diverted are PPE and HCWs. Transport of critical supplies including antimalarial drugs, insecticide, bed nets, and diagnostic supplies are being impacted by restricted movement, flight reductions, and border closures [15]. In addition, manufacturers of chloroquine and hydroxychloroquine have been unable to keep pace with the sudden demand of these drugs for use on COVID-19 patients. Despite numerous reports showing a lack of therapeutic benefit, prescriptions of hydroxychloroquine in the United States increased 80% in the first 6 months of 2020 relative to the same months of 2019 [28], resulting in drug shortages for patients with autoimmune diseases [29]. It is not clear that a similar impact would be felt by malaria patients due to the global burden of chloroquine-resistant *Plasmodium* strains limiting its use; however, this possibility should be acknowledged and accommodated for.

Co-Infections with COVID-19 and the Big Three

Our understanding of pathogen-pathogen or pathogen-host-pathogen interactions between HIV and SARS-CoV-2 is evolving [30,31]. A systemic review evaluating a total of 252 COVID-19 patients across studies who are PLHIV did not indicate dramatically different outcomes from the general population. However, 98% of the included patients were on ART, and 99% of those patients whose viral load was reported (233 out of 256 patients) had loads of < 1000 copies per mL

[32]. It is not clear that enhanced COVID-19 disease would have been predictable in those patients, because their immune function was essential intact. Extrapolating those findings to PLHIV who are not on ART would be highly ill-advised. Adherence to ART as measured by both patient reporting and direct pill counts inversely correlates with both HIV viral load and progression to AIDS (*i.e.*, CD4+ T cell count < 200 cells/μL or occurrence of opportunistic infection) [33,34]. It is reasonable to expect that people living with HIV/AIDS (PLWHA) whose access to ART is disrupted or eliminated will experience progression of their underlying disease. This in turn will likely lead to more severe COVID-19 disease with a higher CFR, in addition to other opportunistic infections.

Interactions between tuberculosis (TB) and COVID-19 have been explored by multiple groups. Diverse outcomes and conclusions have been reported, indicating that the sequence of infection and ongoing host-pathogen interactions may complicate interpretations of cases [35,36]. A cohort of TB patients in Italy reported higher-than-expected COVID-19 mortality, but that mortality was concentrated in older adults. Younger patients experienced similar mortality rates to non-TB patients, indicating that TB may not significantly alter COVID-19 outcomes in the absence of other comorbidities [37]. It is important to note that this paradigm may not apply to though those infected with more aggressive *M. tuberculosis* lineages such as MDR-TB, XDR-TB, and TDR-TB. In addition, the potential for symptomatic treatment for severe COVID-19 disease (such as immunomodulatory therapies) to adversely affect TB prognosis. A recent case report described a 38-year-old patient with no apparent comorbidities whose decline accelerated upon administration of hydroxychloroquine sulfate to control inflammation, potentially due to drug-induced activation of latent TB [38]. Further, hepatic and renal toxicity are potential effects of both the antimycobacterials isoniazid and rifampicin, and the antiviral remdesivir, indicating that toxic drug interactions during co-infections are predictable. As COVID-19 disease burden is increasing exponentially in India, which is highly endemic for TB, the complex interactions between these diseases remains a topic of importance.

In comparing the pathophysiologies of severe COVID-19 and malaria, it is predictable that the two diseases could potentially exacerbate each other. Both can induce cytokine storm, and it is plausible that an uncomplicated case of either malaria or COVID-19 would be intensified by a severe case of the other [39]. Unfortunately, the number of described malaria/COVID-19 co-infections is vanishingly small. A case of *Plasmodium vivax* malaria in an adult with concurrent, PCR-confirmed SARS-CoV-2 infection presented exclusively with malaria symptoms and resulted in full recovery after treatment [40]. A second pediatric case of (dormant) vivax malaria/COVID-19 has been described wherein respiratory symptoms preceded reoccurrence of malaria symptoms, prompting the authors to suggest that SARS-CoV-2 infection caused the malaria relapse [41]. Given the paucity of clinical reports describing co-infection, it is not possible to discern patterns of malaria/COVID-19 co-infection at this time.

Conclusion

A recent modeling study predicted that death associated with HIV, TB, and malaria could increase by 10%, 20%, and 36% (respectively) due to the COVID-19 pandemic [42], and studies focusing on the individual diseases are similarly dire [43]. Syndemic interactions between HIV, malaria, TB, and COVID-19 are likely exacerbating each disease. Increased HIV, malaria, and TB morbidity and mortality from *indirect* effects of the COVID-19 pandemic including restricted movement, supply shortages, and access to maintenance or preventative medications are predictable, and require specific/mindful intervention to ensure continuity of care and blunt the coming surge of cases.

Acknowledgement

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