COVID-19 Clinical Presentation Among HIV-Infected Persons in China: A Systematic Review

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Abstract

Purpose of Review The impact of HIV infection on the natural history of COVID-19 is unknown, given the recency of the human spread of SARS-CoV-2 (CoV). We reviewed published case series/reports of CoV-HIV coinfections to clarify epidemiologic and clinical features in China, the first nation with pandemic experience.

Recent Findings Assuming that HIV-infected persons were at average risk of CoV infection in Wuhan, we estimated HIV-CoV coinfected persons to number 412 (95%CI: 381-442); our review encompassed an estimated 16.7% (69/412) of Wuhan. Men (many of whom reported sex with other men) accounted for 71.1% (54/76) of the cases reported in China. The median age was 48.0 years old (range 24-77, interquartile:37-57). The median CD4+ cell count at the last clinical visit was 421 cells/µL; 83.0% had an undetectable viral load. Among 31 patients with clinical details reported, fatigue (41.9%), respiratory distress (41.9%), and gastrointestinal symptoms (26.7%) were most common. Among the 52 cases reporting COVID-19 clinical severity, 46.2% were severe, 44.2% mild, and 9.6% asymptomatic COVID-19. Late antiretroviral therapy (ART) was reported by 30.4% (7/23) among whom 57.1% (4/7) were confirmed as severe COVID-19. The case fatality rate was 9.1% (3/33). Severe disease and death were less common among persons who took ART prior to the COVID-19 diagnosis. Of 16 reported IL-6 results, 68.7% were within the normal range.

Summary Earlier use of ART was associated with a better COVID-19 prognosis with CoV-HIV co-infection reported from China through early 2021, but small sample sizes limit definitive conclusions.

Keywords SARS-COV-2 · HIV · Coinfection · COVID-19 · Clinical presentation · China

Introduction

The first cases of COVID-19 were reported in China in December of 2019 in the city of Wuhan [1]. Through February 2022, over 434 million COVID-19 cases have been reported with 5.94 million deaths (1.4%) though substantial underreporting is a certainty. The majority of COVID-19 cases are asymptomatic or have mild symptoms like a typical influenza infection. Moderate to severe cases can lead to organ failure, shock, and death associated with pneumonia, systemic inflammation, and coagulopathies. COVID-19 pneumonia presents with tracheobronchitis, diffuse alveolar damage, and vasculitis, including pulmonary micro- and macrothrombi and inflammation exacerbated by the cytokine storm phenomenon.

Given that individuals with advanced age, immunocompromised status, and co-morbidities are at increased risks of severe COVID-19, co-infection with HIV might increase SARS-CoV-2 pathogenicity. In China, persons living with HIV (PLHIV) number about one million. An estimated 6000 PLHIV lived in Wuhan at the time of COVID-19 outbreak in Wuhan [2,3] Due to the depletion of CD4+ T-lymphocytes, PLHIV are more susceptible to opportunistic infections, which might well include more severe SARS-CoV-2 (CoV)

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infections [4, 5]. According to Vizcarra et al. in Spain [6] and Hu et al. [7] in China, PLHIV who developed COVID-19 did not have an increased risk of severe diseases or mortality compared to the general population, but small sample sizes of early studies limited inferences. COVID-19 clinical presentation and radiological images have resembled those HIV-infected persons [8]. One hypothesis is that with compromised T-cell responses, HIV-CoV patients' inflammatory cytokine storms may be down-modulated such that PLHIV might paradoxically have less severe COVID-19 [2, 5]. In contrast, some co-infected PLHIV have presented with significantly elevated IL-6 levels, a predictor of greater COVID-19 severity and mortality [4].

In the rapidly evolving pandemic, COVID-19's impact on PLHIV is still being established. To mitigate clinical harms, it is important to clarify how HIV infection and its treatment affect the outcome of COVID-19. Therefore, we conducted a systematic review of the epidemiological characteristics and clinical presentation of coinfected patients in China, as well as laboratory indicators, antiretroviral therapy status, and disease outcomes in PLHIV coinfected with CoV. Viral spread has been contained in China in mid-2020, such that published CoV-HIV co-infection reports to date may represent full documentation of reported co-infections.

Methods

Data Source and Search Strategies

Guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Table S1 and Fig. S1), we searched PubMed, Web of Science, and three Chinese databases—Wanfang, CNKI, and SinoMed—for studies published between December 1, 2019, and December 10, 2021. We used Boolean operators and included subject heading terms/keywords as follows: (COVID-19 OR SARS-CoV-2 OR Coronavirus Disease 2019 OR severe acute respiratory syndrome coronavirus 2 OR coronavirus infection) AND (HIV OR human immunodeficiency virus OR AIDS OR acquired immunodeficiency syndrome) AND China (see Table S2). Additional references were extracted and screened from citations of publications included in our review.

Selection Criteria

We followed Consensus-Based Clinical Case Reporting (CARE), STROBE (Strengthening the Reporting of Observational Studies in Epidemiology), and PRISMA guidelines of the Cochrane Collaboration for the review of publications. Our search included all reported cases of HIV-CoV

coinfections in China, regardless of study type, in either English or in Chinese languages. Any case reports or case series were eligible for inclusion (Table S4). We developed a summary table of the demographic information and clinical presentations from the retrieved literature and removed duplicate cases across studies with the assistance of the Wuhan CDC. After data and reference triangulation, we eliminated duplicated cases using data on their age, sex, date, and location of admission (if relevant), and details of clinical presentations. This was productive since we found that some individual cases were reported (up to four times) across different studies (Table S5).

Data Abstraction and Synthesis

Three authors (HD, GJ, HY) screened the studies for reported coinfections of HIV and COVID-19 in China. HD and GJ did initial identification, HD reviewed all the full papers and abstracted the following data: first author, city, reported times, sex, age, sex orientation, time of confirmed HIV diagnosis, time of initiating ART, ART-regimen, last CD4+ cell count, last viral load (VL), peak temperature (if febrile), IL-6, co-morbidities, any gastrointestinal symptoms, any other coinfections, clinical presentation, definitive clinical outcome on a WHO 7-category ordinal scale, time to clinical improvement in days, any advanced HIV characteristics, overall clinical symptoms, CT scan imaging, CoV RNA test, and IgG/IgM, if tested. Given limited literature, HD and HY validated and confirmed all information through full-text reviews.

Quality Assessment of Evidence

HD and HY independently conducted quality appraisal of included case series using Joanna Briggs Institute Case Series Checklist (Table S3).

Operational Definitions

The patients were identified by investigators from community surveys or from clinical encounters. Some were confirmed to have SARS-CoV-2 infection after reading the interim guidelines on diagnosis and treatment issued by China National Health Commission [9] or the World Health Organization (2020b). The clinically suspected cases were confirmed through the following: (1) typical COVID-19 clinical presentation at the very earliest stage of the outbreak when testing was unavailable; (2) reverse transcription-polymerase chain reaction (RT-PCR) from throat swab, sputum, or lower respiratory tract secretion; or (3) positive immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies against CoV. The Wuhan CDC identified cases through matching between two independent notifiable

disease symptoms systems of HIV and SARS-CoV-2 [3, 7]. Since the same 35 cases (28 cases with clinical information) were published twice for different research purposes [3, 7], we cite the 28 cases that previously reported individual information.

Statistical Approach and Data Synthesis We did descriptive analysis on demographic information and clinical presentations, as well Fisher exact Chi-square testing on categorical variables. A two-tailed p value of 0.05 was used to determine statistical significance. All data were analyzed using Statistical Analysis System (V.9.4, SAS Institute Inc., Cary, NC, USA).

Results

Results of Search Strategy

We identified 120 records: 48 from PubMed, 22 from Web of Science, 14 from Sinomed, 23 from CNKI, and 13 from WanFang. We removed 26 duplicate records, 12 records deemed ineligible by automation tools, and 18 records that were not relevant. Among the remaining 64 reports, we further excluded 15 reports as not eligible,14 reports without specific cases information, 3 reports on laboratory technique only, and 14 secondary publications. This left 18 eligible publications for inclusion in the systematic review.

Epidemiological Characteristics of HIV-CoV Coinfections

Our review identified 76 reported unique co-infection cases; 69 HIV-CoV cases were reported in Wuhan [2, 3, 7, 10–16], and seven more were reported from seven other cities—Beijing [17], Shenzhen in Guangdong Province [18], Chibi in Hubei [19], Liuzhou in Guangxi [20], Hangzhou in Zhejiang [21], unspecified city in Shaanxi Province [22], and Guiyang in Guizhou Province [23] (Table 1). The serological prevalence of CoV infection has been estimated to be 6.9% (95% CI: 6.4–7.4) in the Wuhan general population [24]; we estimated that the number of HIV-CoV coinfections among 6000 HIV-infected persons in Wuhan would be 412 (95% CI: 381–442) based on an assumption that PLHIV had the same cumulative CoV incidence rate as the general population. Hence, our reports from Wuhan may have represented about 16.7% (69/412) of the total PLHIV with CoV in the city. The average age was 46.7 years old, and the median age was 48.0 years old (range 24–77, interquartile: 37–57). Men accounted for 72.0% (54/75) of the reported cases, most of whom were men who had sex with men (MSM). European and US data have suggested that MSM may have had a higher risk of SARS-CoV-2 infection, perhaps from social mixing before the evidence of

human-to-human transmission was clear [25, 26]. Both older age and male gender have been associated with increased severity and mortality risk [27, 28]. The crude case fatality rate was 9.1% (3/33) of the HIV-CoV coinfected persons for whom survival was reported.

Clinical Presentation of HIV-CoV Coinfections

As best we could derive from the publications, 44.2% had mild COVID-19, 9.6% were asymptomatic, 46.2% had severe COVID-19 among 52 co-infected persons for whom this was reported. In short, 53.8% of the patients exhibited mild or asymptotic. There was no moderate cases reported. The median time it took for clinical improvement in 30 cases with clinical follow-up data was 14 days (IQR 10–23). World Health Organization-recommended definitive clinical outcome categories were reported by 33 of 76 (44.0%) cases; among these, 9.1% were not hospitalized, resuming normal activities promptly (category 1); 48.5% were hospitalized, not requiring supplemental oxygen (category 3); 30.3% were hospitalized, requiring supplemental oxygen (category 4); 3.0% were hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both (category 5); and 9.1% died of COVID-19 (category 7).

The most prevalent presentations among 31 cases on whom clinical information was reported included fatigue (41.9%) and respiratory syndrome (41.9%), and had gastrointestinal symptoms (25.8%), including nausea, abdominal discomfort, diarrhea, anorexia, and poor appetite. The most common clinical presentations were fever (73.5%) and cough (41.9%), though among 34 persons with reported body temperature, nine (26.5%) were afebrile.

Comorbidities were reported in 37.5% (12/32) of HIV-CoV coinfected persons, hypertension (18.8%) most commonly. Comorbid conditions elevated the risk of severe COVID-19, particularly hypertension, chronic lung diseases, and poor cardiopulmonary functions in older adults predicted poorer prognosis. Out of the three deaths reported in co-infected persons, two had hypertension and one had chronic obstructive pulmonary disease (COPD).

Among the 33 co-infected patients, six (18.2%) had other important infections, three with syphilis, one with hepatitis C virus, and two with tuberculosis. Acknowledging this tiny sample, these six patients were no more likely to suffer severe COVID-19. We found older age, hypertension, and chronic respiratory diseases to be associated with an increased risk of death.

Immunity Indicators and Prognosis of HIV-CoV Coinfections

The median time of diagnosis of HIV infection was June of 2012, and 5 (22.7%) of the cases was diagnosed in the year

Table 1 Epidemiological characteristics and clinical presentation of SARS-COV-2-HIV coinfections in China

Variables (consecutive data)	$\bar{x} \pm s$		M(q1-q3)
Age (n = 75)	46.7 ± 13.1		48 (37–57)
Last CD4 + cell count (n = 51)	434.9 ± 286.2		421 (216–658)
Time to clinical improvement in days (n = 30)	-		14 (10–23)
Variables (categorical data)	N (n = 76)	Percentage (%)	Percentage (%, NA excluded)
City			
Wuhan	69	90.8	90.8
Beijing	1	1.3	1.3
Chibi	1	1.3	1.3
Guiyang	1	1.3	1.3
Shenzhen	1	1.3	1.3
Liuzhou	1	1.3	1.3
Shaanxi	1	1.3	1.3
Hangzhou	1	1.3	1.3
Reported times*			
1	39	51.3	51.3
2	22	29.0	29.0
3	13	17.1	17.1
4	2	2.6	2.6
Sex			
Female	21	27.6	28.0
Male	54	71.1	72.0
NA	1	1.3	-
Sex orientation			
HET	4	5.3	14.8
MSM	23	30.3	85.2
NA	49	64.4	-
Time of confirmed HIV diagnosis			
Before 2020	17	22.4	77.3
2020	5	6.6	22.7
NA	54	71.0	-
Time of initiating ART			
Before2020	16	21.1	69.6
2020	7	9.2	30.4
NA	53	69.7	-
ART regimen			
EVG/c + FTC+TAF	1	1.3	1.8
Lopinavir + Ritonavir	2	2.6	3.6
RPV+TDF+FTC	1	1.3	1.8
STRIBILD	1	1.3	1.8
TDF+EFV+3TC	11	14.5	20.0
TDF+LPV/r+3TC	4	5.3	7.3
ZDV+3TC+EFV	7	9.2	12.7
ZDV+3TC+NVP	6	7.7	10.9
Unspecified but on ART	21	27.6	38.2
None	1	1.3	1.8
NA	21	27.6	-
Last viral load (VL)			
Detectable	5	6.6	10.6
< 20	15	19.7	31.9

Table 1 (continued)

Variables (consecutive data)	x̄ ±s		M(q1-q3)
Age (n = 75)	46.7 ± 13.1		48 (37–57)
Last CD4 + cell count (n = 51)	434.9 ± 286.2		421 (216–658)
Time to clinical improvement in days (n = 30)	-		14 (10–23)
Variables (categorical data)	N (n = 76)	Percentage (%)	Percentage (%, NA excluded)
TND	24	31.6	51.1
Don't know	3	4.0	6.4
NA	29	38.1	-
Peak temperature, if fever			
< 37.5 and normal	9	11.8	26.5
37.5 ≤ t ≤ 39.5	22	29.0	64.7
> 39.5	3	4.0	8.8
NA	42	55.2	-
CT scan			
Normal	2	2.6	8.7
Bilateral patchy shadowing	2	3.9	13.1
Bronchiectasia, bilateral pleural effusion	1	1.3	4.4
Ground-glass opacities	16	21.1	69.6
Right lower pneumonia	1	1.3	4.4
NA	53	69.7	-
IL-6			
Elevated (9.87–688.4)	5	6.6	31.3
Normal	11	14.4	68.7
NA	60	78.0	-
Co-morbidities			
Chronic obstructive pulmonary disease (COPD)	1	1.3	3.1
Chronic nephritis	1	1.3	3.1
Diabetes	2	2.6	6.3
Lymphoma	1	1.3	3.1
Hypertension	6	7.9	18.8
Kaposis sarcoma	1	1.3	3.1
Bronchiectasia	1	1.3	3.1
Anemia	1	1.3	3.1
Cerebral infarction	1	1.3	3.1
No	20	26.3	62.5
NA	44	57.9	-
Any gastrointestinal symptoms (abdominal discomfort, anorexia, diarrhea, nausea, poor appetite)			
Yes	16	21.1	48.5
No	17	22.4	51.5
NA	43	56.6	-
Any other coinfections			
HCV	1	1.3	3.0
Syphilis	3	4.0	9.1
TB	2	2.6	6.1
No	27	35.5	81.8
NA	43	56.6	
Clinical presentation			
Abdominal discomfort	5	6.6	16.1
Anorexia	4	5.3	12.9
Cough	13	17.1	41.9

Table 1 (continued)

Variables (consecutive data)	x̄ ±s		M(q1-q3)
Age (n = 75)	46.7 ± 13.1		48 (37–57)
Last CD4 + cell count (n = 51)	434.9 ± 286.2		421 (216–658)
Time to clinical improvement in days (n = 30)	-		14 (10–23)
Variables (categorical data)	N (n = 76)	Percentage (%)	Percentage (%, NA excluded)
Diarrhea	6	7.9	19.4
Dizziness	2	2.6	6.5
Dyspnea	7	9.2	22.6
Fatigue	13	17.1	41.9
Nausea	3	4.0	9.7
Poor appetite	1	1.3	3.2
No	6	7.9	19.4
NA	45	59.2	-
Definitive clinical outcome on a WHO seven-category ordinal scale**			
1	3	4.0	9.1
3	16	21.1	48.5
4	10	13.2	30.3
5	1	1.3	3.0
7	3	4.0	9.1
NA	43	56.6	-
Any advanced HIV syndrome			
PCP	2	2.6	10.0
No	18	23.7	90.0
NA	56	73.7	-
Overall clinical symptoms***			
1	24	31.6	46.2
2	23	30.3	44.2
3	5	6.6	9.6
NA	24	31.6	-
SARS-COV-2 RNA test			
Yes	37	48.7	94.9
No	2	2.6	5.1
NA	37	48.7	-
IgG/IgM, if tested			
IgG	8	10.5	32.0
IgM	3	4.0	12.0
IgM/IgG	5	6.6	20.0
Negative	9	11.8	36.0
NA	51	67.1	-

*Using Wuhan CDC reports as reference to validate repeated reports. Percentages are added up not equal to100 due to round to 1 digit

**WHO recommended category: (1) not hospitalized with resumption of normal activities; (2) not hospitalized but unable to resume normal activities; (3) hospitalized, not requiring supplemental oxygen; (4) hospitalized, requiring supplemental oxygen; (5) hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; (6) hospitalized, requiring invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO) or both; and (7) death

***1 = severe, 2 = mild, 3 = no symptoms

ART regimen abbreviations: RPV for rilpivirine; EVG/c + FTC + TAF for Elvitegravir/Cobicista/tEmtricitabine/Tenofovir_Alafenamide; TDF for tenofovir disoproxil fumarate, EFV for efavirenz, 3TC for lamivudine, ZDV for zidovudine, NVP for nevirapine, LPV/r for lopinavir/ritonavir; STRIBILD for combination of cobicistat, elvitegravir, emtricitabine, tenofovir

of 2020. Advanced HIV or AIDS were present in 10% (2/20) of co-infected persons for which this element was reported.

The median CD4+ count at the last clinical encounter was 421 (IQR 216–658), and the mean was 435. Undetectable (< 20 copies/mL) viral load was noted in 83.0% (39/47) of co-infected persons. Examining different CD4+ cell counts ($\geq$ 200 [$n = 40$] vs. < 200 [$n = 11$]) and clinical symptoms (mild/asymptomatic [$n = 28$] vs. severe [$n = 24$]; 24 missing values), neither CD4+ cell count nor clinical symptoms predicted death prognosis ($p = 0.3$). Among the 16 reported IL-6 results, 68.7% (11/16) were within the normal range (< 7 pg/mL) and five presented with elevated values (range 9.9–688.4 pg/mL). Virus load (detectable [$n = 5$] vs. undetectable/< 20 [$n = 39$]) did not predict overall clinical symptoms (mild and asymptomatic [$n = 28$] vs. severe [$n = 24$]; $p = 0.3$). Low CD4+ cell count and high virus load did not predict poor prognosis among the coinfected patients, though low sample sizes inhibit definitive conclusions.

A severe HIV-CoV case occurred in a 60-year-old man with lymphoma and other comorbidities; he was hospitalized and needed supplemental oxygen but recovered in 18 days [3, 7, 10, 11]. Previous studies reported HIV-CoV coinfection patients who had low CD4+ counts, but eventually recovered [10, 25]. CD4+ count was not associated with in-hospital death [29]. Low CD4+ count has been suggested as a protective factor from hyperimmune response in the critical stage of SARS-CoV-2 infection, but a study on HIV-induced hemophagocytic syndrome (HLH) suggested that low CD4+ cell count was not protective against inflammatory cytokine storms in people with HIV[30]. So far, no consensus has been reached on whether CD4+ cells play a role in the severity of HIV-CoV coinfection.

Late ART and Prognosis of HIV-CoV Coinfections

Among the 34 persons for whom ART details were reported, 11 were on a tenofovir disoproxil fumarate+efavirenz+lamivudine (TDF+EFV+3TC) regimen and three were on newer ART regimens: elvitegravir+cobicistat+ emtricitabine+tenofovir alafenamide (EVG/c+FTC+TAF), rilpivirine+tenofovir+emtricitabine (RPV+TDF+FTC), and cobicistat+elvitegravir+emtricitabine+tenofovir (STRIBILD). Two cases who initiated ART upon admission were prescribed boosted protease inhibitors lopinavir/ritonavir before their limited efficacy against CoV was published [1].

Out of the 23 patients who reported the timing of ART initiation, 30.4% (7/23) reported late initiation of ART around the same time of their COVID-19 diagnosis and 4 (4/7, 57.1%) were confirmed having $\geq$ 4 WHO definitive clinical outcome categories or severe clinical symptoms. Among 16 patients who had early ART initiation, only four cases (25.0%) were confirmed with a $\geq$ 4 WHO definitive

clinical outcome categories ($p = 0.058$). One case was reported by Hu Y [2], Hu R [7], and Wang M [15] who experienced a long-haul hospitalization of COVID-19 over 2 months, perhaps linked to immunosuppression and late commencement of ART.

Discussion

Our review contributes to the limited knowledge of COVID-19 clinical course in PLHIV. The study thoroughly assessed all publications from China, given that incidence cases of SARS-CoV-2 have been rare since April 2020.

Based on an assumption of HIV-infected persons at average risk of CoV infection in Wuhan, the number of HIV-CoV coinfections was estimated about 412 persons (95%CI: 381–442); therefore, our review encompasses an estimated 16.7% (69/412). The average and median ages were 46.7 and 48 years old, respectively. Men accounted over 2/3 of the cases reported. The median CD4+ cell count at the last clinical encounter was 421 cells/μL, and 83.0% had an undetectable viral load. Late ART was reported by 30.4% among whom 57.1%(4/7) were confirmed as severe COVID-19.

Given limited sample size, the impact of CD4+ cell counts, HIV viral loads, and adherence to ART among PLHIV coinfected with SARS-CoV-2 will not be determined by Chinese data and will need further global research [7]. In which circumstances the relative immunosuppression in PLHIV may decrease or increase the severity of COVID-19 disease remains an unresolved issue that will need larger epidemiological studies with appropriate counterfactual populations to resolve. Less than one third of HIV-CoV patients are affected by inflammatory cytokine storms with elevated levels of IL-6 in serum. Acknowledging a limited sample size, we did not observe any increased risk of COVID-19 disease severity or mortality associated with tuberculosis. The comorbidities conditions of HIV and COVID-19 coinfected persons might be the cause of severe illness in this population [6, 31, 32].

A large sample size (2409 coinfected with CoV among 2988 PLHIV) of New York City findings [29] suggested that HIV-CoV coinfections might increase the risk of hospitalization ((standardized rate ratio(sRR), 1.38 [95% CI, 1.29–1.47]) and elevated mortality (sRR, 1.23 [95% CI, 1.07–1.40]), compared with patients who are not infected with HIV [3]. However, the comorbidities conditions of HIV and COVID-19 co-infection might be the cause of severe illness in this population[6, 31, 32]. Only about 10% of the reported cases were asymptomatic, comparable to global systematic reviews with sample sizes over 1000 (1.2–13%) [33–35] and to another health workers' cohort study in Wuhan [36].

According to our study, hypertension was most commonly comorbidity among HIV-CoV coinfected persons. Comorbid conditions elevated the risk of severe COVID-19, particularly hypertension, chronic lung diseases, and poor cardiopulmonary functions in older adults predicted poorer prognosis. An Italian study found that patients with chronic obstructive pulmonary disease were at greater risk for severe forms of COVID-19 [27]. In a meta-analysis of seven studies conducted in China among COVID-19 patients free of HIV suggested a significant association between COVID-19 and hypertension, chronic respiratory disease, and cardiovascular disease [37]. Out of the three deaths reported in co-infected persons, two had hypertension and one had chronic obstructive pulmonary disease (COPD). Given the limited number of HIV-CoV patients studies, it is impossible to tease out the role of HIV per se compared to other comorbid factors in multivariable analysis.

There are some limitations to our study. A majority of case studies come from hospitals, and our conclusions may be biased compared to conclusions that may have emerged from community-based studies. The limited number of co-infected persons in each report should be taken into consideration when interpreting the results. Since there was an abrupt ending to the COVID-19 epidemic in China, a standardized diagnosis and treatment were not adopted in many medical facilities. According to the literature we retrieved (in English and Chinese), all the cases occurred before April 30, 2020. However, compared with other countries' SARS-Cov-2 epidemic situation, only Wuhan among all cities in China had high enough COVID-19 incidence to enable identification of substantial numbers of HIV-coinfected persons. Information bias surely exists in our systematic review. Due to ingrained social prejudices against HIV/AIDS and homosexuality, even matching between two databases may not provide a comprehensive picture of coinfections. For example, three patients chose self-paid ART to protect their confidentiality, even though the government provides ART free-of-charge. Some participants would rather disclose their positive COVID-19 status, but keep private their HIV status [2]. Therefore, we suspect that there are unreported HIV-CoV coinfection cases, while the very low incidence of SARS-CoV-2 in China is a general firewall for protecting PLHIV from COVID-19 infection.

Conclusions

Earlier use of ART was likely associated with a better COVID-19 prognosis with CoV-HIV co-infection reported from China through 2021, but small sample sizes limit definitive conclusions. As a result of China's strict social distancing epidemic control strategy ("whack-a-mole" strategy Zero-Covid Strategy) [38], there were likely far fewer cases of coinfection compared to countries that failed in efforts to control COVID-19 in early 2020. During the literature review, though we cautiously appraised the quality of each study, and tried to triangulate the reliability, there are still some inconsistencies. The pandemic of COVID-19 is still serious globally with still-inadequate distribution efforts of effective vaccines. More infectious variants of SARS-CoV-2 and lack of vaccines for low- and middle-income countries make uncertain the prospects of ending the COVID-19 pandemic. A systematic review in Africa [37] reported less severe disease in hospitalized coinfected patients, and we hope this will indicate salutary outcomes for persons in Africa where the preponderance of PLHIV reside.

Data Sharing Statement We will share all the available data upon request.

Declarations

Conflict of Interest The authors declare no competing interests. Statement
Systematic reviews and meta-analyses (PRISMA) and protocols (Prisma-P) were followed for this systematic review.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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