



Coronavirus disease 2019 (COVID-19) outcomes in HIV/AIDS patients: a systematic review

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Objectives

The aim of the study was to systematically review current studies reporting on clinical outcomes in people living with HIV (PLHIV) infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Methods

We conducted a systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. A comprehensive literature search was conducted in Global Health, SCOPUS, Medline and EMBASE using pertinent key words and Medical Subject Headings (MeSH) terms relating to coronavirus disease 2019 (COVID-19) and HIV. A narrative synthesis was undertaken. Articles are summarized in relevant sections.

Results

Two hundred and eighty-five articles were identified after duplicates had been removed. After screening, eight studies were analysed, totalling 70 HIV-infected patients (57 without AIDS and 13 with AIDS). Three themes were identified: (1) controlled HIV infection does not appear to result in poorer COVID-19 outcomes, (2) more data are needed to determine COVID-19 outcomes in patients with AIDS and (3) HIV-infected patients presenting with COVID-19 symptoms should be investigated for superinfections.

Conclusions

Our findings suggest that PLHIV with well-controlled disease are not at risk of poorer COVID-19 disease outcomes than the general population. It is not clear whether those with poorly controlled HIV disease and AIDS have poorer outcomes. Superimposed bacterial pneumonia may be a risk factor for more severe COVID-19 but further research is urgently needed to elucidate whether PLHIV are more at risk than the general population.

Keywords: AIDS, coronavirus disease 2019, HIV, severe acute respiratory syndrome coronavirus

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Introduction

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in the city of Wuhan, China. SARS-CoV-2 causes coronavirus disease 2019 (COVID-19), which has resulted in the most catastrophic pandemic in modern history [1].

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Presentation can be asymptomatic or consist of mild symptoms, from cough and fever to severe and life-threatening acute respiratory distress syndrome (ARDS), sepsis, multi-organ failure and death [2]. There is no current specific treatment for COVID-19 but rather organ support is provided, and severe cases require admission to hospital for supportive management including mechanical ventilation.

Evidence is emerging that suggests that increasing age, hypertension and diabetes are risk factors that correlate with worse outcomes [3,4]. However, it is not clear if people living with HIV (PLHIV) are at greater risk than the general population [5]. Left untreated, HIV infection results in a reduced number of CD4 T cells, leading to

AIDS. AIDS is defined as a CD4 T-cell count < 200 cells/ μ L [3] or the presence of an AIDS-defining illness [6]. In 2018, it was estimated 37.9 million people worldwide have HIV infection, 23.3 million of whom are on treatment with antiretroviral therapy (ART) [7]. Eighty-six per cent of those on treatment have successful viral suppression, resulting in undetectable viral load and untransmissible disease, known as U = U [8–10]. If ART is maintained and adhered to, PLHIV are not immunocompromised. [11]. Despite this, PLHIV may be at risk of severe COVID-19, especially in areas where HIV infection is poorly controlled.

Limited evidence is available on the impact of HIV on SARS-CoV-2 infection and on whether it has any effect on COVID-19 outcomes [12]. There is a need to understand whether PLHIV are at greater risk of severe illness so that adequate preventative measures can be put in place.

The aim of this systematic review was to identify studies that discuss PLHIV who have been infected with SARS-CoV-2 and that report whether coinfection results in a greater risk of adverse outcomes and, furthermore, whether controlled HIV infection *vs.* uncontrolled HIV infection or AIDS results in different COVID-19 disease outcomes. We define controlled HIV infection as an undetectable viral load and a CD4 count \geq 200 cells/ μ L.

Materials and methods

Search strategy

A comprehensive literature search was carried out in Global Health, SCOPUS, Medline and EMBASE to identify articles that discussed HIV-positive patients and the clinical implications of HIV infection in COVID-19 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [13]. Keywords were deconstructed into two categories (Table 1). Pertinent keywords and Medical Subject Headings (MeSH) terms related to these categories were used to maximize the output from the literature search. All relevant articles were identified and screened by two authors; the results are summarized in a narrative manner in each relevant section within the text of this review.

Inclusion and exclusion criteria

Inclusion and exclusion criteria are outlined in Table 2. Studies were included if they discussed the correlation between confirmed HIV infection and the diagnosis or prediction of severity of COVID-19.

Table 1 Search terms divided into two categories, coronavirus disease 2019 (COVID-19) and HIV

Category	Search terms
COVID-19	"coronavirus" OR "nCoV" OR "2019-nCoV" OR "COVID" OR "SARS-CoV"
HIV	"HIV" OR "human immunodeficiency virus" OR "AIDS" OR "acquired immunodeficiency syndrome"

Table 2 Inclusion and exclusion criteria for the search

Inclusion criteria	Exclusion criteria
Exposure: confirmed diagnosis of COVID-19	Editorials, letters to the editor, consensus documents, commentaries, and studies discussing the psychosocial impacts of COVID-19 on HIV-infected patients
Population/outcome: HIV-positive patients and COVID-19 disease outcomes	Published before January 2019
Date range: papers published from 2019 to present	Does not contain primary data
In the English language	In languages other than English

COVID-19, coronavirus disease 2019.

Data extraction

All articles were screened by two authors and any disagreement was resolved by consensus or the involvement of a third author. Data were extracted by two authors and validated by a third author.

Quality assessment

The quality of each publication was evaluated by two independent reviewers according to a predefined scoring system, using the National Heart Lung and Blood Institute (NIH) quality assessment tool for case series and case-control studies, as appropriate (Table 3) [14].

Statistical analysis

It was not possible to conduct an appropriate meta-analysis because there were not enough research data in the studies on this subject.

Results

A PRISMA flow chart for the literature search is shown in Figure 1. A total of 445 articles were found. After removal of duplicates, a total of 285 articles were used for full-text screening and, finally, only eight studies were included in our analysis. Table 3 summarizes the study characteristics and the data extracted. A narrative

Table 3 Summary of data extracted from studies included in review

First author and pub. year	Article title	Location	Study design (quality score)	Population	Population and outcomes
Blanco <i>et al.</i> , 2020	COVID-19 in patients with HIV: clinical case series	Spain, Barcelona	Case series (12/18)	<ul style="list-style-type: none"> • 5 patients with HIV and SARS-CoV2 infection <ul style="list-style-type: none"> ○ 4 with undetectable HIV viral loads and normal CD4 counts • 1 patient with AIDS and ART naive • Ages < 50 • 4 Male, 2 Transgender 	<ul style="list-style-type: none"> • Symptoms of COVID-19 were the same as the general population (cough, fever, malaise and dyspnoea) • All patients were given ART regimens with boosted protease inhibitors • 4 patients given Hydroxychloroquine, 3 Azithromycin, 2 given steroids <p>Outcomes</p> <ul style="list-style-type: none"> • 2 Admissions to ICU • 4 cured, 1 remained in ICU at the end of the study <ul style="list-style-type: none"> ○ The patient with low CD4 was cured but also had a Pneumocystis jirovecii infection which was successfully treated with antibiotics
Härter <i>et al.</i> , 2020	COVID-19 in people living with human immunodeficiency virus: a case series of 33 patients	Germany	Case series, Retrospective (13/18)	<ul style="list-style-type: none"> • 32 HIV patients co-infected with SARS-CoV2 <ul style="list-style-type: none"> ○ 4 patients with AIDS • Mean age 48 (26–82) 	<p>Main symptoms did not differ from general population</p> <p>Outcomes</p> <ul style="list-style-type: none"> • 90% made a full recovery at final follow up (<i>n</i> = 29) • 9% mortality (<i>n</i> = 3) <ul style="list-style-type: none"> ○ 1 patient was 82 with a high HIV viral load, 1 patient had a low CD4 count, 1 patient had comorbidities including hypertension, type 2 diabetes and COPD. • 76% mild cases • Death, hospitalisation and critical infection rate were higher than the general population • 4 patients with AIDS (low CD4 T-Cell counts) tested positive for SARS-CoV-2 and were symptomatic. 1 died, 3 recovered.
Guo <i>et al.</i> , 2020	A survey for COVID-19 among HIV/AIDS patients in two districts of Wuhan, China	China, Wuhan	Case series (8/18)	<ul style="list-style-type: none"> • 1178 HIV/AIDS Patients <ul style="list-style-type: none"> ○ 9 HIV and SARS-CoV2 coinfecting patients ○ 1 of these patients had AIDS ○ Median age 57 ○ 8 Male 1 female 	<ul style="list-style-type: none"> • Of 1178 PLHIV contacted, 12 had symptoms of COVID-19 and 8 tested positive for SARS-CoV2; 6 via nasopharyngeal swab and 2 via Chest CT Scan (0.68%) <ul style="list-style-type: none"> ○ All were on ART prior to this study and had undetectable HIV viral loads ○ All had normal CD4 counts ○ Slightly higher infection rate than in Wuhan (0.5%) ○ 6 mild cases, 1 critical case and 1 death • Of those who were asymptomatic, 9 had close contact with a known case of COVID-19. 1 PLHIV tested positive for SARS-CoV2 via nasopharyngeal swab. <ul style="list-style-type: none"> ○ This patient had AIDS defining Kaposi's Sarcoma and CD4 count of 27 • Median was higher than the median age of Wuhan; however this was consistent with the epidemic in Wuhan.

Table 3 (Continued)

First author and pub. year	Article title	Location	Study design (quality score)	Population	Population and outcomes
Wang <i>et al.</i> , 2020	Case report: one case of Coronavirus disease 2019 (COVID-19) in patient co-infected by HIV with a low CD4 T cell count	China, Wuhan	Case report (7/18)	<ul style="list-style-type: none"> • 1 HIV (AIDS) and SARS-CoV2 coinfecting patient ○ Low CD4 count (34 cells/mm³) ○ 37 Male 	<ul style="list-style-type: none"> • Patient presented with symptoms of COVID-19. • Long disease course of 2 months, not consistent with COVID-19 • CT Chest confirmed changes consistent with viral pneumonia • RT-PCR tests from Nasopharyngeal swabs for SARS-CoV2 tested negative on 4 occasions <ul style="list-style-type: none"> ○ One test was positive for ORF1ab gene but not n-gene • Patient tested negative for IgM and IgG to SARS-CoV2 on two occasions • Patient later tested positive for SARS-CoV2 IgM, which was a delayed response • No other tests for other causes of viral pneumonia were mentioned • Received 15% oxygen and then Methylprednisolone and Moxifloxacin after developing a fever • Patient recovered without ICU or ventilation
Zhao <i>et al.</i> , 2020	Early virus clearance and delayed antibody response in a case of COVID-19 with a history of co-infection with HIV-1 and HCV	China, Shenzhen	Case report (12/18)	<ul style="list-style-type: none"> • 1 HIV and SARS-CoV2 coinfecting patient ○ CD4 count > 200 ○ Undetectable HIV viral load ○ 38 Male 	<ul style="list-style-type: none"> • CT Chest and clinical assessment confirmed viral pneumonia • 3 negative SARS-CoV2 tests • RNAs for Flu A and respiratory viruses also negative • Later tested positive for SARS-CoV2 Antibody IgM and IgG • IgM titre was low after 42 days, significantly different to Non-HIV patients at this point • Patient made a full recovery without admission to ICU or need for ventilation
Yang <i>et al.</i> , 2020	The reflection on an AIDS patient with asymptomatic COVID-19	China, Wuhan	Case report (10/18)	<ul style="list-style-type: none"> • 1 HIV (AIDS) and SARS-CoV2 coinfecting patient ○ AIDS defining Kaposi's Sarcoma ○ CD4 count of 21 (low) ○ Taking ART prior to COVID-19 • 29 Male • Patient was also Guo <i>et al.</i>, 2020 	<ul style="list-style-type: none"> • Asymptomatic • Blood tests showed lymphopenia • No abnormal findings on chest CT • Test positive for COVID Nasopharyngeal swab and contact tracing was +ve in January. Not retested on that date. • Tested in February twice and both swabs negative. • He recovered without treatment but was quarantined in hospital
Haddad <i>et al.</i> , 2020	Encephalopathy and seizure activity in a COVID-19 well controlled HIV patient	USA	Case report (14/18)	<ul style="list-style-type: none"> • 1 HIV patient with SARS-CoV-2 ○ CD4 T-Cell Count of 604/mm³ (Normal) ○ Undetectable viral load ○ 41-year-old, Male 	<ul style="list-style-type: none"> • Patient experienced typical symptoms of COVID-19 at home and was then hospitalised on day 7 of his illness with confusion and agitation • Lumbar puncture was negative • He started cefepime, ampicillin, vancomycin, and acyclovir for empiric bacterial meningitis and herpes encephalitis coverage which was discontinued. • There was marked leukopenia induced by COVID-19 • He then had a seizure on day 8 and required intubation for 4 days. • The patient made a full recovery

Table 3 (Continued)

First author and pub. year	Article title	Location	Study design (quality score)	Population	Population and outcomes
Karmen-Tuohy <i>et al.</i> , 2020	Outcomes among HIV-positive patients hospitalized with COVID-19	USA, New York	Case control (22/24)	<ul style="list-style-type: none"> • 21 HIV and SARS-CoV2 coinfecting patients <ul style="list-style-type: none"> ○ 6 patients CD4 T-Cell count < 200 • Matched to 42 HIV negative and SARS-CoV2 positive patients 	<ul style="list-style-type: none"> • HIV positive patients had a Higher absolute white cell count and CRP level on admission <ul style="list-style-type: none"> ○ This did lead to worse outcomes in these patients • No statistically significant different in outcomes but a trend toward an increased need for ICU admission and ventilation as well as longer stays in hospital compared to matched HIV negative patients <ul style="list-style-type: none"> ○ This was within the expected normal reported from other sites • No statistical difference in need for oxygen therapy between the two cohorts • 4 patients had superimposed bacterial pneumonia (3 HIV positive and 1 HIV negative) <ul style="list-style-type: none"> ○ All 4 patients died. • Did not find a statistical difference in mortality rate and last reported CD4 T-Cell count

ART, antiretroviral therapy; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computed tomography; ICU, intensive care unit; Ig, immunoglobulin; PLHIV, people living with HIV; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

synthesis was conducted as a consequence of the qualitative nature of the studies analysed. The themes that emerged were (1) controlled HIV infection does not appear to result in poorer COVID-19 outcomes than those found in the general population, (2) more data are needed for COVID-19 outcomes in AIDS patients and (3) HIV-infected patients presenting with COVID-19 symptoms should be investigated for superinfections. These themes are explored in a narrative manner in the sections below.

Discussion

Controlled HIV infection (undetectable viral load and normal CD4 T-cell count) and COVID-19 outcomes

Of the studies analysed, one case report reported a difference between the symptoms of COVID-19 in PLHIV and the symptoms of COVID-19 as defined by the WHO [15]. Haddad *et al.*, reported encephalopathy and seizure activity in a patient with controlled HIV on day 8 of their symptoms with COVID-19. This was not seen in any other studies, and the patient made a full recovery [16]. The other studies included in our review all reported that symptoms of COVID-19, such as cough, fever, malaise

and breathlessness, in PLHIV were not dissimilar to the normal population [15]. This indicates that co-infection HIV and SAR-CoV-2 does not appear to cause a different presentation. Two studies reported that one patient in Wuhan was asymptomatic despite a positive RT-PCR test for SAR-CoV-2 RNA from a nasopharyngeal swab [17,18]. No other study tested asymptomatic PLHIV and therefore it is not clear what proportion of PLHIV experience asymptomatic infection and how this compares to the general population. The rate of asymptomatic infection in PLHIV is likely to be underestimated.

Blanco *et al.* [19], studied five patients in Barcelona; they report four patients with controlled HIV, three recovered from COVID-19, one patient did not need treatment and recovered well, whilst another patient had developed severe COVID-19 and required mechanical ventilation in ICU. This patient was 49 with hypothyroidism. All patients were on ART before they were admitted.

Härter *et al.* [20], investigated the outcomes of 32 patients coinfecting with HIV and SARS-CoV-2 in a retrospective case series in Germany. Ninety percent of the cohort made a full recovery with 76% experiencing mild symptoms, while the reported mortality was 9%. Mortality, hospitalisation and critical case rate was higher than

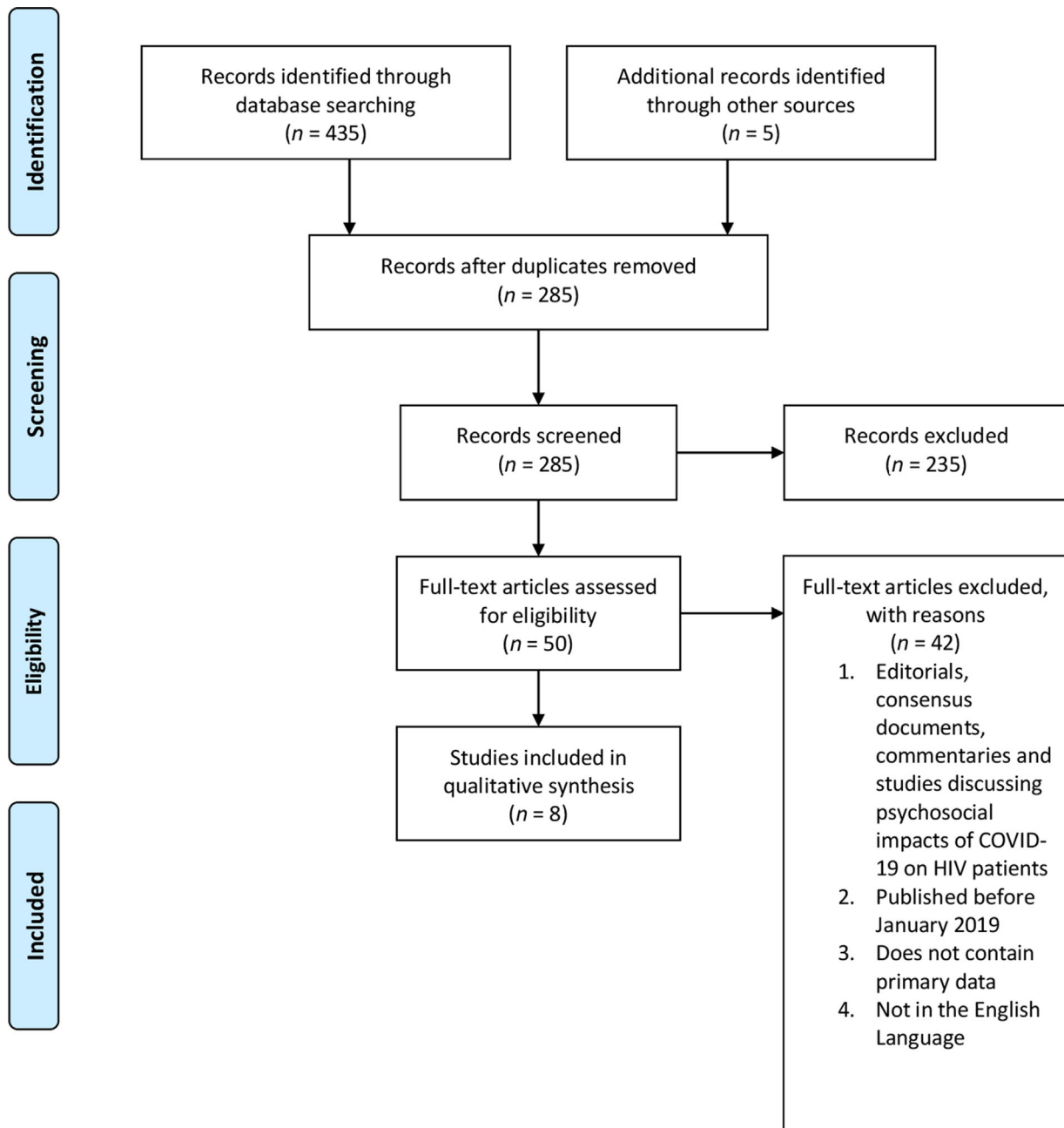


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) chart for the literature search.

the control population. The study only looked at symptomatic patients, so this is likely an overestimation. Of the three patients that died, one patient was 82 years old, another had a CD4 T-Cell count of $69/\text{mm}^3$ and the other patient had multiple comorbidities including hypertension, type 2 diabetes and chronic obstructive pulmonary disease (COPD). The mean age of those included in the

study was 48 years old and 90% (30) of the patients were male, therefore this is not representative of the older population or females with HIV. Confounding factors were not accounted for in the methodology.

The findings are supported by a similar study in Wuhan, China by Guo *et al.* [17] of 1178 patients with HIV. Eight patients with symptoms were diagnosed with

COVID-19 (six via Nasopharyngeal swab and two via CT Chest). This represented 0.68% of patients with HIV who were surveyed, slight but not significantly higher than the percentage of people diagnosed with COVID-19 in Wuhan (0.5%). Outcomes for were that six recovered fully after mild illness, one experienced severe illness but recovered and one patient died. All patients had HIV controlled with ART. Neither study was controlled or matched for HIV negative patients, however the mortality rates do not appear to be different to those in the general population in Wuhan [21]. Zhao *et al.* [21], also highlighted a case study of a HIV patient with SARS-CoV2 co-infection, diagnosis of viral pneumonia was made on clinical examination and chest CT findings. Three nasopharyngeal swabs SARS-CoV-2 were negative. SARS-CoV-2 infection was confirmed with antibody testing at a later date. The patient made a full recovery without the need for admission to ICU or ventilation.

Furthermore, Karmen-Tuohy *et al.* [22] showed no statistical difference in outcomes of COVID-19 between PLHIV and the general population. Twenty-one patients with HIV and SARS-CoV-2 co-infection were matched to 42 HIV negative patients with SARS-CoV-2, with no difference in demographics or comorbidities. Twenty of the 21 patients with HIV had normal CD4 T-Cell counts and were virally suppressed. These patients are not representative of AIDS patients.

COVID-19 outcomes in patients with AIDS (CD4 T-Cell Count < 200 cells/mm³)

Blanco *et al.* [19], reported one case of SARS-CoV-2 in a patient who was ART naïve and a late diagnosis of HIV. The patient presented with a CD4 T-Cell count of 13 cells/mm³ and had superimposed *Pneumocystis jirovecii* pneumonia (an AIDS defining organism) but no other comorbidities [23]. The patient was admitted to ICU and required non-invasive ventilation (NIV), responded well to treatment with oxygen, antibiotics, corticosteroids and hydroxychloroquine and was discharged after 12 days. Härter *et al.* [20], reported that one patient out of three who died had a low CD4 T-Cell count of 69 cells/mm³ with no other stated comorbidities. The study also included three other patients with low CD4 T-Cell counts who recovered from COVID-19, but no further information regarding treatment, disease was given.

Yang *et al.* [18], presented a case of a patient with a low CD4 T-Cell Count (21 cells/mm³) and Kaposi's Sarcoma; this patient was also discussed by Guo *et al.* [17] The patient tested positive for SARS-CoV-2 and remained asymptomatic until two negative tests, with no abnormal findings on CT chest. In contrast, Wang *et al.*, reported a patient with

34 CD4 T Cells/mm³ who experienced a 2-month disease course, far exceeding the typical natural history of COVID-19 [24]. Viral pneumonia was confirmed via CT chest but SARS-CoV-2 RT-PCR was negative on four occasions. One positive test for ORF1ab (but not the N-gene) confirmed SARS-CoV-2. The patient tested negative twice for SARS-CoV-2 antibodies, but later tested positive for IgM antibodies, indicating a delayed immune response which may explain the prolonged disease course.

It is not clear if there is an increased risk of worse outcomes of COVID-19 for AIDS patients. Outcomes in included studies have ranged from asymptomatic infection to death. Until more good quality, case-controlled studies are produced, conclusions cannot be drawn on this point.

The risk of superimposed bacterial pneumonia

We found reports of superimposed bacterial pneumonia with COVID-19. These patients generally had poorer outcomes irrespective of controlled HIV or AIDS. Blanco *et al.* [19], described a case of *Pneumocystis jirovecii* in a patient with AIDS and COVID-19 which responded well to antibiotics, as discussed earlier in this review. They raised the issue of ensuring that pulmonary opportunistic infections are considered in the differential diagnoses of SARS-CoV-2 and HIV co-infection, particularly in AIDS patients. This was supported by Karmen-Tuohy *et al.* [22], who found three patients with HIV and COVID-19 developed superimposed non-AIDS related bacterial pneumonia, compared to only one HIV negative patient with COVID-19. All of the patients who developed a superimposed bacterial pneumonia died in this study, despite receiving antibiotic treatment. Whilst this is a small cohort of patients, it highlights potentially worse outcomes for patients who have a superimposed bacterial pneumonia with COVID-19. Patients with HIV show a higher incidence of bacterial pneumonia, which is inversely proportional to CD4 T-Cell count, when compared to the general population. Thus, superimposed bacterial pneumonia with COVID-19 is a significant consideration in PLHIV [25–29].

Discussion

Recommendations

Current guidelines for PLHIV

At present, the COVID-19 guidelines for well-controlled HIV infection state that it is unlikely that PLHIV are at any greater risk of contracting COVID-19 or experiencing

more severe disease than the general population [12,13]. Our findings support this conclusion, but the data are currently very limited. The recommendations in both the UK and USA are in line with the infection control measures provided to the general public [30]. Specific recommendations include ensuring at least a 30-day supply of ART and advising up-to-date vaccinations including pneumococcal and influenza vaccines [12–14]. Clinicians should reassure PLHIV that, if the HIV infection is controlled, their risk of serious complications of COVID-19 and therefore poor outcomes is likely to be low. However, the presence of known COVID-19 risk factors may put them at greater risk of worse outcomes. The same cannot be said for poorly controlled HIV infection or AIDS.

SARS, Middle East respiratory syndrome (MERS) and H1N1

In previous outbreaks of SARS, H1N1 and Middle East respiratory syndrome (MERS), HIV infection was not associated with increased disease severity. In the SARS and MERS outbreaks, there were only a few reports of mild disease among PLHIV [31,32]. The risk factors for these outbreaks were similar to those being observed for SARS-CoV-2. H1N1 outcomes were similar to outcomes for SARS-CoV-2, whereby clinical outcomes of those with well-controlled HIV infection were similar to those of the general population [33,34]. A literature review by Cooper [35] further highlighted that HIV-infected patients and patients who were immunocompromised for other reasons recovered from H1N1 infection without complications.

SARS-CoV-2 cannot be presumed to be the same as these viruses. We do not know enough about its mechanisms of action to be sure of the impact of HIV infection in those coinfecting with SARS-CoV-2 and HIV. However, data from previous outbreaks are reassuring at least in that well-controlled HIV infection did not pose a greater risk of more severe disease compared with the general population.

PLHIV with undiagnosed HIV infection and those with a confirmed diagnosis not being treated with ART

We identified a small number of studies specifically looking at PLHIV and COVID-19. We identified two patients who were diagnosed with HIV infection at the same time as SARS-CoV-2 infection who were ART naïve [19,24]. Both patients had low CD4 T-cell counts. In 2018, an estimated 8.1 million cases of HIV infection globally were undiagnosed and 28% of patients known to be infected were not on treatment [7]. We recommend that, if a clinical picture suggests viral pneumonia, such as symptoms of COVID-19 or typical viral pneumonitis on a computed

tomography (CT) scan (including mild and severe cases of COVID-19), patients should be offered testing for HIV to rule out undetected HIV infection.

Confirmation of COVID-19, differential diagnosis and coinfection

We found a disparity in methods of COVID-19 diagnosis between studies. In six studies, SARS-CoV-2 was confirmed by reverse transcriptase–polymerase chain reaction (RT-PCR) [16–20, 22], and in two studies COVID-19 was diagnosed using CT thorax findings [17, 21]. In order to ensure that the diagnosis of COVID-19 is correct and other differential diagnosis are ruled out, we suggest that future studies reporting detection of the virus should use a consistent method of diagnosing COVID-19. Also, other causes of pneumonia should be screened for and ruled out to ensure that data are accurate both to confirm the causative agent and to identify any coinfection that may exacerbate symptoms and severity of COVID-19.

Viral pneumonia is generally more severe if a concurrent bacterial pneumonia is present, in both the normal population and PLHIV. This is a plausible reason why some patients included in this review had more severe COVID-19 [25–29]. We recommend that sputum and blood cultures should be taken early for detection of superimposed bacterial pneumonia and the presence of other causative agents.

Wider considerations for PLHIV during the COVID-19 pandemic

Telemedicine

The continuation of out-patient care for PLHIV presents unique challenges as hospitals deal with COVID-19 patients. PLHIV could be deterred from accessing HIV care as a consequence of the perceived risks of attending hospitals, and also the risk that out-patient services may be affected by the re-deployment of health care professionals to other areas of the hospital. This presents an opportunity for the advancement of telemedicine, the remote diagnosis and treatment of a patient using technology. Young *et al.* [36] and Ohl *et al.* [37] both found that, where telemedicine was available to patients, greater viral suppression was achieved. Rogers *et al.* [38] have described an effective implementation of telemedicine in a clinic in the USA, to ensure continuity of care during the COVID-19 pandemic. Clinics who implemented telemedicine also reported fewer missed appointments and higher patient engagement. Furthermore, studies showed that text message services resulted in significant improvements in ART adherence and rates of viral suppression in sub-Saharan Africa [39,40].

Telemedicine can therefore be effectively used to manage patients with HIV infection, without the need for them to attend clinic, allowing patients to avoid unnecessary journeys to hospitals and clinics and to maintain social distancing. Having said this, as stressed by Mgbako *et al.* [41], this must be led by a patient-centred approach, ensuring good communication as well as a good professional–patient relationship.

The psychological impact of COVID-19 on PLHIV

The disruption in the continuity of care for PLHIV, increased social isolation and the psychological stress of living through a pandemic are all factors that could worsen the mental health problems that PLHIV are at a higher risk of experiencing [42]. PLHIV are more likely to experience social isolation; however, as a consequence of measures to prevent the spread of COVID-19, this experience may be amplified, which may have a negative effect on mental health [43]. Furthermore, COVID-19 will potentially exacerbate other psychological stressors such as food insecurity and increased societal stigma [42,44,45]. These psychosocial stressors further may increase the risk of adverse health outcomes among PLHIV as a consequence of reduced medication adherence, leading to failure to achieve adequate HIV management [42].

Future research

Whilst further high-quality studies would be beneficial to confirm that there is no difference in outcomes of COVID-19 between PLHIV who have controlled HIV infection and the general population, as a consequence of the gap in knowledge about outcomes in AIDS patients with COVID-19, there needs to be an urgent focus on high-quality research looking at outcomes for patients with AIDS and COVID-19. Furthermore, more research into the impact and incidence of superimposed bacterial pneumonia is needed in both the general population and PLHIV. This would help to influence management and provide a good basis for developing treatment pathways that may reduce the trend towards higher mortality.

Limitations

The limitations of this review were the small number of studies included in our analysis that were relevant to our outcomes. The studies included were all case series or case reports with small sample sizes, and confounding variables were not accounted for in the reporting of such data. We acknowledge that, in view of the nature of the

study designs included in our analysis, our interpretations and conclusions should be treated with caution.

Conclusions

Our findings indicate that currently PLHIV are not likely to be at increased risk of poorer outcomes of COVID-19 disease than the general population if they have an undetectable viral load and an adequate CD4 count. This suggests that well-managed HIV infection is not a risk factor for more severe COVID-19. However, it is unknown if poorly controlled HIV infection and AIDS put people at a greater risk of severe COVID-19. Bacterial superinfection appears to be a potential risk factor for poorer outcomes in PLHIV. Therefore, our findings highlight the need for further investigation to elucidate the impact of HIV infection in COVID-19.

Conflicts of interest: None to be declared.

Financial disclosure: None to be declared.

References

- 1 European Centre for Disease Prevention and Control. Event background COVID-19. Available at <https://www.ecdc.europa.eu/en/novel-coronavirus/event-background-2019> (accessed 18 May 2020).
- 2 Zaim S, Chong J, Sankaranarayanan V, Harky A. COVID-19 and Multiorgan Response. *Current Problems in Cardiology*. 2020; 45: 8: 100618 <http://dx.doi.org/10.1016/j.cpcardiol.2020.100618>.
- 3 Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. *BMJ* 2020; 368: m1198.
- 4 Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, Li Q, Jiang C, Zhou Y, Liu S, Ye C, Zhang P, Xing Y, Guo H, Tang W. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. *Journal of Infection*. 2020; <http://dx.doi.org/10.1016/j.jinf.2020.04.021>.
- 5 Vishnevetsky A, Levy Mi. Rethinking high-risk groups in COVID-19. *Mult Scler Relat Disord* 2020; 42: 102139.
- 6 Siedner MJ, Triant V. Undetectable = untransmittable and your health: the personal benefits of early and continuous therapy for HIV infection. *J Infect Dis* 2019; 219: 173–176.
- 7 HIV.gov. Global statistics. 2019. Available at <https://www.hiv.gov/hiv-basics/overview/data-and-trends/global-statistics> (accessed 18 May 2020).
- 8 Alison R, Tina B, Matthew W *et al.* Partners of people on ART - a new evaluation of the risks (The PARTNER Study): design and methods. *BMC Public Health* 2012; 12: 296.
- 9 Rodger AJ, Cambiano V, Bruun T *et al.* Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a

- multicentre, prospective, observational study. *Lancet* 2019; **393**: 2428–2438.
- 10 Irini S, Gulick RM, Sonya K *et al.* ART in HIV-positive persons with low pretreatment viremia: results from the START trial. *J Acquir Immune Defic Syndr* 1999; **81**: 456–462.
 - 11 Joob B, Wiwanitkit V. SARS-CoV-2 and HIV. *Journal of Medical Virology*. 2020; <http://dx.doi.org/10.1002/jmv.25782>.
 - 12 AIDSinfo. Interim guidance for COVID-19 and persons with HIV COVID-19 and persons with HIV (Interim Guidance). Available at <https://aidsinfo.nih.gov/guidelines/html/8/covid-19-and-persons-with-hiv-interim-guidance-/554/interim-guidance-for-covid-19-and-persons-with-hiv> (accessed 18 May 2020).
 - 13 Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097.
 - 14 National Heart, Lung, and Blood Institute (NHLBI). Study Quality Assessment Tools. Available at <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools> (accessed 19 May 2020).
 - 15 WHO. Coronavirus [online]. Available at <https://www.who.int/westernpacific/health-topics/coronavirus> (accessed 18 May 2020).
 - 16 Haddad S, Tayyar R, Risch L *et al.* Encephalopathy and seizure activity in a COVID-19 well controlled HIV patient. *IDCases* 2020; **21**: e00814.
 - 17 Guo W, Weng HL, Bai H *et al.* [Quick community survey on the impact of COVID-19 outbreak for the healthcare of people living with HIV]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2020; **41**: 663–667.
 - 18 Yang R, Gui X, Gao S, Mo P, Ke H, Zhang Y, Xiong Y. The reflection on an AIDS patient with asymptomatic COVID-19 - abstract - Europe PMC. Available at <https://europepmc.org/article/ppr/ppr129367> (accessed 18 May 2020).
 - 19 Blanco JL, Ambrosioni J, Garcia F *et al.* COVID-19 in patients with HIV: clinical case series. *The Lancet HIV* 2020; **7**: e314–e316.
 - 20 Härter G, Spinner C, Roeder J, Bickel M, Krznanic I, Grunwald S, Schabaz F, Gillor D, Postel N, Mueller M, Müller M, Römer K, Schewe K, Hoffmann C. COVID-19 in people living with human immunodeficiency virus: a case series of 33 patients. *Infection*. 2020; <http://dx.doi.org/10.1007/s15010-020-01438-z>.
 - 21 Zhao J, Liao X, Wang H, Wei L, Xing M, Liu L, Zhang Z. Early Virus Clearance and Delayed Antibody Response in a Case of Coronavirus Disease 2019 (COVID-19) With a History of Coinfection With Human Immunodeficiency Virus Type 1 and Hepatitis C Virus. *Clinical Infectious Diseases*. 2020; <http://dx.doi.org/10.1093/cid/ciaa408>.
 - 22 Karmen-Tuohy S, Carlucci PM, Zacharioudakis IM *et al.* Outcomes among HIV-positive patients hospitalized with COVID-19. *MedRxiv*. Available at <https://www.medrxiv.org/content/10.1101/2020.05.07.20094797v1> (accessed 18 May 2020).
 - 23 Huang L, Cattamanchi A, Davis JL *et al.* HIV-associated pneumocystis pneumonia. *Proc Am Thorac Soc* 2011; **8**: 294–300.
 - 24 Wang M, Luo L, Haiji B, Xia H. Case report: one case of coronavirus disease 2019(COVID-19) in patient co-Infected by HIV with a low CD4+ T cell count. *Int J Infect Dis* 2020; **96**: 148–150.
 - 25 Cillóniz C, García-Vidal C, Moreno A, Miro JM, Torres A. Community-acquired bacterial pneumonia in adult HIV-infected patients. *Expert Rev Anti Infect Ther* 2018; **16**: 579–88.
 - 26 Feikin DR, Feldman C, Schuchat A, Janoff EN. Global strategies to prevent bacterial pneumonia in adults with HIV disease. *Lancet Infect Dis* 2004; **4**: 445–455.
 - 27 Sogaard OS, Reekie J, Ristola M *et al.* Severe bacterial non-aids infections in HIV-positive persons: incidence rates and risk factors. *J Infect* 2013; **66**: 439–446.
 - 28 Kohli R, Lo Y, Homel P *et al.* Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV epidemiologic research (HER) study. *Clin Infect Dis* 2006; **43**: 90–98.
 - 29 Croxford S, Kitching A, Desai S *et al.* Mortality and causes of death in people diagnosed with HIV in the era of highly active antiretroviral therapy compared with the general population: an analysis of a national observational cohort. *Lancet Public Health* 2017; **2**: e35–e46.
 - 30 Coronavirus (COVID-19) and HIV – update from the British HIV Association (BHIVA). Available at <https://www.bhiva.org/BHIVA-statement-on-COVID-19> (accessed 13 March 2020).
 - 31 Al-Omari A, Rabaan AA, Salih S, Al-Tawfiq JA, Memish ZA. MERS coronavirus outbreak: implications for emerging viral infections. *Diagn Microbiol Infect Dis* 2019; **93**: 265–85.
 - 32 Moni MA, Liò P. Network-based analysis of comorbidities risk during an infection: SARS and HIV case studies. *BMC Bioinformatics* 2014; **15**: 333.
 - 33 Feldman C. Potential Impact of SARS-CoV-2 infection in HIV-positive patients in South Africa. *Wits J Clin Med* 2020; **2**: 19–24
 - 34 Sheth AN, Patel P, Peters PJ. Influenza and HIV: lessons from the 2009 H1N1 influenza pandemic. *Curr HIV/AIDS Rep* 2011; **8**: 181–191.
 - 35 Cooper CL. Pandemic H1N12009 Influenza and HIV: a review of natural history, management and vaccine immunogenicity. *Curr Opin Infect Dis* 2012; **25**: 26–35.
 - 36 Young JD, Patel M, Badowski M *et al.* Improved virologic suppression with HIV subspecialty care in a large prison system using telemedicine: an observational study with historical controls. *Clin Infect Dis* 2014; **59**: 123–126.

- 37 Ohl ME, Richardson K, Rodriguez-Barradas MC *et al.* Impact of availability of telehealth programs on documented HIV viral suppression: a cluster-randomized program evaluation in the veterans health administration. *Open Forum Infect Dis* 2019; **6**: ofz206.
- 38 Rogers B, Coats C, Adams E, Murphy M, Stewart C, Arnold T, Chan P, Nunn A. Development of Telemedicine Infrastructure at an LGBTQ+Clinic to Support HIV Prevention and Care in Response to COVID-19, Providence, RI. *AIDS and Behavior*. 2020; <http://dx.doi.org/10.1007/s10461-020-02895-1>.
- 39 Bigna JJR, Noubiap JJN, Kouanfack C, Plottel CS, Koulla-Shiro S. Effect of mobile phone reminders on follow-up medical care of children exposed to or infected with HIV in Cameroon (MORE CARE): a multicenter, single-blind, factorial, randomized controlled trial. *Lancet Infect Dis* 2014; **14**: 600–608.
- 40 Lester RT, Ritvo P, Mills EJ *et al.* Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomized trial. *Lancet* 2010; **376**: 1838–1845.
- 41 Mgbako O, Miller E, Santoro A, Remien R, Shalev N, Olender S, Gordon P, Sobieszczyk M. COVID-19, Telemedicine, and Patient Empowerment in HIV Care and Research. *AIDS and Behavior*. 2020; **24**: 7: 1990–1993. <http://dx.doi.org/10.1007/s10461-020-02926-x>.
- 42 Shiau S, Krause K, Valera P, Swaminathan S, Halkitis P. The Burden of COVID-19 in People Living with HIV: A Syndemic Perspective. *AIDS and Behavior*. 2020; <http://dx.doi.org/10.1007/s10461-020-02871-9>.
- 43 Marziali M, Card K, McLinden T, Wang L, Trigg J, Hogg R. Physical Distancing in COVID-19 May Exacerbate Experiences of Social Isolation among People Living with HIV. *AIDS and Behavior*. 2020; <http://dx.doi.org/10.1007/s10461-020-02872-8>.
- 44 The Lancet HIV. The syndemic threat of food insecurity and HIV. *Lancet HIV* 2020; **7**: e75.
- 45 Sun S, Hou J, Chen Y, Lu Y, Brown L, Operario D. Challenges to HIV Care and Psychological Health During the COVID-19 Pandemic Among People Living with HIV in China. *AIDS and Behavior*. 2020; <http://dx.doi.org/10.1007/s10461-020-02903-4>.