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Abstract

Background: There are conflicting reports of the interaction between COVID-19 and HIV infection among coinfected individuals, and there is a particular dearth of evidence among populations in the Middle East.

Aim: To determine if living with HIV and use of antiretroviral therapy increases susceptibility to, and severity of, COVID-19.

Methods: This cross-sectional study was based on telephone survey of COVID-19 symptoms duration and clinical course among 200 people living with HIV (PLWHs) and a review of medical records in Beirut, Lebanon, during Spring 2021. Data were collected from consenting patients using standardized forms. The laboratory and medical characteristics of PLWHs with and without COVID-19 were compared and the outcomes of COVID-19 were described. A binary logistic regression model for contracting COVID-19 was constructed based on clinically relevant covariates consistently associated with COVID-19. Significance level was set at 0.05 and statistical analysis was performed using SPSS version 27.0. The Lebanese American University Institutional Review Board approved the study protocol.

Results: Fifty-two of 200 PLWHs contracted COVID-19 but only 4 progressed to severe COVID-19. No significant differences were found with respect to gender, time since HIV diagnosis, most recent CD4 count, viral load, substance use, comorbidities, or use of antiretroviral therapy. Older PLWHs were at lower risk of contracting COVID-19; COVID-19 infection was significantly associated with younger age.

Conclusions: COVID-19 infection was associated with younger age among PLWHs in Lebanon, possibly due to behavioural and socioeconomic factors.

Keywords: COVID-19, HIV infection, antiretroviral agents, antiretroviral therapy, people living with HIV, COVID-19/HIV coinfection, Lebanon

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Introduction

The COVID-19 pandemic still poses a considerable threat to the lives of billions of people, despite vaccination efforts (1). Patient groups with specific comorbidities are suggested to be at higher risk of COVID-19, such as patients with cancer and solid organ transplant recipients (2,3). However, data on people living with HIV (PLWHs) were inconclusive (3) until a recent meta-analysis found a higher incidence and more severe clinical outcomes than among persons without HIV. This risk is increased with progression of HIV and uncontrolled infection (4). The analysis also reported an 80% excess mortality rate among PLWHs compared with people without HIV. However, there was a significant difference between the pooled mortality rates from different countries. This suggests that multiple factors contributed to the mortality rate in these countries. Factors such as age, cardiovascular disease, and metabolic disorders may increase the risk of morbidity and mortality due to COVID-19 regardless of HIV status (5).

Since the beginning of the COVID-19 pandemic, studies from different cities have reported conflicting results on the severity of COVID-19 symptoms among PLWHs (6–14). Some studies reported increased severity of symptoms and hypothesized that frailty of the immune system among PLWHs may have contributed to the severity (7,10). A cohort study from the United Kingdom of Great Britain and Northern Ireland (UK) reported a significantly increased risk of mortality due to COVID-19 among PLWHs compared with people without HIV (14). Also, confounding factors related to HIV infection, such as socioeconomic status and under-reported comorbidities, have been suggested to contribute to the increased severity of COVID-19 in these patients (10). COVID-19 was associated with severe outcomes and hospital admission among PLWHs compared with people without HIV. COVID-19 was also associated with the risk of progression of HIV infection (11). In contrast, other studies from different countries found a negligible difference in clinical features of COVID-19 between PLWHs and patients without HIV (8,12,13).

Other studies have found a significantly decreased risk of COVID-19 among PLWHs compared with people without HIV (6,9). Some researchers have argued that antiretroviral medication, specifically nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), may have contributed a protective effect (6,9). Others have suggested that the suboptimal immune system in these patients worked in their favour, resulting in a less destructive cytokine storm (15). However, one study suggested that a lower CD4 count was associated with more severe COVID-19 outcomes (8) but the results were not statistically significant.

Although several studies have investigated the incidence, prevalence, and clinical outcomes of COVID-19 infection among PLWHs (6–13), no consistent relationship between the conditions has been established. These conflicting results can be attributed to many factors such as sample size, confounding biases, and geographical, social, and healthcare disparities. To our knowledge, no such studies have been conducted in Lebanon. This study aimed to investigate the association between HIV status and susceptibility to COVID-19, the role of antiretroviral

therapy in COVID-19, and whether PLWHs are at increased risk of severe COVID-19 symptoms and outcomes.

Methods

Data sources

Data sources included patients' hospital records and a telephone survey conducted by 1 of the investigators. Three investigators were involved in data collection using a standardized questionnaire for the telephone survey and hospital records. After receiving consent and completing the telephone survey, data were extracted from hospital records. Demographic details and phone numbers collected from the telephone surveys were compared with the hospital records to confirm participant identity and match data collected from the telephone survey and hospital records.

Information collected from the hospital records included date of HIV diagnosis, most recent viral load, most recent CD4 count, other infections, antiretroviral treatment, and other comorbidities. Information collected by telephone survey in May 2021 included ever having a diagnosis of COVID-19, onset and duration of symptoms, type of treatment, disease severity, types of symptoms during infection, and persistent symptoms after infection. Data were collected from a single centre in Beirut. The study sample was assumed to be representative because the clinic provides care to PLWHs with different ages, gender, and backgrounds. The number of PLWHs in Lebanon is estimated to be 3000 [95% confidence interval (CI) = 2600–3400], mostly aged > 15 years, with a male predominance (16).

Patients

Inclusion criteria were: (1) all HIV-positive patients being followed up at the HIV Clinic of the Lebanese American University Medical Center–Rizk Hospital; and (2) HIV-positive patients with COVID-19 infection confirmed by polymerase chain reaction (PCR) or serology. Exclusion criteria were: (1) HIV-positive patients no longer being followed up at the clinic (including patients switching care providers, those lost to follow-up, and those that did not update their contact information at the clinic); (2) HIV-positive patients with reported COVID-19 symptoms but COVID-19 not confirmed by PCR or serology; (3) nonconsenting patients; and (4) deceased patients.

Definitions

Data were collected on symptoms experienced within 14 days of COVID-19 infection. Post-COVID-19 symptoms were defined as symptoms experienced after 14 days. Severe COVID-19 was defined as hospitalization, need for oxygen, admission to intensive care unit

(ICU), or death. The diagnosis of COVID-19 was confirmed by PCR or serology.

Statistical analysis

We used descriptive statistics to describe the main outcomes and covariates. Comparisons for continuous variables were made using the independent samples t test, whereas categorical variables were assessed using the $\chi 2$ test. Binary logistic regression was conducted and the unadjusted odds ratios (ORs) along with their 95% CIs were reported. Multivariate logistic regression analysis was then conducted and adjusted ORs and 95% CIs were obtained. All clinically relevant covariates that were consistently shown in the literature and by expert opinion to be associated with COVID-19 were included in the model to obtain associations between each covariate and COVID-19 status. These covariates included age, gender, CD4 count, smoking status, time since HIV diagnosis, and ART. Significance level was set at 0.05 and statistical analyses were performed using SPSS version 27.0.

Ethical considerations

All research was conducted according to the Declaration of Helsinki. The study protocol was approved by the Lebanese American University Institutional Review Board. Initial consent was obtained from potential participants through SMS text message, followed by oral consent. We contacted 578 HIV patients, 222 responded, and 200 consented. Finalized data sheets were deidentified and special ID numbers were issued to participants to ensure anonymity. All personal information of the participants was kept confidential, and access to the collected data was restricted to the principal investigator only.

Results

Fifty-two of the 200 (26.0%) patients in our sample were diagnosed with COVID-19. Baseline characteristics of PLWHs with and without COVID-19 were compared (Table 1). There were 182 males (91.0%) and 18 females (9.0%). There were no significant differences between PLWHs with or without COVID-19 for mean time since HIV diagnosis, CD4 count, viral load, smoking status, alcohol consumption, illicit drug abuse, hypertension, diabetes mellitus, dyslipidaemia, cardiovascular disease, malignancy, history of other infections, or specific antiretroviral drug or drug class. The average age of PLWHs who contracted COVID-19 was 35.33 (6.61) years, compared with 42.22 (10.14) years among those who were not infected with COVID-19. Five (9.6%) of the PLWHs who contracted COVID-19 were females. Forty-seven of 52 (90.4%) participants who contracted COVID-19 reported symptoms. The most common symptoms were loss of taste or smell, fever, myalgia, chills, arthralgia, and cough. On average, symptoms lasted for 7.81 (7.77) days. Only 2 (3.8%) patients were admitted to hospital for COVID-19, while the rest were treated as outpatients. Only 3 (5.8%) patients required supplemental oxygen therapy. No ICU admissions, intubations, or deaths were reported among PLWHs with COVID-19.

The results of the unadjusted and adjusted logistic regression analyses are presented in Table 2 . The variables used in the regression analysis included: age, gender, CD4 count, smoking status, time since HIV diagnosis, and ART. Patients who were older were 9.0% less likely to have COVID-19 (OR = 0.91, 95% CI = 0.88–0.95) as seen in the unadjusted analysis. Similarly, in the adjusted model, older patients with HIV were significantly less likely to have COVID-19 (OR = 0.89, 95% CI = 0.84–0.95). None of the other variables were associated with COVID-19.

Twenty-five (48.1%) patients who contracted COVID-19 developed symptoms after the disease. The most common symptoms were fatigue, dyspnoea, loss of smell or taste, and anxiety, but only 1 patient developed deep vein thrombosis. No patients developed acute kidney injury, chronic kidney disease, arrhythmias, myocarditis, pericarditis, lung fibrosis, pulmonary embolism, pneumothorax, or hair loss, and none required dialysis. No ICU admissions were noted. Most patients that contracted COVID-19 were treated symptomatically. In decreasing order of frequency, the most commonly reported symptoms during the course of COVID-19 were anosmia and/or ageusia (57.7%), fever (50.0%), and myalgia (46.2%).

Discussion

We found no significant differences between PLWHs with and without COVID-19 in Lebanon, except for age. The most common symptom during COVID-19 infection was loss of taste and/or smell. To our knowledge, this is the first study on outcomes of COVID-19 infection among PLWHs in the Middle East, and adds to the growing literature on COVID-19 and HIV coinfection.

COVID-19 in our study was associated with younger age. This contrasts with a large cohort study from Spain during the first few months of the pandemic, which reported an increased risk of COVID-19 among individuals aged > 70 years, who were all HIV positive and receiving ART (9). Our study was conducted later during the pandemic when PCR testing was readily available and performed regardless of symptom status and as part of COVID-19 case finding (i.e. contact tracing or tracking symptomatic people). The mean age of PLWHs infected with COVID-19 differed among countries (8,9,15,17,18). For instance, a single centre prospective cohort study from Spain reported a mean age of 53.3 years (8), which is markedly higher than 35.33 years in our study. Guo et al. (15) reported that PLWHs who contracted COVID-19 were older than those who did not. These variations may have been influenced by the demographic and social differences among countries. For example, Luan et al. (19) reported that income inequality, binge drinking, and history of sexually transmitted infections were associated with both COVID-19 and HIV infection. A population-based cohort study from the UK also reported a 4.3-fold higher risk of mortality from COVID-19 among PLWHs of black ethnicity (14). We suspect that physiological processes related to different genetic backgrounds played a role in

this increased risk (20), although socioeconomic factors may also have been involved. Socioeconomic disadvantage is associated with worse outcomes and risk of hospitalization in COVID-19 and HIV infection alone (21–23). Thus, such factors may play an important role in the outcomes of coinfection. Another potential explanation is the theory of reverse causality, which has been reported with HIV and other sexually transmitted infections (24). When PLWHs develop a false sense of security, they may be more inclined to engage in activities that carry a risk of contracting COVID-19, such as social gatherings.

Differences in COVID-19 diagnosis or severity among PLWHs with respect to type of ART received have been observed in previous studies. Conflicting results have been reported on the clinical outcomes and severity of COVID-19 among PLWHs (6–14). Some authors have suggested that PLWHs are at lower risk of severe COVID-19 and are expected to have milder symptoms and fewer complications, suggesting that ART plays a role in limiting the ability of SARS-CoV-2 to damage host cells (25). This is supported by the results of a Spanish cohort study in which PLWHs receiving tenofovir/emtricitabine were at decreased risk of COVID-19 diagnosis and severe outcomes (9). However, it is possible that the results were skewed because of selective COVID-19 testing or selective prescription of ART in these individuals rather a true decreased risk of COVID-19.

In vitro studies on the role of NRTIs in inhibiting the docking site of SARS-CoV-2 have suggested that NRTIs have stronger affinity for the active site of SARS-CoV-2 RNA-dependent RNA polymerase than the virus itself, thus decreasing the risk of COVID-19 severity (26–30). Another study on COVID-19 infection among PLWHs from Wuhan by Guo et al. (15) reported similar results. A Chinese randomized controlled trial involving 199 patients (without a history of HIV) with COVID-19 and treated with lopinavir/ritonavir for 14 days found no difference between the treatment and control groups (31). Similar studies also reported no difference in COVID-19 outcomes among PLWHs receiving protease inhibitors and those who were not (17,32).

We found no difference in severity of COVID-19 among PLWHs in terms of CD4 count and viral load. However, only 4 patients who contracted COVID-19 met the definition of severe disease. Conflicting results on the role of immunosuppression in COVID-19 among PLWHs have been reported (8,15,17,33). Guo et al. (15) suggested that immunosuppression predisposed by HIV infection may be protective against COVID-19. Lower CD4 counts among PLWHs downgraded the excessive immune response induced by SARS-CoV-2 infection, thus leading to milder symptoms, if any, among these individuals.

Conversely, other studies reported worse outcomes and delay in symptom resolution in COVID-19 among PLWHs (8, 17, 33). Yang et al. (33) reported lower SARS-CoV-2 IgG levels

among PLWHs coinfected with COVID-19. Also, the CD4+ T-cell count was lower among PLWHs coinfected with COVID-19 than among COVID-19 patients without HIV infection. It is suggested that PLWHs have a weaker immune response and thus decreased ability to produce the necessary levels of SARS-CoV-2 IgG antibodies to limit the infection. In comparing PLWHs with severe and mild-to-moderate COVID-19, Vizcarra et al. (8) reported lower CD4 counts in the severe COVID-19 group. Although the difference was not significant, the results support the theory that immunosuppression caused by HIV infection predisposes PLWHs to an increased risk of severe COVID-19. Hoffmann et al. (17) studied the association between CD4 count and COVID-19 severity among PLWHs. CD4+ T cell count

It is worth mentioning that the studies reporting severe outcomes of COVID-19 among PLWHs were conducted on diverse samples, in which some of the participants had uncontrolled HIV infection (8,17). This represents a striking difference from our sample, which comprised mainly PLWHs with well-controlled HIV infection. One factor contributing to this major difference is that ART is heavily subsidized by the Lebanese National AIDS Control Program, and PLWHs are usually compliant with the treatment provided.

Our findings did not indicate any difference in COVID-19 diagnosis among PLWHs with comorbidities as compared to those with none. In contrast, Vizcarra et al. (8) reported an increased prevalence of comorbidities among PLWHs coinfected with SARS-CoV-2 as compared with HIV infection alone. However, this difference could be because more follow-up opportunities were offered to patients with comorbidities than the healthy individuals (8). From a pathophysiological point of view, these comorbidities do not seem to predispose PLWHs or the general population to increased risk of COVID-19 (1). The role of comorbidities, such as hypertension, diabetes, coronary artery disease, and malignancy, in COVID-19 among PLWHs should be investigated carefully.

This is believed to be the first study to examine COVID-19 among PLWHs in Lebanon. These original data help shed light on the effect of the pandemic on an often-marginalized segment of Lebanese society. Although our data do not provide conclusive results on the role of HIV infection and ART in COVID-19 infection, they do provide a preliminary look at the interaction of the 2 infections, and could help direct further study in this area.

Our study had some limitations. This cross-sectional study presented data collected from hospital records and a telephone survey; therefore, some of the data were self-reported and subject to possible information and recall bias. A significant number of individuals with HIV were excluded because they were lost to follow-up, and this may have had some effect on our analysis. However, the probability of selection bias was low considering that the distribution of excluded participants was likely to have been random. Data collected from clinical records were mainly retrospective; therefore, laboratory analysis, including CD4 count and viral load referred

to different dates of collection. Some variables, such as comorbidities, were missing from some of the participants' records and may have altered the analysis. Missing data from records were secondary to errors of documentation and were probably random. However, an effect of these missing data on the analysis cannot be fully excluded. A comparison group without HIV was not available. Confounding factors such as vaccination status could not be captured because of the study design, although the likelihood of COVID-19 vaccination being a confounding factor was low. The vaccination campaign in Lebanon started later and progressed slower than in the United States of America and Europe. Also, our study coincided with the early phase of the vaccination campaign, and only 3 participants were fully vaccinated at the time of data collection. The probability that these individuals contracted COVID-19 after receiving the vaccine is low considering the timeline of the study. Lastly, this was a single centre study and it is not therefore possible to generalize the results.

Conclusion

In our study of PLWHs, age was the only baseline characteristic that differed significantly between individuals who contracted COVID-19 and those who did not. Younger people living with well-controlled HIV infection had an elevated risk of contracting COVID-19. Only 4 of the 52 cases of COVID-19 were defined as severe, and no deaths were encountered. In this group of PLWHs, ART did not protect against COVID-19, and all the severe cases had well-controlled HIV infection. Further studies are required to determine if HIV diagnosis and severity are associated with COVID-19 severity, and to ascertain the effect of behavioural factors on contracting COVID-19.

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Competing interests: None declared.

La COVID-19 chez les personnes vivant avec le VIH au Liban

Résumé

Contexte : Des informations contradictoires ont été rapportées concernant l'interaction entre la COVID-19 et l'infection à VIH chez les personnes co-infectées, et les données probantes sont particulièrement manquantes parmi les populations du Moyen-Orient.

Objectif : Déterminer si le fait de vivre avec le VIH et de suivre un traitement antirétroviral augmente la sensibilité à la COVID-19 et sa gravité.

Méthodes : La présente étude transversale est basée sur une enquête téléphonique concernant la durée et l'évolution clinique des symptômes de COVID-19 auprès de 200 personnes vivant avec le VIH ainsi que sur une revue des dossiers médicaux à Beyrouth (Liban) au cours du printemps 2021. Les données ont été recueillies auprès de patients consentants à l'aide de formulaires standardisés. Les caractéristiques médicales et biologiques des personnes vivant avec le VIH et atteintes ou non de COVID-19 ont été comparées et ses conséquences ont été décrites. Un modèle de régression logistique binaire pour la COVID-19 a été élaboré à partir de covariables cliniquement pertinentes qui lui sont systématiquement associées. Le niveau de signification a été fixé à 0,05 et l'analyse statistique a été réalisée à l'aide du logiciel SPSS version 27.0. Le Comité d'examen institutionnel de l'Université libano-américaine a approuvé le protocole de l'étude.

Résultats : Cinquante-deux personnes vivant avec le VIH sur 200 ont contracté la COVID-19, mais seulement quatre en ont développé une forme grave. Aucune différence significative n'a été observée pour ce qui concerne le sexe, le temps écoulé depuis le diagnostic du VIH, le nombre le plus récent de CD4, la charge virale, l'utilisation de substances psychoactives, les comorbidités ou le suivi d'un traitement antirétroviral. Les personnes plus âgées vivant avec le VIH étaient moins exposées au risque de contracter la COVID-19. Le risque lié à ce type d'infection était fortement lié à un jeune âge.

Conclusion : L'infection COVID-19 était associée à un âge plus jeune chez les personnes vivant avec le VIH au Liban, probablement en raison de facteurs comportementaux et socioéconomiques.

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