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Biomedical Risk Factors for COVID-19 among People Living with HIV during the First Wave of the Pandemic

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Objective: We assessed the associations between testing positive for COVID-19 and HIV viral load, and access to and adherence to antiretroviral therapy during the initial phase of the COVID-19 pandemic. **Methods:** We conducted a secondary analysis of data, where we extracted complete information for 904 participants self-identifying as HIV positive. The dataset encompassed the dependent variable (testing positive for COVID-19), independent variables (HIV viral load, access to a 90-day supply of antiretroviral drugs, adherence to antiretroviral therapy), and confounding variables (age, sex assigned at birth, living with HIV co-morbidities, and self-reported depression). **Results:** Adherence to antiretroviral therapy (AOR: 0.364; 95% CI: 0.231-0.574; $p < .001$) was significantly association with decreased odds of testing positive for COVID-19. We found no statistically significant associations between HIV viral load or access to a 90-day supply of antiretroviral drugs and testing positive for COVID-19. **Conclusion:** The results underscore the necessity for ongoing HIV treatment adherence counseling for individuals with HIV during the COVID-19 pandemic. Further research is warranted to elucidate the paradox wherein adherence to antiretroviral therapy was associated with testing positive for COVID-19, but HIV viral load was not.

Key words: COVID-19; HIV; viral load; antiretroviral therapy; co-morbidities; infectious diseases
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The likelihood of contracting the SARS-CoV-2 infection, responsible for COVID-19, is elevated among individuals with HIV due to heightened exposure to social and structural factors associated with COVID-19.[1,2] Concerns have been raised regarding the potential for more severe illness and increased mortality rates from COVID-19 among people living with HIV compared to those without HIV.[1] This is attributed to higher rates of underlying health conditions such as hypertension, diabetes mellitus, obesity, and chronic obstructive pulmonary disease among

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individuals with HIV, further amplifying the risk of severe COVID-19.[4,5] Additionally, individuals living with HIV who contract COVID-19 are more prone to requiring hospitalization.[2,6] Whereas certain studies have not established a direct link between HIV and heightened COVID-19 mortality,[7-9] global data from the World Health Organization (WHO) indicate that the risk of developing severe and fatal COVID-19 is 38% higher for individuals with HIV compared to those without HIV.[2]

Factors that increase the risk of co-infection with COVID-19 and HIV include being male, being over age 50, and having multiple concurrent health conditions.[5-7] Additionally, a heightened risk for COVID-19 is associated with poor virological suppression and not being on antiretroviral therapy, as HIV-induced immune suppression can exacerbate the impact of COVID-19 on health outcomes.[8] Conversely, it has been suggested that individuals undergoing antiretroviral treatment may experience a reduced risk of COVID-19 infection.[9,10]

There is, however, little known about how the presence of poor mental health may mediate the risk for COVID-19 among individuals living with HIV. COVID-19 is associated with depression,[11] living with HIV is associated with depression,[12] and depression affects adherence to antiretroviral therapy and HIV viral suppression.[13] Therefore, it is plausible that depression may be a confounding factor for the associations found between COVID-19 and HIV status.

Therefore, in this study, we aimed to assess the associations between biomedical markers of HIV infection and COVID-19. We analyzed a global dataset collected from 152 countries as part of a broader study on mental health and well-being during the pandemic[14] to determine the associations between testing positive for COVID-19 and HIV viral load, as well as access to and adherence to antiretroviral therapy during the first wave of the COVID-19 pandemic. We hypothesized that people living with HIV who did not adhere to their antiretroviral therapy and who had a high viral load were more likely to have tested positive to COVID-19.

METHODS

Study Design

This study conducted a secondary analysis of data obtained from a broader research project focused on gathering insights into mental health and well-being amid the COVID-19 pandemic. The data of the primary study were collected online between July and December 2020. Before participating, all individuals involved were introduced to the study team, the study's objectives, and the anticipated time commitment. Participants were assured that their responses would be kept confidential, and their involvement in the study was voluntary. The study adhered to relevant guidelines and regulations, and participants were required to provide informed consent by checking a checkbox before proceeding with the survey.

Study Population

The study encompassed adults aged 18 years and above from diverse countries who engaged in the online survey during the initial phase of the COVID-19 pandemic. No exclusion criteria were applied. Details regarding the survey design and the tools used for data collection in the primary study have been published previously.[14-20] Overall, 22,106 participants were recruited using non-probability sampling methods and administering a questionnaire that had an overall content validity index of 0.83.[14] For the current analysis, data from 904 people living with HIV were extracted from the primary database for analysis.

Study Dependent Variable

The dependent variable was testing positive for COVID-19. This was assessed by asking respondents if they had tested positive for COVID-19. The response options were *yes* or *no*.

Study Independent Variables

The independent variables were HIV viral load, having access to a minimum 90-day supply of antiretroviral drugs, and adherence to antiretroviral therapy. Participants were presented with the following questions and asked to select an appropriate response by marking a checkbox for each question: (1) What is your current HIV viral load (detectable, undetectable, do not know)? (2) At present, do you have a 90-day supply of your HIV medications (yes/no)? and (3) Some individuals occasionally forget to take their medications for managing their HIV. Did you miss any of your HIV medications during COVID-19 (yes/no)?

Table 1
Factors Associated with Testing Positive for COVID-19 among Individuals Living with HIV during the First Wave of the Pandemic (N = 904)

Variables	Total N = 904 n (%)	Tested positive to COVID-19		AOR (95% CI)	p-value
		Yes (N = 101) (11.2%) n (%)	No (N = 803) (88.8%) n (%)		
Viral load					
Detectable	190 (21.0)	35 (18.4)	155 (81.6)	1.66 (0.98-2.80)	.059
Undetectable	482 (53.3)	46 (9.5)	436 (90.5)	1.00	--
I don't know	232 (25.7)	20 (8.6)	212 (91.4)	0.81 (0.44-1.50)	.499
Had 90 days ARV supplies					
Yes	684 (75.7)	72 (10.5)	612 (89.5)	0.70 (0.43-1.15)	.156
No	220 (24.3)	29 (13.2)	191 (86.8)	1.00	--
Adherence to ARV					
Yes	696 (77.0)	54 (7.8)	642 (92.2)	0.36 (0.23-0.57)	<.001
No	208 (23.0)	47 (22.6)	161 (77.4)	1.00	--
Living with HIV and comorbidity					
HIV + comorbidity	208 (7.6)	38 (18.3)	170 (81.7)	1.86 (1.11-3.12)	.019
HIV alone	696 (92.4)	63 (9.1)	633 (90.9)	1.00	--
Mean Age (SD)	39.0 (11.1)	36.4 (11.0)	39.3 (11.0)	0.97 (0.96-0.99)	.013
Sex at birth					
Female	508 (56.2)	52 (10.2)	456 (89.8)	0.79 (0.51-1.23)	.294
Male	396 (43.8)	49 (12.4)	347 (87.6)	1.00	--
Depression					
Yes	160 (17.7)	27 (16.9)	133 (83.1)	1.08 (0.6201.88)	.789
No	744 (82.3)	74 (9.9)	670 (90.1)	1.00	--
Education level					
No formal education	39 (4.3)	5 (12.8)	34 (87.2)	0.90 (0.30-2.67)	.852
Primary	74 (8.2)	8 (10.8)	66 (89.2)	0.69 (0.30-1.61)	.394
Secondary	331 (36.6)	28 (8.5)	303 (91.5)	0.64 (0.37-1.07)	.090
University	460 (50.9)	60 (13.0)	400 (87.0)	1.00	--
Employment status					
Retired	28 (3.1)	4 (14.3)	24 (85.7)	2.35 (0.62-8.90)	.210
Student	71 (7.9)	9 (12.7)	62 (87.3)	1.00 (0.41-2.41)	.990
Employed	570 (63.1)	62 (10.9)	508 (89.1)	0.99 (0.59-1.67)	.967
Unemployed	235 (26.0)	26 (11.1)	209 (88.9)	1.00	--

Note.
ARV = Antiretroviral; SD = standard deviation; AOR = adjusted odds ratio; 95% CI = 95% confidence interval

Study Confounding Variables

Factors considered as potential confounders encompassed age at the last birthday,[21,22] sex assigned at birth (female or male),[21,23,24] educational status (no formal education, primary, secondary, university), employment status (retired, student, employed, unemployed), self-reported depression (yes/no),[25,26] and the presence of co-morbidities (yes/no). Re-

spondents were prompted to specify whether they had experienced any of the 10 listed emotions during the pandemic, with one of them being depression. Those who did not mark the checkbox next to *depression* were classified as not having experienced depression throughout the pandemic. Participants indicating *yes* to any of the following health conditions were deemed to have co-morbidities: infectious diseases (hepatitis, herpes, pneumonia, shingles, and other sexually transmitted infections), non-infectious diseases (diabetes, cancer, dermatologic problems, heart condition, hypertension, kidney problem, migraines, neurological problems, neuropathy, respiratory problems, and stroke), and geriatric syndromes (arthritis, broken bones, depression, hearing loss, and vision loss).[14]

Data Analysis

The dataset underwent cleaning and was then imported into SPSS version 23.0 (IBM Corp, Armonk, NY) for analysis. From a statistical modeling perspective, having a minimum of 10 participants with complete responses for each of the dependent variables in the study allows for the execution of regression analyses with a statistical significance level (p-value) of .05 or lower.[27] In this study, data from 904 participants (4.1% of the total 22,106 respondents) with complete responses were extracted. Subsequently, binary logistic regression analysis was conducted to explore associations between the dependent and independent variables, adjusting for confounding variables. Adjusted odds ratios (AOR) and 95% confidence intervals (CI) were calculated, with statistical significance set at .05.

RESULTS

Table 1 presents findings based on 904 study participants, among whom 508 (56.2%) were females. The age of participants ranged from 18 years to 77 years with a mean age of 39.0 (SD = 11.1) years. Additionally, 160 participants (17.7%) reported experiencing depression, 208 (7.6%) were living with co-morbidities, 190 (21%) had detectable viral loads, 684 (75.7%) possessed a 90-day supply of antiretroviral (ARV) drugs, and 696 (77.0%) adhered to ARV therapy.

We found a statistically significant association between adherence to antiretroviral therapy and testing positive for COVID-19. Participants who adhered to the therapy exhibited significantly lower odds of testing positive for COVID-19 (AOR: 0.364; 95% CI: 0.231-0.574; $p < .001$). However, no statistically significant associations were found between viral load or access to a 90-day supply of antiretroviral therapy and testing positive for COVID-19.

DISCUSSION

The study outcomes offer additional insights into the factors influencing the risk of COVID-19 among individuals with HIV. Although HIV viral load and access to antiretroviral therapy do not appear to impact the likelihood of testing positive for COVID-19, adherence to antiretroviral therapy does. This presents a paradox whereby HIV viral load depends on adherence to antiretroviral therapy, adherence to antiretroviral therapy seems to affect the likelihood of a COVID-19 diagnosis but the HIV viral load did not. Therefore, the study hypothesis was only partially supported by the study findings.

This study provides a global perspective concerning the associations between testing positive for HIV and having COVID-19 while addressing the confounding role of mental health. However, it had some limitations which include the use of non-probability sampling, an online data collection method, and language restrictions in the survey, affecting the generalizability of the findings. The online data collection was justified due to movement restrictions during the initial wave of the COVID-19 pandemic.[28,29] The cross-sectional study design hampers the establishment of direct cause-effect relationships. Additionally, the self-reporting of health status and HIV parameters, without verification, raises accuracy concerns as there was no clarity on where the test was administered (home/clinic/hospital), when the test was administered in the clinical spectrum, and the type of test used by respondents from the different nations. However, a previous study demonstrated the reliability of self-reports of HIV-related health status among individuals with higher education.[30] Secondary data analysis also comes with inherent challenges with comprehensive data access,[31] and for this study, the measure of antiretroviral medication access was limited to the question on access to 90 days supply; we did not measure the several

dimensions of access, namely – availability, affordability, accessibility, acceptability, and quality.[32] The research was undertaken during the pandemic to generate timely insights into disease processes.[33]

Despite these limitations, the study findings align with a systematic review supporting the use of antiretroviral therapy in reducing adverse COVID-19 outcomes.[34] Adherence to antiretroviral therapy not only decreases the risk of adverse COVID-19 outcomes,[35] but the antiviral properties of these drugs also may protect individuals with HIV from severe COVID-19 outcomes. Although there is currently insufficient evidence to support the use of antiretroviral therapies for managing COVID-19,[36] this does not discount their potential minimal benefits in reducing COVID-19 risk.[37-40] Our study suggests that individuals with HIV who adhere to drug therapy have a lower risk of COVID-19, and those with co-existing health conditions face a higher risk. Therefore, special attention should be given to individuals with HIV who are not taking antiretroviral medication during the COVID-19 pandemic.

Despite the WHO's recommendation for providing long-term supplies of antiretroviral drugs as a precautionary measure against COVID-19, our findings do not seem to support the recommendation.[36] However, this does not negate the importance of ensuring an adequate supply of antiretroviral medication to improve treatment adherence, reduce costs per patient, and enhance clinic efficiency.[41-43] Promoting the multi-month scripting of antiretroviral drugs for managing individuals with HIV should be encouraged.

The observed paradox prompts inquiries, and one plausible explanation could be the interaction between antiretroviral drugs and the SARS-CoV-2 virus, leading to the inverse relationship observed between adherence to antiretroviral therapy and testing positive for COVID-19. Antiretrovirals have demonstrated various interactions with the SARS-CoV-2 virus, such as exhibiting affinity for the SARS-CoV-2 RNA-dependent RNA polymerase, acting as terminators in the catalyzed reaction by the SARS-CoV-2 RNA-dependent RNA polymerase, reducing SARS-CoV-2 particle production, binding to the SARS-CoV-2 through molecular docking, displaying inhibitory potential against the SARS-CoV-2 3-chymotrypsin-like cysteine protease and non-structural proteins14-non-structural proteins10, or terminating RNA synthesis catalyzed by the SARS-CoV-2 RNA-dependent RNA polymerase.[44] There is no evidence of interactions between HIV and SARS-CoV-2. Thus, our result may reflect this molecular interaction between the drug and the virus, and non-interactions between the viruses. This postulation needs to be explored further.

There is a scarcity of studies reporting on the association of the HIV viral load and testing positive to COVID-19. One study, however, suggests there is an association between HIV viral load and COVID-19 re-infection with people living with HIV who were virally suppressed having a higher risk for COVID-19 re-infection.[45] The study suggests the need for further studies to understand the finding.

We postulate that the study findings may indicate that risk-taking behaviors could play a role in the observed association between adherence to antiretroviral medication and a lower risk of COVID-19 infection. A previous study by our team suggested that the connection between poor adherence to antiretroviral therapy and a lack of adherence to COVID-19 preventive measures may be linked to risk-taking behavior.[46] It is plausible to consider that individuals with HIV who are less prone to taking risks are more likely to adhere to their antiretroviral therapy and engage in better COVID-19 preventive behaviors, thereby reducing their risk of COVID-19 infection. However, further research is needed to explore this hypothesis in more detail.

Our findings provide valuable insights into the complex relationship between HIV and COVID-19 risks among individuals living with HIV with a plausibility that this risk may be biomedically mediated. Yet, risk-taking behaviors that affect adherence to antiretroviral medication and poor adherence to COVID-19 preventive behaviors introduce risks that can hamper the protective role of antiretroviral for COVID-19. Further research is needed to explore the complex interplay of behavioral and biomedical factors influencing the risk for COVID-19 among people living with HIV. In addition, these study findings contribute to the evolving understanding of the intricate dynamics between HIV and COVID-19 in individuals living with HIV.

In conclusion, our study identifies adherence to

antiretroviral therapy as a potential indicator for a reduced risk of testing positive for COVID-19 among individuals with HIV. Whereas this finding may suggest that treatment adherence counseling should be intensified during pandemics like that of COVID-19, our hypothesis suggests that focal attention should be placed on people living with HIV with a high propensity for risk-taking and a poor treatment adherence profile as they are the ones at higher risk for contracting COVID-19. Further studies are needed to explore our findings.

IMPLICATIONS FOR HEALTH BEHAVIOR AND POLICY

The study contributes to the goal of reduced rates of infectious diseases and improved health for people with chronic infections. Specifically, it explores COVID-19 infection among individuals with HIV. The findings suggest that there could be a potential relationship between risk-taking behaviors, adherence to antiretroviral medication, and the risk of COVID-19 infection among individuals with HIV.

- *Integrating risk-reduction strategies:* The WHO is one of the organizations with a global HIV strategy that is aligned with sustainable development goal (SDG) target 3.3 for ending the HIV epidemic by 2030.[47] Promoting interventions and counseling that address risk-taking behaviors among individuals with HIV, may have a positive impact on both antiretroviral medication adherence and adherence to COVID-19 preventive measures, thereby responding to the WHO-SDG target.
- *Enhancing adherence support:* By providing resources and interventions to support adherence to antiretroviral medication during a pandemic like COVID-19, there could be a potential benefit in terms of better adherence to COVID-19 preventive measures, potentially leading to a reduced risk of COVID-19 infection.
- *Public health messaging:* Messages could highlight the potential link between risk-taking behaviors and the increased risk of COVID-19 infection. By emphasizing the importance of adhering to both antiretroviral medication and COVID-19 preventive measures, policymakers may encourage behavior change and promote overall health and well-being. A WHO policy brief[48] emphasizes the importance of building trust through targeted risk communication and community engagement.
- *Interdisciplinary approach:* Collaboration between HIV treatment providers and COVID-19 prevention teams could be beneficial, as it allows for a holistic understanding of patients' behaviors and needs, leading to more effective interventions and support.
- *Health equity considerations:* Policymakers need to be mindful of potential disparities in risk-taking behaviors and access to healthcare among individuals with HIV. Addressing social determinants of health, such as poverty, stigma, and discrimination, is essential in ensuring that vulnerable populations receive appropriate support and resources to enhance adherence to medications and preventive measures. A WHO objective calls upon the health sector to take the lead in monitoring inequitable distribution of power and resources and other health inequities through monitoring health outcomes and health service delivery – as well as working with other sectors to monitor people's living conditions.[49]

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Human Subjects Approval Statement

Approval for the ethical conduct of this study was granted by the Human Research Ethics Committee at the Institute of Public Health, Obafemi Awolowo University in Ile-Ife, Nigeria (HREC No: IPHOAU/12/1557) as the lead partner for this study. Additional ethical approvals were obtained from authorities in India (D-1791-uz and D-1790-uz), Saudi Arabia (CODJU-2006F), Brazil (CAAE N° 38423820.2.0000.0010), and the United Kingdom (13283/10570). The protocol was in accordance with international and national research guidelines. All participants provided written informed consent before taking the survey.

Conflict of Interest Disclosure Statement

All authors declare no conflict of interest.

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