





ORIGINAL RESEARCH

Immune deficiency is a risk factor for severe COVID-19 in people living with HIV

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Objectives

A prior T cell depletion induced by HIV infection may carry deleterious consequences in the current COVID-19 pandemic. Clinical data on patients co-infected with HIV and SARS-CoV-2 are still scarce.

Methods

This multicentre cohort study evaluated risk factors for morbidity and mortality of COVID-19 in people living with HIV (PLWH), infected with SARS-CoV-2 in three countries in different clinical settings. COVID-19 was clinically classified as to be mild-to-moderate or severe.

Results

Of 175 patients, 49 (28%) had severe COVID-19 and 7 (4%) patients died. Almost all patients were on antiretroviral therapy (ART) and in 94%, HIV RNA was below 50 copies/mL prior to COVID-19 diagnosis. In the univariate analysis, an age 50 years or older, a CD4+ T cell nadir of < 200/μl, current CD4+ T cells < 350/μl and the presence of at least one comorbidity were significantly associated with severity of COVID-19. No significant association was found for gender, ethnicity, obesity, a detectable HIV RNA, a prior AIDS-defining illness, or tenofovir (which was mainly given as alafenamide) or protease inhibitor use in the current ART. In a multivariate analysis, the only factor associated with risk for severe COVID-19 was a current CD4+ T cell count of < 350/μl (adjusted odds ratio 2.85, 95% confidence interval 1.26–6.44, $p=0.01$). The only factor associated with mortality was a low CD4 T cell nadir.

Conclusions

In PLWH, immune deficiency is a possible risk factor for severe COVID-19, even in the setting of virological suppression. There is no evidence for a protective effect of PIs or tenofovir alafenamide.

Keywords: antiretroviral therapy, COVID-19, HIV infection, immune deficiency, SARS-CoV-2

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Introduction

In the current COVID-19 pandemic, older age and several comorbidities have been identified as risk factors for severe disease and death, including hypertension, cardiovascular disease and diabetes, but also chronic pulmonary diseases and obesity [1–4]. For people living with HIV (PLWH), preliminary data from the UK, the US and Spain have suggested no elevated incidence of COVID-19 [4–6]. However, data on the clinical course of COVID-19 in this

population are still scarce. The cellular immune deficiency seen in PLWH is of potential concern as dysfunctional immune responses contribute to disease progression and dysregulated T-cell responses can result in immunopathology [7]. Moreover, there is growing evidence of a transient depletion of T cells during COVID-19, indicating that a pre-existing T-cell depletion induced by HIV may carry deleterious clinical consequences [8,9]. Others groups, however, have speculated that a defective cellular immunity could paradoxically be protective for severe cytokine dysregulation, preventing the cytokine storm seen in severe COVID-19 cases [10–11]. A recent review of five studies found that immunodeficiency was associated with a 1.55-fold increased risk of severe COVID-19 disease. However, the statistical difference was not significant, due to the small numbers of immunodeficient patients [12].

In our early case series from Italy, Spain and Germany, we described the clinical characteristics of PLWH with COVID-19 [13–15]. In all three cohorts, the numbers of patients with severe COVID-19 with severe immune deficiency were too low to draw definite conclusions. Despite the absence of data, according to several organisations such as the British HIV Association (BHIVA), Deutsche AIDS Gesellschaft (DAIG), European AIDS Clinical Society (EACS), Grupo de Estudio del SIDA (GESIDA) and the Polish Scientific AIDS Society [16], “it has to be assumed that immune suppression, indicated by a low CD4 T-cell count, or not receiving antiretroviral treatment, will be associated with an increased risk for a more severe disease presentation”. In order to verify this assumption and to identify potential risk factors for severe disease, we have combined and updated our cohorts of patients with documented HIV and confirmed SARS-CoV-2 infection.

Methods

This retrospective analysis included all cases of PLWH with SARS-CoV-2 infection enrolled by 12 June 2020 in three European countries. In Italy, patients were diagnosed at the Department of Infectious Diseases, ASST Fatebenefratelli Sacco University Hospital, Milan. In Spain, patients were diagnosed at the Hospital Universitario Ramón y Cajal (Madrid, Spain), a tertiary university hospital. In Germany, patients were diagnosed at 16 different centres, representing university hospitals, other hospitals and general practitioners throughout the country. Details of the three cohorts, including ethical approvals, have been described previously [13–15].

Anonymized data were collected by the treating physicians and included age (using 10-year categories), ethnicity, gender and body mass index (BMI). In addition, HIV-

associated parameters such as the last CD4 T-cell count (absolute cells/ μ L, as assessed by local laboratories) at least 4 weeks prior to SARS-CoV-2 infection (as defined by onset of disease) and the CD4 T-cell nadir and the last HIV RNA viral load (copies/mL, as assessed by local laboratories) were evaluated as well as prior AIDS-defining illnesses. With regard to the last antiretroviral therapy (ART) prior to COVID-19 diagnosis, it was evaluated whether the regimen included either tenofovir [as alafenamide (TAF) or disoproxil fumarate (TDF)] or an HIV protease inhibitor (PI).

Parameters were documented categorically as follows: male *vs.* female gender, Caucasian ethnicity *vs.* non-Caucasian ethnicity, older (≥ 50 years) *vs.* younger age (< 50 years), obesity *vs.* no (BMI ≥ 30 *vs.* < 30 kg/m²), current CD4 T-cell count (< 350 *vs.* ≥ 350 cells/ μ L), CD4 T-cell nadir (< 200 *vs.* ≥ 200 cells/ μ L), HIV RNA (≥ 50 *vs.* < 50 copies/mL). Comorbidities included cardiovascular disease, diabetes mellitus, hypertension, cancer, kidney diseases and pulmonary diseases.

Laboratory confirmation of SARS-CoV-2 infection was performed by qualitative real-time polymerase chain reaction (PCR) assay of nasopharyngeal swabs, sputum or lower respiratory tract aspirates, or by serology testing.

Severity of disease was classified as mild-to-moderate (i.e. non-pneumonia and mild pneumonia), severe (either respiratory frequency ≥ 30 /min, blood oxygen saturation $\leq 93\%$, or lung infiltrates $> 50\%$ within 24–48 hours), and critical (either respiratory failure, septic shock, or multiple organ dysfunction or failure) [17], and outcomes (alive and recovered or deceased at the last follow-up) were collected.

We calculated and reported patient characteristics as absolute numbers and percentages. Potential associations between baseline characteristics and severity of disease were assessed using a univariate and a multivariate logistic regression model. Due to presumed multicollinearity we included only current CD4 T cells (and not CD4 T-cell nadir) in the model. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of the association. The level of significance was $P < 0.05$.

Results

Among 175 PLWH (65 patients from Milan, 61 from Germany and 49 from Madrid), SARS-CoV-2 infection had been confirmed by positive SARS-CoV-2 PCR in 118 cases, by serology in 52 cases and by both PCR and serology in five cases. The number of patients diagnosed by SARS-CoV-2 serology only was higher in Milan (32/65, 49%), compared with the German cohort (13/61, 21%) and with Madrid (7/49, 14%). The clinical case definition

Table 1 Baseline characteristics and COVID-19 severity

	Total	Mild to moderate	Severe or critically ill
<i>N</i>	175	126	49
Age [<i>n</i> (%)]			
20–40 years	45 (26)	38 (30)	7 (14)
40–49 years	36 (21)	28 (22)	8 (16)
50–59 years	66 (38)	43 (34)	23 (51)
60–69 years	24 (14)	15 (12)	9 (18)
≥ 70 years	4 (2)	2 (2)	2 (4)
Gender [<i>n</i> (%)]			
Male	143 (82)	102 (81)	41 (84)
Female	32 (18)	24 (19)	8 (16)
HIV-associated parameters			
Median (range) current CD4 T-cell count (cells/ μ L)	663 (69–1,715)	717 (161–1,715)	449 (69–1,100)
Current CD4 T-cell count \geq 500 cells/ μ L [<i>n</i> (%)]	120 (69)	96 (77)	24 (49)
Current CD4 T-cell count < 350/ μ L [<i>n</i> (%)]	32 (18)	16 (13)	16 (33)
Median (range) nadir CD4 T-cell count (cells/ μ L)	256 (1–1,336)	304 (4–1,336)	185 (1–650)
Nadir CD4 T-cell count < 200 cells/ μ L [<i>n</i> (%)]	63 (39)	39 (34)	24 (52)
HIV RNA copies < 50 copies/mL [<i>n</i> (%)]	164 (94)	119 (94)	45 (92)
AIDS-defining illness [<i>n</i> (%)]	53 (31)	34 (27)	19 (40)
Number of comorbidities			
0	69 (39)	57 (45)	12 (24)
1	48 (27)	33 (26)	15 (31)
2	25 (14)	16 (13)	9 (18)
>2	33 (19)	20 (16)	13 (27)
Body mass index \geq 30 kg/m ²	26 (16)	18 (16)	8 (16)
Pre-existing antiretroviral regimen consisting of:			
Tenofovir	101 (58)	74 (59)	27 (55)
Protease inhibitor	35 (20)	22 (17)	13 (27)

of COVID-19 was mild-to-moderate in 126 (72%) cases and severe in 49 cases (28%), among them 16 critically ill cases. Reflecting the different settings of the three cohorts, the rates of patients with severe or critical COVID-19 was higher in Madrid (17/49, 35%) and Milan (23/65, 35%) than in Germany (9/61, 15%) where more patients had been diagnosed while being not hospitalized. At the last follow-up, 168 (96%) patients had recovered from COVID-19 while seven (4%) patients had died.

The baseline characteristics are displayed in Table 1. The majority of the patients were male (82%), of Caucasian ethnicity (88%) and < 60 years of age (84%). The median current CD4 T-cell count was 663 cells/ μ L and 69% had a CD4 T-cell count \geq 500 cells/ μ L. Only 18% had a current CD4 T-cell count < 350 cells/ μ L. However, 39% had a CD4 T-cell nadir < 200 cells/ μ L and 31% had had a history of a prior AIDS-defining illness. Except for one, all patients were on ART and in 94% the last documented viral load was < 50 HIV RNA copies/mL prior to COVID-19 diagnosis. Of the patients with a detectable HIV RNA, eight out of 11 had a low plasma viraemia of < 1000 copies/mL. Of the 101 patients who were treated with tenofovir at the time of COVID-19 diagnosis, 92 received TAF and nine received TDF. Of the 35 patients who were treated with a boosted PI-based antiretroviral regimen, 29 received darunavir. Three, two and one patients were treated with atazanavir, lopinavir and fosamprenavir, respectively.

Patients with severe COVID-19 had a lower current CD4 T-cell count and a lower nadir CD4 T-cell count, compared with patients with mild-to-moderate COVID-19. Lower T-cell counts were also found for patients who died from COVID-19 (Fig. 1).

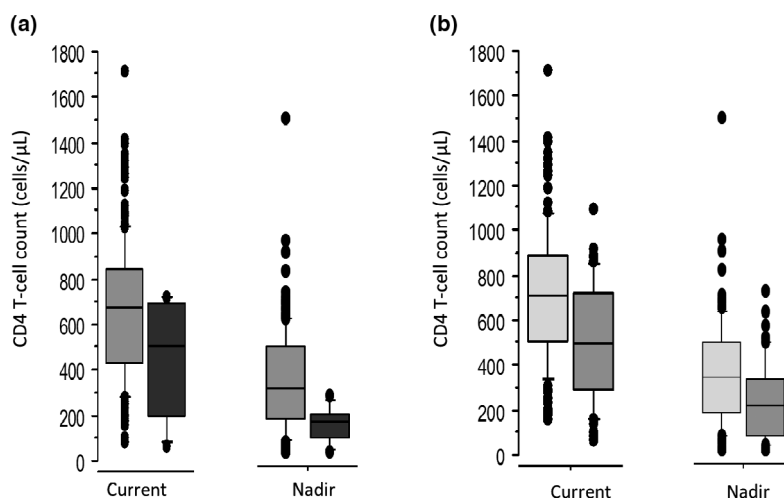


Fig. 1 (a) Mortality: CD4 T cells of recovered and deceased (dark grey) patients. (b) Morbidity: CD4 T cells of patients with mild-to-moderate and severe (dark grey) COVID-19.

Table 2 Association between baseline characteristics and severe/critical COVID-19

	Univariate analysis OR (95% CI)	P-value	Multivariate analysis OR (95% CI)	P-value
Male gender (vs. female)	1.21 (0.50–2.90)	0.68	–	–
Caucasian ethnicity (vs. black)	2.12 (0.58–7.75)	0.25	–	–
Age ≥ 50 years (vs. < 50)	2.49 (1.24–5.03)	0.011	2.02 (0.96–4.22)	0.06
Nadir CD4 T-cell count < 200 cells/μL (vs. ≥ 200)	2.10 (1.05–4.21)	0.037	–*	–
AIDS-defining illness (vs. no)	1.82 (0.90–3.67)	0.096	–	–
Current CD4 T-cell count < 350 cells/μL (vs. ≥ 350)	3.30 (1.49–7.31)	0.0032	2.85 (1.26–6.44)	0.01
Viral load ≥ 50 HIV RNA copies/mL (vs. < 50)	1.51 (0.42–5.41)	0.52	–	–
At least one comorbidity (vs. no)	2.04 (1.03–4.03)	0.04	1.53 (0.74–3.17)	0.25
Tenofovir (vs. no)	0.86 (0.44–1.68)	0.66	–	–
Protease inhibitor (vs. no)	1.71 (0.78–3.74)	0.18	–	–
Body mass index ≥ 30 kg/m ² (vs. < 30)	1.01 (0.41–2.51)	0.97	–	–

OR, odds ratio; CI, confidence interval.

*Variable excluded from multivariate analysis due to multicollinearity.

In the univariate analysis, an age of 50 years or older, a nadir CD4 T-cell count < 200 cells/μL, current CD4 T-cell count < 350 cells/μL and the presence of at least one comorbidity were found to be significantly associated with severity of COVID-19. As shown in Table 2, there was no significant association between severity of COVID-19 and gender, ethnicity, obesity, a detectable HIV RNA, a prior AIDS-defining illness, or use of tenofovir or PI in the current antiretroviral regimen. In the multivariate analysis, the only factor significantly associated with a risk for severity of COVID-19 was a current CD4 T-cell count < 350 cells/μL. The adjusted OR for severe COVID-19 was 2.85 (95% CI: 1.26–6.44) ($P = 0.01$). Results were consistent in the three countries and did not change when only patients with PCR-confirmed diagnosis were analysed. This was also true when analysis was restricted to patients with virological suppression or patients without comorbidities (data not shown).

The only factor that was found to be significantly associated with case fatality was a nadir CD4 T-cell count of < 200 cells/μL (OR = 10.11, 95% CI: 1.19–86.10, $P = 0.03$). However, the number of deaths observed in the three cohorts was relatively low and a multivariate analysis was not performed.

Discussion

In this combined cohort of 175 PLWH with a confirmed SARS-CoV-2 infection diagnosed in three countries during the first months of the pandemic, patients with severe COVID-19 had a lower current CD4 T-cell count and a lower CD4 T-cell nadir, compared with patients with mild-to-moderate COVID-19. A current immune deficiency consisting of CD4 T-cell count < 350 cells/μL was identified to be independently associated with an almost

three-fold risk for severe disease. A lower nadir CD4 T-cell count of < 200 cells/μL was associated with mortality and morbidity.

There has been some speculation that a defective cellular immunity could paradoxically be protective for severe cytokine dysregulation, preventing the cytokine storm seen in severe COVID-19 cases [10–11]. Although we did not collect data on the inflammatory response, our clinical study clearly shows that this is not the case, at least when it comes to T cells. T cells are required for controlling exuberant and overzealous early innate responses to coronaviruses and other respiratory viruses [18–20]. Virus-specific CD4 and CD8 T cells play a critical role in clearing viral infections, and dysfunctional immune responses contribute to disease progression [7]. A recent study identified robust SARS-CoV-2 – specific CD4 and CD8 T-cell responses in almost all COVID-19 convalescent patients, correlating with the magnitude of immunoglobulin G titres [21]. In line with these studies, our clinical data indicate that a robust T-cell immunity may be important for efficient SARS-CoV-2 control. It is notable that immune deficiency remained associated with severity even when only patients with virological suppression or patients without comorbidities were included in the analyses.

Besides immune deficiency, we saw other factors that were associated with morbidity. In the univariate analysis, this was seen for comorbidities, but also for age. It is noteworthy that the majority of our patients with severe disease were < 60 years old. Except for one patient, all were on ART and only very few had a detectable viraemia. Nevertheless, we did not obtain data showing whether viraemia in these patients was due to an insufficient, or an interruption in, ART regimen. It remains to be seen whether uncontrolled HIV viraemia brings a risk for severe disease.

Overall, mortality in our cohort was 4%. Whether this corresponds to mortality rates in HIV-uninfected populations remains to be elucidated. Carefully designed seroprevalence studies are needed that have to adjust for important risk factors such as age and comorbidities. It also remains to be seen whether PLWH with SARS-CoV-2 infection differ from PLWH in general.

We found no evidence of any protective effect of tenofovir or PIs regarding the severity of disease. The percentage of subjects with severe COVID-19 did not differ between patients treated with these antiretroviral drugs or with other regimens, indicating that a potential therapeutic effect, as suggested by molecular docking studies [22], is limited. However, a selection bias cannot be ruled out as we have only included patients who had acquired SARS-CoV-2 infection in the presence of these drugs. Moreover, almost all patients on PI-based regimens were treated with darunavir, a PI which seems to be without any *in vitro* activity against SARS-CoV-2 [23]. Of note, the number of patients treated with TDF in our cohorts was too low to draw definitive conclusions. More recently, it has been reported that HIV-positive patients receiving TDF/emtricitabine (FTC) have a lower risk for COVID-19 and related hospitalization than those receiving other therapies such as TAF/FTC or abacavir/lamivudine [24].

There is no doubt that our study has further important limitations. First, this was a retrospective and uncontrolled case series of patients diagnosed with SARS-CoV-2 during the first 5 months of the pandemic. We only had data on absolute CD4 T cells; data on other lymphocyte subpopulations such as CD8 T cells were lacking. Other important data were not available, including socioeconomic status, time of HIV infection and duration of ART and of virological suppression, but also transmission, exposure conditions and treatment of SARS-CoV-2 infection. In addition, detailed information about the onset, duration of follow-up, hospitalization and intensity of the symptoms, and virological data were not obtained. No further information on the precise causes of death were available in the seven deceased patients. We did not specify comorbidities and the clinical manifestation, and the relevance of a condition such as diabetes may be very heterogeneous. Reflecting the HIV-infected population in the three countries, female patients and patients with ethnicity other than Caucasian were under-represented. Given the restrictions of conducting SARS-CoV-2 confirmatory testing in the three countries, we were also unable to estimate the incidence and prevalence of severe and fatal cases. It seems likely that testing policies and restrictions may have had an impact on clinical presentation of the patients in this

uncontrolled cohort. However, we believe that our uncontrolled data obtained until June 2020 give a first picture on the clinical situation of PLWH co-infected with SARS-CoV-2.

During recent months, some cohort studies have reported on an increased mortality risk due to HIV-positive status [25,26] while others have reported similar outcomes of PLWH compared with those without HIV [27–29]. However, many studies have been limited by small sample sizes or the lack of HIV-related parameters, by lack of direct comparative data from people without HIV or by the inability to adjust for comorbidities. In one multicentre registry including 286 patients mainly from the US, a lower CD4 count (< 200 cells/ μ L) was associated with poor outcomes, including higher hospitalization rates and overall survival [30].

In conclusion, these early data of 175 PLWH from three countries revealed cellular immune deficiency as a possible risk factor for severe SARS-CoV-2 infection. Mortality was 4% and the only factor associated with mortality was a low CD4 T-cell nadir. Although there was no evidence of any direct therapeutic effect of tenofovir (mainly used as TAF) and HIV PIs, data strongly argue against any interruption or delayed initiation of ART in the current pandemic, in order to prevent even moderate cellular immune deficiency.

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The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Author contributions

CH, JLC, PV and CG were instrumental in the study conception and design. CH wrote the manuscript and performed the statistical analysis. GH, AM, DC, PM, CDS, FS and SG participated in the acquisition, analysis and interpretation of the data. All authors revised the paper critically for important intellectual content and gave final approval of the version to be published.

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