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SUBSTANTIVE REVIEW

COVID-19 Among People Living with HIV: A Systematic Review

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Abstract
This systematic review summarizes the evidence on the earliest patients with COVID-19-HIV co-infection. We searched PubMed, Scopus, Web of Science, Embase, preprint databases, and Google Scholar from December 01, 2019, to June 1, 2020. From an initial 547 publications and 75 reports, 25 studies provided specific information on COVID-19 patients living with HIV. Studies described 252 patients, 80.9% were male, the mean age was 52.7 years, and 98% were on antiretroviral treatment (ART). Co-morbidities in addition to HIV and COVID-19 (multimorbidity) included hypertension (39.3%), obesity or hyperlipidemia (19.3%), chronic obstructive pulmonary disease (18.0%), and diabetes (17.2%). Two-thirds (66.5%) had mild to moderate symptoms, the most common being fever (74.0%) and cough (58.3%). Among patients who died, the majority (90.5%) were over 50 years old, male (85.7%), and had multimorbidity (64.3%). Our findings highlight the importance of identifying co-infections, addressing co-morbidities, and ensuring a secure supply of ART for PLHIV during the COVID-19 pandemic.

Keywords HIV · COVID-19 · SARS-CoV-2 · Co-infection · Systematic review

Introduction

Coronavirus disease 2019 (COVID-19) was declared a pandemic on March 11th, 2020 [1]. As of July 10th, 2020, 12,102,328 COVID-19 patients and 551,046 COVID-19-related deaths have been reported worldwide [2]. The World Health Organization (WHO) and Center for Disease Control and Prevention (CDC) have issued health alerts and prevention guidelines for people at increased risk for severe health outcomes and death due to COVID-19 [3, 4]. These guidelines are generally based on the outcomes and characteristics of patients affected early in the course of the COVID-19 pandemic. Emerging patterns point to elevated risk for older persons, people living in long-term care facilities, men, and racial/ethnic minorities who have long experienced disparities in health outcomes for many chronic diseases [5]. Chronic disease co-morbidities, especially multimorbidity, appear to be driving factors for COVID-19 mortality. Warnings to take extra precautions include persons with asthma, chronic lung disease, diabetes, serious cardiovascular conditions, chronic kidney disease, obesity, chronic liver disease, and persons who are immunocompromised, such as people living with HIV (PLHIV) [3–5].

The concern over increased risk for severe COVID-19 disease for PLHIV may be based on the assumption that PLHIV are more likely to be immunosuppressed. HIV infection is associated with abnormal humoral and T-cell–mediated immune responses, resulting in increased susceptibility to numerous opportunistic infections [6]. Under this rationale, particular caution is warranted for PLHIV with low CD4 cell count, advanced disease, high viral load, and those not taking antiretroviral treatment (ART). As PLHIV are living longer with ART, many will also have chronic conditions associated with severe COVID-19 disease [7]. However, there have not been large observational studies specifically measuring symptoms, disease severity, complications,

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multimorbidity, and the proportion of death in reported COVID-19-HIV co-infected patients. It is also not known if people with HIV who are clinically and virologically stable will experience any greater risk for COVID-19 complications than the population without HIV infection. At present, the available data mainly appear in case reports and case series of COVID-19-HIV co-infected patients.

Given the urgency of the COVID-19 pandemic and the rapidly changing information about the disease, a high degree of vigilance is needed on the course of infection among PLHIV. As there are 37.9 million PLHIV and 1.7 million new infections each year [8], patients of COVID-19-HIV co-infection are likely to increase. This systematic review was therefore undertaken to bring together the existing evidence on the earliest known case reports to provide a baseline for what is known and to alert providers around the world of any emerging patterns.

Methods

Details of inclusion criteria and our analytical approach were conceptualized a priori and are documented in Open Science Framework (https://osf.io/zj2hu/).

Literature Search

Following the Systematic Reviews and Meta-Analyses (PRISMA) checklist (see the Supplementary File S1) and the Peer Review of Electronic Search Strategies [9] guideline [10, 11], we searched PubMed, Scopus, Web of Science, Embase, preprint databases (medRxiv, bioRxiv, Preprints), the references of publications found, and the "cited by" feature of Google Scholar from December 1, 2019, to June 1, 2020, for studies published in English. Search terms were combined using appropriate Boolean operators and included subject heading terms/keywords relevant to COVID-19 (e.g., SARS-CoV-2 OR Coronavirus Disease 2019 OR COVID-19 OR severe acute respiratory syndrome coronavirus 2 OR coronavirus infection) and HIV (e.g., HIV OR human immunodeficiency virus OR AIDS OR Acquired Immunodeficiency Syndrome). Please see the Supplementary File S2 for a sample search strategy.

Inclusion Criteria and Study Selection

Empirical studies including any study design (i.e., case report, case series, cross-sectional, case–control, cohort, and clinical trial) that reported individual- or aggregate-level data on COVID-19 among PLHIV were considered for this review. Studies that included a mixed sample of HIV-positive and HIV-negative COVID-19 patients were only considered if subgroup analyses for PLHIV were reported or could be extracted. Studies were excluded if they did not present original empirical data (e.g., editorials, commentaries, letters to editors, and reviews) or did not report any clinical data on patients with HIV and COVID-19 co-infection. The title, abstract, and full-text screening were completed in duplicate and independently by two reviewers. Duplicate records were excluded and disagreements over the inclusion of studies for data extraction were resolved through discussion or feedback from the senior author.

Data Extraction

Data extraction was completed in duplicate, and discrepancies were resolved through discussion or feedback from the senior author. Data were extracted on publication date, study type, location, sample size, participants' age, and sex, as well as HIV-related characteristics such as CD4 count (cells/mm3), viral load (copies/ml), and antiretroviral therapy before COVID-19 diagnosis. Data were also extracted for COVID-19-related clinical symptoms (e.g., fever, cough, myalgia, dyspnea, headache, sore throat, fatigue, and gastrointestinal symptoms). Comorbidities other than HIV included atrial fibrillation, chronic kidney disease, congestive heart failure, chronic liver disease, cerebrovascular accident, cardiovascular disease, dyslipidemia, diabetes mellitus, hyperlipidemia, hypertension, obstructive sleep apnea, pulmonary embolism, obesity, and smoking. The severity of COVID-19 disease was classified as mild (i.e., non-pneumonia and mild pneumonia), severe (i.e., dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation $\leq 93\%$, and/or lung infiltrates $> 50\%$ within 24–48 h), and critical (i.e., respiratory failure, septic shock, and/or multiple organ dysfunction or failure) [12]. Admission to the intensive care unit (ICU) and recovery status (cured, died, still in hospital) were also assessed and reported.

Quality Assessment

The Joanna Briggs Institute's critical appraisal tools were used to assess the methodological quality of the included papers [13]. Selected studies were examined for inclusion criteria, sample size, description of study participants, setting, and the appropriateness of the statistical analysis. Methodological quality was independently assessed by two reviewers, and disagreements were resolved through discussion. The tool was modified to provide a numeric score [14, 15]. Quality assessments were done with different tools based on different study designs. Tools had nine items for case reports, ten items for case series, nine items for cross-sectional studies, and eleven items for cohort studies. Quality assessment tools and scores are presented in the Supplementary File S3.

Statistical Analysis

Descriptive analyses were used for reporting results. Continuous variables were summarized using mean and standard deviation (SD) with differences compared using a two-tailed student's *t* test. Categorical variables were summarized by frequency and percentage and differences were measured using the Fisher's exact test. P-values less than 0.05 were considered as statistically significant. For combining data from studies that reported aggregated data with those reported individual data, aggregated data were weighted by the number of patients. The proportion of death among reported patients in studies included in the review was also measured. The denominator and nominator for this measure are based on people living with HIV whose COVID-19 was diagnosed and reported. We also conducted a subgroup analysis by sex.

Results

The combined search strategy identified 622 potential publications on COVID-19 infection among PLHIV (Fig. 1). After screening and removing duplicate studies ($n=222$) and those not relevant to COVID-19-HIV co-infection ($n=343$), the full-texts of 57 reports were sought to assess for eligibility. Of these, eight did not report information about patients with co-infection; 23 were editorials, commentaries, or reviews; and the full-text for one abstract was unavailable. The search found 25 studies that met our inclusion criteria and were included in the systematic review (Table 1).

Of the 25 studies on COVID-19-HIV co-infection, 19 reported information on an individual-level, and six reported on an aggregate-level. Eleven studies were case reports (i.e., describing one patient), ten studies were case series including 2–33 patients. Two studies were cross-sectional investigating COVID-19 status among PLHIV. Two cohort studies were found. Eight studies were from the US, seven from China, three from Italy, two from Spain, and the remaining five studies were from Turkey, Germany, the UK, Republic of Cyprus, and Uganda. Publication dates ranged from March 12, to June 1, 2020. The Joanna Briggs Institute critical appraisal tools assessment scores ranged from 4 to 7 for case reports (out of 8 possible points), and 4–8 for the case series (out of 10 possible points), 6–7 for cross-sectional (out of 9 possible points), and 8–9 for cohort studies (out of 11 possible points). As quality assessments were done with different tools based on different study designs, scores cannot be directly compared.

Summed across all studies, 252 patients with COVID-19-HIV co-infection were described with varying completeness of demographic and clinical data (Table 2). The mean age of the patients was 52.7 years. Most patients (204, 80.9%) were male; 46 (18.3%) were female, and two (0.8%) were transgender women. Of 251 patients in studies reporting ART status, only 2.0% were not taking ART. Low CD4 count (< 200 cells/mm^3) was reported for 23 of 176 patients (13.1%). The viral load was high (> 1000 copies per ml) for two of 233 patients (0.9%) with viral load data. Multimorbidity included hypertension (96 of 244 patients reporting on co-morbidities, 39.3%), obesity or hyperlipidemia (as reported, 19.3%), chronic obstructive pulmonary disease (18.0%), and diabetes (17.2%). Smoking was reported in 53 patients (21.7%).

Table 2 also presents reported symptoms and severity of COVID-19 disease patients with HIV infection. The most common symptoms were fever (165 of 223, 74.0%), cough (130 of 223, 58.3%), and dyspnea (68 of 223, 30.5%). Less common were headache (44 of 223, 19.7%), arthralgia/myalgia (33 of 223, 14.8%), and sore throat (18 of 223, 8.1%). Any gastrointestinal symptoms were reported by 13.0%. COVID-19 was reported as mild to moderate in 141 of 212 (66.5%), severe in 46 patients (21.7%), and critical in 25 patients (11.8%). The majority of patients (158 of 244, 64.7%) were hospitalized; 16.8% were admitted to the intensive care unit.

Of all 252 reported cases of COVID-19-HIV co-infection, 36 (14.3%) were reported as having died. Supplementary File S4 presents further information on patients where available. Information on the sex of the deceased was available for 14 of 36 patients, with 85.7% being male. Information on the age of the deceased was available for 21 of 36 patients, with 38.1% of deaths occurring in patients over 65 years of age and older, 52.4% in patients age 50–65 years of age, and 9.5% in patients younger than 50 years. Information about multimorbidity, was available for 14 of 36 the deceased patients, with 64.3% reporting multimorbidity. Additional information on ART regimen, CD4 count, viral load, and indicators of the severity of the disease can be found in the Supplementary File S4.

Based on the available data, no significant differences between male and female patients were observed with regards to age, clinical characteristics, the severity of COVID-19, and health outcomes of COVID-19-HIV co-infected patients (Table 3).

Discussion

In this systematic review, we summarized available data from 252 patients co-infected with COVID-19 and HIV. The majority of patients with co-infection of HIV and COVID-19 were male. Also, in line with HIV-negative persons [16–19], data point to higher morbidity and mortality among male patients and higher mortality when multimorbidity is present. The main clinical symptoms of COVID-19 in PLHIV

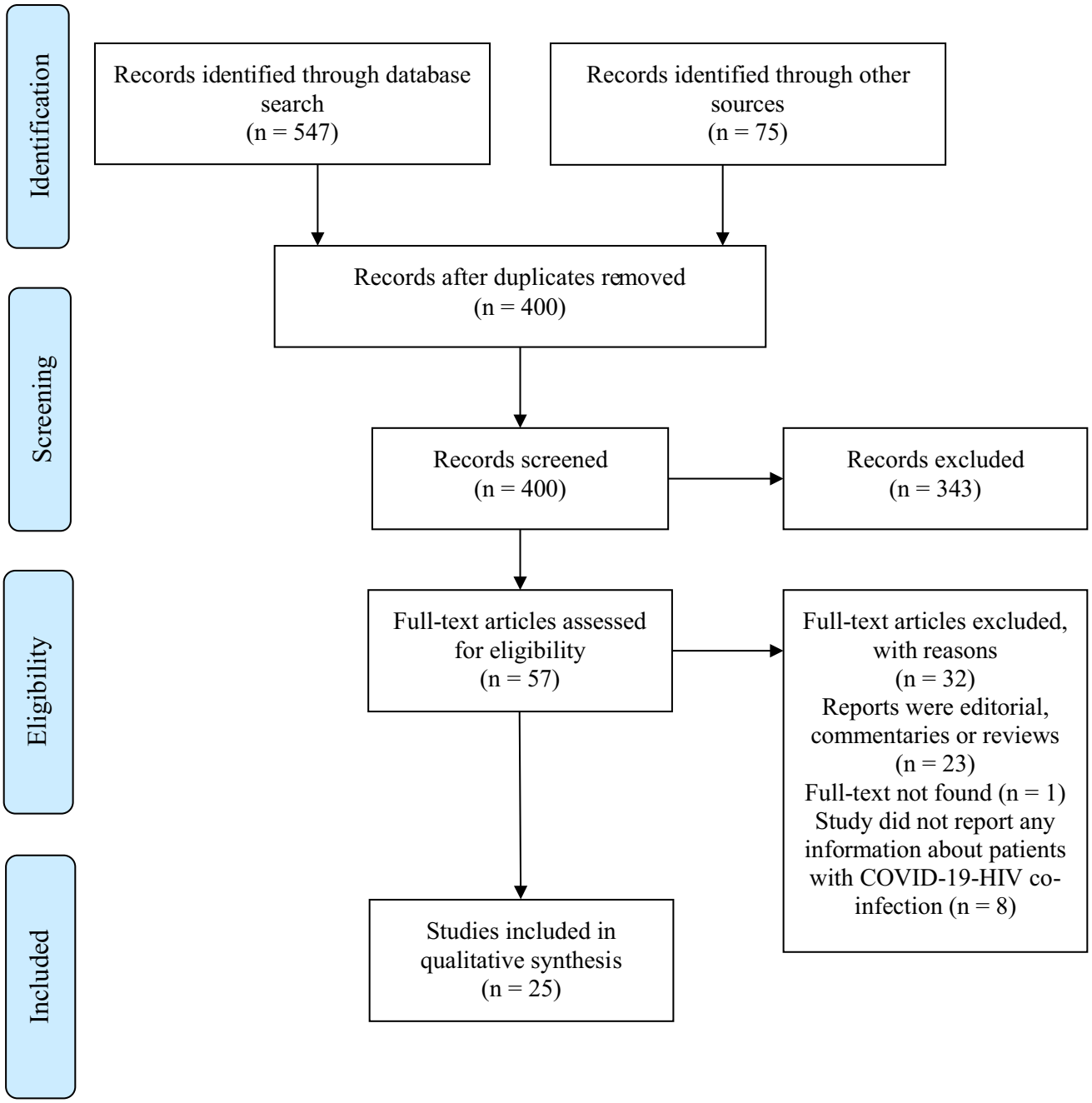

Fig. 1 Flowchart of studies included in the systematic review of COVID-19-HIV co-infection

were cough and fever, and comparable to HIV-negative people, the majority had mild COVID-19 disease [16–19].

Nonetheless, the proportion of reported PLHIV with COVID-19 appears to have higher multimorbidity, severity of disease, and a potentially higher proportion of death. Multimorbidity was reported in nearly two-thirds of co-infected patients. The most common co-morbidities among patients with HIV and COVID-19 were hypertension, obesity or hyperlipidemia, chronic obstructive pulmonary disease, and diabetes. Results of a cohort study showed that multimorbidity (mostly hypertension and diabetes) was more prevalent in COVID-19-HIV co-infected patients than PLHIV without COVID-19 [20]. When data were available, the proportion of death among reported COVID-19-HIV co-infected patients appears high (14.3%) in our pooled estimate. The result might be confounded by other factors. For example, PLHIV may be at increased risk of mortality or severe illness with COVID-19 based on their age and other medical conditions. Among those who died for whom individual data were recorded, multimorbidity and

Table 1 Characteristic of studies included in the review of COVID-19-HIV co-infection

First author (Reference)	Setting	Publication date	Study type	Data type[a]	Sample size	Case definition	Quality assessment
Zhu [22]	Wuhan, China	12/03/20	Case report	Individual	1	Confirmed	5/8
Guo [23]	Wuhan, China	03/04/20	Cross-sectional	Aggregate	8	Confirmed	7/9
Zhao [24]	Shenzhen, China	10/04/20	Case report	Individual	1	Confirmed	6/8
Chen [25]	Guizhou, China	15/04/20	Case report	Individual	1	Confirmed	6/8
Su [26]	China	17/04/20	Case report	Individual	1	Confirmed	6/8
Schweitzer [27]	Italy	18/04/20	Case report	Individual	1	Confirmed	4/8
Blanco [28]	Barcelona, Spain	19/04/20	Case series	Individual	5	Confirmed	8/10
Riva [29]	Italy	24/04/20	Case series	Individual	3	Confirmed	4/10
Wang [30]	Wuhan, China	27/04/20	Case report	Individual	1	Confirmed	6/8
Altuntas Aydin [31]	Istanbul, Turkey	30/04/20	Case series	Individual	4	Confirmed	7/10
Haerter [32]	Germany	01/05/20	Case series	Individual	33	Confirmed	8/10
Karmen [33]	New York, USA	12/05/20	Retrospective cohort	Aggregate	21	Confirmed	8/11
Wu [34]	Wuhan, China	13/05/20	Case series	Individual	2	Confirmed	4/10
Gervasoni [35]	Italy	15/05/20	Cross-sectional	Aggregate	47	Confirmed/Probable	6/9
Benkovic [36]	New York, USA	20/05/20	Case series	Individual	4	Confirmed	4/10
Haddad [37]	Wynnewood, USA	20/05/20	Case report	Individual	1	Confirmed	7/8
Baluku [38]	Uganda	22/05/20	Case report	Individual	1	Confirmed	6/8
Patel [39]	USA	23/05/20	Case report	Individual	1	Confirmed	6/8
Iordanou [40]	Cyprus	25/05/20	Case report	Individual	1	Confirmed	7/8
Kumar [41]	Chicago, USA	27/05/20	Case report	Individual	1	Confirmed	7/8
Childs [42]	UK	28/05/20	Case series	Aggregate	18	Confirmed	4/10
Suwanwongse [43]	New York, USA	29/05/20	Case series	Individual	9	Confirmed	5/10
Ridgway [44]	Chicago, USA	30/05/20	Case series	Individual	5	Confirmed	7/10
Shalev [45]	New York, USA	31/05/20	Case series	Aggregate	31	Confirmed	8/10
Vizcarra [20]	Madrid, Spain	01/06/20	Prospective cohort	Aggregate	51	Confirmed, probable	9/11

[a]Individual: reported information for each patient; Aggregate: reported summary of information for groups of patients

older age were common. Current clinical data suggest the main mortality risk factors are linked to older age and multimorbidity, not particular to HIV, including cardiovascular disease, diabetes, chronic respiratory disease, and hypertension [21]. Another possible explanation is bias due to the preponderance of publications on hospitalized patients with more severe disease.

The observational designs of the available studies and lack of appropriate control do not permit concluding whether ART can prevent the acquisition of COVID-19 or reduce morbidity and mortality from COVID-19. The search for antiviral agents with activity to treat and prevent COVID-19 is an area of active research. For example, a clinical trial in 199 patients showed that ritonavir-boosted lopinavir did not have a benefit over standard care for COVID-19 [15]. A survey in PLHIV in China showed that nucleoside reverse transcriptase inhibitors (NRTI) plus non-nucleoside reverse transfer inhibitors (NNRTI) did not prevent COVID-19 infection [16]. A cohort study showed that there are no differences in previous use of NNRTI, INSTI, or protease inhibitors in individuals with and without COVID-19 diagnosis [17]. Findings of lower morbidity or mortality among persons on ART compared to those not on ART would also need to consider higher CD4 count and better immune status.

We acknowledge additional limitations of our study. First, while a large proportion of COVID-19 patients are asymptomatic or have mild symptoms, all of the patients in this review were symptomatic, and most were admitted to a hospital. This study, therefore, refers only to patients with a confirmed diagnosis of COVID-19 and may overrepresent those with severe COVID-19 disease. Second, the lack of appropriate comparison groups, particularly for the case reports and case series, is a limitation to identifying factors associated with COVID-19-HIV co-infection. Third, many of the studies included in our review had a small sample size. Fourth, without a population- or probability-based survey of PLHIV, the true prevalence of COVID-19 and disease manifestations among PLHIV remain unknown. To the best of our knowledge, no study has yet measured COVID-19-HIV co-infection in a wider

Table 2 Demographic and clinical characteristics of COVID-19 infection in people living with HIV included in the reviewed studies (N = 252 total patients)

Characteristics (n reported)[a]	N (%)
Age (Mean ± SD; n = 244)	52.7 ± 8.6
Sex (n = 252)	
Male	204 (80.9)
Female	46 (18.3)
Transgender	2 (0.8)
On antiretroviral treatment (n = 251)	
Yes	246 (98.0)
CD4 count [cells/mm^3] (n = 176)	
< 200	23 (13.1)
≥ 200	153 (86.9)
HIV viral load [copies per ml] (n = 233)	
≤ 1000	231 (99.1)
> 1000	2 (0.9)
Multimorbidity (n = 244)	
At least one morbidity	145 (59.4)
Hypertension	96 (39.3)
Obesity or hyperlipidemia	47 (19.3)
Chronic obstructive pulmonary disease	44 (18.0)
Diabetes	42 (17.2)
Cardiovascular disease	26 (10.7)
Renal insufficiency	29 (11.9)
HBV/HCV	18 (7.4)
Hypothyroidism	1 (0.4)
Smoking	53 (21.7)
COVID-19 symptoms (n = 223)	
Fever	165 (74.0)
Cough	130 (58.3)
Dyspnea	68 (30.5)
Headache	44 (19.7)
Arthralgia/myalgia	33 (14.8)
Sore throat	18 (8.1)
Gastrointestinal symptoms	29 (13.0)
Severity (n = 212)	
Mild or moderate	141 (66.5)
Severe	46 (21.7)
Critical	25 (11.8)
Hospitalized (n = 244)	
Yes	158 (64.7)
Intensive care unit admission (n = 244)	
Yes	41 (16.8)
Death (n = 252)	
Yes	36 (14.3)

[a]Continuous variables were summarized using mean and standard deviation and categorical variables were summarized using frequency and percentage. Data are n (%) unless otherwise stated

Table 3 Demographic and clinical characteristics of COVID-19 in people living with HIV included in the reviewed studies, stratified by sex

Characteristics[a]	Male	Female	P-value
Age (Mean ± SD)	49.1 ± 10.5	51.9 ± 10.2	0.2
On antiretroviral treatment	n = 204	n = 46	0.6
Yes	198 (97)	46 (100)	
CD4 count [cells/mm^3]	n = 56	n = 10	0.06
< 200	4 (7.1)	0 (0.0)	
≥ 200	52 (92.9)	10 (100)	
Multimorbidity	n = 70	n = 19	0.4
At least one morbidity	43 (61.4)	13 (68.4)	
Hypertension	25 (35.7)	7 (36.8)	
Obesity or hyperlipidemia	8 (11.4)	2 (10.5)	
Chronic obstructive pulmonary disease	9 (12.9)	3 (15.8)	
Diabetes	9 (13.6)	2 (10.5)	
Cardiovascular disease	3 (4.5)	2 (10.5)	
Renal insufficiency	5 (7.6)	0 (0.0)	
HBV/HCV	11 (16.7)	1 (5.3)	
COVID-19 symptoms	n = 70	n = 19	
Fever	59 (84.3)	13 (68.4)	0.4
Cough	41 (58.6)	11 (57.9)	0.1
Dyspnea	20 (28.6)	7 (36.8)	0.6
Headache	5 (7.1)	4 (21)	0.06
Arthralgia/myalgia	10 (14.3)	3 (15.8)	0.5
Gastrointestinal symptoms	13 (18.6)	6 (31.6)	0.3
Severity	n = 57	n = 9	
Mild or moderate	44 (77.2)	8 (88.9)	0.4
Severe	5 (8.8)	1 (11.1)	
Critical	8 (14)	0 (0.0)	
Hospitalized	n = 154	n = 37	0.1
Yes	106 (68.9)	27 (73)	
Intensive care unit admission	n = 57	n = 9	0.4
Yes	10 (17.5)	1 (11.1)	
Death	n = 99	n = 22	0.7
Yes	12 (12.1)	2 (9.1)	

[a]Continuous variables were summarized using mean and standard deviation with differences compared using a two-tailed student's *t* test. Categorical variables were summarized using frequency and percentage and differences were measured using the Fisher's exact test. P-values less than 0.05 were considered as statistically significant. Data are n (%) unless otherwise stated

or representative cross-section of the population. Fifth, since most of the patients included in the studies reviewed were immunologically and virologically stable, we could not conduct subgroup analyses based on low CD4 cell count or high viral load to directly measure the association of HIV-related immunosuppression and severity of COVID-19 disease. Such subgroup analyses should be investigated in future studies. Finally, in the context of urgent care for large numbers of patients, HIV may not

be divulged, asked for, or recorded and therefore, under-assessed among COVID-19 patients.

Conclusions

The data available to date indicate that PLHIV can be infected with COVID-19 and are largely affected by similar features of disease risk and progression as HIV-uninfected patients. The presence of multimorbidity and older age appear to be the important factors for severe morbidity and mortality with COVID-19-HIV co-infection. Results suggest that healthcare providers need to address multimorbidity among PLHIV, ensure their ART supply is secure, and continue to consider PLHIV as a population for whom precautions are needed to prevent the COVID-19. Given the number of PLHIV worldwide, there are likely many more patients with COVID-19-HIV co-infection than suggested by the scant literature to date. Clinicians and researchers could help fill the data gap by being vigilant to patients who may be co-infected with SARS-CoV-2 and HIV.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

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