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Overview of SARS-CoV-2 infection in adults living with HIV

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Around 2·5 million deaths and more than 110 million COVID-19 cases have been reported globally. Although it initially appeared that HIV infection was not a risk factor for COVID-19 or more severe disease, more recent large studies suggest that people living with HIV (particularly with low CD4 cell counts or untreated HIV infection) might have a more severe clinical course than those who are HIV-negative. Moreover, the COVID-19 pandemic has disrupted HIV prevention and treatment services worldwide, creating huge challenges to the continuity of essential activities. We have reviewed the most relevant features of COVID-19 in people living with HIV and highlighted topics where further research is required.

Introduction

On Dec 31, 2019, a pneumonia cluster of 44 patients was reported by Chinese authorities.[1] Since then, SARS-CoV-2, the novel coronavirus that causes COVID-19, has caused a devastating pandemic with over 2·5 million deaths reported globally.[2] According to the estimates of the Johns Hopkins University tool,[2] there are more than 110 million confirmed cases of COVID-19 to date, with the most affected countries being the USA, India, and Brazil, followed by several countries in Europe. The highest number of deaths has been reported in the USA, Brazil, and Mexico. With the exception of South Africa, the African continent has been affected less severely, although underdiagnosis and under-reporting cannot be excluded.[2]

At present, more than 38 million people worldwide are living with HIV, approximately 25 million of those in sub-Saharan Africa. Although 26 million people living with HIV are estimated to be receiving antiretroviral therapy (ART), most of those not receiving ART, and those who are immunosuppressed, live in sub-Saharan Africa.[3] There has not yet been a clear geographical overlap of the COVID-19 and HIV pandemics, which is fortunate because evidence suggests poor clinical outcomes in people living with HIV who become infected with SARS-CoV-2, particularly in those who are immunosuppressed or not receiving ART.[4–6] However, the direct clinical effects of COVID-19 should not only be considered at the individual level but also at the populational level. It has been estimated that disruptions to HIV prevention and treatment services might have caused an excess of HIV/AIDS mortality in 2020 of around 400 000 people.[7]

Current evidence indicates that people living with HIV represent around 1·0% (95% CI 0·0–3·0) of total hospitalised COVID-19 cases,[8–10] whereas SARS-CoV-2 infection prevalence in people living with HIV is between 0·68–1·8%, similar to the SARS-CoV-2 prevalence (0·6–0·8%) reported in the general population.[11–13] In people living with HIV and with symptoms following SARS-CoV-2, 66·5% had mild symptoms, 21·7% reported severe symptoms, and 11·8% needed critical care.[11,12] However, asymptomatic infection rates in people living with HIV are most likely underestimated.[11] The epidemiology of COVID-19 in people living with HIV and the overlap between the two pandemics might be affected in the future by SARS-CoV-2 vaccination, depending on the vaccine coverage, vaccination priorities for people living with HIV, and the responses of this population to immunisation by the range of available vaccines. Despite an increasingly consolidated body of evidence on COVID-19 in the general population, the interaction between SARS-CoV-2 and HIV infection is still unclear and data are, at times, conflicting.[11,14]

Pathogenesis

Immune status in people living with HIV and SARS-CoV-2 response

A favourable clinical course of COVID-19 has been associated with appropriate class-I interferon responses and timely production of neutralising antibodies and specific cell-mediated immunity.[15] On the contrary, low or delayed immune responses allow viral dissemination and are associated with hyperinflammatory states, or cytokine storms, leading to massive pneumonia, respiratory failure, and death.[16] However, much remains to be learned regarding SARS-CoV-2 immunity,[17] and reports suggest that, in patients with severe COVID-19 infection, sustained interferon responses in combination with IL-1 and tumour necrosis factor production in lung monocytes could exacerbate the cytokine storm.[18] Therefore, the effect of immunodeficiency in chronic HIV infection on the appropriate immune response to COVID-19 might be a matter of concern or might offer potential protection against severe forms of disease.

Immune response to SARS-CoV-2 mediated by interferon in people living with HIV

Interferon is the first barrier to infection, which SARS-CoV-2 is sensitive to in vitro. In response, SARS-CoV-2 has developed several mechanisms to counteract the interferon response.[19] Accordingly, poor COVID-19 prognosis has been associated with decreased interferon response,[20] frequently observed in older patients, genetic defects in interferon-associated pathways, and anti-interferon antibody generation.[20,21] HIV infection triggers interferon responses in acute infection, contributing to HIV-replication control and transmitted/founder virus selection.[22] However, in chronic phases of HIV infection,

persistently high interferon concentrations and interferon-stimulated gene activation might correlate with disease progression, low CD4 counts, and long-term immunoactivation. These factors could suggest a detrimental role of chronic interferon signalling in HIV infection, normalised by ART.[23]

HIV-infected response: adaptive immunity and potential gaps against SARS-CoV-2

Early generation of robust functional IgG antibodies against the SARS-CoV-2 spike protein is associated with survival in severe COVID-19 infection.[24] In addition, broad, strong CD4 and CD8 memory cell responses are observed in recovered patients, suggesting that coordinated antigen-specific B-cell and T-cell responses provide protective immunity against severe COVID-19 infection and death.[24]

In people living with HIV, active replication of HIV is associated with T-cell activation, increased CD8 T cells, inflammation, and lymphocytic exhaustion.[25] These parameters are normalised by ART, particularly when treated early. Profound defects in B-cell function have been reported—eg, polyclonal activation, absence of and dysfunction of memory B cells, and defective follicular helper T-cell activity.[26] Some of these defects are not fully recovered after ART, and long-term antibody production and decreased responses to neoantigens or recall antigens can persist in patients with HIV, representing a potential threat to vaccine response. These defects in T-cell and B-cell functions can potentially result in severe clinical course and poor COVID-19 prognosis in patients with HIV, particularly when low CD4 counts and viral replication persist despite ART. Two studies have shown that the concentration and duration of IgG, IgM, and neutralising antibodies in people living with HIV after SARS-CoV-2 infection are similar to the population that are HIV-negative,[27,28] although a third study showed a lower rate of neutralising antibodies in people living with HIV.[29]

Proinflammatory status in people living with HIV

Patients with COVID-19 and severe clinical course develop dysfunctional immune responses characterised by profound lymphopenia (including both low CD4 and CD8 T-cell counts), increased cytokines and chemokines, massive natural killer cell and lymphocytic activation, and subsequent exhaustion. At the pulmonary level, macrophage activation and endothelial damage lead to cellular recruitment, increased inflammation, and activation of complement and coagulation pathways, leading to aggravated viral pneumonia, respiratory failure, systemic injury, and death. This cytokine storm is also present with lower intensity in acute HIV infection in which strong immune-system activation is triggered by high viraemia.[25,30] ART restores interferon, cytokine, and chemokine concentrations, although some patients present low-level persistent activation and inflammatory markers. Although evidence is scarce, restoration of interferon concentrations might be beneficial for responses to SARS-CoV-2.

Overall, full viral suppression with ART ensures near-complete immune recovery in people living with HIV. Therefore, for well controlled infections in people with well controlled HIV infection, SARS-CoV-2 infection should be managed as in the HIV-negative population. However, persistent viral replication, low CD4 counts, and increased concentrations of inflammatory markers have been described in a subgroup of patients treated with ART, a scenario potentially leading to severe COVID-19 disease progression. Additionally, defective B-cell functioning, not completely recovered by ART, might contribute to decreased COVID-19-vaccine response. Moreover, increased rates of cancer, neurological disease, and cardiovascular disease have been described in people living with HIV, adding potential risk factors to COVID-19 disease progression.[31,32] There is also a progressive increase in the median age of people living with HIV, particularly in high-income countries,[33] and the natural immune-senescence process should be also considered in older people living with HIV, which might also impair immune responses.[34]

Advantages and disadvantages of immune HIV status in tackling COVID-19

People living with HIV with CD4 counts less than 200 cells per µL, unsuppressed HIV RNA, or opportunistic illnesses in the preceding 6 months, have been considered an at-risk population since the COVID-19 pandemic began.[35] As declining CD4 cells are associated with COVID-19 severity, people living with HIV with low CD4 cells might face a higher risk of severe COVID-19 infection.[36,37] Similarly, untreated HIV infections might worsen the immunological effect of COVID-19 infection.[38] At present, effective ART is universally recommended and immunological recovery is expected in most patients with HIV infection,[39] but COVID-19 might occur in people living with HIV unaware of their HIV status. In the largest published cohorts, the potentially higher risk for poorer COVID-19-related outcomes in people living with HIV with lower CD4 cell counts[40,41] might be driven by concomitant comorbidities,[42] more common in people living with HIV than in uninfected people,[43] the prevalence of which is inversely proportional to CD4 counts in people living with HIV.[44]

Virological and immunological issues of SARS-CoV-2 in people living with HIV

Nasopharyngeal and oropharyngeal samples are most widely used for laboratory diagnosis of COVID-19.[45] SARS-CoV-2 can also be detected in other respiratory and non-respiratory samples including in plasma, stool, and urine.[46] In general, no differences in SARS-CoV-2 viral load have been observed between people that are HIV-negative and people living with HIV. However, in specific scenarios—eg, in advanced disease, low CD4 cell counts,

	Country	Study design	Number of participants	Age (years)	Sex (men)	Confirmed SARS-CoV-2 infection	CD4 count (cells per µl)	Undetectable HIV viral load	Prevalence of comorbidities
Inciarte et al (2020)[62]	Spain	Single-centre retrospective cohort	53	44	81%	79·2%	618	96·2%	At least 1 comorbidity (43%)*
Vizcarra et al (2020)[61]	Spain	Single-centre retrospective cohort	51	53·3	84%	69%	565	98%	Liver disease (47%), hypertension (35%), cardiovascular disease (27%)†
Sigel et al (2020)[40]	US	Multicentre case-control study	88	61	75%	100%	44% higher than 500	81%	Hypertension (38%), diabetes (27%), chronic kidney disease (22%)
Ho et al (2021)[37]	US	Muticentre retrospective cohort	93	58	72%	100%	554	83·8%	Hypertension (52·7%), diabetes (34·4%), respiratory disease (26·9%)
Etienne et al (2020)[63]	France	single-centre prospective cohort	54	54	61·1%	70·3%	583	96·2%	Cardiovascular disease (46·3%), hypertension (29·6%), respiratory disease (9·3%)‡
Dandachi et al (2020)[41]	US and Spain	COVID-19 in people living with HIV registry	286	51·1	74·1%	100%	531	88·7%	Hypertension (46·5%), obesity (32·3%), diabetes (21·3%)
Boulle et al (2020)[4]	South Africa	Population cohort study	2895	20–39 (57% of participants)	21%	100%	24% higher than 200	NR (60% viral load more than 1000 copies)	NR
Miyashita et al (2021)[64]	US	Muticentre retrospective cohort	161	51–65 (51% of participants)	78%	NR	NR	NR	Hypertension (46%), dyslipidaemia (34%), diabetes (29%)
Del Amo et al (2020)[65]	Spain	Muticentre retrospective cohort	236	50–59 (42% of participants)	75%	100%	NR	NR (100% on ART)	NR
Geretti et al (2020)[5]	UK	Muticentre prospective cohort	122	56	66·1%	90·5%	NR	NR (91·8% on ART)	Chronic kidney disease (18·1), cardiovascular disease (17·1%), obesity (17%)§
Cabello et al (2021)[57]	Spain	Muticentre retrospective cohort	63	46	88·9%	49·2%	605	NR (96·8% on ART)	Hypertension (19%), obesity (13%), cardiovascular disease (12·7%)

ART=antiretroviral therapy. NR=not reported. *Comorbidity details not described in study. †63% chance of having at least one comorbidity. ‡55·6% chance of having at least one comorbidity. §74·6% chance of having at least one comorbidity.

Table 1: **Main epidemiological and clinical results of studies (published until Nov 1, 2020) reporting at least 50 cases of people living with HIV and COVID-19 infections**

or uncontrolled HIV replication—people living with HIV might show prolonged SARS-CoV-2 shedding, which has been described in other immunosuppressed populations, and might eventually promote the emergence of SARS-CoV-2 variants.[47,48] As described in other acute infections[49,50] and vaccination,[51] acute COVID-19 infection might lead to transient increases in HIV RNA due to overall T-cell activation and mobilisation of HIV reservoirs.[52] No major consequences on progression in people living with HIV receiving ART are expected, but there is an absence of data for long-term follow-up.[52,53]

Standard confirmation of acute SARS-CoV-2 infection relies on detecting unique viral sequences by nucleic acid amplification tests, such as real-time RT-PCR. The assay targets include regions on the *E*, *RdRP*, *N*, and *S* genes of SARS-CoV-2. Optimal diagnostics consist of nucleic acid amplification test assay with at least two independent targets on the SARS-CoV-2 genome. Given the extensive SARS-CoV-2 transmission, a simple algorithm might be adopted with one single discriminatory target.[54] No data describe nucleic acid amplification tests in people living with HIV compared with individuals that are HIV-negative. Coinfections are common in immunocompromised patients (eg, people living with HIV) and might be associated with greater morbidity and mortality than in immunocompetent individuals. The use of multiplex PCR against multiple common human respiratory pathogens in parallel might facilitate single-test differential diagnosis.[55]

Antibody testing is dependent on host immune responses to infection; hence antibody responses to infection and vaccination might be expected to be impaired in immunosuppressed people living with HIV, despite the low number of studies on antibody responses in people living with HIV. Knowledge gaps include the duration of detectable IgG and total antibodies, the relationship of seropositivity to infectious virus shedding during convalescence, and factors affecting antibody response (eg, age, comorbid medical conditions, and immunocompromised status, including HIV infection).[56]

Clinical manifestations and disease progression

Since the first reported series of COVID-19 in people living with HIV,[8] a stream of single-centre or multicentre case-series have been published.[13,37,40,41,57–63] These series report epidemiological features, clinical presentation, and outcomes in people living with HIV (table 1). Globally, the initial series showed no clear evidence for higher COVID-19 infection rates or different disease course in people living with HIV. However, these series were limited by small sample sizes. Most studies reported a younger age population compared with hospitalised patients who are HIV-negative and had COVID-19 but reported similar rates of comorbidity. The patients had

a good overall immunological status; however, with a high proportion of these patients receiving ART, evaluations of clinical course in more immunosuppressed patients and in those not taking ART were hampered (table 1).

As with individuals that are HIV-negative, the risk of severe COVID-19 illness in these series was reported to increase with age, affected by sex (men in particular), and by certain chronic medical problems, such as arterial hypertension, cardiovascular disease, chronic lung disease, obesity, and diabetes. Many of these comorbidities are more prevalent among people living with HIV at any given age, particularly in high-income countries. Not surprisingly, a more severe outcome was described in people living with HIV who also had three or more comorbidities (table 1).[41] However, larger cohort studies were published soon after, some suggesting poorer outcomes for individuals with HIV compared with the smaller series,[64] but other studies did not report these outcomes.[65] A cohort study from the UK[5] and, in particular, a study from South Africa[4] found a higher risk of poor outcome (which resulted in admission to the intensive care unit [ICU] or mortality, or both) in coinfected patients compared with individuals that are HIV-negative. The South African study was much larger and from a country with high HIV seroprevalence; most of the patients who were infected with SARS-CoV-2 were women, and people living with HIV were much younger with more pronounced immunodeficiency. Consequently, this study was probably capable of detecting an HIV-infection effect unnoticed in smaller studies.[4] In a large New York study,[6] previous HIV diagnosis was associated with higher rates of severe disease requiring hospitalisation, and the risk of hospitalisation (but not death) increased with progression of HIV disease stage. The only significant factor associated with in-hospital mortality among hospitalised patients living with HIV was age, with those aged 40 years or older being three to four times more likely to die in hospital.[6] Recent cohort studies indicated increased age and different comorbidities (such as diabetes and renal insufficiency) and low CD4 cell count as risk factors for hospitalisation in people living with HIV infected with SARS-CoV-2 in the USA.[66–68]

In studies comparing people living with HIV with individuals that are HIV-negative, clinical COVID-19 presentation was no different to typical reports in the general population. Fever, cough, fatigue, and dyspnoea were consistently the most frequently reported signs and symptoms in most of these series. Fever and cough were sometimes significantly more frequent in people living with HIV than in those who are HIV-negative.[41,61,62] Headache, myalgia, and odynophagia (or sore throat) were also very prevalent and rates of anosmia or dysgeusia seem to be similar in people living with HIV compared with HIV-negative individuals. Radiological findings of people living with HIV were also similar to HIV-negative patients, presenting mostly with patchy bilateral alveolo-interstitial infiltrates. Among laboratory abnormalities, as expected, lymphopenia was more frequent in people living with HIV,[5,37] CD4 and CD8 T-cell counts could be very low during the disease[36] as a result of COVID-19-induced lymphopenia, and patients with poor outcome (ie, ICU admission, mechanical ventilation, and death) had higher concentrations of inflammatory markers.[37]

Nevertheless, drawing definite conclusions from these studies is difficult; some studies aggregated confirmed and suspected cases,[5,61–63] others focused only on hospitalised patients,[5,40] and some reported no relevant clinical data. The possibility of HIV infection and late presentation as a differential diagnosis of COVID-19 must always be considered. The most relevant differential diagnosis with COVID-19 is pneumonia caused by *Pneumocystis jirovecii*,[69] but chest x-ray infiltrates in COVID-19 are frequently more peripheral than central; the opposite occurs with pneumonia caused by *P jirovecii*. Nevertheless, *P jirovecii* should always be excluded when CD4 cell counts are low. Likewise, COVID-19 causes a deep lymphopenia, and therefore, patients with severe disease can have very low CD4 and CD8 T-cell counts,[36] thus increasing the risk of pneumonia caused by *P jirovecii*. Although, reports of high frequency of pneumonia caused by *P jirovecii* resulting from COVID-19-induced lymphopenia are scarce. Finally, concomitant diagnoses should be considered, such as COVID-19 and tuberculosis,[70] pneumonia caused by *P jirovecii*,[69,71] or cryptococcosis.

No clear evidence indicates that HIV infections prolong or spread SARS-CoV-2 infections; hence monitoring SARS-CoV-2 shedding durations has not been recommended for people living with HIV. However, as in other immunocompromised individuals,[47,48] it is reasonable to consider a longer viral shedding in severely immunosuppressed people living with HIV. No specific differences exist regarding infection prevention and control measures for people living with HIV, and those measures indicated for immunosuppressed patients, in general, should be followed.

Prognostic factors for ICU admission and death

For series reporting only hospitalisations, ICU admission for people living with HIV ranged between 17% and 33%.[5,40] In instances when outpatients were included, overall rates of ICU admission ranged between 3% and 22%.[57,64] As previously explained, severe illness increases with age and multimorbidities, and is increased in men,[11,12] with multimorbidities being reported in nearly two-thirds of patients coinfected with HIV and SARS-CoV-2.[12] The risk of mortality in hospitalised patients in the UK showed an adjusted hazard ratio of 1·69 (95% CI 1·15–2·48; p=0·008),[5] whereas in the UK, in primary care alone, after adjustment for age, sex, deprivation, ethnicity, smoking and obesity, the adjusted hazard ratio was 2·59 (1·74–3·84; p<0·0001). Although, most deceased people with HIV had other comorbidities.[9] Similar results were found in

	Hospitalisation	Intensive care unit admission	Mechanical ventilation	Mortality rate	Other relevant results and conclusions
Inciarte et al (2020)[62]	49%	8%	4%	4%	No HIV or ART role identified as prognostic factor
Vizcarra et al (2020)[61]	55%	12%	9·8%	4%	No differences in COVID-19 presentation due to HIV status
Sigel et al (2020)[40]	NA*	17%	18%	21%	Smoking and comorbidities more frequent in people living with HIV than in people who are HIV-negative, but both groups had similar outcomes
Ho et al (2021)[37]	NA*	26·4%	20·8%	26·4%	Higher inflammatory markers in people living with HIV with poor outcome
Etienne et al (2020)[63]	NR	9·3%	NR	2%	Sub-Saharan African ethnicity and metabolic disorders associated with critical outcome; CD4 cell count not related
Dandachi et al (2020)[41]	57·3%	28·7%	22·6%	16·5%	CD4 counts of less than 200 cells per µL was associated with intensive care unit admission, mechanical ventilation, or death
Boulle et al (2020)[4]	20·75%	NR	NR	3·6%	Higher mortality in people living with HIV compared with people who are HIV negative
Miyashita et al (2021)[64]	NR	22%	12%	14%	Poor outcomes related to comorbidities
Del Amo et al (2020)[65]	64%	6·35%	NR	8·5%	Incidence of COVID-19 not higher than in the general population; tenofovir might be protective
Geretti et al (2020)[5]	NA*	33%	16·4%	24%	After adjusting for age and other variables, higher mortality seen in people living with HIV
Cabello et al (2021)[57]	32·3%	3·2%	3·2%	3·2%	Prognosis related to age and comorbidities

ART=antiretroviral therapy. NR=not reported. NA=not applicable. *Studies included only hospitalised patients.

Table 2: **Summary of outcomes in studies reporting on more than 50 people living with HIV who have been infected with COVID-19**

Western Cape, South Africa, where after adjusting for other risk factors, HIV increased the risk of death in patients with COVID-19 by a factor of 2·14 (1·70–2·70).[4] However, global mortality varied considerably across studies, depending on the design. Mortality was as high as 24% in the UK series (only hospitalisations)[5] and as low as 2% in the French series,[63] and 3·6% in the South African cohort study[4] with a higher number of patients and the inclusion of outpatients (table 2).

Prognosis, according to HIV status and CD4 cell count, is difficult to evaluate because most studies from Europe and the USA on levels of immunity reported an overall high CD4 cell count.[37,41,61–63] In these virologically suppressed patients with good immune status, poor outcomes remained relating to comorbidities and age (as in the general population). Other studies, with larger cohorts did not provide CD4 T-cell count. Nevertheless, in the South African cohort study (with a larger number of patients, but also with the most immunosuppressed population), HIV was an independent prognosis factor for poor outcome, suggesting people living with HIV with low CD4 counts have a more severe COVID-19 clinical course than those who are HIV-negative.[4] Dandachi and colleagues[41] reported poor outcomes for patients with CD4 count of less than 200 cells per µL. A 2021 cohort study from the UK (CD4 data were not provided) and another multicentre cohort study also found people living with HIV to be at higher risk of poor outcome.[9,72] In a case-control study from Spain, people living with HIV had higher mortality (9·8% *vs* 3·4% compared with HIV-negative individuals), related mostly to the presence of comorbidities but not to virological or immunological factors, or ART use.[73] In other studies, a poorer outcome was not noticed.[74–76]

The potential relationship of antiretroviral drugs to improve or worsen outcomes remains controversial. Although Del Amo and colleagues[65] reported lower COVID-19 incidence in patients taking tenofovir, a selection bias might have existed, because most patients with comorbidities do not take tenofovir. Furthermore, Boulle and colleagues[4] reported the use of tenofovir being associated with reduced mortality compared with other therapies. In a Spanish study, the use of tenofovir–emtricitabine was associated with lower seropositivity against SARS-CoV-2, suggesting a lower infection rate.[77] Although no other published study reported any antiretroviral drug to be protective or associated with poor outcomes in people living with HIV and COVID-19, there are ongoing studies that are researching this.

Drug therapies

Antiretroviral drugs with potential anti-SARS-CoV-2 activity

Some antiretroviral drugs have been investigated for their potential action against SARS-CoV-2. Data suggest tenofovir might be active in vitro[65,78] due to its tight union with a critical SARS-CoV-2 lifecycle enzyme, the RNA-dependent RNA polymerase.[79] However, conflicting results have emerged from clinical trials and observational studies investigating the anti-SARS-CoV-2 activity of the enzyme in treatment and prevention.[65,78] Lopinavir–ritonavir and darunavir, both protease inhibitors, have also been evaluated. In-vitro activity of darunavir was identified but no anti-SARS-CoV-2 activity at clinically relevant concentrations (EC50 >100 µM) was shown. Lopinavir–ritonavir showed no efficacy

in reducing mortality and mechanical ventilation in hospitalised patients in the RECOVERY study (<1% of people living with HIV) and in the large Solidarity trial.[80,81] Trials with maraviroc and cenicriviroc (CCR5 inhibitors) are ongoing (NCT04441385 and NCT04500418).

State-of-the-art COVID-19 treatment

Remdesivir (a viral RNA-dependent RNA polymerase inhibitor) in monotherapy or combined with baricitinib (a selective JAK inhibitor with dual antiviral and anti-inflammatory activity) improved time to recovery compared with standard of care or placebo among patients with stages 4–6 on the US National Institutes of Health severity scale (figure 1).[81–86] However, the Solidarity trial, which analysed stages 5 and 6, did not find improvement in survival.[81] This finding has led to contradictory positions held by the US Food and Drug Administration and the European Medicines Agency, which approved remdesivir use, and by WHO, which does not recommend its use. Convalescent plasma and some specific neutralising antibody administration in mild disease in the community has shown to prevent progression and hospital admission compared with placebo.[87–90] However, data are scarce on all antivirals used by people living with HIV. Many off-label antimicrobial agents, such as ivermectin or sofosbuvir, are under evaluation.

Steroids, other anti-inflammatory drugs, and anticoagulants

Anti-inflammatory drugs, such as systemic corticosteroids, IL-6 inhibitors (eg, tocilizumab, siltuximab, and sarilumab), IL-1 inhibitors (eg, anakinra), colchicine, and baricitinib (JAK inhibitor), might act in virus-driven hyperinflammation and cytokine storms occurring in severe COVID-19 infection and many of these drugs are under investigation.[91] Dexamethasone (at low doses of 6 mg per day for up to 10 days, or equivalent doses of hydrocortisone or methylprednisolone) is the only drug that reduces mortality in patients requiring oxygen therapy.[92] To date, no data indicate that anti-inflammatory drug use increases the risk of reactivation of opportunistic infections in people living with HIV or that drug use should differ from the general population. Prophylactic anticoagulation is generally recommended in all hospitalised patients with COVID-19 and should be used similarly in people living with HIV.[93]

Relevant drug–drug interactions are available for many anticoagulants and systemic steroids when pharmacokinetic enhancers (eg, ritonavir and cobicistat) are provided in ART regimens. Dose adaptation or changes in the concomitant medication might be necessary. With immunomodulatory drugs (eg, tocilizumab), drug–drug interactions are less relevant, but evidence is scarce. Online resources, such as the University of Liverpool's interaction checker, can be consulted.

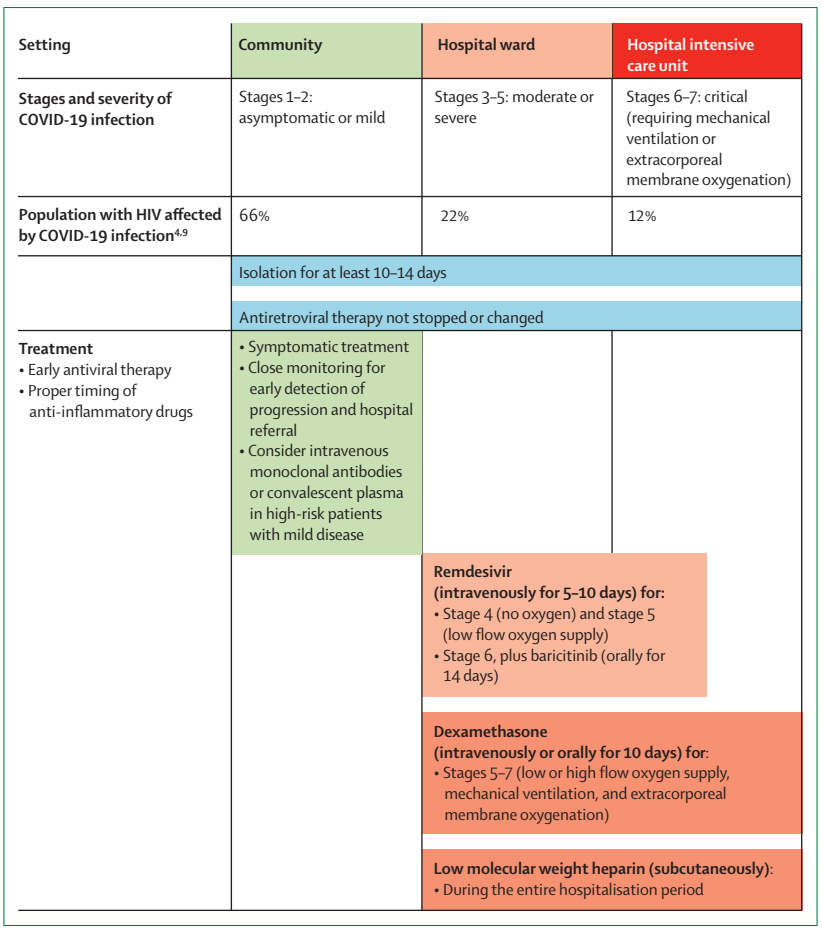

Figure 1: **Therapeutic management of COVID-19 in patients with HIV in January, 2021**
Adaptive COVID-19 Treatment Trial scores on the ordinal scale: 1=not hospitalised, no limitations of activities; 2=not hospitalised, limitation of activities, home oxygen requirement, or both; 3=hospitalised, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalisation was extended for infection control reasons); 4=hospitalised, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19-related or other medical conditions); 5=hospitalised, requiring any supplemental oxygen; 6=hospitalised, requiring non-invasive ventilation or use of high-flow oxygen devices; 7=hospitalised, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; and 8=death. Asymptomatic or presymptomatic infections=individuals positive for SARS-CoV-2 with a virological test (ie, a nucleic acid amplification test or an antigen test), but with no symptoms consistent with COVID-19. Mild illness=individuals with any of the various signs and symptoms of COVID-19 (eg, fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, and loss of taste and smell) but without shortness of breath, dyspnoea, or abnormal chest imaging. Moderate illness=individuals with evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation of 94% or higher in room air at sea level. Severe illness=individuals who have oxygen saturation of less than 94% in room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of less than 300 mm Hg, respiratory frequency of more than 30 breaths per min, or lung infiltrates of more than 50%. Critical illness=individuals who have respiratory failure, septic shock, or multiple organ dysfunction. Remdesivir is approved by the regulatory agencies (ie, US Food and Drug Administration and European Medicines Agency) but is currently not recommended by WHO for COVID-19 treatment (regardless of HIV status).

Monitoring HIV infection in outpatient and care facilities

Disruption in health-care services has affected the prevention and care of various illnesses, including HIV. In the short term, there have been decreases in testing and diagnoses of new cases of HIV infection and other transmittable infections; and limitations in laboratory monitoring, clinical visits, and access to ART might have resulted in suboptimal care of HIV infection and other

For more on **the University of Liverpool's interaction checker** see https://www.hiv-druginteractions.org/checker

comorbidities in people living with HIV.[94–96] The real long-term consequences are not completely known, and time will be necessary for accurate evaluations. Infrastructure for HIV consultations has been adapted to the constraints of the pandemic in most institutions.

In-person visits have been the rule for monitoring HIV infection. Before the COVID-19 pandemic, telehealth interventions had been used satisfactorily but were restricted, at least, partly due to major technical issues and costs. The COVID-19 pandemic has brought a renewed need for remote care. Simple telephone calls and email messages replaced in-person visits at first. The Spanish HIV association, GeSIDA, has established a minimum set of recommendations for telehealth for patients with HIV.[97] More sophisticated systems (eg, videoconferencing) have developed during the COVID-19 pandemic, and this option, alongside in-person visits, will most likely remain in the future for stable and non-complicated cases. Consultation for post-exposure prophylaxis or symptomatic sexually transmitted infections need to be maintained by in-person visits, as well as the initiation of ART for newly diagnosed individuals. In the follow-up of people living with HIV, approaches to screening asymptomatic SARS-CoV-2 infection, isolation, and quarantine rules should be the same as in the general population.

People with drug addictions are particularly susceptible to COVID-19, due to poorer social health determinants. Social isolation might increase the risks of addiction and deaths caused by drug overdose. People using substances might have reduced access to harm reduction and treatment services.[98] There might be disruptions in illicit drug supplies, affecting availability and cost, and increasing the risk of drug adulteration.[99] Individuals with addictions have been at higher risk of multimorbidity and mortality during the COVID-19 pandemic.[100] Some centres have ensured a sufficient quantity of take-home doses for patients on methadone maintenance treatment to maximise their adherence during COVID-19-related lockdowns.[101]

The COVID-19 pandemic has affected mental health, particularly in patients with pre-existing psychiatric disorders.[102] The consequences were substantially higher among people living with HIV, in racial and ethnic minorities, immigrants, transgender people, sex workers, and socioeconomically disadvantaged groups.[103] Women were especially affected in some studies.[104,105] Other studies (but not all) have described substantial reductions in sex with non-steady partners during the first weeks of lockdown among men who have sex with men (MSM).[106–109] These studies describe MSM as indicating fewer sexual partners or fewer opportunities for having sex. Reduced sexual activity with sexual partners external to the household is more likely to result in reduced sexual transmitted infections among HIV-positive MSM.[106] A Belgian study described MSM who had sex with non-steady partners were significantly more likely to be HIV positive, to use pre-exposure prophylaxis (PrEP), or to have engaged in sexual practices such as group sex, chemsex, and sex work, before the first national lockdown, compared with their counterparts.[106]

Lockdown restrictions and reducing in-person visits during the COVID-19 pandemic might have interrupted both pre-exposure prophylaxis for adults at high-risk of HIV infection and antiretroviral treatment for people living with HIV. Hence outreach programmes for treatment and prevention of HIV have become increasingly relevant and should be rapidly implemented in case of further waves. Developing remote pharmacy visits alongside the widespread use of commercial home delivery services ensured continued ART access for people living with HIV. As with remote medical visits, there were technical and legal obstacles to overcome. The Spanish Society of Hospital Pharmacy released a document on telepharmacy and medication home delivery.[110]

SARS-CoV-2 vaccines and HIV infection

All licensed, virally effective vaccines are based on the induction of neutralising antibodies directed against viral envelope surface proteins and the spike receptor binding domain. Although cellular responses are probably important in establishing a protective response, vaccines that are unable to induce antibodies that block infection are no longer considered for clinical development.[111,112] This principle has targeted the SARS-CoV-2 spike protein in all COVID-19 vaccines,[113] even if some prototypes also hope to induce cellular immunity. HIV preventive vaccine research is focusing on the induction of broadly neutralising antibodies.[114,115] Many HIV-preventive prototypes under development (eg, RNA, adenovirus vectors, or trimeric envelopes) have been translated to the coronavirus field, enabling the rapid results observed in SARS-CoV-2 vaccinology.[113]

Few people living with HIV have been included in reported phase 3 vaccine trials, so the readiness of their immune systems remains unknown.[116] Predictions and potential concerns are based on two sets of data: the immune damage to B-cell compartments and antibody generation caused by HIV infection that could potentially decrease humoral responses to neoantigens (eg, the SARS-CoV-2 spike protein); and the scarce response of people living with HIV to other vaccines, particularly in patients with low CD4 T-cell count. People living with HIV display lower or delayed responses to several vaccines, including pneumococcal, influenza and hepatitis B vaccines.[117] Accordingly, specific recommendations have been generated, including repeated vaccine doses or vaccination with particular prototypes.[118,119] Studies analysing the response of patients with HIV to COVID-19 vaccines are needed to define the potential advantage of some prototypes or the need for additional vaccine doses to achieve full protective immunity.

There is debate on whether people living with HIV should be considered as an at-risk group requiring prioritisation for COVID-19 vaccination. No evidence supports

this indication, but patients with comorbidities or those with low CD4 counts (less than 200 cells per µL) might be at higher risk of developing severe COVID-19, and hence should benefit from early COVID-19 vaccination. The European AIDS Clinical Society statement on COVID-19 in people living with HIV also supports the vaccination priority scheme.[120] Unfortunately, data on people living with HIV included in approved phase 2 and 3 vaccine trials so far are scarce: in the Moderna vaccine trials, only 0·6% of participants were people living with HIV[121] and only 0·5% in the Pfizer trials.[122] In the Novavax phase 2b study in South Africa, responses in people living with HIV seem to have been much lower than in individuals that do not have HIV. Although, the final results remain unavailable.[123] ART should be continued during vaccination of people living with HIV.

Future trends in SARS-CoV-2 and HIV infections

Unfortunately, clearly establishing the interplay between the HIV/AIDS and COVID-19 pandemics will require a higher quality of evidence than is available. Emerging evidence seems to indicate a moderately increased risk of death and severity of COVID-19 in people living with HIV.[4–6,124] Many aspects of COVID-19 and HIV/AIDS interaction need to be elucidated (figure 2). Although data are insufficient to determine whether HIV viral load, CD4 T-cell count, or ART use are associated with COVID-19-related death, there are some signs that low CD4 counts (less than 200 cells per µL) might potentially be associated with poor outcomes. As the data are not unequivocal, a large dataset comparing outcomes in HIV-positive and HIV-negative cohorts with broader geographical representation is required. Among other initiatives, the WHO Global COVID-19 Clinical Platform[125] is gathering anonymised and standardised individual-level clinical data from people living with HIV and the general population hospitalised with COVID-19. One ongoing discussion is whether the use of specific antiretroviral drugs might protect against COVID-19. Although evidence on the potential protective role of tenofovir–emtricitabine[65] on SARS-CoV-2 acquisition and progression is conflicting, PrEP should continue to be provided to protect against HIV-infection acquisition. Similarly, no evidence suggests people living with HIV should be managed differently in preventing COVID-19 clinical progression. Modifications switching to protease inhibitor-based ART or including any antiretroviral drug increasing protection for COVID-19 are not justified.

When health-care systems are overwhelmed, deaths from manageable conditions, such as HIV, might increase substantially due to disruptions in essential health services. Lockdown measures and stigmatisation have affected the functioning of HIV clinics in many settings, particularly in low-income and middle-income countries. A survey by WHO done between April and June, 2020, showed that 34 of 127 countries reported ART disruptions. In a subsequent update, 12 countries reported ART stock availability of 3 months or less for the major first-line drugs.[126] To support countries in reorganising and maintaining access to high-quality essential health services for all, WHO has published updated guidance, including a set of immediate targeted actions that countries should consider.[127] WHO also recommends clinically stable people living with HIV to benefit from multiple refills (every 3–6 months) of antiretroviral drugs and other medications, such as opiate substitution and tuberculosis preventative therapies.

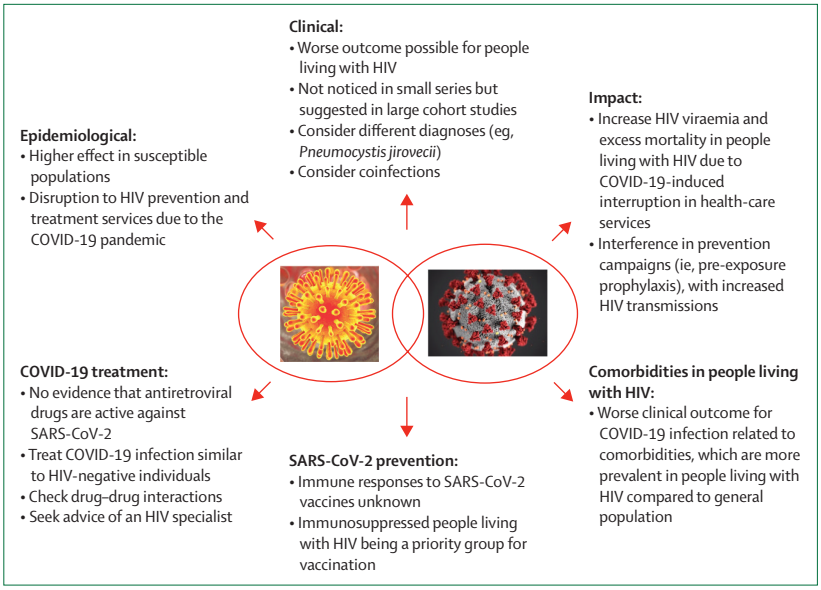

Figure 2: **Interaction of the HIV and SARS-CoV-2 pandemics and unanswered questions**

Panel: General principles of COVID-19 management in people living with HIV

Studies on therapeutics were mostly done in HIV-negative individuals, and no evidence indicates different therapeutic approaches should be considered in people living with HIV. Some general principles are applicable when treating COVID-19 infection in people living with HIV:

- Treatment, including antiviral, anti-inflammatory, and anticoagulant therapies, should be the same as for HIV-negative individuals (figure 1)
- Antiretroviral therapy (ART) regimens should not be stopped or modified to promote anti-SARS-CoV-2 activity
- Initial ART should be started with regimens that have high barriers to resistance and low drug–drug interactions, and treatment changes should be delayed unless strictly necessary
- Drug–drug interactions should be considered, particularly with boosted protease inhibitors or boosted integrase-strand-transfer inhibitors. Non-boosted integrase-strand-transfer inhibitors (eg, raltegravir, dolutegravir, and bictegravir) have no major drug–drug interactions
- ART dispensary practice should allow for 3–6-month drug supplies, and monitoring might be deferred with good adherence and absent new toxicity or drug–drug interactions
- Consider consulting infectious disease or HIV specialists in complex cases or for questions on ART and drug–drug interactions
- Although data are scarce for pregnant women living with HIV, COVID-19 prevention and treatment should be identical to treatment given to HIV-negative pregnant women

Search strategy and selection criteria

We identified references searching PubMed using a Boolean strategy with the terms: "COVID-19", "SARS-CoV-2" and "HIV-infection" and "epidemiology", "clinical manifestations", "pathogenesis", "diagnosis", "prognosis", "prevention", "treatment", "antiretrovirals", "vaccines", and "low-, middle- and high-income countries". We searched for papers from Jan 1 to Nov 1, 2020, including cohort studies, case-series and clinical trials; duplicates were eliminated. This period had 73 094 COVID-19 publications, including 963 (1·32%) that were HIV related. The first case series was published on April 15, 2020. Only publications in English were reviewed and only published data were analysed. Preprint publications were not considered. Given rapid developments, we also considered relevant printed publications between Nov 1, 2020, and Feb 3, 2021, (there were approximately 500 additional publications) and specific relevant data presented in important conferences (ie, the 2021 Conference on Retroviruses and Opportunistic Infections). The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

Considering the social determinants of health, accessibility to health systems and to ART should be a priority in any further waves of the COVID-19 pandemic (panel).

To protect people living with HIV from COVID-19, a vaccine should be promptly available and accessible. Despite initial concerns on whether a vaccine with the adenovirus 5 platform might increase the risk of acquiring HIV,[128] no evidence suggests that the vaccines approved might increase the risk of HIV infection or that people with HIV have a different response; although data on this are scarce. Therefore, there is an urgent need to know the response of patients with HIV to different COVID-19 vaccines and whether two doses are enough to achieve full protective immunity.

In conclusion, although emerging data on COVID-19 epidemiology and physiopathology and its intersection with HIV infection continue to accumulate, knowledge gaps remain and should be a focus for the global research community.

Contributors

JMM contributed to the study conception and design of this paper. All authors contributed to the acquisition, analysis, and interpretation of data. All authors contributed to the drafting of this paper and the revision of this paper for important intellectual content. All authors approved the final version of this paper for publication. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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