The Journal of Infectious Diseases

REVIEW ARTICLE

Human Immunodeficiency Virus/AIDS in the Era of Coronavirus Disease 2019: A Juxtaposition of 2 Pandemics

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The coronavirus disease 2019 (COVID-19) pandemic has significantly impacted persons with human immunodeficiency virus (HIV), interfering with critical health services for HIV prevention, treatment, and care. While there are multiple profiles of persons living with HIV and the impact of COVID-19 may differ for each, the severity of COVID-19 in persons with HIV is related strongly to the presence of comorbidities that increase the risk of severe disease in COVID-19 patients in the absence of HIV. An effective response to the juxtaposition of the HIV and COVID-19 pandemics requires a novel coordinated and collaborative global effort of scientists, industry, and community partners to accelerate basic and clinical research, as well as implementation science to operationalize evidence-based interventions expeditiously in real-world settings. Accelerated development and clinical evaluation of prevention and treatment countermeasures are urgently needed to mitigate the juxtaposition of the HIV and COVID-19 pandemics.

Keywords. HIV and COVID-19 dual pandemics.

The Joint United Nations Programme on HIV/AIDS recently reported that in 2019 there were 1.7 million new human immunodeficiency virus (HIV) infections globally with approximately 700 000 AIDS-related deaths, figures that have fallen 37% and 50%, respectively, since 2000. More than 26 million people with HIV were receiving antiretroviral therapy (ART), which has substantially reduced the burden of HIV disease [1]. Despite this substantial progress, programs at the local, national, regional, and global levels are now facing a new and unforeseen challenge—the coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The juxtaposition of the HIV and COVID-19 pandemics has impacted persons with HIV indirectly by interfering with critical services and directly by adding an additional potentially lethal threat to the health of the individual.

INTERFERENCE WITH ESSENTIAL SERVICES

Certain public health measures required to control the spread of SARS-CoV-2 have led to societal restrictions that have negatively impacted the economy and also have limited access to routine nonemergent healthcare. Specifically, with regard to persons with HIV or at risk for HIV, the COVID-19 pandemic has had a negative effect on HIV testing, linkage to care, and treatment access [1]. The disruption of these and other HIV-related healthcare services, including HIV testing, treatment of opportunistic infections, availability of preexposure prophylaxis (PrEP), and other HIV prevention strategies likely already has led to increased HIV incidence, morbidity, and mortality [2]. A recent global cross-sectional survey of 10 000 men who have sex with men (MSM) with HIV found that 18% of the respondents were either unable to refill or access their ART prescriptions or had difficulty in doing so between 16 April 2020 and 4 May 2020. These difficulties were greater for men in racial or ethnic minority groups. Disruptions in ART access, resulting in poor virologic control of HIV during the COVID-19 pandemic, suggest that strategies such as multimonth dispensing of ART will be essential [3].

As a result of these disruptions, the COVID-19 pandemic could result in a 10% increase in HIV-related deaths over the next 5 years in low- and middle-income nations with high HIV burdens [4]. However, maintaining critical HIV prevention services could significantly reduce this toll. Ongoing access to PrEP and other prevention and treatment tools will be essential to MSM [5] and other vulnerable populations at increased risk for HIV acquisition. In a cross-sectional online survey of 204 MSM, a national lockdown was associated with a decrease in daily PrEP use among 1 in 4 MSM [6]. The PrEP in Pregnant and Postpartum women cohort study showed that the number of missed PrEP antenatal visits by pregnant women without HIV increased by 63% at the 1-month visit and 55% at the 3-month visit during a COVID-19 related lockdown in South Africa [7].

Received 21 January 2021; editorial decision 24 February 2021; accepted 9 March 2021; published online April 7, 2021.

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The Journal of Infectious Diseases® 2021;224:1455–61

DOI: 10.1093/infdis/jiab114

The COVID-19 pandemic and resulting national lockdowns/shutdowns also have negatively impacted the number of prescriptions for HIV postexposure prophylaxis (PEP) as reported by major HIV and sexually transmitted infection public health clinics in both London and Melbourne. An 80% reduction of PEP prescriptions in London [8] and a 66% reduction in Melbourne [9] were reported during the first 4 weeks after implementation of lockdowns in these cities. Such studies underscore the critical need to continue HIV testing services and providing access to PEP in the COVID-19 pandemic era. The decreased utilization of PrEP and PEP during COVID-19 lockdowns also may be due to decreased risk behaviors.

RISK OF INFECTION WITH SARS-COV-2 IN PERSONS WITH HIV

Black/African American and Hispanic/Latinx populations in the United States (US) are disproportionately at risk for HIV acquisition. These same populations and other minority ethnic groups are at increased risk of acquiring SARS-CoV-2 infection and have worse clinical outcomes (eg, hospitalizations, admissions to intensive care units [ICUs], and mortality), compared with white individuals. Contributing factors include long-standing systemic health disparities and socioeconomic inequalities, as well as multigenerational households, frontline jobs not permitting social distancing, and remote work conditions that may make exposure to SARS-CoV-2 more likely [10, 11]. These also are the same populations in the US who have limited access to HIV treatment and achieving viral suppression [5, 12]. These populations also have a higher burden of comorbidities that place them at increased risk of severe COVID-19 [13].

Mascolo et al [14] propose a possible correlation between HIV-associated immune impairment with susceptibility to SARS-CoV-2 infection and the clinical manifestations and severity of COVID-19. They speculate that individuals with HIV who are not receiving ART develop lymphopenia that may protect them from severe COVID-19, although they remain susceptible to SARS-CoV-2 infection. Others have proposed that individuals with HIV who are not receiving ART or are not virally suppressed may be at increased risk of contracting SARS-CoV-2 due to a compromised immune system and that these individuals are then at increased risk of serious COVID-19 and death [12].

Initial reports of HIV and SARS-CoV-2 coinfection came from Wuhan, China, during the early days of the COVID-19 pandemic. An initial report [15] of coinfection described a 61-year-old man, with diabetes and a history of heavy smoking, who presented in January 2020 with the now-recognized symptoms of COVID-19 confirmed with chest computed tomography results that indicated multiple ground-glass opacities in both lungs. The patient was newly diagnosed with HIV during admission for COVID-19, subsequently recovered, and returned home. On the basis of this case, the authors proposed that immunocompromised patients, including those individuals with HIV, should be considered a vulnerable population group at increased risk of COVID-19 [15].

While additional single-case reports of HIV and SARS-CoV-2 coinfection emerged from Wuhan, information was limited until a large cohort survey of 1174 individuals with HIV in 2 districts of Wuhan was conducted in late February to determine the risk of SARS-CoV-2 in this population and the potential role of ART in the prevention or treatment of COVID-19 [16]. The data showed that the rate of SARS-CoV-2 infection in persons with HIV was 0.68%, slightly higher than among the general population (~0.5%) in Wuhan at the end of February 2020. In contrast, a systematic review of 25 published studies recently showed no increased risk for incident SARS-CoV-2 infection or disease progression for individuals with HIV receiving ART and virally suppressed as compared to individuals without HIV [17]. The findings indicated that the percentage of individuals with HIV and SARS-CoV-2 coinfection was similar to that of the general population with SARS-CoV-2 monoinfection.

SEVERITY OF COVID-19 IN PERSONS WITH HIV

Studies Indicating Lack of Increased Risk of Severe COVID-19

Many questions remain as to whether persons with HIV are more at risk for severe COVID-19 and death as reports are in some cases contradictory. Mounting evidence indicates that the presence of comorbidities in persons with HIV is the predominant determining factor as to the severity of COVID-19. In this regard, a meta-analysis [18] showed a high prevalence of comorbidities in individuals with HIV who developed severe COVID-19. The findings underscore the critical role of comorbidities as a key factor in morbidity and death for individuals with HIV and SARS-CoV-2 coinfection as they are for COVID-19 patients who are not infected with HIV [18]. Similar findings were reported from an analysis of the multicenter TriNETX research network that included data on 50 167 patients with COVID-19 in the US, including 404 persons with HIV [19].

However, when comorbidities are removed from the calculation, HIV infection itself does not appear to be a risk factor for severe COVID-19. A systematic review involving an analysis of 8 studies, totaling 70 persons with HIV, including 13 with AIDS and 57 individuals who were on ART and virally suppressed, showed that persons with controlled HIV infection do not appear to be at increased risk of poorer outcomes of COVID-19 than the population at large [20]. Similarly, Calza et al [21] reported that COVID-19 in individuals with uncontrolled HIV had a clinical presentation similar to individuals with controlled HIV infection and patients without HIV, and did not have greater severity and worse outcomes of COVID-19. A systematic review of the literature [22] that described 164 adults coinfected with both

HIV and SARS-CoV-2 concluded that there was no clear evidence that coinfected individuals have a different risk of severe disease or course of disease than individuals with SARS-CoV-2 monoinfection. However, to complicate the situation, the study showed that some persons with HIV, especially males who have ART-related complications, may be at increased risk for severe COVID-19 [22].

In the largest cohort-based study so far in the US, an analysis of SARS-CoV-2 infection among 189 individuals with HIV and 380 individuals without HIV in the Veterans Aging Cohort Study showed similar rates of incident SARS-CoV-2 infection regardless of HIV status [23]. The study found that COVID-19 patients with HIV and those without HIV had similar rates of hospitalizations, admissions to ICUs, intubation for mechanical ventilation, and death rates (10% vs 11%). The authors concluded that individuals with HIV were not at an increased risk of severe COVID-19 compared to individuals without HIV [23].

Studies Indicating Increased Risk of Severe COVID-19

In contrast to the above reports, several studies have shown that individuals with HIV are at increased risk for severe COVID-19 and death. A population retrospective study using the OpenSAFELY database in the United Kingdom involving 17.3 million adults, including >27 000 who had HIV, showed that persons with HIV had 2.9 times the risk of COVID-19 death compared to people without HIV after accounting for age and sex [24]. This risk decreased slightly to 2.3 times for individuals with HIV when adjusting for comorbidities. The findings also showed that HIV infection was associated with a 4.3-fold higher risk of COVID-19 death among individuals with black ethnicity [24].

Two additional analyses of large cohorts showed increased risk of severe COVID-19 and mortality among SARS-CoV-2/HIV-coinfected individuals. An analysis of the International Severe Acute Respiratory and Emerging Infections Consortium database of >47 000 hospitalized COVID-19 patients, 0.26% with confirmed HIV status and >90% receiving ART found an age-adjusted 47% increased risk of 28-day mortality from COVID-19 among persons with HIV compared to the general population with COVID-19 [25]. Among hospitalized COVID-19 patients <60 years of age, the risk of mortality doubled for those patients with HIV compared to patients without HIV [25]. Another multicenter analysis involving 286 patients coinfected with HIV and SARS-CoV-2 showed that severe clinical outcomes were common, with decreased survival rates associated with age, lung disease, and hypertension [26]. Lower $CD4^+$ T-cell counts (<200 cells/μL), despite HIV viral suppression due to ART, were associated with higher rates of hospitalizations, lower rates of ICU-free survival, and overall survival [26].

In a large population cohort study of >3.4 million adults [27], an analysis in the Western Cape Province of South Africa showed that HIV was associated with an approximate doubling of COVID-19 mortality risk. The authors suggested that individuals with HIV should be considered a high-risk population for COVID-19, regardless of viral suppression, when they have other comorbidities [27]. Sax [28] suggested that the negative outcomes in individuals with HIV and SARS-CoV-2 coinfection may be due to their comorbidities, including cardiovascular disease (CVD) or renal disease, which are common high-risk factors associated with severe COVID-19 [10].

A population-level analysis of registry-matched surveillance data of >200 000 COVID-19 cases in New York City involving 2410 HIV/SARS-CoV-2–coinfected individuals had a higher rate of hospitalization (42% vs 26% of all cases), ICU admission (5% vs 3% of all cases), and/or death (13% vs 8% of all cases) [29]. A larger proportion (54%) of coinfected individuals had at least 1 underlying health condition compared to individuals with COVID-19 monoinfection (35.4%). Persons with HIV/SARS-CoV-2 coinfection with unsuppressed HIV and low $CD4^+$ T-cell counts (<500 cells/μL) or who were diagnosed with HIV prior to 2000 had poorer COVID-19 outcomes, including increased rates of ICU admission and mortality, compared to coinfected persons who were virally suppressed [29].

A recent analysis of medical records of 8912 patients with COVID-19, including 161 patients with HIV, showed that coinfected patients had a higher prevalence of hypertension, diabetes, dyslipidemia, heart failure, and chronic kidney disease compared to the COVID-19 patients without HIV infection. Coinfected patients <50 years of age had higher relative risks of intubation (2.97) and death (4.36). However, the study found there were no significant differences between COVID-19 patients with or without HIV among the older age groups or for the relative risk for admission to the ICU [30].

COMORBIDITIES IN PERSONS WITH HIV AND THE RISK OF SEVERE COVID-19

Persons with HIV may experience various comorbidities, many of which also have emerged as risk factors for severe COVID-19. The etiology for development of many HIV-associated comorbidities is multifactorial and is in certain cases not clearly established. The following comorbidities have emerged as risk factors for severe COVID-19 (defined as hospitalization, admission to the ICU, intubation or mechanical ventilation, or death) [10] and represent a significant burden in persons with HIV.

Cancer

There is an increased incidence of certain cancers in persons with HIV, including several non–AIDS-defining cancers [31]. A large prospective cohort study among US military veterans with HIV demonstrated that individuals with viral suppression still had excess cancer risk [32]. Cancer also is associated with an increased risk of severe COVID-19 [10]. The aspects of various types of cancers and their treatments that confer a risk for

severe COVID-19, as well as the underlying pathophysiology, will require further study [33, 34].

Chronic Kidney Disease

In the US, the prevalence of HIV-associated kidney diseases, such as HIV-associated nephropathy and thrombotic microangiopathy, associated with high viral loads and low CD4 T-cell counts, has decreased. In contrast, among people with HIV who are effectively treated with ART, kidney disease associated with diabetes, hypertension, nephrotoxic effects of medication, and aging is becoming more prominent [35]. Chronic kidney disease (CKD) is associated with severe COVID-19 [10]. The mechanisms underlying the association of CKD with severe COVID-19 are not fully understood and may be heterogeneous depending on the nature of the underlying illness leading to CKD.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is prevalent in people with HIV. HIV is increasingly recognized, apart from smoking, as an independent risk factor for COPD, with HIV-related immune activation possibly involved in the pathogenesis of this condition [36, 37]. COPD also is recognized as a risk factor for development of severe disease in COVID-19 [10]. Certain aspects of COPD, such as host immune responses, structural damage of the lung, microbiome imbalance, and mucous production, may predispose the individual to development of pneumonia from a variety of causes [38]. Factors unique to SARS-CoV-2, such as differential expression of ACE2, also may potentially play a role [39].

Cardiovascular Disease

Persons with HIV, including those receiving ART, have an increased risk of developing ischemic heart disease and certain other cardiovascular conditions. While the underlying etiology of this excess risk is likely to be multifactorial, chronic immune activation due to HIV may play a role [40]. Preexisting CVD is linked to an increased risk of severe illness and poor outcomes in patients with COVID-19 [10, 41]. In addition, COVID-19 can cause various acute presentations of CVD, including acute coronary syndrome, arrythmia, myocarditis, and thromboembolic disease. Myocardial injury during acute COVID-19 is associated with increased mortality [41].

Obesity

The strong tendency toward obesity in the US, the effects of certain antiretrovirals (ARVs), and an aging population are all potential contributing factors to the growing problem of obesity among persons with HIV [42]. One study utilizing cross-sectional data from 2 US surveys estimates that obesity affects 2 in 5 women and 1 in 5 men with HIV [43]. Obesity (body mass index [BMI] $\geq$30 kg/m^2) and severe obesity (BMI $\geq$40 kg/m^2) are underlying conditions that increase risk of severe disease from COVID-19 [10]. A recent meta-analysis [44] showed that obese individuals with COVID-19 had a higher risk of hospitalization (odds ratio [OR], 2.13 [95% confidence interval {CI}, 1.74–2.60]; $P < .0001$); ICU admission (OR, 1.74 [95% CI, 1.46–2.08]; $P < .0001$), and death (OR, 1.48 [95% CI, 1.22–1.80]; $P < .001$). Mechanisms to explain this increased risk are not fully understood but may include metabolic and immune alterations, chronic inflammation, and physical features of obese individuals that impact respiratory function [44].

Type 2 Diabetes Mellitus

In addition to traditional risk factors for development of type 2 diabetes mellitus, persons with HIV may also face metabolic effects of certain ARVs, lipodystrophy, and hepatitis C coinfection [45]. In the general population, type 2 diabetes mellitus is associated with severe COVID-19 [10]. The etiology of this poorer prognosis is likely multifactorial and complex, with hypothesized contributing factors being concomitant comorbidities and a proinflammatory and procoagulative state [46].

PREMATURE AGING AND HIV

Several studies have noted that persons with HIV and COVID-19 coinfection have a median age about 10 years younger than COVID-19 patients without HIV infection [47]. This may reflect that persons with HIV have an advanced biological age compared to the general population. Early onset or "premature" aging has been described in individuals with HIV, even those who are virally suppressed. This phenomenon is associated with the biological age of the individual compared to their chronological age and may be characterized by appearance of comorbidities that occur in individuals without HIV at a chronological age of 10–13 years older. Persistent inflammation, immunosenescence, and innate immune activation characteristic of chronic HIV infection causes premature aging of the immune system despite the beneficial effects of ART suppression on HIV replication [48, 49]. These immunologic abnormalities have been causally associated with premature onset of non-AIDS complications including heart disease, cancer, and end-stage liver and renal diseases, among other end organ diseases [48].

Guaraldi et al [50] reported the occurrence of noninfectious comorbidities and multiple comorbidities occurring in persons with HIV approximately 10 years earlier than in the general population, at 41–50 years of age compared to 51–60 years of age. They noted certain risk factors associated with the occurrence of these comorbidities, including low nadir CD4$^+$ T-cell counts and prolonged ART exposure [50]. Cross-sectional analysis of the Co-morBidity in Relation to AIDS (COBRA) cohort study demonstrated that persons with HIV and undetectable HIV RNA may experience accelerated aging by 13.2 years compared to individuals without HIV based on a series of validated biomarkers of aging [51]. They reported that the factors

associated with advanced aging in persons with HIV include historic severe immunosuppression and certain ARVs, as well as potential viral coinfections with chronic hepatitis B virus and cytomegalovirus [51].

CONCLUSIONS

Although the totality of the data is somewhat contradictory, it is nonetheless clear that the COVID-19 pandemic has had a negative impact on persons with HIV. The most consistent finding is that the severity of COVID-19 in persons with HIV is related strongly to the presence of comorbidities that increase the risk of severe disease in COVID-19 patients in the absence of HIV. There are multiple profiles of persons living with HIV and the impact of COVID-19 may differ for each; although the data are somewhat contradictory, certain general patterns emerge (Table 1).

With COVID-19 pandemic engulfing the globe, there is an even higher priority and urgency to accelerate the development and clinical evaluation of prevention and treatment countermeasures to mitigate the juxtaposition of the HIV and COVID-19 pandemics. The COVID-19 pandemic is overwhelming already overstretched healthcare systems and resources and threatens to reverse progress made in ending the HIV pandemic in the US and worldwide.

An effective response to these dual pandemics requires an unprecedented coordinated and collaborative global effort of scientists, industry, and community partners to accelerate basic and clinical research, as well as implementation science to operationalize evidence-based interventions expeditiously in real-world settings. Clearly, the most definitive approach to these 2 pandemics is the development of safe and effective vaccines. It is highly likely that the effective implementation of efficacious vaccines for COVID-19 will end this global pandemic within a reasonable period of time. While individuals with HIV were initially excluded from participating in phase 3 COVID-19 vaccine trials, this was later changed to allow those with stable disease to enroll in these critical studies. The development of a vaccine for HIV has been much more challenging [52]. Apart from vaccines, additional research on the pathogenesis, immunology, and basic biology of SARS-CoV-2 infection is urgently needed. Similarly, research on the interactions between HIV and SARS-CoV-2 at both the cellular and molecular levels is crucial. It will be important to determine if SARS-CoV-2 amplifies inflammatory pathways and whether these pathways are differentially enhanced among persons with HIV compared to individuals without HIV. Large-scale cohort studies are needed to describe the natural history and outcomes in individuals coinfected with both HIV and SARS-CoV-2, including the impact of comorbidities. Findings from these studies will inform the continued development of the National Institutes of Health COVID-19 treatment guidelines [53] and the Department of Health and Human Services interim guidelines for treatment of COVID-19 and persons with HIV [54]. Although this research agenda represents an enormous challenge, it is one that we can and must meet in order to adequately address and hopefully end both the HIV and COVID-19 pandemics.

Table 1. Profiles of Persons With Human Immunodeficiency Virus and Potential for Severe Coronavirus Disease 2019

Profile of Person With HIV	Potential for Severe COVID-19[a]
Uncontrolled viremia, immunosuppressed with comorbidities	++++
Uncontrolled viremia, immunosuppressed without comorbidities	+++
On ART, virologically suppressed, immunocompetent with comorbidities	++
On ART, virologically suppressed, immunocompetent without comorbidities	+

Abbreviations: ART, antiretroviral therapy; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus.

[a]Given the somewhat conflicting data regarding each of these situations, the assignment of a risk from + to ++++ is based on a broad interpretation of the weight of the data.

Notes

Acknowledgments. The authors thank Gregory K. Folkers for his careful and thorough editing of this manuscript.

Financial support. This work was supported by the Office of the Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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