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People Living with HIV and Neurocysticercosis Presenting Covid-19: A Systematic Review and Crosstalk Proposals

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Abstract

Background: Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) is associated with the risk of death due to Coronavirus Disease 19 (COVID-19) which is undefined. Therefore, we aimed to investigate this comorbidity in a large-scale population-based study to identify the relationship with the risk of mortality among People Living With HIV/AIDS (PLWHA) presenting COVID-19 and Neurocysticercosis (NCC), which is largely unknown. Based on the previous background information, we identify three research questions: 1. How often the comorbidity of HIV/NCC/COVID has been reported in the medical literature? 2. What is the most typical clinical presentation of this comorbidity? 3. What is the most probable pathogenesis of this comorbidity and its consequences?

Method: A systematic review of COVID-19/HIV/AIDS/NCC publications written in English, Spanish, and Portuguese was performed to answer the first research questions. We included case reports, case series, observational cohort studies, systematic review and meta-analysis, cross-sectional studies, and clinical trials on the comorbidity of NCC/HIV/AIDS/COVID-19. During the initial search, we looked for all articles published between December 1, 2019 and October 31, 2021.

Results: From searched retrospective cohort studies, case reports, case series and case-control studies, we found a total of 905, 620 PLWHA infected by SARS-CoV-2 cases with reported clinical presentations. The commonest clinical manifestations of HIV patients infected by SARS-CoV-2 were fever (n:690-994, 76.3%). tiredness (n:595-903, 65.8%), dry cough (n:537-037, 59.3%), headache (n418-021, 46.15%), ashes/pain (n:153-145, 16.8%), diarrhea (n:129-504, 14.3 %), sore throat (n:85-129, 14.3%).

Comments: No case report/case series on PLWHAN and associated COVID-19 has been reported, and no other analysis of this comorbidity has been published. We have hypothesized a novel mechanism for this comorbidity based on novel combinations of pro and anti-inflammatory elements aggravated by an increased capacity of viral replication and transmission, sustainable stress due to prolonged pandemic leading to a decreased immunological response.

Conclusion: We recommend a mandatory plan to vaccinate all PLWHA as a matter of maxima priority and do not prescribe anti-parasitic medication for cysticercosis for PLWHA on the risk of being infected SARS-CoV-2.

Keywords: COVID-19 • HIV • AIDS • Meta-analysis • PLWHAN • NEURO-COVID-19

Abbreviations: AC-1: Activate Caspase-1; BD: Brainstem Dysfunction; BVEMF: Binding and Viral Entry (Membrane Fusion); C: Cytoplasm; CAM: Cell Adhesion Molecules; CCC2-3: Chemokine C-C Motif Ligands 2 and 3; CRS: Cytokine Release Syndrome; Dy: Dysbiosis; E: Epilepsy; ES: Epileptic Seizure; SE: Status Epilepticus; DNAv: Deoxyribonucleic Acid Viral; IFN-γ: Interferon Gamma; IL: Interleukin, G-CSF: Granulocyte Colony-Stimulating Factor; LC: Long COVID-19; RT: Reverse Transcriptase; HPAaa: Hypothalamic-Pituitary-Adrenal Axis Activation; RNAp: Ribonucleic Acid Polymerase; RNAg: Ribonucleic Acid Genome; R: Ribosome, MSOF: Multi-System Organ Failure; NA: Neuro-AIDS; NC: Neuro-COVID-19; ND: Neurotransmitters Disorder; NVC: New Virus Copy; ORFx: Open Reading Frames (a,b,3,6,7a,7b,8,10); PIE: Pro-Inflammatory Enzymes; PE: Prostaglandin-Ethanolamides; RNAr: Ribonucleic Acid Replication; CA: Cell Apoptosis; IE: Inflammatory Environment; HEIF16: High Expression of IF16; VI: Viral Integrase; TNFα: Tumour Necrosing Alpha; IL-1β: Interleukin 1-beta; TSC: Taenia Solium Cysticercosis; A/M A: Astrocytes/Microglia Activation; B: Bacteroidetes; DNA: Deoxyribonucleic Acid Viral; F: Firmicutes; HEIF16: High Expression of IF16; IFN-γ: Interferon-Gamma; TYMP: Thymidine Phosphorylase; VEGF-A: Vascular Endothelial Growth Factor-A.

Introduction

An increasing number of Coronaviruses 19 (COVID-19) patients worldwide will elevate the frequency of comorbidities with a broad spectrum of combinations of viral, bacterial, and parasitic diseases. Neurocysticercosis (NCC) and Human Immunodeficiency Virus (HIV) are pretty common in several places; therefore, its association with SARS-CoV-2 infection is not surprising. Unfortunately, insufficient information on patients living with HIV/AIDS and NCC (PLWHAN) and COVID-19 motivated us to investigate this issue.

At the beginning of the COVID-19 pandemic, the presence of SARS-CoV-2 in patients living with HIV/AIDS (PLWHA) was documented, and the first case was reported in Wuhan in January 2020, followed by other subsequent reports from Barcelona (5 cases), Madrid (51 patients), Italy (47 cases) and Rode Island (27 patients) on March, April, and July respectively [1-5]. At this time, those PLWHA on HAART infected by SARS-CoV-2 reported by the Italian authors had better clinical outcomes than another COVID-19 patient with no HIV/AIDS [4], while other authors found more comorbidities in PLWHA and SARS-CoV-2 co-infection [2,3].

As a piece of general information has been reported that PLWHA and COVID-19 did not differ remarkably in clinical manifestations, blood test results and imagenology from the group of patients presenting SARS-CoV.2 infection alone, but it has been confirmed that the first group has a higher rate of illness severity and worse outcome [6], including higher risks of cardiomyopathies and heart failure and cardiomyopathies [7,8], chronic renal disorders [9,10], recurrent exacerbations of chronic obstructive pulmonary disease [11,12]. Some authors highlight that PLWHA, when infected by SARS-CoV-2, may have severe COVID-19 independently of HAART, while others denied it [13]. On the other hand, some authors based on systematic review and meta-analysis also confirm that there is no remarkable impact on COVID-19 mortality between a group of PLWHA and a group of non-HIV/AIDS patients infected by SARS-CoV-2 [RR 0.99 (95% CI 0.82–1.19)] [14]. Nevertheless, a higher risk of COVID-19 mortality has been found in PLWHA [HR 1.95 (95% CI 1.62–2.34)], compared with the general population [15]. Without a doubt, PLWHA and COVID-19 in the UK have a high mortality rate [16]. Two postulations have been supported

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before and after by other authors [17,18]. Probable, those PLWHV and COVID-19 not had a poor prognosis because of Antiretroviral Treatment (ARTs) such as Tenofovir, Emtricitabine, Raltegravir, and Dolutegravir, which can reduce SARS-CoV-2 proliferation, as has been proved *in vivo* [19-22]. Furthermore, Tenofovir disoproxil fumarate therapy provides a better clinical outcome in PLWHA infected by SARS-CoV-2 than other ARVs [23]. On top of that, almost all studies were done in developed countries where most of the patients had easy access to ARVs and good national HIV/AIDS health programmes, fewer economic restrictions, and better facilities to manage COVID-19 cases [24]. It has been demonstrated that around two-thirds of PLWHA co-infected by SARS-CoV-2 presented multimorbid complications [25].

Correlation among comorbidities and COVID-19 has been in focus recently . It is reported that approximately 2/3 of COVID-19 co-infected PLWHA had multimorbid complications. In PLWHA, we can see comorbidities like diabetes mellitus, chronic heart disease, and chronic renal disease, among others, which can aggravate COVID-19, and some authors report the highest incidence of COVID-19 in this group [26], although these results have been denied by others [27]. Again, poor HIV management seen in impoverished countries contributes to the frequency of poor outcomes, including mental well-being or fatal COVID-19 [28,29]. Unfortunately, it is still not clear-cut the fundamental relationship between poor outcome COVID-19 and viral load, CD4 level, adequate ARTs in different settings of PLWAH.

Neurocysticercosis is a zoonotic disease secondary to the infection of the central nervous system by the cysticercus' larval stage infection (Cysticercus cellulose) of the pig tapeworm, *Taenia solium* (Ts). The presence of secondary epilepsy in a person living in or visiting a region where Ts is endemic or even in close contact with people who have taeniosis should suggest a diagnosis of NCC. This pathological disorder may remain asymptomatic for months or even years until the diagnosis is confirmed when performing neuroimaging studies. Symptoms and signs are related to the parasite, which can vary from one country to another and the host's inflammatory-immunological response [30-32]. This parasite is transmitted among humans and between humans and pigs. Taeniosis is acquired only by humans after eating raw or undercooked pork meat contaminated with cysticerci, the parasite's larval form. When ingested, the cysticerci migrate to the human intestine, becoming a mature parasite (Taeniosis). These adult worms shed eggs through human faeces that can infect other humans and pigs through direct ingestion or indirect water and food contamination. In developing countries, pigs are often allowed to roam freely, and they can eat human faeces containing eggs or proglottids of Ts. Ingested eggs result in larvae migrating to different parts of the pig or the developing human cysticercosis. A leading migration site in humans is the CNS (brain parenchymal, brainstem, spinal cord, and optic nerve). Epilepsy is NCC's most common clinical manifestation, affecting 66% to 90% of cases [30]. Recently, we studied the clinical manifestations, pathophysiology, management, and complication of the comorbidity of NCC/COVID-19, and we concluded that low or delayed immune responses allow massive dissemination of SARS-CoV-2, leading to hyperinflammatory states and a long list of complications including brainstem dysfunction, massive pneumonia, dysbiosis, and death among others [31].

Now nobody has an idea when this pandemic will end. Nobody knows how many mutations the current SARS-CoV-2 will have. Nobody knows what the consequences of forthcoming comorbidities are going to be. In our opinion, nobody will be able to predict what will happen with the world population because of the complexity of our planet.

Today the Delta variant of SARS-CoV-2 predominate all around the world. However, because the virus continues affording different immunological scenarios from millions of people with dysregulated immune systems worldwide, the virus needs to keep its vital capacity for replication under several immunocompromised conditions like diabetes mellitus, tuberculosis, HIV/AIDS and NCC, which are pretty standard in low incomes countries with inferior health educational programme, with inadequate infrastructure for sanitation, and even miserable living condition and meagre percentage of complete vaccination. The virus is forced to mutate infinitely. Therefore, a part of the new arriving variant (Omicron) probably other variants will arrive if the whole population is not vaccinated with safe and accurate vaccines. Fortunately, many developing countries have the capacity (transparency) to inform other communities about these new mutations at due time.

Based on the previous background information, we identify three research questions: 1. How often the comorbidity of HIV/NCC/COVID has been reported in the medical literature? 2. What is the most typical clinical presentation of this comorbidity? 3. What is the most probable pathogenesis of this comorbidity and its consequences?

Materials and Methods

A systematic review of COVID-19/HIV/AIDS/NCC publications written in English, Spanish, and Portuguese was performed to answer the first research questions.

Literature search strategy

We included case reports, case series, observational cohort studies, systematic review and meta-analysis, cross-sectional studies and clinical trials on the comorbidity of NCC/HIV/AIDS/COVID-19. During the initial search, we looked for all articles published between December 1, 2019, and October 31, 2021. We search the following databases: Medline EMBASE, Scopus online databases, Google Scholar, Science Direct, Scielo, LILACS, BIREME, Search of Sciences, BioRxiv, medRxiv and Cochrane library. Studies were retrieved using MeSH-derived topical terms and Medical Subject Headings (MeSH).

All items about "COVID-19" OR "2019 coronavirus disease" OR "COVID-19" OR "COVID pandemic" OR "SARS-CoV-2 infection" OR "COVID-19 virus disease" OR "2019 novel coronavirus infection" OR "neuro-COVID" OR "2019-CoV infection" OR "coronavirus disease 2019" OR "2019-nCoV disease" OR "COVID-19 virus infection") Moreover, ("HIV" OR "Human Immunodeficiency Virus*" OR "Human T Cell Lymphotropic Virus Type III" OR "Human T-Cell Leukaemia Virus Type III" OR "LAV-HTLV-III" OR "Lymphadenopathy-Associated Virus*" OR "Human T Lymphotropic Virus Type III" OR "AIDS Virus*" OR "Acquired Immunodeficiency* Syndrome Virus" OR "HTLV-III" where * is the PubMed Central wild card for every possible word beginning or ending. We did not include other clinical manifestations beyond the current work scope. Articles published after October 31, 2021 was not included in this review.

Study and cohort selection

We select prospectively, and retrospective cohort studies, case reports, case series, case-control studies, controlled clinical trials, review and meta-analysis reported data on COVID-19/HIV/AIDS/NCC, clinical features, therapy and outcome.

Risk of bias of individual studies: We applied the Joanna Briggs Institute checklist for the case series [32] for the quality assessment of the case series rating the quality of selection, measurement, and comparability of studies from 0 to 10. We selected case series and cohort studies for assessing the risk of bias. Moreover, the average score for included studies was six points out of nine (between 5 and 9 individually). The cases series was 9/10 because these studies did not report demographic features and the follow-up. Biases for cohort studies were assessed using the Newcastle–Ottawa Scale (NOS), which included outcome reporting bias, comparability issues, and ratings of selection bias [33]. Another collaborator assessed the risk of bias for each study independently, but finally, Lourdes de Fatima Ibanez Valdes was not listed as co-author due to new regulations of the Department of Research for a non-staff member of this University. All disagreements were resolved through analytical discussions before reaching a final consensus. The disadvantages of case-series studies were improperly reporting of participant recruitment, their demographic presentation, and a short time for follow-up duration and the recruitment methodology was not confident.

Results

After the first searching process, found 44 eligible publications, 14 of which were cohort, 10 were case series, 2 case reports and nine systematic reviews and meta-analyses on Medline, Scopus, and EMBASSY. Three hundred fourteen thousand three hundred fifty-five patients with COVID-19 were identified (12-901 PLWHA *vs*. 301-454 non-PLWHA). Meta-analyses established the prevalence and mortality rate of COVID-19 in PLWHA was 0.914% [95% Confidence Interval (CI) 0.00451–0.01819] and 12.169% (95% CI 0.06061–0.5428 respectively. COVID-19 co-infected PLWHA seem to be associated with a high mortality rate, as compared to non-PLWHA [relative risk (RR) 0.13 (95% CI 0.91–1.01)].We found a number of comorbidities such as hypertension and chronic cardiac disease, RR: 5.1 (95% CI 0.96–12.01), diabetes mellitus, RR: 7.4 (95% CI 5.65–7.91), chronic renal disorders, RR: 9.03 (95% CI 6.19–13.20), and an associated increase mortality rate in PLWHA co-infected by SARS-CoV-2. From searched retrospective cohort studies, case reports, case series, and case-control studies, we found 905-620 PLWHA infected by SARS-CoV-2 cases with reported clinical presentations. The commonest clinical manifestations of HIV patients infected by SARS-CoV-2 were fever (n:690 994, 76.3%). tiredness (n:595 903, 65.8%), dry cough (n:537 037, 59.3%), headache (n418 021, 46.15%), ashes/pain (n:153 at the prevalence of COVID-19 in PLWHA and its mortality (n:129 504, 14.3%), sore throat (n:85 129.14.3%) (Figure 1). The total percentage of epileptic patients identified was very low because only anecdotal COVID-19 patients who presented epileptic seizures were found, and no NCC cases were included in those reports.

Study selection

This study aims rate. Three thousand five hundred seven manuscripts were retrieved from electronic databases until October 30, 2021. After removing irrelevancy and duplicates, 1429 articles were taken for full-text screening, and, finally, 64 studies providing outcomes information were included for review [34-47]. Of these included studies, 11 were peer-reviewed; a PRISMA flow chart for the literature search is shown below Figure 1.

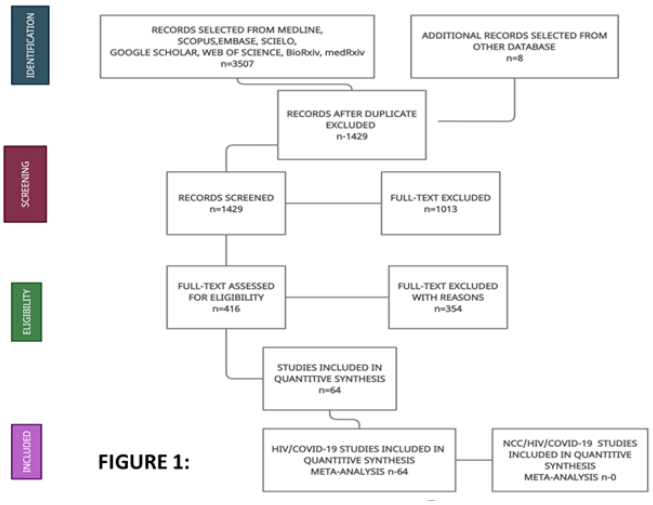

Figure 1. Flow diagram of included publications.

Study findings

Thirteen studies were of cohort design and eight case series were identified [37,39,42,46,47]. Unfortunately, one cohort study used matched population design when comparing PLWHA and non-PLWHA [44]. Seven of the studies were conducted in European countries (UK [41], Italy [37,43], Spain [36], France [40], Germany [41], and Central/East European countries [42]. The others publication released came from Asia (China [5]), Africa (Western Cape [34]), North America (United States [39, 44-46], and South America (Chile [38]). Only, four of the cohort studies used a mass database (provincial/national) for population recruitment [34,35,41,45], another two had a multi-center involvement [36,38], and three studies had a single-center involvement [40,43,44]. Also only, four out of the five case series were of a multicentre design [37,39,42,47]. In a published systematic review [48], these authors found another three were case series and four case reports, with 16 reported patients. The rest of included cases were extracted from systematic reviews and meta-analyses. One case died, whereas (15/16) patients were discharged home, but they did not find other observational or interventional clinical studies or systematic reviews of similar scope.

Based on the results from seven cohort studies, other investigators reported an incidence proportion of COVID-19 among PLHIV as 0.9% (95% CI 0.6%, 1.1%), among them 28.4% of cases were hospitalized, 2.5% were critically ill, and 3.5% needed intensive care management. The overall mortality rate was 5.3%, and the most common comorbidity was arterial hypertension (24.0%) [49]. In South Africa, Boullet and collaborators found that tuberculosis and HIV were independently associated with elevated COVID-19 mortality rates [50]. On the other hand, Liang, et al. from meta-analysis estimation of prevalence and mortality rate of COVID-19 in PLWHA confirmed 0.774% [95% confidence interval (CI) 0.00393–0.01517] and 8.814% (95% CI 0.05766–0.13245) respectively. However, associated hypertension and chronic cardiac disease, RR: 4.2 (95% CI 1.09–16.10), chronic renal disease, RR: 8.43 (95% CI 5.49–12.93), and diabetes mellitus, RR: 5.2 (95% CI 4.25–6.36), were associated with a high mortality rate in COVID-19 co-infected PLWHA [51]. One cohort study made from March 1 to June 7, 2020, in New York State reported 108-062 PLWHA, among of them, 2988 (2109 men [70.6%]; 2409 living in New York City [80.6%]; mean [SD] age, 54.0 [13.3] years) a diagnosis of COVID-19 was confirmed at a rate of 27.7 per 1000, which was higher than among non-HIV/AIDS persons (rate, 19.4 per 1000; RR, 1.43 [95% CI, 1.38-1.48]) concluding that PLWHA leads poorer COVID-related outcomes compare to cases living without HIV/AIDS/COVID-19, and it also increases a risk of HIV stage worsening progression [52].

Other investigators found that the median age of cases was 56 years on average, 66.0% of patients were male, and the most common comorbidities were hypertension, diabetes, chronic obstructive pulmonary disease and chronic renal. On the other hand, a remarkably higher risk of SARS-CoV-2 infection (RR: 1.24, 95% CI 1.05–1.46; Fig. 2) was also confirmed. Between-study variation was elevated (I2=85, p=0.0003). The pooled prevalence of PLWHA and COVID-19 patients was 1.22% (95% CI 0.61–2.43%; I2=98%; p<0•01). In this study, the prevalence of PLWHA and COVID-19 patients ranged from a low level in Catalonia (Spain) of 0.26% (95% CI 0.23–0.29%) to a high level in Seattle (USA) of 4.17% (95% CI 0.58–24.35%) [53].

Some authors from Poland analysed 82 patients with the SARS-CoV-2 infection, hospitalized from May 5 to December 2, 2020, plus 31 patients with a required course of COVID-19 hospitalized in ICU and the male cases comprised 65% of the ICU patients. The most common comorbidity was arterial hypertension and diabetes mellitus type 2, the only comorbidity with a remarkably higher prevalence in critical COVID-19 cases (p=0.039). In this study, the mortality rates were significantly higher in the ICU COVID-19 patients than in non-ICU COVID-19 patients (77% and 8%, respectively). These investigators also demonstrated that the IL-2/INFγ ratio is exceptionally high in the critically ill COVID-19 patients (p<0.001 and p=0.007, respectively). Finally, they established that the IL-2/INFγratio above the cut-off value of 0.09 is the best marker of T cell activity which is significantly higher in the COVID-19 patients with fatal outcomes (p<0.001) [54]. A group of investigators from Rome conducted a cross-sectional study on 1389 stored cryopreserved samples from 1106 PLWHA between March 1, 2020, and November 30, 2020. Sixty-nine per cent of cases were males with median age 53 years, 94% on antiretroviral treatment, 93% with HIV-RNA<50 copies/mL, and median CD4 cell count 610 cell/μL. These authors found an overall seroprevalence of 0.72% (8/1106, 95% CI 0.37–1.42) and concluded that IgG SARS-CoV-2 prevalence among PLWH is low compared with the general population [55].

Nasreddine and colleagues described the clinical characteristics and outcomes of PLWHA and COVID-19 in Belgium. Overall, 9% of patients died, while 77% of patients made a full recovery. PLWHA with COVID-19

presented a high degree of hospitalization despite having high CD4+ cell counts level and a high rate of virologic suppression. The age average median age was 51.3 years (IQR 41.3–57.3), and many patients were female (44%). The most frequent comorbidities were hypertension (34%), diabetes mellitus (13%), and dyslipidaemia (13%), and 25% of cases had more than or equal to two comorbidities [56]. This year, Dong, et al. conducted a meta-analysis study with 18,122,370 COVID-19 patients from ten publications to estimate the association of PLWAH and the risk of COVID-19 mortality and their pooled overall effect size (OR) finding was 1.252 (95% CI 1.027–1.524, Z=2.22, p=0.026<0.05) confirming that PLWHA had a higher risk of mortality from COVID-19 than those non-HIV cases (OR=1.252, 95% CI 1.027–1.524) [57].

Ambrosio and collaborators reported a recent large study confirming that PLWHA with untreated HIV infection or low CD4 counts might have a more severe COVID-19 clinical course than those who non-HIV [58]. Recently, Bhaskaran et al. performed a population-based cohort study of United Kingdom primary care data linked national death registrations and found 17-282, 905 cases of whom 27-480 (0.16%) were PLWHA commonly Black male peoples with Hazard Ratio (HR) 4.31 (95% CI 2.42–7.65) versus 1.84 (1.03–3.26) in non-Black individuals (p-interaction=0.044), living in more disadvantage geographical areas than the general population. Among these cases, 14-882 COVID-19 died, confirming once again that PLWHA have a higher risk of COVID-19 death compared with those non-HIV with a Hazard Ratio (HR) 2.90 (95% CI 1.96–4.30; p<0.0001) [59]

The overall number of patients and the percentage of clinical manifestations found in searched publications reporting this available data are graphically shown in Figure 2. In this graphic, fever, tiredness, dry cough short of breath was the most familiar manifestations observed, but because NCC cases were not included, then the absence of seizures disorder is evident. These findings are the answer to the second research question. Looking for the prevalence of COVID-19 in PLWHA, we found other studies with 757,103 cases and for fourteen publications reporting a total of 5626 cases [34-48]. Six studies with 5,090 PLWHA and 195,812 non-PLWHA patients were included in determining the mortality rate by SARS-CoV-2 infection between PLWHA and non-HIV patients.

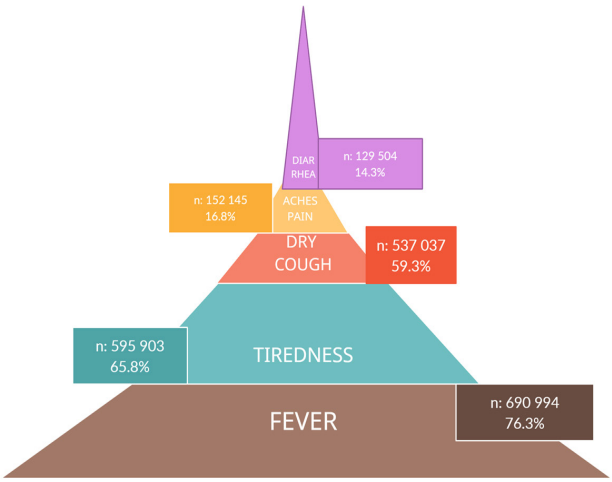

Figure 2. Graphic representation of the most common clinical manifestation of COVID-19 in PLWHA reported in the medical literature.

On top of those publications, another four studies delivered comorbidities data among PLWHA and non-HIV patients, which allow us to compare the risk of SARS-CoV-2 co-infection based on various comorbidities in the two groups. Unfortunately, only two studies reported data on HIV viral load and CD4 count before/during hospitalization between COVID-19 patients and non-COVID-19-infected PLWHA [35,43]. However, because the published data of these two groups were not standardized, this led to the infeasibility of distinguish the role of either of the two crucial factors in the risk of SARS-CoV-2 co-infection in this population.

Meta-analysis

Primary outcome: The results found on the mortality rate and prevalence of PLWHA infected by SARS-CoV-2 were interesting. The pooled prevalence of co-infection with COVID-19 in PLWHA from the six selected publications was 0.774% (95% CI 0.00393–0.01517). Looking for the level of mortality of COVID-19 in PLWHA and associated COVID-19, pooled results from fourteen studies showed a rate of 8.814% (95% CI 0.05766–0.13245) [46]. Nevertheless, these authors arrived at their conclusions based on single studies, and only scarce systematic reviews and meta-analyses estimated the odds comprehensively and quantitatively. On the other hand, some authors made a separate systematic review and meta-analysis reporting a prevalence and mortality rate of 1.22% and 12.35%, respectively, in PLWHA/COVID-19. The last study was not published, but it can be found at the following address: Sentongo, Heilbrunn, Ssentongo, Advani, et al. "Prevalence of HIV in patients hospitalized for COVID-19 and: a systematic review and meta-analysis". MedRxiv.2020:2020.07.03.20143628. doi: 10.1101/2020.07.03. 20143628. We did not find publications concerning NCC/COVID-19/HIV/AIDS in our searching process, as shown in the PRISMA flow chart Figure 1.

Discussion

No case report/case series on PLWHAN and associated COVID-19 has been reported, and no other analysis of this comorbidity has been published. Therefore, we could not respond to the first research question regarding how often the association of NCC/SARS is-CoC-2/HIV/AIDS is, concluding that it is the first publication related to this issue.

Today (December 03, 2021) the number of people infected by SARS-CoV-2 is 264,709,360 worldwide with 5,240,453 deaths [60]. The World Health Organization reported an estimated 2.5–8.3 million cases of NCC every year with a disability-adjusted life year burden of 2.8 million approximately (the values of prevalent neglected tropical diseases are always underestimated) [61]. Globally, there are more than 38 million PLWHA, and more than 68% are from Sub-Saharan Africa, and they are not on HARRT. Untreated HIV patients may cause CD4 lymphocytopenia leading to chronic inflammation due to immune dysfunction [62,63]. On the other hand, leukopenia is a hallmark of severe course of COVID-19, and a low level of lymphocytes is a predictor factor to higher mortality rate due to impairment of both adaptive and innate immunity [64-69]. As before-mentioned, there is no available information on the effect of NCC, HIV and COVID-19 on clinical features, management, or morbid-mortality rate in the world populations. As a result of this comorbidity, other clinical disorders, complications and death may result. Unfortunately, we did not find accurate information published in the medical literature based on this topic. Therefore, below we will deliver our hypotheses on the pathogenesis of this process, trying to answer the last research question.

The dysregulation of the innate and adaptive responses to SARS-CoV-2 have a remarkable impact on the clinical outcome of COVID-19 and its mortality rate. In an investigation made with two weeks admitted COVID-19 patients for analyzing the T cell subset with Treg cells, TCRα/β and γ/δ, B cells, and NK cells, the authors confirmed marked reductions in leukocytes subpopulations, especially in those critically ill and diminished levels of Th, Ts cells, Treg cells (both naïve and induced), TCR α/β and γ/δ cells. On top of that, +CD16+CD56+NK cells and secreted cytokines were reduced more in critically ill patients than non-critically ill COVID-19 cases [54]. As we mentioned before, the role played by the IL-2/INFγ ratio to confirm bad prognosis/fatal outcomes is mandatory. The levels of TCRα/β and TCRγ/δ were decreased in moderate and critical levels of COVID-19 cases; the levels of both populations were significantly lower in the ICU COVID-19 patients (both p<0.001) [54].

Apart from the well know structural proteins (N, S, M) of the coronavirus, it is essential to highlight the role of the non-structural eight open reading frames (ORF1a, ORF1b, ORF3, ORF6, ORF7a, ORF7b, ORF8 and ORF10)

encoding the RNA, able to induce apoptosis as has been shown in Figure 3. The cytokine release syndrome observed in SARS-CoV-2 infections is quite similar to the significant release of cytokine seen in NCC patients characterized by increased production of pro-inflammatory elements such as IL-1B, IL-1RA, IL-7, IL-8, IL-9, IL-10, basic FGF, GCSF, GMCSF, IFN-y, IP-10, MCP-1, MIP 1-a, MIP 1-B, PDGF, TNF-a and VEGF [31]. As hypothesized, there is little interaction among all those elements produced by NCC, HIV/AIDS, and SARS-CoV-2 independently.

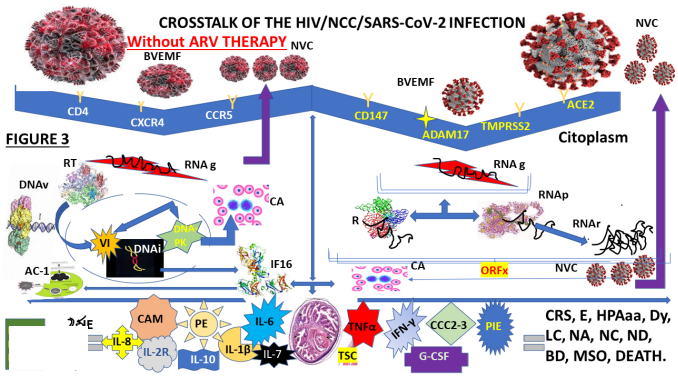

Figure 3. Crosstalk of the infection mechanism of NCC, HIV/AIDS, COVID-19.

The first experience in Wuhan has documented higher levels of IL-2, IL-7, IL-10, GCSF, IP-10, MCP-1, MIP 1-a and TNFα in critically ill Covid-19 patients compared with mild/moderate cases [54,70]. This cytokine storm by itself and loss of ACE2 contributes to multiple systems organ failures in severe cases [71]. This complicated picture is even worse in PLWHA because of the associated process of T lymphocyte exhaustion and its closed relationship with the progression of HIV patients.

Other investigators studied the T cell profile, cytokine dynamics and the role of exhausted lymphocytes performing immunological cell blood analyses after measuring INFγ IL-2, IL-10, and TNFα and TGFβ levels with ELISA kits from Protein Contour [72]. These authors found an increased IL-10 and TGFβ serum concentrations plus a rapid augmentation of the process of T-cell exhaustion. It was seen in PLWHA, and COVID-19 and this T cell degradation were mainly identified in untreated HIV patients. Nevertheless, the same author reported a decreasing $CD4^+/CD8^+$ cell and Th1/Th2 cell ratios typically seen in HIV progression accompanied by a surge in exhausted T cell count associated with simultaneous aggravation COVID-19-related respiratory complications. SARS-CoV-2 accelerate of T cell exhaustion mechanism by diminishing the capability of T cells to produce enough INFγ, IL-2, and TNFα or even completely interrupted because it is well known that exhausted T cells lose their ability to produce INFγ, IL-2, and TNFα during the process exhaustion. In the beginning, T cells stop producing IL-2, followed by slow synthesizing of TNFα and finally interrupting INFγ fully. Recent evidence proves that HIV/SARS-CoV-2 co-infection rise the process of T cell exhaustion [72], and increased concentrations of the immunosuppressive cytokines IL-10 and TGFβ in serum cause T cell exhaustion augmentation further [73]. Fortunately, it was convincingly documented in PLWH [74]. If comorbidity co-exists, this process will be extensive and prolonged with unfortunate consequences. Therefore, untreated PLWH will have very bad comorbidity of SARS-CoV-2 infection; the immunity of PLWHAN on HAART is not affected by SARS-CoV-2, and HIV-1 and SARS-CoV-2 have a synergic effect. Nevertheless, exhausted T lymphocyte dynamics may be an accurate biomarker [72].

In PLWHANC, the AIDS-defining events start from the cut-off from CD4 count below 200 l/μl, and it has characterized by recurrent viral, fungal, bacterial, or protozoan pneumonia, mainly the Histoplasma capsulatum-related disease, Pneumocystis carinii-associated pneumonia, plus *Moraxella catarrhalis* and *Legionella pneumophila* as well. In such cases (NCC/HIV/COVID-19), the occurrence of AIDS-defining events is quite frequent compared with non-HIV cases, and the mortality rate is even higher [72].

Finally, we agreed with those authors who consider that HIV infection is not an independent risk factor for being infected by SARA-CoV-2 [72-75] if that PLWH are appropriately treated with ARV medications and are virologically suppressed, with $CD4^+$ lymphocyte count higher than 500 l/μl and less than 50 copies per millilitre of viral load in serum, and if they ARV treatment is not discontinued for two months or more during lockdown period, pharmaceutical supply chain disruptions or other impediments. In addition, most of the postulates before-mentioned have been validated by other authors previously [76-102].

Hypotheses on Crosstalk of NCC/HIV/AIDS/Omicron SARS-CoV-2

All previous investigations on alpha, beta, and delta variants of SARS-CoV-2 were done. In those cases, neurological manifestations of COVID-19 like anosmia and ageusia were related to the entry of the virus into the nervous system. On the other hand, in delta variant, the mechanisms of invasion through the nervous system have been documented *via* ascending vagus nerves, lungs; gastrointestinal tract (gut-lung-brain axis), hematogenous route (blood-brain-barrier), and direct invasion (smell and gustatory receptor, area postrema) of SARS-CoV-2 are well documented. However, a new variant (Omicron) arrives at the current scenario. However, it seems to be presenting attenuated clinical manifestations compared with the Delta variant and probable that it has a different entry to the nervous system due to the new protein S mutations and a different genetic. While writing this article, novel and updated information on Omicron is still not validated. We are seen more young people (20 to 39 years old) with Omicron variant subjectively compared with Delta. It is well known that the young population has a better immunological capacity to respond to SARS-CoV-2 than older adults. The main problem (in our opinion) is the low percentage of vaccination among South Africans (41.97%) compared with the United Arab Emirates population (98%), which explain why more than 62% of cases infected by Omicron SARS-CoV-2 all over the world remain in South Africa, and it is neighbour Botswana. We did not see enough patients reach accurate clinical observations. However, the neurological manifestation and pathogenesis of Omicron infection seem different, as we proposed in Figure 4.

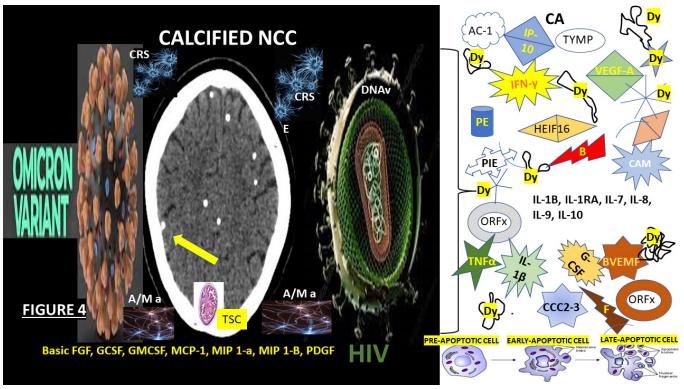

Figure 4. Comorbidity of NCC, HIV/AIDS and Omicron SARS-CoV-2 and elements participating.

We have hypothesized a novel mechanism for this comorbidity based on novel combinations of pro and anti-inflammatory elements aggravated by an increased capacity of viral replication and transmission, sustainable stress due to prolonged pandemic leading to a decreased immunological response. We think this variant enter the host mainly *via* the oropharyngeal route, and the alveolar damage is minimum and probable its ability to pass from the pharynx to the gut supported by GIT secretion, speedy gut motility, and a proper pH with minor CNS damage and mild/moderate dysbiosis secondary to broken balance between Firmicutes and Bacteroidetes.

Probable, the mortality rate will be low and the damage to the country's economy even less, supported by better managing experience on COVID-19 cases and accelerating the national vaccination process.

Recommendation to manage PLWHAN infected by SARS-CoV-2

There is no evidence suggesting a therapeutic approach for PLWHAN and COVID-19 (PLWHANC) published in the medical literature. Therefore, based on our results and own local experience, some recommendations could be considered to manage these cases as follow:

• PLWHANC should receive HAART with immediate effect if the patient were treated before.

• PLWHANC is on HAART; it must not be discontinued under any circumstances except lethal side effects, immune reconstitution syndrome or other strictly necessary situations.

• Anticoagulant therapies, antiviral, anti-inflammatory should be prescribed for non-HIV/NCC cases.

• Low drug-drug interaction and high barriers to resistances therapy should be the first choice.

• Medication supply should be granted despite lockdown restrictions.

• Par parasitic medication for NCC should be strictly prohibited during COVID-19 management to avoid additional cytokine storms.

• Because of the high risk of lethal complications and death, all PLWHAN should be vaccinated as a significantly higher priority.

Strengths and limitation

The strength of the current study was to identify the most common clinical manifestation, pathogenesis, and mortality rate among patients presenting NCC/HIV/AIDS/COVID-19 searching the medical literature based on PRISMA systematic review methodology. We also established the main difference between HIV/AIDS/COVID-19 patients and non-HIV cases. However, the scarce sociodemographic information and confident statistical information from large series of patients and cross-sectional investigations did not allow us to conduct subgroup and meta-regression analyses looking for the role of different HIV stages, viral load values, CD4 counts and ARV medications in PLWHA its incidence and prevalence. As a result, we acknowledge that our extensive searching had several limitations. Mainly many studies were either case series or case reports, with no observational cohort studies and no cross-sectional investigations. In addition, many of these publications were considered relatively poor in quality with reporting bias. Unfortunately, due to space limitations, other deep analyses should be transferred to forthcoming publications on the same matter.

Conclusion

After extensive searching of the medical literature, we found no publication on PLWHANC up to date. Therefore, as far we know, this is the first article related to PLWHANC. The clinical manifestations of COVID-19 among PLWHA are like to the clinical feature seen in non-HIV/COVID-19 cases if their ARV therapy is not discontinued for more than 2 or 3 months. The risk of poor outcome and death secondary to COVID-19 in PLWHA with ARV therapy is like the general population. Other studies should be done to determine the prevalence and outcome of PLWHAC, We recommend a mandatory plan to vaccinate all PLWHA as a matter of maxima priority. We recommend we do not prescribe anti-parasitic medication for cysticercosis to any PLWHA at risk to be infected by SARS-CoV-2. PLWHAC should follow the international guidelines of social distancing, health education, hygiene, and self-isolation. Special care should be provided to PLWHAC and other comorbidities like diabetes mellitus or immunocompromised disorders. Specialized medical care should be implemented in PLWHAC and lymphopenia. We have hypothesized on the crosstalk of NCC/HIV/AIDS/COVID-19 infections without ARV therapy as a cause of multiple medical consequences and death. Following the arrows is possible to understand the self-explanatory proposal.

Finally, we hypothesized the interactions of NCC, HIV/AIDS, and Omicron-SARS-CoV-2 on patients without ARV therapy, as can be graphically represented. The role of SARS-CoV-2 accelerating the mechanism of T cell exhaustion and its capacity to decrease the production of INFγ, IL-2, and TNFα should not be ignored in future medical research. Of course, more investigation will clarify doubts and establish curative therapy with safe and sustainable accurate prophylaxis.

Ethical approval

Ethical approval for this review was no necessary because all the data were extracted from previously published articles and did not include any studies of human participants or animals performed by the author. Therefore, the Institutional Ethical committee did not consider this study for additional ethical approval.

Competing interest

The author has not any conflict of interest to disclose. The authors declare that they researched the absence of any commercial or financial relationships construed as a potential conflict of interest.

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Declaration of anonymity

The author certifies that he did not reveal the names, surnames, initials, or other identity issues of any case in this publication, and complete anonymity is guaranteed. Availability of data and material: The data that support the findings of this study are available on reasonable request from the corresponding author.

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