Infection and Drug Resistance

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REVIEW

HIV and SARS-CoV-2 Co-Infection: What are the Risks?

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Abstract: The dramatic increase of the global pandemic of SARS-CoV-2 infection represents a critical issue that needs to be investigated to evaluate the associated risk factors for acquisition and worse outcome. The interplay between immune activation and immune depression during SARS-CoV-2 infection is an intriguing topic that still needs to be clarified. The role of HIV in SARS-CoV-2 infection is not well defined. Chronic inflammation linked to HIV infection could be a driver for a worse prognosis in people living with HIV (PLWH). We explored the role of HIV as a risk factor for SARS-CoV-2 infection and severity and which factors contributed to a worse prognosis when HIV infection was present. PubMed/MEDLINE was searched for "COVID-19" or "SARS-CoV2" and "HIV" or "AIDS" and ("hospitalization" or "intensive care" or "mechanical ventilation" or "death" OR "mortality"), both in MeSH and as free text in all fields. Our review focused on 21 studies that enrolled at least 40 PLWH. In most studies, HIV infection did not represent a risk factor for SARS-CoV-2 infection. On the contrary, the risk of severe COVID-19 and hospitalization was higher in PLWH. Low CD4 cell count consistently emerged as a risk factor for severe COVID-19. Comorbidities, either in people with or without HIV diagnosis, played a key role, especially because of their early development in PLWH.

Keywords: HIV, SARS, CoV-2, COVID-19

Introduction

As of early June 2021, more than 170 million cases of SARS-CoV-2 disease (COVID-19) were diagnosed, with over 3.7 million deaths worldwide (https://covid19.who.int/).

High mortality rates are associated with progressive respiratory failure and acute kidney injury[1] and are linked to systemic microvascular thrombosis and generalized coagulopathy, both related to high inflammatory response and continuing complement activation.

Previous health conditions have been consistently identified as risk factors for severe COVID-19 outcomes, mainly obesity, hypertension, diabetes, and chronic pulmonary disease. Due to the accelerated aging linked to persistent inflammation, cardiovascular comorbidities are more frequent among people living with HIV (PLWH) than in the general population.[2] Given this disproportionate burden, a larger number of severe cases and deaths are expected among PLWH.

HIV-1 and SARS-CoV-2 infection share CD4+T cells (CD4) loss in association with disease outcome and immunodeficiency. In both diseases, immune activation, direct attacks on CD4, and redistribution of CD4 contribute, in quite different proportions, to CD4 lymphopenia. Like for HIV, lymphopenia and marked CD4

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Received: 19 July 2021
Accepted: 8 September 2021
Published: 28 September 2021

count reduction in COVID-19 patients have been linked with poor clinical outcomes. However, when HIV and COVID-19 meet, no additional decrease of CD4 count has been observed.[3] PLWH could even experience protection from the most serious sequelae of COVID-19, because of their history of immune response or the hypothesized activity of Anti-Retroviral Treatment (ART) against SARS-CoV-2.[4,5]

The interplay between SARS-CoV-2 and HIV is affected by several conflicting aspects. The residual chronic inflammation, present even in suppressed PLWH, and the immune deficiency due to HIV may exert opposite effects. The age might also affect the outcomes in coinfected COVID-19-HIV patients, who may be younger and monitored for comorbidities at an earlier age than their HIV-negative counterparts. The conflicting evidence about their interaction may be due to the relative weight of these factors.[6]

However, evidence regarding the clinical outcome of SARS-CoV-2 in PLWH is still inconsistent.

For example, in a single-center cohort study, PLWH diagnosed with COVID-19 was not different from the COVID-19 patients without known HIV diagnosis.[7] Clinical presentation, severity of the disease, and mortality did not depend on HIV-related or ART-related factors. The standardized incidence rate of COVID-19 was lower in PLWH than in the Barcelona general population, although no comparison of mortality rate was performed between the two groups. Similarly, a propensity matched analysis revealed no difference between HIV+ and HIV- subjects, suggesting that higher mortality was likely driven by a higher number of comorbidities.[8]

On the contrary, a comparison between HIV-negative and positive patients, admitted in 207 hospitals across the United Kingdom, showed higher day-28 mortality in PLWH, after considering potential risk factors such as age, sex, comorbidities and need for oxygen at presentation. In particular, in people aged less than 60 years the adjusted hazard ratio (aHR) was 2.87 (95% confidence interval, CI, 1.70–4.86), increased risk due to HIV status.[9]

The objective of this review was to explore the role of HIV infection as risk factor for COVID-19 diagnosis, hospitalization, and death, and to investigate the risk factors for COVID-19 severity in PLWH.

Methods

Database Search

PubMed/MEDLINE was searched for "COVID-19" or "SARS-CoV-2" and "HIV" or "AIDS" and ("hospitalization" or "intensive care" or "mechanical ventilation" or "death" OR "mortality"), both in MeSH and as free text in all fields (limits: Human, English). The search was limited to articles published in English until 15 May 2021, retrieving 552 results in PubMed/MEDLINE.

We excluded papers that reported protocols, no information about HIV status, laboratory studies, case reports, and editorials.

Among 47 studies reporting on COVID-19 outcomes in PLWH, we evaluated 21 studies with at least 40 PLWH enrolled and analyzed HIV infection as risk factor for the different considered outcomes.

Bibliography from the retrieved articles was manually searched to identify further relevant literature about the relationship between SARS-CoV-2 and HIV.

HIV Infection and Its Impact on SARS-CoV-2 Infection

The main characteristics of selected studies are reported in Tables 1 and 2.

HIV Infection and COVID-19 Diagnosis

Most cohort studies did not show a higher incidence of COVID-19 in PLWH than in the general population (Table 1).[7,10–13]

In a large cohort study[10] that involved 2988 COVID-19 positive PLWH, similar diagnosis rates for COVID-19 were observed in PLWH and in people not living with known HIV diagnosis (PNLWH) after standardization (standardized rate ratio, sRR, 0.94, 95% CI, 0.91–0.97). In an adjusted model, PLWH of older age, not white non-Hispanic race/ethnicity, and living in the regions of metropolitan New York City (NYC) were significantly more likely to receive a diagnosis of COVID-19. No significant differences were observed between the main HIV transmission groups. In adjusted analysis, stage 3 HIV infection was related with an increased rate of COVID-19 diagnosis (vs stage 1: adjusted RR 1.22, 95% CI 1.07–1.38).

Cabello et al[11] described an infection rate between 0.86 (confirmed cases) and 1.68 (confirmed and suspected cases), similar to Madrid general population.

An observational prospective study[14] conducted on 2873 PLWH observed 51 COVID-19 infections (incidence 1.8%, 95% CI, 1.3–2.3). Although the rate of suspected and confirmed cases in the general population was higher (4.02%, 95% CI 4.01–4.03%), the rate of confirmed diagnosis was similar among PLWH and the general

Table 1 Main Characteristics of Selected Studies Estimating HIV as a Risk Factor for COVID-19 Infection and Negative Outcomes

First Author, Year	Country, Study Period	Study Design	Population	Sample Size	Outcome Variable(s)	Outcome(s)	Sample Characteristics	Risk Factors used for adjustement	HR or RR (95% CI) for HIV vs Non-HIV
Bhaskaran et al[18] 2021	England, Feb 1, 2020-Jun 22, 2020,	Retrospective cohort from OpenSafely database	All adults (aged ≥18 yrs) alive and in follow-up on Feb 1, 2020, with at least 1 year of continuous registration with a GP	17,255,425 without HIV record, 27,480 with HIV record	COVID-19 death	14,857 in subjects without HIV record, 25 in pts with HIV record	49.9% males in non-HIV pts, median age 49 yrs (IQR 34–64) 64.7% males among HIV pts, median age 48 yrs (IQR 40–55),	Age and sex Age, sex, deprivation, ethnicity, smoking and obesity	HR 2.90 (1.96–4.30) 2.59 (1.74–3.84) If Black: 4.31 (2.47–7.65) If non-Black 1.84 (1.03–3.26)
Boulle et al[15] 2020	South Africa, Mar 1, 2020- Jun 6, 2020	Cohort study, Western Cape Provincial Health Data Centre	Public-sector pts aged ≥20 yrs, alive before 1 March 2020	2,920,380 without HIV, 540,552 with HIV	COVID-19 death	510 in HIV-negative pts, 115 in HIV pts	43.9% males among non-HIV pts, 33.5% males among HIV pts	Age and sex Age, sex, Diabetes, hypertension, tuberculosis, CKD, CPD	HR 1.97 (1.59–2.45) All subjects 2.14 (1.70–2.70) Hospitalized 1.45 (1.14–1.84)
Braunstein et al[12] 2021	New York City, March 1, 2020 – June 2, 2020	NYC Department of Health and Mental Hygiene's (DOHMH) HIV surveillance registry, the NYC DOHMH COVID-19 surveillance system	People with confirmed diagnosis of COVID-19	202,012 NYC residents with COVID-19 infection, 2,410 PWH with COVID-19	Hospitalization, ICU admission, death	26% vs 42%, 3% vs 5%, 8% vs 13%	51.1% NYC male residents (45–64 yrs 36.1%, ≥ 75 yrs 11.8%), 71.4% PWH (45–64 yrs 56.1%, ≥75 yrs 5.1%)		NYC HIV prevalence 1.5%, COVID-19 cases in PWH 1.06%: PWH were not overrepresented among COVID-19 cases in NYC

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https://doi.org/10.2147/IDR.S277899

Table 1 (Continued).

First Author, Year	Country, Study Period	Study Design	Population	Sample Size	Outcome Variable(s)	Outcome(s)	Sample Characteristics	Risk Factors used for adjustement	HR or RR (95% CI) for HIV vs Non-HIV
Cabello et al[11] 2021	Spain, Feb 1, 2020-May 20, 2020	Retrospective cohort study, Quirónsalud network of public hospitals in the Community of Madrid and registry	Non-HIV and HIV individuals with probable or confirmed SARS-CoV-2 infection	6,663,394 living in the Community of Madrid, 3,738 PLWH regularly followed up in the network	Rate of COVID-19 diagnosis, suspected or confirmed	18,790 diagnoses in non-HIV group; 63 diagnoses in the HIV group. 7,030 (903 deaths) and 31 (1 death) with confirmed infection			Confirmed infection Non-HIV 1.00% HIV 0.86% Mortality rate Non-HIV 12.8% HIV 3.2%
Geretti et al[9] 2020	United Kingdom, Jan 21, 2020-Jun18, 2020	Prospective cohort study, ISARIC WHO CCP-UK, 207 hospitals in UK	Pts aged ≥18 years hospitalized with laboratory-confirmed or highly likely SARS CoV-2 infection	47,470 without HIV, 122 with HIV	Admission to intensive Care Unit, Day-28 mortality	13,969 non-HIV pts, 30 HIV pts	57.1% males among non-HIV pts, median age 74 yrs (IQR 60–84), 66.1% males among HIV pts, median age 56 yrs (IQR 49–62)	Age, sex, ethnicity, baseline date, indeterminate/ probable hospital acquisition of COVID-19, comorbidities, and hypoxia/receiving oxygen at presentation	HR 1.69 (1.15–2.48) Age <60 yrs: 2.87 (1.70–4.86)
Hadi et al[8] 2020	USA, period not published	Cohort study, unspecified number of centers in southern (44% of pts), northeast (22% of pts) and other geographic areas	Pts aged >10 yrs in the multicenter research network TriNETX	49,763 HIV-negative, 404 HIV-positive	COVID-19 death and hospitalization within 30 days from diagnosis	Death: 1,585 and 20 Hospitalization: 5,254 and 78	44.9% males, mean age 48.8 ± 19.2 in HIV-negative cohort, 70.6% males, mean age 48.2 ± 14.2 yrs in the HIV cohort		RR[a]: mortality 1.55 (1.01–2.39) hospitalization 1.83 (1.50–2.24)

Hadi et al[8] 2020	USA, period not published	Nested case-propensity-matched controls study, unspecified number of centers in southern (44% of pts), northeast (22% of pts) and other geographic areas	Pts aged >10 yrs in the multicenter research network TriNETX	404 HIV negative, 404 HIV positive	COVID-19 death and hospitalization within 30 days from diagnosis	Death: 15 and 20 Hospitalization: 46 and 78	70.3% males, mean age 47.8 ± 15.9 in HIV-negative controls; 70.6% males, mean age 48.2 ± 14.2 yrs in HIV cases	Crude, after matching for BMI, diabetes, hypertension, chronic lung diseases, chronic kidney disease, race, history of nicotine dependence and sex	RR[a]: mortality 1.33 (0.69–2.57) hospitalization 1.70 (1.21–2.38)
Inciarte et al[7] 2020	Spain, Mar 1, 2020-May 10, 2020	Prospective study, Hospital Clinic of Barcelona	Pts aged ≥ 18 yrs, known diagnosis of HIV and laboratory-confirmed COVID-19	Incidence rate in Barcelona inhabitants, standardized incidence rate in PLWH	Confirmed infection incidence rate ratio	Incidence rate 282/10,000 in Barcelona inhabitants, 107/10,000 in PLWH		Age and sex standardized	Standardized incidence RR[b] 0.38 (027–0.52)
Miyashita et al[17] 2021	USA, Mar 1, 2020-Apr 30, 2020	Retrospective cohort, New York Hospital and ambulatory care unit network	Pts with laboratory-confirmed or highly likely SARS CoV-2 infection	8751 HIV negative, 161 PLWH	ICU admission, intubation, or death	ICU admission: 1946 and 36; Intubation: 733 and 19; death: 1235 and 23	55.0% males, ≤50 yrs 34% 51–65 yrs 28% ≥66 yrs 38% in non-HIV pts; 78% males, ≤50 yrs 24% 51–65 yrs 51% ≥66 yrs 25% in PLWH		No significant overall effect of HIV Pts ≤50 yrs: 2.97 (1.29–6.84) for intubation 4.36 (1.43–13.30) for death
Patel et al[16] 2021	USA, Mar 10, 2020-May 11, 2020	Retrospective cohort, Montefiore Health System	Pts aged ≥18 yrs with laboratory-confirmed SARS CoV-2 infection	4513 non-HIV pts, 100 PLWH	Intubation, acute kidney injury (AKI), length of hospitalization stay (LOS), and in-hospital death.	Intubation: 6363 and 21; AKI: 2072 and 46; LOS (days): both 5 (IQR 3–9); Death: 1104 and 22	53% males, median age 65 yrs (IQR 54–76); 44.8% males, median age 61 yrs (IQR 52–69)	Age, sex, race/ethnicity, history of chronic lower respiratory disease, BMI, calendar time, and accounting for competing risks	Intubation HR 1.73 (1.12–2.67) AKI HR 1.21 (0.96–1.52) Death HR 1.20 (0.78–1.83)

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https://doi.org/10.2147/IDR.S277899 DovePress

Table 1 (Continued).

First Author, Year	Country, Study Period	Study Design	Population	Sample Size	Outcome Variable(s)	Outcome(s)	Sample Characteristics	Risk Factors used for adjustement	HR or RR (95% CI) for HIV vs Non-HIV
Sachdev et al[13] 2021	USA, Mar 24, 2020-Sep 3, 2020	Retrospective cohort, San Francisco Department of Public Health	Pts with laboratory-confirmed SARS CoV-2 infection	272,555 HIV-negative subjects, 4252 PLWH	Positivity rate	9626 non-HIV subjects, 183 HIV subjects	Only PLWH: 91.2% males, mean age 48 (IQR 37–57)		Positivity rate 3.5% vs 4.5%, p=0.00004 Housing as a risk factor
Sigel et al[19] 2020	USA, Mar 12, 2020-Apr 23, 2020	Retrospective cohort, 5 hospitals in the Mount Sinai Health System, New York	Hospitalized non-HIV and HIV pts with laboratory-confirmed SARS CoV-2 infection	404 HIV-negative, 88 PLWH (match 5:1)	Mechanical ventilation, death	Mechanical ventilation: 23% and 18% Death: 20% and 21%	76% males, median age 60 yrs (IQR 55–67) in PNLWH 75% males, median age 61 yrs (IQR 54–67) in PLWH	Demographics, COPD, smoking, baseline ferritin level, baseline white blood cell count	Death HR 1.13 (0.62–2.08)
Tesoriero et al[10] 2021	USA, Mar 1, 2020-Jun 7, 2020	Retrospective cohort, HIV surveillance Registry, Electronic Clinical Laboratory ReportingSystem, and State Health Information Network for NY, New York State (NYS)	Pts in public health information exchange network connecting NYS health care institutions	19,345,499 pts without diagnosed HIV, 108,062 PLWH	COVID-19 diagnosis, hospitalization, in-hospital death	Diagnosis rate: 19.4/1000 and 27.7/100 Hospitalization rate: 3.15/1000 and 8.29/1000 Death rate: 0.75/1000 and 1.92/1000	48.4% males, <40 yrs 51.2% 40–59 yrs 25.5% ≥60 yrs 23.3% in PNLWH; 71.9% males, <40 yrs 25.1% 40–59 yrs 49.6% ≥60 yrs 25.2% in PLWH	Age, sex, region of residence	**sRR per population** Diagnosis 0.94 (0.91–0.97) Hospitalization 1.38 (1.29–1.47) In-hospital death 1.23 (1.07–1.40) **sRR per diagnosis** Hospitalization 1.47 (1.37–1.56) in-hospital death 1.30 (1.13–1.48) **sRR per hospitalization** in-hospital death 0.96 (0.83–1.09)

Vizcarra et al[14] 2020	Spain, Mar 1, 2020-Apr 30, 2020	Prospective cohort study at the Hospital Universitario Ramón y Cajal, Madrid	Non-HIV and HIV infected individuals aged ≥18 yrs with suspected or confirmed COVID-19	Community of Madrid general population, HIV-infected individuals regularly followed up at the Hospital Universitario	COVID-19 diagnosis	269,417 in non-HIV and 51 in HIV suspected diagnoses; confirmed in 35 and 61,577 respectively	Mean age 59.7 ± 19.3 yrs in PNLWH; 53.6 ± 10.0 yrs in PLWH	–	Confirmed COVID-19 rate 0.92 (0.91–0.93) vs. 1.22 (0.85–1.68)

Notes: [a]risk ratio; [b]rate ratio.

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; CPD, chronic pulmonary disease; GP, general practitioner; HR, hazard ratio (aHR, adjusted HR); ICU, intensive care unit; IQR, interquartile range; LOS, length of hospital stay; OR, odds ratio; pts, patients; PLWDH, people living with diagnosed HIV; PLWH, people living with HIV; RR, risk ratio or rate ratio; SHR, subhazard ratio for death; sRR, standardized rate ratio; VL, viral load; yrs, years.

population (0.92%, 95% CI 0.91–0.93%, and 1.22%, 95% CI 0.85–1.68% respectively).

On the same line, Braunstein et al[12] observed that COVID-19 did not disproportionately affect the PLWH in NYC, since the diagnosed HIV with COVID-19 represented 1.06% of all confirmed COVID-19 cases, and the overall prevalence of HIV in the NYC population was 1.5% in 2018.

On the contrary, in the analysis from Inciarte et al,[7] the incidence of confirmed COVID-19 cases in a cohort of 5683 PLWH was 62% lower than in the Barcelona population.

On the other hand, Sachdev et al[13] found a significantly higher diagnosis rate in 4252 PLWH compared to PNLWH (4.5% vs 3.5%, p=0.00004).

Finally, we considered the prevalence of comorbidities in PLWH with or without COVID-19. Boulle et al[15] described a slightly lower prevalence of diabetes (4% vs 11%) and hypertension (12% vs 19%) in PLWH without COVID-19 vs PLWH with COVID-19. Vizcarra et al[14] confirmed the lower prevalence of diabetes and hypertension in PLWH without COVID-19, also finding a lower percentage of patients with chronic kidney disease and liver disease in this subset of patients.

HIV Infection and Hospitalization for COVID-19

Many studies demonstrated a higher rate of hospitalization in PLWH than in PNLWH (Table 1). [8,10,12,14]

Tesoriero et al[10] observed population-level rates of COVID-19 hospitalization significantly higher among PLWH (8.28 per 1000) than among PNLWH (3.15 per 1000; sRR 1.38, 95% CI, 1.29–1.47). In the adjusted analysis, older age and region were associated with hospitalization. This study observed an increasing hospitalization risk across stage 1, 2 and 3 of HIV infection: more in detail, a per-person hospitalization standardized rate analysis was conducted by stage of HIV disease. Compared to people living without HIV infection, hospitalization risk was progressively higher by HIV stage 1 infection: sRR was 1.19 (95% CI 1.08–1.30) for stage 1, 1.60 (95% CI 1.42–1.78) for stage 2, and 2.66 (95% CI 2.20–3.13) for stage 3 infection. Hadi et al[8] with their large analysis conducted on more than fifty thousand COVID-19 patients (404 with preexisting HIV diagnosis) confirmed a significantly higher proportion of hospitalization in the HIV-positive group (19.3% vs 11.4%; risk ratio 1.70, 95% CI 1.21–2.38), after propensity score matching for body mass index (BMI), diabetes, hypertension, chronic lung

Table 2 Main Characteristics of Selected Studies Exploring Risk Factors for COVID-19 Infection and Negative Outcomes in HIV-Positive Subjects

First Author, Year	Country, Study Period	Study Design	Population	Sample Size	Outcome Variable(s)	Outcome(s)	Sample Characteristics	Risk Factors used for adjustment	HR or RR (95% CI)
Boulle et al[15] 2020	South Africa, Mar 1, 2020- Jun 6, 2020	Cohort study, Western Cape Provincial Health Data Centre	Public-sector pts aged ≥20 yrs, alive before 1 March 2020	601 HIV pts hospitalized	COVID-19 death	105 deaths	–	Adjusted estimates, unclear if complete model or only age and sex-adjusted	CD4 (n=199) <200 cells/μL vs ≥350 aHR 1.97 (1.14–3.40) pts on TDF vs ABC/AZT aHR, 0.41 (0.21–0.78)
Braunstein et al[12] 2021	New York City, March 1, 2020 – June 2, 2020	NYC Department of Health and Mental Hygiene's (DOHMH) HIV surveillance registry, the NYC DOHMH COVID-19 surveillance system	People with confirmed diagnosis of COVID-19	2410 PWH with COVID-19, 113,907 PWH without COVID-19	Hospitalization, ICU admission, death	1101 hospitalized, 124 ICU, 312 deaths	–	–	By latest CD4 cell count, most hospitalized PWH had ≥500 cells/μL; those with ICU admission, had <200 cells/μL. VL did not differ by outcome. Socio-economic status and ethnicity were strong determinants of severe outcome
Cabello et al[11] 2021	Spain, Feb 1, 2020-May 20, 2020	Retrospective cohort study, Quirónsalud network of public hospitals in the Community of Madrid	HIV-infected patients with probable or confirmed SARS-CoV-2 infection	PLWH regularly followed up in the network	Severity of COVID-19	63 PLWH with COVID-19, 45 with non-severe, 18 with severe disease	48.9% males, median age 46 yrs (IQR 37–56)	Age, comorbidities	Age associated with severe COVID-19 Current and nadir CD4, ART N.S.
Dandachi et al[23] 2020	USA, Apr 1, 2020- Jul 1, 2020	Cohort study, COVID-19 in PLWH Registry	Pts aged ≥ 18 yrs, known diagnosis of HIV and laboratory-confirmed COVID-19	286 PLWH	COVID-19 severity: composite endpoint (intensive care admission, invasive mechanical ventilation, or death)	164 hospitalizations, 47 ICU admissions, 27 deaths	74.1% males, mean age 51.4 ± 14.4 yrs	Age, sex, ethnicity, CD4 count, HIV viral load suppression, hypertension, diabetes, CLD, CKD, chronic liver disease	**Hospitalization** CD4 <200 vs CD4>500 cells/mm^3 OR 3.67 (1.64–17.10) **Severe outcome:** CD4 <200 vs CD4>500 cells/mm^3 OR 2.80 (1.02–7.67) Viral load suppression N. S.

Del Amo et al[26] 2021	Spain, Feb 1, 2020-Apr 15, 2020	Cohort study, cases identified in 60 ID clinics	Pts aged ≥ 18 yrs, known diagnosis of HIV and laboratory-confirmed COVID-19	236 PLWH with COVID-19 diagnosis, from a population of 77,590 HIV-positive persons receiving ART	Hospital admission, ICU admission, death	151 hospital admission, 15 ICU admission, 20 deaths	75% males, 20–39 yrs 18%, 40–49 yrs 23%, 50–59 yrs 36%, 60–69 yrs 15%, 70–79 yrs 9%	Age and sex	Diagnosis and hospitalization greater in men, increased in those older than 70 yrs. Pts on TDF/FTC had the lowest risk for COVID-19 diagnosis and hospitalization
Di Biagio et al[25] 2020	Italy, Feb 21, 2020-May 12, 2020	Retrospective cohort, cases identified in 14 ID clinics	Pts aged ≥ 18 yrs, known diagnosis of HIV and laboratory-confirmed COVID-19	69 PLWH	Hospital admission, death	38 hospital admission, 7 deaths	72.4% males, median age 54 yrs (IQR 47–59)	Age and sex	Hospitalization: CD4 nadir (by 50 cells/mm^3) OR 0.83 (0.72–0.96) VL suppression N.S.
Etienne et al[21] 2020	France, Mar 1, 2020-Apr 30,2020	Prospective cohort, cases identified in one ID clinic	Pts aged ≥ 18 yrs, known diagnosis of HIV and COVID-19	54 PLWH (38 laboratory-confirmed, 16 clinical diagnosis)	Severity of COVID-19	35 moderate, 14 severe, 5 critical	61.5% males, median age 54 yrs (IQR 57–60)	–	Increased risk of severe form with older age, higher BMI, cardiovascular comorbidities. Nadir CD4, last CD4, CD8 and VL N.S.
Geretti et al[9] 2020	United Kingdom, Jan 21, 2020-Jun18, 2020	Prospective cohort study, ISARIC WHO CCP-UK, 207 hospitals in UK	PLWH aged ≥18 years hospitalized with laboratory-confirmed or highly likely SARS CoV-2 infection	122 PLWH	Day-28 mortality	30 deaths	66.1% males, median age 56 yrs (IQR 49–62)	–	Age (by 1 year) 1.05 (1.01–1.09) Diabetes 2.18 (1.02–4.66) Obesity 2.89 (1.28–6.53) Recorded ART 0.39 (0.15–1.01)

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https://doi.org/10.2147/IDR.S277899 DovePress

Table 2 (Continued).

First Author, Year	Country, Study Period	Study Design	Population	Sample Size	Outcome Variable(s)	Outcome(s)	Sample Characteristics	Risk Factors used for adjustment	HR or RR (95% CI)
Gervasoni et al[24] 2020	Italy, Feb 21, 2020-Apr 16, 2020	Retrospective cohort, cases identified in one ID clinic	Pts aged ≥ 18 yrs, known diagnosis of HIV and laboratory-confirmed COVID-19	47 PLWH, from a population of about 6000 HIV-positive persons	Severity of COVID-19	13 hospitalizations, 2 mechanical ventilations, 2 deaths	77% males, mean age 51 ± 11 yrs	–	No increased risk of severe outcome in comparison with non-HIV
Ho et al[27] 2021	USA, Mar 2, 2020-Apr 15, 2020	Retrospective cohort, cases identified in 5 New York emergency department	Pts aged ≥ 18 yrs, known diagnosis of HIV and laboratory-confirmed COVID-19	93 PLWH, 72 with hospital admission	ICU admission, use of mechanical ventilation, or death	19 ICU care, 15 mechanical ventilation, 19 deaths	72% males, median age 58 (IQR 52–65)	-	No association with CD4 at presentation, nadir CD4 or viral load
Hoffmann et al[20, a] 2021	Europe, Feb 21, 2020-Jun12, 2020	Retrospective analysis, cases identified in ID centers in Germany, Italy, Spain	Pts aged ≥ 18 yrs, known diagnosis of HIV and laboratory-confirmed COVID-19	175 PLWH	Severity of COVID-19	126 mild/ moderate 49 severe/ critically ill (7 deaths)	82% males, 20–39 yrs 26%, 40–49 yrs 21%, 50–59 yrs 38%, 60–69 yrs 14%, ≥70 yrs 4%	Age, current CD4 cell count, comorbidity (Y/N)	**Severity** CD4 <350 vs ≥350 cells/ mm^3 OR 2.85 (1.26–6.44) VL suppression N.S. **Mortality** Nadir CD4 <200 cells/ mm^3 Crude OR 10.11 (1.19–86.10)
Inciarte et al[7] 2020	Spain, Mar 1, 2020-May 10, 2020	Prospective study, Hospital Clinic of Barcelona	Pts aged ≥ 18 yrs, known diagnosis of HIV and laboratory-confirmed COVID-19	53 cases among 5863 PLWH	Severity of COVID-19	26 hospital admissions, 6 severe disease, 4 ICU admissions, 2 deaths	85% males, median age 44 yrs (IQR 36–52)	-	No HIV or ART factor significantly associated with COVID-19 diagnosis or severity (CD4, nadir CD4, ART)

Maggiolo et al[22] 2021	Italy, Mar 1, 2020-Jun15, 2020	Retrospective cohort, Division of Infectious Diseases, Bergamo	Pts aged ≥18 years known diagnosis of HIV	124 PLWH	Laboratory-confirmed or highly likely SARS CoV-2 infection	55 with COVID-19, 69 without SARS-CoV-2 infection	75.8% males, median age 51 yrs (IQR 46–59)	-	No associations detected for infection, 4 deaths associated with higher age and comorbidity (CD4, nadir CD4, CD8, VL, ART, yrs of HIV)
Patel et al[16] 2021	USA, Mar 10, 2020-May 11, 2020	Retrospective cohort, Montefiore Health System	Pts aged ≥18 yrs with laboratory-confirmed SARS CoV-2 infection	100 HIV pts, 15 with unsuppressed VL, 81 with suppressed VL	Intubation, acute kidney injury (AKI), length of hospitalization stay (LOS), and in-hospital death.	Intubation: 0 and 21; AKI: 7 and 38; LOS (days): 7 (IQR 4–12) and 5 (IQR 3–8); Death: 0 and 22	53% males, median age 65 yrs (IQR 54–76); 44.8% males, median age 61 yrs (IQR 52–69)	Age, sex, race/ethnicity, history of chronic lower respiratory disease, BMI, calendar time, and account for competing risks	Intubation: CD4 (by 100) HR 1.13 (1.06–1.20); LOS higher in unsuppressed pts; Unadjusted comparison for intubation and death p=0.04 and 0.02 respectively (favorable to unsuppressed pts)
Sigel et al[19] 2020	USA, Mar 12, 2020-Apr 23, 2020	Retrospective cohort, 5 hospitals in the Mount Sinai Health System, New York	Hospitalized non-HIV and HIV pts with laboratory-confirmed SARS CoV-2 infection	88 PLWH	COVID-19 death	18 deaths	75% males, median age 61 yrs (IQR 54–67)	Age, sex, race/ethnicity	Organ transplant recipient status: SHR 3.85 (1.87–7.94) NRTI use: SHR 0.31 (0.12–0.80) CD4, VL N.S.

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https://doi.org/10.2147/IDR.S277899

Table 2 (Continued).

First Author, Year	Country, Study Period	Study Design	Population	Sample Size	Outcome Variable(s)	Outcome(s)	Sample Characteristics	Risk Factors used for adjustment	HR or RR (95% CI)
Tesoriero et al[10] 2021	USA, Mar 1, 2020- Jun 7, 2020	Retrospective cohort, HIV surveillance Registry, Electronic Clinical Laboratory Reporting System, and State Health Information Network for NY, New York State	Pts in public health information exchange network connecting NYS health care institutions	108,062 PLWH	COVID-19 diagnosis, hospitalization, in-hospital death	2988 COVID-19 diagnoses, 896 hospitalizations, 207 deaths	71.9% males, Mean age 54.0 ± 13.3	-	**For diagnosis** CD4 cell count Stage 2 aRR 1.02 (0.94–1.11) Stage 3 aRR 1.22 (1.07–1.38) VL unsuppressed RR 0.74 (0.65–0.84) **For hospitalization** CD4 cell count Stage 2 RR 1.29 (1.11–1.49) Stage 3 aRR 1.69 (1.38–2.07) VL unsuppressed RR 1.37 (1.11–1.68) **For in-hospital death** CD4 cell count Stage 2 RR 1.11 (0.81–1.51) Stage 3 RR 1.26 (0.85–1.86) VL unsuppressed 0.84 (0.54–1.32)
Vizcarra et al 2020	Spain, Mar 1, 2020-Apr 30, 2020	Prospective cohort study at the Hospital Universitario Ramón y Cajal, Madrid	HIV infected individuals aged ≥18 yrs with suspected or confirmed COVID-19	HIV infected patients with updated data on clinical variables	COVID-19 diagnosis, hospitalization, outcome	51 PLWH with COVID-19, 1288 PLWH without COVID-19; 28 hospitalizations, 2 deaths	84% males, mean age 53.3 ± 9.5 yrs; 77% males, mean age 53.5 ± 10.2 yrs	Age, gender, nadir CD4 cell counts, and years of HIV infection.	For diagnosis OR 3.7 (1.6–8.7) for tenofovir use CD4 and VL N.S.

Notes: [a] partially includes Gervasoni[24] and Vizcarra.[13]

Abbreviations: ABC; abacavir; AKI, acute kidney injury; ART, antiretroviral therapy; AZT, zidovudine; CI, confidence interval; CKD, chronic kidney disease; CPD, chronic pulmonary disease; FTC, emtricitabine; HR, hazard ratio (aHR, adjusted HR); ICU, intensive care unit; IQR, interquartile range; LOS, length of hospital stay; FTC, emtricitabine; NRTI, nucleoside reverse transcriptase inhibitors; OR, odds ratio; pts, patients; PLWDH, people living with diagnosed HIV; PLWH, people living with HIV; RR, rate ratio (aRR, adjusted RR); SHR, subhazard ratio for death; sRR, standardized rate ratio; TDF, tenofovir disoproxil fumarate; VL, viral load; yrs, years.

disease, chronic kidney disease, race, nicotine dependence and sex.

In their observational prospective study, Vizcarra et al[14] observed a high hospitalization rate (55%), but their sample was small (51 patients).

A retrospective observational study conducted by Cabello et al[11] analyzed 63 HIV-positive patients with COVID-19, observing a lower hospitalization rate in PLWH confirmed cases compared with PNLWH (48.4% vs 63.5%).

Braunstein et al[12] demonstrated that, in comparison with all diagnosed COVID-19 cases in NYC, a higher proportion of PLWH were hospitalized for COVID-19 (42% vs 26%).

HIV Infection and ICU Admission for COVID-19

In the first three months of the SARS-CoV-2 infection outbreak in NYC, Braunstein et al[12] showed a rate of ICU admission of 5% in 2410 PLWH vs 3% in 202,012 PNLWH with confirmed COVID-19.

Patel et al[16] conducted a retrospective cohort study on 4613 COVID-19 positive patients; 100 were PLWH. In an analysis adjusted for age, sex, race/ethnicity, BMI, history of chronic lower respiratory diseases and calendar time, PLWH had an increased risk of intubation compared to PNLWH (aHR 1.73, 95% CI 1.12–2.67; p= 0.01).

Miyashita et al[17] also carried out a retrospective study on 8912 patients with COVID-19; 161 had also HIV infection. The author observed a higher risk of intubation in the age group under 50 years (relative risk 2.97, 95% CI, 1.29–6.84), whilst no differences were observed in the other age groups.

On the contrary, Geretti et al[9] reported no differences between HIV-negative patients and PLWH in the risk of admission to ICU, after adjustment for sex, ethnicity, age, baseline date, indeterminate/probable hospital acquisition of COVID-19 and comorbidities, regardless of HIV status (odds ratio, OR 1.22, 95% CI, 0.80–1.87; p=0.35).

HIV Infection and Mortality for COVID-19

A very large retrospective cohort study, reported by Bhaskaran et al[18] compared the risk of COVID-19 death among PLWH and PNLWH: crude mortality risk was similar between the two groups (HR 1.03, 95% CI 0.7–1.52); after adjusting for age and sex, HIV infection was associated with a higher risk of COVID-19 death (HR 2.90, 95% CI 1.96–4.30; p < 0.0001), with a slight attenuation after further adjustment for index of multiple deprivation, ethnicity, obesity and smoking (HR 2.59, 95% CI, 1.74–3.84; p < 0.0001).

The Western Cape Department of Health (South Africa) performed a study on 223,080 COVID-19 positive patients[15], 625 of them died. A greater proportion of COVID-19 death was observed in PLWH younger than 50 years compared with same age PNLWH (39% vs 13%). After adjusting for age, sex, and other comorbidities, HIV was associated with increased COVID-19 mortality (aHR 2.14, 95% CI 1.70–2.70), irrespectively of viremia or immunosuppression prior to the COVID-19 infection.

In the large Tesoriero cohort study[10] (2988 patients), no differences were observed in in-hospital death between people living with diagnosed HIV infection, and people without diagnosed HIV infection (adjusted rate ratio 0.98, 95% CI 0.85–1.12). Anyway, a significantly higher mortality rate per person and per diagnosis was observed in PLWH (case fatality rate, 69.28 per 1000 vs 38.70 per 1000: sRR 1.30, 95% CI, 1.13–1.43).

Hadi et al[8] performed an analysis on all patients diagnosed with COVID-19 (total 50,167), who were divided into two cohorts, based on the presence or absence of HIV infection: 49,763 patients without concurrent HIV infection and 404 with preexisting HIV diagnosis. In the unmatched analysis, PLWH had higher mortality at 30 days from COVID-19 diagnosis (4.95% vs 3.2%, risk ratio 1.55, 95% CI, 1.01–2.39), while after matching for BMI, diabetes, hypertension, chronic lung diseases, chronic kidney diseases, race, nicotine dependence and sex, no difference in mortality was found between the two groups (5.0% vs 3.7%, risk ratio 1.33, 95% CI, 0.69–2.57%). These observations are probably due to the demographic characteristics of PLWH (greater proportion of men, African American race, obesity, and the other listed comorbidities). No differences in mortality were found even in two subgroup analyses, including only (1) patients with HIV-associated diseases (risk ratio 1.12, 95% CI 0.59–2.12) or (2) patients with antiretroviral therapy history (risk ratio 1.22, 95% CI 0.68–2.18), compared to non-HIV subjects.

On the other hand, Braunstein et al[12] reported a mortality of 13% vs 8% in PLWH vs PNLWH.

The retrospective observational study that was conducted by Cabello et al[11] observed a lower global mortality rate in PLWH (3.22% vs 13.3%), including severe cases (6.7% vs 21.0%). No association was observed between HIV-related factors and COVID-19 severity.

Considering studies that enrolled less than 200 PLWH, most did not report higher mortality in the overall PLWH population (Table 1),[9,16,17,19] whereas some differences were observed in patients aged less than 60 years in the study of Geretti et al[9] and in patients aged less than 50 years in the study of Miyashita et al.[17]

Risk Factors for COVID-19 Severity in PLWH

Risk Factors for Severe COVID-19

In PLWH, rates of severe COVID-19 ranged from 11% to 28% (Table 2).[7,14,19–22] Severe SARS-CoV-2 Infection was associated mostly with age and presence of comorbidities (see Table 3).

In a cohort of 175 PLWH, Hoffman et al[20] reported a 28% rate of severe COVID-19 (49/175). Severity of COVID-19 was associated with age equal or higher than 50 years (OR 2.49, 95% CI 1.24–5.03), nadir CD4 <200 cells/μL (OR 2.10, 95% CI 1.05–4.21) and current CD4 <350 cells/μL (OR 3.30, 95% CI 1.49–7.31).

On the other hand, Inciarte et al[7] showed a severity rate of 11.3% (6/53) in a cohort of PLWH with a median age of 44 years (interquartile range, IQR, 36–52), nadir CD4 303 (IQR 140–434) and last CD4 624 (IQR 462–838) with a 43% prevalence of comorbidities (23/43, mainly hypertension and diabetes). No association was found with immune-virological parameters and anti-retroviral treatment.

In most studies, patients had high CD4 (usually >500 cells/μL) and suppressed HIV-viral load (VL).

Hospital Admission

The reported hospitalization rates ranged from 27% to 63% (Table 2).[10,23–26] Age, low CD4 nadir and low current CD4 were the most frequent risk factors.

In Italy, Gervasoni et al[24] showed a hospitalization rate of 27.7% (13/47) in PLWH with mean CD4 of 636 ± 290 cells/μL, mostly with undetectable HIV-VL (94%<20 copies/mL) with mean age of 51±11 years. Di Biagio et al[25] showed a higher rate of hospitalization in PLWH with lower nadir CD4 and lymphocytes.

Del Amo et al[26] described a hospitalization rate of 63.9% (151/236), with a higher risk for men and subjects older than 70 years, and a lower risk in patients receiving tenofovir/emtricitabine.

Two large cohorts[10,15] described hospitalization rates lower than 30%.

Tesoriero et al[10] showed a hospitalization rate of 30% in 2988 PLWH in New York State, with a higher risk in patients with lower CD4 and unsuppressed VL, while Boulle et al[15] described a low percentage of hospital admission in PLWH (601/3978, 15.1%) in South Africa, with a higher risk in patients with low CD4. These significant differences could be due to different socio-economic status and to significantly lower age in Boulle's study. However, lower CD4 were consistently reported as a risk factor for hospitalization in PLWH.

ICU Admission

Rates of ICU admission ranged from 5% to 28.7% (Table 2).

Dandachi et al[23] showed an ICU admission rate of 28.7% (47/286) in a sample of PLWH aged 51.4 years on average, with a higher risk in patients with CD4<200 cells/μL.

Ho et al[27] reported an ICU admission rate of 26.4% (19/72) in patients with median CD4 554 (IQR 339–752) and HIV-VL <50 copies/mL at last visit. The median age was 58 years (IQR 52–65).

Patel et al[16] showed a risk of intubation in 26% (21/81) of PLWH, independently of HIV-VL suppression, in a sample with median age of 65 years (IQR 54–76). Moreover, in this study, increased CD4 were related with an increased risk of intubation (aHR 1.13, 95% CI 10.6–1.20, by 100 cells/mmc increase in CD4).

On the other hand, Braunstein et al[12] described a 5% rate of ICU admission, with a higher risk in patients with CD4 less than 200 cells/μL.

Vizcarra et al[14] described an ICU admission rate of 12% (6/51) in a cohort of PLWH with a mean age of 53.3 (±9.5) years, with 63% of patients affected from at least one comorbidity, median CD4 nadir 224 (IQR 101–437), recent CD4 565 (IQR 296–782) and HIV-VL <50 copies in 98% of patients.

Death

The reported mortality rates are extremely variable, depending on sample characteristics, region of origin and socio-economic factors (Table 2).

Evaluating HIV-related risk factors, Boulle et al[15] showed data about 199 hospitalized patients with available CD4: 70 had CD4 <200 cells/μL. In this group, a higher mortality was demonstrated (aHR 1.97, 95% CI 1.14–3.40) in comparison to PLWH with CD4≥350 cells/μL. A protective role of tenofovir disoproxil-fumarate vs abacavir was also found (aHR 0.41, 95% CI 0.21–0.78).

Dandachi et al[23] described a sample of PLWH mostly (95%) on antiretroviral therapy (ART) and with viral

Table 3 Comorbidities and Antiretroviral Treatments in HIV Subjects

First Author, Year	Risk factors	Overall Prevalence in HIV/COVID-19 (%)	Prevalence in Severe[a] COVID-19 (%)	Prevalence in Mild/Moderate[b] COVID-19 (%)	Association with Outcome (Results or Authors' Conclusion)
Bhaskaran et al.[18] 2021	**Comorbidities in PWH with COVID-19 diagnosis (n=27,480)**		**N=25 (death)**		
	Hypertension	19.3	60.0	19.2	The relatively small number of deaths among individuals with HIV, reflecting the young age distribution of the HIV group, prevented definitive conclusions about the role of comorbidities in HIV subjects
	Diabetes	9.8	56.0	9.8	
	Reduced Kidney function	5.7	36.0	5.6	
	ART	NA[c]	NA	NA	NA
Boulle et al.[15] 2020	**Comorbidities in PWH with COVID-19 diagnosis (n=3978)**		**N=115 (deaths)**		
	Diabetes	11.0	50	10	No separate estimates for HIV subjects. However, diabetes, hypertension, chronic kidney disease, and tuberculosis represented risk for COVID-19 death irrespectively of HIV status
	Hypertension	19.0	42	18	
	Chronic kidney disease	2.6	18	2	
	Lung disease/asthma	5.7	9	6	
	Previous tuberculosis	23.0	37	22	
	Current tuberculosis	4.7	14	4	
	ART	NA	NA	NA	**Death: Adjusted HR (95% CI)**
	TDF vs ABC or ZDV				0.57 (0.31–1.04)
	LPV vs EFV				0.68 (0.29–1.63)
	ATV vs EFV				1.09 (0.25–4.82)
	DTG vs EFV				0.62 (0.17–2.22)
	ART duration	NA	NA	NA	**Death: adjusted HR (95% CI)**
	ART 1–2 years vs < 1 year				1.28 (0.37–4.42)
	ART >2 years vs <1 year				0.55 (0.21–1.42)
Braunstein et al.[12] 2021	**Comorbidities in PWH with COVID-19 diagnosis (n=1549)**		NA	NA	NA
	Asthma	4.6			
	Cancer	9.3			
	Diabetes	27.6			
	Hepatic disease	24.9			
	Heart disease	29.1			
	HT	24.1			
	Kidney disease	10.9			
	Lung disease	14.2			
	ART	NA	NA	NA	NA

(*Continued*)

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Table 3 (Continued).

First Author, Year	Risk factors	Overall Prevalence in HIV/COVID-19 (%)	Prevalence in Severe[a] COVID-19 (%)	Prevalence in Mild/ Moderate[b] COVID-19 (%)	Association with Outcome (Results or Authors' Conclusion)
Cabello et al.[11] 2021	**Comorbidities in PWH with COVID-19 diagnosis (n=63)**		**n=18 (severe disease)**		
	Hypertension	19.0	38.9	11.1	No association with severity of COVID-19 after adjusting for age
	Diabetes	9.5	22.2	4.4	
	Overweight	13.1	29.4	6.7	
	Cardiovascular disease	12.7	27.8	6.7	
	Chronic obstructive pulmonary disease	4.8	16.7	0	
	Renal chronic failure (CrCl < 30 mL/min)	3.2	NA	NA	
	ART in PWH with COVID-19 diagnosis				
	PI-based therapy	9.8	0	13.3	No association with severity of COVID-19 after adjusting for age
	INSTI-based therapy	63.9	NA	NA	
	NNRTI-based therapy	26.2	NA	NA	
	TDF-containing regimen	14.8	0	20	
	TFV (TAF or TDF)-containing regimen	26.2	16.7	28.8	
Dandachi et al.[23] 2020	**Comorbidities in PWH with COVID-19 diagnosis (n=286)**		NA	NA	**Severe outcome: adjusted OR (95% CI)**
	Hypertension	46.5			Hypertension 2.43 (1.20–4.93)
	Diabetes	21.3			
	Chronic lung disease	17.1			Diabetes 3.37 (1.63–6.97)
	Chronic kidney disease	16.8			
	Cardiovascular disease	10.5			
	Chronic liver disease	9.8			
	Active malignancy	4.5			
	Obesity	32.3			No other significant association
	ART in PWH with COVID-19 diagnosis		NA	NA	
	INI+2 NRTI	61.3			No association between the class of ART or the use of darunavir-containing regimens on outcome severity
	NNRTI + 2 NRTI	7.2			
	PI + 2NRTI	7.2			
	Dual regimen	7.9			
	Other	10.8			

Del Amo et al.[26] 2021	**Comorbidities in PWH with COVID-19 diagnosis (n=236)**	NA	NA	NA	NA
	ART		**n=20 (deaths)**	[d]	**Risk for death/10,000 diagnoses of COVID-19 (95% CI)**
	NRTI				
	TDF/FTC	9	0	10	0 (one-sided 97.5% CI −2.9)
	TAF/FTC	42	50	42	3.9 (1.9–7.2)
	ABC/3TC	24	40	23	4.0 (1.7–7.8)
	Others	25	10	26	1.0 (0.1–3.7)
	Third drug				
	NNRTI	15	25	14	No significant association
	PI	15	25	13	
	INI	60	45	62	
	Other	10	1	10	
Di Biagio et al.[25] 2020	**Comorbidities in PWH with COVID-19 diagnosis (n=69)**		**n=38 (hospitalization)**		
	Hypertension	44.9	52.6	35.5	No significant association
	Diabetes	14.5	18.4	9.7	
	Cardiovascular diseases	13.0	15.8	9.7	
	ART[e]				
	PI based	24.6	21.1	29.0	No significant association
	NNRTI based	33.3	31.6	35.5	
	INI based	46.4	52.6	38.7	
	TDF-containing	59.4	52.6	67.7	
Etienne et al.[21] 2020	**Comorbidities in PWH with COVID-19 diagnosis (n=54)**		**n=19 (severe +critical)**		
	Diabetes	9.3	26.3	0	No significant association
	Hypertension	29.6	47.4	20.0	
	Renal insufficiency	7.4	15.8	0	
	Respiratory disease	9.3	10.5	8.6	
	ART				
	PI-based	16.7	8.6	31.6	No significant association
	NNRTI-based	46.3	48.6	42.1	
	NRTI-based	79.6	77.1	84.2	
	INI-based	61.1	65.7	52.6	

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Table 3 (Continued).

First Author, Year	Risk factors	Overall Prevalence in HIV/COVID-19 (%)	Prevalence in Severe[a] COVID-19 (%)	Prevalence in Mild/Moderate[b] COVID-19 (%)	Association with Outcome (Results or Authors' Conclusion)
Geretti et al.[9] 2020	**Comorbidities in PWH with COVID-19 diagnosis (n=122)**		**n=30 (death)**		
	Chronic pulmonary disease	10.8	3.5	13.2	PWH had lower prevalence of chronic pulmonary disease, due to their younger age. HIV-positive people who died were more likely to suffer from obesity and diabetes with complications than those who survived to discharge
	Diabetes, with complications	7.7	16.7	4.6	
	Obesity	17.0	28.6	13.1	
	ART	NA	NA	NA	NA
Gervasoni et al.[24] 2020	**Comorbidities in PWH with COVID-19 diagnosis (n=47)**		NA	NA	
	Dyslipidemia	30.6			No significant association
	Hypertension	28.6			
	Hepatitis B/C	10.2			
	Renal disease	8.2			
	Diabetes	6.1			
	Cardiovascular diseases	4.1			
	Neoplasms	6.1			
	Chronic obstructive pulmonary disease	4.1			
	ART		NA	NA	
	TAF/FTC/bictegravir	20.4			Antiretroviral therapy apparently does not play a key role
	ABC/3TC/dolutegravir	20.4			
	TAF/FTC/INI	12.2			
	3TC/dolutegravir	10.2			
	Dolutegravir+boosted PI	10.2			
	TAF/FTC+boosted PI	10.2			
Ho et al.[27] 2021	**Comorbidities in PWH with COVID-19 diagnosis (n=93)**		NA	NA	
	Diabetes	34.4			
	Heart disease	18.3			
	Lung disease	26.9			
	(n=72 hospitalized)		**n=19 (death)**		p=0.53
	Obesity	23.2	16.7	25.5	
	ART				
	TDF-containing	69.0	55.5	73.6	p=0.15
	PI-containing	14.1	16.7	13.2	p=0.71

Hoffmann et al.[20, f] 2021	**Comorbidities in PWH with COVID-19 diagnosis (n=175)**		**n=49 (severe)**		
	0	39	24	45	No effect of at least 1 comorbidity after accounting for age (aOR 1.53, 95% CI 0.74–3.17) univariate OR 1.01 (95% CI 0.41–2.51)
	1	27	31	26	
	2	14	18	13	
	>2	19	27	16	
	Obesity	16	16	16	
	ART				
	TDF-containing	58	55	59	Univariate OR 0.86 (95% CI 0.44–1.68)
	PI-containing	20	27	17	Univariate OR 1.71 (95% CI 0.78–3.74)
Inciarte et al.[7] 2020	**Comorbidities in PWH with COVID-19 diagnosis (n=53)**		**n=6 (severe)**		
	Cardiovascular disease	9	67	4	p=0.0008
	Hypertension	39			
	Diabetes	22			
	Chronic renal disease	9			
	Chronic obstructive pulmonary disease	13			
	Fatty liver syndrome	13			
	Neoplasia	12			
	At least one	43			
	ART		NA	NA	
	Any	96			No antiretroviral factors significantly associated with COVID-19 severity
	Triple therapy	83			
	INI-based	55			
	PI-based	28			
	NNRTI-based	25			
	TDF-containing	66			
	ABC-containing	17			
Maggiolo et al.[22] 2021	**Comorbidities in PWH with COVID-19 diagnosis (n=55)**		**n=4 (death)**		
	0	49	0	53	The number of comorbidities was statistically associated with the outcome in the multivariate model
	1	29	25	29	
	2	11	25	10	
	>2	11	50	8	
	ART		NA	NA	
	NRTIs	85			The use of specific antiretrovirals did not result protective
	NNRTIs	36			
	PIs	20			
	INIs	58			

(*Continued*)

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Table 3 (Continued).

First Author, Year	Risk factors	Overall Prevalence in HIV/COVID-19 (%)	Prevalence in Severe[a] COVID-19 (%)	Prevalence in Mild/ Moderate[b] COVID-19 (%)	Association with Outcome (Results or Authors' Conclusion)
Patel et al.[16] 2021	**Comorbidities in PWH with COVID-19 diagnosis (n=100)**		NA	NA	NA
	Obesity	34			
	Chronic lower respiratory disease	31			
	Hypertension	70			
	Diabetes	41			
	Ischemic heart disease	16			
	Heart failure	17			
	ART		NA	NA	NA
	Any TDF use	64			
Sigel et al.[19] 2020	**Comorbidities in PWH with COVID-19 diagnosis (n=88)**		**n=18 (death)**		
	Diabetes	27	22	29	Adjusting for age, sex, and race/ethnicity, organ transplant recipient status represented a risk factor for death (subhazard ratio, SHR, 3.85; 95% CI 1.87–7.94)
	Hypertension	38	33	39	
	Obesity	10	6	11	
	Chronic obstructive pulmonary disease	9	11	9	
	Cirrhosis	6	6	6	
	Coronary artery disease	7	0	9	
	Chronic kidney disease	22	33	19	
	Cancer	17	6	20	
	Organ transplant recipient	5	17	1	
	ART				
	INI	78	72	80	Adjusting for age, sex, and race/ethnicity, significance persisted for NRTI use (SHR, 0.31; 05% CI, 0.12–0.80) as predictor of death for PLWH
	PI	17	28	14	
	NNRTI	9	0	11	
	NRTI	97	89	89	
Tesoriero et al.[10] 2021	**Comorbidities in PWH with COVID-19 diagnosis (n=2988)**	NA	NA	NA	NA
	ART	NA	NA	NA	NA

Vizcarra et al,[14] 2020	**Comorbidities in PWH with COVID-19 diagnosis (n=51)**		**n=13 (severe)**		No significant association
	Any	63	69	61	
	Hypertension	35	38	34	
	Diabetes	14	8	16	
	Chronic kidney disease	12	15	32	
	Chronic liver disease	47			
	ART				No significant association
	PI	22	15	24	
	NNRTI	16	8	18	
	INI	80	77	82	
	TAF or TDF	73	69	74	

Notes: [a] Severe defined as: hospitalized, ICU admission, severe cases, or death. [b] Mild/moderate defined as: non hospitalized, non-ICU admission or survivors. [c] Not available. [d] survivors, calculated as COVID-19 infected – deceased from published numbers. [e] calculated from published numbers. [f]partially includes Gervasoni[24] and Vizcarra.[14].

Abbreviations: ABC, abacavir; ART, antiretroviral treatment; ATV, atazanavir; CI, confidence interval; DTG, dolutegravir; EFV, efavirenz; HR, hazard ratio (aHR, adjusted HR); INI, integrase strand transfer inhibitor; LPV, lopinavir; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; PWH, people with HIV; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarato; ZDV, zidovudine.

suppression (88.7%). At the multivariable analysis, CD4<200 cells/μL (OR 3.32, 95% CI 1.11–9.93), chronic lung disease (OR 3.65, 95% CI 1.56–8.56) and three or more comorbidities (OR 5.09, 95% CI 1.05–24.76) were associated with a severe outcome (composite endpoint including ICU admission, use of mechanical ventilation and death).

Geretti et al[9] reported that age (OR 1.05, 95% CI 1.01–1.09), diabetes (OR 2.18, 95% CI 1.02–4.66) and obesity (OR 2.89, 95% CI 1.28–6.53) were risk factors for SARS-CoV-2-related mortality, at multivariable analysis.

Ho et al[27] reported that a lower lymphocyte nadir was significantly associated with death in a sample of PLWH with median CD4 554 (IQR 339–752) and HIV-VL <50 copies/mL at the last visit, with a median age of 58 (IQR 52–65).

Sigel et al[19] described a cohort of PLWH with a median age of 61 years (IQR 54–67) with 44% of patients with CD4>500 cells/μL and 81% with undetectable HIV.

In the multivariate analysis, organ transplant recipient status was a risk factor for death (sub-hazard ratio, SHR, 3.85, 95% CI 1.87–7.94), while nucleoside reverse transcriptase inhibitors (NRTI) use was a protective factor (SHR 0.31, 95% CI 0.12–0.80).

Patel et al[16] described a 22% death rate (22/100) in a cohort of HIV patients, without any significant differences between the group with suppressed HIV-VL vs unsuppressed HIV-VL.

Smaller studies usually reported a mortality rate ≤10%,[14,22,24,26] showing older age and comorbidities as risk factors. In these studies, most patients were on ART, had CD4>500 cells/μL and undetectable HIV-VL.

Discussion

In most studies, HIV infection did not represent a risk factor for SARS-CoV-2 infection.

Evidence from larger studies[7,10–12] did not support a higher risk of SARS-CoV-2 infection in PLWH.

Only Sachdev et al[13] described a higher risk of SARS-CoV-2 in PLWH than in PNLWH, but 45% of PLWH in their sample experienced unstable housing, a factor that could have influenced the rate of infection. In the study by Tesoriero et al,[10] a higher risk of SARS-CoV-2 diagnosis was reported in older age, black race, and Hispanic individuals, with a probable link with socioeconomic status rather than HIV infection per se.

So far, in the published literature, data were scarce and inconsistent about the effect of ART regimen on the chance of SARS-CoV-2 infection and clinical outcome of

COVID-19 in PLWH. Large studies are needed to confirm or exclude the role of ART.

Del Amo et al[26] and Boulle et al[15] found a lower risk of infection in patients on tenofovir therapy, suggesting a possible inhibiting effect on RNAdRNAp of SARS-CoV -2,[28] whereas Sigel et al[19] observed a lower risk in PLWH on current NRTI therapy, but did not differentiate among individual drugs.

The protective role of tenofovir is a matter of debate, with conflicting evidence about its possible effect on COVID-19 prevention and treatment.[4]

Protease inhibitors, which had a role in treating the MERS-CoV infection, did not seem effective in preventing or treating SARS-CoV-2.[29]

Once SARS-CoV-2 infection is acquired, risk of severe COVID-19 and hospitalization is higher in PLWH. Low CD4 are consistently reported as a risk factor for severe COVID-19. Tesoriero et al[10] demonstrated an increasing risk of hospitalization across the three stages of HIV infection (CD4 ≥500 vs 200–499 vs <200 cells/μL). Age older than 50 years and the presence of comorbidities are other strong risk factors for the disease severity. Uncontrolled HIV-VL was not reported as a risk factor for COVID-19 severity in three studies,[15,16,23] although PLWH with uncontrolled VL represented less than 15% of enrolled patients.

Few data are available on PLWH younger than 50 years, which are underrepresented in the studies on COVID-19 severity.

Inciarte et al[7] described a low prevalence of severe SARS-CoV-2 infection in a population mostly younger than 50 years.

Many studies[14,19,21,22] reporting a prevalence of severe cases higher than 20% showed a median age between 52 and 61.

From the published evidence, PLWH aged 50 or more years appear more at risk of severe COVID-19, especially in the presence of severe immune suppression (CD4<200 cells/micrL). This could be due both to the higher burden and early development of comorbidities in this group of PLWH[2,30] and to the immune dysfunction occurring in PLWH with CD4<200 cells/μL.

Low CD4 have been also associated with poor outcomes in the general population.[31]

We can hypothesize that CD4 at diagnosis of SARS-CoV-2 infection were extremely low as a consequence of SARS-CoV-2 infection. However, in most studies, CD4 during the course of COVID-19 were not available. "Current CD4" were usually defined as retrospectively collected, from three years to four weeks before SARS-COV-2 infection diagnosis. Only Patel et al[16] stated that they included CD4 during hospitalization only when a previous measure was unavailable; nonetheless, they did not stratify their results according to time of CD4 measurement. Thus, we were unable to evaluate the possible role of fast CD4 loss during SARS-CoV-2 infection.

However, there are several reasons for inappropriate immune response in HIV infection.

A prompt and hard CD4 response has been reported to be necessary for IgG and IgA response to SARS-CoV-2.[32]

Immune activation has been demonstrated to persist in HIV chronic infection with alteration in kynurenine-tryptophan ratio, a marker of defective adaptive immunity, even in patients treated early for HIV infection.[33,34]

On the other hand, HIV and SARS-CoV-2 share a common evasion of innate immunity,[35] that could explain a deficient response to Interferon.

Inflammation and immune-activation related to severe HIV infection (CD4 <200) could explain the worse prognosis of SARS-CoV-2 infection in this subset of patients.

The risk of ICU admission was reported as higher than in people not living with HIV in most studies.[12,16,17] CD4 <200 were a risk factor for ICU admission in the study of Dandachi et al[23] while the increase in current CD4 (per 100 cells/μL) was a risk factor for Patel et al.[16] The two studies included a slightly different number of intubated patients with significantly different ages: Dandachi et al enrolled 47 intubated patients (twice as much than Patel et al) with significantly younger age. This difference could partially explain the inconsistency of their findings. The immune reconstitution as a risk factor could be an interesting hypothesis in the development of cytokine storm in COVID−19, but high CD4 were not frequently associated with severity of disease, even if most patients enrolled in these studies had CD4 >500 cells/μL and suppressed HIV-VL. However, as previously discussed, low and dysfunctional CD4 are not the only immune dysfunction in HIV infection.

PLWH with high CD4 (>500) did not show a higher risk of cytokine storm in most studies, suggesting that, in this group of patients, the role of comorbidities could be stronger than that of CD4.

In PLWH, higher mortality rates were reported in two large studies.[12,15]

It is interesting that in the study of Tesoriero et al[10] they did not find a significantly higher mortality rate in

PLWH per hospitalization, but when they analyzed per population and per diagnosis, HIV infection represented a risk factor for death. These results were likely due to the higher percentage of PLWH with severe disease.

On the other hand, Hadi et al[8] demonstrated a higher mortality in PLWH but adjusting for BMI, diabetes, hypertension, chronic lung diseases, chronic kidney diseases, race, nicotine dependence and sex, no differences were found between PLWH vs PNLWH.

CD4<200 cells/μL, age and comorbidities were the most documented risk factors for mortality in PLWH.

The role of comorbidities has been demonstrated to be crucial. In particular, in Miyashita's study[17] most PLWH who deceased younger than 50 years old were male, with hypertension and other comorbidities. In the study by Geretti et al,[9] a higher risk of mortality was also reported in PLWH aged <60 years, especially if associated with obesity and diabetes.

Besides median age and number of comorbidities that are increasing in cohorts of PLWH, especially in Europe,[36] another concern is that chronic airway abnormalities and pulmonary inflammation are highly prevalent in HIV infection, even in non-smokers.[37,38]

This review has some limitations. First, we did not perform a meta-analysis and we cannot evaluate the impact of statistical power in the selected studies. Secondly, we did not evaluate all the studies on HIV and SARS-CoV-2 but only those including more than 40 PLWH.

In conclusion, HIV infection did not seem a risk factor for SARS-CoV-2 infection, but when PLWH acquire COVID-19 a worse outcome was more frequent than in PNLWH, especially in case of severe immune deficiency (CD4<200) and in presence of multiple comorbidities.

Disclosure

Dr Nicola Squillace reports personal fees from ViiV Healthcare, outside the submitted work. The authors report no other conflicts of interest in this work.

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