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To the Editor:

How HIV-1 infection affects risk of severe COVID-19 outcome is poorly investigated. Evidence from different studies does not support a higher risk of SARS-CoV-2 infection in HIV-1 infected patients [1]; however, it has been reported that COVID-19 has a negative impact on HIV-1 individuals, especially in the presence of comorbidities that increase the risk of serious illness [2]. Moreover, there are multiple immunological profiles of HIV-1 infected individuals, and the impact of SARS-CoV-2 infection can vary for each patient [2]. A dysregulation of innate immunity has been observed in both HIV-1 infected individuals and severe COVID-19 patients. In particular, type I Interferon (IFN-I) signaling has been reported to exert a dichotomous role in the pathogenesis of acute vs. chronic HIV-1 infection [3]. Additionally, severe COVID-19 is characterized by a delayed or suppressed IFN-I response, in part due to evasive strategies employed by SARS-CoV-2 [4], as well as IFN genetic defects [5] and anti-IFN neutralizing antibodies (NAB) [6,7]. Increasing evidence showed a dominant role of cell-mediated immunity in the clearance of SARS-CoV-2 in HIV-1 infected patients [8], while little is known about the impact of co-infection with SARS-CoV-2 and HIV-1 on antiviral innate immune responses.

We evaluated the presence of anti-IFN-I NAB in 8 HIV-1 positive individuals co-infected with SARS-CoV-2. During March 2020 to April 2021, blood samples were collected at the time of hospital admission for COVID-19 from 6/8 HIV-1 patients seen at the Policlinico Umberto I hospital in Rome, Italy. For 2/8 patients, blood was collected at the time they first tested positive for SARS-CoV-2. No other common respiratory infections were observed: hypertension (pt No. 7 and pt. No. 8), hypercholesterolemia (pt No. 7), diabetes (pt No. 8). Six out of eight (75%) NAB positive patients were hospitalized for a median of 52 days (range 21–110 days, Table 1). SARS-CoV-2/HIV-1 co-infected patients with the highest NAB titer (≥2100 TRU/ml, pt. No. 2, 3 and 4) had values of a COVID-19 severity Index [9] considered critical (8–11). Levels of laboratory biomarkers associated with major risks for severe COVID-19 (lactate dehydrogenases (LDH), C-reactive protein (CRP), fibrinogen and D-Dimer) [7] were high in all hospitalized patients, and further increased in those with higher NAB titers (Table 1). Levels of CD4 T cells were lower than 500 cells/μl in those patients (range CD4 T cell values: 86–304 cells/μl, patients No. 2, 3 and 4) with elevated NAB titer against IFN-α and IFN-β (Table 1). The only patient with no detectable anti-IFN-I NAB was a female; all the male patients had detectable anti-IFN-I NAB. Two NAB positive patients died: one of whom (pt No. 4) showed a fatal outcome related to COVID-19, while the other one (pt No. 1) had a cerebral non-Hodgkin’s lymphoma (Table 1). The following comorbidities were observed: hypertension (pt No. 7 and pt. No. 8), hypercholesterolemia (pt No. 7), diabetes (pt No. 8).

The presence of anti-IFN neutralizing antibodies (NAB) has been reported in critically ill COVID-19 patients. We found that 87.5% (7/8) of HIV-1 patients co-infected with SARS-CoV-2 had serum anti-IFN-I NAB against IFN-α subtypes, IFN-β and/or IFN-ω. Anti-IFN-I NAB were also detected in oropharyngeal samples. Patients with NAB were males, and those with high serum anti-IFN-α/ω NAB titer had severe illness and exhibited reduction in the expression of IFN-stimulated genes. Thus, high titer of anti-IFN-α/ω NAB may contribute to the greater severity of COVID-19 in HIV-1 infected patients.

**Keywords**
HIV-1
SARS-CoV-2
Neutralizing antibodies
Interferon
ISGs
HIV-1 and SARS-CoV-2 co-infection

**Abstract**

The presence of anti-IFN neutralizing antibodies (NAB) has been reported in critically ill COVID-19 patients. We found that 87.5% (7/8) of HIV-1 patients co-infected with SARS-CoV-2 had serum anti-IFN-I NAB against IFN-α subtypes, IFN-β and/or IFN-ω. Anti-IFN-I NAB were also detected in oropharyngeal samples. Patients with NAB were males, and those with high serum anti-IFN-α/ω NAB titer had severe illness and exhibited reduction in the expression of IFN-stimulated genes. Thus, high titer of anti-IFN-α/ω NAB may contribute to the greater severity of COVID-19 in HIV-1 infected patients.

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We evaluated the presence of anti-IFN-I NAB in 8 HIV-1 positive individuals co-infected with SARS-CoV-2. During March 2020 to April 2021, blood samples were collected at the time of hospital admission for COVID-19 from 6/8 HIV-1 patients seen at the Policlinico Umberto I hospital in Rome, Italy. For 2/8 patients, blood was collected at the time they first tested positive for SARS-CoV-2. No other common respiratory infections were observed: hypertension (pt No. 7 and pt. No. 8), hypercholesterolemia (pt No. 7), diabetes (pt No. 8). Six out of eight (75%) NAB positive patients were hospitalized for a median of 52 days (range 21–110 days, Table 1). SARS-CoV-2/HIV-1 co-infected patients with the highest NAB titer (≥2100 TRU/ml, pt. No. 2, 3 and 4) had values of a COVID-19 severity Index [9] considered critical (8–11). Levels of laboratory biomarkers associated with major risks for severe COVID-19 (lactate dehydrogenases (LDH), C-reactive protein (CRP), fibrinogen and D-Dimer) [7] were high in all hospitalized patients, and further increased in those with higher NAB titers (Table 1). Levels of CD4 T cells were lower than 500 cells/μl in those patients (range CD4 T cell values: 86–304 cells/μl, patients No. 2, 3 and 4) with elevated NAB titer against IFN-α and IFN-β (Table 1). The only patient with no detectable anti-IFN-I NAB was a female; all the male patients had detectable anti-IFN-I NAB. Two NAB positive patients died: one of whom (pt No. 4) showed a fatal outcome related to COVID-19, while the other one (pt No. 1) had a cerebral non-Hodgkin’s lymphoma (Table 1). The following comorbidities were observed: hypertension (pt No. 7 and pt. No. 8), hypercholesterolemia (pt No. 7), diabetes (pt No. 8). Six out of eight (75%) NAB positive patients were hospitalized for a median of 52 days (range 21–110 days, Table 1). SARS-CoV-2/HIV-1 co-infected patients with the highest NAB titer (≥2100 TRU/ml, pt. No. 2, 3 and 4) had values of a COVID-19 severity Index [9] considered critical (8–11). Levels of laboratory biomarkers associated with major risks for severe COVID-19 (lactate dehydrogenases (LDH), C-reactive protein (CRP), fibrinogen and D-Dimer) [7] were high in all hospitalized patients, and further increased in those with higher NAB titers (Table 1). Levels of CD4 T cells were lower than 500 cells/μl in those patients (range CD4 T cell values: 86–304 cells/μl, patients No. 2, 3 and 4) with elevated NAB titer against IFN-α. No patients included in this study were previously treated with IFN-α/β preparations or received COVID-19 vaccines before testing positive for SARS-CoV-2.
Table 1
Neutralizing antibodies (NAB) to IFN-1 in SARS-CoV-2 and HIV-1 co-infected patients.

| Item | Patient No. 1 | Patient No. 2 | Patient No. 3 | Patient No. 4 | Patient No. 5 | Patient No. 6 | Patient No. 7 | Patient No. 8 | SARS-CoV-2 and HIV-1 co-infected patients (n = 8) | HIV-1 positive patients without SARS-CoV-2 infection (n = 16) | Healthy donors (n = 16) |
|------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|-----------------------------------------------|----------------------------------------------------|---------------------|
|      | Gender | male | male | male | female | male | male | male | male/female | male/female | male/female |
| Age (years) | 42 | 78 | 57 | 50 | 47 | 51 | 58 | 80 | 54 (42-80) | 56 (40-82) | 57 (41-82) |
| HIV-1 RNA (copies/ml) | <37 | <37 | <37 | <37 | <37 | <37 | <37 | <37 | <37 | 14 (3-21) | 15 (8-25) | NA |
| Years from HIV-1 diagnosis | 21 | 13 | 8 | 18 | 15 | 13 | 17 | 3 | 13 (3-21) | 12 (6-23) | NA |
| Anti-HIV-1 drug class | | | | | | | | | | | | |
| CD4 T cell count (cells/μl) | >500 | 304 | 304 | 86 | >500 | >500 | >500 | >500 | >500 (86-500) | >500 (210-1053) | NA |
| Hospitalization (days) | 110 | 44 | 60 | 60 | 0 | 0 | 21 | 21 | 52 (21-110) | NA | NA |
| CRP (mg/dl) | 25.47 | 15.52 | 13.46 | 1.66 | NA | NA | 2.90 | 0.23 | 8.18 (0.23-25.47) | NA | NA |
| Biochemical parameters | | | | | | | | | | | | |
| Fibrinogen (mg/dl) | 401 | 591 | 555 | 532 | NA | NA | 555 | 412 | 543.5 (401-591) | NA | NA |
| D-dimer (μg/l) | 1918 | 2997 | 501 | 33933 | NA | NA | 238 | 240 | 1209.5 (238-33933) | NA | NA |
| COVID-19 Severity Index | 3 | 11 | 9 | 8 | 1 | 1 | 5 | 4 | 4.5 (1-11) | NA | NA |
| COVID-19 therapy* | Decadron, Velklury, Heparin | Decadron, Velklury, Heparin | Decadron, Velklury, Heparin | Decadron, Velklury, Heparin | Bamlanivimab, Etesevimab, Heparin | Bamlanivimab, Etesevimab, Heparin | Decadron, Velklury, Heparin | Decadron, Velklury, Heparin | – | – | – |
| Outcome of COVID-19 NAB status** | Dead | Survival | Survival | Dead | Survival | Survival | Survival | Survival | – | NA | NA |
| IFN-α2 (TRU/ml)* | Serum Oropharyngeal swab | 53 | 530,000 | <10 | 5689 | <10 | <10 | <10 | <10 | 3/8 (53-530,000) | 0/16 (<10) | 0/16 (<10) |
| IFN-α1 (TRU/ml)* | Serum Oropharyngeal swab | 13 | 136,500 | <10 | 8960 | <10 | <10 | <10 | <10 | 3/8 (13-136,500) | 0/16 (<10) | 0/16 (<10) |
| IFN-β (TRU/ml)* | Serum Oropharyngeal swab | <10 | <10 | <10 | <10 | <10 | 10 | 13 | 26 | 3/8 (10-26) | 0/16 (<10) | 0/16 (<10) |
| IFN-ω (TRU/ml)* | Serum Oropharyngeal swab | <10 | 2100 | 2100 | <10 | <10 | 17 | 10 | 10 | 5/8 (10-2100) | 0/16 (<10) | 0/16 (<10) |

Data are expressed as single value for each patient (Patient No 1–8) or as median (range) and percentage. NAB positive patients are in bold. *COVID-19 Severity Index [9] was indicated for each patient. There are four risk categories based on values of COVID-19 Severity Index (0–2 = low; 3–5 = moderate; 6–7 = high; ≥8 = critical). *Decadron (Sigma Aldrich, St. Louis, MO, USA) was injected at 6 mg per day for 8 days. Velklury (Gilead Sciences, Foster City, CA, USA) was administered at 200 mg during the first dose, and at 100 mg in the following 4 days. Patients received a single administration of a monoclonal antibody-based combination therapy, which included a single infusion of Bamlanivimab and a double infusion of Etesevimab (Lilly, Indianapolis, IN, USA) at 700 mg/20 ml. All patients received low molecular weight heparin for prophylaxis of deep vein thrombosis as recommended at the time by the Italian Society of Infectious Diseases. **NAB detection was carried out at the time of hospitalization for patients No.1, 2, 3, 4, 7 and 8 or before starting Bamlanivimab-Etesevimab therapy for patients No.5 and 6 who were not hospitalized. Anti-IFN-α NAB were detected against IFN-α2 subtype and multiple IFN-α subtypes contained in the natural IFN-α preparation (IFN-α1). NAB titers were calculated using the Kawade's method, and the titers were expressed in Tenfold Reduction Units (TRU)/ml. No NAB were detected in the serum of HIV-1 mono-infected individuals and healthy donors. Abbreviations: ART = antiretroviral therapy; NA = not available; LDH = lactate dehydrogenase; CRP = C-reactive protein.
Previous studies have reported that at least 10% of patients with severe COVID-19 exhibit anti-IFN-I NAB [6,7]. We showed that the proportion of HIV-1 and SARS-CoV-2 co-infected patients with NAB to IFN-I is much higher (87.5%). NAB against IFN-α are uncommonly detected in HIV-1 infected patients, except in those receiving IFN-α preparation with the aim of inducing anti-IFN-α antibodies to counteract IFN-α overproduction [10]. Thus, although none of our patients had been previously treated with IFN-α, therapy, 3/8 patients had NAB against IFN-α and produced NAB against IFN-α (Table 1), suggesting that those patients might have developed a broad spectrum of NAB with specificity against different IFN-α subtypes.

Because anti-IFN-I NAB have recently been detected in respiratory samples of SARS-CoV-2 positive patients [7], we measured NAB in respiratory samples from 3 SARS-CoV-2 and HIV-1 co-infected patients (Table 1). NAB against IFN-ω were detected in two oropharyngeal swab samples (Table 1); anti-IFN-α NAB were detected in one of these samples (Table 1). No anti-IFN-β NAB were detected in oropharyngeal samples (Table 1).

High titres of serum NAB have been associated with reduction and/or abrogation of the endogenous induced IFN response in COVID-19 patients [7]. Therefore, we performed gene expression analysis of IFN stimulated genes (ISGs) that have been reported to be involved in immunopathogenesis of HIV-1 or are considered important antiretroviral restriction factors, such as ISG15 [11], APOBEC3G and APOBEC3F [12]. We compared mRNA levels in PBMCs from SARS-CoV-2 and HIV-1 co-infected patients positive for anti-IFN-I NAB (n = 7), with levels in gender and age matched HIV-1 infected individuals (n = 16) without SARS-CoV-2 infection and healthy donors (n = 16, Table 1). None of the healthy controls and HIV-1 mono-infected patients had detectable NAB in serum samples. The mRNA levels of ISGs were measured in PBMCs by quantitative RT/real time PCR assays using LightCycler480 instrument (Roche, Basel, Switzerland) as previously reported (S1). Primers and probes for APOBEC3G (Hs.PT.58.27074917) and APOBEC3F (Hs. PT.58.2507020) were purchased from Integrated DNA Technologies. The following primers and probe were used for ISG15: ISG15 Forward 5′-TGCGGGCAACGAATT-3′; ISG15 Reverse 5′-TGATCTGCGCCTTCA-3′; ISG15 Probe 5′-6FAM-TGAGCAGCTCCATGTC-TAM-3′ [7]. Transcript levels of APOBEC3G and APOBEC3F were strongly reduced (p < 0.001 for both genes using Mann Whitney test) in anti-IFN-I NAB positive co-infected patients [supplementary file 2 (S2)] [13]. A trend toward lower expression of ISG15 in NAB positive patients was observed compared to HIV-1 patients uninfected with SARS-CoV-2 (p = 0.50) and healthy individuals (p = 0.77) (S2). Moreover, we found an inverse correlation between ISG15 mRNA expression and the titer of NAB against IFN-α (p = 0.030, Spearman rho = −0.544) and the natural IFN-α preparation (p = 0.041, Spearman rho = −0.516) respectively. These results are consistent with those of our previous investigation, in which we reported decreased levels of ISGs in COVID-19 patients who had anti-IFN-ω NAB [7]. By contrast, no significant correlation was observed between NAB titer and APOBECs transcript levels, despite their mRNA levels were highly reduced in the presence of NAB (S2). The reason for these results remains unclear. Remarkably, SARS-CoV-2 has been shown to utilize the APOBEC-mediated mutations for fitness and evolution [14]; on the other hand, APOBEC levels were found to be downregulated in severe COVID-19 [13], highlighting the complexity of the phenomenon analyzed.

Our findings demonstrated for the first time a high rate of a broad spectrum of NAB with specificity against IFN-α subtypes, IFN-β, and IFN-ω in SARS-CoV-2 and HIV-1 co-infected patients. It is unknown whether the presence of anti-IFN-I NAB reflects pre-existing autoimmunity contributing to severe disease in some patients or if the appearance of NAB is in response to SARS-CoV-2-induced increase of IFN.

Detection of anti-IFN-I NAB might have value as a prognostic indicator for severe COVID-19 disease in HIV-1 infected patients. The presence of a high level of serum NAB against IFN-α and IFN-ω was associated with severe illness, although the range of NAB levels was very broad. Further studies with larger number of SARS-CoV-2 and HIV-1 co-infected patients, across the spectrum of SARS-CoV-2 associated disease, are needed to better characterize the clinical and biological significance of NAB in HIV-1 patients. Moreover, virus induced cytopathic effect (CPE) based neutralization assay, such as that used in this study, has been the favored approach for NAB determination, until to date. However, variations in assay conditions between laboratories and the increasing use of novel methods including the high throughput luciferase test described by Bastard et al. [15], have highlighted the need to develop standardized assay for the detection of anti-IFN neutralizing autoantibodies to better define the overall diagnostic value of assessing NAB status in COVID-19 patients.

Author contributions

All authors participated in the conception and design of the study. All authors revised and approved the final letter.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinimm.2022.109068.

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Letter to the Editor

P. Bastard, L.B. Rosen, Q. Zhang, E. Michailidis, H.H. Hoffmann, Y. Zhang, K. Dorgham, Q. Philippott, J. Rosain, V. Bezát, J. Maney, E. Shaw, L. Haljsamagi, P. Peterson, L. Lorenzo, L. Bizien, S. Trouillet-Assant, E. Dubbs, A.A. de Jesus, A. Belot, A. Kallaste, E. Kathiron, Y. Tandjaoui-Lambotte, J. Le Pen, G. Kermer, B. Bigio, Y. Seeleuthner, R. Yang, A. Bolze, A.N. Spaan, O.M. Delmonte, M.S. Abers, A. Aiuti, G. Casari, V. Lampasonza, L. Piemonti, F. Ciceri, R. Bilguvar, A. Bolze, A. N. Spaan, O. M. Delmonte, M. S. Abers, A. Belot, K. S. Hallberg, K. T. Jensen, I. Meyts, A. H. Dyer, S. P. Kennelly, N. M. Bourke, R. Halwani, N. S. Sharif-Askari, K. Dorgam, J. Sallette, S. M. Sedrakus, S. Allhaster, R. B. Yon, M. Roman, F. Morandeau, L. Dus, F. S. Gavrielson, K. S. Hallberg, B. Fardesman, D. Hagan, J. Wauters, I. Meyls, A. Dyer, S. P. Kennelly, N. M. Bourke, R. Halwani, N. S. Sharif-Askari, K. Dorgam, J. Sallette, S. M. Sedrakus, S. Allhaster, R. B. Yon, 101, https://doi.org/10.1016/j.immuni.2021.49574.

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