American Journal of Epidemiology

Vol. 190, No. 1
DOI: 10.1093/aje/kwaa158
Advance Access publication:
July 22, 2020

Data-Driven Commentary

HIV and COVID-19: Intersecting Epidemics With Many Unknowns

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Initially submitted July 1, 2020; accepted for publication July 17, 2020.

As of July 2020, approximately 6 months into the pandemic of novel coronavirus disease 2019 (COVID-19), whether people living with human immunodeficiency virus (HIV; PLWH) are disproportionately affected remains an unanswered question. Thus far, risk of COVID-19 in people with and without HIV appears similar, but data are sometimes contradictory. Some uncertainty is due to the recency of the emergence of COVID-19 and sparsity of data; some is due to imprecision about what it means for HIV to be a "risk factor" for COVID-19. Forthcoming studies on the risk of COVID-19 to PLWH should differentiate between 1) the unadjusted, excess burden of disease among PLWH to inform surveillance efforts and 2) any excess risk of COVID-19 among PLWH due to biological effects of HIV, independent of comorbidities that confound rather than mediate this effect. PLWH bear a disproportionate burden of alcohol, other drug use, and mental health disorders, as well as other structural vulnerabilities, which might increase their risk of COVID-19. In addition to any direct effects of COVID-19 on the health of PLWH, we need to understand how physical distancing restrictions affect secondary health outcomes and the need for, accessibility of, and impact of alternative modalities of providing ongoing medical, mental health, and substance use treatment that comply with physical distancing restrictions (e.g., telemedicine).

COVID-19; engagement in care; HIV; mental health; substance use; telemedicine

Abbreviations: ART, antiretroviral therapy; COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; PLWH, people living with HIV; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Editor's note: *The opinions expressed in this article are those of the authors and do not necessarily reflect the views of the* American Journal of Epidemiology.

People living with human immunodeficiency virus (HIV; PLWH) might be at particularly high risk for infection with and poor clinical outcomes from severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the novel coronavirus that causes coronavirus disease 2019 (COVID-19), and for adverse health outcomes associated with physical distancing measures introduced to mitigate the SARS-CoV-2 epidemic. It is critical that we understand these risks to modify ongoing HIV care accordingly and to update future pandemic preparedness plans. Herein, we outline several research questions to frame this research agenda, and we highlight existing data and future opportunities to answer these questions. We focus mainly on the intersecting epidemics of SARS-CoV-2 and HIV in the United States, but many of the questions we pose apply to other settings as well.

INCIDENCE AND PREVALENCE OF SARS-COV-2 IN PLWH

It is unclear whether or not PLWH are at higher risk for infection with SARS-CoV-2 or for poor clinical outcomes subsequent to infection. There are reasons to hypothesize that PLWH are a high-risk group: Antibody responses to an immune system challenge are impaired in PLWH, and PLWH have high prevalence of risk factors for severe SARS-CoV-2 infection, including hypertension, diabetes, cardiovascular disease, obesity, lung disease and smoking, male sex, and older age (1, 2). Alternatively, worse COVID-19 outcomes might be due to immune (over)activation, and thus PLWH might actually be at lower risk for poor outcomes following SARS-CoV-2 infection due to their reduced immune response (3). However, there are not yet sufficient data to support or refute either of these hypotheses.

Early in the course of an epidemic of a novel pathogen, evidence is scarce, and the most practical or indeed the only epidemiologic study design available to us is the case report or case series (4–8). Early case reports and case series of COVID-19 in PLWH told of an occasionally atypical, but not more severe, disease course relative to people living without HIV (7–13). Some case series suggested that PLWH with COVID-19 might be younger than persons with COVID-19 in the general population (11, 12). However, incidence and mortality rates for COVID-19 will be a function of the age structure of the underlying populations of people with versus without HIV; thus, it is difficult to compare rates without age standardization.

Data on the incidence of COVID-19 in PLWH is slowly amassing from population- (i.e., surveillance) and clinic-based cohorts of PLWH. While important, absolute risk estimates will reflect: 1) SARS-CoV-2 infection dynamics such as the force of infection in a community and duration of follow-up (cumulative risk infection increases monotonically); 2) demographic and clinical characteristics of PLWH in the population (presumably, higher prevalence of comorbidities would be associated with higher risk of COVID-19, independent any direct causal effect of HIV infection on COVID-19); and 3) excess risk of COVID-19 attributable to HIV infection. Among 1,174 PLWH living in the Wuchang or Qinshan districts of Wuhan, China, 8 had confirmed COVID-19 (0.7%, as of the end of February or beginning of March 2020), which was comparable to the risk in the general population in Wuhan (0.5%) (14). Among 1,339 PLWH engaged in regular care in Madrid, Spain, 51 (3.8%) were diagnosed with COVID-19 as of April 30, 2020. The risk of COVID-19 in Madrid for the same period (4.0%) was comparable (15). Finally, the SARS-CoV-2 positivity rate among PLWH tested in a medical center in Chicago, Illinois (15%), was comparable to the positivity rate among people without HIV (19%) (16). In contrast to these cohorts suggesting similar infection rates in people with and without HIV, unpublished surveillance data from South Africa's Western Cape province through June 9, 2020, suggest that PLWH were 2.3 times as likely to die from COVID-19 as people without HIV, after age and sex standardization (17).

Certainly, more information is needed. Surveillance data, such as those available from South Africa or Wuhan, will provide the most complete picture of COVID-19 risk among PLWH (e.g., by not restricting to PLWH who are in care and who are more likely to have well-controlled HIV disease); however, clinical data, such as those from Madrid, might provide the most depth (e.g., by allowing examination of the role of comorbidities, medications, and COVID-19 treatments) as long as potential selection bias is considered. Perhaps the most fruitful investigation would be one that merged clinical and surveillance data.

SURVEILLANCE FOR SARS-COV-2 IN PLWH

Strict initial guidance for testing for SARS-CoV-2 infection—restricting testing to people with a history of travel to Wuhan, and then to China, or to people with a known epidemiologic connection to a confirmed case—limits our ability to accurately describe incidence of SARS-CoV-2 in PLWH. Even if testing were widely available, incidence estimates would be plagued by nonrandomly missing data from people with poor access to health care, people who are avoiding health-care settings for fear of contracting or transmitting SARS-CoV-2, and people who do not believe themselves to be infected.

New serological assays for past exposure to SARS-CoV-2 are rapidly becoming available (18). Sensitivity of serological tests in PLWH with compromised immune systems, who might not mount a vigorous antibody response, could be lower than the nominal sensitivity; unless test and patient characteristics are taken into account, serosurveys of PLWH might underestimate the true burden of SARS-CoV-2 infection. As with estimation of incidence, attempts to estimate prevalence of past SARS-CoV-2 infection in PLWH must take into account who is, and is not, included in any serosurvey. Some states are randomly sampling residents for serosurveys (19); if sampling strategies considered groups of special interest, including PLWH, these serosurveys might be an opportunity to get estimates of prior SARS-CoV-2 infection in PLWH.

HIV AS A "RISK FACTOR"

Useful epidemiologic investigations into the impact of COVID-19 on PLWH will need to carefully consider the research question of interest and how results will be used. There is justified concern about labeling HIV as an "independent risk factor" for poor COVID-19 outcomes based on an arbitrary multivariable model given that it might then be inappropriately used to ration care or guide treatment decisions. Ambiguity about the meaning of the term "independent risk factor" makes it highly likely that results will be misinterpreted and misapplied (20, 21). If interest is in identifying groups that should be monitored more closely for SARS-CoV-2 infection, this is a descriptive epidemiology question, and crude analyses (or perhaps age- and sex-adjusted analyses) might be sufficient (22). While the most appropriate adjustment set for descriptive epidemiology is an unresolved question, associations from a multivariable model are interpretable as hypothetical assumptions that would exist if we could "hold constant" the other covariates in the model and thus are necessarily not descriptive of the world as it exists (22). If interest is in estimating the etiological influence of the HIV virus and associated immune activation/immune system suppression on the progression of COVID-19, other analyses are warranted.

In particular, for etiological questions, we need to be thoughtful about the role of comorbidities in our analyses. The prevalence of some comorbidities, such as alcohol and other drug use disorders, is higher among PLWH because they are causal factors for HIV acquisition and are therefore confounders in any etiological analysis. The prevalence of other comorbidities, such as depleted bone and kidney health, might be higher among PLWH because of the effects of the virus and antiretroviral therapy, and are mediators of any effect of HIV on poor COVID-19 outcomes; adjusting for these comorbidities would be inappropriate. The role of other comorbidities, such as cardiovascular disease and diabetes, is more complex. For example, tobacco use increases the risk of cardiovascular disease that might precede HIV infection (implying cardiovascular disease is a confounder), but uncontrolled viremia and some antiretroviral medications themselves increase the risk of cardiovascular disease (implying cardiovascular disease is also a mediator).

Existing studies examining the relationship between HIV and COVID-19 outcomes have not always been clear about their research question. In a retrospective matched cohort of PLWH and people without HIV hospitalized for COVID-19 in New York, outcomes were similar. Matching factors included some confounders of the effect of HIV, such as admission date, age, gender, and tobacco history, but also included variables that might be considered mediators, such as body mass index and history of chronic kidney disease, hypertension, asthma, chronic obstructive pulmonary disease, and heart failure (23). In another matched cohort in New York, outcomes of people with and without HIV hospitalized for COVID-19 were similar even without adjusting for higher prevalence of chronic obstructive pulmonary disease, prior cancer, cirrhosis, and current smoking among PLWH (24).

Markers of HIV disease that might be expected to be the strongest mediators of a direct effect of HIV infection on COVID-19 outcomes, such as HIV viral load and CD4 cell count, have not been strongly associated with COVID-19 morbidity among PLWH (15, 17, 24). However, these data should be interpreted cautiously because, as yet, only SARS-CoV-2 infections that resulted in symptomatic disease have been studied; HIV might influence whether SARS-CoV-2 infections are detected, either because PLWH might have more or less access to screening or because HIV might increase the proportion of infections that are symptomatic. Furthermore, HIV-infected patients without updated clinical data (presumably because they are out of care) have generally been excluded for having missing data; the prevalence of HIV viral suppression in identified COVID-19 cases has been high, which might indicate that PLWH who are not well-linked to HIV care are less likely to be diagnosed with COVID-19 or identified as HIV-infected in the data.

THE ROLE OF ANTIRETROVIRAL MEDICATIONS IN COVID-19 DISEASE PROGRESSION

Certain antiretroviral medications, such as lopinavir-ritonavir (a protease inhibitor), were proposed and partially evaluated as treatments for other, similar coronaviruses (25). However, a trial of 199 patients randomized to lopinavir-ritonavir versus standard of care found only small differences in time to clinical improvement (hazard ratio = 1.24, 95% confidence interval: 0.90, 1.72) and 28-day mortality (risk difference = −5.8%, 95% confidence interval: −17.3%, 5.7%) (26). There was some hint that the impact of lopinavir-ritonavir on mortality was stronger if treatment was administered closer to symptom onset, although results were imprecise. Results were reported as indicative of "no benefit" of lopinavir-ritonavir, although associations were suggestive of a potentially protective effect (26). While these results do not support initiating treatment with lopinavir-ritonavir in patients with SARS-CoV-2, they might suggest some benefit to PLWH on a lopinavir-ritonavir-containing antiretroviral therapy (ART) regimen who continue on treatment while infected with SARS-CoV-2.

Darunavir (another protease inhibitor) has also been hypothesized to potentially have therapeutic action against SARS-CoV-2; however, no trial results are yet available.

Thus far, in cohort studies of COVID-19 among PLWH, ART regimen has not been consistently associated with disease incidence or severity. In a small cohort ($n = 88$) of PLWH hospitalized with COVID-19 in New York, New York, being on a nucleoside reverse transcriptase inhibitor was protective against death (24). In a cohort of over 77,000 PLWH receiving ART in Spain, being on a regimen containing tenofovir/emtricitabine (a nucleotide reverse transcriptase inhibitor and a nucleoside reverse transcriptase inhibitor, respectively) was protective against COVID-19 diagnosis and hospitalization (27). Data on the association between ART regimen and COVID-19 outcomes are still too limited to support or exclude an effect of any particular regimen.

MODIFYING, MEASURING, AND MONITORING ENGAGEMENT IN CARE

Engagement in ongoing care is essential to the health of PLWH. HIV viral load and CD4 cell count should be monitored every 3–6 months (28). In light of the risk of SARS-CoV-2 transmission associated with face-to-face contact, particularly in medical settings, many clinical encounters (for all people, including for PLWH) were rapidly changed to telehealth visits starting in March 2020 as SARS-CoV-2 cases started increasing rapidly (29).

While telehealth visits eliminate potential exposure to SARS-CoV-2 and thus might be necessary for some period, the costs and benefits associated with telemedicine need to be enumerated and weighed. Prior to the SARS-CoV-2 outbreak, telehealth was studied as a potential intervention to increase access to care (30) particularly for PLWH with transportation difficulties and those living in rural settings (31). However, offering telehealth to persons who opt in is a different intervention from requiring telehealth visits to all persons in the midst of a pandemic, and it might result in different outcomes.

There is, as yet, little data on the short- and long-term impacts of the transition to telehealth on engagement in care and ART adherence for PLWH. In a narrative report, >90% of patients in a Missouri HIV clinic (presumably among those who successfully completed a telehealth visit) reported that their telehealth visit during COVID-19 physical distancing restrictions was as good as or better than a traditional in-clinic visit (29). Not provided was the number of patients who failed to complete a telehealth visit. At a clinic in Chicago, from late March to mid-April, only 21% of scheduled visits were carried out virtually; 31% were rescheduled, 2% occurred in person, and 46% were not attended (16). The impact of telehealth on high-need patients and new patients who have not yet established rapport with their providers has yet to be described (7).

Despite some good telehealth outcomes for some PLWH, telehealth has the potential to exacerbate disparities in care for people with lower socioeconomic status: Lack of necessary technology and services, technology literacy, or safe, confidential surroundings to participate fully in telehealth might be barriers to engagement in care (32). There are not good, representative data on the prevalence of smartphone ownership and internet use among PLWH (33). Among a sample of predominantly low-income women of color seeking HIV-related social or clinical services in the Bronx in 2014, 87% owned a cellphone, compared with 90%–92% of persons in the general population at the same time (34). In a sample of PLWH in British Columbia, Canada, recruited in 2012, only 60% owned a cellphone at enrollment (35). In the general US population, demographic characteristics associated with limited access to smartphones and home broadband services match the demographics of people with high prevalence of HIV infection: non-White persons, older adults, and persons with less education or lower income (34, 36). In addition, for telehealth to be effective, simply owning a cell phone is not sufficient. Patients might incur additional monetary costs for telehealth visits if they do not have access to unlimited telephone or internet service.

Additionally, PLWH could face privacy concerns engaging in medical care from outside the clinic, where they might not have control of their surroundings (37). In a survey of PLWH about attitudes towards telehealth generally, nearly a quarter had concerns about their ability to express themselves in the absence of a face-to-face interaction, and over a quarter had concerns about the privacy of their health information over the internet (38).

From a practical standpoint, to track ongoing engagement in care of PLWH and long-term impacts of telehealth, healthcare systems must be proactive in ensuring that all scheduled patient encounters (attended, rescheduled, and missed) and the modality of the attended encounters (i.e., in-person, video conference, or telephone call) are being captured by the electronic medical system. Potential risks and benefits of, and preferences for, telehealth are likely heterogeneous across PLWH, and this heterogeneity will need to be considered to inform clinical practice (e.g., by prioritizing patients for in-clinic versus continued telehealth visits as clinics reopen but maintaining low in-clinic patient volume to accommodate physical distancing) (38). In particular, those factors likely to modify the effect of telehealth on engagement in care (access to internet and private, safe space from which to call in and distance and transportation to the clinic) should be routinely collected.

An additional factor likely to interrupt engagement in care in the United States is the economic crisis precipitated by the pandemic, in which millions lost their jobs and employer-sponsored insurance (39). PLWH who previously had private insurance might experience gaps in care if they find themselves suddenly without means of paying for care. Clinical cohorts have a unique opportunity to track changes in insurance status and impact on engagement in care, access to ART, and viral suppression. This might require some additional follow-up of patients who are lost-to-clinic to determine why they have not returned.

SUBSTANCE USE/MENTAL HEALTH COMORBIDITIES

PLWH have a high prevalence of alcohol use, other drug use, and mental health disorders that might present unique risks and challenges during the SARS-CoV-2 pandemic. Physical distancing restrictions and related depression and anxiety might lead to increased alcohol and other drug use. Epidemiologists should consider novel data sources to track some of these trends. For example, Nielsen Retail Measurement Services reports dramatic increases (+234%) in online alcohol sales and sales of larger volumes of alcohol (40). We will continue to need to rely on more traditional surveys about alcohol and other drug use, however, to know whether individual PLWH are increasing their consumption (to go beyond ecological inference) and whether they are shifting where and how they use alcohol and other drugs. Even shifts in where and with whom alcohol and other drugs are consumed could have consequences for PLWH related to the venues and networks in which alcohol and drug use occurs, including sexual risk behaviors, sharing of needles or drug paraphernalia, and exposure to violence (41). Finally, persons with alcohol use disorder or substance use disorder might be less likely or able to comply with physical distancing restrictions if they need to go outside their homes to access alcohol or other drugs or, critically, medication-assisted treatments (such as methadone or buprenorphine).

Poor baseline mental health is likely to be exacerbated by physical distancing restrictions (42). PLWH, particularly older PLWH, are already at high risk of social isolation (43, 44), and social structures and creative outlets that have helped people cope in the past might be dismantled under physical distancing restrictions. Breaking with physical distancing policy to seek out these coping outlets might be associated with additional stress due to fears of SARS-CoV-2 exposure or stigma. Accurate estimates of the risk associated with such activities for PLWH are critical to help individuals weigh the risk and benefits of participating in them but are not currently available. People able to shelter in place in their homes might face additional stressors at home if they are alone in their home, if being at home imposes additional caregiving responsibilities, or if they live with someone who poses a physical or emotional threat.

For persons with diagnosed mental health disorders, physical distancing restrictions and the transition to telehealth might lead to difficulty receiving or fully engaging in behavioral treatments for those disorders. Indeed, while delivery of mental health counseling might be one of the medical services most amenable to delivery via video conferencing, it might also serve as a “canary in the coal mine” for emergent disparities due to access to technology and private, safe spaces to participate in counseling (30, 45). For example, one HIV clinic in Chicago, Illinois, reported that some patients who had been receiving mental health counseling prior to the institution of physical distancing measures temporarily discontinued services when they were offered via telehealth, but other patients engaged in telecounseling for the first time. Engagement in telecounseling was universal among patients with stable income and housing but entirely absent among patients who were unstably housed with no steady source of income; in lieu of telecounseling, the latter group of patients received peer counseling, which was more flexible with respect to the time and locations in which it could occur (16). In addition to exacerbated mental health symptoms as a result of physical distancing, persons with severe mental health symptoms might be at higher risk for SARS-CoV-2 infection if their understanding of public health messaging is impaired or if they do not understand their risk and how to mitigate it (46).

STRUCTURAL VULNERABILITIES

The HIV epidemic has disproportionately affected marginalized communities: people belonging to minority racial or ethnic groups, and in particular women of color, young men of color who have sex with men, people who inject drugs, transgender individuals, and people with a history of incarceration. The same structures that placed these groups at higher risk for HIV—including racism, stigmatization, limited economic opportunities, and oppression—also place them at higher risk for SARS-CoV-2, such that the term syndemic has been used to describe these overlapping epidemics and vulnerabilities (47, 48). Less than 6 months into the COVID-19 pandemic, we are already seeing staggering disparities in the proportion of confirmed SARS-CoV-2 infections and COVID-19 deaths among Black Americans and persons in homeless shelters and prisons (49–52). Persons with limited income are less likely to be able to take some precautions that require financial resources, such as driving in lieu of taking public transportation (53), stockpiling groceries, or paying for grocery delivery. Indeed, even in the first 2 weeks of implementation of physical distancing regulations in Alabama, there was increased need for wraparound social services such as provision of nutritional and personal care items (54). There is likely to be increased need for services among PLWH who were already receiving such services, as well as an increasing number of people in need of services.

CURRENT AND FUTURE DIRECTIONS: OPPORTUNITIES AND CHALLENGES

Data that can help answer many of these questions are already being collected (or their collection is planned) but are not yet available for analyses. Because many cohorts of PLWH predate the emergence of SARS-CoV-2, the research infrastructure exists to quickly expand and adapt data collection to monitor changes in health, health-care access and engagement, and risk behaviors associated with all phases COVID-19 pandemic and the implementation and relaxation of physical distancing policies.

Interval and clinical cohorts are working overtime to implement questions designed to address some of the unknowns about HIV and COVID-19, including documenting the impact of SARS-CoV-2 in PLWH and the impact of the physical distancing regulations and associated economic challenges on the lives of PLWH, with special attention to PLWH with comorbid conditions, including mental health and substance use disorders. Some challenges to these efforts include the need to administer focused questionnaires over the internet or telephone and to compensate individuals for their time electronically, particularly when they don't have bank accounts to accommodate those transactions through some of the most common methods.

Clinical cohorts and electronic health systems are in a unique position to document some of the health impacts of SARS-CoV-2 in PLWH by capturing clinical illness, severity, and outcomes in a well-defined population, including (as time and testing capacity increases) seropositivity. Beyond estimating the association between HIV-specific indicators (CD4 cell count, HIV viral load, ART regimen) and COVID-19 outcomes, these clinical cohorts already collect data on other comorbidities and structural vulnerabilities hypothesized to be associated with COVID-19 outcomes based on other studies, and those hypotheses could be rigorously tested. Such analyses should clearly state whether they are descriptive, and then avoid overadjustment, or whether they seek to identify the causal effects, and then choose their adjustment set appropriately. Additionally, clinical cohorts are potentially well-positioned to document impacts of the COVID-19 pandemic on modifications to and interruptions in HIV care.

CONCLUSIONS

The COVID-19 pandemic will affect the health and health care of all people. PLWH are likely to be uniquely vulnerable to both the direct and indirect effects of the pandemic. Some as-yet unanswered research questions of interest for PLWH in the United States include: Should PLWH be monitored more closely for COVID-19? Does HIV infection affect the risk of SARS-CoV-2 infection or affect the risk of poor COVID-19 outcomes among people who are infected with SARS-CoV-2? What are the impacts of physical distancing measures on PLWH, particularly as related to their engagement in HIV care, substance use and mental health outcomes, and other structural influences on health outcomes? A robust research infrastructure around HIV provides many opportunities to answer some of these outstanding questions, as long as we adhere to good epidemiologic principles with regard to asking well-defined questions. Leveraging these opportunities to inform public health practice requires that the specific research question being addressed is clearly stated and that appropriate analyses for answering that questions are applied.

ACKNOWLEDGMENTS

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This work was funded by the National Institutes of Health (grants K01 AA028193 and R00 MH112413).

The authors thank Dr. Geetanjali Chander for helpful comments on earlier versions of this manuscript.

Conflicts of interest: none declared.

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