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REVIEW

Dangerous liaisons? The role of inflammation and comorbidities in HIV and SARS-CoV-2 infection

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ABSTRACT

Introduction: In people living with HIV (PLWH), immune activation and inflammation levels are high even when viral suppression is maintained, potentially contributing to several comorbidities, and hampering the immune response to infections such as the recent SARS-CoV-2 disease 2019 (COVID-19).
Areas covered: Immune activation and inflammation play a role in SARS-CoV-2 infection. Severe COVID-19 patients may experience cytokine release syndrome (CRS), leading to alveolar damage, pulmonary fibrinolysis, dysregulated coagulation, and pulmonary injury. Into the systemic circulation, cytokines in excess might leak out of pulmonary circulation, causing systemic symptoms and possibly a multiple-organ dysfunction syndrome. Preexisting comorbidities are also linked to worse COVID-19 outcome: studies suggest that diabetes and hypertension are linked to higher mortality rates. Such comorbidities are more frequent in PLWH, but it is unclear if they have worse outcomes in the case of COVID-19. The literature was searched in PubMed/MEDLINE and EMBASE, and manually in COVID-19 resources.
Expert opinion: A body of evidence shows that HIV and SARS-CoV-2 are able to activate inflammatory pathways, acute in the case of SARS-CoV-2, chronic in the case of HIV, while the comorbidities seem to represent, in the first case, a contributory cause, in the second an effect of the virus-induced damage.

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Comorbidity; hiv; immune response; inflammation; SARS-CoV-2

1. Introduction

In persons living with HIV (PLWH), levels of immune activation and inflammation remain elevated even when viral suppression is maintained, and this may contribute to the insurgence of several comorbidities. On the other hand, residual immune dysregulation can hamper the immune response to infections. Immune activation and inflammation seem to play a pivotal role also in SARS-CoV-2, and some comorbidities are tied to a worse outcome in this disease, although it is still unclear if PLWH experience a worse outcome in the case of COVID-19 [1,2].

Several confounders make it difficult to correctly interpret the interplay between SARS-CoV-2 and HIV. On the one hand, the residual chronic inflammation evidenced also in PLWH on stable viral suppression should favor the cytokine storm. On the other hand, in patients with more severe disease, immune deficiency should exert a protective effect. In all this, the role of antiviral therapy seems irrelevant. In particular, the RECOVERY trial showed that, in patients admitted to hospital with COVID-19, lopinavir-ritonavir, used in the first phase of the pandemic, was not associated with reduction in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death [3].

Also, behavioral aspects could play a role and make it even more difficult to evaluate the SARS-CoV-2-HIV interaction. In fact, many PLWH are aware of their immune deficiency conditions and may protect themselves better than the general population. Furthermore, in several countries, the median age of PLWH is lower than non-coinfected COVID-19 patients. Finally, PLWH are frequently more treated and monitored for hypertension and diabetes at an earlier stage than their non-co-infected counterparts.

Knowledge of the intricate interaction between HIV, SARS-CoV-2, comorbidities and host immune system will be pivotal to understand the pathogenic mechanisms, to clarify the effects of the SARS-CoV-2-HIV coinfection, and to develop new strategies to manage both the diseases.

1.1. Database search

PubMed/MEDLINE and EMBASE were searched for specific comorbidities (hypertension, diabetes, hyperglycemia, metabolic syndrome, coagulation disturbances) or 'proinflammatory cytokines' and COVID-19 or SARS-CoV-2 and HIV, both in MeSH and as free text in all fields (limits: Human, English). The search was limited to articles published in English until 11 January 2021, retrieving 122 results from PubMed/MEDLINE and 67 in EMBASE, after excluding duplicates. Bibliography of the retrieved articles was manually searched to identify the relevant literature regarding inflammation

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Article highlights

- HIV and SARS-CoV-2 can both activate inflammatory pathways
- Cytokine release syndrome (CRS) might occur in severe COVID-19 patients and represents a negative prognostic factor for survival
- Treatment for CRS seems less effective in presence of hyperglycemia, both in diabetic and non-diabetic subjects
- SARS-CoV-2 disease has a worse outcome in subjects with concurrent diabetes, hypertension and coagulation disorders
- Cardiovascular comorbidities are frequent among persons living with HIV, suggesting that COVID-19 may have a worse outcome than in HIV-negative people

markers and SARS-CoV-2 or HIV. Since this was not a systematic review, articles were selected according to authors' opinion about their relevance.

2. Proinflammatory cytokines and SARS-CoV-2 disease

Various evidence confirms that cytokine release syndrome (CRS), a negative prognostic factor for survival, might occur in severe COVID-19 patients [4–6]. In alveolar epithelial and in airway cells, CRS dampens type-1 interferon (IFN) responses, by allowing rapid viral replication whilst attracting a disproportionate number of inflammatory monocytes, macrophages, neutrophils, natural-killer cells, and dendritic cells into the lungs [6]. As a consequence, innate responses could be overactivated, through a vicious cycle driven by cytokines [4]. Moreover, the overwhelmingly present proinflammatory chemokines and cytokines might lead to alveolar damage, pulmonary fibrinolysis, and dysregulated coagulation, resulting in pulmonary injury [4]. Furthermore, cytokines in excess might leak out of pulmonary circulation, causing systemic symptoms and possibly a multiple-organ dysfunction syndrome [4]. Interestingly, in most severe cases, proinflammatory cytokines, including IL-2 receptors (IL-2Rs), IL-6 and tumor necrosis factor (TNF)-a, showed increased serum concentrations that were markedly higher than in mild-moderate cases. This suggested an association between cytokine storms and disease severity [7].

Summary table. Markers of inflammation and comorbidities in SARS-CoV-2 and HIV infection.

Marker	SARS-CoV-2	HIV
IL-2 r	Increased	Reduced
IL-6	Increased	Increased
TNF-a	Increased	Increased
IL-17	Increased	Reduced
D-dimer	Increased	Increased
DC SIGNS	Favors CRS	Favors HIV access
CD4+ cells	Decreased	Decreased
Th17	Increased	Decreased
Comorbidity		
Diabetes	Favors CRS	Favored by HIV
Cardiovascular disease	Favors CRS	Favored by HIV
Coagulation disturbances	Favors CRS	Favored by HIV
Metabolic syndrome	Favors CRS	Favored by HIV
Vitamin D deficiency	Favors CRS (?)	Favors disease progression

Similarly, exuberant inflammatory responses and pulmonary damage also characterized SARS [4]. Using a mouse model of SARS, a previous study indicated that inflammatory monocyte and macrophage accumulation was promoted by a delay in type-1 IFN signaling and by the rapid kinetics of SARS-CoV replication. This accumulation resulted in elevated pulmonary cytokine/chemokine levels, vascular leakage, and suboptimal T-cell responses [8].

IL-17 plays a key role in the cytokine storm observed in acute respiratory distress syndrome of any cause and is associated with alveolar inflammation and a poor prognosis. In severe compared to non-severe COVID-19, increased levels of IL-17-regulated cytokines were observed. However, IL-17 was only increased in severe cases compared to non-infected controls and correlated positively with an increased lung injury severity score. Furthermore, IL-17 plays a role in facilitating early neutrophil recruitment into the lungs, a deleterious phenomenon associated with poor prognosis in severe cases of COVID-19 [9].

DC-SIGN (Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin) also known as CD209 (Cluster of Differentiation 209) is a protein which in humans is encoded by the CD209 gene [10]. Dendritic cells (DCs) are the first immune cells to encounter the HIV, and being the main antigen presenting cells, HIV-1 uses DCs to gain faster and more efficient access to CD4 T cells [11]. On the other hand, an interaction between SARS-CoV-2 spike protein S and the DC-SIGN receptor on the respiratory dendritic cell and associated endothelial cells has been demonstrated and could in part explain the mechanism of the cytokine storm [12,13].

3. SARS-CoV-2 and comorbidities

Comorbidities seem tied to a worse outcome in SARS-CoV-2 disease: in a systematic review and meta-analysis aimed at estimating whether preexisting comorbidities were associated to COVID-19 mortality, Ssentongo et al. [14] found that the presence of cancer, cardiovascular disease (CVD), congestive heart failure, hypertension, diabetes, and chronic kidney disease increased the mortality risk in COVID-19 patients. Similarly, in a cohort of 3894 unselected COVID-19 subjects, admitted to 30 Italian clinical centers [15], machine learning analysis revealed that, besides older age, the major predictors of in-hospital death were elevated C reactive protein levels and kidney damage, as estimated by glomerular filtration rate. A Cox survival analysis, accounting for sex, age, comorbidities, smoking habits, and other relevant confounders, confirmed these findings although it did not detect any relation with obesity, tobacco use, or CVD.

Cardiometabolic multimorbidity, rather than single cardiovascular comorbidities, was associated with high risk of negative COVID-19 outcomes, in a retrospective study comparing data from hospitalized subjects with and without cardiometabolic multimorbidity, and with and without diabetes [5]. In this experience, patients hospitalized for COVID-19 experienced an increased risk, attributed to the clusterization of diabetes and hypertension and/or dyslipidemia.

4. The role of diabetes and hyperglycemia

A body of evidence shows that hyperglycemia has an impact on several components of the host response, such as cytokine regulation and immune cell function [16]. Tocilizumab (TCZ) treatment was widely used in the early period of the pandemic for the treatment of moderate and severe COVID-19 pneumonia. This reduced cytokine release and targeted interleukin-6 receptors (IL-6Rs), allowing us to understand the fundamental relations between SARS-CoV-2 disease and diabetes. Nonetheless, despite this therapy, diabetic patients have an adverse disease course as compared to non-diabetic ones. Indeed, glucose homeostasis affected the outcomes of diabetic subjects with concomitant infectious diseases. In a study conducted by Marfella et al. [17] on 475 patients positive for COVID-19, it was observed that hyperglycemic patients (even if non-diabetic) vs. normoglycemic patients had higher IL-6 levels, persisting after TCZ administration. In an adjusted Cox regression analysis, in hyperglycemic individuals TCZ did not diminish the risk of severe outcomes whereas it did in normoglycemic ones. In hyperglycemic patients, higher IL-6 levels lessened the effects of TCZ while the TCZ effect lost significance when IL-6 levels were added to the Cox regression model. In both diabetic and non-diabetic patients, evidence suggested that COVID-19 was not optimally managed during hyperglycemia. Previous observations by Capes et al. [18] were consistent with these findings: patients admitted for acute myocardial infarction and with stress hyperglycemia, were at greater risk of in-hospital mortality if not previously diagnosed with diabetes, in comparison with patients with previous diabetes diagnosis.

This observation may be explained by several mechanisms. Insulin and/or oral antidiabetic drugs for hyperglycemia are more likely administered, before and during acute illness, to subjects with known diabetes [18], and such treatments may reduce the free radicals and inflammation surge, and also reduce coagulability since they cause a decreased the production of proinsulin-like molecules and plasminogen activator inhibitor type-1 (PAI-1) activity [19]. Conversely, several observations have shown that higher IL-6 plasma levels may blunt the effects of TCZ in hyperglycemic patients.

5. Hypertension and coagulation disturbances

The most common comorbidity and death cause in patients with COVID-19 infection is hypertension [20]. The negative relationship between clinical prognosis in COVID-19 patients and hypertension has been thoroughly investigated in recent studies [20,21]. Angiotensin converting enzyme 2 (ACE2), involved in the molecular pathways leading to hypertension, is a central co-factor that mediates the entry of SARS-CoV-2 into host cells [22]. In fact, the SARS-CoV-2 spike proteins have a strong binding affinity for ACE2, mainly expressed in the endothelial cells of the lung and the upper respiratory tract [17]. Moreover, angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) were demonstrated to up-regulate ACE2 levels that mediates, in part, their cardiovascular protective effects [23]. Nevertheless, recent evidence suggested that ACEi/ARB therapy did not increase the risk of COVID-19 infection in patients with treated hypertension [4]. Therefore, ACEi/ARB therapy discontinuation was not recommended since it could lead to endothelial dysfunction and hyperinflammation [4] that could cause alterations of the coagulation, thus worsening the prognosis of the disease [17,22].

The role of AB0 blood group is strictly related to the problem of high blood pressure and vascular damage. The AB0 blood group plays a functional role in some viral infections, such as Norwalk virus infection [24] or SARS [25]. It has also been observed that individuals with 0 blood group had lower risk of being infected with COVID-19 when compared to individuals with non-0 blood groups [26], and that AB0 groups may affect the coagulation processes [27,28]. However, the underlying pathogenic mechanisms have not been entirely explored, despite their great potential for clinical applications. In a prospective study including hypertensive patients with COVID-19 infection, Sardu et al. [29] compared 0 and non-0 blood groups, evaluating thrombotic and inflammatory statuses, heart damage, and deaths. The study evidenced that values of D-dimer, activated prothrombin time, and thrombotic indexes (as Factor VIII and Von Willebrand factor) were significantly different by blood group. Furthermore, 0 individuals had lower rates of heart damage and death. In the multivariate analysis, non-0 blood group and IL-6 independently predicted heart damage in patients with concomitant hypertension and COVID-19. Similarly, non-0 blood group, D-dimer and IL-6 were independently predicting death events. Overall, these data indicate that individuals with hypertension and COVID-19 had significantly higher values of prothrombotic indexes, as well as higher rates of cardiac injury and deaths, if they were in the non-0 blood group, in comparison to the 0 group. Lastly, COVID-19 prognosis was associated with AB0 blood group in hypertensive patients with COVID-19 infection [29].

A mathematical model of the virus transmission dynamics that takes into account the protective effect of AB0 natural antibodies was built by Guillon et al. [30]. The model indicated that the AB0 polymorphism could contribute to substantially reduce the virus transmission, affecting both the number of infected individuals and the kinetics of the epidemic.

6. Inflammation and comorbidity in HIV

It is well known that, even if HIV suppression has been achieved and maintained for many years, immune activation and inflammation levels stay elevated in PLWH on ART, and may play a role in increasing the risk of morbidity and mortality [31,32]. In particular, persistent inflammation likely contributes to comorbidities in PLWH, including CVD, kidney, neurocognitive diseases, and malignancies. Soluble TNF receptors 1 and 2, D-dimer, IL-6, sCD14, sCD163, that is biomarkers of immune activation and inflammation, are largely associated with development and/or progression of these comorbidities in PLWH [31,32]. In treating HIV infection, conclusive evidence is lacking if the role of inflammation in driving disease risk is causal, although this possibility is supported by several lines of evidence. A clinical trial of the IL-1β inhibitor canakinumab, performed in HIV-uninfected individuals with previous

myocardial infection, showed that patients in the treated arms experienced a reduction in high-sensitivity C-reactive protein level and showed a lower incidence of cardiovascular events and mortality from cancer as compared to the placebo arm [33]. On the same line, studies comparing progressive and non-progressive simian immunodeficiency virus (SIV) infections suggested that SIV-induced inflammation played a role in the development of CVD and other comorbidities [34]. Persistent inflammation and 'inflammaging' (inflammation concomitant with aging) are also likely contributing to frailty [35,36], a geriatric phenotype associated with advancing age. It is still unclear if there are differences between PLWH and non-HIV populations, in terms of inflammatory profiles correlated with risk increase of age-related comorbidities, and if potential mediators and pathways are similar in these two groups.

Over time, studies in PLWH identified many potential drivers of chronic inflammation, such as low-level residual HIV expression during successful ART, dysbiosis and microbial translocation, coinfections with hepatitis C virus, Epstein-Barr virus, and cytomegalovirus (CMV) [4,37]. Elevated cholesterol and/or triglycerides, inflammatory oxidized lipids, and lifestyle factors were also linked to comorbidities in PLWH [4,37].

In the general population, cigarette smoking, recreational drug use, unhealthy diet, and low levels of physical activity, with genetics and coinfections (particularly CMV), were associated with low-grade inflammation and age-related diseases development (cognitive decline, CVD, diabetes, hepatic disease). Notably, several among these lifestyle factors are concurrent among PLWH [38–41]. Besides other key drivers, residual inflammation and immune activation may differ by sex [42], ethnicity [43], and geographic areas [44]. Moreover, they are likely affected by genetic [45] and environmental factors [46].

Other important aspects still need to be understood. In fact, the incidence of some age-related morbidities, such as prostate, colon, and breast cancer, is not increased by concurrent HIV infection. Additionally, starting an ART treatment with high CD4 cell count may confer some protection toward several comorbidities (CVD, neurocognitive dysfunction), but it does not seem to affect the abnormally high risk for coinfections and infection-related cancers [47].

Inappropriate activation and retention of immune cells within liver tissues, blood vessels, adipose tissues, and the central nervous system (CNS) may be driven by immune system dysregulation due to coinfection or to HIV itself. In PLWH, population of circulating immune cell, including activated monocytes that express pro-coagulants such as tissue factor, high levels of mature activated $CD8^+$ T cells, which can home to endothelial surfaces via expression of homing receptors, lymphocyte function-associated antigen 1, macrophage-1 antigen [48,49], C-C chemokine receptor type 2, and C-C chemokine receptor type 5 [50], have all been detected and associated to the development of CVD and several other comorbidities [51–55].

Development of other end-organ diseases may also be affected by altered migration of activated immune cells to liver tissues, blood vessels, and the central nervous system. In addition, in PLWH T- cell subsets may be inappropriately held within lymph nodes [56], possibly contributing to heightened lymph node inflammation, fibrosis, and immune cell reconstitution failure [57,58].

A last point worth considering was that among PLWH vitamin D deficiency is a very frequent condition. Vitamin D reduces the risk of microbial infection and death, through several mechanisms: cellular natural immunity, adaptive immunity, and physical barrier. Vitamin D supplementation has shown favorable effects in HIV and other viral infections, like influenza, although the effects of vitamin D supplementation during COVID-19 infection remain still controversial [59].

7. Metabolic syndrome, COVID-19 and HIV

A body of evidence suggest that metabolic syndrome (MetS) and its components (hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol, diabetes or hyperglycemia, overweight – expressed as waist circumference) are associated with the severity of COVID-19. In fact, patients with MetS are highly susceptible to SARS-CoV-2 infection. Recent meta-analyses have shown that MetS is significantly associated with the development of severe COVID-19. Enhanced ACE2 expression, preexisting endothelial dysfunction, and procoagulant state induced by adipocytokine dysregulation in MetS may play a crucial role for the development of severe COVID-19 [60].

MetS is one of the major comorbidities among PLWH. Several studies have investigated the pathophysiology of MetS and cardiovascular complications in HIV infection. Evidence shows that both HIV infection per se and HIV-related chronic immune activation, despite antiretroviral therapy (ART), are critical factors linking MetS and cardiovascular complications. Lipotoxicity and adipokines have been focused as key issues for explaining MetS in HIV patients. Although metabolic disorders have been associated indirectly with ART, directly with HIV infection *per se* or with host conditions, current circumstances could change the framework of MetS in the HIV setting: for example, the aging of the HIV population and newer, less metabolically toxic antiretroviral drugs [61].

8. COVID-19 in PLWH

Both HIV-1 and SARS-CoV-2 infection share CD4 T cell loss in association with disease outcome and immunodeficiency. In both diseases, immune activation, direct attacks on CD4 T cells, and redistribution of CD4 T cell contribute, in very different proportion, to CD4 T cell lymphopenia. Like for HIV, lymphopenia and marked CD4 T cell count reduction in COVID-19 patients have been linked to poor clinical outcomes. However, when HIV and COVID-19 meet, no additional decrease of CD4 T cell count has been observed [62].

T helper 17 cells (Th17)–polarized CD4 T (Th17) cells bridge innate and adaptive immunity against pathogens at mucosal barrier surfaces. Th17 cells are located at portal sites of HIV entry and represent the first targets of infection. The paucity of Th17 cells during HIV infection is caused by the infection itself, but also by an altered Th17 differentiation, survival, and

trafficking into mucosal sites. This causes major alterations in mucosal barrier integrity, microbial translocation, and disease progression. Unless initiated during the early acute infection phases, ART fails to restore the frequency and functionality of mucosal Th17 cells [63]. On the contrary, it has been recently hypothesized that the altered functional characteristics of COVID-19 patient-derived neutrophils result in skewed Th1/Th17 adaptive immune response, thus contributing to disease pathology. In the COVID-19 neutrophil/T cell cocultures, neutrophils caused a strong polarity NOS-dependent shift toward Th17. Neutrophils, the known modulators of adaptive immunity, skew the polarization of T cells toward the Th17 promotion and Th1 suppression in COVID-19 patients, contributing to the dyscoordinated orchestration of immune response against SARS-CoV-2. As IL-17 and other Th17-related cytokines have previously been shown to correlate with the disease severity, targeting neutrophils and/or Th17 could represent a potentially beneficial therapeutic strategy for severe COVID-19 patients [64].

Data regarding the clinical outcome of SARS-CoV-2 in PLWH are still inconsistent.

Di Biagio et al. [65] described the epidemiological, clinical features and the outcomes of 69 HIV patients with confirmed SARSCoV-2 in a network of Italian centers. Characteristics of patients and median days between symptoms and diagnosis were similar by hospital admission. Admitted patients had lower current lymphocytes count and nadir CD4 cells, values that also correlated to the worse outcome of COVID-19. Antiretroviral drugs and disease severity did not seem to be associated.

According to Inciarte et al. [66], PLWH diagnosed with COVID-19 were not different from the rest of the Barcelona HIV cohort. 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 rates was performed between the two groups.

In a study comparing COVID-19 outcome between PLWH and non-HIV subjects [67], crude COVID-19 mortality resulted higher in PLWH. However, as regards COVID-19 outcomes, propensity matched analyses revealed no difference in HIV infection status, suggesting that higher mortality was likely driven by higher number of comorbidities.

This finding was further confirmed in a study comparing 42 HIV-negative and 21 HIV-positive COVID-19 patients, matched by admission date, age, gender, body mass index, tobacco history, and a history of hypertension, chronic kidney disease, chronic obstructive pulmonary disease, asthma, and heart failure [1]. SARS-CoV-2-HIV coinfection did not have a significant impact on clinical features, course of hospitalization, or outcomes (in terms of days of hospitalization, need for intensive care unit, invasive ventilation) as compared to SARS-CoV-2 infection alone.

On the contrary, a comparison between HIV-negative and positive patients, admitted in 207 hospitals across the United Kingdom, showed a 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 was 2.87 (95% confidence interval 1.70–4.86), an increased risk due to HIV status [2].

Considering older PLWH and HIV-negative controls with a similar lifestyle, the Elixhauser Comorbidity Index (ECI), the Comorbidity Burden Index, and the Charlson Comorbidity Index were compared [68]. These indices were higher in PLWH than in HIV negative individuals, although the size of differences was small. In particular, HIV patients had more frequently higher ECI scores, thus driving the higher ECI associated with worse COVID-19 outcomes.

9. Conclusion

In conclusion of this brief and, necessarily, not exhaustive analysis of the relationship between these two very important viral infections, and of the role of inflammation and comorbidities in their presentation and outcome, we should conclude that, in both diseases, the correlations are extremely relevant although several aspects still need to be clarified. A body of evidence shows that both these viruses are able to activate inflammatory pathways (Summary table). This capacity influences the acute or hyperacute phase of SARS-CoV-2 while, in the case of HIV, inflammation dominates the entire chronic phase of the disease for several years. Moreover, the comorbidities seem to represent, in the case of SARS-CoV-2, a contributory cause of primary importance in the outcome of the disease, in the case of HIV an effect of the virus-induced damage.

10. Expert opinion

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

Undoubtedly, both these cases put in evidence how inflammation and comorbidities represent nowadays two fundamental aspects in the pathogenesis of several infectious diseases, previously generally underestimated. Probably, the first and most important consequence of this awareness is that, from now on, an in-depth knowledge of immune mechanisms at the base of several viral diseases will be mandatory, aimed both at preventing the negative outcomes of these diseases and at designing effective therapeutic strategies, especially for new pathogens, such as SARS-CoV-2. We can hypothesize that, in the near future, therapies targeted to interfere with inflammatory patterns will be associated with antiviral or antibiotic treatments. In addition, a new approach based on a thorough knowledge of the interactions between inflammatory patterns and infectious agents will allow us to deal with one of the last challenges of HIV infection: the problem of the residual

inflammation and its contribution to premature aging and comorbidities.

The role of comorbidities in modifying the natural history of viral diseases is another crucial point: nowadays it is mandatory to obtain, from our first clinical approach to the patient, a comprehensive awareness of his comorbidities, even at subclinical stages. Moreover, a body of evidence shows that a prompt and effective treatment of comorbidities could substantially modify the clinical outcome of a number of infections and could prevent the most severe complications: the example of the role of diabetes in SARS-CoV-2 will become a paradigm of this concept. From this point of view, the coinfection with HIV and SARS-CoV-2 is an extremely intriguing issue although still poorly understood. In regards to clinical outcomes, the World Health Organization is currently collecting individual data from researchers who have published on the issue of HIV-COVID-19 patients, hopefully providing more comprehensive results on this still uncertain issue.

Of concern is the recent diffusion of the 501Y Variant 2 (also named B.1.1.7, 20B/501Y.V1 and VOC-202,012/01), that is estimated to present an R0 1.75 times higher than the previous variant 501 N, meaning it is 75% more transmissible. This variant became the dominant strain in England in November/December 2020, and it is diffusing worldwide. Moreover, in South Africa, a new variant with 501Y but not Δ69/Δ70 has emerged and spread rapidly since late October [69]. No evidence at present has emerged that these new, more transmissible strains are responsible for more severe diseases; however, a close monitoring of their diffusion and clinical outcome is warranted among PLWH.

An important consequence of the increasing role of inflammation and comorbidities in infections is that infectious diseases are increasingly becoming a multidisciplinary territory: currently, it is clearly evident that the contribution of immunology to infectious disease research is essential, but we should also be aware that only interactive teams composed by infectious disease specialists supported by cardiologist, diabetologists, geriatricians, could effectively address all the diagnostic and therapeutic needs of these patients.

Four decades ago, some experts predicted the extinction of the greatest part of infectious diseases due to the introduction of new potent anti-infective drugs. In the following years, many new infections emerged, and old ones reemerged. Moreover, the problem of the extensive resistance to anti-infective drugs was raised. Probably, infectious disease is the medical specialty that has undergone the greatest changes in the last few years, especially after the HIV pandemic. The present SARS-CoV-2 pandemic, evaluated in the light of the experience gained with HIV, will impose an unprecedented cultural revolution on this medical specialty.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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