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Severity of COVID-19 manifestations in HIV patients: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: The incidence of coronavirus disease 2019 (COVID-19) pandemic among people living with HIV (PLWH) is experiencing major increases. This demographic is vulnerable due to compromised immune function, but the individuals are subjected to antiretroviral therapy (ART), which shows potential as a treatment for the pandemic. Therefore, this study aimed to investigate the severity of various forms of COVID-19 in PLWH as opposed to the general population.

MATERIALS AND METHODS: The study followed PRISMA guidelines and included a systematic review of literature from Pubmed, Science Direct, and Cochrane Library, comprising English-language articles from 2019 to 2022. This study included articles discussing HIV and COVID-19 case prevalence data by severity. A random effect model was used to demonstrate the pooled prevalence of COVID-19 among PLWH, as well as the prevalence of moderate and critical severity of COVID-19 among PLWH. The Joanna Briggs Institute checklist was used to assess the quality of studies. This study is registered in INPLASY No. INPLASY2023100063.

RESULTS: Out of a total of 1,965 articles relevant to the specified keyword combination, 13 articles conformed with inclusion and exclusion criteria. For HIV and non-HIV COVID-19 patients, the mean age was 52.98 ± 6.45 years and 55.84 ± 9.73 years, respectively. Approximately 73% of HIV COVID-19 patients were male. Symptoms among PLWH included fever (57%), cough (48.9%), and shortness of breath (37%). The pooled prevalence of COVID-19 among PLWH was 3.0% (95% CI, 1.0 - 8.5%), with critical, moderate, and mild severity in 4.8% (95% CI, 1.6 - 13.3%), 24.4% (95% CI, 1.9 - 29.8%), and 9.9% (95% CI, 1.9 - 38%), respectively.

CONCLUSIONS: PLWHs and HIV-negative individuals showed comparable rates and intensity of COVID-19. ART users exhibited immunological health comparable to immunocompetent people, demonstrating the essential role of ART in reducing the severity and mortality of PLWH with COVID-19.

Key Words:
COVID-19, HIV, Severity.

Introduction

The global expansion of preventive measures in response to the COVID-19 pandemic has posed significant challenges for approximately 2.8 million children and adolescents aged 0 to 19, as well as 1.3 million pregnant women living with HIV. These individuals have encountered difficulties in accessing essential antiretroviral therapy (ART) through healthcare facilities. According to a report by UNESCO, the estimated number of pregnant women and children infected with HIV who received ART in 2019 was only 2.1 million[1].

The rapid transmission of the coronavirus has led to the declaration of COVID-19 pandemic status by the WHO[2]. The first confirmed case in Indonesia was reported in March 2020, although the initial case was adequately documented in February 2020[3]. A study[4] conducted at Cipto Mangunkusumo Hospital in Jakarta found that the prevalence of COVID-19 among adults with HIV by the end of 2021 was 0.083 (95% CI, 0.074 - 0.092). This incidence was higher compared to similar cases in Madrid, which reported 0.067 (95% CI, 0.057 - 0.079)[4,5]. The current findings show a greater outcome compared to a previous meta-analysis encompassing seven trials, with an incidence rate of 0.009 (95% CI, 0.006 - 0.011)[4,6].

Empirical data derived from an evidence-based study[7] indicate that COVID-19 manifestations in individuals living with AIDS or people living with HIV (PLWHs) were comparable to individuals without HIV/AIDS with similar rates and intensity. Due to limitations in immune cells, such as T cells and humoral cells, their weakened immunological status renders them more susceptible to contracting various opportunistic infections[5]. PLWH on ART can restore their immunological competence, leading to an immune system closely resembling an immunocompetent population. However, COVID-19 infection among

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PLWHs is showing rapid progression. There were no comprehensive investigations conducted into the severity of cases among people living with HIV. Therefore, this study aims to calculate the COVID-19 prevalence based on the severity in PLWH compared to the general population.

Materials and Methods

The study followed the PRISMA guideline and focused on articles discussing the number of HIV patients infected with COVID-19 in both children and adults. A systematic literature search across multiple databases, including Pubmed, Science Direct, and Cochrane Library, was conducted. The search terms adopted were "2019-nCoV", "2019 Novel Coronavirus", "2019 Novel Coronavirus", "Acute Respiratory Disease", "Novel coronavirus", "2019-nCoV infection", "COVID-19", "SARS-CoV-2", "HIV", "AIDS", "human immunodeficiency virus", "acquired immunodeficiency virus", "PLWH", "PLHIV", and "severity", using Boolean operators "OR" and "AND". This study analyzed articles written in English and published in international journals between the years 2020 and 2022. The analysis focused exclusively on studies using a descriptive research design without any intervention, providing comprehensive explanations regarding the demographic features, clinical symptoms, comorbidities, severity, and outcomes of both HIV and non-HIV individuals affected by COVID-19. Relevant outcomes and no contradictory findings about the impact of COVID-19 co-infection on PLWH were discussed.

Two authors, AA and AAS, contributed to reviewing and screening each record retrieved, as well as establishing the inclusion and exclusion criteria. RAS and AAS conducted individual reviews, with AA taking the lead in making the final decision. LAC performed the statistical analysis and drew conclusions. The visualization, validation, writing, and reviewing of the original draft of the manuscript were performed by RAS, while AA contributed to supervision and reviewed the manuscript. A risk of bias analysis was carried out using the Joanna Briggs Institute (JBI) checklist for observational studies to critically appraise systematic reviews. Low, moderate, and high risks of bias were determined when > 85%, 70-85%, and < 70% answer was "Yes".

Statistical Analysis

The statistical analysis was conducted using the meta-package of RStudio software (Posit PBC, MA, USA). A random effect model was employed to demonstrate the pooled prevalence of COVID-19 among people with HIV, as well as the prevalence of critical and moderate severity of COVID-19 among HIV patients. The pooled prevalence was presented with a 95% CI, and a p-value of lower than 0.05 was used to determine statistical significance. The heterogeneity test of involved studies was measured using the inverse variance (I^2) statistics, with a Forest plot displaying the prevalence.

This research protocol was registered in International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) (No. INPLASY2023100063).

Results

A total of 1,965 articles were identified using the specified keywords within the search results. Of these, 1,489 articles were considered ineligible due to irrelevant outcomes, and 104 were found in three journals. After screening the titles and abstracts, 320 studies were excluded from the analysis, leaving 54 for eligibility assessment. From these, a further 3 and 38 studies were excluded due to presenting contradictory results about the impact of COVID-19 coinfection on PLWHs and irrelevance to the primary objective, respectively. A total of 13 articles[8-20] were identified to investigate the occurrence of COVID-19 co-infection among individuals living with HIV, and the methodology for selection is depicted in Figure 1.

Table I outlines the key characteristics of the investigation. Out of the 13 publications that met the requirements, 11 were original study articles[8,9,10-18] while the remaining 2 were letters to the editor[19,20]. Six investigations were conducted in the United States[10,12-15,20] and two in South Africa[8,17], respectively. Additionally, two studies were conducted in Italy[16,19] and the remaining studies were distributed between the United Kingdom[11] and Chile[18]. This study encompassed a sample size of 13 articles and involved a total of 14,306 individuals diagnosed with HIV compared to 1,552,317 individuals without HIV.

The study primarily consisted of adult patients, with the exception of two studies[12,15] which respectively included children aged 10 and 13 years and above. Each study was critically appraised using the JBI tool. Out of 13 articles, 10[8-11,13,16-20] and 3[12,14,15] articles were included as low and moderate risk, respectively. Detailed answers to the

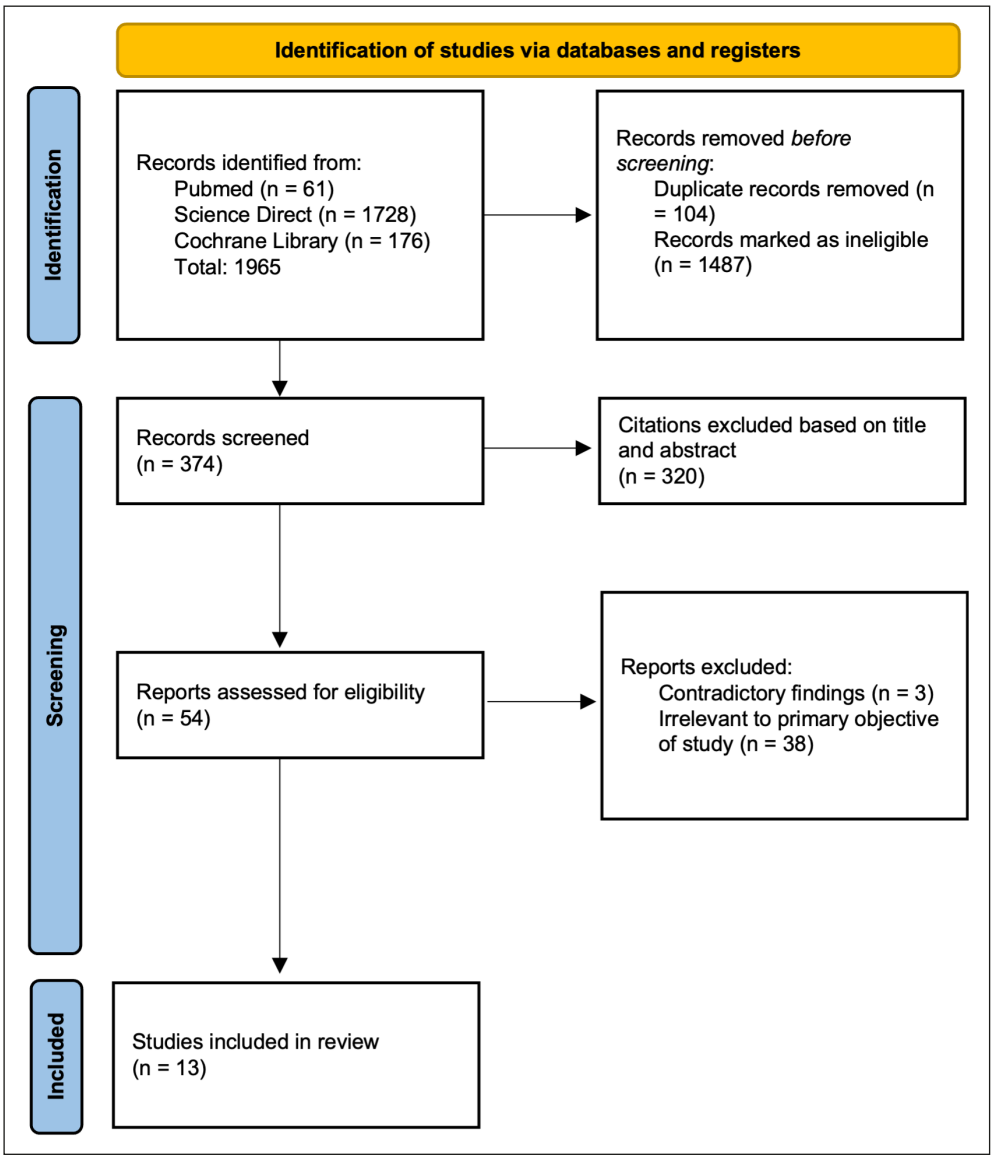

Figure 1. Flowchart of study selection according to PRISMA guidelines.

JBI critical appraisal tool for each study are available in **Supplementary Table I**. In conclusion, the confidence in the results of the review for our study was moderate, indicating that although the systematic review has more than one weakness, no critical flaws were found.

Subject Characteristics

Table II presents the subject characteristics that were included in the study. In people with and without HIV, the mean age of the participants was 52.98 ± 6.45 years and 55.84 ± 9.73 years, respectively. In PLWH, men and women showed higher and lower degrees of dominance, accounting for 73% and 27% of the total.

The most common comorbidities among PLWH and non-HIV patients were diabetes mellitus (23% and 16.6%), whereas smoking history was found in 28.6% PLWH and 17.7% in non-HIV COVID-19 patients. Figure 2a-b illustrates the prevalence of comorbidities among COVID-19 patients in people with and without HIV.

Among individuals who contracted COVID-19, fever affected 57% of PLWH, followed by cough and shortness of breath at 48.9% and 37%, respectively. Meanwhile, the most common symptoms in the non-HIV population were cough at 64.3%, followed by shortness of breath and fever at 61.3% and 60.4%, respectively (Figure 3).

Table I. Characteristics of included studies.

No.	Author	Year	Place	Journal	Study design	Population	COVID-19 Test	JBI Critical Appraisal
1	Ventura et al[6]	2021	South Africa	Journal Of Infection	Retrospective analysis (cross-sectional)	HIV-positive = 108 HIV-negative = 276	RT-PCR	Low risk
2	Yang et al[7]	2021	USA	Lancet HIV 2021	Case control	-	-	Low risk
3	Shalev et al[12]	2020	USA	Oxford	Descriptive	HIV-positive = 31	RT-PCR	Low risk
4	Sigel et al[1]	2020	USA	IDSA	Cross-sectional	HIV-positive = 88 HIV-negative = 405	Laboratory confirmed	Moderate risk
5	Sachdev et al[14]	2020	USA	Wolters Kluwer Health	Descriptive	-	-	Moderate risk
6	Calza et al[17]	2021	Italy	Journal Acquired Immune Deficiency Syndrome	Letter to editor (Case Series)	HIV-positive = 26	RT-PCR	Low risk
7	Stoeckle et al[9]	2020	USA	Open forum infectious diseases	Retrospective cohort	HIV-positive = 30 HIV-negative = 90	-	Low risk
8	Gervasoni et al[15]	2020	Italy	Clinical Infectious disease	Retrospective descriptive study	HIV-positive = 47	Probable or proven SARS-CoV-2	Low risk
9	Geretti et al[10]	2020	United Kingdom	-	Prospective cohort study	HIV-positive = 122 HIV-negative = 47,592	RT-PCR	Low risk
10	Parker et al[16]	2020	South Africa	SAMJ	Descriptive study	HIV-positive = 24 HIV-negative = 89	RT-PCR	Low risk
11	Okoh et al[18]	2020	Israel	JAIDS	Letter to editor (Case Series)	HIV-positive = 27	RT-PCR	Low risk
12	Hadi et al[1]	2020	USA	Wolters Kluwer Health	Comparison cohort	HIV-positive = 404 HIV-negative = 49,763	- risk	Moderate
13	Ceballos et al[8]	2021	Chile	International Journal of STD & AIDS	Observational cohort	HIV-positive = 36 HIV-negative = 18,285	RT-PCR	Low risk

HIV: human Immunodeficiency Virus; RT-PCR: real time polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; STD: sexually transmitted disease; AIDS: acquired immunodeficiency syndrome.

Prevalence of COVID-19 Among PLWH

The Random effect model (I^2 = 100%, t^2 = 3.45, $p < 0.01$) showed the pooled prevalence of COVID-19 among people with HIV was 3.0% (95% CI, 1.0 - 8.5%) (Figure 4). From 1,566,549 patients with COVID-19, there were 14,232 people with HIV. The highest and lowest prevalence occurred in the study by Venturas et al[6] and Ceballos et al[16] with 28.1% and 0.2%, respectively.

Severity and Outcome of COVID-19 Among PLWH

To assess the severity of COVID-19, a study[8] used the CURB-65 (confusion, uremia, respiratory rate, BP, age > 65 years) score, National Early Warning Score 2 (NEWS 2), and The Coronavirus Clinical Characterization Consortium Mortality Score (4C Mortality Score). Another article[9] used the WHO Clinical Progression Score (WHO-CPS), and five[10,11,13,14,16] utilized the type of oxygenation support to assess the severity of COVID-19. The remaining articles[12,15,17-20] determined severity based on the type of admission room provided for patients. To generalize the severity of COVID-19, WHO disease severity divided into mild, moderate, severe, and critical was used[21].

Patients were classified as mild cases when there was no evidence of hypoxia and did not require oxygen supplementation. Conversely, moderate

Table II. Subject characteristics, clinical symptoms, and comorbidities.

Characteristics	HIV (n = 14,298)		Non-HIV (n = 1,550,804)	
	n	%	n	%
Age (mean ± SD)	52.98 ± 6.45		55.84 ± 9.73	
Sex				
Male	10,460	73%	709,301	46%
Female	3,838	27%	829,019	54%
Length of stay	9.3		N/A	
Comorbidity				
Cardiovascular	2,844	20%	209,323	13.5%
Chronic kidney disease	1,912	13.4%	99,836	6.4%
Hypertension	308	2.2%	30,089	2%
Chronic liver disease	2,185	15.3%	72,256	4.6%
Chronic lung disease	3,145	22%	225,688	14.5%
Tuberculosis	16	0.1%	11	< 0.01%
Diabetes mellitus	3,282	23%	257,419	16.6%
Dyslipidaemias	20	0.14%	20	< 0.01%
Obesity	2,636	18.4%	235,925	15.1%
Thyroid disease	4	0.03%	5	< 0.01%
Malignancy	1,235	8.6%	82,344	5.3%
Neuropsychiatry	276	1.9%	37,441	2.4%
Rheumatology	522	3.6%	51,266	3.3%
Smoking History	4,087	28.6%	274,803	17.7%
Stroke	878	6.1%	67,298	4.3%
Symptoms	**HIV (n = 343)**		**Non-HIV (n = 65,934)**	
	n	%	n	%
Fever	305	57%	39,856	60.4%
Sore throat	43	8%	6,047	9.2%
Cough	262	48.9%	42,376	64.3%
Dyspnea	198	37%	40,452	61.3%
Runny nose	36	6.7%	839	1.3%
Diarrhea	66	12.3%	8,830	13.4%
Nausea/vomit	34	6.3%	8,827	13.4%
Ageusia	31	5.8%	762	1.2%
Anosmia	10	1.9%	893	1.4%
Fatigue/Myalgias	183	34%	30,128	45.7%

n: number; SD: standard deviation; HIV: human immunodeficiency virus.

cases received oxygen supplementation through a nasal cannula or venturi mask due to clinical signs of pneumonia but were not severe or had oxygen saturation ≥ 90% on room air. Severe cases were individuals with pneumonia and were provided with oxygen supplementation through a non-rebreather mask and high-flow nasal cannula. In critical cases, individuals experienced acute respiratory distress syndrome (ARDS) and required non-invasive or mechanical ventilation[21].

Among these patients, 50.4% of mild cases were from the HIV population, and 33.8% were from the non-HIV population. Meanwhile, 4.1% of the HIV population and 2.2% of the non-HIV population contracted critical COVID-19 cases (Table III). Out of the 14,218 individuals who were diagnosed with COVID-19 and were identified as PLWH, 516 (3.6%) of the total succumbed to the disease. Meanwhile, 96.4% or 13,702 PLWH who contracted COVID-19 managed to recover (Table III and Figure 5).

From a total of 31,323 patients with critical cases, 562 were HIV positive. The pooled prevalence of critical COVID-19 using the random effect model ($I^2 = 97\%$, $t^2 = 2.13$, $p < 0.01$) showed a number of 4.8% (95% CI, 1.6 - 13.3%), with the highest and lowest prevalence occurred in the study by Stoeckle et al10 and Ceballos et al[18] in 17.9% and 0.4%, respectively (Figure 6).

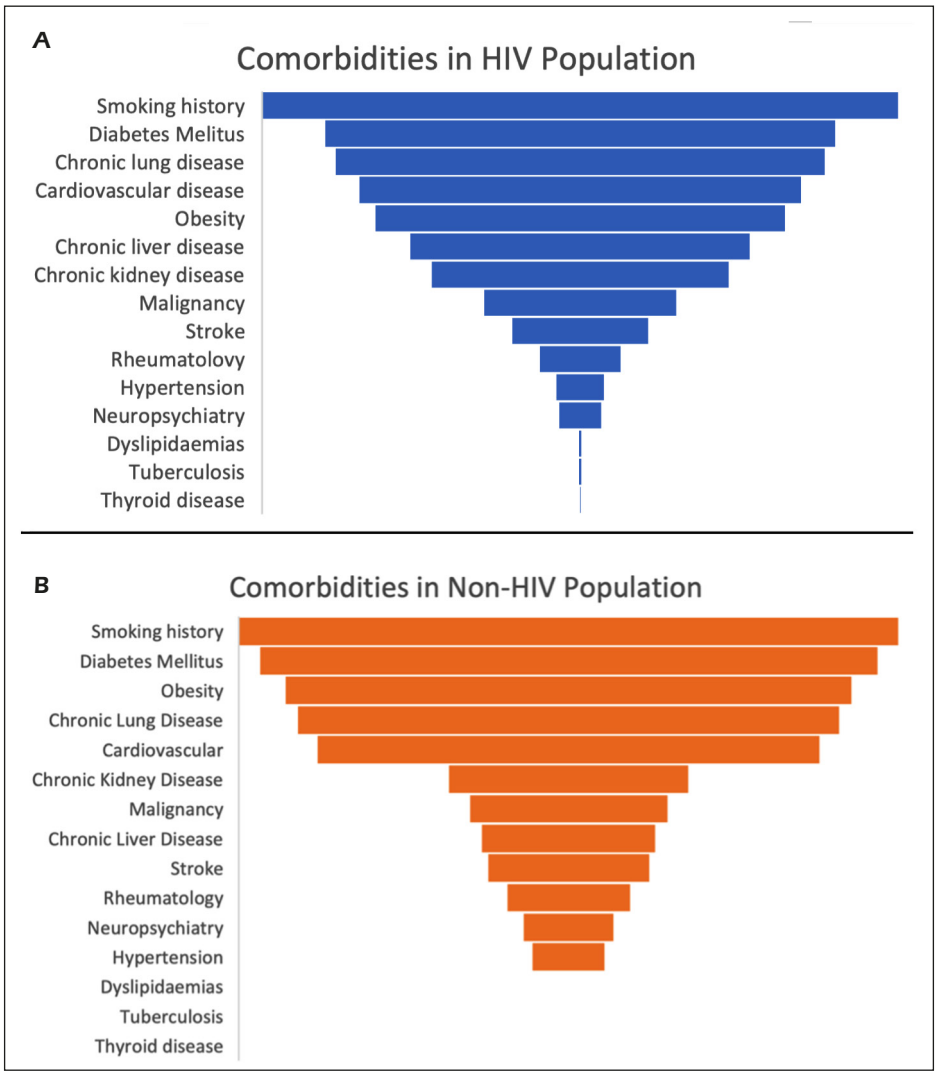

Figure 2. Comorbidities among PLWH (**A**) and Non-HIV (**B**) subjects.

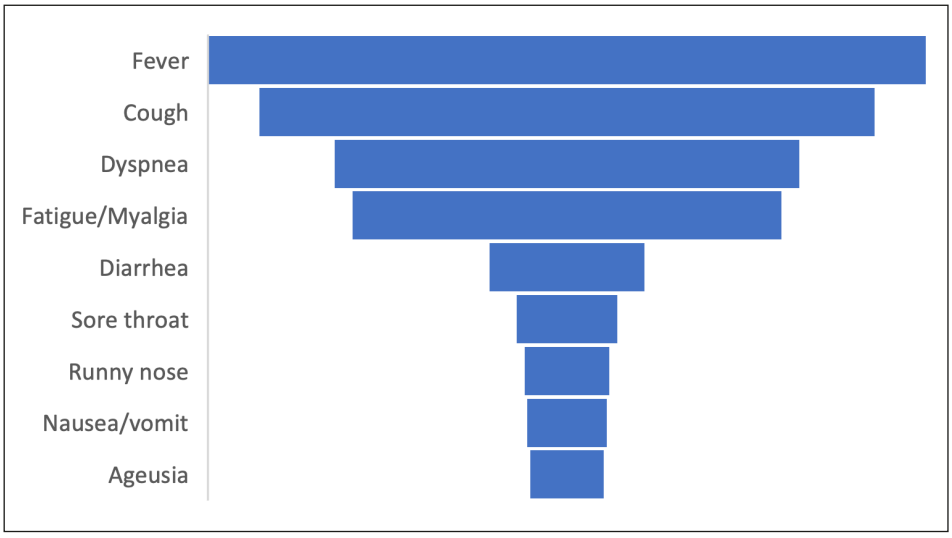

Figure 3. Clinical manifestations in HIV population.

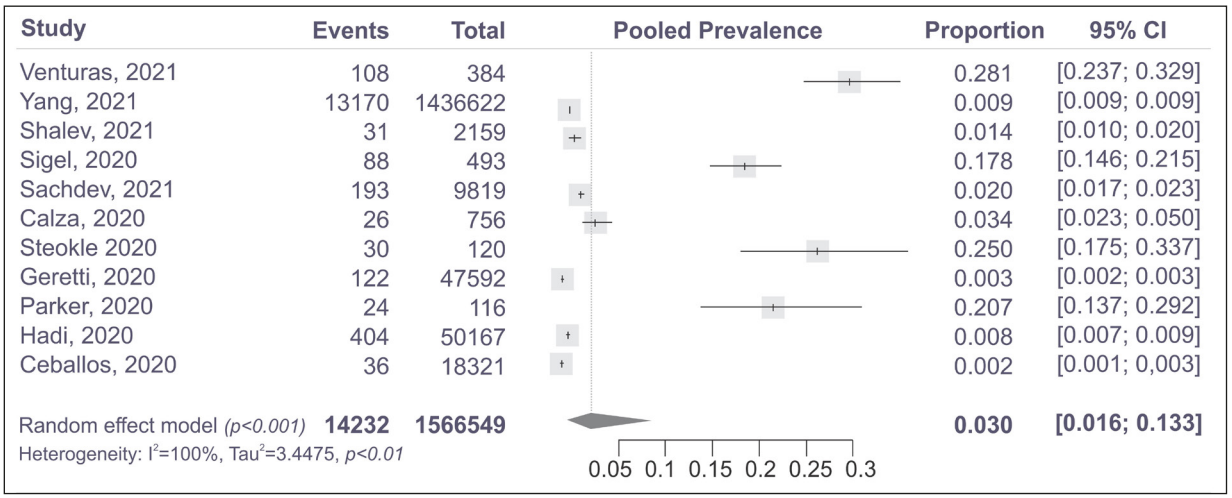

Figure 4. Pooled prevalence of total COVID-19 infection in people living with HIV.

Table III. Classification of COVID-19 severity and outcome in HIV and non-HIV patients.

	HIV Positive (n = 14,028)		HIV Negative (n = 1,390,335)	
Classification	**n**	**%**	**n**	**%**
Mild	6,956	50.4%	469,970	33.8%
Moderate	68	0.5%	211	0.02%
Severe	6,224	45.1%	889,380	63.9%
Critical	562	4.1%	30,761	2.2%
	HIV Positive (n = 14,218)		**HIV Negative (n = 1,491,955)**	
Outcome	**n**	**%**	**n**	**%**
Alive	13,702	96.4%	1,460,235	97.9%
Died	**516**	**3.6%**	**31,720**	**2.1%**

HIV: human immunodeficiency virus.

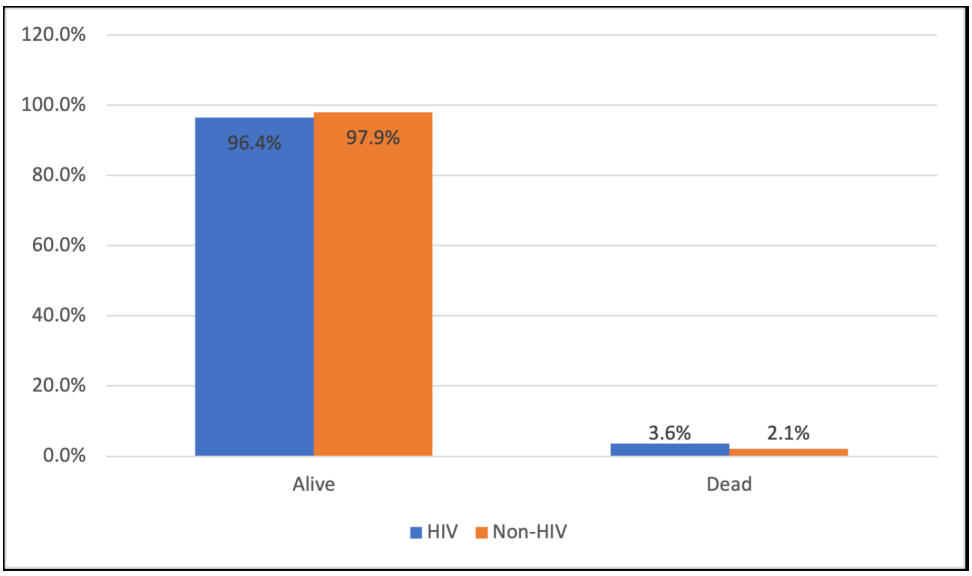

Figure 5. Outcome of HIV and Non-HIV subjects.

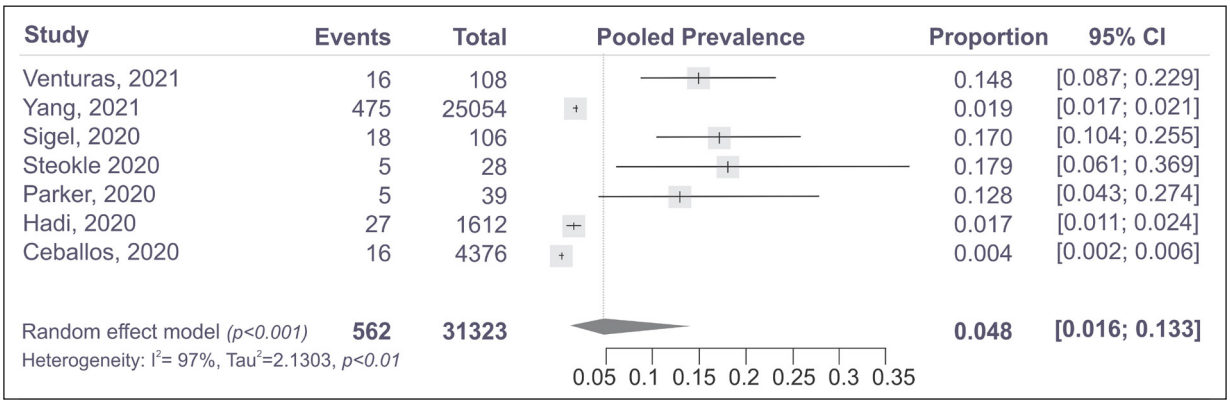

Figure 6. The pooled prevalence of HIV-positive infection in critical COVID-19.

A total of three studies[10,14,16] described 279 moderate cases, with 68 being HIV positive. The pooled prevalence using the random effects model (I^2 = 0%, t^2 = 0, p < 0.85) was 24.4% (95% CI, 1.9 - 29.8%) (Figure 7). Studies by Stoeckle et al[10] and Sigel et al[14] showed the highest and lowest numbers at 27.0% and 23.2%, respectively.

Only three articles[9,10,14] described the 476,926 cases of mild severity of COVID-19. In this context, 6,956 cases were HIV positive, while the remaining were HIV negative. The pooled prevalence of mild COVID-19 cases (I^2 = 99%, t^2 = 2.25, p < 0.01) among PLWH was 9.9% (95% CI, 1.9 - 38%) (Figure 8). The study by Stoeckle et al[10] showed the highest number of mild HIV COVID-19 patients at 35.7%, while the lowest was by Yang et al[9] at 1.5%.

The Utilization of ART Among PLWH

The use of ART among PLWH was also described in several studies[8,10,14,18] (Table IV). The collective sum of HIV-positive patients across the four publications amounts to 262 individuals. Out of the total sample, 232 received ART, accounting for 88.5% of the HIV-positive population.

Discussion

Our study found the prevalence of COVID-19 in PLWH is 3.0%, with only 4.8% of them yielding critical severity. Studies[14,22-30] have demonstrated diverse results about the effect of COVID-19 on PLWH. Some research[14,22-25] suggests that PLWH are not more susceptible to developing COVID-19,

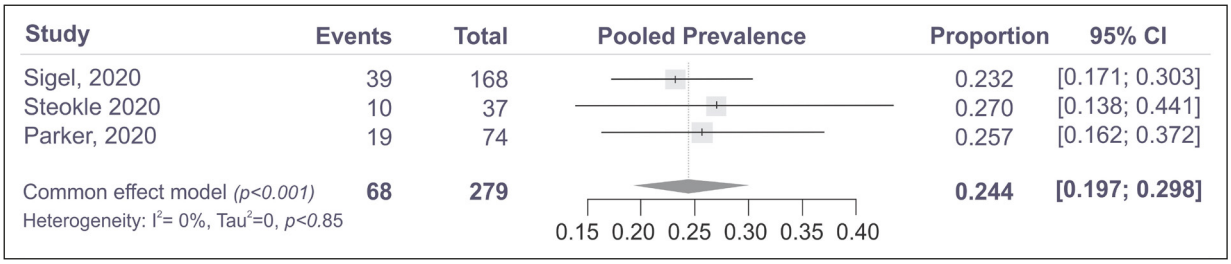

Figure 7. The pooled prevalence of HIV-positive infection in moderate COVID-19.

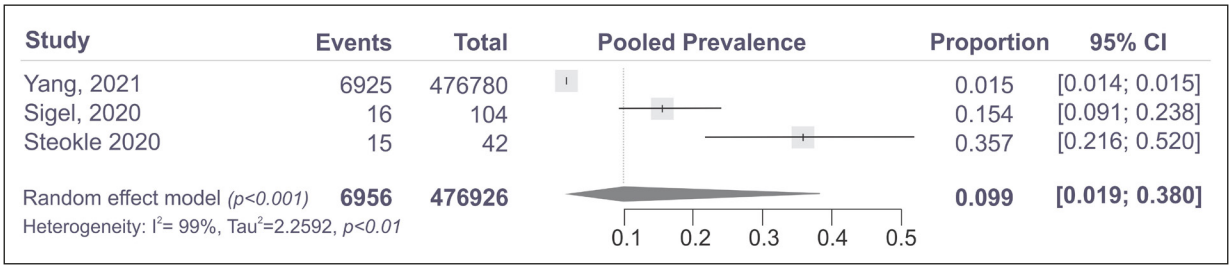

Figure 8. The pooled prevalence of HIV-positive infection in mild COVID-19.

Table IV. ART usage profile.

Author	Positive HIV sample (n)	Use of ART (%)	Type (%)
Ventura et al[6]	108	79 (82.3)	-
Ceballos et al[8]	36	1st: 30 (83.3) 2nd: 6 (16.6)	-
Sigel et al[13]	88	88 (100)	Integrase: 69 (78.4) Protease inhibitor: 15 (17) NNRTI: 8 (9) NRTI: 85 (96.5)
Stoeckle et al[9]	30	29 (97)	Protease inhibitor: 6 Non-protease inhibitor: 23
Total	262	232 (88.5)	

ART: antiretroviral therapy; HIV: human immunodeficiency virus; NNRTI: non-nucleoside reverse transcriptase inhibitors; NRTI: nucleoside reverse transcriptase inhibitors.

and there is no significant difference in the rate of mortality compared to individuals without HIV. On the contrary, different studies[26-28] described an increase in SARS-CoV-2 infection and mortality among PLWH with COVID-19. A systematic review[29] from China reported that PLWH had a comparable risk of SARS-CoV-2 infection and developing into severe COVID-19 compared to HIV-negative patients. Meanwhile, another systematic review[30] from Belgium described an opposite result by finding a higher incidence of COVID-19 in PLWH, leading to increased hospitalization rates, but not linked to greater severity. These results may be attributed to the use of ART, as the previous studies[26] with higher mortality did not mention the adherence data regarding ART use or having comorbidities despite being adherent to ART. Whereas in our study, about 88.5% of PLWH who contracted COVID-19 adhered to ART treatment.

In South Africa, PLWH who contracted COVID-19 have a 15% elevated risk of mortality. This region is characterized by a high prevalence of HIV infection and limited accessibility to ART treatment[31]. Meanwhile, studies[32] following long-term use of ART have shown an increase in median CD4 count and CD4/CD8 ratio compared to the time of initiation. A study[4] in Indonesian suggested that the utilization of ART, having an absolute CD4 count of less than 200 cells/mm, and having any comorbidities were all linked to severe COVID-19 infection. This pattern may indicate that poor compliance to ART and having serious comorbidities among PLWH are causally linked to a serious outcome upon contracting COVID-19.

A previous study[33] suggested that ART has a similar mechanism to reduce the viral load of SARS-CoV-2. Some of the ARTs, such as Lopinavir (protease inhibitor) and Ritonavir, have *in-vitro* activities in resisting SARS-CoV-2. The use of nucleoside reverse transcriptase inhibitor (NRTI) is also related to the low mortality rate in COVID-19 coinfection cases[14]. A previous study[34] in Spain also showed a decreased risk of COVID-19 infection and hospitalization due to COVID-19 infection in PLWHs that have consumed ARTs such as Disoproxil and Emtricitabine compared to other NRTI components. This mechanism is associated with the viral replication process and mechanism of drug action. In the coronavirus replication process, there is a major protein (M^{pro}), also known as 3C-like proteinase (3CLpro) or nsp5, that plays an important role in activating viral replication. M^{pro} has a secondary function and can interact with histone deacetylase 2 (HDAC2), enabling M^{pro} to stop the core transport of HDAC2 and inhibit the inflammation effect, thus producing an anti-inflammatory effect. Direct M^{pro} inhibition will affect the replication cycle and other functions in inhibiting inflammation. As a result, protein inhibitors that could directly target these protein structures will be effective in inhibiting SARS-CoV-2 infection[35]. This explains why some protease-inhibitor class HIV drugs, such as lopinavir and ritonavir, are currently being studied for COVID-19 therapy[35,36].

Some of the other ARTs, such as remdesivir, homoharringtonine, and emetine dihydrochloride, inhibit SARS-CoV-2 *in vitro* on Vero E6, but the use of ART therapy in combination is also suspected to hinder the concentration effectiveness. Remdesivir has been in the computational screening phase as a drug candidate against SARS-CoV-2 along with hydroxychloroquine, OEW, and N3. These drugs were reported as some of the best candidates for each known ligand pharmacophore for *in vitro* and *in vivo*[34-36]. Remdesivir, as well as ribavirin, sofosbuvir,

galidesivir, and tenofovir, have also been proposed as effective medications against SARS-CoV-2 because of their ability to bind tightly to RNA-dependent RNA polymerase (RdRp), a viral enzyme that is important to the life cycle of RNA viruses and has been targeted in a variety of viral infections[38]. Even though these regimens do not necessarily become the drug of choice for COVID-19, a randomized-control trial in Hong Kong[39] with a combination of 400 mg lopinavir and 100 mg ritonavir every 12 hours, and 400 mg ribavirin every 12 hours, as well as 3 doses of 8 million IU of interferon beta-1b on alternate days, resulted in shorter median time to negative nasopharyngeal swab.

A greater proportion of men was reported than women. The results are consistent with other studies[11,16,18,34,40,41], which have shown a higher incidence of COVID-19 infection among men with HIV. In contrast, among those who do not have HIV, there is a higher proportion of women compared to men. Men have been reported as having the highest HIV prevalence, with 81% contracting the virus by birth and 81% from male-to-male contact[42].

Our study revealed that a significant number of PLWH encountered mild symptoms of COVID-19 in comparison to individuals without HIV (50.4% *vs.* 33.8%). The data is consistent with a previous study[43] that reported 88.2% of HIV patients with COVID-19 experiencing mild or moderate symptoms, while only 10.6% experienced severe symptoms. In cases of severe COVID-19, PLWH had a lower prevalence compared to individuals without HIV (45.1% *vs.* 63.9%). However, those with HIV exhibited a greater incidence of critical severity and mortality as compared to those without HIV (critical prevalence among PLWH: 4.1% *vs.* non-HIV: 2.2%; mortality among PLWH: 3.6% *vs.* non-HIV: 2.1%). These presentations suggest that PLWH suffers similar prevalent symptoms as the general population, and the immune response is nearly as robust as that of the general population. However, HIV suppresses the immune system and results in immunodeficiency. This immunological deficit can reduce the intensity of the immune system's response, such as cytokine storm and its related symptoms[44]. Hence, in this study, a lower percentage of PLWH experienced respiratory difficulties.

The prevalence of COVID-19 among PLWH is lower (2%) compared to the general population with comorbidities such as cardiovascular disease and obesity[31]. The presence of comorbidities such as hypertension and smoking history would impact PLWHs when they are infected with COVID-19, which is found to be the most common comorbid in both PLWH and people without HIV[7,8,13,14,45-47]. Patients with hypertension had a higher risk of death, with a hazard ratio of 2.679. This poor outcome is speculated to have been associated with a significant decrease in peripheral blood of CD3, CD4, and CD8 T-cells that caused impairment of immune function[48]. A study[49] conducted in the United Kingdom highlights that the death rate among PLWH infected with COVID-19 is higher when they have comorbidities such as hypertension and diabetes mellitus, as well as a low CD4 count.

Nevertheless, each PLWH differs in its immune suppression and viral load, leading to different outcomes based on the population studied[50]. The variation of SARS-CoV-2 itself may influence the incidence and outcome in PLWH. In Africa, the mortality of PLWH during the alpha, beta, delta, and omicron variants was higher than in the general population[51]. However, China reported a lower prevalence of SARS-CoV-2 Omicron variant infection in PLWH than HIV-negative people[52]. Furthermore, although the median viral load was greater for a longer period, China has also reported that there is no significant difference in clinical manifestations prior to SARS-CoV-2 Delta infection in PLWH. The computed tomography (CT) imaging also showed rapid lesion absorption without sequelae[53].

The phenomenon could be influenced by the scope of the COVID-19 vaccine, where only 32% of the South African population was fully vaccinated. The COVID-19 vaccine is safe for PLWH, with the first dose of vaccine giving PLWH seroconversion that was comparable to healthy individuals, and an increase in vaccine effectiveness escalated for up to 89.3%[54,55]. Furthermore, a study[56] examining the occurrence following vaccination in individuals with HIV and the general population has similarly shown a greater proportion of asymptomatic cases among PLWH (78.9%) compared to the general population (74.3%).

However, despite being vaccinated, a lower CD4+ count < 350 cells/mL or advanced HIV stage has been associated with an increased risk of moderate to severe COVID-19 infection and re-infection, and those less than 200 cells/mL have an elevated risk of ICU admission and death[57,58]. Early innate response to SARS-CoV-2 infection is mediated by CD4 and CD8+ T cells. PLWH, with a low CD4+ cell count, has a lower response to mRNA COVID-19 vaccines, which are crucial in destroying the virus. During COVID-19 infection itself, CD4+ specific cell activity increases. However, serious COVID-19 infection reduces

the CD4+ count. SARS-CoV-2 infection also causes modification of circulatory leukocytes, namely interleukin-1 (IL-1), IL-6, IL-10, IL-17, tumor necrosis factor (TNF), and granulocyte-macrophage colony-stimulating factor (GM-CSF), which cause cytokine storm. Fortunately, ART is found to decrease cytokinemia to baseline level, as shown by a reduction of interleukin concentrations following 12 months of ART[57]. This was supported by the case of a 67-year-old ART-compliant HIV patient who recovered from COVID-19 infection after a sharp decline in CD4 count. After two months, the CD4 count was back to normal[59].

Other than COVID-19, it is widely observed that PLWH are more susceptible to contracting other infections compared to the general population. Viruses are the most common cause of opportunistic infections, with Rhinovirus and influenza A being the most prevalent. About 41% of PLWH with a respiratory virus required intensive management, and more than half of PLWH with secondary viral infection exhibit moderate to severe diarrhea and fatigue[60,61]. Studies[62-63] also indicate that PLWH had an increased risk of mortality from seasonal influenza. Humoral and cellular immunosuppression in PLWH are found to be the causal mechanism.

It is also an interesting question to understand the impact of COVID-19 on other immunocompromised-non-HIV patients, such as those with systemic lupus erythematosus (SLE) and rheumatoid disease (RD), where studies[64,65] stated that around 46% and 32.9% of individuals with RD and SLE with COVID-19 required hospitalization. Individuals with immunocompromised conditions experience a reduction or complete lack of antibodies that inhibit the spread of the virus within the lungs, hence increasing the likelihood of a more extensive infection[46]. A meta-analysis[66] among autoimmune patients showed that prior glucocorticoid use increased the risk of SARS-CoV-2 infection, hospitalization, and death. Patients diagnosed with RD showed the most elevated rates of hospitalization and mortality[67-69]. The event rate for hospitalization and fatality was determined to be 0.54 and 0.097, resepectively[66].

This finding seemed to be linked with long-term administration of glucocorticoids. Prolonged usage of prednisone at a dosage exceeding 10 mg per day was found to be correlated with an increased likelihood of hospitalization64. Corticosteroids are known to induce a reduction in the numbers of T cells and B cells. During the extended administration of corticosteroids, a decrease in the CD4 and CD8 subsets of T cells has been seen, and the CD19 subset of B cells also remained consistently low[70,71]. Meanwhile, in COVID-19, there is an observed rise in the number of neutrophils and leukocytes, but there is a decrease in the overall count of lymphocytes, including CD4+ T cells, CD8+ T cells, regulatory T (T reg) cells, memory T cells, natural killer cells, and B cells. The utilization of long-term corticosteroids may potentially contribute to poor outcomes in autoimmune diseases diagnosed with COVID-19[72]. Therefore, non-HIV immunocompromised patients may have a higher prevalence of contracting COVID and a higher hospitalization rate.

Limitations

This study, while valuable, has certain limitations. The reliance on published literature may not fully capture the complete impact of COVID-19 on PLWH. The effects of different ART regimens, adherence levels among PLWH, or the disparities in healthcare access and quality among various populations are not extensively explored. Future analyses should focus on understanding the specific role of ART in mitigating COVID-19 severity and its potential impact on the pandemic management of vulnerable populations. Additionally, further studies are needed to examine the variability in COVID-19 severity among PLWH who used various ART regimens in these contexts.

Conclusions

In conclusion, the prevalence of PLWH to contract COVID-19 is low, and the symptoms often resemble those of the general population, predominantly displaying milder forms of the disease. The use of ART in PLWH has been associated with a reduction in severe cases and lower mortality rates from COVID-19.

This study enhances our understanding of COVID-19 in PLWH and other immunocompromised persons and emphasizes the importance of ART and comorbidity management in lowering disease severity.

Informed Consent

Not applicable.

Ethics Approval

Not applicable.

Conflict of Interest
The authors declare that they have no conflict of interest to disclose.

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Data Availability
All data generated or analyzed during this study are included in this published article and/or its supplementary material.

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