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Human Immunodeficiency Virus and Severe Acute Respiratory Syndrome Coronavirus 2 Coinfection: A Systematic Review of the Literature and Challenges

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Abstract

The concurrence of infection with human immunodeficiency virus (HIV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), presents an intriguing problem with many uncertainties underlying their pathogenesis. Despite over 96.2 million cases of COVID-19 worldwide as of January 22, 2021, reports of patients coinfected with HIV and SARS-CoV-2 are scarce. It remains unknown whether HIV patients are at a greater risk of infection from SARS-CoV-2, despite their immunocompromised status. We present a systematic review of the literature reporting cases of HIV and SARS-CoV-2 coinfection, and examine trends of clinical outcomes among coinfected patients. We systematically compiled 63 reports of HIV-1 and SARS-CoV-2 coinfection, published as of January 22, 2021. These studies were retrieved through targeted search terms applied to PubMed/Medline and manual search. Despite scattered evidence, reports indicate a favorable prognosis for HIV patients with strict adherence to combined antiretroviral therapy (cART). However, the presence of comorbidities was associated with a poorer prognosis in HIV/SARS-CoV-2 patients, despite cART and viral suppression. Studies were limited by geographic coverage, small sample size, lack of patient details, and short follow-up durations. Although some anti-HIV drugs have shown promising *in vitro* activity against SARS-CoV-2, there is no conclusive evidence of the clinical efficacy of any anti-HIV drug in the treatment of COVID-19. Further research is needed to explain the underrepresentation of severe COVID-19 cases among the HIV patient population and to explore the possible protective mechanisms of cART in this vulnerable population.

Keywords: HIV, COVID-19, SARS-CoV-2, coinfection, cART, antiviral

Introduction

The ongoing global pandemic of novel coronavirus disease 2019 (COVID-19), which originated from Wuhan in the Hubei province of China, has rapidly spread throughout the world, causing great uncertainty in various dimensions.[1,2] The etiological agent responsible for this disease, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), shares many similarities with the SARS coronavirus outbreak of 2003, triggering, for the most part, a range of respiratory symptoms but in a subset of patients, both neurological and cardiovascular symptoms[3] are reported along with a variety of other clinical manifestations.[4] There has been inconclusive evidence of human immunodeficiency virus (HIV)-1 protease inhibitors showing *in vitro* clinical efficacy against the SARS-CoV outbreak and other coronavirus infections.[5] It is also assumed that SARS-CoV-2 may not effectively disrupt the complement system and trigger cytokine storm in pre-existing dysfunctional immune systems of people living with HIV (PLWH), making them less susceptible to the severe form of COVID-19.[6] Although combined antiretroviral therapy (cART) in HIV patients may influence COVID-19 progression, the persistent innate immune defects that accompany cART may be involved in limiting the hyperinflammatory state seen as a characteristic of SARS-CoV-2 infection than cART itself. Recent studies

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have shown an inflammatory response and persistent complement activation as a marker of severe COVID-19 progression linked to microvascular injury and thrombosis, supporting that cART does not entirely suppress this chronic inflammatory state.[7]

The elderly patients (>60 years), and those with underlying comorbidities such as hypertension, respiratory disease, cardiovascular disease, diabetes, and chronic kidney disease present with a more severe form of COVID-19 and have adverse outcomes.[8] The majority of PLWH/AIDS worldwide are over the age of 50 and generally have some form of comorbidities, which poses a greater risk for developing a severe sequelae of symptoms from COVID-19.[9] Although some reports have found anti-HIV drugs such as atazanavir, lopinavir/ritonavir, nelfinavir, and tenofovir[10–12] to be effective against SARS-CoV-2, there is conflicting evidence regarding the benefits of cART in HIV patients and its relation with the severity of COVID-19 clinical symptoms. Therefore, we systematically compiled the available literature regarding patients with HIV and SARS-CoV-2 coinfection. Our review aims to better understand the interactions of cART in HIV patients infected with SARS-CoV-2 and provide details regarding the clinical efficacy of antiretroviral therapy (ART) to accelerate the search for optimal treatment. Given the plethora of emerging reports regarding HIV and SARS-CoV-2 coinfection, it becomes important to systematically compile all available evidence to assess the impact of COVID-19 clinical presentation in this vulnerable patient population and corroborate the importance of maintaining the HIV care continuum during this challenging time.

Materials and Methods

We conducted a systematic review of the literature to identify all available studies reporting HIV and SARS-CoV-2 coinfection patients. This search was conducted to include all studies published between December 1, 2019, and January 22, 2021.

Search strategy

Studies were identified through a systematic search of PubMed/Medline and a manual search for gray literature. The following targeted search terms were applied in combination across all databases: ''HIV,'' ''SARS-CoV-2,'' ''COVID-19,'' ''human immunodeficiency virus,'' ''coronavirus disease 2019,'' ''severe acute respiratory syndrome coronavirus disease 2,'' and/or ''coinfection.'' We conducted a thorough search to locate targeted search terms within the articles' title, abstract, and keywords.

Study selection

To maximize inclusion, there were no geographic or language limitations applied. All titles from the search results were preliminarily screened to determine eligibility for inclusion. Next, each title, abstract, and full text (when necessary) of the search results were further examined to determine the following inclusion criteria satisfaction. Studies that described the clinical course of HIV patients who were coinfected/hospitalized with SARS-CoV-2/COVID-19 were included. Studies that were commentaries, editorials, unpublished/peer-reviewed manuscripts, or those that did not describe any clinical details of patients with coinfection (behavioral studies) were excluded from the review. The contents described in this systematic review does not involve human subjects and do not require *IRB* review.

Data extraction

We reviewed each of the eligible articles and extracted/sorted the relevant data. The first category is comprised of the case reports that described two patients or less, and provided anecdotal experiences of HIV patients coinfected with SARS-CoV-2 (Table 1). The second category is comprised of the remaining more extensive studies, which described three or more patients and provided a statistical analysis of the clinical outcomes in coinfected patients, and included single- or multicenter studies (Table 2). The following information was collected from the studies: author details, article title, geographic location, number of patients reported, age of patients, comorbidities of patients (if noted), statistical information, cART regimen of patients, presence of severe clinical outcomes [intensive care unit (ICU) admission or mechanical ventilation], CD4+ T-cell counts, and HIV viral RNA loads, and outcomes. This information was synthesized and divided into Tables 1 and 2 based on the article type.

Assessment of risk of bias

We evaluated all possible methodological bias sources in the identification of studies per the Cochrane Handbook for Systematic Reviews of Interventions.[13] Given the independence of both reviewers and agreement of the limited results, after a careful evaluation, no sources of methodological bias were identified.

Analysis of data

After compiling the data through systematic review, we explored trends of mortality, ICU admission, hospitalization, the severity of the clinical course, and the impact of comorbidities in HIV patients coinfected with SARS-CoV-2. These factors were discussed in a descriptive review of the articles included in each study category. We also discuss cART and comorbidities' role in the prognosis of HIV patients with SARS-CoV-2 infection based on trends demonstrated by the limited studies.

Results

Based on our targeted search terms, 349 studies were identified from PubMed/Medline. Since we used many inclusive search terms, there were many false hits of studies, which fell outside of the inclusion criteria. Based on a review of the title of these studies, 228 were excluded based on irrelevance. The remaining abstracts of the 121 studies were reviewed, and 66 of these were excluded as they did not describe clinical details of coinfection, duplications of preprints, or due to other irrelevancies. Also, several studies solely reported social and behavioral responses of HIV patients to COVID-19 experiences and did not include any relevant clinical data, leading to their exclusion. After a manual hand search of peer-reviewed and unindexed articles was performed, an additional eight studies that satisfied the inclusion criteria were found. This led to a final sample of 63 total studies, which fully satisfied our inclusion criteria.

Table 1. Systematic Review Findings of Twenty-Eight Case Reports (≤2 Patients) Describing Patients with Human Immunodeficiency Virus and Severe Acute Respiratory Syndrome Coronavirus 2 Coinfection

Author	*Title*	*Number of Patients*	*Age (years)*	*Location*	*Comorbidities*	*CD4+ T-cell count at the time of admission*	*HIV viral RNA at the time of admission*	*cART regimen*	*Outcome*
Zhao *et al.*[14]	Early virus clearance and delayed antibody response in a case of COVID-19 with a history of coinfection with HIV-1 and HCV	1	38	Wuhan, China	HCV infection	250 cells/μL	<500 HIV-1 RNA, copies/mL	Lamivudine, tenofovir, and efavirenz	Recovered with mild symptoms
Zhu *et al.*[15]	Coinfection of SARS-CoV-2 and HIV in a patient in Wuhan city, China	1	61	Wuhan, China	Type II diabetes	—	—	Lopinavir/ritonavir	Recovered with mild symptoms
Chen *et al.*[16]	Computed tomography imaging of an HIV-infected patient with COVID-19	1	24	Wuhan, China	—	—	—	Lopinavir/ritonavir	Recovered with moderate symptoms
Wang *et al.*[17]	One case of COVID-19 in patient coinfected by HIV with a low CD4+ T-cell count	1	37	Wuhan, China	—	34 cells/μL	—	—	Recovered after moderate symptoms
Wu *et al.*[18]	Recovery from COVID-19 in two patients with coexisted HIV infection	2	P1:60 P2:47	Wuhan, China	P1: stage IV diffuse large B-cell lymphoma and pulmonary tuberculosis P2: —	—	—	P1: tenofovir, disoproxil, fumarate, lamivudine, and efavirenz P2: —	P1, P2: recovered after mild symptoms
Nakamoto *et al.*[19]	A case of SARS-CoV-2 infection in an untreated HIV patient in Tokyo, Japan	1	28	Tokyo, Japan	Hepatitis B	194 cells/μL	100 copies/mL	—	Recovered after moderate symptoms
Iordanou *et al.*[20]	Severe SARS-CoV-2 pneumonia in a 58-year-old patient with HIV: a clinical case report from the Republic of Cyprus	1	58	Republic of Cyprus	None	1,640 cells/μL	Undetectable	Elvitegravir, cobicistat, emtricitabine, tenofovir, alafenamide, fumarate	Recovered after severe symptoms
Baluku *et al.*[21]	HIV and SARS-CoV-2 coinfection: a case report from Uganda	1	34	Uganda	None	965 cells/mm^3	<1,000 copies/mL	Tenofovir, disoproxil, fumarate, lamivudine, and efavirenz	Recovered after mild symptoms
Louisa *et al.*[22]	A case of HIV and SARS-CoV-2 coinfection in Singapore	1	37	Singapore	None	680 cells/μL	Undetectable	Tenofovir, lamivudine, and efavirenz	Recovered after mild symptoms
Li *et al.*[23]	Letter to the Editor: the characteristics of two patients coinfected with SARS-CoV-2 and HIV in Wuhan, China	2	P1: 37 P2: 24	Wuhan, China	—	—	—	P1: umifenovir P2: —	Both patients recovered after severe symptoms
Patel and Pella[24]	COVID-19 in a patient with HIV infection	1	58	United States	Chronic bronchitis, hypertension	497 cells/mm^3	—	Emtricitabin, tenofovir, atazanavir, ritonavir	Recovered after mild symptoms
Kumar *et al.*[25]	COVID-19 in an HIV-positive kidney transplant recipient	1	50	United States	End-stage renal disease	435 cells/μL	<20 copies/mL	Dolutegravir, emtricitabine, and tenofovir alafenamide	Recovered after mild symptoms
Di Giambenedetto *et al.*[26]	SARS-CoV-2 infection in a highly experienced person living with HIV	1	75	Italy	Hepatitis B virus infection (resolved), hypertension (undergoing treatment)	159 cells/μL	Undetectable	Darunavir/cobicistat/ emtricitabine/tenofovir alafenamide	Recovered after severe symptoms
Sasset *et al.*[27]	Coinfection of severe acute respiratory syndrome coronavirus 2 and HIV in a teaching hospital: still much to learn	2	61, 62	Italy	Patient 1: myocardial infarction, atrial fibrillation, HCV. Patient 2: hypertension	Patient 1: 421 cells/μL, Patient 2: 217 cells/μL	<40 copies/mL for both patients	Tenofovir alafenamide/ emtricitabine + raltegravir	Patient 1: discharged and cured after mild symptoms; Patient 2: still at hospital in ICU
Menghua *et al.*[28]	Case report: one case of COVID-19 in a patient coinfected by HIV with a normal CD4 + T-cell count	1	49	China	Syphilis	Normal	Undetectable	Efavirenz 600 mg, zidovudine 300 mg, and lamivudine 150 mg	Patient recovered after moderate symptoms (47 days hospitalization period)

(*continued*)

Table 1. (Continued)

Author	Title	Number of Patients	Age (years)	Location	Comorbidities	CD4+ T-cell count at the time of admission	HIV viral RNA at the time of admission	cART regimen	Outcome
d'Ettorre *et al.*[29]	Analysis of type I IFN response and T cell activation in severe COVID-19/HIV-1 coinfection: a case report	1	52	Italy	—	242 cells/μL	<37 HIV-1 RNA copies/mL	Darunavir/cobicista	Recovered after mild symptoms
Rivas *et al.*[30]	Case report: COVID-19 recovery from triple infection with *Mycobacterium tuberculosis*, HIV, and SARS-CoV-2	2	29, 53	Panama	—	P1: 133 cells/μL, P2: 294 cells/μL	P1: 78,100 copies/mL, P2: 461,000 copies/mL	Tenofovir, lamivudine, and dolutegravir	P1: recovered after 2 months of nosocomial pneumonia; P2: recovered after mild symptoms
Gadelha Farias *et al.*[31]	Case report: coronavirus disease and pulmonary tuberculosis in patients with HIV: report of two cases	2	39, 43	Brazil	P1: Hepatitis B, Tuberculosis	P1: CD4 cell count 145/mm^3, P2: 407/mm^3	P1: 293,313 copies/mm^3, P2: 9,054 copies/mm^3	None in both patients	P1: recovered after moderate symptoms P2: recovered after mild symptoms
Tian *et al.*[32]	An HIV-infected patient with COVID-19 has a favorable prognosis: a case report	1	24	China	None	552 cells/μL	—	Lopinavir/ritonavir	Recovered after moderate symptoms
Cipolat and Sprinz[33]	COVID-19 pneumonia in an HIV-positive woman on ART and undetectable viral load in Porto Alegre, Brazil	1	63	Brazil	Systemic arterial hypertensio	426 cells/mm^3	Undetectable	Atazanavir/ritonavir	Recovered after mild symptoms
Farinacci *et al.*[34]	PLWH in the COVID-19 era: a case report	1	59	Italy	—	10 cells/mm^3	—	None	Death after 5 days of severe clinical symptoms with ICU admission
Chowdary *et al.*[35]	Experience of SARS-CoV-2 infection in two kidney transplant recipients living with HIV-1 infection	2	41, 49	United Kingdom	Kidney transplant in both patients	<100 cells/mm^3	Undetectable	Ritonavir, abacavir, lamivudine, and raltegravir	Recovered with mild-moderate symptoms
Foster *et al.*[36]	It is complicated: a case report on a COVID-19-positive HIV patient presenting with rhabdomyolysis and acute kidney injury	1	40	United States	Rhabdomyolysis and acute kidney injury	—	47 HIV-1 RNA copies/mL	Lopinavir and ritonavir	Recovered with mild-moderate symptoms
Qasim *et al.*[37]	A case of COVID-19 in acquired immunodeficiency syndrome patient: a case report and review of the literature	1	37	United States	Chronic hepatitis C, syphilis, anxiety, and depression, Kaposi's Sarcoma, pneumocystis pneumonia	67 cells/μL	517 copies/mL	Nonadherent	Recovered with mild symptoms
Bessa *et al.*[38]	Ischemic stroke related to HIV and SARS-CoV-2 coinfection: a case report	1	56	Brazil	Diabetes	1,163 cells/μL	Undetectable	Tenofovir, lamivudine, and efavirenz	Recovered with mild symptoms
Chiappe Gonzalez *et al.*[39]	Hospital-acquired SARS-CoV-2 pneumonia in a person living with HIV	1	38	Peru	—	438 cells/μL	Undetectable	Tenofovir-DF/emtricitabine + atazanavir/ritonavir	Passed away after severe clinical course
Basso *et al.*[40]	COVID-19-associated histoplasmosis in an AIDS patient	1	43	Brazil	Neurotoxoplasmosis	113 cells/mm^3	38,503 RNA copies/mL	Tenofovir/lamivudine and atazanavir/ritonavir	Recovered with mild symptoms
Messina *et al.*[41]	COVID-19 in a patient with disseminated histoplasmosis and HIV—a case report from Argentina and literature review	1	36	Argentina	Chronic coccidioidomycosis	3 cells/mm^3	356,000 copies/mm^3	Atazanavir/ritonavir, tenofovir/emtricitabine	Recovered with mild symptoms

HIV, human immunodeficiency virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ART, antiretroviral therapy; cART, combined antiretroviral therapy; HCV, hepatitis C virus; IFN, interferon; ICU, intensive care unit; COVID-19, coronavirus disease 2019.

Table 2. Systematic Review Findings of Thirty-Five Larger Case Studies (>2 Patients) Describing Patients with Human Immunodeficiency Virus and Severe Acute Respiratory Syndrome Coronavirus 2 Coinfection

Author	*Title*	*Number of patients*	*Median age (range)*	*Location*	*Comorbidities*	*Median CD4+ T-cell counts at the time of admission (range)*	*HIV viral RNA at the time of admission*	*cART regimen*	*Outcomes*
Blanco *et al.*[42]	COVID-19 in patients with HIV: clinical case series	5	38 (29–49)	Barcelona, Spain	P2: Hyperthyroidism P4: Asthma	P1: 616 cells/μL P2: 445 cells/μL P3: 604 cells/μL P4: 1,140 cells/μL P5: 13 cells/μL	P1–P4: <50 copies/mL P5: 45,500 copies/mL	P1, P3: Tenofovir alafenamide, emtricitabine, and darunavir-boosted cobicistat P2, P4: Abacavir, lamivudine, and dolutegravir P5: None	P1, P3, P4, P5: Recovered after mild symptoms P2: Severe symptoms, still at hospital
Altuntas Aydin *et al.*[43]	HIV/SARS-CoV-2 coinfected patients in Istanbul, Turkey	4	37 (34–44)	Istanbul, Turkey	P1: HBV infection P2: Diabetes, COPD, hypertension P3: None P4: None	P1: 2.8/mm^3 P2: 1,385/mm^3 P3: 449/mm^3 P4: 396 mm^3	P1: 434,782 copies/mL P2: Negative P3: Negative P4: Negative	P1: Tenofovir, emtricitabin, lopinavir/ritonavir P2: TDF/FTC + dolutegravir P3, P4: TAF/FTC + elivitegravir/cobicistat	P1, P3, P4: Recovered after mild symptoms P2: Died after severe respiratory symptoms
Harter *et al.*[44]	COVID-19 in PLWH: a case series of 33 patients	33	48 (26–82)	Germany	20/33 patients had arterial hypertension ($n=10$), COPD ($n=6$), diabetes mellitus ($n=4$), cardiovascular disease ($n=3$), and renal insufficiency ($n=2$)	670/mm^3 (range 69–1,715/mm^3)	In 30/32 cases, the last HIV-RNA was <50 copies/mL	Mainly tenofovir alafenamide (16 cases), tenofovir disoproxilfumarate (6 cases), and a cytidine analog, either emtricitabine ($n=22$) or lamivudine ($n=9$)	3/33 patients died, 29/33 recovered with mild-moderate symptoms
Vizcarra *et al.*[45]	Description of COVID-19 in HIV-infected individuals: a single-center, prospective cohort	51	53.3 (31–75)	Spain	32/51 (18 with hypertension, 7 with diabetes, 6 with CKD, 24 with chronic liver disease)	224 (120–437) cells/μL	<50 copies/mL	51/51 on cART. 11 on PI, 8 on NNRTI, 41 on INSTI, 37 on tenofovir	44 recovered, 2 deaths, 5 still admitted
Ridgway *et al.*[46]	A case series of five PLWH hospitalized with COVID-19 in Chicago, Illinois	5	48 years (38–53)	United States	P1: DM, HTN, obesity, OSA, HLD P2: Obesity P3: — P4: bronchoesophageal fistula, Addison's disease P5: CHF s/p ICD, CVA, PE, COPD, HTN, morbid obesity	>200 cells/mm^3	P1, 2, 3, 5: <20 copies/mL P4: 25 copies/mL	P1: ABC, DTG, 3TC P2: BIC, FTC, TAF P3: EVG, COBI, FTC, TAF P4: BIC, FTC, TAF, RTV, DRV P5: TDF, FTC, DRV, RTV, RAL	5/5 recovered after moderate symptoms
Benkovic *et al.*[47]	Four cases: HIV and SARS-CoV-2 coinfection in patients from Long Island, New York	4	59.7 (56–65)	United States	P1: HLD P2: HTN P3: HCV, HLD, HTN P4: A. Fib, HLD, HTN, T2DM	P1: 1,206 cells/μL P2: 794 cells/μL P3: 1,412 cells/μL P4: 929 cells/μL	P1: 5,454 copies/mL P2, P3, P4: <20 copies/mL	P1, P2: emtricitabine, tenofovir, dolutegravir, maraviroc P3: emtricitabine, tenofovir, dolutegravir P4: emtricitabine, tenofovir, elvitegravir, cobicistat	All recovered with mild symptoms
Childs *et al.*[48]	Hospitalized patients with COVID-19 and HIV: a case series	18	52 (49–58)	United Kingdom	—	97 (45–143) cells/μL	17/18 had <50 copies/mL	All on NRTI	12 recovered, 1 remains inpatient, 5 died
Okoh *et al.*[49]	COVID-19 pneumonia in patients with HIV—a case series	27	58 (50–67)	United States	59% had systemic hypertension, 33% had diabetes, 27% had CKD	551 (286, 710) cells/μL	11/27 had <20 copies/mL. 15/27 had 20–120 copies/mL, 1 had >120 copies/mL	Nine had integrase-based ART, five had NNRTI, five had PI + Integrase, four were not available, three had NNRTI + Integrase, one had PI based	22 patients recovered after mild symptoms, 3 required ICU admission, 2 died
Suwanwongse and Shabarek[50]	Clinical features and outcomes of HIV/SARS-CoV-2 coinfected patients in the Bronx, New York City	9	58 (31–76)	United States	6/9 had HTN, HLD, 2/9 had obesity, 2/9 had DM, 4/9 had COPD	179–1,827/mm^3	4/9 Undetectable, 5/9 < 20 copies/mL	8/9 on HAART, 1/9 not available	2/9 recovered after mild symptoms, 7/9 died due to COVID-19 ARDS

(*continued*)

Table 2. (Continued)

Author	Title	Number of patients	Median age (range)	Location	Comorbidities	Median CD4+ T-cell counts at the time of admission (range)	HIV viral RNA at the time of admission	cART regimen	Outcomes
Gervasoni *et al.*[51]	Clinical features and outcomes of HIV patients with COVID-19	47	51 (40–62)	Italy	30/47 had ~1 comorbidity (dyslipidemia, HTN, HCV, HBV, renal disease, epilepsy, cardiovascular disease, COPD)	636 ± 290 cells/mm^3	44/47 had <20 copies/mL	80% on integrase-inhibitor-based ART, 11% on PI-based regimen, 42% on tenofovir-based regimen	45/47 fully recovered, 2/47 died
Shalev *et al.*[52]	Clinical characteristics and outcomes in PLWH hospitalized for COVID-19	31	60.7 (23–89)	United States	22/31 had ~1 comorbidity, 21/31 had hypertension, 13/31 had diabetes, 9/31 had obesity	396 (89–924) cells/μL	31/31 had <200 copies/mL	20/31 had integrase-inhibitor-based ART, 17 on tenofovir prodrugs, 7 on PI-based regimen	21 recovered after moderate symptoms, 2 remain in patient, 8 died
Karmen-Tuohy *et al.*[53]	Outcomes among HIV-positive patients hospitalized with COVID-19	21	60.04 (48–72)	United States	All had at least one comorbidity, 7/21 had hypertension, 4/21 had hyperlipidemia, 4/21 had diabetes, COPD	298 cells/μL	15/17 had viral load of <50 copies/mL, all others undetectable	21/21 on HAART	28.6% died, 23.8% had severe symptoms
Hu *et al.*[54]	Coinfection with HIV and SARS-CoV-2 in Wuhan, China	12	36 (33–56.3)	Wuhan, China	One with TB, two with HTN, one with chronic nephritis	500 (339–745) cells/μL	Undetectable	10/12 on ART, 5 on TDF, EFV, ZDV, NVP, 2 on ZDV, EFV	9 recovered with mild symptoms, 2 recovered with severe symptoms (no prior ART), 1 died before admission
Toombs *et al.*[55]	COVID-19 in three PLWH in the United Kingdom	3	55 (46–62)	United Kingdom	P1: Renal transplant 2012, DM, HTN, LTB P2: G6PD deficiency P3: HTN, DM, obesity	P1: 180 cells/μL P2: 50 cells/μL P3: 890 cells/μL	P1, P3: Undetected P2: >1 million copies/mL	P1: Raltegravir, lamivudine, abacavir P2: Emtricitabine/tenofovir, dolutegravir P3: Emtricitabine/tenofovir, nevirapin	P1: Died, P2, P3: Recovered with moderate symptoms
Del Amo *et al.*[56]	Incidence and severity of COVID-19 in HIV-positive persons receiving ART	236	(20–79)	Spain	—	—	—	236/236, tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC), tenofovir alafenamide (TAF)/FTC, abacavir (ABC)/lamivudine (3TC)	20 died, 82 recovered with mild symptoms, 10 recovered after ICU admission, 124 recovered after mild-moderate symptoms
Davies and Boulle[57]	HIV and risk of COVID-19 death: a population cohort study from the Western Cape Province, South Africa	2,352	63 (30-71)	South Africa	—	—	<1,000 copies/mL	69% of survived PLWH were on ART, 66% of deceased PLWH were on ART	79/2352 died
Molina-Iturritza *et al.*[58]	COVID-19 in patients with HIV in the province of Araba, Basque Country, Spain	8	47.5	Spain	Hepatitis C coinfection, arterial hypertension, diabetes mellitus, COPD, obstructive sleep apnea, stable Hodgkin's lymphoma stadium IV(1), SCC	50% had CD4+ cell counts >500/μL, three with CD4+ cell counts between 500 and 200/μL one had <200/μL	6/8 had <20 copies/mL (including deceased patient), 1 had 446 copies/mL, 1 had 2,000 copies/mL	3/8—darunavir, ritonavir. 1/8—NRTI, 4/8—2 NRTI and integrase inhibitor	7/8 recovered with mild-moderate symptoms, 1/8 died
Calza *et al.*[59]	COVID-19 in patients with HIV-1 infection: a single-center experience in northern Italy	26	54	Italy	73% had comorbidities (hypertension and diabetes)	566 (304–821) cells/mm^3	22 patients had <50 copies/mL	Six patients (23%) were receiving a PI-based cART, including darunavir–cobicistat in five cases and darunavir–ritonavir in one case. Sixteen patients (61.5%) were receiving a cART, including tenofovir, disoproxil, fumarate, or tenofovir alafenamide	22 patients recovered, 4 patients improved clinically, no deaths and no ICU admissions

(*continued*)

Table 2. (Continued)

Author	Title	Number of patients	Median age (range)	Location	Comorbidities	Median CD4+ T-cell counts at the time of admission (range)	HIV viral RNA at the time of admission	cART regimen	Outcomes
Maggiolo *et al.*[60]	SARS-CoV-2 infection in persons living with HIV: a single-center prospective cohort	55	52 (49–58)	Italy	—	904 (557–1,110) cells/μL	<54 (98.1%) copies/mL	47—NRTI, 20—NNRTI, 11—PI, 32—INI	51 recovered with moderate symptoms, 4 died after respiratory complications
Guo *et al.*[61]	Patterns of HIV and SARS-CoV-2 coinfection in Wuhan, China	14	56 (31–71)	China	HTN, diabetes mellitus, HTN, atrial fibrillation, Kaposi's sarcoma, COPD	141–817/μL	<20 copies/mL	2—no prior ART, 12—tenofovir, lopinavir/ritonavir, emtricitabine	2 died, 12 recovered with moderate symptoms
Byrd *et al.*[62]	SARS-CoV-2 and HIV coinfection: clinical experience from Rhode Island, United States	27	49	United States	—	1,441 cells/μL	<200 copies/mL	All on prior ART	Nine of the 27 were hospitalized for one to thirteen days; of those, three lived in a nursing home, six received remdesivir through a clinical trial or emergency use authorization and tolerated it well; eight recovered and one died
Stoeckle *et al.*[63]	COVID-19 in hospitalized adults with HIV	30	60.5 (56–70)	United States	COPD, hepatitis B, HTN, DM, CAD, stroke, CKD, asthma, cirrhosis, HCV	332 (123–526) cells/μL	<200 cells/μL	Atazanavir, ritonavir, emtricitabine, and tenofovir to dolutegravir, emtricitabine, and tenofovir	2 died, 28 recovered after mild-moderate symptoms
Miyashita and Kuno[64]	Prognosis of COVID-19 in patients with HIV infection in New York City	161	≤50 years = 38, 51–65 years = 82, ≥66 years = 41 years	United States	HTN, DM, heart failure, CKD, dyslipidemia	—	—	—	23 died, 138 recovered after ICU admission or moderate symptoms
Liu *et al.*[65]	Effect of a previous history of antiretroviral treatment on clinical picture of patients with coinfection of SARS-CoV-2 and HIV: a preliminary study	20	46.5	China	15/20 had comorbidities	237.0 (142.5–346.8) cells/μL	Not measured	NRTIs ($n = 12$), PIs ($n = 8$), and Non-NRTIs ($n = 6$). NRTIs were mainly lamivudine ($n = 12$), tenofovir disoproxil fumarate ($n = 9$), and zidovudine ($n = 2$). PI was mainly kaletra (lopinavir/ritonavir) and non-NRTI was mainly efavirenz	19 discharged after recovery with moderate symptoms, 1 died
Huang *et al.*[66]	Epidemiological, virological, and serological features of COVID-19 cases in PLWH in Wuhan City: a population-based cohort study	35	52, IQR: 36–57 years	China	—	200–499 cells/μL	<20 copies/mL	NNRTI, PI, NRTI	15 (42.86%) had severe illness, with 2 deaths, remaining patients recovered with mild-moderate symptoms
Hadi *et al.*[67]	Characteristics and outcomes of COVID-19 in patients with HIV: a multicenter research network study	404	48.2 years	United States	HTN, CKD, DM, ischemic heart disease, chronic lower respiratory diseases	—	—	Most patients had a history of treatment with antiretroviral agents (284 patients, 70%), and many patients had documentation of antiretroviral treatment within 6 months of COVID diagnosis (187 patients, 46%).	27 required critical care, 78 required inpatient services

(*continued*)

Table 2. (Continued)

Author	Title	Number of patients	Median age (range)	Location	Comorbidities	Median CD4+ T-cell counts at the time of admission (range)	HIV viral RNA at the time of admission	cART regimen	Outcomes
Etienne *et al.*[68]	HIV infection and COVID-19: risk factors for severe disease	54	54 (IQR: 47–60) years	France	25—cardiovascular comorbidities, 5—diabetes, 16—HTN, 3—renal insufficiency, 5—respiratory disease	215 cells/μL	<40 copies/mL		
Madge *et al.*[69]	Descriptive account of 18 adults with known HIV infection hospitalized with SARS-CoV-2 infection	18	63 Years (47–77)	United States	17/18 had COPD, CVA, DM, HTN, CKD	200 cells/mm^3	<40 copies/mL	Three were receiving two-drug (dual) ART, one of whom died and one had protease inhibitor monotherapy; 7 had Truvada or Descovy; 4 had abacavir/lamivudine within NNRT backbone; 11 included an integrase strand transfer inhibitor; and 5 had a protease inhibitor (all boosted darunavir)	15/18 recovered after moderate symptoms, 3/18 died
Dandachi *et al.*[70]	Characteristics, comorbidities, and outcomes in a multicenter registry of patients with HIV and coronavirus disease-19	286	51.4 (SD, 14.4)	United States	HTN, DM, CLD, CKD, obesity	41 to <200 cells/mm^3, 98 to 200–500 cells/mm^3, 129 to >500 cells/mm^3	Darunavir, atazanavir, lopinavir	43 cured, 1 still hospitalized, 5 unknown, 1 death	27 died, 50 recovered after severe symptoms, remainder recovered after mild-moderate symptoms
Nagarakanti *et al.*[71]	Clinical outcomes of patients with COVID-19 and HIV coinfection	23	59	United States	Hypertension (65%), chronic kidney disease (48%), or DM (30%)	>200 cells/μL	22/23 undetectable, 1/23 had 26,900 copies/mL	Ten patients on tenofovir, four patients on TDF, six on TAF, three patients on NRTI/NNRTI combination	3 died, 2 required mechanical ventilation, 2 required ICU admission, 16 recovered after mild symptoms
Swaminathan *et al.*[72]	COVID-19 in HIV-infected patients: a case series and literature review	6	64	United States	—	P1: 491 P2: 1,500 P3: 500 P4: 772 P5: 678 P6: 651 (in cells/mm^3)	Undetectable for all six patients	EVG c/TAF/FT C/TDF	4 discharged after mild symptoms, 2 died
Akyala and Iwu[73]	Novel SARS-CoV-2 coinfection with HIV: clinical case series analysis in North Central Nigeria	4	30	Nigeria	Diabetes, chronic sinusitis, pulmonary tuberculosis	200 cells/μL	P1: >50 copies/mL P2: 600,000 copies/mL P3: 12,650 copies/mL P4: 30,030 copies/mL	Abacavir, lamivudine, tenofovir, emtricitabine	All patients discharged after mild symptoms
Yang *et al.*[74]	Clinical characteristics of COVID-19 patients with HIV coinfection in Wuhan, China	3	40	China	—	P1: 420 cells/μL P2: 550 cells/μL P3: 21 cells/μL	—	TRUVADA (emtricitabine and tenofovir disoproxil fumarate) + TYBOST (cobicistat) + VITEKTA (elvitegravir).	All patients discharged after mild symptoms

(*continued*)

Table 2. (Continued)

Author	*Title*	*Number of patients*	*Median age (range)*	*Location*	*Comorbidities*	*Median CD4+ T-cell counts at the time of admission (range)*	*HIV viral RNA at the time of admission*	*cART regimen*	*Outcomes*
Kowalska *et al.*[75]	The characteristics of HIV-positive patients with mild/asymptomatic and moderate/severe course of COVID-19 disease—a report from Central and Eastern Europe	34	40.5	Eastern and Central Europe	Cardiovascular disease (5), chronic lung disease (2), diabetes (2), hypertension (2), other (7)	557 cells//μL	4.93 copies/mL	Darunavir/cobicistat, lopinavir/ritonavir, bictegravir	Asymptomatic courses of COVID-19 were reported in 4 (12%) cases, 11 (32%) patients presented with mild disease not requiring hospitalization, moderate disease with respiratory and/or systemic symptoms was observed in 14 (41%) cases, and severe disease with respiratory failure was found in 5 (15%) patients
Sachdev *et al.*[76]	COVID-19 susceptibility and outcomes among PLWH in San Francisco	193	48	United States	Diabetes, cardiopulmonary disease, lung disease, chronic renal disease (78)	121 (62.7%) had a CD4 count >500 cells/mm,^{3} 60 (31.1%) had a CD4 count of 200–500, and 12 (6.2%) had a CD4 count <200	85 suppressed, 108 not suppressed	—	Only 7.7% required hospitalization, and only 2 patients required admission to the ICU. None of the HIV/COVID-19 coinfected patients died

TAF, tenofovir, alafenamide; FTC, emtricitabine; 3TC, lamivudine; PI, protease inhibitor; INI, integrase inhibitor; HTN, hypertension; HCV, hepatitis C virus; HBV, hepatitis B virus; LTN, latent tuberculosis; HLD, hyperlipidemia; A. Fib, atril fibrillation; G6PD, glucose-6-phosphate dehydrogenase; NNRTI, non-nucleoside reverse transcriptase inhibitor; HAART, highly active antiretroviral therapy; DM, diabetes mellitus; SD, standard deviation; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; PLWH, people living with HIV; CKD, chronic kidney disease; INSTI, integrase strand transfer inhibitor; OSA, obstructive sleep apnea; HLD, hyperlipidaemia; CHF s/p ICD, congestive heart failure status post implantable cardioverter defibrillator; CVA, cerebrovascular accident; PE, pulmonary embolism; T2DM, type 2 diabetes mellitus; ARDS, acute respiratory distress syndrome; HAART, highly active antiretroviral therapy; LTB, laryngotracheobronchitis; CAD, coronary artery disease; DTG, dolutegravir; BIC, bictegravir; EVG, elvitegravir; COBI, cobicistat; RTV, ritonavir; DRV, darunavir; TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; RAL, raltegravir; ZDV, zidovudine; NVP, nevirapine; EFV, efavirenz.

The full texts of these 63 studies were reviewed, and the findings were then compiled and divided into two subcategories. The first category included 28 case reports of anecdotal evidence, consisting of two patients or fewer.[14–41] The second category included 35 case series or single-, multicenter studies of HIV patients hospitalized with COVID-19.[42–76] Figure 1 demonstrates the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram of the selection process of inclusion for this systematic review.

Case report studies

In total, 28 studies were identified as case report studies with ≤2 HIV patients who developed SARS-CoV-2 infection (Table 1). These studies reported clinical progression, outcomes, and implications for the coinfected patients. However, several of these reports left out important details, including the CD4+ T-cell counts, HIV RNA viral loads, and presence of comorbidities. These 28 studies collectively represented a total of 34 HIV/SARS-CoV-2 coinfected patients. Eighteen of 28 studies reported favorable outcomes for patients with recovery after mild symptoms (64.3%).[14,15,18,21,22,24,25,27,29–32,35–38,40,41] Six of 28 studies reported recovery after moderate symptoms (21.4%).[16,17,19,28,30,31] Another 4 of 28 studies reported recovery after severe symptoms (14.3%).[20,23,26,39] Remarkably, only one case report reported mortality of a single coinfected patient after severe clinical symptoms.[34] These studies' geographic scope included the following: China, the Republic of Cyrus, Turkey, the United States, Africa, Singapore, Brazil, Panama, Peru, Argentina, and Italy. The mean combined patient age among these studies was 44.7 years (range, 24–75). The most common comorbidities described included hepatitis B virus infection and hypertension.

Large case studies

The remaining 35 studies were classified as more extensive studies describing a case series of three HIV patients or more who developed SARS-CoV-2 infection.[44–76] The number of patients reported in studies of this category ranged from 3 to 2,352. In total, these studies encompass a collective population of 4,259 patients. The majority of these studies also reported clinical progression, outcomes, and implications for coinfected patients in depth. Also, these studies provided details regarding median CD4+ T-cell counts and HIV viral RNA loads at the time of admission. Geographic locations represented within these studies included the following: Spain, Turkey, Germany, the United States, Italy, the United Kingdom, France, South Africa, Nigeria, Eastern Europe, and China. The most common comorbidities reported in coinfected patients included hepatitis B virus infection, diabetes mellitus, hypertension, hyperthyroidism, chronic obstructive pulmonary disease (COPD), and obesity. Median patient age ranged from 36 to 79 years.

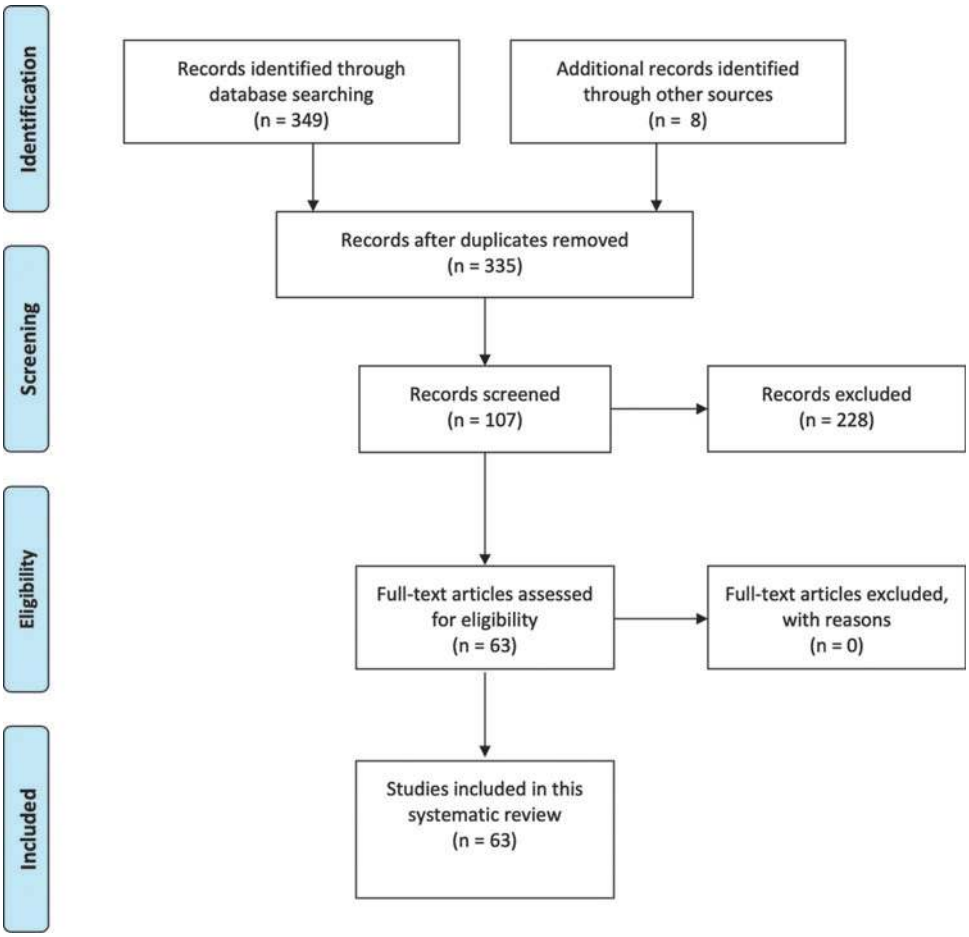

FIG. 1. Flow diagram of the selection process for a systematic review of the literature.

Discussion

Our systematic review includes all available reports of HIV/SARS-CoV-2 coinfection as of January 22, 2021. After a careful analysis, we aimed to identify the trends and interrelationships between comorbidities, CD4+ T-cell counts, HIV viral RNA loads, and ART regimen in the outcomes of coinfected patients.

There are numerous similarities between SARS-CoV-2 and HIV, both being RNA viruses accumulate mutations and undergo recombination due to selection pressure within the host (Fig. 2).[56] During the previous SARS-CoV epidemic, the HIV-1 protease inhibitor nelfinavir was found to strongly inhibit the cytopathic effects of SARS-CoV infection.[5] Several other protease inhibitors were previously reported to have substantial but inconclusive evidence of *in vitro* activity against SARS-CoV.[57] Other HIV-1 protease inhibitors, including lopinavir/ritonavir and darunavir, have been reported as efficacious treatment options in case reports of patients coinfected with COVID-19 and HIV by reducing SARS-CoV-2 viral loads and accelerating recovery.[16,42] Lopinavir was also found to show efficacy *in vivo* and *in vitro*, reducing viral titers and shortening disease progression in Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infected animals.[6,77] Tenofovir was also recently found to be effective against SARS-CoV-2 through potently inhibiting SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) as demonstrated by a molecular docking study.[6,78] Given that tenofovir is used widely as an HIV treatment and pre-exposure prophylaxis (PrEP) drug and our review of case reports found that patients who recovered with only mild symptoms had tenofovir as part of their cART regimen, it may hold promising benefits as an anti-SARS-CoV-2 drug.

Among the case report study category (Table 1), 18 of 28 cases described HIV patients who recovered after experiencing mild COVID-19 clinical symptoms. Notably, in this

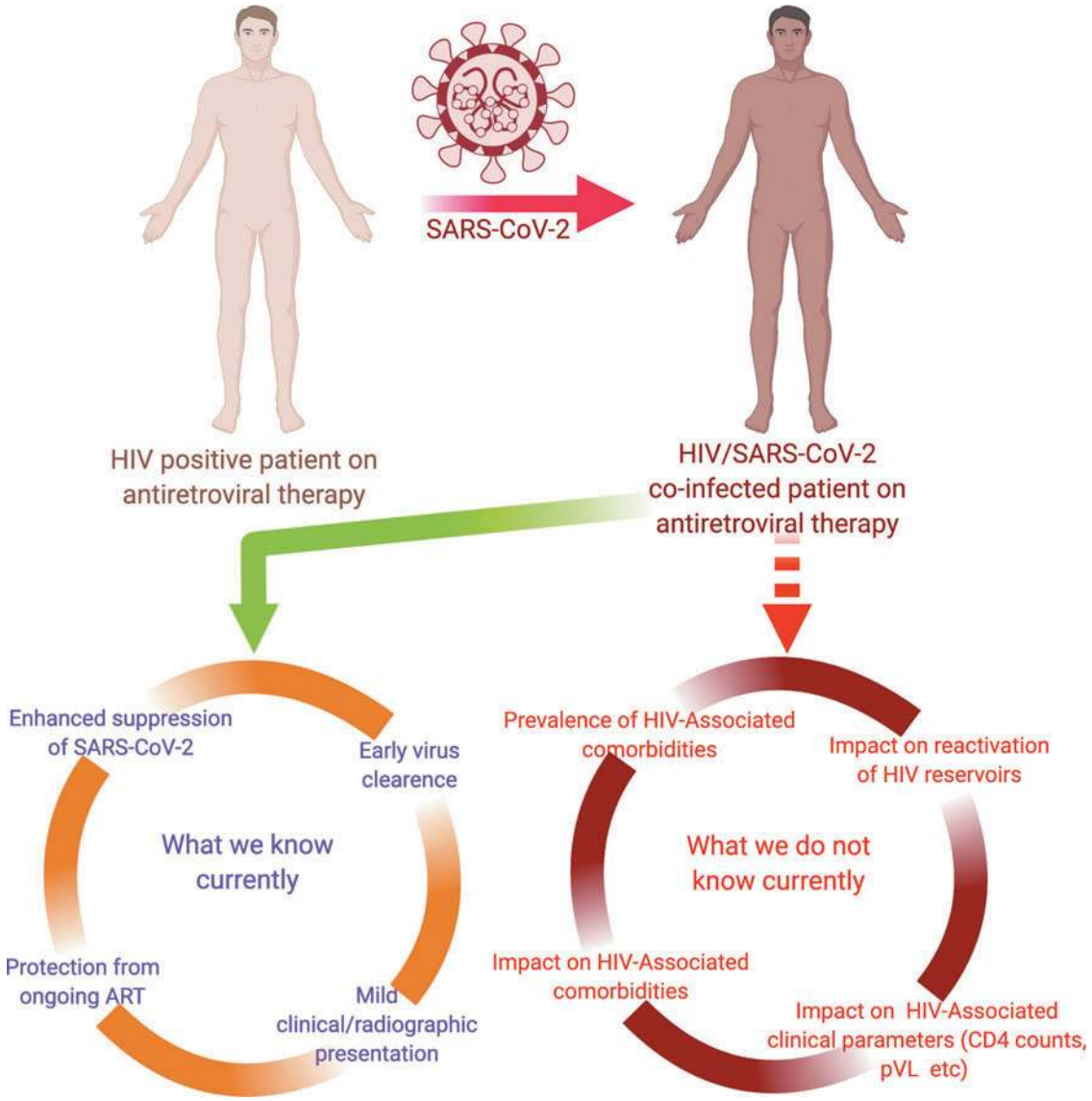

FIG. 2. Similarities and differences between HIV patients and HIV/SARS-CoV-2 coinfection patients on antiretroviral therapy. HIV, human immunodeficiency virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

category, all but one case included tenofovir as part of the cART regimen. On the contrary, one case study by Zhu *et al.* reported recovery with mild symptoms that did not include tenofovir as part of the cART regimen.[15] This study received significant criticism for unclear details, lack of adequate patient background information, lack of a COVID-19 test, and administration of an unwarranted antigen/antibody combination HIV test, which presented questionable findings.[15,79,80] In patients who recovered after moderate or severe symptoms (6/28 studies), there was a lack of adequate detail to effectively analyze any trends for the impact of comorbidities or CD4+ T-cell counts. Four of 28 comprehensive case reports demonstrated a recovery after severe symptoms. Two case reports described mortality, one of which was 59-year-old patient who died after 5 days of severe clinical symptoms, which involved ICU admission and the second which reported a patient who passed away after hospital-acquired SARS-CoV-2 pneumonia.[34,39] The first patient was not under prior ART, and HIV viral loads were not described. The second was adherent to ART, but comorbidities were unknown. Two of the case reports reported an interesting phenomenon in HIV/SARS-CoV-2 coinfected patients. The first is a report of a 24-year-old man who was coinfected with HIV and SARS-CoV-2 with atypical clinical presentation and radiographic findings.[16] This patient recovered from the continuation of his anti-HIV treatment regimen supplemented with lopinavir/ritonavir for COVID-19 and was only moderately symptomatic.

However, radiographic findings found in the patient's chest computed tomography (CT) scan showed patchy shadows in the peripheral lungs, which were different from the classic COVID-19 CT findings of the ground-glass opacity along with consolidation and interlobular septal thickening. This patient's pulmonary lesions were also recognized earlier than those observed during the classical presentation of COVID-19. The authors of this study concluded that this could be explained by the ART regimen that the patient was already on before being admitted for COVID-19.[16] Zhao *et al.*, who reported the first known case of SARS-CoV-2 and HIV coinfection in China, also described atypical findings.[14] This report described a patient who had persistent undetectable SARS-CoV-2 RNA, with only one positive plasma test, which detected the presence of SARS-CoV-2 antibody and confirmed the diagnosis of COVID-19 along with clinical symptoms.[14] Several other reports also acknowledged the possible benefits of strict adherence to cART in their patients with favorable outcomes, even in cases with moderate-to-severe symptoms.[17,20,23,26] One report of an undiagnosed HIV patient infected with SARS-CoV-2, who was not treated with ART before admission for COVID-19, demonstrated a smooth clinical progression with moderate symptoms that resolved within 9 days; however, the authors note that HIV viral loads and infection were not well controlled due to the lack of prior ART.[9]

Thirty-five case series studies were identified to have larger patient samples (>3 patients), and consisted primarily of case series or retrospective cohort studies. Blanco *et al.* reported the first case series of five HIV/SARS-CoV-2 coinfected patients in Spain.[42] In this study, three of five patients recovered with only mild symptoms and disease progression, and underwent <4 days of hospitalization. These three patients were on ART at the time they tested positive for COVID-19. The remaining two patients, one not on antiretroviral treatment before admission, required noninvasive and invasive ventilation, and was admitted to the ICU and later recovered. Another case series from Turkey by Altuntas Aydin *et al.*, reporting four patients with SARS-CoV-2 and HIV infection, found that COVID-19 clinical symptoms improved in HIV-infected patients using regular ART medications that suppressed vial loads, even in advanced HIV-infected cases without any symptomatic treatment for COVID-19.[43] The authors also reported that the presence of other comorbidities was a significant factor that predicted mortality in coinfected cases. Harter *et al.* reported 33 patients with HIV/SARS-CoV-2 coinfection, and found that only 3 of the 33 patients died with 91% recovered, and 76% presented with only mild clinical symptoms.[44] All 33 patients were on prior ART. This study concluded that morbidity and mortality rates were low in PLWH who reported COVID-19 positivity. In a similar study of 47 coinfected patients published by Gervasoni *et al.*,[51] HIV patients hospitalized with SARS-CoV-2 infection generally had favorable outcomes. They did not experience severe symptoms requiring ICU admission and mechanical ventilation.[51] Shalev *et al.* also reported that HIV patients with COVID-19 shared similar clinical manifestations and outcomes comparable with other hospitalized cohorts in their report of 31 coinfected patients.[52]

Vizcarra *et al.* reported 51 HIV-infected individuals diagnosed with COVID-19, of which 6 were critically ill and 2 died.[45] Notably, previous administration of ART, CD4 T-cell counts, CD4/CD8 ratio, and pre-existing comorbidities were not significantly different in recovered patients than the hospitalized individuals in this study. The authors concluded that HIV-infected individuals should not be considered protected from SARS-CoV-2 or to have a lower risk of developing severe COVID-19 disease. In another study by Suwanwongse and Shabarek, of nine HIV/SARS-CoV-2 coinfected patients from New York City, seven died from COVID-19 related respiratory failure, despite low HIV viral loads and previous ART regimen.[50] In a recent case series comprising 18 PLWH with COVID-19, Childs *et al.* reported that five patients died from severe respiratory symptoms, and the rest presented with moderate symptoms during hospitalization.[48] In contrast to other studies, the authors noted that substantial morbidity and mortality were seen in these patients, of which the majority had distinctive comorbidities, despite suppressive ART. Most notably, 17 of the 18 patients were of African American origin. The authors further noted that African American PLWH were at an increased risk of severe disease, and darunavir (or any other ART class) failed to protect against moderate-to-severe COVID-19 disease.

Similarly, another case study by Ridgway *et al.* reported that five African American HIV-positive women were tested positive for COVID-19.[46] All of them were on ART with suppressed viremia while testing positive for SARS-CoV-2. Of all five patients admitted to the hospital for managing their COVID-19 disease, four received azithromycin and a cephalosporin, and two were given hydroxychloroquine. All patients recovered and were released after a median hospital stay of 3 (2–7) days. Karmen-Tuohy *et al.* reported a case series of 17 patients, among them, 15 notably had viral loads measuring <50 copies/mL, with the other 2 patients having undetectable plasma viral loads.[53] All patients were on prior

ART medication. However, most patients within this case series had comorbidities, including COPD, hyperlipidemia, and hypertension. Five died, and four survived after developing severe clinical symptoms of COVID-19. Hu *et al.* reported 12 patients in which 9 recovered after showing mild symptoms, 2 recovered after developing severe symptoms, and 1 died.[54] In this study, the patients with severe symptoms and the patient who died had comorbidities. However, HIV viral loads were undetectable in all patients. Thus, it is likely that underlying conditions significantly impacted the morbidity and mortality of patients within this study.

Based on an analysis of the more extensive case series studies (>2 patients), the presence of comorbidities and higher HIV viral RNA loads was found to influence the severity of COVID-19 symptoms that might have led to a greater risk of morbidity and mortality. The impact of comorbidities, particularly in male patients and patients of older age, is likely to overwhelm any impact of HIV and ART. Another possible factor worthy of consideration is the geographic setting of each of the studies and how this may influence patients' COVID-19 prognosis due to the resources and differences of the HIV care continuum. Every country has had its unique challenges with maintaining regular care for HIV patients while also effectively treating the overload of COVID-19 patients. These impacts can affect the prognosis of this vulnerable population when infected with SARS-CoV-2 due to the lack of adequate health care resources. Thus, the prognosis of HIV/SARS-CoV-2 patients is not entirely generalizable to all parts of the world due to other confounding socioenvironmental factors. Nevertheless, these findings suggest a possible crossprotective mechanism offered by antiretroviral therapy against COVID-19 in HIV patients, which could be lowering the risk of severe COVID-19 infection, and the similarities between all reported cases should not go unnoticed (Table 2). Although these reports are subject to various biases and present limited patient samples, they still provide invaluable insights into the outcomes for HIV patients with COVID-19.

Another essential piece of information missing from several of these studies, predominantly from studies within the case report category (Table 1), is the HIV RNA viral load data, CD4+ T-cell counts, and presence of any non-AIDS-associated comorbidities. Further, it must be determined if the systemic inflammation triggered by COVID-19 can cause the latent HIV reservoir's reactivation and transiently increase viral loads. The brain, intestine, and lymph nodes severely impacted by HIV also serve as sanctuary sites for SARS-CoV-2.[81–83] Thus, the impact of COVID-19 on latent HIV reactivation in these sites is a clinically important question to be addressed in future studies. Animal models are urgently needed to shed light on these questions. To *et al.* recently reported that SARS-CoV-2 viral loads do not correlate with disease severity, which may explain the limited efficacy of the anti-SARS-CoV-2 drug, remdesivir.[84] PLWH not on antiretroviral treatment or are not virally suppressed may be immunocompromised, thereby predisposing them to severe illness or opportunistic infections. PLWH are also at a higher risk of developing comorbidities than the general population due to immune activation and chronic inflammation from HIV, ART side effects, and higher usage of illicit drugs prevalent in this population.[43] In two of the currently available reports, which show an interesting pattern of delayed antibody response to SARS-CoV-2 in HIV-infected patients, it is also possible that these patients may have developed viral suppression from ART, and thus experienced a less severe form of the illness and presented with atypical radiographic findings that were inconsistent with the classical presentation of COVID-19.[14,17] It has also been proposed that HIV-related lymphopenia could protect against the severe clinical manifestation of COVID-19 in PLWH.[85]

Given the significantly improved outcomes of HIV patients on ART infected with COVID-19, PLWH must have continued access to antiretroviral treatment during this time.[84] The COVID-19 pandemic has presented challenges and barriers to the HIV care continuum. It has reduced access to HIV testing in many parts of the world due to nationwide lockdowns, quarantines, and social distancing measures.[86–88] Manufacturing and production of ART drugs have significantly been interrupted, and have seen increased demand due to COVID-19, which has left PLWH who required daily ART drug treatment in a state of uncertainty. Some countries such as Indonesia have reported complete ART stock-outs for HIV patients, including difficulty accessing ART due to shortages caused by the COVID-19 outbreak and nationwide quarantines and lockdowns.[89] These shortages present significant barriers for PLWH due to the grave circumstances associated with discontinuing ART, especially given the risk of COVID-19 transmission. There is no more significant urgent time than now to inform PLWH about the importance of ART therapy as HIV-related immunosuppression may pose substantial risks of SARS-CoV-2 infection and associated comorbidities. International institutions and governments need to sustain medical services and ART medications for HIV patients, and should continue providing treatment and care for individuals who fall in this group.[90]

Given the rapidly evolving nature of the COVID-19 pandemic, it is urgent to consider the impact of the disease on the HIV population, which represents >37.9 million people across the world.[87] Information on how SARS-CoV-2 impacts immunocompromised patients, especially those living with HIV, is important to manage better and develop treatment strategies for this patient population. This is even more important considering the stigma that the HIV-infected population already face and the additional health burdens of COVID-19 on PLWH.[88] Although more studies are needed, it is undeniable that there is a constant influx of new data on HIV/COVID-19 coinfected patients demonstrating the positive effects of ART in dampening COVID-19 severity. It is known that chronic systemic inflammation and immune dysfunction persist among aviremic PLWH receiving ART.[91] It is assumed that SARS-CoV-2 may not effectively disrupt the complement system and trigger a cytokine storm in the already dysfunctional immune systems of PLWH, which makes them less susceptible to the severe form of COVID-19.[6] The molecular mechanism of this assumption needs to be confirmed in future studies. People who are unaware of their HIV diagnosis and do not have access to ART represent a vulnerable population who could be severely impacted by COVID-19.

Limitations

Our review is not without limitations. As a continually evolving subject, we recognize that there may be unreported

or unpublished data regarding HIV and SARS-CoV-2 coinfection that has yet to surface. Despite this, our review includes a systematic analysis of all studies reported from December 2019 to January 22, 2021. Second, although there were no limitations of geographic location or language placed during our search, it is apparent that not all countries that have been significantly impacted by COVID-19 have described HIV/SARS-CoV-2 coinfection. Notably, this includes Iran, Australia, African subcontinent, and parts of Europe. Third, many of the case report studies described in this review do not have CD4+ T-cell counts and HIV viral RNA load data, which can be crucial in analyzing the trends of outcomes and prognosis. Fourth, we did not assess the reporting or methodological quality in each of the reviewed studies. Some of the case reports and case series, which we reviewed, have been criticized through letters to the editor regarding their absence of key patient details such as cART regimen, T-cell counts, and the reported patients' comorbidities.[92,93]

In addition, we believe it is essential to recognize the influence of geographic and cultural results on both the outcomes of coinfected patients and the differences in population infection rates from SARS-CoV-2. For example, prevalence and severity of HIV, policies for facial coverings and social gatherings, and the accessibility to COVID-19 testing and treatment differ across nations. Further, factors such as social determinants of health can contribute to our reported outcomes and results.[94] Thus, it is crucial to consider the presence of these limitations in the interpretation of our systematic analysis. Nevertheless, the present systematic review includes substantial extrapolatable details for the clinicians and researchers to enable them better understand the underlying mechanisms, and for comprehending the trends among HIV patients who have been infected with SARS-CoV-2.

Overall, further studies are urgently needed to thoroughly evaluate the impact of COVID-19 infection among HIV patients who are on long-term ART and to better understand the mechanisms behind the perceivable ART-mediated protection in this specific patient population. Results from ongoing clinical trials of remdesivir, the most active antiviral drug against the SARS-CoV-2 to date, have also shown promise in nonhuman primate studies.[91,95,96] Remdesivir may prove useful for PLWH, as this drug does not have intersecting pharmacokinetics with ART drugs.[97–100] Experience from prior coronavirus outbreaks, including SARS-CoV and MERS-CoV, suggests that both viruses had limited pathogenicity in HIV-coinfected patients, implying that PLWH are not at any higher risk of infection or mortality from SARS-CoV-2.[85]

Authors' Contributions

R.H.P. performed literature search and wrote the article draft; A.A. formatted and edited the article; H.S.C. edited and reviewed the article; M.M. edited and reviewed the article; S.N.B. conceived the study, wrote, and edited the article.

Author Disclosure Statement

No competing financial interests exist.

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