Outcomes of patients with HIV and COVID-19 co-infection: a systematic review and meta-analysis

Celestin Danwang1*, Jean Jacques Noubiap2, Annie Robert1 and Jean Cyr Yombi3

Abstract

Background: Data on the association of human immunodeficiency virus (HIV) infection with adverse outcomes in patients with COVID-19 are conflicting. This systematic review and meta-analysis aimed to summarize the available information on the risk of hospitalization, severe disease, and death attributable to HIV in patients with COVID-19.

Methods: PubMed, EMBASE, Web of Science, and SCOPUS were searched through October 25, 2021, to identify relevant studies, without language restriction. A random-effects model was used to pool estimates.

Results: We included 44 studies reporting information from 38,971,065 patients with COVID-19. The pooled prevalence of HIV among COVID-19 patients was 26.9 ‰ (95% CI 22.7–31.3) and was significantly higher in studies conducted in Africa compared to those conducted elsewhere (118.5‰ [95% CI 84.8–156.9, 11 studies] vs 10.9‰ [95% CI 8.8–13.2, 27 studies]). In pooled analyses of unadjusted odds ratio, HIV-positive individuals were more likely to be admitted to hospital (OR: 1.49; 95% CI 1.01–2.21, 6 studies) compared to HIV-negative individuals. In the adjusted (for age and sex) analyses, HIV was associated with an increased risk of death (hazard ratio: 1.76, 95% CI 1.31–2.35, 2 studies). However, HIV was not associated with the severity of the disease (OR: 1.28; 95% CI 0.77–2.13, 13 studies), or death (OR: 0.81; 95% CI 0.47; 1.41, 23 studies) in patients with COVID-19 in the meta-analysis of unadjusted odds ratio.

Conclusion: Our findings suggest that patients with HIV have an increased risk of hospital admission for COVID-19. HIV seems to be independently associated with increased risk of mortality in COVID-19 patient in adjusted analysis. However, this evidence was derived from only two studies.

Keywords: Outcomes, HIV, Systematic review, Meta-analysis

Introduction

The coronavirus 2019 (COVID-19) pandemic is imposing to the world a huge health, societal and economic burden [1–3]. Despite all the efforts that have been made to reduce the spread of the virus and limit its lethality, the death rate from COVID-19 remains high. Indeed, as of 3 November 2021, approximately 246,951,274 cases of COVID-19 have been diagnosed worldwide and 5,004,855 associated deaths have been recorded [4]. Results from vaccination campaigns are promising, with a marked reduction in new infections regardless of the variant in vaccinated individuals compared to unvaccinated or partially vaccinated people [5–8].

Although all ages and profiles are likely to be affected by COVID-19, studies suggest that patients with co-morbidities are particularly at risk of adverse outcomes compared to those without [9–11]. For instance, patients with hypertension, obesity and diabetes are more likely to die, be admitted to intensive care units and have severe forms of the infection [9–11]. For some other diseases such
HIV, the information on their association with adverse outcomes in patients with COVID-19 are conflicting [12–17]. However, some regions of the world like sub-Saharan Africa are at risk of having a burden of COVID-19 drive by the proportion of HIV patients. Sub-Saharan Africa for example bore the highest burden of HIV and patients not receiving antiretroviral therapy (ART) [18–21]. Among the 38 millions of patients living with HIV globally, 26 million are in this part of the continent, with a relatively high proportion not receiving ART compare to other region of the world [18, 19].

HIV causes immunodepression by depleting CD4 cells, thus reducing the capacity of the organism to defend against bacterial, fungal, parasitic, and viral infections such as COVID-19 [20, 22]. This vulnerability to infection is greater when the immunodepression is severe and the patient is not on ART making the patient at risk of opportunistic infections [23, 24]. The presence of 38 million people worldwide with HIV during this period of COVID-19, could therefore be challenging for health systems worldwide as more aggressive preventive and therapeutic measures might be needed for this population. It is therefore necessary for programmatic purposes, optimal allocation of public health interventions and prioritisation of care in a context of scarce resources due to the pandemic [25], to know whether, given the state of the art, people living with HIV are proportionally more affected than people without the disease, and whether they are at greater risk of pejorative outcome when affected by COVID-19.

Hence, this study aimed to summarize the available information on the risk of hospitalization, severe disease, and death attributable to HIV in patients with COVID-19 and to determine the proportion of patients co-infected with HIV among patients with COVID-19.

**Methods**

This review is reported in accordance with the PRISMA guidelines and is registered with PROSPERO CRD42021255993.

**Search strategy and eligibility criteria**

PubMed, EMBASE, Web Sciences, and SCOPUS were searched from 1 December 2019 to 25 October 2021 without language restriction for studies reporting the outcome of COVID-19 according to HIV status. Only studies involving patients with confirmed COVID-19 infection (polymerase chain reaction or rapid diagnostic test) were included. HIV positivity/negativity was defined as per reported by each study. Both study reporting on patients with a known HIV status prior to the COVID-19 pandemic, and those in which the diagnostic of HIV was made in patients with COVID-19 during hospitalisation were considered. Severe COVID-19 was defined as the presence of blood oxygen saturation ≤ 93%; multiple organ dysfunction; respiratory failure; septic shock; dyspnoea; respiratory rate greater than 30/min, PaO2/FiO2 ratio < 300, and/or lung infiltrates > 50% of the lung field within 24–48 h [26]. For duplicates or studies published in more than one report, or conducted on the same database, the one reporting the largest sample size was considered.

The detailed search strategy is presented in the Appendix (Additional file 1: Tables S1–S3). We included all studies with at least 20 participants in each group (with and without HIV) and reporting sufficient information to determine the number of hospital admissions, severe cases, or deaths in each group.

After removing duplicates, two investigators (CD, JJN) assessed the eligibility of the retrieved articles, first based on the title and abstract, then on full text. Disagreements between the two investigators were resolved by discussion and consensus.

**Data extraction and quality assessment**

In each study, we extracted the name of the first author, the year of publication, the country, the characteristics of the study population (proportion of men, age distribution), the total number of patients with and without HIV in the study, the number of patients with each outcome between those with and without HIV. For all studies reporting prevalence data, the Joanna Briggs Institute (JBI) critical appraisal tool for prevalence studies was used to assess the risk of bias [27], with the following ranges 0–3, 4–6 and 7–9 indicating high, moderate and low risk of bias, respectively. For the remaining studies, the JBI tool corresponding to the study design was used [28].

**Statistical analysis**

To obtain the overall proportion of HIV patients among COVID-19 patients, a DerSimonian-Laird random-effects model for meta-analysis within the "meta" package of R was performed. Then, to estimate the overall risk of hospital admission, severe COVID-19, and the risk of death among HIV and COVID-19 co-infected patients, a random-effects model was run. A subgroup analysis was performed according to country location (USA vs. Non-USA, and Africa vs. Non-Africa).

In addition, adjusted odds ratios (OR) or hazard ratio (HR) when available (with their standard error) were pooled to obtain an adjusted estimate for each outcome where there were at least two studies. We have assessed the association between mortality and death with the two ways of measuring methods of associations, the odds ratio and the hazard ratio. Cochran and I² statistics were
used to assess and estimate the degree of heterogeneity in the meta-analysis [29, 30]. I² ranging from 0 to 40%, 40–75%, 75–100% was considered as indicative of low, moderate, and substantial heterogeneity respectively. Visual inspection of the funnel plot and Egger’s test were used to assess publication bias. A sensitivity analysis was performed to detect influential studies. A p-value of ≤ 0.05 was considered statistically significant. All analyses were performed with R software, version 4.0.2.

Results
Study selection and characteristics
We found 8537 studies from literature searches, and finally included 44 studies reporting information from 38,971,065 patients with COVID-19 in the meta-analysis (Additional file 1: Fig. S1). Thirteen (41.9%) studies were conducted in the USA. Twenty-eight studies were cross-sectional studies, eight were cross-sectional analyses of a cohort study, three were case series and five were case controls. Twenty-eight of the 44 studies were multicentre. All studies included in the systematic review and meta-analysis were in English. The sex ratio, and age distribution of patients according to HIV status was greatly variable according to study as summarized in Table 1.

Prevalence of HIV among patients with COVID-19
Thirty-eight studies were included in the meta-analysis of prevalence information. The pooled prevalence of HIV among COVID-19 patients was 26.9 % (95% confidence interval [CI] 22.7–31.3) (Fig. 1) and was significantly higher in studies conducted in Africa compared to those conducted elsewhere (118.5% [95% CI 84.8–156.9, 11 studies] vs 10.9% [95% CI 8.8–13.2, 27 studies]). The pooled prevalence of HIV among COVID-19 patients was 12.9% (95% CI 7.7–19.5, 13 studies) in the USA and was significantly lower compare with the figure outside the USA (49.2% [95% CI 24.0–82.2, 25 studies] (P value: 0.002). The pooled prevalence of HIV among studies conducted on hospital records was 24.6% (95% CI 20.4–29.1, 33 studies), while the figure for population-based studies was 56.8% (95% CI 11.9–129.7, 5 studies) (Additional file 1: Figs. S1–S4).

Risk of in-hospital admission associated with HIV infection
Based on the meta-analysis of six studies, HIV-positive COVID-19 participants were more likely to be admitted to hospital than HIV-negative patients (OR: 1.49; 95% CI 1.01–2.21) (Fig. 2).

Risk of severe COVID-19 associated with HIV infection
A meta-analysis of 13 studies including 13,016 HIV-infected individuals with COVID-19, and 1,744,014 HIV-uninfected individuals with COVID-19, shows that HIV does not increase the likelihood of having severe COVID-19 (OR: 1.28; 95% CI 0.77–2.13) (Fig. 3), even after stratification according to study’s country of recruitment (Additional file 1: Figs. S5, S6).

Risk of death from COVID-19 associated with HIV infection
Twenty-three studies were included in the unadjusted risk ratio meta-analysis and two (one from South Africa, and one multicentric) in the adjusted HR meta-analysis. In unadjusted pooled analyses, there was no association between death from COVID-19 and HIV (OR: 0.81; 95% CI 0.47; 1.41, 23 studies). However, in analyses adjusted for age and sex, HIV was associated with an increased risk of death (hazard ratio 1.76, 95% CI 1.31–2.35; 2 studies) (Fig. 4).

There was no significant difference in the risk of death of patients co-infected with HIV and COVID-19, compare with those without HIV even when the analysis was stratified by country (Additional file 1: Figs. S7, S8).

Publication bias and sensitivity analysis
The funnel plot of the studies included in the prevalence meta-analysis shows some asymmetry which was confirmed by Egger’s test (p-value=0.01) (Additional file 1: Fig. S9), suggesting the presence of publication bias. However, neither the funnel plot nor the Egger test indicated publication bias for studies included in the meta-analysis conducted to assess the risk of in-hospital admission, severe disease, or death (Additional file 1: Figs. S10–S12).

In the leave-one-out analysis, none of the studies included when omitted change the overall effect-size in all analyses except in the meta-analysis pertaining to mortality risk (Additional file 1: Figs. S13–S16). In the latter, the omission of the Jassap et al. study strongly influences the overall OR, without changing the direction of the association between HIV and COVID-19 mortality, which remains non-significant (Additional file 1: Fig. S16).

Discussion
The results of the current study suggest that co-infection with HIV is associated with an increased risk of hospital admission in people with COVID-19. Furthermore, based on the analysis of a limit number of studies, the meta-analysis of adjusted (for age and sex) hazard ratio showed that HIV increases the risk of death in patients with COVID-19. However, HIV was not associated with an increased risk of death or of developing severe disease in the unadjusted analysis. The influence of age and sex on the outcome of patients with COVID-19 is well known and has been previously published [31, 32]. The lack of evidence of higher risk of death in HIV patients
| Author              | Year of publication | Country      | Period of inclusion          | State/city/region       | Number of Centre | Registry Setting | Mean/Median age (yrs.) | Min. age | Max. age | %Males | Nber of patients with COVID-19 | Nber of patients with COVID-19 and HIV | RoB |
|---------------------|---------------------|--------------|------------------------------|-------------------------|------------------|-------------------|-----------------------|-----------|-----------|--------|-------------------------------|----------------------------------------|-----|
| Bakamutu-maho       | 2021                | Uganda       | March to December 2020       | Entebbe                 | Single-Site study| HR, HB            | 35 (IQR:27–47)       | NR        | NR        | 83     | 270                           | 27                      | Low |
| Bhaskaran           | 2021                | UK           | Feb 1, 2020                  | National                | Multi-Site study | Yes, HB           | HIV positive: 48 (40–55), HIV negative: 49 (34–64) | 18        | NR        | HIV positive: 64.7, HIV negative: 49.9 | 17,282,905, 27,480 | Low |
| Blanco              | 2020                | Spain        | March 9, 2020                | Barcelona               | Single-Site study| HR, HB            | HIV positive: 3.78   | HIV positive: 29 | HIV positive: 49 | 60     | 543                           | 5                       | Low |
| Boulle              | 2020                | South Africa | 1 March to 9 June 2020       | Western Cape            | Multi-Site study | HR, HB            | 20                    | NR        | HIV positive: 22.0, HIV negative: 33.7 | 22,308, 3978 | Low |
| Braunstein          | 2020                | USA          | June 2, 2020                 | New York                | Multi-Site study | Yes, PB           | NR                    | 0         | NR        | HIV positive: 71.4, HIV negative: 51.1 | 204,442, 2410 | Low |
| Byrd                | 2020                | USA          | 30 March and 20 May 2020     | Rhode Island            | Single-Site study| Yes, PB           | NR                    | 30        | 71        | 74.1   | 150                           | 27                      | Low |
| Cabello             | 2021                | Spain        | February 1 until May 20, 2020| Madrid                  | Multi-Site study | HR, HB            | 46 (IQR: 37–56)     | NR        | NR        | 88.9   | 7061                          | 31                      | Low |
| Calza               | 2020                | Italy        | March 1, 2020, and April 30, 2020 | Bologna               | Single-Site study| HR, HB            | 53.8 (IQR: 42.5–64.7) | NR        | NR        | 73.1   | 756                           | 26                      | Low |
| Ceballos            | 2021                | Chile        | 16 April and 23 June 2020    | 23 hospitals all over the country | Multi-Site study | HR, HB            | 44 (IQR: 26–85)     | NR        | NR        | HIV positive: 92 | 18,321 | 36 | Low |
| Charre              | 2020                | France       | March to April 2020          | Lyon                    | Unclear/Not described | Yes, PB           | HIV positive: 53.0 (41.3–58.6), HIV negative: 546 (35.6–75.7) | NR        | NR        | HIV positive: 67.5, HIV negative: 40.5 | 3648 | 12 | Low |
| Collins             | 2020                | USA          | 8 March 2020 to 23 April 2020| Atlanta                 | Multi-Site study | HR, HB            | 57 (IQR: 48–62)     | NR        | NR        | HIV positive: 65 | 530 | 20 | Low |
| Cucurulli-Canosa    | 2021                | Spain        | Up to 15 May 2020            | Madrid                  | Single-Site study| HR, HB            | HIV:22.7             | HIV:4       | HIV:35               | HIV58.3 | 317 | 12 | Low |
| Author          | Year of publication | Country               | Period of inclusion          | State/city/region                      | Number of Centre | Registry | Setting     | Mean/Median age (yrs.) | Min. age | Max. age | %Males | Nber of patients with COVID-19 | Nber of patients with COVID-19 and HIV | RoB |
|-----------------|---------------------|-----------------------|-----------------------------|---------------------------------------|------------------|----------|-------------|------------------------|----------|----------|--------|--------------------------------|---------------------------------|-----|
| Diez            | 2021                | Spain                 | Up to 30 June 2020         | 13 hospitals of the 17 regions of the country | Multi-Site study | HR       | HB          | HIV:53; HIV negative:53 | Q1: HIV:46; HIV negative:46 | Q3: HIV:56; HIV negative:56 | HIV:90.5; HIV negative:90.5 | 126 | 21 | Low |
| Durstenfeld     | 2021                | USA                   | Up to December 2020        | 107 hospitals in USA                 | Multi-Site study | Yes      | HB          | HIV:56.0 ± 130; HIV negative: 62.3 ± 17.9 | NR       | NR       | HIV:72.3; HIV negative:53.9 | 21,528 | 220 | Low |
| Esfahanian      | 2021                | Iran                  | From 20 February to 19 April 2020 | Tehran                              | Multi-Site study | HR       | HB          | NR                     | NR       | NR       | 664 | 500 | 4 | Low |
| Geretti         | 2020                | England, Scotland, and Wales | June 2020 | Multi-countries | Multi-Site study | Yes      | HB          | HIV positive: 56 (IQR: 49, 62); HIV negative: 74 (60, 84) | NR       | NR       | HIV positive:66.1; HIV negative: 57.1 | 47,592 | 122 | Low |
| Gudipati        | 2020                | USA                   | March 20, 2020, and April 30, 2020 | Michigan                            | Multi-Site study | HR       | HB          | HIV positive:49; HIV negative:52 | NR       | NR       | HIV positive:81; HIV negative:47 | 65,549 | 278 | Low |
| Hadi            | 2020                | USA                   | NR                         | Massachusetts                        | Multi-Site study | Yes      | HB          | HIV positive:48.2; HIV negative:48.8 | 10       | NR       | HIV positive:70.6; HIV negative:44.9 | 50,167 | 404 | Low |
| Jassat          | 2021                | South Africa          | Up to March 27, 2021       | 393 public and 251 private hospitals | Multi-Site study | Yes      | HB          | NR                     | NR       | NR       | HIV:7.2; HIV negative:92.8 | 151,779 | 13,793 | Low |
| Lee             | 2021                | UK                    | From 1 February 2020 to 31 May 2020 | London, Manchester, and Leicester  | Multi-Site study | HR       | HB          | HIV:57; HIV negative:56 | Q1: HIV:50; HIV negative:51 | Q3: HIV:63; HIV negative:62 | HIV:61.8; HIV negative:63 | 249 | 68 | Low |
| Molina-Iturritza| 2020                | Spain                 | 1 March to 30 April 2020   | Arabia                              | Multi-Site study | HR       | HB          | NR                     | NR       | NR       | HIV positive:78; HIV negative:55 | 8912 | 161 | Low |
| Mwanan-yanda    | 2021                | Zambia                | Up to September 2020       | Lusaka                              | Single-Site study | HR       | HB          | 48                     | Q1:36     | Q3:72    | 69 | 70 | 16 | Low |
| Author          | Year of publication | Country | Period of inclusion | State/city/region | Number of Centre | Registry | Setting | Mean/Median age (yrs.) | Min. age | Max. age | %Males | Nber of patients with COVID-19 | Nber of patients with COVID-19 and HIV | RoB |
|-----------------|---------------------|---------|---------------------|-------------------|------------------|----------|---------|------------------------|----------|----------|--------|-------------------------------|----------------------------------|-----|
| Karmen-Tuohy   | 2020                | USA     | March 2, 2020, and April 23, 2020 | New York Multi-Site study | Yes | HB | NR | NR | NR | NR | NA | NA | Low |
| Kirenga         | 2020                | Uganda  | 16 May 2020         | Entebbe Multi-Site study | HR | HB | 34.2 | NR | NR | 679 | 203 | 15 | Low |
| Mash            | 2021                | South Africa | March and June 2020 | Western Cape Multi-Site study | HR | HB | 46.3 | NR | NR | 1376 | 195 | Low |
| Mbarga          | 2021                | Cameroon | April 01, 2020 to July 31, 2020 | Yaoundé Single-Site study | HR | HB | 46 | NR | NR | 625 | 259 | 7 | Low |
| Migisha         | 2020                | Uganda  | March 21–April 12, 2020 | National Multi-Site study | Yes | PB | 35 | NR | NR | 63 | 54 | 2 | Low |
| Tshikung        | 2021                | Switzerland | 1 May 2020 | Geneva Single-Site study | HR | HB | NR | NR | NR | NR | 1024 | 8 | Low |
| Venturas        | 2021                | South Africa | March 6, 2021, to September 11, 2020 | Johannesburg Single-Site study | HR | HB | HIV: 45; HIV negative: 52.5 | Q1: HIV: 38; HIV negative: 39.8 | Q3: HIV: 56; HIV negative: 61 | HIV: 50; HIV negative: 54 | 384 | 108 | Low |
| Nagarakanti     | 2021                | Israel   | March 2020 and April 2020 | Newark Beth Single-Site study | HR | HB | HIV: 59; HIV negative: 49 | HIV: 51; HIV negative: 41 | HIV: 67; HIV negative: 73 | HIV: 61.0; HIV negative: 34.8 | 66 | 23 | Low |
| Silva           | 2020                | Portugal | March 02 and July 14, 2020 | Porto Single-Site study | HR | HB | 48 | NR | NR | NR | 2092 | 8 | Low |
| Sultan          | 2021                | Ethiopia | Up to August 20, 2020 | Addis Ababa Multi-Site study | HR | HB | 59 | 17 | 92 | 71 | 85 | 15 | Low |
| Sun             | 2021                | USA      | Up to 21 May 2021 | National Multi-Site study | Yes | HB | HIV: 50; HIV negative: 47 | Q1: HIV: 36; HIV negative: 32 | Q3: HIV: 59; HIV negative: 61 | HIV: 44.8; HIV negative: 72.5 | 1,446,913 | 8270 | Low |
| Wyk             | 2020                | South Africa | 3 July 2020 | National Multi-Site study | Yes | PB | 61 | NR | NR | NR | 2457 | 342 | Low |
| Yang            | 2020                | China    | February 14 | Wuhan Multi-Site study | HR | HB | NR | NR | NR | NR | 188 | 3 | Low |
| Author       | Year of publication | Country | Period of inclusion | State/city/region  | Number of Centre | Registry Setting | Mean/Median age (yrs.) | Min. age | Max. age | %Males | Number of patients with COVID-19 | Number of patients with COVID-19 and HIV | RoB |
|--------------|---------------------|---------|---------------------|--------------------|------------------|-----------------|-----------------------|----------|----------|--------|-------------------------------|--------------------------------------------|-----|
| Shalev       | 2020                | USA     | 15 April 2020       | New York           | Single-Site study| Yes              | HB 60.7              | 23       | 89       | NR     | 2159                          | 31                           | Low |
| Ouyang       | 2020                | USA     | 3/1 to 5/15, 2020  | New York           | Single-Site study| HR               | HB NR               | NR       | NR       | NR     | 1092                          | 22                           | Low |
| Parker       | 2020                | South Africa | 25 March to 11 May 2020 | Cape Town          | Single-Site study| HR               | HB HIV positive: 46.2; HIV negative: 49.1 | NR       | NR       | HIV positive: 250; HIV negative: 427 | 116                          | 24   |
| Rosenthal    | 2020                | USA     | April 1 and May 31, 2020 | National           | Multi-Site study | Yes              | HB 55.5              | NR       | NR       | 493    | 64,781                        | 252                          | Low |
| Sachdev      | 2021                | USA     | March 24, 2020, to September 3, 2020 | San Francisco | Multi-Site study | Yes              | PB 48               | 13       | NR       | 912    | 9819                          | 193                          | Low |
| Sigle        | 2020                | USA     | 12 March and 23 April 2020 | Mount Sinai       | Multi-Site study | Yes              | HB HIV positive: 61; HIV negative: 60 | NR       | NR       | HIV positive: 75; HIV negative: 76 | 4402                         | 88   |
| Stoeckle     | 2020                | USA     | March 3, 2020, and May 15, 2020 | New York           | Single-Site study| HR               | HB HIV positive: 60.5; HIV negative: 60.5 | NR       | NR       | HIV positive: 80; HIV negative: 80 | NA                           | NA   |
| Tesorieres   | 2021                | USA     | March 1 and June 15, 2020 | New York           | Multi-Site study | Yes              | HB 54.0              | NR       | NR       | NA     | 19,453,561                    | 2409                         | Low |
| Yendewa      | 2021                | USA     | January 1 to December 1, 2020 | 44 healthcare centers in the USA | Multi-Site study | Yes              | HB HIV 48.34 ± 13.59; HIV negative 48.34 ± 13.59 | NR       | NR       | HIV69.4 | 297,194                       | 1638                         | Low |

HB: Hospital-based; PB: population-based; HR: hospital records; Max age: maximum age; Min age: minimum age; RoB: risk of bias
Fig. 1 Proportion of HIV positive patients among patients with COVID-19

| Study                     | HIV+ | Total | Prevalence (per 1000) | [95% CI] | Weight | Prevalence (per 1000) |
|---------------------------|------|-------|------------------------|----------|--------|------------------------|
| Blanco, 2020              | 5    | 543   | 9.2 [3.0; 21.4]        | 2.5%     |        |                        |
| Boulle, 2020              | 3978 | 22308 | 178.3 [173.3; 183.4]   | 3.3%     |        |                        |
| Byrd, 2020                | 27   | 150   | 180.0 [122.1; 251.0]   | 1.5%     |        |                        |
| Calza, 2020               | 26   | 756   | 34.4 [22.6; 50.0]      | 2.6%     |        |                        |
| Charre, 2020              | 12   | 3648  | 3.3 [1.7; 5.7]         | 3.1%     |        |                        |
| Collins, 2020             | 20   | 530   | 37.7 [23.2; 57.7]      | 2.4%     |        |                        |
| Geretti, 2020             | 122  | 47592 | 2.6 [2.1; 3.1]         | 3.3%     |        |                        |
| Gudipati, 2020            | 278  | 65549 | 4.2 [3.8; 4.8]         | 3.3%     |        |                        |
| Hadi, 2020                | 404  | 50167 | 8.1 [7.3; 8.9]         | 3.3%     |        |                        |
| Kirenga, 2020             | 15   | 203   | 73.9 [41.9; 118.9]     | 1.7%     |        |                        |
| Migisha, 2020             | 2    | 54    | 37.0 [4.5; 127.5]      | 0.7%     |        |                        |
| Molina–Iturriza, 2020     | 161  | 8912  | 18.1 [15.4; 21.0]      | 3.2%     |        |                        |
| Ouyang, 2020              | 22   | 1092  | 20.1 [12.7; 30.3]      | 2.8%     |        |                        |
| Parker, 2020              | 24   | 116   | 206.9 [137.3; 292.0]   | 1.3%     |        |                        |
| Rosenthal, 2020           | 252  | 64781 | 3.9 [3.4; 4.4]         | 3.3%     |        |                        |
| Shalev, 2020              | 31   | 2159  | 14.4 [9.8; 20.3]       | 3.0%     |        |                        |
| Sigle, 2020               | 88   | 4402  | 20.0 [16.1; 24.6]      | 3.2%     |        |                        |
| Silva, 2020               | 8    | 2092  | 3.8 [1.7; 7.5]         | 3.0%     |        |                        |
| Wyk, 2020                 | 342  | 2457  | 139.2 [125.7; 153.5]   | 3.1%     |        |                        |
| Yang, 2020                | 3    | 188   | 16.0 [3.3; 45.9]       | 1.7%     |        |                        |
| Bakamutumaho, 2021        | 27   | 270   | 100.0 [66.9; 142.2]    | 2.0%     |        |                        |
| Bhaskaran, 2021           | 27480| 17282906| 1.6 [1.6; 1.6]       | 3.3%     |        |                        |
| Cabello, 2021             | 31   | 7061  | 4.4 [3.0; 6.2]         | 3.2%     |        |                        |
| Caballos, 2021            | 36   | 18321 | 2.0 [1.4; 2.7]         | 3.3%     |        |                        |
| Cucurull–Canosa, 2021     | 12   | 317   | 37.9 [19.7; 65.2]      | 2.1%     |        |                        |
| Durstenfeld, 2021         | 220  | 21528 | 10.2 [8.9; 11.7]       | 3.3%     |        |                        |
| Esfahanian, 2021          | 4    | 500   | 8.0 [2.2; 20.4]        | 2.4%     |        |                        |
| Jassat, 2021              | 13793| 151779| 90.9 [89.4; 92.3]      | 3.3%     |        |                        |
| Mash, 2021                | 195  | 1376  | 141.7 [123.7; 161.3]   | 2.9%     |        |                        |
| Mbarga, 2021              | 7    | 259   | 27.0 [10.9; 54.9]      | 1.9%     |        |                        |
| Mwananyanda, 2021         | 16   | 70    | 228.6 [138.7; 344.5]   | 0.9%     |        |                        |
| Sachdev, 2021             | 193  | 9819  | 19.7 [17.0; 22.6]      | 3.2%     |        |                        |
| Sultan, 2021              | 15   | 85    | 176.5 [102.3; 274.3]   | 1.0%     |        |                        |
| Sun, 2021                 | 8270 | 1446913| 5.7 [3.8; 5.8]        | 3.3%     |        |                        |
| Tesoriero, 2021           | 2409 | 19453561| 0.1 [0.1; 0.1]       | 3.3%     |        |                        |
| Tshikung, 2021            | 8    | 1024  | 7.8 [3.4; 15.3]        | 2.8%     |        |                        |
| Venturas, 2021            | 108  | 384   | 281.2 [236.8; 329.1]   | 2.2%     |        |                        |
| Yendewa, 2021             | 1638 | 297194| 5.6 [5.2; 5.8]        | 3.3%     |        |                        |

Pooled 38971065 26.9 [22.7; 31.3] 100.0%

Fig. 2 Risk of hospital admission according to HIV status among COVID-19 patients

| Study                     | Events | HIV+ Events | Total | HIV+ Events | Total | Weight | MH, Random, 95% CI | Odds Ratio | MH, Random, 95% CI |
|---------------------------|--------|-------------|-------|-------------|-------|--------|-------------------|------------|-------------------|
| Gudipati, 2020            | 58     | 278         | 13054 | 65271       | 16.0% | 1.05   | [0.79; 1.41]      |            |                   |
| Hadi, 2020                | 78     | 404         | 5254  | 49763       | 17.1% | 2.03   | [1.58; 2.60]      |            |                   |
| Cabello, 2021             | 15     | 31          | 4060  | 7030        | 7.4%  | 0.69   | [0.34; 1.39]      |            |                   |
| Sun, 2021                 | 545    | 8466        | 59648 | 1450815     | 20.4% | 1.60   | [1.47; 1.75]      |            |                   |
| Tesoriero, 2021           | 896    | 2988        | 61371 | 375260      | 20.6% | 2.19   | [2.02; 2.37]      |            |                   |
| Yendewa, 2021             | 269    | 1635        | 218   | 1609        | 18.5% | 1.26   | [1.04; 1.52]      |            |                   |

Total (95% CI) 13802 1949748 100.0% 1.49 [1.01; 2.21]

Heterogeneity: Tau² = 0.0703; Chi² = 65.12, df = 5 (P < 0.01); I² = 92%
with COVID-19 in previous meta-analyses on the topic is probably because these meta-analyses pooled unadjusted estimators [14, 33].

Indeed, in our study, when pooling the unadjusted risk ratios, no difference in terms of mortality is observed. This contradictory result draws attention on the need to consider homogeneously adjusted estimators in the meta-analyses rather than raw estimators [11]. The possibility that the effect observed in the unadjusted analysis is attributable to sex cannot be excluded, as sex is known to influence the outcome of COVID-19 patients [34–40]. Our findings could have been different if the analyses had been stratified according to CD4 count or ARV protocol. Indeed, some ARVs such as tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) are reported to be potentially effective against COVID-19 and could have a protective effect in patients on these drugs, thus modifying the natural history of the disease in patients treated with these medications [41–44]. In addition, CD4 count and lymphopenia, are known to be associated with disease severity and could have an impact on the evolution of COVID-19, as one of the main mechanisms underlying COVID-19-related morbidity and mortality is cytokine storm [45]. Deep immunodepression and low CD4 count could therefore increase the probability of having lymphopenia and a pejorative course of COVID-19 in HIV patients. Indeed in two recent studies presented in the conference on retrovirus and opportunistic infections (CROI), the mortality rate between HIV-positive and HIV-negatives patients with COVID-19 was not statistically different in treated and well-controlled patients [46, 47].

The relationship between age and increased comorbidities in HIV-positive patients compared to their negative counterparts is well established. The presence of inflammation in patients with HIV, even under effective ART, is thought to be the cause of renal, cardiovascular, and neurological diseases [48, 49]. These comorbidities are associated with poor outcomes of COVID-19 [44, 49].

Our results point to a potential increased risk of admission for COVID-19 in HIV-infected individuals. This probably reflects the conservative approach used by physicians for this category of patients, given the inconsistent evidence regarding their outcome. Indeed, knowing the vulnerability of HIV patients to infections due to the pathophysiology of the disease [43], physicians may be inclined to admit HIV-positive individuals more easily than HIV-uninfected individuals, in order to better monitor them in hospital and anticipate the occurrence of any potential complications.

Our results also shows that co-infection with HIV does not increase the risk of presenting severe forms of COVID-19 as previously found by other authors [12]. Several hypotheses have been suggested to explain this phenomenon. The most plausible of which is the presence of immunodepression, which prevents patients from triggering and maintaining the cytokine storm responsible for the inflammatory manifestations of the disease, and which intensity is correlated with the severity of the disease. However, this claim would only be valid in HIV-immunocompromised patients with low CD4 counts and high viral load. A meta-analysis stratifying the outcomes according to CD4 count would therefore make it possible to distinguish whether severely immunocompromised patients are less likely to present severe COVID-19 compared with patients on ARVs with a CD4 count above 200 cells/mm³. This especially because some studies have shown a worser
prognosis in patients with CD4 counts below 200/mm\(^3\) [48]. Unfortunately, few studies included in our meta-analysis stratified their results according to CD4 count, making it difficult to pooled studies according to CD4 count and to assess the veracity of this hypothesis using available evidence.

The current study highlights the need to consider HIV patients as a sub-population at high risk of hospital admission. They also call for more studies stratifying their analyses according to the different conditions (gender, age) and comorbidities known to influence the course of COVID-19, to clarify the contribution of HIV in disease progression.

Several reviews have attempted to synthesise outcome information for HIV patients with COVID-19 [12–17, 50]. However, these studies have either included preprints and therefore unpublished articles in peer-reviewed journals, or they have meta-analysed unadjusted estimators, ignoring the potential difference in the composition of the study populations and, more importantly, the presence of factors such as co-morbidities other than HIV that could influence outcomes in

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**Fig. 4** Risk of death among COVID-19 patients according to HIV status. Meta-analysis of adjusted and unadjusted estimates

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**A-Meta-analysis of unadjusted Odds ratio (OR)**

| Study          | HIV+ Events | HIV+ Total Events | HIV− Events | HIV− Total Events | Odds Ratio | Odds Ratio |
|----------------|-------------|-------------------|-------------|-------------------|------------|------------|
| Boulle, 2020   | 115         | 3978              | 510         | 18330             | 1.04 [0.85; 1.28] |            |
| Geretti, 2020  | 30          | 122               | 13969       | 47470             | 0.78 [0.52; 1.18] |            |
| Gudipati, 2020 | 23          | 278               | 5942        | 65271             | 0.90 [0.59; 1.38] |            |
| Hadi, 2020     | 20          | 404               | 1585        | 49763             | 1.58 [1.01; 2.49] |            |
| Molina−Iturrita, 2020 | 23          | 106               | 1235        | 8751              | 1.69 [1.06; 2.69] |            |
| Nagarakanti, 2020 | 3           | 22                | 23          | 23                | 0.42 [0.09; 1.96] |            |
| Ouyang, 2020   | 4           | 22                | 213         | 1070              | 0.89 [0.30; 2.67] |            |
| Parker, 2020   | 6           | 24                | 22          | 89                | 1.02 [0.36; 2.88] |            |
| Rosenthal, 2020| 37          | 252               | 7318        | 64529             | 1.35 [0.95; 1.91] |            |
| Sigle, 2020    | 18          | 88                | 81          | 405               | 1.03 [0.58; 1.82] |            |
| Stoeckle, 2020 | 2           | 30                | 14          | 90                | 0.39 [0.08; 1.82] |            |
| Bhaskaran, 2021| 25          | 27480             | 14857       | 17255425          | 1.08 [0.71; 1.68] |            |
| Cabello, 2021  | 1           | 31                | 903         | 7030              | 0.23 [0.02; 1.56] |            |
| Ceballos, 2021 | 5           | 36                | 4369        | 18285             | 0.52 [0.20; 1.33] |            |
| Díez, 2021     | 2           | 21                | 12          | 105               | 0.82 [0.17; 3.95] |            |
| Durstenfeld, 2021| 36        | 220               | 3290        | 21308             | 1.07 [0.75; 1.53] |            |
| Esfahani, 2021 | 4           | 4                 | 151         | 496               | 93.64 [0.18; 49784.41] |          |
| Jassat, 2021   | 3407        | 34104             | 30697       | 34104             | 0.01 [0.01; 0.01] |            |
| Lee, 2021      | 13          | 68                | 35          | 181               | 0.99 [0.49; 2.00] |            |
| Sun, 2021      | 196         | 6270              | 23831       | 1426984           | 1.43 [1.34; 1.88] |            |
| Tesoriero, 2021| 207         | 2409              | 145222      | 375266            | 2.34 [2.02; 2.70] |            |
| Venturas, 2021 | 16          | 108               | 54          | 276               | 0.71 [0.39; 1.31] |            |
| Yendoa, 2021   | 46          | 1635              | 61          | 1609              | 0.73 [0.50; 1.08] |            |

Total (95% CI) 79713 19936854 100.0% 0.81 [0.47; 1.41]

Heterogeneity: \(\tau^2 = 4.871; \chi^2 = 10947.49, \text{df} = 22 (P = 0); I^2 = 100\%

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**B-Meta-analysis of adjusted Hazard ratio**

| Study          | TE    | SE    | Weight | Hazard Ratio | Hazard Ratio |
|----------------|-------|-------|--------|--------------|--------------|
| Boulle, 2020   | 0.68  | 0.1103| 62.9%  | 1.97 [1.59; 2.45] |              |
| Geretti, 2020  | 0.37  | 0.1917| 37.1%  | 1.45 [1.00; 2.11] |              |

Total (95% CI) 100.0% 1.76 [1.31; 2.35]

Heterogeneity: \(\tau^2 = 0.0230; \chi^2 = 1.92, \text{df} = 1 (P = 0.17); I^2 = 48\%\)

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primary studies. The strength of our study was to give for the first time a meta-analysis of adjusted estimators and to included only articles published in peer review journals. Furthermore, the pooled sample size in our meta-analysis was high (38,971,065 patients with COVID-19). However, some limitations of the current study are the absence of the stratification of the analysis according to ART regimen, and the level of CD4. This was due to the lack of sufficient information to conduct these subgroup analyses. Secondly the number of studies included in the meta-analysis of adjusted point estimates was low.

Conclusion
Findings of the current review suggest that patients with HIV have an increased risk of hospital admission. Although crude analysis did not show an association between HIV infection and an increased risk of death or of developing severe disease in patients with COVID-19, adjusted data from two studies suggest that HIV infection increased the risk of mortality due to COVID-19. However, this later evidence was weak as it was derived from only two studies.

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Authors’ contributions
JC conceived the original idea of the study. CD and JJN selected the studies, extracted the relevant information, and synthesized the information. CD and JJN did the literature search. CD performed analyses and wrote the first draft of the paper with inputs from JC, AR and JJN. All authors critically revised successive drafts of the paper. All authors read and approved the final manuscript.

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We declare no competing interests.

Author details
1 Epidemiology and Biostatistics Unit, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium. 2 Centre for Heart Rhythm Disorders, University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia. 3 Department of Internal Medicine and Infectious Diseases, HIV/AIDS Reference Center, Cliniques Universitaires Saint-Luc, Avenue Hippocrate 10, 1200 Brussels, Belgium.

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