Review article

Gastrointestinal manifestations of human immunodeficiency virus and coronavirus disease 2019: Understanding the intersecting regions between the two epidemics

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ABSTRACT

In March 2020, the World Health Organization declared coronavirus disease (COVID-19) a pandemic. As of February 2021, there were 107 million COVID-19 cases worldwide. As a comparison, there are approximately 38 million people living with human immunodeficiency virus (PLHIV) worldwide. The coexistence of both epidemics, and the syndemic effect of both viruses could lead to a delirious impact both at individual and community levels. Many intersecting points were found between severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative agent of COVID-19, and HIV; among which, gastrointestinal (GI) manifestations are the most notable.

GI manifestations represent a common clinical presentation in both HIV and SARS-CoV-2. The emergence of GI symptoms as a result of SARS-CoV-2 infection provides a new dynamic to COVID-19 diagnosis, management, and infection control measures, and adds an additional diagnostic challenge in case of coinfection with HIV. The presence of GI manifestations in PLHIV during the COVID-19 pandemic could be referred to HIV enteropathy, presence of opportunistic infection, adverse effect of antiretrovirals, or coinfection with COVID-19. Thus, it is important to exclude SARS-CoV-2 in patients who present with new-onset GI manifestations, especially in PLHIV, to avoid the risk of disease transmission during endoscopic interventions.

Structural similarities between both viruses adds a valuable intersecting point, which has mutual benefits in the management of both viruses. These similarities led to the hypothesis that antiretrovirals such as lopinavir/Rironavir have a role in the management of COVID-19, which was the target of our search strategy using the available evidence. These similarities may also facilitate the development of an efficient HIV vaccine in the future using the advances in COVID-19 vaccine development.

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Introduction

Both severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and human immunodeficiency virus (HIV) infections can cause multisystemic diseases of variable presentations. Several factors have been shown to affect the severity of illness, and racial and ethnic variations appear to be similar in both diseases. The incidence of HIV is 20-fold higher in Black women than Caucasians

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and 4-fold higher than Hispanics [1]. Similarly, early reports on coronavirus disease (COVID-19; the disease resulting from SARS-CoV-2 infection) demonstrated a higher rate of infection and hospitalization among African American and Hispanic communities [2]. A higher prevalence of comorbities and a lack of access to heathcare are believed to be the main causes of this finding in addition to genetic susceptibility, risky sexual behavior in HIV, and angiotensin-converting enzyme 2 expression in COVID-19 [3].

Gastrointestinal (GI) manifestations are considered to be a primary presentation in both HIV and SARS-CoV-2 infection [4]. COVID-19 can cause a wide spectrum of GI manifestation, ranging from diarrhea in 3.8–34% of patients, followed by nausea, vomiting, and abdominal pain (1.1–2.2%). Other GI symptoms such as anorexia, and dysgeusia have been reported in a smaller proportion of patients [5]. As for HIV, most of the GI manifestations in PLHIV are secondary to opportunistic infection, which explains the crucial role of the immune status in PLHIV with GI manifestations. Moreover, HIV per se can cause a wide spectrum of GI manifestations from the mouth to anus [4].

The presence of GI manifestations in both HIV and SARS-CoV-2 infection will likely serve to provide greater understanding of the intersecting regions between the two epidemics. As chronic diseases and immunodeficiency are important risk factors for morbidity and mortality in COVID-19, PLHIV are at a high risk of a poor outcome following COVID-19 [6]. SARS-CoV-2 and HIV have dual tropism for both the lung and gut, and GI manifestations are the first symptoms for both diseases, which poses a clinical challenge for diagnosis [4].

As a result, further study of the pathogenesis, and clinical and endoscopic picture of GI manifestations in both viruses is essential to the efficient use of antiretrovirals in the management of COVID-19.

Literature search

We performed a search of PubMed and Google for all published articles using the search terms "COVID-19," "SARS-CoV-2," "gastrointestinal," and "diarrhea" to extract data for this review.

We searched for articles in PubMed that discussed the clinical impact of the COVID-19 pandemic on PLHIV and its consequences. Relevant keywords and Medical Subject Headings terms concerning "COVID-19" and "HIV" were included to ensure the maximum output from the literature search. The search terms were divided into two categories and were written as follows: COVID-19 "COVID-19" OR "SARS-COV2" OR "2019-nCOV" and HIV "HIV" OR "AIDS" OR "acquired immunodeficiency virus." All pertinent studies were identified and screened by two authors, and any discrepancy was resolved by involving a third author.

The exposure was clinically and laboratory-confirmed cases of COVID-19, while the outcome was the clinical status of infected patients with HIV and COVID-19 confirmed cases and its consequences. We searched for articles written in the English language only, from December 2019 to December 2020. We excluded all editorials, letters to the editor, and studies that discussed the psychological and social burden of COVID-19 on HIV confirmed cases.

Approximately 315 articles were found. After full-text screening and removal of duplicates, 19 studies were included. Table 1 summarizes the included studies addressing the outcome of COVID-19 in PLHIV.

Structural similarities and immunological interaction between HIV and COVID-19

Previous studies have shown structural similarities between HIV and the SARS-associated coronavirus (SARS-CoV). Both viruses

have been suggested to follow an analogous membrane fusion mechanism, as the 3D structure of the S2 subunit of SARS-CoV spike protein (S) and gp41 from HIV-1 share the same two α helices. In addition, ligand-binding analysis has suggested that the two inhibitors GGL and D-peptide from HIV-1 gp41 serve as inhibitors for SARS-CoV entry [25]. Analysis of SARS-CoV-2 showed that amino acid residues of a unique four insertion in the S protein are similar to those in HIV-1 gp120 or HIV-1 Gag. Although these inserts are discontinuous on the primary amino acid sequence, 3D-modeling of SARS-CoV-2 suggests that they converge to constitute the receptor binding site; thus highlighting a relationship between SARS-CoV-2 S protein and gp120 and Gag protein of HIV. These proteins are important for viral binding and assembly, and formed part of the rationale of using HIV antiretroviral therapies (ARTs) in the management of COVID-19 [26].

While still not conclusive, data on the pathogenesis of SARS-CoV-2 in PLHIV suggests that a healthy immune system could facilitate the pathogenetic alterations responsible for the appearance of symptoms, and that, conversely, immunocompromised individuals with low counts of CD4+ cells and alteration of CD8+ T-lymphocytes mitigates the symptoms [8]. Some studies reported that PLHIV might benefit from the HIV-induced cellular immunity dysfunction protecting against the cytokine storm (paradoxical prevention). This evidence contradicts the basic hypothesis, which anticipates a more severe COVID-19 outcome due to HIV-induced immunocompromised states, which coronavirus can augment transiently. This was concluded in the UK cohort study that reported an increased risk of COVID-19 death among patients complaining of immunosuppressive comorbidities, including PLHIV [27–29]. A recent study exhibited at the 23rd International AIDS Conference (AIDS 2020: Virtual) showed that PLHIV is capable of inducing a strong inflammatory response to the SARS-COV-2 virus, as measured by higher than normal levels of C-reactive protein, fibrinogen and D-dimer, and cytokines including interleukin 6 (IL-6), IL-8, and tumor necrosis factor alpha, but not IL-1b. However, PLHIV remain at risk of severe COVID-19 due to the possibility of a cytokine storm [30].

GI manifestations of HIV and COVID-19

COVID-19 is primarily a disease affecting the respiratory system, it has a wide spectrum of severity, ranging from asymptomatic or mild to life-threatening, the pulmonary symptoms are the main presentations, including cough, and dyspnea with constitutional symptoms [31]; however, the spread of COVID-19 leads to the evolution of new symptoms. Accumulating evidence has shown that COVID-19 is a multisystem disease with extrapulmonary involvement, including GI, hepatobiliary, neurological, cardiovascular, dermatologic system, and others [31,32]. Several studies have reported GI manifestations of COVID-19, including patients presenting with either pulmonary symptoms with concurrent GI symptoms, the onset of GI symptoms before respiratory symptoms, or GI symptoms in the absence of respiratory symptoms [33].

The incidence of GI manifestations ranges from 12% to 61% in patients with COVID-19 [32]. SARS-CoV-2 can affect the entire GI tract, starting from the oral cavity. Indeed, dysgeusia has been described as one of the first oral symptoms, and could be attributed to the direct consequence of SARS-CoV-2 infection; however, further studies are needed to determine the exact pathophysiological mechanisms [34,35]. Other oral manifestations have been described in patients with COVID-19, including oral ulcers, desquamative gingivitis, and petechiae in the palate, but it is unclear if these lesions result from direct SARS-CoV-2 infection or if COVID-19 predisposes individuals to opportunistic infections

Table 1
List of published studies on COVID-19 cases in HIV-positive populations.

Study	Country of origin	Study design	Study size	Age (years)	Sex	Results
Blanco JL *et al.* [6]	Spain	Case series	5 confirmed HIV/COVID-19 cases admitted to Hospital Clinic Barcelona	Median (IQR): 40 (15)	3 male, 2 transgender	- All were given ART: 2 on protease inhibitors, 2 on integrase-inhibitors, and 1 ART naïve - 4/5 had CD4 > 400 cells/μL, with undetected VL < 50 copies/mL - 2/5 had severe infection, and were admitted to the ICU and ventilated - All were discharged, except one who remained in the ICU at the end of the study
Härter G *et al.* [7]	Germany	Case series	33 COVID-19/HIV cases in 12 German HIV centers	Mean (IQR): 48 (26–82)	30 male, 3 female	- All were receiving ART, 29/33 made a full recovery and 3 died: 1 with a very low CD4/CD8 ratio, 1 was 82 years old, and 1 had multiple comorbidities) - 24% severe and critical cases: 14/33 were hospitalized, 6/14 were transferred to the ICU, 1 remains hospitalized, and 3 died
Guo W *et al.* [8]	China	Cross-sectional study (survey)	1,178 HIV patients in two central districts in Wuhan, 9 HIV/COVID-19 patients	Median (IQR): 57 (47.5–61.5)	8 male, 1 female	- No differences in hospitalization and death rate were observed between PLWH who were virally suppressed and the general population - Among 1,178 HIV cases, 12 had symptoms of COVID-19; 6 were confirmed through PCR and 2 via chest CT - All patients were on the NRTI/NNRTI regimen, had CD4 > 350 cells/μL and VL < 20 copies/mL. - 6 mild and 2 critical cases; all patients recovered, except 1 who died - Among the asymptomatic cases, 9 PLHIV who had contact with a confirmed COVID-19 case, 1 tested positive via PCR
Wu Q *et al.* [9]	China	Case series	2 COVID-19 cases with HIV co-infection	60 (1st case) and 47 years old (2nd case)	2 male	**Case 1:** Stage IV diffuse B-cell lymphoma, type 2 diabetes, and pulmonary TB; cured and discharged 2 weeks after admission. **Case 2:** Pneumocystis pneumonia, diarrhea, lymphopenia; discharged 1 month after admission. - Both cases had multiple ground-glass opacities; case 1 is on a long-term ART, while case 2 is treatment-naïve - No difference in the clinical outcome among HIV positive and negative patients regarding COVID-19
Gervasoni C *et al.* [10]	Italy	Cross-sectional	Out of 6,000 HIV-positive patients, 47 probable and confirmed cases of COVID-19 infection	Mean, SD (51 ± 11)	36 male, 11 female	- 44/47 had viral load < 20 copies/mL - Dyslipidemia and hypertension were the most common comorbidities (15/47 and 14/47, respectively) - 28/47 (60%) were confirmed with PCR and IgG/IgM Rapid Test, 19 were home isolated,13/28 were hospitalized, and 6/28 had severe lung deterioration - Two cases required mechanical ventilation; one was discharged and one died - ARV is thought to be protective to PLHW against severe outcomes of COVID-19
Ridgway JP *et al.* [11]	United States	Case series	5 HIV/COVID-19 cases	Mean age: 48 (range 38–53) years	1 male, 4 female	4/5 African, all cases were taking ART, had a CD4 count > 200 cells/μL, and suppressed HIV viral loads < 20 copies/mL - 3 had diarrhea,1 had cardiac symptoms

Table 1 (*continued*)

Study	Country of origin	Study design	Study size	Age (years)	Sex	Results
Shalev N *et al* [12]	United States	Case series	2,159 confirmed COVID-19 cases, 31 were HIV/COVID-19 positive	Mean age: 60 (range 23–89) years	24 male, 7 female	- All were hospitalized, 2 required supplemental oxygen, and none were ventilated; all were discharged 16/31 non-Hispanic; all HIV cases were taking ART with a mean CD4 396 cells/μL, and 96% had suppressed viral loads < 200 copies/mL - The most common comorbidities were hypertension in 21 (67.7%), and diabetes mellitus in 13 (41.9%). - 8/31 (25%) died, 2 remain in the ICU - Hospitalized PLHW with COVID-19 have the same characteristics and outcomes with other hospitalized patients
Vizcarra P *et al* [13]	Spain	Prospective cohort	1,339 HIV-positive cases, followed up for COVID-19 progression	Mean (SD) age: 53.3 ± 9.5 years	43 male, 8 female	- 51 HIV-positive individuals with probable COVID-19, 35 confirmed by PCR, 28/51 hospitalized, 21/28 recovered, 5 remain admitted, and 2 died - 25/51 had hypertension and diabetes - No significant differences in clinical and radiological presentation among HIV-positive individuals versus the general population
Byrd, KM, *et al.* [14]	United States	Case series	27 patients infected with HIV/COVID-19 presenting to Miriam Hospital Infectious Diseases and Immunology Center	Mean (SD) age: 49 ± 10.6 years	20 male, 6 female, and 1 transgender	-13/27 were Hispanic and 9/27 were African American. - All were on ART, with a viral load < 20 copies/mL, and a CD4 range of 87–1,441 cells/μL - 9/27 were hospitalized for 1–13 days; 8 recovered and 1 died - The clinical characteristics of COVID-19 are similar between HIV positive and negative patients
Aydin Altuntas O *et al.* [15]	Turkey	Case series	Four HIV/COVID-19 cases admitted to a hospital in Istanbul were extracted and analysed	Mean (SD): 37.25 (4.5) years	4 male	- 3/4 cases were taking integrase inhibitors; 3 were discharged and 1 died
Okoh AK *et al.* [16]	United States	Case series	27 HIV/COVID-19 co-infected patients in Neward, New Jersey	Median age: 58 years (IQR, 50–67)	15 male, 12 female	- Mortality in HIV/COVID-19 co-infected cases is associated with comorbidities 25/27 were black American, with a median CD4 count of 551 cells/μL - >50% had hypertension, 33% had diabetes mellitus, and 27% had chronic kidney disease - 2/3 patients who were admitted to the ICU died - No significant difference in clinical presentation compared to the general population
Hu Y *et al.* [17]	China	Case series	12 HIV/COVID-19 patients (2 diagnosed with late stage HIV in hospital)	Median age: 36 years (IQR, 33–56; range, 25–66)	10 male, 2 female	A total of 9 mild COVID-19 cases were taking long term ART, 2 severe cases admitted to the ICU were ART naive, and 1/12 died. - Adherence to ART might aid in reducing the severity of COVID-19
Karmen-Tuohy S *et al.* [18]	United States	Retrospective matched cohort study	21 HIV/COVID-19 patients matched to 42 HIV-negative and COVID-19 positive patients at NYU Langone Health with COVID-19 between March and April 2020	Mean age: 60.04 ± 11.77 years (HIV group); 61.48 ± 20.13 years (non-HIV group)	19 male, 2 female (HIV group), versus 38 male, 4 female (non-HIV group)	- Among HIV-positive patients, 24% were African American, and all were taking ART - The median CD4 count was 298 cells/μL; 6/19 had CD4 < 200 cells/μL, and 15/17 had VL < 50 copies/mL - No statistical differences between the two groups regarding the length of hospital stay, need for oxygenation, and mortality - A higher proportion of the HIV group required admission to the ICU and mechanical ventilation versus the non-HIV group - 4 patients (3 HIV positive and 1 HIV negative) died

Table 1 (continued)

Study	Country of origin	Study design	Study size	Age (years)	Sex	Results
Patel VV et al. [19]	United States	Case report	100 HIV/COVID-19 patients compared to 4,513 HIV-negative patients with COVID-19 admitted to the tertiary healthcare system between March 10, 2020, and May 11, 2020	Median (IQR) of the HIV and non-HIV groups: 62 years (53–68) and 65 years (54–76), respectively	Proportion of males of the HIV and non-HIV groups was 55% and 53%, respectively	from superimposed bacterial pneumonia The HIV group comprised 43% black, 37% Hispanic, 4% white. There was a higher intubation rate among PLHIV (21% versus 14%), and a 50% risk of intubation among HIV group, although not statistically significant (aHR, 1.54; p = 0.055). No significant differences in time until death or discharge between groups Among the HIV group, 94% were on ART, 81% had suppressed VL < 40 copies/mL, 21% had CD4 < 200 cells/μL No association between CD4 count and death or time until discharge between the two groups f 81 patients with an undetectable load, 21 (26%) were intubated, and 22 (27%) died in hospital
Ho H et al. [20]	United States	Retrospective cohort	93 HIV/COVID-19 cases were admitted to 5 emergency departments between March 2, 2020 and April 15, 2020	Median (IQR): 58 (52–65) years	67 male, 23 female, and 3 transgender	38/93 black, 29/93 Hispanic/Latino 49/93 (52%) had hypertension, 34.4% had diabetes, and 25% had prior opportunistic infection 57/68 (83.8%) were virally suppressed (VL < 50 copies/mL), and had a median CD4 count of 554 cells/μL prior to COVID-19 diagnosis Approximately 70% (62/89) of patients were taking tenofovir-based regimens 2/93 PLHIV hospitalized with COVID-19, 19/72 (26.4%) required ICU-level care, and 15/72 (20.8%) required mechanical ventilation Overall, 19/72 individuals (26.4%) died, and 53/72 (73.6%) recovered
Del Amo J et al. [21]	Spain	Cohort	77,590 HIV-positive persons receiving ART at 60 HIV clinics between February 1 and April 15, 2020 were collected from the national COVID-19 Health Information System	20–79 years old	204 male, 32 female	- 236 confirmed COVID-19 cases; among whom, 151 (64%) were hospitalized, with 15 (6%) admitted to the ICU, and 20 (8%) died. - Higher risk of COVID-19 and hospitalization was observed among men and age > 70 years old - HIV positive patients who were receiving TDF/FTC had a lower risk of acquiring COVID-19
Sigel K et al. [22]	USA	Retrospective cohort study	4,402 COVID-19 positive individuals were compared to 405 negative HIV and positive COVID-19 12 March to 23 April.	Median age: 61 (54–67) years	22 female (HIV +VE), 97 (HIV –ve)	- 88 PLWH/COVID-19 matched with 405 HIV negative and SARS COVID positive - No significant difference in COVID-19 severity among HIV negative and positive groups - No significant difference in poor outcome (18% required mechanical ventilation and 21% died during follow-up [compared to 23% and 20%, respectively]).

Table 1 (continued)

Study	Country of origin	Study design	Study size	Age (years)	Sex	Results
Etienne N et al. [23]	France	Prospective cohort	54 HIV/COVID-19 positive cases compared to 4,000 HIV positive patients	Median age: 54 (47–60) years	33 male, 21 female	- 38 confirmed and 16 patients with probable HIV/COVID-19, all of whom were on ART - 96% with undetected VL - Moderate cases (64.8%) - 19 (14 severe and 5 critical cases), 1 died. 13/19 were black African. - Metabolic disorder, older age, black ethnicity, and male sex were significantly associated with poor outcomes of COVID-19
Childs K et al. yyyy [24]	United kingdom	Case series	18 HIV/COVID-19 confirmed cases from the medical records of Kings College Hospital	Median age: 52 (49–58) years	12 male, 6 female	- 5 died, 12 discharged, 1 remains hospitalized - 2 cases acquired COVID-19 as a nosocomial infection - Black PLWH were thought to be at a higher risk of severe disease - Darunavir and other ART were not protective against moderate/severe COVID-19 - Increased COVID-19 morbidity and mortality among PLHIV

[34,36]. Other upper GI symptoms of COVID-19 include nausea, vomiting, loss of appetite, and abdominal pain. The pooled prevalence of nausea/vomiting and abdominal pain across different studies was 7.8% and 3.6% respectively [37]. Few aspects of abdominal pain require consideration; it can range from mild nonspecific epigastric pain to generalized abdominal pain, and some reports attribute abdominal pain to COVID-19-induced pancreatitis [38–40], SARS-CoV enters the pancreatic islet cells using ACE2 and causes damage to the endocrine part of the pancreas, as shown by increased ACE2 in pancreatic islets during SARS-CoV infection [41]. Moreover, genome sequencing has shown that SARS-CoV-2 shares 79.6% homology with SARS-CoV, further suggesting that SARS-CoV-2 can cause acute pancreatitis [38,42]. Upper GI bleeding (GIB) in the form of hematemesis and melena was reported in different case series of COVID-19 patients [43,44], in a matched case-control study of 41 patients with COVID-19 with GIB, the most common upper GIB etiologies were gastric or duodenal ulcers (80%) [45].

Regarding lower GI symptoms associated with COVID-19, diarrhea was one of the most common symptoms, and the pooled prevalence of diarrhea across different studies was 7.7% (5.8–18.3%) [37]. In most studies, diarrhea was described as loose or watery stools ranging from 2 to 10 bowel movements per day [38]; however, bloody diarrhea was reported in some case reports of COVID-19 patients without IBD. In one such case, bleeding was caused by colitis, evident by wall thickening of the ascending, transverse, and descending colon, which was compatible with colitis; however, endoscopic assessment was not performed [46]. Another patient with COVID-19 presented with bloody diarrhea due to acute hemorrhagic colitis, as confirmed by endoscopic evidence of colonic injury [47]. Variable data exist on the correlation between GI manifestations and COVID-19 severity. In a study conducted on 150 patients with COVID-19, there was no significant difference in the length of hospital stay, need for mechanical ventilation, or mortality between patients with and without GI symptoms [48,49]. Moreover, a pooled analysis of multiple studies showed that abdominal pain was associated with 4-fold increased odds of severe disease, marginally increased odds with nausea/vomiting, and no correction with diarrhea [50,51].

PLHIV demonstrate pronounced GI complaints throughout the disease course, with approximately 50–70% of PLHIV reporting GI symptoms. HIV can affect the entire GI tract [4,52], and there is a wide spectrum of GI symptoms in PLHIV, including nausea, vomiting, dysphagia, odynophagia, and abdominal pain, in addition to lower GI symptoms such as diarrhea and tenesmus. Pancreatitis is another well-described complication of HIV [53]. These disorders are common, potentially due to viral effects, opportunistic infections, or drug-induced symptoms [54,55]. Table 2 shows the prevalence/incidence of the common symptoms of COVID-19 and HIV among studies.

Pathophysiology of HIV- and COVID-19-induced diarrhea

COVID-19 diarrhea

Several mechanisms have been proposed to explain COVID-19-induced diarrhea, including viral cytopathic or non-cytopathic mechanisms [38,60]. Moreover, angiotensin-converting enzyme-2 (ACE2) is the receptor of entry of SARS-CoV-2 into the host cell and is highly expressed in the GI tract, especially in intestinal epithelial cells. SARS-CoV-2 attacks the GI tract through binding of the S1 subunit of the viral spike glycoprotein to the ACE2 receptors on the membrane of enterocytes, whereas S2 favors the fusion of the two cell membranes; this process requires priming by cellular serine proteases (TMPRSS2), which allow protein cleavage, reg-

Table 2
Prevalence/incidence of common COVID-19 symptoms.

Prevalence/incidence of gastrointestinal symptoms	COVID-19	HIV
Abdominal pain	8/138 (5.7%) [56]	27.9% [57]
Nausea/vomiting	55/1099 (5.0%) [58]	16.8% [57]
Diarrhea	42/1099 (3.8%) [58]	23.6% [57]
Pancreatitis	32/11,883 (0.27%) [59]	17 to 30 cases per 100 000 [53]
Anorexia	83/204 (40.6%) [49]	

ulating the entire mechanism. After viral entry, replication of the virus can cause a cytopathic effect on enterocytes [38]. Histological analysis of the GI epithelium shows infiltration by plasmacytic cells and lymphocytes, with interstitial edema, mainly in the stomach, duodenum, and rectum, and more patchy lymphocytic infiltration in the esophagus [61,62]. Other proposed non-cytopathic mechanisms of COVID-19-induced diarrhea include alterations to gut flora and gut motility, largely due to the increased level of proinflammatory cytokines released during a cytokine storm in severe COVID-19 (IL-2, IL-6, IL-7, granulocyte monocyte colony-stimulating factor [GM-CSF], and tumor necrosis factors [TNF-α]) [38,60,63]. In addition, several antivirals and antibiotics used in the management of COVID-19 patients can directly cause diarrhea as an adverse effect [38,64].

HIV-induced diarrhea

HIV can directly cause structural, functional, and immunological abnormalities of the GI tract; this leads to HIV enteropathy, which is diagnosed by exclusion after a thorough work-up of all other potential causes [4,65]. Viral gp120 causes enterocyte apoptosis through decreased tubulin depolymerization and induction of local cytokines such as IL-6, IL-10, and TNF [4,66]. This results in small intestinal villous atrophy and colonic crypt hyperplasia, epithelial hyperproliferation, and CD4+ depletion within the lamina propria; even after the era of HAART, the reconstitution of CD4 T cells is incomplete and slower in the gut-associated lymphoid tissue than in the peripheral blood [4,67–69]. All of these factors cause diarrhea through gut inflammation, increased permeability, and malabsorption of bile acids and vitamin B12 [70].

Fecal shedding of SARS-CoV-2 and HIV

COVID-19 spreads mainly by droplet transmission; however, recent evidence has shown that viral shedding in feces is another potential route of transmission [71]. Indeed, the reported pooled prevalence for stool SARS-CoV-2 RNA positivity was 48.1% (95% confidence interval [CI], 38.3–57.9%) in a systematic review of 12 studies [72]. Furthermore, a study of 73 patients with COVID-19 in China showed that 53.42% of patients tested positive for SARS-CoV-2 RNA in the stool. Positive stool results ranged from 1 to 12 days, and 23.29% of patients had persistent viral fecal shedding after negative respiratory samples [73]. In addition, prolonged shedding of viral RNA in feces was observed for at least 2 weeks, and in some cases, for more than a month, even with negative viral RNA in respiratory samples [74]. In a study conducted on 59 patients with COVID-19 from Hong Kong, 15.3% of had positive stool viral RNA, and patients without diarrhea also tested positive for stool viral RNA, but at a lower rate [72]. Tracing the GI manifestations of COVID-19, and the possible risk of feco-oral transmission, are crucial not only for the early diagnosis of COVID-19 but

also for public health to prevent the spread of the pandemic through dissemination via GI endoscopy units [38,75].

Few studies have described the fecal shedding of HIV-1 and its impact on HIV-induced diarrhea. In a study investigating the cause of diarrhea in HIV-positive patients, stool samples of 196 HIV-infected persons, including 29 persons with diarrhea, HIV-1 RNA was detected in 66% of patients with diarrhea compared to 45% of patients without. Moreover, 34% were enteropathogen-negative cases, and HIV-1 RNA shedding in stool was found in 80% enteropathogen-negative cases compared to 47% in enteropathogen-positive cases, indicating that HIV-1 itself is the most likely candidate to be involved in diarrhea [76]. Another study found that infants and children with HIV infection shed HIV nucleic acids in fecal samples, and that those with persistent diarrheal disease were more likely to shed detectable levels of HIV nucleic acids than those with no evidence of GI dysfunction [61,62].

Endoscopic in HIV and COVID-19

Endoscopic features

Esophagitis, gastritis, and duodenitis are the most common endoscopic findings in PLHIV. With regard to colonoscopy, PLHIV were significantly more likely to have adenomas 6–9 mm in diameter than hyperplastic polyps [77]. However, an African study concluded a lower prevalence of colorectal adenomas in 263 PLHIVs compared to 657 non-PLHIV (20.5% vs. 27.1%, p = 0.04), tubular adenomas > 10 mm (0.4% vs. 2.9%, p = 0.02) and serrated adenomas (0.0% vs. 2.6%, p $\leq$ 0.01) [78]. Moreover, advanced neoplastic lesions and colorectal adenocarcinomas were more common in PLHIV. However, all of these results lacked statistical significance. Another study revealed a high prevalence of adenocarcinoma in PLHIV compared to non-PLHIV (1.5% vs. 0.8%, p = 0.29) [77,78].

Despite the high prevalence of GI disorders in COVID-19, data on GI histologic and endoscopic findings due to COVID-19 are limited, and therefore the association remains unconfirmed [79,80]. In a multicenter retrospective study, 38 patients with COVID-19 from Lombardy, Italy who underwent endoscopic examination were enrolled. The endoscopic findings of these patients showed considerable heterogeneity; endoscopic lesions were observed in 75% (18/24) of patients who underwent esophagogastroduodenoscopy (EGD) and 70% (14/20) of patients who underwent colonoscopy. The main upper GI findings were esophagitis in 20.8%, bulbar ulcer in 20.8%, erosive gastritis in 16.6%, neoplasm in 8.3%, and Mallory–Weiss tear in 4.1%. As for colonoscopic findings, colitis was the most common finding, ranging from mild to severe ulcerations, either on top of segmental colitis due to diverticulosis, or colonic ischemia [80]. The these findings suggest a role of SARS-CoV-2 in the induction of ischemic injuries to the GI tract, which may occur as a result of a cytokine storm, leading to systemic inflammation, endothelial dysfunction, and subsequent thrombosis [81].

Risk of endoscopic transmission

Gastrointestinal endoscopy is widely accepted as an aerosol-generating procedure (AGP) [82]. Although aerosolized droplets are the primary route of SARS-CoV-2 transmission, fecal-oral transmission is another possible route [83]. Although healthcare professionals in endoscopy units are at increased risk of infection from SARS-CoV-2, it is unclear whether SARS-CoV-2 can be transmitted by endoscopes. In theory, this is a possibility due to direct contact with mucous membranes, GI secretions, and the generation of aerosols as a result of suctioning during endoscopy. However, no cases of endoscope-related COVID-19 transmission have been

reported so far [71]. Delivery of GI endoscopy has been affected by the COVID-19 pandemic, and during the first wave of the pandemic, studies showed a reduction in endoscopic procedures of up to 99% of pre-pandemic levels [84]. This reduction is because joint GI societies strongly recommend rescheduling non-urgent endoscopic procedures. However, with resumption of the workflow, strict precautions have been implemented, including screening for COVID-19 symptoms, pre-procedural testing, and a stratified approach to PPE and infection control policies such as air exchange, room cleaning, and the use of negative pressure rooms, especially for patients infected with SARS-CoV-2 [85–88].

Regarding the risk of HIV transmission during endoscopy, there are no documented cases of HIV transmission related to GI endoscopy [89,90]. Although in theory, HIV may be inoculated during contact of contaminated endoscopy to traumatized GI mucosa [89], HIV is readily destroyed by high-level disinfection, and therefore, the virus is eliminated in all cases by using standard manual cleaning and high-level disinfection protocols [91]. The Center for Disease Control stated that currently recommended procedures for disinfection of endoscopes are adequate for instruments contaminated with HIV [92].

Effect of medications on the GI tract

Patients with COVID-19 are exposed to multiple medications, including antivirals, antibiotics, proton pump inhibitors (PPIs), anticoagulants, steroids, and anti-interleukins in severe cases [51]. All of these pharmacological interventions have an impact on the GI tract. Several antibiotic regimens used for the treatment of COVID-19 can cause antibiotic-associated diarrhea due to disturbances of the GI microbiota [93], and antivirals are also implicated in the development of GI symptoms. In a randomized trial of 150 patients with mild-to-moderate COVID-19, 16% of patients who received hydroxychloroquine developed GI symptoms, of whom, 10% had diarrhea [94]. Moreover, a higher rate of GI adverse effects (30% of patients versus 3.1% in the control group) were reported with lopinavir/ritonavir in a randomized trial including 199 patients with COVID-19 [95]. However, a low prevalence of non-significant GI adverse effects (diarrhea, nausea, vomiting) were reported with remdesivir [96]. In contrast, frequent use of PPIs in hospitalized patients with COVID-19 can lead to the development of GI symptoms; importantly, hypochlorhydria resulting from PPI use has been shown to abolish the neutralizing effect on SAR-CoV-2, resulting in increased positivity of COVID-19 [51,97]. Furthermore, small intestinal bacterial overgrowth and *Clostridium difficile* infection are associated with long term PPI use, leading to diarrhea [98,99]. A retrospective study on the pre-hospitalization exposure to PPIs in patients hospitalized with COVID-19 showed that PPI use was associated with worse clinical outcomes and higher mortality [48].

Patients with HIV receive high doses of several categories of medications that can affect the GI tract, and aggravate the presence of GI symptoms [91]. ARTs can cause many adverse drug reactions, primarily hepatotoxicity, although GI disturbance is also frequently encountered [91,100]. Diarrhea, vomiting, and abdominal pain were the most frequently observed adverse drug reactions during ARTs [91,101]. Diarrhea is commonly reported with lopinavir/ritonavir therapy, and can lead to treatment discontinuation; however, this adverse effect was less commonly associated with efavirenz [102]. GI disturbance was also reported with nevirapine, nelfinavir, saquinavir, and didanosine, which is also associated with a change in treatment [103–106]; however, no discontinuation of treatment was reported with atazanavir/ritonavir due to GI intolerance [107]. Moreover, pancreatitis has been observed

with didanosine [108], and nevirapine has been associated with pancreas-related toxicities [109].

Antiretrovirals as an option for COVID-19 treatment

Among the previously reported similarities between SAR-CoV-2 and HIV, the shared GI manifestations and underlying pathogenesis highlighted the importance of investigating the efficacy of antiretroviral drugs, especially boosted protease inhibitors, against SARS-CoV-2.

Several studies have reported the recovery of patients after treatment with lopinavir/ritonavir (LPV/r) alone or in combination with oseltamivir. These studies were mostly conducted in a small number of HIV-negative individuals and had important limitations (timing, duration and dosing for treatment were highly variable and most patients received co-interventions/co-treatments) that may have contributed to the reported outcomes.

At this time, two recent publications should be mentioned. The first is a randomized clinical trial with LPV/r, which demonstrated no benefit over standard care in 199 hospitalized adults with severe COVID-19 [95]. GI adverse events were more common in the LPV/r group and caused treatment discontinuation in approximately 14% of patients.

Additionally, based on a systematic review of the efficacy and safety of antiretroviral drugs against coronaviruses [110], it is uncertain whether LPV/r and other antiretroviral drugs improve clinical outcomes or prevent COVID-19 among patients at high risk of acquiring SARS-CoV-2.

Many prospective studies are currently underway to evaluate the efficacy and safety of LPV/r or darunavir and cobicistat for treating COVID-19 pneumonia, as well as to assess the impact of long term protease inhibitors in PLHIV on the incidence of COVID-19. A list of these clinical studies is shown in Table 3.

The pre-exposure prophylaxis combination of TDF/FTC and low-dose hydroxychloroquine has been suggested in a large Spanish clinical trial for prophylaxis for COVID-19 in healthcare workers, but no specific recommendations have been proven useful. There is also no evidence that switching a patient from their usual ART would be beneficial, nor is there evidence that HIV pre-exposure prophylaxis is effective against COVID-19 [111–114].

One further matter that warrants consideration in the similarity between the two viruses is stigma. PLHIV already face significant stigma, and fear of further stigmatization may prevent them from visiting healthcare facilities for testing, treatment, and monitoring, as well as fear of COVID-19, the full impact of which on PLHIV is still unknown and will unfold over the coming months with subsequent waves.

COVID-19 vaccine... could it pave the way for an HIV vaccine?

The herd immunity threshold is defined as the percentage of the population that are required to have immunity before virus transmission declines, and for COVID-19, it is approximately 82.5% [115]. Developing a safe and effective COVID-19 vaccine is a worldwide priority to control this pandemic, where achieving herd immunity through natural infection is neither ethical nor rational. Government agencies and pharmaceutical companies have made significant efforts to develop a COVID-19 vaccine rapidly, and many vaccines are now competing to be approved for large-scaled distribution. Generally, there are different vaccine group "platforms," including the traditional attenuated or inactivated whole viruses, genetically engineered proteins, and the modern mRNA (mRNA) technique, which is the backbone of Pfizer and Moderna vaccines [116].

Table 3
List of ongoing clinical trials of antiretroviral therapy (ART).

Product	Study identifier	Study location	Study design	Primary outcome	Status of trial
Lopinavir/ritonavir versus hydroxychloroquine sulfate	NCT04307693	Korea	Phase 2, randomized controlled, open label parallel-group, multicenter study (n = 65)	Time to clinical improvement among mild COVID-19 cases through assessment of change in viral load, time to clinical improvement, and need for oxygenation	Terminated
Lopinavir/ritonavir + hydroxychloroquine sulfate	NCT04403100	Brazil	Phase 3, randomized trial, 4 arms, quadruple masking, factorial assignment (n = 1,968)	Proportion of patients who were hospitalized or died due to COVID-19	Recruiting
Lopinavir/ritonavir	NCT04321174	Canada	Phase 3, randomized trial, single blind, parallel-group (n = 1,220)	Assessment of microbiological evidence of infection	Recruiting
Darunavir/cobicistat versus lopinavir/ritonavir	NCT04425382	Qatar	Retrospective observational study (n = 200)	Time to clinical improvement, and/or virological clearance	Recruiting
Lopinavir/ritonavir	NCT04455958	United States	Phase 2, randomized , double-blinded, parallel group, placebo-controlled (n = 75)	Improvement in clinical outcome	Not yet recruiting
Favipiravir + hydroxychloroquine + lopinavir/ritonavir	NCT04376814	Islamic Republic of Iran	Non-randomized trial, parallel assignment, open-label (n = 40)	Admission to ICU and mortality	Completed
Hydroxychloroquine versus lopinavir/ritonavir	NCT04328285	France	Phase 3, randomized, double blinded, placebo-controlled, triple masking, parallel assignment (n = 1,200)	Occurrence of COVID-19 infection among healthcare workers	Active, not recruiting
Lopinavir/ritonavir	NCT04372628	United States	Phase 2, multicenter sequential randomized trial, placebo-controlled, triple masking (n = 600)	Hospitalization, mechanical ventilation, death	Recruiting
Standard care versus lopinavir/ritonavir	NCT04409483	Niger	Phase 3, randomized trial, parallel assignment, open-label	Hospitalization and mortality	Withdrawn
Lopinavir/ritonavir + hydroxychloroquine	NCT04386070	India, Ghana, Nigeria, South Africa, United Kingdom	Phase 3, randomized, four-armed, parallel assignment, open-label trial (n = 6,400)	Occurrence of postoperative pulmonary complications and death	Not yet recruiting
Azithromycin versus lopinavir/ritonavir versus hydroxychloroquine	NCT04365582	France	Phase 3, randomized trial, parallel assignment, open-label (n = 640)	Hospitalization, ICU admission, death	Suspended
Emtricitabine/tenofovir + colchicine pill + rosuvastatin	NCT04359095	Columbia	Phase 2/3, randomized trial, open label, parallel assignment (n = 1,200)	Time to ICU admission and death	Recruiting
Lopinavir/ritonavir + losartan	NCT04328012	United States	Multicenter phase 2/3, randomized, controlled trial, parallel assignment, quadruple masking, double blind (n = 4,000)	Hospital length of stay, ICU admission, mechanical ventilation, mortality	Recruiting
Lopinavir/ritonavir versus abidol hydrochloride versus oseltamivir	NCT04255017	China	Phase 4, randomized trial, parallel assignment, single masking (n = 400)	Time to remission and recovery	Recruiting
Lopinavir/ritonavir	NCT04364022	Switzerland	Phase 3, randomized trial, open-label, parallel assignment (n = 300)	Incidence and severity of COVID-19 outcomes	Recruiting
Remdesivir versus lopinavir/ritonavir + interferon beta-1A versus hydroxychloroquine	NCT04315948	Austria, Belgium, and others	Multicenter randomized trial, parallel assignment, open-label, phase 3 (n = 3,100)	Hospitalization, oxygenation, mechanical ventilation, and death	Recruiting
(Asc09/ritonavir versus lopinavir/ritonavir)	NCT04261907	Hospital of Zhejiang	Multicenter, randomized clinical	Incidence of adverse outcome, time to resolution of symptoms	Not yet recruiting

Table 3 (*continued*)

Product	Study identifier	Study location	Study design	Primary outcome	Status of trial
		University	trial, parallel assignment, open-label (n = 160)	and recovery	
Chloroquine or hydroxychloroquine versus lopinavir/ritonavir, rivaroxaban, heparin, candestartan, non-ras-blocking antihypertensive, clazakizumab	NCT04351724	Austria	Multicenter, phase 2/3 active randomized controlled trial, 3 arms, parallel assignment, open label (n = 500)	Clinical improvement	Recruiting
Wharton's jelly derived mesenchymal stem cells versus hydroxychloroquine, lopinavir/ritonavir or azithromycin	NCT04390152	Colombia	Randomized clinical trial, parallel assignment, quadruple, phase ½ (n = 40)	Intergroup mechanical ventilation, hospitalization, mortality difference	Not yet recruiting
Lopinavir/ritonavir versus corticosteroid hydroxychloroquine, azithromycin, plasma, tocilizumab, immunoglobulin versus aspirin	NCT04381936	United Kingdom	Randomized clinical trial, factorial assignment, open label, phase 2/3 (n = 20,000)	Need for hospitalization, ventilation and renal replacement therapy	Recruiting
Hydroxychloroquine + lopinavir/ritonavir + interferon beta-1A + interferon beta-1B	NCT04343768	Islamic Republic of Iran	Phase 2, randomized trial, parallel assignment, 3 arms, open-label (n = 60)	Time to clinical improvement and mortality	Completed
Lopinavir/ritonavir + ribavirin + interferon beta-1B	NCT04276688	Hong Kong	Phase 2, randomized controlled trial, parallel assignment, open-label (n = 127)	Time to clinical improvement	Completed
Emtricitabine/tenofovir disoproxil + hydroxychloroquine	NCT04334928	Spain	Phase 3, randomized double-blind trial, parallel assignment (n = 4,000)	Number and severity of confirmed COVID-19 cases	Recruiting
Tenofovir alafenamide	NCT04405271	Argentina	Phase 3, randomized, double-blind, placebo-controlled, parallel assignment, quadruple masking (n = 1,378)	Incidence and severity of COVID-19	Not yet recruiting
Darunavir/cobicistat	NCT04252274	China	Phase 3, randomized trial, open label, parallel assignment (n = 30)	Virological clearance rate and mortality	Recruiting
Favipiravir versus lopinavir/ritonavir	NCT04499677	United Kingdom	Phase 2, randomized trial, double-blind, 2*2 factorial placebo-controlled, triple masking (n = 240)	Virological clearance of COVID-19, ICU admission and deaths	Recruiting
Lopinavir/ritonavir + telmisartan + atorvastatin	NCT04466241	Côte d'ivoire	Phase 2/3, multicenter randomized trial, open-label, parallel assignment (n = 294)	Clinical recovery, mortality	Not yet recruiting
Umifenovir + interferon-β 1A + lopinavir/ritonavir + hydroxychloroquine	NCT04350684	Iran	Phase 4, randomized trial, parallel assignment, double-blind, placebo-controlled (n = 40)	Time to clinical improvement, hospitalization ventilation, mortality	Enrolling by invitation
Hydroxychloroquine versus lopinavir/ritonavir versus convalescent plasma	NCT04483960	Australia	Phase 3, multicenter randomized trial, factorial assignment, open-label (n = 2,400)	Survival rate, length of hospital stay, ICU admission, and ventilation	Recruiting
Ascorbic acid, hydroxychloroquine sulfate, azithromycin, folic acid versus lopinavir/ritonavir	NCT04354428	United States	Phase 2/3, randomized, multi-center, parallel assignment, double masking (n = 300)	Change in viral shedding, incidence of hospitalization or mortality	Active, not recruiting
Hydroxychloroquine + azithromycin + ritonavir + lopinavir	NCT04459702	United States	Phase 2, randomized controlled trial, parallel assignment, double masking (n = 200)	Efficacy and safety of treatment via reduction of COVID-19 symptoms	Not yet recruiting
Lopinavir/ritonavir, hydroxychloroquine, azithromycin, piperacillin/tazobactam, heparin, corticosteroid injection, tocilizumab	NCT04394182	Spain	Single group assignment, open label, multicenter clinical trial (n = 15)	Oxygen saturation status	Recruiting
Ivermectin versus hydroxychloroquine + darunavir/ritonavir	NCT04435587	Thailand	Phase 4, randomized trial, parallel assignment, single masking (n = 80)	Incidence of adverse events, efficacy for shortening the duration of detection by PCR	Not yet recruiting
Oseltamivir, hydroxychloroquine, darunavir/ritonavir, lopinavir/ritonavir, favipiravir, chloroquine	NCT04303299	Thailand	Phase 3, multicenter, randomized trial, open label, parallel	Time to COVID-19 eradication, death	Recruiting

Table 3 (continued)

Product	Study identifier	Study location	Study design	Primary outcome	Status of trial
Tenofovir/emtricitabine	NCT04519125	Colombia	assignment (n = 320) Phase 2/3, randomized trial, triple masking, parallel assignment (n = 950)	Incidence of COVID-19 infection and occurrence of adverse events	Not yet recruiting

Both HIV and COVID-19 pandemics represent considerable global burden, leading to devastating effects, a high death rate (especially in middle- and low-income countries), and the need for an effective cure and vaccine, at least until recently, when the Pfizer and Moderna vaccines were approved for COVID for Emergency Use Authorization [117]. Therefore, one of the major goals of combating HIV disease is the development of effective and safe vaccines blocking HIV-1 infection. Following on from the success achieved in the development of COVID-19 vaccines, it may now be possible, after 30 years of active HIV research and vaccine trials, to have a licensed HIV vaccine available.

Conclusions

COVID-19 has had a devastating impact across the globe; however, its impact on PLHIV is still unclear and will continue to unfold over the coming months. The structural and immunological similarities between the two viruses, particularly their GI manifestations, have provided insights about how COVID-19 may impact PLHIV, and the rationale behind suggesting the use of ARTs for COVID-19 treatment and prevention. It is also reasonable to pay close attention to COVID-19 in patients presenting for endoscopy for HIV and to follow the suggested infection control interventions.

The stigma against both viruses, as a shared barrier to care, can impact health systems and this is likely to be particularly obvious in low- and middle-income countries. The great success achieved in the rapid development of the COVID-19 vaccine provides a certain level of optimism regarding the research and development of an HIV vaccine in the near future.

Competing interests

AV has received research institutional grants from Gilead Sciences, travel grants from Gilead Sciences and Janssen-Cilag, speaker's honoraria from Janssen-Cilag and MSD, GE is a speaker, advisory board member and investigator for Gilead Science, GSK and AbbVie. MM reports grants from USAID, grants from Unitaid, personal fees from Gilead Sciences, AbbVie, Cipla, Johnson and Johnson, Sanofi, Pfizer, ViiV Healthcare, Mylan and Southern African HIV Clinicians Society, other from Johnson and Johnson, BD, Gilead, Merck, Cipla, Mylan and Canopy Growth, outside the submitted work.

Authors' contributions

AC, GE, SM, were responsible for the study concept, design and implementation; SO and MA were responsible for the study execution; AC and MA were responsible for the data collection, AV, MM, were responsible for the data verification; YG, MM, KB, SA, MK, MC, MA, AV and AC are responsible for medical writing; all authors critically reviewed and approved the manuscript.

List of abbreviations

- ACE: Angiotensin-converting enzyme

- ART: Antiretroviral
- COVID-19: Coronavirus Disease 2019
- FTC: Emtricitabine
- EGD: Esophagogastroduodenoscopy
- IL: Interleukin
- IQR: Interquartile Range
- LPV/r: Lopinavir/ritonavir
- NNRTI: Non-nucleoside reverse transcriptase inhibitor
- NRTI: Nucleoside reverse transcriptase inhibitors
- PLHIV: People living with HIV
- RT: Reverse transcription
- SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
- SD: Standard deviation
- TDF: Tenofovir disoproxil fumarate

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