HIV and COVID-19: review of clinical course and outcomes

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Background: Understanding the relationship between HIV and SARS-CoV-2 has important public health implications.

Objective: To summarize current research on COVID-19 among people with HIV (PWH) as published through 15 July 2021.

Methods: We conducted a search of PubMed, Scopus, preprint databases (medRxiv, bioRxiv), and the references of publications found using key terms relevant to COVID-19 ('COVID-19' OR 'SARS-CoV-2' OR 'coronavirus') AND to HIV ('HIV' OR 'Human Immunodeficiency Virus' OR 'AIDS' OR 'Acquired Immunodeficiency Syndrome'). We summarized all articles that reported data or opinions on SARS-CoV-2 and HIV coinfection.

Conclusions: Although many initial case series and cohort studies found no increased risk for SARS-CoV-2 infection or severe COVID-19 outcomes among PWH, recent studies have signaled an increased risk for severe COVID-19 disease progression even in the setting of well-controlled HIV. Whether this is due to the increased prevalence of comorbidities in PWH and other social determinants of health is unknown. These conflicting findings highlight the continued need for COVID-19 related research among PWH that addresses COVID-19 disease course as well as exacerbation of existing comorbidities already disproportionately represented among PWH.

KEYWORDS: Human immunodeficiency virus, SARS-CoV-2, COVID-19, coinfection

Introduction

When COVID-19, the disease caused by the novel coronavirus SARS-CoV-2, began to surface in late 2019 and early 2020, healthcare officials and providers assumed that individuals with Human Immunodeficiency Virus (HIV) infection and other immunocompromising conditions would be at particularly high risk of both acquisition and severe disease.¹ Without effective antiretroviral therapy (ART), HIV leads to depletion of CD4 T-lymphocytes, resulting in a weakened adaptive immune response.² In the presence of effective ART, the cellular immune response recovers to variable degrees; however, individuals with HIV appear to remain at greater risk for many infections, including pneumococcal pneumonia, influenza,

meningococcal disease, herpes virus infections, and tuberculosis. $^{\rm 2-7}$

As COVID-19 precipitated widespread closures of businesses, schools, and community gatherings, healthcare agencies, and other critical operations scrambled to determine how to provide essential services to patients while protecting their employees. In an attempt to limit potential spread to patients and employees, many clinics converted to virtual or telephone-based visits.⁸ However, as businesses, schools, and healthcare facilities have gradually resumed inperson services, the ongoing risk for acquiring SARS-CoV-2 infection, or developing severe disease, remain somewhat elusive.

While increasing age, obesity, diabetes, and Black or Hispanic race/ethnicity have consistently been linked to acquisition and severe disease in U.S. populations, the role of other factors, such as HIV, in contributing to risk of COVID-19 acquisition and disease

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severity have been less certain.^{9–14} Furthermore, people with HIV (PWH) frequently have overlapping risk factors for COVID-19, often at rates higher than the general population. These risks include being male, Black or Hispanic, smoking, older age, and medical comorbidities.^{15–23} Lastly, despite effective ART, PWH have higher levels of inflammation, one of the key factors driving the development of severe respiratory disease, thromboembolic disease, and other poor outcomes with COVID-19.^{24,25} Parsing out the added risk of HIV with or without ART in the setting of these other epidemiologic and physiologic risks is therefore challenging.

Methods

To better understand what is currently known about the relationship between HIV and COVID-19 acquisition and disease severity, we conducted a search of PubMed, Scopus, preprint databases (medRxiv, bioRxiv), and the references of publications found using key terms relevant to COVID-19 ('COVID-19' OR 'SARS-CoV-2' OR 'coronavirus') AND to HIV ('HIV' OR 'Human Immunodeficiency Virus' OR 'AIDS' OR 'Acquired Immunodeficiency Syndrome') between 1 March 2020 and 15 July 2021. Of 2210 initial results we considered each study that reported data or opinions on COVID-19 among PWH, applying extra filters to access articles related to 'symptoms', 'severity', 'hospitalization', 'mental health', 'access to care', and 'ART'. This resulted in the 212 articles presented in this review. We then summarized the risk for acquiring COVID-19, presenting symptoms of COVID-19, severity of COVID-19 illness, and impacts on mental health and access to care during the COVID-19 pandemic. We also report findings on the effects of antiretroviral therapy on COVID-19 risk and outcomes for PWH.

Discussion

Are people living with HIV more likely to contract SARS-CoV-2?

Many experts initially considered individuals living with HIV as a vulnerable group with regards to SARS-CoV-2 infection due to a greater burden of some comorbidities, higher systemic inflammation despite effective ART, and some degree of immune alteration even among those on effective ART with immune reconstitution.^{26–32} Whether this is true remains unclear. PWH account for approximately 0.7% of the general population of adults in the world, and roughly 0.5–1.5% of COVID-19 cases in various COVID-19 case series and cohort studies.^{28,33–36}

It is important to note that multiple studies have attempted to distinguish the difference between test positivity and disease incidence. In a recent analysis of over 30,000 PWH in the USA, PWH were more likely to be tested for SARS-CoV-2 but did not have an increased percentage of COVID-19 positivity compared to individuals without HIV.44 However, the authors note that testing shortages and the potential for differential adherence to stay-at-home guidance by immunosuppression status could have influenced the outcome of the study. In contrast, researchers in Southern Italy found that PWH were more reluctant to obtain SARS-CoV-2 testing and thus were likely underdiagnosed with COVID-19, though this was an opinion piece and the conclusion was not backed by data.45

have HIV.43

Do the presenting symptoms of COVID-19 differ among people with or without HIV?

One prospective cohort study of 5683 PWH

observed a lower incidence of COVID-19 among PWH compared to the general population, suggesting a

possible protective effect of HIV, ART, or less expos-

ure through physical isolation and consistent use of

personal protective equipment.³⁷ However, this study

was limited in that it did not control for ART use.

Multiple other prospective cohort studies, limited by

their study sizes, have found similar rates of SARS-

CoV-2 among PWH and the general population.³⁸⁻⁴¹

A study from San Francisco of 4252 PWH suggested

that PWH were more susceptible to SARS-CoV-2

infection than those without HIV.42 Numerous other

confounders, however, may have explained these differences: for example, 8% of PWH in San Francisco

experience unstable housing as compared to the 1% of

the San Francisco general population.⁴² As of 28 July

2020, the Centers for Disease Control and Prevention

concluded that based on the limited data available,

PWH on effective ART appear to have a similar risk

for acquisition of SARS-CoV-2 as people who do not

In the general population, the most common presenting symptoms of COVID-19 include fever, cough, or shortness of breath (70%) and less commonly muscle aches (36%), headaches (34%), and loss of smell or taste (8%).⁹ A cohort of 286 PWH showed similar symptoms: cough (76.2%), fever (70.7%), and fatigue (66.0%).²⁰ This study was especially strong as it took data from multiple states and countries. These results have been supported by numerous other studies.^{46–53} Besides one review, these studies are limited in their small sample size. Of note, other individual case studies have found that PWH may present with COVID-19

and opportunistic infections such as *Pneumocystis jirovecii* pneumonia and AIDS-related disseminated histoplasmosis, perhaps exacerbated by or contributing to presenting symptoms of COVID-19.^{54–60}

Are people living with HIV more likely to present with severe disease and/or be hospitalized for COVID-19?

Similar to the general population, age and co-morbidities appear to be the strongest predictors of severe disease and mortality in PWH.^{22,46,61–73} Most PWH who develop symptomatic COVID-19 have at least one comorbidity, most commonly hypertension, dyslipidemia, or type 2 diabetes mellitus.^{28,38,46,51,61,64,74–78} Per Dandachi et al. (n = 286), 81% of PWH had at least one co-morbidity which impacted their COVID-19 clinical course.²⁰

Data describing the likelihood of hospitalization due to COVID-19 among PWH is limited and mixed: rates of hospital admission among people living with HIV range from 0.8% to 1.8%.^{33,38,74,79} Notably, these rates derive from cohorts in numerous countries including Spain, China, and the United States, which may differ demographically with varying rates of comorbidities and clinical threshold for hospitalization. A retrospective, matched cohort study at a New York health system indicated PWH (n = 21) had a significantly higher rate of hospital admission but not intensive care unit admission, mechanical ventilation, or mortality, compared to people without HIV (n = 42).⁸⁰ All PWH in this cohort were on ART, the majority had an undetectable viral load, and only six of 19 had a CD4 count < 200 cells/uL, thus limiting the ability to determine the effect of HIV severity of COVID-19 outcomes. A separate small analysis of 31 PWH hospitalized at a New York, NY hospital also found similar rates of hospitalization among those with or without HIV.35 In a much larger Veteran cohort of 107,636 patients with COVID-19, risk of hospital admission among PWH did not differ from those without HIV, although these results have not yet been published in a peer-reviewed paper.44

In a retrospective study in New York comparing 21 PWH with 42 matched-uninfected controls admitted with COVID-19, a similar burden of comorbidities and similar admission laboratory values were seen between PWH and uninfected controls.⁸⁰ In addition, no statistically significant differences were seen between PWH and the uninfected controls when comparing consolidation, infiltrate, or opacity on chest imaging.⁸⁰ Although the study was small, findings are strengthened by matching PWH and controls by admission date, age, body mass index, gender, tobacco history, and a

history of chronic kidney disease, hypertension, asthma, chronic obstructive pulmonary disease, and heart failure. In summary, among PWH, risk factors for hospitalization and clinical presentation at the time of hospitalization appear to be influenced more by comorbidities or demographic risk factors seen in the general population (race/ethnicity, socio-economic status), and less by HIV-specific factors.

Are people with HIV more likely to have severe outcomes?

A number of studies on HIV and SARS-CoV-2 coinfection have addressed the question whether PWH have more severe outcomes than the general population (as defined by more ICU admissions, greater need for mechanical ventilation, and higher mortality rates). As summarized in Table 1, many large studies and smaller case reports have found greater likelihood of ICU admission and higher mortality rates among PWH than the general population.^{76,81–91} Indeed, of 3.460.932 patients in the public sector in South Africa, 16% were PWH and 22,308 (0.6%) were diagnosed with COVID-19. In this large study, HIV infection was associated with a doubling of COVID-19 mortality risk, independent of CD4 count or HIV viral load (though >90% were virologically suppressed).⁹¹. In a study of 17,282,905 adults (including 27,480 PWH) in the United Kingdom, a substantially higher risk of mortality was seen with COVID-19 in PWH than in the general population, although the actual number of deaths among PWH was only 25, thus limiting some of the conclusions.¹⁹ Furthermore, data were available on some comorbidities and demographics but not HIVrelated characteristics (ART, CD4 count, or viral load). A landmark report by the World Health Organization (WHO) included 15,522 PWH and 168,649 adults without known HIV hospitalized with suspected or confirmed SARS-CoV-2 from 24 countries (96% from the WHO African Region).⁹² HIV was associated with an increased risk of severe or critical disease at admission compared to uninfected controls, after adjusting for age, sex, and underlying comorbidities. HIV was also independently associated with higher mortality risk. The majority of persons included were from South Africa, and no data were presented on ART, CD4 count, or virologic suppression.⁹² Two systematic reviews/meta-analyses also concluded that PWH had a higher risk of mortality, though only in studies of PWH from Africa and the United States.^{93,94} A smaller study of PWH in Brazil (n = 255) found that being Black/Mixed race and having lower education were associated with greater mortality in adjusted models, while age, sex, CD4 count, viral load, and

Table 1.	Summary of 2020-2021	publications (through	n 15 July 2021)) related to HIV and COV	D-19.

First author	Population	Location	Publication date	Journal	Description or findings
Zhu, F. ²⁶	1 PWH	China	11-Mar-20	J Med Virol	Described how PWH should be regarded as a vulnerable population in regard to
Chen, J. ¹⁹⁹	1 PWH	China	14-Apr-20	J Med Virol	Described a coinfected PWH with atypical CT imaging of the chast
Blanco, J.L. ³³	5 PWH	Spain	15-Apr-20	Lancet HIV	Described clinical course of
Wang, M. ⁸²	1 PWH	China	23-Apr-20	Int J Infect Dis	COVID-19 and HIV (low CD4 count) led to a longer disease course
Aydin, O.A. ²³	4 PWH	Turkey	29-Apr-20	J Med Virol	Comorbidities are an important factor in mortality for coinfected PWH
Ridgway, J.P. ⁴¹	8 PWH/1061 HIV negative controls	USA	7-May-20	AIDS Behav	PWH did not test positive for COVID-19 at a different rate than the general population
Härter, G. ⁴⁷	33 PWH	Germany	11-May-20	Infection	PWH did not have more severe morbidity or mortality than the general population
Gervasoni, C. ¹⁰⁵	47 PWH	Italy	14-May-20	Clin Infect Dis	PWH coinfected with COVID-19 had favorable outcomes as compared to the general population
Patel, R.H. ¹⁰⁶	1 PWH	USA	22-May-20	J Med Virol	Coinfected patient under treatment with ART had a less severe clinical presentation than the general hospitalized population
lordanou, S. ⁸¹	1 PWH	Republic of Cyprus	25-May-20	J Med Virol	Coinfected (PWH/COVID-19) patient had a prolonged need for mechanical ventilation and increased risk for thrombotic complications
Childs, K. ⁴⁹	18 PWH	United Kingdom	27-May-20	Clin Infect Dis	Black PWH were at higher risk of severe disease; ARTs did not appear to provide protection against COVID-19 severity
Vizcarra, P. ³⁸	51 PWH and COVID-19 positive/ 1288 PWH	Spain	28-May-20	Lancet HIV	Clinical presentation in PWH was similar to the general population, however, lower CD4 counts affected disease severity; PWH had a higher prevalence of comorbidities
Okoh, A.K. ¹⁴²	27 PWH	USA	28-May-20	J Acquir Immune Defic Syndr	Coinfected PWH presented similarly to the general population
Ridgway, J.P. ⁵⁰	5 PWH	USA	29-May-20	AIDS Patient Care STDS	A similar COVID-19 clinical course was seen in PWH as in the general population
Shalev, N. ³⁵	31 PWH	USA	30-May-20	Clin Infect Dis	HIV coinfection did not lead to increased rates of hospitalization; outcomes for PWH were similar to the general population
Suwanwongse, K. ²⁷	9 PWH	USA	9-Jun-20	J Med Virol	PWH did not have more favorable COVID-19 outcomes especially when their CD4 counts were low
Coleman, H. ⁵⁵	1 PWH	United Kingdom	10-Jun-20	AIDS	Pneumocystis jirovecii pneumonia and COVID-19 infection were observed in a PWH
Karmen- Tuohy, S. ⁸⁰	21 PWH/42 HIV negative controls	USA	12-Jun-20	J Acquir Immune Defic Syndr	PWH had a higher admission rate for COVID-19 but did not show significant differences in ICU admissions, mechanical ventilator use, or mortality
Benkovic, S. ¹¹³	4 PWH	USA	16-Jun-20	J Med Virol	Clinical severity was not different in uncomplicated cases of

First author	Population	Location	Publication date	Journal	Description or findings
	-				COVID-19 and HIV coinfection
Byrd, K.M. ¹¹⁵	27 PWH	USA	19-Jun-20	J Int AIDS Soc	as compared to the general population Clinical course and severity appeared similar in PWH as the
Meyerowitz, E.A. ⁷⁵	47 PWH	USA	25-Jun-20	AIDS	general public Coinfected PWH were on average 53 4 years old and a substantial
Del Amo, J. ²⁰²	236 PWH and COVID-19 positive/77,590 PWH receiving ART	Spain	26-Jun-20	Ann Intern Med	proportion had comorbidities, were non-Hispanic Black, and lived or worked in a congregate setting The risk for COVID-19 hospitalization was 20.3 among patients receiving TAF/FTC, 10.5 among those receiving TDF/FTC, 23.4 among those
Sigel, K. ⁷⁴	88 PWH/405 HIV negative controls	USA	28-Jun-20	Clin Infect Dis	receiving ABC/3TC, and 20.0 for those receiving other regimens There was no difference in COVID-19 severity on admission by HIV status and PWH did not have more severe COVID-19 outcomes than the
Toombs, J.M. ¹²⁹	3 PWH	United Kingdom	29-Jun-20	J Med Virol	general population PWH may be protected from severe COVID-19 if they are
Ho, H. ⁸⁴	72 PWH	USA	30-Jun-20	J Infect Dis	PWH were at higher risk for severe COVID-19 outcomes, especially those with increased markers of inflammation and
Guo, W. ⁷⁶	14 PWH	China	1-Jul-20	J Int AIDS Soc	immune dysfunction HIV and COVID-19 coinfection led to a higher mortality rate and higher proportion of severe cases than the
Park, L.S. ⁴⁴	30,891 PWH/ 76,745 HIV negative controls	USA	6-Jul-20	AIDS 2020 Conference	general population PWH had higher COVID-19 testing rates but no evidence to support increased positivity or
Ruan, L. ¹⁰²	4 PWH	China	6-Jul-20	J Med Virol	PWH in the stage of AIDS had a more complicated clinical
Gudipati, S. ¹¹²	14 PWH	USA	15-Jul-20	J Acquir Immune	PWH were not at a higher risk for
Mahmood, K. ¹⁹⁶ Cooper, T.J. ¹⁴⁰	1 PWH 70 PWH	USA United Kingdom	15-Jul-20 15-Jul-20	JACC Case Rep HIV Med	Coinfected PWH on a LVAD PWH with well-controlled disease are not at risk of poorer
Adachi, E. ¹⁴¹	2 PWH	Japan	15-Jul-20	AIDS	general population Transgender PWH have similar clinical course of COVID-19 as compared to the
Charre, C. ³⁹	77 PWH/27 PrEP users/19009 other patients	France	17-Jul-20	AIDS	general population The positivity rate appeared similar in HIV-infected patients, in PrEP users, and in
Maggiolo, F. ⁶¹	55 PWH and COVID-19	Italy	24-Jul-20	J Med Virol	other patients HIV coinfection did not protect from COVID-19 coinfection or
Su, J. ⁵²	postive/69 PWH 1 PWH	China	1-Aug-20	AIDS	trom severe disease Described COVID-19 in a patient with AIDS; speculated that protease inhibitors might have a protective effect for COVID-19
Stoeckle, K. ¹¹⁶	30 PWH/90 HIV- negative controls	USA	1-Aug-20	Open Forum Infect Dis	

First author	Population	Location	Publication date	Journal	Description or findings
					A similar COVID-19 clinical course was seen in PWH as in
Sun, L.J. ¹¹¹	1 PWH	Singapore	1-Aug-20	J Acquir Immune Defic Syndr	He recovered from a mild and uncomplicated clinical course
Calza, L. ⁴⁸	26 PWH	Italy	3-Aug-20	Infection	PWH had a similar COVID-19 clinical presentation to the
Bhaskaran, K. ¹⁹	27480 PWH/17.3 million adults	United Kingdom	7-Aug-20	Lancet	general population PWH had nearly three-fold higher risk of COVID-19 death than those without HIV after
Tian, C. ¹⁰⁸	1 PWH	China	10-Aug-20	Ann Palliat Med	Described favorable outcome in
Guo, W. ¹³⁸	11 PWH	China	10-Aug-20	Res Sq	PWH have comparable COVID-19 morbidity rates as the
Marbaniang, I. ¹⁵⁸	167 PWH	India	13-Aug-20	Res Sq	$I/_4$ of PWH had anxiety during the
Huang, J. ³⁴	35 PWH	China	17-Aug-20	Clin Infect Dis	PWH had similar severity and fatality from COVID-19 as the
Parker, A. ¹³⁶	24 PWH/92 HIV negative controls	South Africa	21-Aug-20	S Afr Med J	general population Coinfected PWH had similar presentations and outcomes as
Boulle, A. ⁹¹	553,749 PWH	South Africa	29-Aug-20	Clin Infect Dis	HIV was independently associated with increased COVID-
Larzábal, F.J. ⁷	1 PWH	Argentina	31-Aug-20	Medicina	Described a PWH hospitalized with Pneumocysti jiroveccii and
Molina- Iturritza, E. ¹³⁹	8 PWH	Spain	1-Sep-20	AIDS	The rate of COVID-19 in PWH is similar to the rate in the
Sasset, L. ⁷⁰	2 PWH	Italy	1-Sep-20	AIDS	PWH had similar demographic and clinical characteristics to the general perulation
Hu, Y. ¹⁹⁷	12 PWH	China	1-Sep-20	J Acquir Immune Defic Syndr	The value of ART for mitigation of COVID-19 infection
Shekhar, R. ¹¹⁰	5 PWH	USA	1-Sep-20	J Acquir Immune Defic Syndr	PWH may have a milder course of COVID-19 than the
Madge, S. ¹¹⁷	18 PWH	United Kingdom	2-Sep-20	Sex Transm Infect	PWH did not have prolonged hospital courses or worse outcomes compared to the
Etienne, N. ⁶⁴	54 PWH and COVID-19 positive/ 4000 PWH	France	3-Sep-20	AIDS	general population PWH had worse COVID-19 outcomes when they were older age, male, had comorbidities, higher BMI, sub- Saharan Africa origins, had
Inciarte, A. ³⁷	53 PWH and COVID-19 positive/ 5683 PWH	Spain	3-Sep-20	AIDS	Incidence rate of COVID-19 was lower in PWH compared to general population; clinical course of COVID-19 was not dependent on any HIV- or
Winston, A. ⁷⁷	699 PWH/304 HIV negative controls	United Kingdom and Ireland	3-Sep-20	AIDS	PWH tended to have more comorbidities which was associated with poorer COVID-
d'Ettore, G. ³¹	1 PWH	Italy	4-Sep-20	Medicine	19 outcomes Coinfection of HIV and COVID-19 showed increased levels of IFN α/β and T-cell activation as compared to healthy individuals with COVID-19
Bertolini, M. ⁵⁴	1 PWH	Argentina	9-Sep-20	Int J STD AIDS	Described a male patient with AIDS-related disseminated

First author	Population	Location	Publication date	Journal	Description or findinas
	-1				histoplasmosis associated with
Dandachi, D. ²⁰	286 PWH	USA	9-Sep-20	Clin Infect Dis	COVID-19 PWH were at higher risk for severe COVID-19 outcomes, especially those with comorbidities and lower CD
Akyala, A.I. ¹⁹⁸	4 PWH	Nigeria	10-Sep-20	Pan Afr Med J	cell counts PWH experienced a mild COVID-
Nagarakanti, S.R. ¹¹⁴	23 PWH/23 HIV negative controls	USA	19-Sep-20	J Med Virol	Among, PWH, there was not higher mortality, ICU admissions, or mechanical ventilation in PWH than in the
Chiappe Gonzalez,	1 PWH	Peru	21-Sep-20	Int J STD AIDS	HIV/COVID-19 coinfection led to a fatal outcome
Mondi, A. ¹²⁰	5 PWH	Italy	25-Sep-20	J Med Virol	PWH did not have more severe COVID-19 outcomes than the
Isernia, V. ⁷⁸	30 PWH	France	26-Sep-20	Int J Infect Dis	general population HIV was not a risk factor for COVID-19
Sun, S. ¹⁵⁰	703 PWH	China	Oct-20	AIDS Behav	PWH reported high rates of anxiety, depression, and incompia
Collins, L.F. ⁴⁶	20 PWH	USA	1-Oct-20	AIDS	PWH with more than 5 comorbidities, who are non- Hispanic Black, are male had more severe COVID- 19 outcomes
Di Biagio, A. ²⁰⁶	4 PWH	Italy	1-Oct-20	AIDS	Protease inhibitor-based regimens were not protective against
Yamamoto, S. ²⁰⁰	5 PWH	Japan	2-Oct-20	J Microbiol Immunol	PWH coinfected with COVID-19 have a similar clinical course as patients without HIV
Kim, J.Y. ¹¹⁸	1 PWH	Korea	12-Oct-20	Korean Med Sci	PWH had a favorable clinical
Gamboa, E. ¹²³	1 PWH	USA	17-Oct-20	Cureus	Noted that CD4+ lymphocytes declined over the course of COVID-19 hospitalization in a PWH
Zhang, J.C. ³²	2 PWH	China	19-Oct-20	BMC Infect Dis	Described the importance of accurate diagnosis for PWH
Geretti, A.M. ⁸⁵	115 PWH/47,424 HIV negative controls	United Kingdom	23-Oct-20	Clinical Infectious Diseases	Following additional adjustment for disease severity at presentation, mortality was
Yang, R. ⁹⁷	3 PWH/53 HIV negative controls	China	27-Oct-20	Expert Review of Respiratory	Low CD4 count was a risk factor for severe COVID-19 outcomes
Cabello, A. ¹³⁷	63 PWH	Spain	27-Oct-20	Int J Infect Dis	Coinfected PWH do not have different outcomes based on severity of HIV or type of ADV tractment
Di Biagio, A. ⁹⁶	69 PWH	Italy	1-Nov-20	AIDS	Lower CD4 counts were associated with higher rates of COVID-19 hospital admission
Hadi, Y.B. ²⁸	404 PWH/49,763 HIV negative controls	USA	1-Nov-20	AIDS	and more severe outcomes Propensity-matched analysis showed no difference in outcomes for PWH compared to the non-HIV controls; higher mortality was related to comorbidition
Siewe Fodjo, J.N. ¹⁵⁷	317 PWH	Belgium, Brazil	1-Nov-20	J Acquir Immun Defic Syndr	23.3% of PWH screened positive for depression and 22.7% screened positive for anxiety during the COV/ID-19 pandemia
Morani, Z. ⁶⁹	43 PWH	Belize, USA	2-Nov-20		
					(Continued)

First author	Population	Location	Publication date	Journal	Description or findings
			*	SN Compr	Comorbidities and advanced age
				Clin Med	make PWH more prone to worse COVID-19 outcomes
Tesoriero, J.M. ⁹⁰	2988 PWH	USA	6-Nov-20	MedRxiv	PWH experienced poorer COVID- 19 related outcomes than those without HIV
Jones, D.L. ¹⁶³	1554 PWH	Argentina, USA	18-Nov-20	Res Sq	PWH who had higher levels of social support reported less depression during the COVID- 19 pandemic
D'Souza, G. ⁵³	2078 PWH/1333 HIV negative controls	USA	19-Nov-20	HIV Res Clin Pract	PWH had similar prevalence and type of COVID-19 symptoms as the general population
Sachdev, D. ⁴²	193 PWH and COVID-19 positive/ 4252 PWH	USA	20-Nov-20	J Acquir Immune Defic Syndr	PWH were more susceptible to COVID-19 than those without HIV
Turken, M. ⁹⁸	4 PWH	Turkey	30-Nov-20	Curr HIV Res	Two patients with normal CD4+ count had mild coinfections, a patient with low CD4+ count died
Braunstein, S.L. ¹⁰³	2410 PWH	USA	30-Nov-20	Clin Infect Dis	More PWH had adverse COVID- 19 outcomes than the general population, perhaps due to comorbidities and other social determinants of health
Swaminathan, N. ¹⁴⁵	6 PWH	USA	1-Dec-20	J Med Virol	PWH had similar mortality when compared to other studies
Hardy, Y.O. ¹²⁷	3 PWH	Ghana	Dec-20	Ghana Med J	PWH with advanced immunosuppression may not have an unfavorable COVID-19 disease outcome
Kowalska, J.D. ¹²²	34 PWH	Central and Eastern Europe	13-Dec-20	Int J Infect Dis	HIV serostatus was not associated with more severe disease
Kuman Tuncel, O. ¹⁵⁹	307 PWH	Turkey	17-Dec-20	Turk J Med Sci	A significant proportion of PWH had anxiety during the COVID- 19 pandemic
Hoffmann, C. ²⁰⁹	175 PWH	Germany, Spain, Italy	27-Dec-20	HIV Med	Virological suppression was possibly related to severe COVID-19 outcomes; no evidence of protective effect by ARTs
Noe, S. ¹³⁵	500 PWH	Germany	2-Jan-21	Infection	There were no marked differences for PWH with and without SABS-CoV-2 co-infection
Cooley, S.A. ¹⁵⁶	54 PWH/133 HIV negative controls	USA	6-Jan-21	J Neurovirol	PWH had increased symptoms of anxiety and depression during the COVID-19 pandemic
Laracy, J. ¹³²	68 PWH/272 HIV negative controls	USA	28-Jan-21	Open Forum Infect Dis	PWH did not did not differ from HIV-uninfected controls by rate of mechanical ventilation or death
Tesoriero, J.M. ⁸⁹	2988 PWH/2409 HIV	USA	1-Feb-21	JAMA Netw Open	PWH experienced poorer COVID- 19 outcomes than the general population
Patel, V.V. ¹³⁴	100 PWH/4513 HIV negative controls	USA	1-Feb-21	Acquir Immune Defic Syndr	PWH had increased risk of intubation but similarly frequent rates of AKI and in-hospital death as those without HIV
Ceballos, M.E. ¹³³	36 PWH	Chile	3-Feb-21	Int J STD AIDS	No differences were found between PWH and the general population in the need for mechanical ventilation and death
Nasreddine, R. ⁶⁵	101 PWH	Belgium	9-Feb-21	J Med Virol	HIV patients with COVID-19 experienced a high degree of hospitalization
Delle Donne, V. ¹⁶²	98 PWH	Italy	1-Mar-21	Infez Med	Almost half of PWH experienced significant distress due to the COVID-19 pandemic
					(Continued)

First author	Population	Location	Publication date	Journal	Description or findings
Eybpoosh, S. ¹²⁴	90 PWH	Iran	10-Mar-21	Med J Islam Repub Iran	HIV infection was not a risk factor for increased COVID-19
Sorbera, M. ¹⁸³	211 PWH	USA	16-Mar-21	J Am Coll Clin Pharm	severity and death Telehealth for pharmacy services did not jeopardize
Weerasuria, M. ¹⁴⁹	153 PWH	Australia	17-Mar-21	AIDS Res Hum Retroviruses	patient outcomes Telehealth was widely used; many PWH experienced negative mental health in the COVID- 10 pagdomic
Farinacci, D. ⁵⁹	1 PWH	Italy	31-Mar-21	AIDS Res Hum	PWH coinfected with
Durstenfeld, M.S. ¹²⁸	220 PWH	USA	7-Apr-21	MedRxiv	HIV was not associated with adverse outcomes of
Mohindra, R. ¹³⁰	1 PWH/1 HIV	India	7-Apr-21	Virus disease	PWH had a similar clinical course
Liu, W. ¹⁴⁶	1 PWH	Taiwan	21-Apr-21	J Formos Med Assoc	The clinical presentation of coinfected PWH were similar to other COVID-19 patients without HIV infection
Diaz, M.M. ¹⁵³	156 PWH	Peru	26-Apr-21	MedRxiv	PWH reported increased anxiety and stress during the COVID- 19 pandemic
Mang, S. ⁶⁰	1 PWH	Germany	26-Apr-21	Clin Infect Dis	PWH coinfected with COVID-19
Siewe Fodjo, J.N. ¹⁵⁴	247 PWH	Brazil	27-Apr-21	Int J Environ Res Public Health	27.1% of PWH screened positive for anxiety, 27.9% screened positive for depression during the COVID-19 pandemic
Spinelli, M.A. ⁸⁷	955 PWH/1062 HIV	USA	29-Apr-21	Lancet HIV	PWH had more cases of severe
Liang, M. ¹⁰⁴	7718 PWH/196,043 HIV	China	3-May-21	Infect Dis Ther	Coinfected PWH were not associated with higher COVID- 19 mortality
Merchant, E.A. ⁵⁸ Charifi, Y. ⁵⁷	1 PWH 1 PWH	USA Morocco	7-May-21 15-May-21	ID Cases Clin Case Rep	Coinfection PWH had PJP Coinfected PWH had pneumocystis with
Massarvva, T. ¹²⁶	730 PWH	Cyprus	17-May-21	Epidemiol Health	Coinfected PWH had comparable clinical outcomes with the
Kumar, S. ¹⁵¹	167 PWH	India	19-May-21	New Microbes New Infect	Many PWH experience fear, anxiety and depression in the
Venturas, J. ¹²⁵	108 PWH/276 HIV	South Africa	26-May-21	J Infect	HIV is not a risk factor for severe
Ader, F. ²¹⁰	583 patients	France	26-May-21	Clin Microbiol	COVID-19 disease of mortality COVID-19 clearance and clinical status were not improved but
Pujari, S. ⁶⁷	86 PWH	India	31-May-21	AIDS Res Hum Retroviruses	Coinfected PWH had similar clinical outcomes as the general population; comorbidities are associated
Pujari, S. ⁹⁵	94 PWH	India	2-Jun-21	Immun Inflamm Dis	With more severe outcomes Long-COVID is common among PWH with moderate-severe
Rocha, S.Q. ⁶³	255 PWH	Brazil	4-Jun-21	AIDS Care	acute COVID-19 Skin color/race, and schooling remained significantly associated with higher COVID-
Chanda, D. ¹⁰¹	122 PWH	Zambia	4-Jun-21	MMWR	19 mortality in PWH Severe HIV is associated with increased risk of COVID- 19 death
Di Castelnuovo,	3,451 patients	Italy	9-Jun-21	Front med	DRV/c was associated with increased mortality
A. Wu, M. ⁵⁶	68 PWH/980 HIV negative controls	China	9-Jun-21	Res Sq	Older age was considered a driving force for coinfection in PWH

			Publication		
First author	Population	Location	date	Journal	Description or findings
Wion, R.K. ¹⁵²	154 PWH	USA	15-Jun-21	AIDS Behav	PWH experienced an increase in social isolation, depression, and stress
Flannery, S. ⁹⁹	99 PWH	USA	22-Jun-21	Int J STD AIDS	Hospitalized coinfected PWH did not have worse outcomes than the general population; PWH who had CD4% <14 or not on treatment for HIV had higher mortality rates
Berenguer, J. ²⁰³	91 PWH	Spain	26-Jun-21	Clin Microbiol Infect	TDF/FTC may prevent SARS- CoV-2 infection among PWH
Dong, Y. ⁹³	41,113 PWH/ 18,081,257 HIV negative controls	China	2-Jul-21	Medicine (Baltimore)	PWH had a higher risk of mortality from COVID-19 than those without HIV infection
Bertagnolio, S. ⁹²	15,522 PWH/ 168,649 negative controls	24 countries	15-Jul-21	WHO	PWH were at increased risk for severe or critical COVID-19

Abbreviations: PWH, person(s) living with HIV; ART, antiretroviral therapy; USA: United States of America.

comorbidities were not.⁶³ To the best of our knowledge, thus far only one study has investigated the risk of post-acute symptoms following COVID-19 and found that moderate to severe disease was associated with an increased risk of persistent symptoms in PWH.⁹⁵

Dandachi et al. (n = 286) noted that patients with lower CD4 counts (<200 cells/mm³) may be at risk for more severe outcomes despite viral suppression and supported by other smaller studthis was ies.^{20,72,84,96-103} The results of Dandachi et al. are strong and generalizable as they pull data from 36 institutions across 21 states and three countries. However, the study did not collect data on social determinants of health or COVID-19 therapies, which may have differed and confounded the results. Greater comorbidity burden in PWH has also been associated COVID-19 with more severe outcomes.^{20,28,46,64,76,77,104}

Other studies suggest that PWH have fewer COVID-19 complications, fewer admissions to the ICU, and lower mortality rates (as seen in Table 1).^{105–111} Larger cohorts from Spain, Italy, and the USA as well as many smaller studies have found no association or an unclear association between severity of outcomes such as ICU admission, need for mechanical ventilation, or mortality rates and HIV serostatus.^{34,38,44,61,74,80,99,112–147}

In general, PWH appear to be at higher risk for severe COVID-19 outcomes even after considering demographic factors and comorbidities associated with severe disease. However, it is important to note that due to the quickly changing testing procedures and requirements for hospitalization throughout the pandemic, as well as the reliance on public health surveillance data and/or medical record review, the ability to truly distinguish severity of outcomes in PWH is difficult and often confounded.¹⁴⁸ Regardless, preventive measures for PWH should be strongly encouraged (particularly vaccination) to limit disease severity.

How does COVID-19 impact the mental health of PWH?

The social distancing and quarantine strategies required to reduce the spread of SARS-CoV-2 have left many feeling isolated and lonely. This is especially impactful to PWH as they have increased worry about physical health (68%), mental health (66%), finances (50%), and accommodation (25%) during the COVID-19 pandemic.¹⁴⁹ One study found that of 703 PWH, 61% of PWH reported depressive symptoms, 50% noted anxiety symptoms, and 39% experienced recent insomnia.¹⁵⁰ Other smaller studies have also found increased rates of depression, anxiety, insomnia, and substance abuse in relation to the COVID-19 pandemic.^{151–162} Importantly, these rates are lower amongst people who report strong levels of social support in a large study from two countries.¹⁶³

How does COVID-19 impact access to care for PWH?

The COVID-19 pandemic has restricted access to care for much of the population by restricting public transportation, suspending routine appointments, and adding financial hardships. PWH specifically are at high risk of treatment interruption due to reduced access to HIV clinics, reduction in primary care or specialty referrals, and difficulties refilling ART prescriptions.^{150,156,157,164–176} Telemedicine has proven to be very effective in many countries as it provides flexibility in scheduling appointments, reduces the need for transportation, and provides privacy for patients not wanting to be seen attending an HIV clinic.^{149,177–184} However, telemedicine also presents barriers including technological challenges, client/provider experiences, digital literacy, low socio-economic status of client population, and reimbursement issues.^{185–187} Many countries have identified this imbalance in access to care both with HIV diagnosis and ongoing care and have provided at-home testing kits, distributed condoms with COVID-19 testing services, and mailed ART to ensure continuity of care.^{188–193}

How does ART influence acquisition of SARS-CoV-2 or severity of COVID-19?

In the USA, an estimated 61.5% of the 1.2 million persons living with HIV are virologically suppressed using ART.¹⁹⁴ Consequently, most PWH who develop COVID-19 will be on suppressive ART. While maintaining suppressed viral load and a normal CD4 Tlymphocyte count likely decreases the risk of severe COVID-19, there is yet to be clear evidence that ART itself prevents the acquisition of SARS-CoV-2 infection or alters the rate of progression to severe disease.^{51,144,195–201} Three observational studies have suggested a potential protective role of tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) among PWH.^{91,202,203} The last of these adjusted for comorbidities, demographics, country of birth, and education level. As TDF/FTC tends to be avoided due to toxicity among older patients with more comorbid conditions, this finding may be due to confounders of younger age and fewer comorbidities, rather than a protective effect of the drug.91,202 Similarly, the HIV protease inhibitor lopinavir-ritonavir has in vitro activity against SARS-CoV-2 and some speculate that it may be protective against COVID-19.204 However, a randomized control trial of this medication in 199 HIV-negative persons with COVID-19 have failed to demonstrate a clinical benefit and other studies, including systemic reviews and meta-analyses, support the conclusion that ART does not serve a protective role against SARS-CoV-2 infection.49,205-212 A study of darunavir/cobicistat actually showed an increased mortality rate.²¹³ However, this was an observational study that may have been affected by confounders.

General management of COVID-19 among PWH

The guidelines for management of care for PWH and COVID-19 does not differ from those without HIV, although the likelihood of severe disease and poor outcomes may be heightened. Thus, we suggest that the following principles of HIV management are important in persons who present with COVID-19²¹⁴:

- Public health precautions including hand hygiene, mask wearing, and physical distancing should be strictly adhered to.
- Compliance with routine vaccinations, including influenza, should be emphasized.
- COVID-19 vaccination should be given.
- Consideration could be given to telehealth visits in place of in-person visits to ensure continuity of care, particularly in areas of high COVID-19 rates and when there are no acute health concerns.
- For persons who are on HIV treatment, ART and opportunistic infection prophylaxis (if applicable) should be continued, if feasible based on the patient's clinical condition.
- ART should not be adjusted in an attempt to treat COVID-19.
- With regards to COVID-19 treatment, there are no significant drug-drug interactions between remdesivir and ART. Dexamethasone is an inducer of hepatic metabolism of drugs and could decrease the levels of some co-administered ART.²¹⁵ As the course of dexamethasone is typically limited to 10 days or less, it is unlikely that this interaction will be significant in most circumstances.
- If there is a need to adjust or change ART, consultation with an HIV specialist is recommended. For critically ill patients who require enteral feeding, some ART are available in liquid formulations and some pills may be crushed. Clinicians should consult an HIV specialist and/or pharmacist to assess the best way for a patient with a feeding tube to continue an effective regimen.
- Regarding prophylaxis for opportunistic infections, whether the lymphopenia associated with COVID-19 places PWH at higher risk for opportunistic infections is not currently known. As this lymphopenia is limited, the risk of acquiring infections is not expected to alter prophylactic therapy.
- As COVID-19 may occur more commonly in people with limited prior access or engagement to the healthcare system, the hospitalization is an opportunity to screen for HIV and other infections (hepatitis C, tuberculosis), as indicated. For persons who present with COVID-19 and a new diagnosis of HIV infection, the timing of starting ART is currently unknown. Currently, the Department of Health and Human Services guidelines recommend immediate initiation of ART in persons with newly diagnosed HIV infection.²¹⁴ Immune reconstitution could help in the management of SARS-CoV-2 infection. In contrast, immune reconstitution could also exacerbate the inflammatory response and worsen respiratory failure or contribute to a hypercoagulable state in others. Other characteristics such as renal failure, thrombosis, or mechanical ventilation might suggest a delay in ART initiation to avoid further exacerbating inflammation. Consultation with an HIV specialist is advised.

Conclusion

Although initial case studies and small cohorts found similar rates of infection and severity in PWH, the growing literature in diverse settings throughout the course of the pandemic now suggests that PWH are at greater risk for severe disease, even with well-controlled HIV. As the pandemic continues, PWH should be counseled regarding the heightened risk from HIV, in addition to other demographic or comorbid factors. Precautions to limit unnecessary exposure and decrease risk for acquisition (i.e. handwashing, physical distancing, mask wearing) should be encouraged particularly during surges in infection rates. While the general care of PWH who also acquire SARS-CoV-2 infection does not differ from people without HIV, certain considerations regarding drug-drug interactions can be guided through consultation with an HIV specialist. Lastly, while separate from the direct complications of COVID-19, the isolation and loneliness experienced during this pandemic, potential interruptions of medication therapy, and reduced access to care may have an even more profound effect on those experiencing the stigma of HIV. Ensuring that PWH are able to stay connected to local resources and monitoring for the impact on mental health and well-being will have important long-term implications.

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