

The incidence and outcome of COVID-19 in patients living with HIV: an umbrella review of systematic reviews and meta-analyses

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Abstract

Introduction: The COVID-19 pandemic has surrogated the world and enforced a massive burden. Several risk factors, such as immunosuppression state, were recognized for severe COVID-19. Human immunodeficiency virus (HIV) is an immunosuppressing virus that deteriorates people living with HIV (PLWH) and makes them vulnerable to pathogens. It is expected that PLWH are more susceptible to severe COVID-19; however, research demonstrates conflicting results. This study aimed to provide conclusive evidence for the incidence and outcome of COVID-19 in PLWH.

Material and methods: A comprehensive search of databases, including Cochrane, PubMed/MEDLINE, Scopus, and Web of Science was conducted from inception to April 13, 2022. Systematic reviews and meta-analysis representing data on the incidence and outcome of COVID-19 in PLWH were included in an umbrella review.

Results: Fever and cough were the most prevalent symptoms. Most research indicated that the mortality rate in PLWH was higher. Commonly prescribed medications included tenofovir disoproxil fumarate, emtricitabine, lamivudine, hydroxychloroquine, oseltamivir, arbidol, and remdesivir. PLWH had higher C-reactive protein, ferritin, interleukin 6, and D-dimer levels. Most hospitalized PLWH suffered from severe symptoms.

Conclusions: Clinical features of underlying AIDS, antiviral treatments received, other underlying comorbidities, and laboratory findings, may affect the mortality risk among COVID-19 patients with HIV. However, more studies are needed to evaluate the risk and long-term effects of the COVID-19 vaccine on the mortality rate of patients with HIV and SARS-CoV-2 co-infection.

HIV AIDS Rev 2026; 25, 3: 169-184
DOI: <https://doi.org/10.5114/hivar/171553>

Key words: COVID-19, SARS-CoV-2, HIV, AIDS, incidence.

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Article history:
Received: 03.05.2023
Revised: 18.08.2023
Accepted: 25.08.2023
Available online: 25.09.2026

International Journal
of HIV-Related Problems
**HIV & AIDS
Review**

Introduction

The COVID-19 pandemic has surrogated the world, and enforced a massive socio-economical and health load on the governments and healthcare systems [1, 2]. Up to now, many efforts have been made to overcome the challenges of COVID-19. However, complications related to COVID-19 remain inspiring to manage [3, 4]. Several risk factors were recognized for more severe COVID-19, including the elderly, immunosuppression state, and underlying diseases, such as cancer, diabetes, cardiovascular disorders, renal failure, and obesity [5-7].

Human immunodeficiency virus (HIV) is a well-known challenging virus that results in acquired immunodeficiency syndrome (AIDS) [8, 9]. HIV is an immunosuppressing virus in nature, and can reduce the count of CD4+ T cells, an essential component of the acquired immune system [10, 11]. It also deteriorates people living with HIV (PLWH) and makes them vulnerable to pathogens, such as viruses, bacteria, parasites, and fungi [12]. It is expected that PLWH is more susceptible to severe COVID-19 [13]; however, studies conducted among PLWH infected with SARS-CoV-2 show conflicting results. Some surveys reported that HIV infection is not a comorbidity factor in patients with COVID-19, which can be attributed to the sub-maximal intense immune reaction that prevents clinical complications of SARS-CoV-2 [14]. Moreover, some of PLWH are under antiretroviral therapy (ART) that has beneficial effects on these patients by inhibiting the function of enzymes essential for proliferation and invasion of HIV. Similarly, it was shown that ART, such as nucleoside reverse transcriptase inhibitors (NRTIs), are effective medical agents in COVID-19 [15]. Conversely, PLWH are expected to face more severe stage of COVID-19 disease due to the higher rate of comorbidities, such as elderly [16], cardiovascular [17], renal [18], and pulmonary diseases [19], which are common risk factors to the severity of COVID-19. Worldwide, there are about 40 million PLWH at present, and living this population during COVID-19 pandemic is disputing [20]. Therefore, for the planned purposes, the optimal allocation of public health interventions, and prioritization of care in the field of scarce resources due to the epidemic [21], it is necessary to know whether the number of PLWH is relatively high or not. People without the disease are at higher risk for unpleasant consequences if they acquire COVID-19. Therefore, knowing how COVID-19 incidence and outcome of this disease in patients with HIV can help prevent its complications is crucial.

Although there is a body of documents regarding the condition of COVID-19 in PLWH, the evidence is conflicting. Therefore, it is essential to conclude the data and highlight the importance of COVID-19 pandemic on PLWH. This umbrella review study aimed to investigate the systematic reviews and meta-analyses conducted on the incidence and outcome of COVID-19 in patients with HIV, to provide conclusive evidence for clinicians

and healthcare systems for better management of this population.

Material and methods

Study design and search strategy

Databases, including Cochrane, PubMed/MEDLINE, Scopus, and Web of Science were searched on April 13, 2022. Key words were acquired using medical subject headings (MeSH) and from previous studies. Supplementary material 1 provides the complete search strategies for all the databases, but the search strategy for PubMed was as follows:

(((((COVID-19 [Title/Abstract]) OR (SARS-CoV-2 [Title/Abstract])) OR (SARS-CoV2 [Title/Abstract])) OR (2019-nCoV [Title/Abstract])) OR (Novel coronavirus Title/Abstract])) AND (((((Human Immunodeficiency Virus [Title/Abstract]) OR (HIV [Title/Abstract])) OR (Acquired Immune Deficiency Syndrome [Title/Abstract])) OR (Acquired Immune Deficiency Syndrome Virus [Title/Abstract])) OR (AIDS [Title/Abstract])) Filters: Systematic review.

Inclusion and exclusion criteria

Systematic reviews and meta-analyses, which discussed the incidence and outcomes of COVID-19 in patients with HIV were included.

Exclusion criteria were as follows: 1) original studies or any other studies, except for systematic reviews and meta-analyses; 2) abstracts or studies without full texts available; 3) studies on populations rather than HIV, e.g., other immunodeficiencies; 4) studies not related to COVID-19.

Study selection

Two reviewers screened relevant records to identify eligible systematic reviews and meta-analyses. In case of disagreement, another independent researcher's opinion was considered. Screening process consisted of two steps; in the first step, titles and abstracts of the studies were screened, while in the second step, they underwent a full-text screening, and all eligible studies were included in this review.

Data extraction

Studies were distributed between three independent reviewers to extract data. Then, another reviewer verified the extracted data to assess their accuracy. Data were entered into a Microsoft Word table consisting of: first author's name, date of the study and its type (systematic review or meta-analysis), searched databases, number of included studies, population of the study, participants' sex and their comorbidities, outcomes reported, and summary of other significant findings (Table 1) [22-46].

Table 1. Description of findings reported in eligible studies

ID	First author [Ref]	Date (MM/YY)	Type of study	Searched databases	Included studies	Total population	Sex	Other comorbidities	Outcome	Summary of findings
1	Cooper TJ [22]	Oct 2020	Systematic review	- Scopus - Embase - MEDLINE	8	70 HIV-infected pts. (13 with AIDS, 57 without AIDS)	N/A	N/A	Symptoms of COVID-19 in HIV-infected pts. are similar to general population	- No risk of poorer COVID-19 in well-controlled HIV - Risk of superinfection exists and might lead to severe COVID-19
2	Costenaro P [23]	Sep 2020	Systematic review	- Embase - MEDLINE - Google Scholar	23	164 adults with COVID-19 and HIV co-infection	84.5% males (n = 120) - Females: 20 - Transgender: 2	101 cases - HTN: 35 - Dyslipidemia: 20 - Diabetes: 20 Other: IHD, COPD, chronic kidney disease, lymphoma, HBV co-infection hepatocarcinoma, hypothyroidism, pulmonary TB - 3 cases in intensive care and 3 cases among pts. who died had comorbidities	- 16 cases died - 15 patients needed intensive care	- No clear evidence of severe COVID-19 or higher rate of infection in HIV-infected pts. - Male HIV pts. with long-term ART may have severe COVID-19 course
3	Danwang C [24]	Jan 2022	Systematic review and meta-analysis	- PubMed - Scopus - Embase - Web of Science	44	38,971,065	N/A	N/A	No increase in severity of COVID-19 was seen in pts. with co-infection of HIV and COVID-19	- Increased risk of hospital admission in HIV-infected pts. - HIV does not increase the mortality and severity of COVID-19
4	de Medeiros KS [25]	Jul 2021	Systematic review	- Medline - Scopus - Embase - Web of Science - CINAHL - LILACS - Cochrane - Clinicaltrials.gov	30	266	209 males 57 females	- Cardiovascular disease - Obesity - HTN - COPD	- No relationship was found between HIV and occurrence of COVID-19 infection	- HIV infection might stop COVID-19 infection due to IFN- λ induction - ART might prevent COVID-19 infection

Table 1. Cont.

ID	First author [Ref]	Date (MM/YY)	Type of study	Searched databases	Included studies	Total population	Sex	Other comorbidities	Outcome	Summary of findings
5	Dolatian M [26]	Oct 2020	Systematic review	- Scopus - Web of Science - Embase - PubMed - Google Scholar	15	N/A	N/A	N/A	Only CD4+ < 200 cells may increase the risk of COVID-19 infection	No significant difference was found in mortality and clinical signs of COVID-19 in HIV-positive individuals
6	Dong Y [27]	Jul 2021	Meta-analysis	- Embase - PubMed - China National Knowledge Infrastructure - WanFang data - Chongqing VIP	10	18,122,370 COVID-19 pts. (41,113 COVID-19 pts. with HIV and 18,081 COVID-19 pts. without HIV)	N/A	N/A	HIV morbidity in COVID-19 could increase mortality	HIV/COVID-19 co-infection may lead to higher mortality risk of COVID-19 infection
7	Gao Y [28]	Aug 2020	Systematic review and meta-analysis	- Embase - PubMed - Web of Science - Cochrane - China National Knowledge Infrastructure (CNKI) - Chinese biomedical literature - WanFang	8	4,007	Males: 2,256 Females: 1,751	N/A	HIV/COVID-19 co-infection leads to severe COVID-19 disease	Immunodeficiency is associated with severe COVID-19 infection
8	Heidary M [29]	Feb 2022	Systematic review	- Embase - PubMed - Scopus	65	N/A	Males: 74.3%	Most common: HTN, DM Other: HBV, HCV	HIV might elevate morbidity and mortality of COVID-19	HIV/COVID-19 co-infected pts. had higher comorbidities (HTN, diabetes) compared with COVID-19 individuals without HIV
9	Huang D [30]	Mar 2022	Systematic review	- PubMed - Web of Science - WanFang - CNKI - SinoMed	18	412 HIV/COVID-19 pts.	Males: 72%	37.5% of pts. had comorbidities - HTN (most common) - Chronic lung disease	HIV/COVID-19 pts. with earlier use of ART had better outcomes	Comorbidities increase the risk of severe COVID-19

Table 1. Cont.

ID	First author [Ref]	Date (MM/YY)	Type of study	Searched databases	Included studies	Total population	Sex	Other comorbidities	Outcome	Summary of findings
10	Kouhpaye H [31]	Dec 2021	Meta-analysis	- PubMed - Scopus	11	19,645,775 COVID-19-infected cases, 59,980 HIV-positive	N/A	HTN, diabetes, cardiovascular disease	COVID-19 caused higher mortality in HIV-positive pts.	Mortality in HIV/COVID-19 co-infection was 21% higher than in pts. without HIV
11	Lee K [32]	Mar 2021	Systematic review and meta-analysis	- PubMed - MEDLINE - CINAHL	82	643,018 HIV pts.	Females: 58.5% Males: 39.8% Unknown gender: 1.5% Transgender: 0.2%	- Cardiovascular: 27.2% (HTN) - DM: 12.2% - Chronic lung disease: 4.2% - Asthma: 4.2% - Dyslipidemia - Obesity - Alcoholism - Smoking - Chronic kidney disease - Liver disease	Long-term HIV might be associated with more severe illness	Mortality rate is higher in HIV/COVID-19 co-infected patients
12	Liang M [33]	Sep 2021	Systematic review and meta-analysis	- Embase - PubMed - medRxiv - BioRxiv	14	203,761 COVID-19 pts.	N/A	- HTN - DM - Chronic cardiac and kidney disease	Comorbidities were related to poorer outcomes	Increased mortality in HIV/COVID-19 co-infection was seen with comorbidities
13	Massarva T [34]	May 2021	Systematic review	- Embase - Scopus - MEDLINE - Cochrane	22	730 COVID-19/HIV pts.	Males: 79.4%	Hypertension	- Comorbidities in HIV/COVID-19 co-infected pts. were associated with poorer outcomes - COVID-19 outcome was better when HIV was controlled	Comorbidities in HIV/COVID-19 co-infection lead to high-risk COVID-19 disease
14	Mellor MM [35]	Mar 2021	Systematic review	- Embase - Medline - medRxiv - Google Scholar - Google - LitCovid - Trip	19	N/A (large number) 10 studies included more than 1,000 individuals	N/A	- Diabetes - Obesity	COVID-19/HIV co-infection leads to higher mortality rate	HIV infection is associated with higher mortality rate

Table 1. Cont.

ID	First author [Ref]	Date (MM/YY)	Type of study	Searched databases	Included studies	Total population	Sex	Other comorbidities	Outcome	Summary of findings
15	Mirzaei H [36]	Jan 2021	Systematic review	- PubMed - Scopus - Web of Science - Google Scholar - Pre-printed database	25	252 pts. with HIV/COVID-19 co-infection	Males: 80.9% Females: 18.3% Transgender women: 0.8%	- HTN - Hyperlipidemia - Obesity - COPD - Diabetes	Presence of comorbidities was associated with severe COVID-19/HIV co-infection and higher mortality	No difference in severity of COVID-19/HIV co-infection and mortality between males or females
16	Oyelade T [37]	Feb 2022	Systematic review and meta-analysis	- Embase - MEDLINE	43	692,032 COVID-19 individuals (9,097 of them with HIV)	N/A	N/A	COVID-19/HIV co-infection may lead to higher mortality risk	HIV infection might cause more severe COVID-19 infection
17	Patel RH [38]	Mar 2021	Systematic review	PubMed/MEDLINE	63	4,259	N/A	- Diabetes - HBV - HTN - Obesity - COPD - Hyperthyroidism	Comorbidities are associated with a poor prognosis of COVID-19 infection	- HIV patients on ART have better COVID-19 outcomes
18	Sarkar S [39]	Dec 2020	Systematic review and meta-analysis	- PubMed/MEDLINE - Embase - Google Scholar - Pre-print platform - medRxiv	20	205,702 pts. 177,186 pts. with COVID-19/HIV co-infection	N/A	N/A	HIV/COVID-19 co-infection does not show any increased mortality risk	No significantly increased mortality risk in COVID-19/HIV co-infection
19	SeyedAlinaghi S [40]	Jul 2021	Systematic review	- PubMed - Scopus - Science Direct - Web of Science	36	3,993,400 COVID-19 pts. (89,343 pts. with COVID-19/HIV co-infection)	Males: 72% Transgenderers: 0.01%	- HTN - DM - Asthma - Renal insufficiency - Cardiovascular disease	Individuals with advanced stage of HIV and low CD4+ count have less severe COVID-19 symptoms and less mortality after COVID-19 infection	Advanced stages of HIV are associated with COVID-19 infection and lower mortality rate
20	Shareef MA [41]	Oct 2020	Systematic review	- PubMed/MEDLINE - WHO registry - Cochrane	7	16	Males: 15 Females: 1	- HTN - DM - Obesity - COPD - CAD	Symptoms of COVID-19 in HIV pts. are similar to individuals without COVID-19	- Older population with comorbidities have poorer outcomes - COVID-19/HIV co-infected individuals on ART have favorable outcomes

Table 1. Cont.

ID	First author [Ref]	Date (MM/YY)	Type of study	Searched databases	Included studies	Total population	Sex	Other comorbidities	Outcome	Summary of findings
21	Ssentongo P [42]	Mar 2021	Systematic review and meta-analysis	- PubMed - Scopus - Ovid - Web of Science - Cochrane - Google Scholar - Pre-print platform medRxiv	22	20,982,498	Males: 66%	- HTN - DM - COPD - Chronic kidney disease	Mortality rate due to COVID-19 is higher in HIV-positive individuals	- Risk of COVID-19 infection is higher in HIV-positive individuals - Vaccination is highly recommended for HIV patients
22	Tamuzi JL [43]	Oct 2020	Systematic review	- Cochrane - PubMed - medRxiv - Google Scholar - WHO COVID database	21	28,387 COVID-19 pts. (1,094 COVID-19/HIV/TB, and 1 SARS-COV/HIV/TB pt.)	N/A	HIV/TB co-infection	HIV/TB co-infection with COVID-19 has more higher mortality rate	COVID-19 associated with HIV/TB co-infection is more common in males, with longer recovery period
23	Varshney K [44]	Jan 2022	Systematic review	- PubMed - Scopus - WHO coronavirus database - Global Health	20	N/A	N/A	- Cardiovascular disease - Diabetes - Obesity - Chronic kidney disease	Mortality rate is about twice in males compared with females	- Older age is related to higher mortality rate - Comorbidities are associated with higher mortality - Lower CD4+ cell count does not affect mortality
24	Wang H [45]	Nov 2021	Meta-analysis	- PubMed - Web of Science - medRxiv	9	N/A	N/A	- Diabetes - HTN - Cardiovascular disease - Chronic kidney disease - Respiratory disease	Comorbidities lead to increased severity of COVID-19 infection	- COVID-19/HIV co-infection increases the severity of COVID-19 infection - Comorbidities also cause experiencing severe course of COVID-19
25	Wang Y [46]	Sep 2021	Meta-analysis	- PubMed - Web of Science - Embase	84	816,678	N/A	N/A	HIV infection is related to increased mortality from COVID-19 infection	- COVID-19/HIV co-infected individuals have higher mortality risk

ART – antiretroviral therapy, CAD – coronary artery disease, COPD – chronic obstructive pulmonary disease, DM – diabetes mellitus, HBV – hepatitis B virus, HCV – hepatitis C virus, HSV2 – Herpes simplex virus type 2, HTN – hypertension, IHD – ischemic heart disease, pts. – patients, TB – tuberculosis

Data synthesis

This was a qualitative umbrella review, and narrative synthesis of data was done through columnar summarizing of extracted data. Quantitative analysis was not available due to the diversity of studies and inconsistency reports of effect sizes. Therefore, the influence of studies was assessed using synthesis without meta-analysis (SWiM) in systematic reviews guideline [47] to provide an appropriate report of the synthesized data.

Quality and risk of bias assessment

Two reviewers independently assessed the quality of studies included in this umbrella review using the AMSTAR 2 assessment tool. AMSTAR 2 has a 16-item checklist to review and evidence the quality of systematic review and meta-analysis. AMSTAR 2 does not generate an overall score; instead, it is meant to classify studies based on seven critical and nine non-critical items (Table 2) [22-46]. Critical domains include the establishment of a review method prior to conduction of the study, providing a comprehensive search strategy, publication bias of meta-analysis studies, using the risk of bias for discussing results, utilizing appropriate statistical analysis in meta-analysis studies, applying an appropriate risk of bias method, stating excluded studies, and explaining each excluded study. Studies were categorized as high, moderate, low, and critically low. High studies had no or one non-critical weakness, moderate ones had more than one non-critical weakness, low studies had one critical flaw with or without non-critical weakness, and critically low studies had more than one critical flaw with or without non-critical weakness [48].

Results

After a comprehensive literature search of online databases (Cochrane, PubMed, Scopus, and Web of Science), 277 studies were initially identified. After removing duplicate studies, 183 articles remained for title and abstract evaluation. One hundred fifty-eight articles were subjected to full-text review. At the full-text screening stage, 133 articles were excluded, and the reasons are listed in the PRISMA flow chart (Figure 1). Following quality assessment, 25 articles that addressed the research questions and met inclusion criteria were included in the umbrella review phase. The geographic distribution of included studies is shown in Figure 2.

The featured investigations were conducted primarily in the United States and Europe, followed by Asia and Africa. These publications were classified according to their sample size, mean age, sex, severity, comorbidities, antiretroviral drug therapy, and CD4+ counts (ranging from 10 to 1,163 cells/mm³). Most COVID-19 cases were diagnosed with PCR, serology (IgM and IgG), chest computed tomography (CT), and according to clinical symptoms. The majority of patients were receiving antiretroviral medications, including integrase strand transfer inhibitors (INSTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs),

protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTIs).

Clinical manifestations

Seven publications discussed clinical symptoms, of which five claimed that fever (ranging from 37.5 to 94%) was the most prevalent symptom. Two of these publications, however, declared that cough (ranging from 37.3 to 88%) was the most prevalent symptom, followed by fever as the second most prominent symptom [34, 29]. Dyspnea was listed as the third most prevalent symptom in five different articles [29, 32, 34, 36, 41]. According to these articles, less frequent symptoms included headaches, myalgia, fatigue [36, 40], and respiratory distress [30]. Lastly, the least frequent symptoms were gastrointestinal indications, including nausea, abdominal pain, diarrhea, and loss of appetite [36, 30].

Mortality and morbidity

Although most studies indicated higher mortality rates among PLWH [24, 25, 27, 31, 33, 35, 37, 49, 50], some emphasized that there is no discernible increase in mortality rate among these patients [22, 51]. However, there was a noticeable difference in mortality rates among different countries. According to one study, HIV infection raised the global risk of death from COVID-19 by 2.3-fold compared with individuals without HIV infection. At the regional level, there was no substantial increase in the mortality risk associated with COVID-19 among PLWH in Africa or Europe. However, according to the included research, a two-fold increase in mortality risk was reported in the United States [37].

Furthermore, another study claimed that PLWH had a greater mortality risk from COVID-19 than HIV-negative individuals. In a study from the United States and South Africa, a sub-group analysis revealed that PLWH had a greater risk of COVID-19 mortality than those without HIV infection; however, no significant association was observed in the United Kingdom [27]. In addition, another study reported that HIV infection was associated with an increased risk of COVID-19 mortality in Asia, Europe, and both the Americas, but not in Africa [50]. Furthermore, in a sub-group analysis, the mortality rate in the United States and Europe showed no significant correlation. According to studies conducted in South Africa, there was a significant correlation between the mortality rate of PLWH and HIV-negative patients [51]. One study claimed that HIV infection increased the risk of death from COVID-19 according to an adjusted pooled analysis for age and sex [24].

Moreover, chronic liver disease, chronic obstructive pulmonary disease (COPD), asthma, and HIV comorbidities were not substantially related to increased mortality risk [49]. On the other hand, some studies claimed that chronic kidney disease, diabetes, hypertension, and chronic cardiovascular disease were strongly associated with higher mortality in patients with HIV due to COVID-19 [25, 32-34, 40].

Table 2. AMSTAR 2 assessment tool for quality assessment of the study

First author [Ref]	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16
Cooper <i>et al.</i> [22]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No meta-analysis conducted	No meta-analysis conducted		Yes	No meta-analysis conducted	No
Dong <i>et al.</i> [27]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Costenaro <i>et al.</i> [23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Danwang <i>et al.</i> [24]	Yes	Yes	Yes	Yes	Yes	Yes	Partial Yes	Yes	No	No	Yes	No	No	Yes	Yes	No
De Medeiros <i>et al.</i> [25]	Yes	No	Yes	Yes	Yes	Yes	Partial Yes	Yes	Yes	No	No meta-analysis conducted	No meta-analysis conducted		Yes	No meta-analysis conducted	No
Dolatian <i>et al.</i> [26]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No meta-analysis conducted	No meta-analysis conducted			No meta-analysis conducted	No
Heidary <i>et al.</i> [29]	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No meta-analysis conducted	No meta-analysis conducted	No	Yes	No meta-analysis conducted	No
Huang <i>et al.</i> [30]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No meta-analysis conducted	No meta-analysis conducted	No	Yes	No meta-analysis conducted	No
Kouhpayeh <i>et al.</i> [31]	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No	No
Lee <i>et al.</i> [32]	Yes	No	Yes	Yes	Yes	Yes	Partial Yes	Partial Yes	No	No	Yes	No	No	Yes	Yes	No
Liang <i>et al.</i> [33]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Mellor <i>et al.</i> [35]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Massarwa <i>et al.</i> [34]	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No
Mirzaei <i>et al.</i> [36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No meta-analysis conducted	No meta-analysis conducted	No	No	No meta-analysis conducted	No
Patel <i>et al.</i> [38]	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No meta-analysis conducted	No meta-analysis conducted	No	Yes	No meta-analysis conducted	No
Shareef <i>et al.</i> [41]	Yes	No	Yes	Yes	Yes	No	Yes	Yes	No	No	No meta-analysis conducted	No meta-analysis conducted	No	Yes	No meta-analysis conducted	No

Table 2. Cont.

First author [Ref]	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16
Sarkar <i>et al.</i> [39]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No
Oyelade <i>et al.</i> [37]	Yes	Yes	Yes	Partial Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No
SeyedAlinaghi <i>et al.</i> [40]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No meta-analysis conducted	No meta-analysis conducted	No	Yes	No meta-analysis conducted	No
Ssentongo <i>et al.</i> [42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes	No
Tamuzi <i>et al.</i> [43]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	No	No
Varshney <i>et al.</i> [44]	Yes	Partial Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No meta-analysis conducted	No meta-analysis conducted	No	No	No meta-analysis conducted	No
Wang H <i>et al.</i> [45]	Yes	No	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	No	Yes	No	No
Gao <i>et al.</i> [28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes	No
Wang Y <i>et al.</i> [46]	Yes	No	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	No	Yes	No	No

Treatments

The majority of patients received ART, and most of ART patients were administered LPV/r at the time of COVID-19 infection [36]. Tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), lamivudine (3TC), hydroxychloroquine, oseltamivir, arbidol, and remdesivir were the most frequently prescribed medications [29]. Some patients were prescribed various drug combinations, including tenofovir plus emtricitabine, and lopinavir plus ritonavir.

Several studies indicated that antiretroviral treatment regimen affected COVID-19 outcome. Patients treated with TDF/FTC had the lowest incidence of COVID-19 diagnosis, hospitalization, intensive care unit (ICU) admission, and mortality rate [35]. Other studies, however, were unable to provide clear evidence of a protective effect of tenofovir and darunavir-based ART [38].

Azithromycin was the most frequently prescribed antibiotic for COVID-19 therapy or prophylaxis against opportunistic infection, followed by sulfonamide. In addition, moxifloxacin, meropenem, linezolid, sulbactam/cefoperazone, cefixime, and ceftaroline were administered. Several patients required anti-inflammatory drugs, such as steroids, interleukin (IL)-6 inhibitors, sarilumab, and tocilizumab. Moreover, 1% of patients were administered anticoagulant medication, including enoxaparin or heparin, whereas 3.5% of patients did not receive pharmacological treatment [23, 32, 41, 42].

Laboratories

Two studies reported elevated levels of C-reactive protein (CRP), ferritin, IL-6, and D-dimer [40]. Biomarkers indicative of inflammation, coagulopathy, and tissue injury were enhanced proportionately. Liver profile results and effect of COVID-19 on these analytes varied considerably. In over two-thirds of studies, serum creatinine levels were within normal range. Most patients had normal hemoglobin levels and leukocytes, but 50% lacked lymphocytes. Those on ART had a much lower viral load than patients who were not on ART. The absence of ART was associated with a more severe HIV infection and a larger degree of cellular immunological malfunctioning. D-dimer and lactate dehydrogenase (LDH) levels were elevated in HIV patient groups [32].

Hospitalization

The majority of hospitalized patients had severe conditions, followed by moderate and mild symptoms [24]. The hospitalization rate and ICU utilization reported by studies varied considerably. While some studies suggested that the majority of PLWH hospitalized with COVID-19 had a lower median CD4+ T cell count, 9 trials found no correlation between CD4+ T cell count and COVID-19 outcomes [40]. According to several studies, CD4+ count did not affect hospital mortality, and low CD4+ count protected against hyperimmune response in COVID-19 infection. Most PLWH hospitalized did not require supplementary

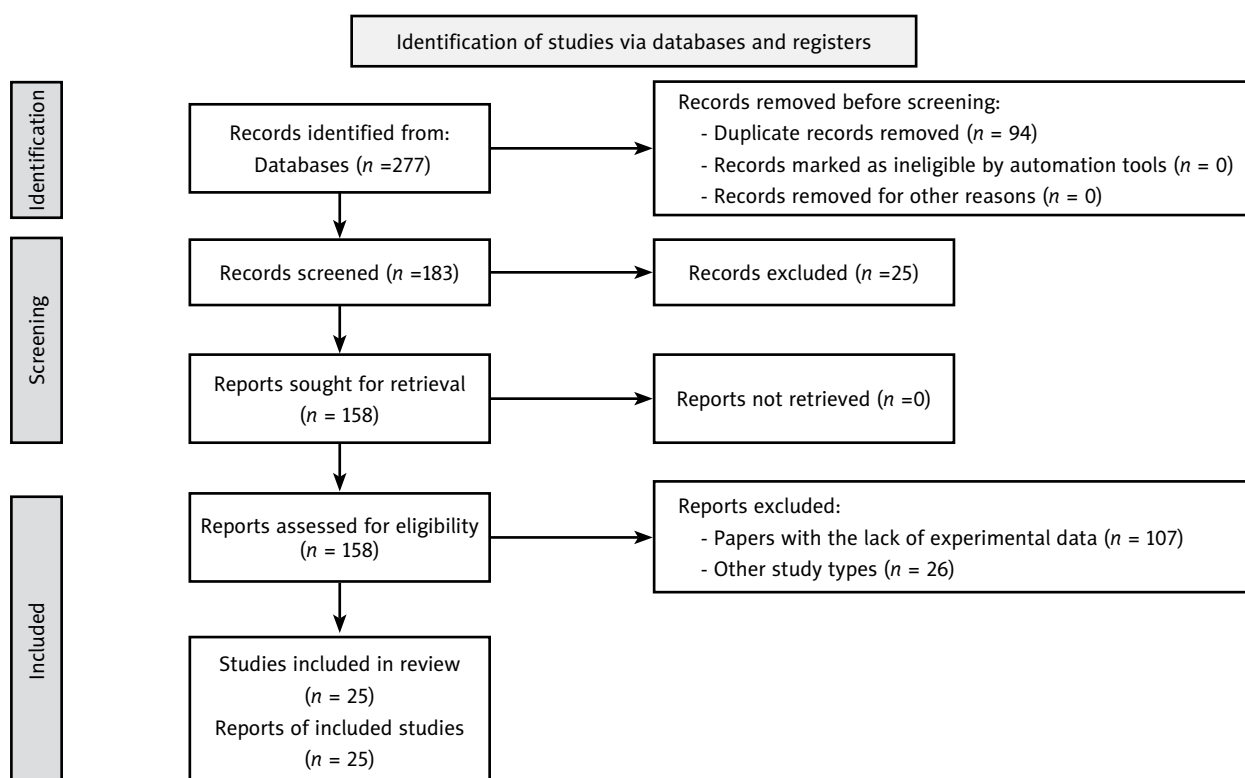


Figure 1. PRISMA 2020 flow diagram of the process of study retrieval

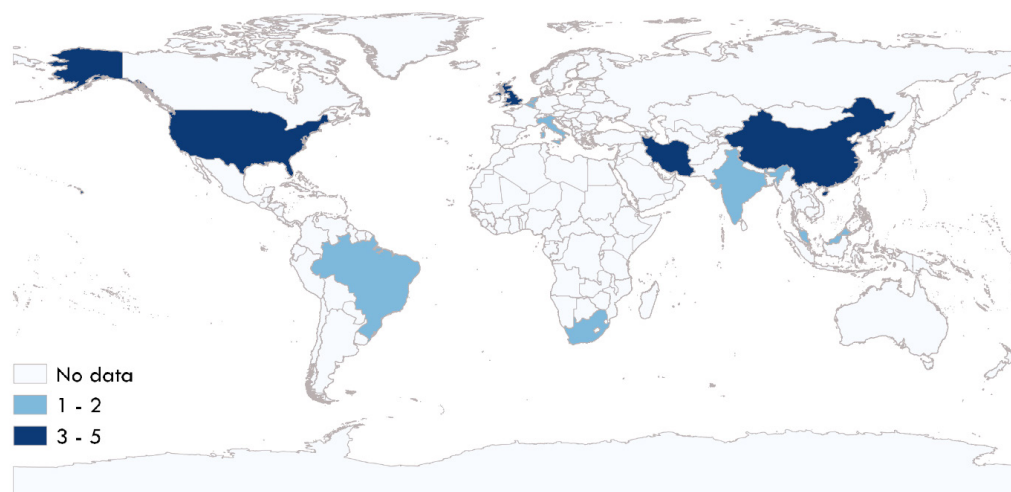


Figure 2. Geographic distribution of the studies

oxygen [23, 25, 30, 32, 35, 36]. According to one study, Black patients with HIV had a higher risk of death and hospitalization from COVID-19 [35].

Discussion

Since December 2019, COVID-19 has been the largest challenge for healthcare systems all over the world. Globally,

there are approximately 38 million PLWH, with an increased risk of contracting COVID-19 and dying from the disease. In addition, there are multiple published systematic reviews and meta-analyses assessing different aspects of PLWH co-infected with COVID-19. In light of this, it is crucial to conduct a holistic review to evaluate and summarize the current evidence for different aspects of this population's care. Based on our included studies, we can assess the interactions

of COVID-19 with HIV in the co-infected population in 5 categories.

Clinical manifestations

COVID-19 patients often exhibit a wide range of systemic and gastrointestinal symptoms, including fever, cough, dyspnea, anosmia (loss of smell), ageusia (loss of taste), headache, fatigue, abdominal discomfort, anorexia, diarrhea, and nausea [52]. According to the findings of our review, fever, cough, and dyspnea were the most frequently observed clinical manifestations of COVID-19 in PLWH [32, 36, 40]. This is consistent with the results of a multicenter case-series study by Cabello *et al.* [53], revealing that the most common symptoms among PLWH co-infected with COVID-19 were fever (66.1%), cough (66.1%), and dyspnea (46.8%). In addition, the reviewed studies showed that other COVID-19 clinical symptoms were less prevalent among HIV patients. Research suggest that this is due to PLWH's low level of CD4+ cells and immunosuppressed health condition, which may shield them from the cytokine storm reported in COVID-19 patients [54]. Furthermore, our review demonstrated that PLWH were more prone to suffer mental health issues during the COVID-19 pandemic [32]. This may be because PLWH are a particularly susceptible population, and COVID-19-induced distance restrictions further exacerbated their vulnerability to mental health problems [55].

Mortality and morbidity

The superinfection of SARS-CoV-2 in individuals with underlying HIV infection may lead to an overall higher burden of morbidity and mortality [31]. It has been reported that the clinical characteristics and symptoms of COVID-19 in people with HIV are not significantly different compared with the general population, and that a large proportion of such patients remain asymptomatic [56, 57]. However, multiple observational studies have shown that HIV patients with COVID-19 tend to be affected by a more severe form of the disease, higher hospitalization rates as well as higher rates of breakthrough infections after receiving a vaccination [25, 33, 35, 57] and even higher likelihood of COVID-related mortality [58-60]. This remained true also after adjusting for age and sex [24].

As shown in the results section, large population studies indicate that geographic distribution may play a role in determining excess mortality in HIV-positive versus non-HIV-positive patients with COVID-19 [27, 50], albeit with some controversies [37]. Interestingly, we found a non-negligible degree of inconsistency with regard to the association between pre-existing comorbidities and overall mortality risk in HIV-positive patients, with some studies reporting higher risk in patients with a common disease, such as diabetes, hypertension, or chronic renal insufficiency [25, 32-34], whereas other authors conversely found that asthma, chronic liver disease, and COPD are not associated with any increased risk [49]. This

remains in line with the existing literature on the topic, which overall reports that amongst HIV-positive people infected by SARS-CoV-2, four main categories of patients may be recognized at higher risk for adverse outcomes and morbidity: first, elderly and more frail patients [61, 62]; second, patients with an underlying burden of comorbidities [58, 63]; third, patients with a higher degree of immunocompromise, meaning a lower CD4+ T cell count [61, 64]; and finally, patients who identify as Black or Hispanic [63].

Paradoxically, Dandachi *et al.* [61], who run a large, multicenter, US-based study on behalf of the HIV-COVID-19 consortium, reported that HIV viral load could not be identified as a significant risk factor in their data or predictor for the development of a severe form of COVID-19. Interestingly, Yang *et al.* [58] showed that people with HIV might show fewer symptoms at the earlier stages of SARS-CoV-2 infection, and speculated that such protection from the most serious sequelae of COVID-19 could perhaps be attributable to the possible anti-SARS-CoV-2 activity of certain anti-HIV medications (such as tenofovir disoproxil fumarate plus emtricitabine). This has also been suggested in other observational studies and randomized controlled trials [62, 65].

An additional potential explanation for these dynamics may be that patients with features, such as advanced HIV infection, immunosuppression, or high viremia, could eventually restrict the immune dysregulation related to COVID-19 and therefore soften the development of cytokine storms that have been linked to the severity of the disease [64]. That said, the authors also claim that an alternative hypothesis may simply be the fact that people with HIV and mild COVID-19 illness might be underrepresented in light of higher chances of stigma, fear of being hospitalized, and overall less effective medical coverage, when compared with people who do not have a diagnosis of HIV infection [58]. As Nomah *et al.* [64] pointed out, the COVID-19 pandemic has highlighted the existing health inequities affecting specific sub-populations based on their social and economic background. When taking care of a COVID-19 patient with HIV, it is therefore of utmost importance to properly stratify the overall morbidity and mortality risk taking into account the afore-mentioned clinical, demographic, and laboratory features.

Treatments

Our review showed that most PLWH with COVID-19 co-infection were receiving antiretroviral (ARV) medications, with LPV/r being the most prevalent regimen [36]. However, our findings were contradictory on the potential effectiveness of ARV medications as preventative measures against COVID-19 infection in PLWH. Although some reviewed studies were unable to provide compelling evidence on the clinical efficacy of tenofovir and darunavir-based ARV therapies against COVID-19, others indicated that TDF/FTC-treated HIV patients had less severe COVID-19 outcomes [38]. This is in line with the findings of another

study conducted in South Africa, which indicated that the COVID-19 mortality rate of PLWH who were on TDF/FTC regimen was lower than that of PLWH who were receiving other ARVs [66]. In a similar vein, another study conducted in Spain found that PLWH who received TDF/FTC had a lower risk of contracting COVID-19 infection and being admitted to hospitals than recipients of other regimens (16.9% and 10.5%, respectively) [62]. However, both the studies were confounded by lower comorbidity rates, which may explain the discrepancies between their findings and existing literature, given that in those studies, PLWH who were TDF/FTC recipients were younger and free of comorbidities [62, 66].

Laboratories

The majority of systematic reviews and meta-analyses found that serum levels of inflammatory markers, such as CRP, ferritin, and IL-6 were elevated among HIV patients with concurrent COVID-19 [32, 40]. Elevated levels of inflammatory markers among COVID-19 patients have been reported by many studies, which could be associated with worse outcomes, disease severity, and mortality [67-69]. Thus, it seems that the rising trend in serum levels of inflammatory markers could be detected among both COVID-19 patients with and without HIV infection. However, some studies demonstrated that serum levels of inflammatory markers were within normal ranges among PLWH with COVID-19. It seems that due to HIV-induced immunosuppression, the immunological reaction may be depressed among these infected patients, which may lead to the production of lower levels of inflammatory markers, such as interleukins and cytokines among PLWH than in patients without HIV infection [70].

Similar to COVID-19 patients who do not suffer from HIV, PLWH may show higher levels of cellular/tissue damage markers, such as LDH, and coagulation markers, such as D-dimer during COVID-19 infection [32]. Although a growing body of evidence has demonstrated that higher serum levels of CRP, ferritin, IL-6, D-dimer, and LDH are associated with worse COVID-19 outcomes and higher risk of mortality, the association between these markers and disease outcomes among PLWH is not fully understood and needs further investigation [67, 68].

The serum levels of hemoglobin and creatinine were within normal ranges among most COVID-19 patients with HIV infection. It seems that hemoglobin and creatinine levels do not change until the severe end stages of COVID-19. Some studies reported lower levels of hemoglobin and/or higher levels of creatinine among severely ill COVID-19 patients, which could be associated with worse outcomes and mortality [71-73].

Lymphopenia is found in majority of patients infected with SARS-CoV-2, which is more prevalent among hospitalized patients with severe COVID-19, and could be associated with a higher rate of mortality among these patients [74, 75]. Similarly, PLWH developing COVID-19, especial-

ly these with a severe form of the disease, may suffer from various degrees of lymphopenia, as shown by several studies [32]. However, little is known about the association between lymphocyte count and mortality risk among PLWH. It is worth noting that HIV causes immune suppression via depleting CD4+ lymphocytes. Therefore, some patients with HIV infection may suffer from leukopenia and/or lymphopenia, even in the absence of other microbial infections. Hence, on the one hand, developing viral infections, such as COVID-19, may deteriorate the immune suppression state among PLWH, and on the other hand, underlying lymphopenia may lead to the development of worse outcomes among HIV patients with COVID-19.

Hospitalization

Studies showed that majority of hospitalized patients with AIDS suffered from severe COVID-19 [24], and more than half of the admitted patients required oxygen supplementation during hospitalization [32, 35, 36]. Many studies have found that underlying comorbidities are associated with an increased risk of COVID-19 severity and mortality [76]. However, it is still unknown if underlying HIV infection is associated with a higher risk of COVID-19-associated mortality among affected patients. While some studies revealed a higher risk of mortality due to COVID-19 in AIDS patients [27, 42], others demonstrated that mortality risk is comparable between COVID-19 patients with and without HIV infection [24, 33]. Thus, data about the mortality rate among AIDS patients suffering from COVID-19 is limited and conflicting. In the one hand, underlying infection with HIV seems to increase the risk of developing unfavorable outcomes, disease severity, and mortality among PLWH who acquire COVID-19. On the other hand, it has been suggested that since COVID-19 symptoms, severity, and outcomes are mainly due to hyperinflammatory state, excess cytokine production, and cytokine storm resulting from immune system reaction, it seems that AIDS patients whose immune system is suppressed may develop mild forms of COVID-19 and suffer from less severe symptoms. In addition, some studies evaluated the association between various factors, such as CD4+ T cell count, underlying comorbidities, and received treatments, with prognosis of COVID-19 among PLWH. However, the results vary and are conflicting. Thus, further research is needed to find risk factors that affect and predict the mortality risk among COVID-19 patients suffering from HIV.

Strengths and limitations

In this umbrella review, we used a systematic search strategy to compile data from a wide range of prior reviews and meta-analyses on the incidence and outcome of COVID-19 in HIV patients. We explored four electronic databases, conducted an exhaustive literature search, and assessed a significant number of relevant publications in order to obtain credible data from the available literature. The AMSTAR 2

assessment tool was then used to assess the quality of included reviews and meta-analyses, with a focus on the results of publications deemed to be of moderate to high quality. Therefore, the results of this umbrella review are crucial for understanding the epidemiology of COVID-19 in HIV patients, and establishing effective disease preventive measures for this population. Our search, however, was confined to English-language papers, and other findings may have been uncovered if we had looked at literature in other languages as well. In light of this, it is recommended that future umbrella reviews examine papers published in other languages on this issue in order to make proper comparisons.

Conclusions

The present study showed that patients with HIV infection are at risk of acquiring COVID-19, partly due to their immunosuppression state. COVID-19 symptoms and presentations are mainly similar between PLWH and those without HIV, with fever, cough, and dyspnea being the most prevalent complaints among both patient groups. In addition, laboratory test results of PLWH with COVID-19 may reveal elevated inflammatory, coagulative and cellular damage markers, and lymphopenia similar to COVID-19 patients without underlying HIV. However, the available data regarding COVID-19 clinical course, outcomes, and prognosis are still very limited and diverse. It seems that AIDS stage, received anti-HIV agents, HIV viral load, CD4+ T cell count, underlying comorbidities, ethnicity, and gender may affect the risk of COVID-19-associated mortality among patients suffering from concurrent SARS-CoV-2 and HIV infection. Although some studies reported a higher risk of mortality due to COVID-19 among HIV patients, others demonstrated a comparable mortality risk among COVID-19 patients with and without underlying HIV infection. It is suggested that future studies be conducted in relation to the risk assessment and long-term effects of the COVID-19 vaccine on the mortality rate of patients with HIV and SARS-CoV-2 co-infection.

Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: The present study was conducted in collaboration with Khalkhal University of Medical Sciences, Iranian Research Center for HIV/AIDS, Tehran University of Medical Sciences, and Tufts University.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.
5. AI use statement: During the preparation of this manuscript, the authors used a large language model (ChatGPT-4) for language editing, grammar checking, and text refinement to improve readability. The authors reviewed, edited, and verified all AI-generated suggestions and take full responsibility for the integrity and accuracy of the final manuscript.

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