"HIV and SARS-COV-2 coinfection: what is the prognosis?"

"Coinfecção HIV e SARS-COV-2: qual é o prognóstico?"

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RESUMO

INTRODUÇÃO: A infecção por SARS-CoV-2 apresentou piores desfechos em idosos/imunocomprometidos até março/2022, causando 655.249 óbitos no Brasil. O HIV infecta linfócitos T CD4 + e os degrada, levando à imunodepressão com 37.7 milhões de infectados até 2020. Portanto, surge a hipótese de que pessoas vivendo com HIV expericiariam piores prognósticos da COVID-19 se comparados aos não-HIV. MÉTODO: Revisão

sistemática horizontal com pesquisa bibliográfica realizada entre 27/março e 13/abril de 2022 nas bases de dados PubMed Central e LILACS, compreendendo artigos do período entre 2020-2022, pelo método PRISMA, para identificar artigos elegíveis que abordassem pacientes coinfectados HIV/COVID-19. Foram utilizados os termos: 'COVID-19', 'HIV', 'AIDS', 'CORONAVIRUS', 'HUMAN IMMUNODEFICIENCY VIRUS', 'SARS COV 2'. RESULTADO: Encontrados 10.224 artigos e, aplicados os métodos de inclusão, restaram 30 artigos. Ao todo, foram estudados 142.790 casos de coinfecção HIV/SARS-CoV-2 de todos os continentes, sendo 95.241 (66,7%) do sexo masculino, com idade média de 51,8 anos, média de TCD4 de 558,1 e os três sintomas mais relatados da COVID-19 foram febre, tosse e dispneia. 103.765 (72,7%) pacientes estavam em terapia antirretroviral (TARV), sendo que 7 estudos não forneciam dados em relação ao número de pacientes co-infectados ou em relação ao desfecho destes. O número de óbitos foi de 7.906 (5,5%). DISCUSSÃO: A maioria dos estudos aponta que os pacientes com a coinfecção HIV/SARS-CoV-2 não apresentam maior risco de morte pela COVID-19 se comparados aos pacientes sem HIV, possivelmente por se tratar de população em tratamento com imunidade compensada. A idade média dos pacientes co-infectados foi cerca de uma década menor do que a média de idade dos pacientes internados pela COVID-19, o que pode ser justificado pelo envelhecimento precoce de pessoas vivendo com o HIV devido à inflamação crônica. A presença de comorbidades como hipertensão, diabetes e doenças cardiovasculares apresenta-se como maior fator de risco para a COVID-19 e, assim como em pacientes sem HIV, provoca maior mortalidade. CONCLUSÃO: A mortalidade pela COVID-19 em coinfectados HIV/SARS-CoV-2 não foi maior do que em pacientes sem HIV. As características e sintomas dos pacientes com coinfecção não diferiram dos pacientes não portadores de HIV. A taxa de mortalidade de pacientes co-infectados foi similar à da população em geral de 50 a 59 anos.

Palavras-chave: HIV, SIDA, síndrome da imunodeficiência adquirida, COVID-19

ABSTRACT

INTRODUCTION: Until march/2022, the SARS-CoV-2 infection in humans resulted in worse outcomes in older adults and immunocompromised patients, causing 655,249 deaths in Brazil. The HIV virus infects and degrades CD4 T lymphocytes, leading to immune depression, and until 2020, 37.7 million people were infected by HIV. Therefore, the hypothesis that people living with HIV experience worse COVID-19 prognosis compared to people without HIV comes up. METHOD: Using the PRISMA guideline and PubMed and LILACS databases, between March 27 and April 13, 2022 we searched systematically for eligible articles published between 2020-2022 that included patients coinfected with HIV/COVID-19. The key words used were: 'COVID-19', 'HIV', 'AIDS', 'CORONAVIRUS', 'HUMAN IMMUNODEFICIENCY VIRUS', 'SARS COV 2'. RESULT: A total of 10,224 articles were found. After applying the inclusion methods, 30 articles remained. In all, 142,790 cases of HIV/SARS-CoV-2 coinfection from all continents were studied, of which 95,241 (66.7%) were male, the mean age was 51.8 years, the mean CD4 T count was 558.1 and the three most reported symptoms of COVID-19 were fever, cough and dyspnea. The total of 103,765 (72.7%) patients were on antiretroviral therapy (ART), and seven studies did not provide any data about the amount of coinfected patients or their outcome . The number of deaths was 7,906 (5.5%). DISCUSSION: Most studies point out that the mortality risk of HIV/SARS-CoV-2 patients is not higher than that of patients without HIV, possibly because they are a population in treatment with compensated immune system. The average age of coinfected patients was approximately a decade younger than the age of COVID-19 hospitalized patients. This can occur because of the early aging due to the chronic inflammation experienced by HIV-infected people. The presence of comorbidities such as hypertension, diabetes and cardiovascular diseases represents

the greatest risk factor for COVID-19 and, as well as in non-HIV patients, causes a higher number of deaths. CONCLUSION: The mortality rate due to COVID-19 in HIV/SARS-CoV-2 coinfected patients was not higher than that in patients without HIV. Characteristics and symptoms of coinfected patients were not different from those of patients without HIV. Coinfected patients' mortality rate was similar to that of the general population aged 50-59 years.

Keywords: COVID-19, acquired immunodeficiency syndrome, HIV, AIDS

1 INTRODUCTION:

SARS-CoV-2 is a coronavirus of the Coronaviridae family, an enveloped RNA virus with a non-segmented, single-stranded, positive genome. **[1]** The novel coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide and several variants of this virus have been reported. **[2, 3]** On March 14, 2022, Brazil had 29,380,063 confirmed cases, 655,249 deaths, an incidence of 13,980.7 per 100,000 inhabitants, 311.8 deaths per 100,000 inhabitants and 2.2 % lethality. **[5]** In the same period, there were 460,355,090 total cases and 6,047,784 deaths worldwide, with the highest concentration of cases in Europe. **[6]**

The Human Immunodeficiency Virus (HIV), in turn, is a retrovirus with two identical RNA strands that infects CD4 T lymphocytes and macrophages of the human immune system and degrades them, which can lead to a condition of immunosuppression called Acquired Immunodeficiency Syndrome. (AIDS). **[9, 10]** AIDS is a serious disease of immunodeficiency that results from the progressive decrease in CD4 T lymphocytes (less than 350 cells/mm^3 of blood) and the emergence of various opportunistic infections. **[9]**. More than 79 million people have become infected with HIV and more than 36 million have died from AIDS-related illnesses since the beginning of the COVID-19 pandemic. **[11]** Although antiretroviral therapy (ART) is highly effective in blocking viral replication, it has no effect on latently infected cells or in populations with proliferating infected cells. **[14, 16]**

Given the above, the hypothesis that people living with HIV experience worse outcomes and prognoses of COVID-19 compared to those who do not live with the immunodeficiency virus arises. **[19, 20]** By mid-2021, most people with HIV had no access to any vaccines against SARS-CoV-2. **[11]** In general, people with HIV infection are believed to be more likely to contract SARS-CoV-2 infection, even though specific information is unavailable. **[19]** Thus, the present systematic review sought to elucidate the relationship between HIV and SARS-CoV-2 coinfection and its respective outcome through a horizontal systematic review, aiming

to answer the question: “Do individuals with HIV have a worse prognosis when affected by COVID-19?”.

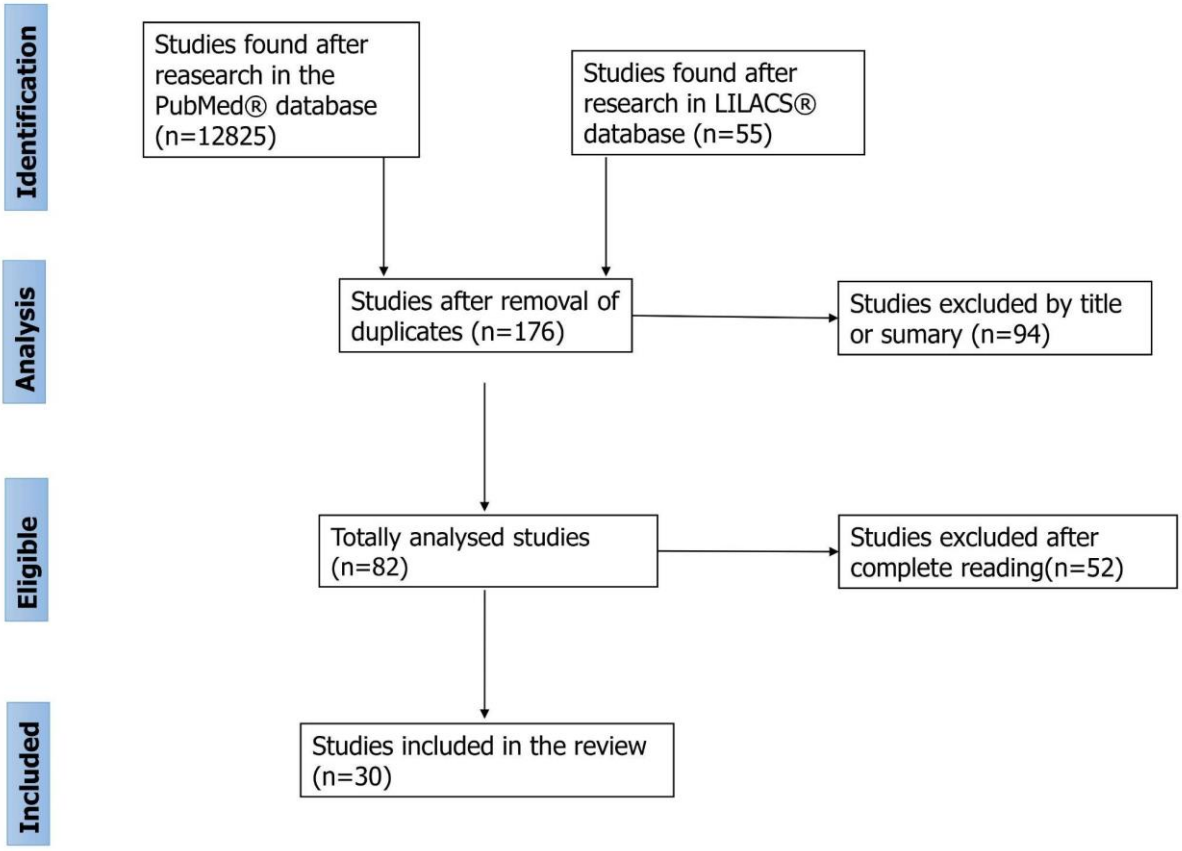
2 METHODS

A horizontal systematic review was performed with four independent reviewers following the PRISMA method, followed by a double check performed by a senior researcher. The final selection of articles was made by the senior researcher. Searches were performed on March 27 and 28, 2022 and on April 13, 2022 in PubMed® and LILACS® databases to identify articles addressing patients with HIV and COVID-19 coinfection. According to DeCS/MeSH, the following terms were used: ‘COVID-19’, ‘HIV’, ‘AIDS’, ‘CORONAVIRUS’, ‘HUMAN IMMUNODEFICIENCY VIRUS’ and ‘SARS-COV 2’.

The study inclusion criteria were articles in Portuguese, English or Spanish, addressing the concomitant infection of HIV and COVID-19 and published between years 2020 and 2022. Articles containing the mean CD4 T lymphocyte count of adult patients, older than 18 years and with a number of patients greater than 20 were selected. Exclusion criteria comprised articles involving children or adolescents under 18 years of age, in a letter or comment, not containing the mean CD4 T of patients, in languages other than Portuguese, English or Spanish and addressing the subject in a qualitative or social way.

Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta Analyzes (PRISMA) checklist based on the reading of articles and abstracts. Initially, 12,825 articles were found in PubMed® and 55 in LILACS®, and 12,594 of these were excluded because they were duplicates and 176 articles remained. After reading the title and abstract, 94 articles were eliminated and 82 articles were analyzed in full. After this complete reading, 52 articles were eliminated and 30 articles were included in this review.

Figure 1: The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist and article selection.



3 RESULTS

Initially, 12,880 articles published between 2020 and 2022 were found in the databases and after applying inclusion methods and filters, 82 articles were selected. Repeated articles addressing the theme in a qualitative or social way were excluded, leaving 40 articles. A final review was performed; articles that did not have data referring to the variables in the tables of the present study were excluded and 30 articles remained. All were published in the previous three years; 18 (60%) in 2021, nine (30%) in 2020 and three (10%) in 2022. Regarding the type of study analyzed, ten (33.3%) were retrospective cohort studies, six (20%) systematic reviews, four (13.3%) observational studies, three (10%) literature reviews, three (10%) multicenter studies, two (6.6%) case series and two (6.6%) systematic reviews and meta-analysis. Table 1 displays more information about the articles covered.

Table 1. Analysis of the number of articles selected, year of publication, type of study, author, country and number of people coinfected with HIV and SARS-CoV-1.

Nr Article	Year of Publication	Type of Article	Author	Country	Nr of Patients
1	2021	Literature review	*Gatechopol et al.*	USA, Italy, Spain, United Kingdom, China	435
2	2021	Literature review	*Ssentongo et al.*	USA, Germany, Spain, Italy, China, South Africa, France, United Kingdom	34,324
3	2020	Case series	*Kanwugu et al.*	Austria, China, Cyprus, Germany, Italy, Japan, Singapore, South Africa, Spain, Turkey, Uganda, United Kingdom and USA	378
4	2021	Case series	*Calza et al.*	Italy	26
5	2021	Retrospective cohort	*Chang et al.*	USA	61
6	2021	Literature review	*Ambrosioni et al.*	Spain, USA, United Kingdom, France, Spain, South Africa	4102
7	2021	Systematic review	*Medeiros et al.*	Not informed	266
8	2021	Retrospective cohort	*Nomah et al.*	Spain	749
9	2021	Systematic review	*Schaurich et al.*	China, USA, Spain, Italy, Japan, Turkey, United Kingdom, South Africa, Germany, Cyprus, Austria, Singapore, El Salvador, India and Uganda	106
10	2020	Retrospective cohort	*Nagarakanti et al.*	USA	23
11	2021	Retrospective cohort	*Jiao Huang et al*	China	35
12	2021	Multicenter study	*Dima Dandachi et al*	USA	286
13	2020	Observational study	*Inciarte et. al*	Spain	53
14	2021	Retrospective cohort	*Viraj V Patel et al*	USA	96
15	2020	Systematic review and meta-analysis	*Hossein Mirzaei et al*	Not informed	250
16	2020	Retrospective	*Georg Härter et al*	USA	33

		cohort			
17	2020	Multicenter study	*Lauren F. Collins et al*	USA	19
18	2020	Retrospective observational	*Gervasoni et. al*	Italy	47
19	2022	Systematic review	*Bousis et. al*	Not informed	831
20	2021	Systematic review	*Tael et. al*	Multicenter study	4.259
21	2021	Systematic review	*SeyedAlinaghi et al*	Multicenter study	89.343
22	2021	Systematic review	*Costenaro et al*	China, USA, Brazil, Italy, Switzerland, France, Spain, Turkey	164
23	2021	Systematic review and meta-analysis	*Lee et. al*	Multicenter study	6128
24	2020	Observational study	*Byrd et. al*	USA	26
25	2022	Retrospective cohort	*Durstenfeld et. al*	USA	220
26	2021	Retrospective cohort	*Flannery et al*	USA	99
27	2020	Retrospective cohort	*Kowalska et. al*	Multicenter study	34
28	2022	Retrospective observational	*Guembe et. al*	Spain	177
29	2021	Multicenter study	*Hoffmann et. al*	Italy, Spain, Germany	175
30	2021	Retrospective cohort	*Díez et. al*	Spain	45

Regarding the number of patients coinfected with HIV and Sars-CoV-2, only studies describing more than 20 cases (n > 20) were selected. Thus, five studies with less than 20 patients and two articles including children under 18 years of age were excluded. The 30 selected studies totaled 142,790 cases of coinfection, of which 42,570 (29.8%) were female and 95,241 (66.7%) were male. The sex of patients was not informed in three studies. The male predominance can be explained by the fact that they comprise the oldest population affected by the HIV virus. Although two out of the 30 articles did not present the mean age of participants, among the remaining studies the mean age was of 51.8 years.

Six out of the 30 articles did not explain any data on comorbidities. The most frequently reported comorbidities were systemic arterial hypertension (SAH), diabetes mellitus, cardiovascular disease and the presence of some type of kidney injury. Regarding SAH, in a

total of 23,435 patients in which this variable was analyzed, 3,308.72 had this condition, accounting for 14.11% of patients. In relation to diabetes mellitus, in a total of 23,543 patients, 1,662.53 had this condition, representing 7.06% of patients. Regarding cardiovascular disease, of the 22,464 patients analyzed for this condition, 2,347.65 had this disease, or 10.45% of patients. About kidney injuries, in a total of 23,072 patients analyzed for this condition, 855.04 patients had the disease, or 3.70% of patients. The number of patients with chronic obstructive pulmonary disease was reported in 19 articles, representing 22,809 patients in which this condition was evaluated, and 801.08 patients had the disease, representing 3.51% of patients. The number of patients with some type of neoplasm was reported in 13 articles; in a total of 2439 patients analyzed for this condition, 133.18 had the disease, accounting for 5.46% of patients.

Regarding the mean CD4 T lymphocyte count, in 12 studies it was not reported. Among those that reported, the average count was 571.3 cells/mm^3; 764 was the highest number found among individual averages and 265 the lowest. Among the 23 studies that reported patients using ART, 103,765 out of 137,165 patients were on this type of therapy, corresponding to 75.65% of the total number of patients. In six studies, this information was not reported and in one study (*Gatechopol et al)* it was reported that the majority of patients were using ART. Regarding the mortality rate in coinfected patients, it could not be calculated in 11 studies. In the remaining studies, rates ranged between 2.3% and 25.5%, a median of 11%. Only three articles reported data on relative risk and results were as follows: the first study with 1.78; the second with 16.86 for people over 50 years old discontinuing ART and 3.74 for people over 50 years old in general; and the third study with 2.3 for those under 60 years old and 7.4 for those over 60 years old. Information about symptoms of COVID-19 was presented in 23 studies. Fever and cough were cited in 22 articles, dyspnea in 20, myalgia in eight, headache in six, anosmia in four, arthralgia and fatigue in three, malaise and tachypnea in two, and odynophagia, diarrhea, hypoxemia, asphyxia and hyperventilation in one. The analysis of outcomes of coinfected patients is shown in Table 2.

Table 2: Analysis of outcomes, including hospitalization, discharge and death, and the mortality rate of coinfection.

Article	Hospitalizations	Discharge	Death	Mortality rate
1	12	328	67	Not informed
2	2	32	4289	12.65%
3	109	269	53	14%
4	5	26	0	Not informed
5	10	9	1	Not informed
6	1293	12541	273	Not informed
7	Not informed	Not informed	30	11%
8	103	Not informed	13	Not informed
9	Not informed	Not informed	7	Not informed
10	4	20	3	Not informed
11	Not informed	Not informed	2	5.71%
12	164	Not informed	27	16.50%
13	4	47	2	Not informed
14	Not informed	Not informed	21	22%
15	244	Not informed	36	14.30%
16	14	10	3	9%
17	20	13	3	15%
18	0	45	2	17%
19	276	349	56	6.70%
20	140	3933	186	Not informed
21	13.401	68.794	7.147	Not informed
22	15	133	16	Not informed
23	1773	Not informed	328	5.30%
24	9	8	1	3.70%
25	220	Not informed	36	16.40%
26	99	74	25	25.25%
27	19	11	2	5.90%
28	80	Not informed	4	2.30%

29	Not informed	Not informed	7	4%
30	21	Not informed	2	9.50%

Of the 30 articles that had data on death (total of 697,199 patients), 12,888 patients died (approximately 1.8%). The mean recovery time, considering five studies in which data was available, was 8.5 days. The average time to death, considering the four studies that had this information, was 16.5 days.

4 DISCUSSION

Some four decades after the first AIDS cases were reported, according to data from the 2021 UNAIDS report, several countries achieved the targets set by the United Nations General Assembly in 2016. **[21]** Only three studies in the present review did not indicate the country studied, although most of them are from developed or developing countries, such as the USA, Italy, Spain, United Kingdom, China, Germany, France, Japan, Austria, Switzerland and others. This shows that the population with HIV is not restricted to underdeveloped countries or the African continent, but is divided across the five continents. Furthermore, this systematic review did not include studies from countries with little access to health care or with punitive laws in relation to HIV. Therefore, it was not possible to analyze patients without access to ART, who consequently end up evolving to the most severe form of the disease, AIDS.

A determinant component of HIV infections involves not only the CD4 T count but also viral load and access and adherence to ART, which remains an essential aspect of long-term outcomes, including progression to AIDS and survival of patients with HIV. **[22]** According to 2020 data from UNAIDS, people living with HIV experience more severe outcomes and have more COVID-19-related comorbidities than people without HIV. **[11]** As individuals studied in the present review had a mean CD4 T lymphocyte count of 571.3 cells/mm³ (265 - 764), they are considered non-AIDS immunocompromised patients. This fact corroborates the explanation for the low mortality from the infection, also evidenced in this systematic review; if patients are more compensated for HIV, there is less risk for SARS-CoV-2 coinfection.

4.1 COMORBIDITIES

Severe cases of COVID-19 are strongly related to comorbidities such as hypertension, followed by diabetes mellitus, coronary heart disease, obesity and others. **[23]** After all, most deaths were in patients over 60 years old who had at least one of these comorbidities and as a

consequence, the vaccination plan introduced in early 2021 gave preference to this group of people. Some studies demonstrate that a well-regulated innate immune response is essential for a better prognosis of COVID-19 infection. **[24]** Note that such comorbidities deregulate the response, causing an exacerbated predominance of pro-inflammatory cytokines, which mark the worst prognosis of the disease.

As a result, patients living with HIV are in a constant inflammatory state and have a certain degree of immunosuppression, even those with good CD4 T levels who have always adhered properly to ART, that is, these individuals have deficient innate immune response. **[24]** In addition, this constant inflammatory state causes premature aging and advances the onset of comorbidities such as diabetes and hypertension. Furthermore, medications used in ART also increase the incidence of these comorbidities. **[25]** As observed in this study, the mean age of patients analyzed was 51.8 years and 14.11% of them had SAH, 7.06% had diabetes mellitus and 10.45% had some type of cardiovascular involvement. This mean age is about 10 years younger than that of patients with the worst prognosis at the beginning of the pandemic and 30 years younger than patients with the worst prognosis at the current time of the pandemic.

The study conducted by Noiman A et al. suggested that some patients, even those who acquire viral suppression with the use of ART, cannot achieve satisfactory levels of CD4 T due to non-immune response. Although the etiology of this phenomenon is unclear, it increases the predisposition to cardiovascular diseases, SAH and diabetes. The study also suggests that the onset of SAH and the onset of this condition are related. **[26]**

Therefore, it is a fact that the presence of comorbidities, both in people living with and without HIV, has an impact on the evolution of COVID-19. In both groups of patients, comorbidities are risk factors for a worse outcome. Note that people living with HIV are more likely to have these comorbidities and have them when they are younger; their rates of cardiovascular disease, hypertension, lung disease and smoking are higher. **[27]**

4.2 ART VS MORTALITY AND SEVERE OUTCOMES

At the beginning of the pandemic, there was doubt if HIV patients would be more affected by COVID-19. In the present study, the mortality rate in coinfected patients ranged from 2.3 to 25.5%, a median of 11%, which does not significantly differ from the rates of patients who contracted only SARS-CoV-2. **[28]** Low mortality rates may be associated with the fact of the CD4 T lymphocyte level being compensated and most patients being on ART, which is supported by studies that demonstrate a 10% increase in mortality in individuals who discontinue ART. **[27]** A low CD4 T lymphocyte count, in turn, is associated with worse

prognosis for COVID-19 in people living with HIV. **[29]** The mean age of 51.8 years also plays an important role, as it may be a risk factor for more severe disease and mortality. **[19, 30]** Furthermore, some components of ART used in the treatment of AIDS are suspected to have a beneficial effect on SARS-CoV-2 infection. Lopinavir, for example, is a protease inhibitor that has been shown to inhibit SARS-CoV-2 replication in vitro, although there is no evidence of better clinical outcomes or lower mortality in randomized controlled trials. **[29, 31]**

In a large study in South Africa, a developing country, the fact of living with HIV posed as a risk factor for having severe illness or death. These patients have a lower mean age at death, the number of deaths in people under 50 years old is greater, only 55% of people living with HIV were on ART, and the numbers of patients with uncontrolled diabetes and active tuberculosis infection are high. **[33]** In other words, the current review allows us to infer that the factor really causing worse outcomes of COVID-19 in HIV patients is the immune status of these individuals, and not the infection itself. If the disease is controlled by the adequate performance of ART with adequate levels of CD4 T, HIV infection alone will not represent a modifying factor in the evolution of the disease. Many different factors can impact the severity with which COVID-19 will manifest in people with HIV, such as associated biological, economic factors, social structures and access to adequate treatment, and further studies are needed to assess the different aspects. **[34]**

5 CONCLUSION

Based on data obtained with this review, in general, the prognosis of patients with HIV and SARS-CoV-2 coinfection did not differ from that of patients infected only with SARS-CoV-2. The worse outcomes were associated with the comorbidities presented by patients, like in the general population with COVID-19, and not with the fact of patients being HIV positive. This is probably a result of the fact that most patients in the study had compensated disease, a normal number of CD4 T lymphocyte count and were on regular and adequate use of ARTs, that is, their immunological response was similar to that of non-HIV individuals. However, it is noteworthy that HIV-positive people are more susceptible to developing the main comorbidities associated with COVID-19, such as cardiovascular disease, diabetes mellitus, SAH and pulmonary diseases. The present study has certain limitations, such as not involving AIDS patients (immunosuppressed), hence the need for further studies with more comparisons.

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