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False-positive HIV results and COVID-19 infection or vaccination?

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Abstract

Recently, there have been reports of false-positive HIV results associated with COVID-19 infections and vaccination, which require attention. The similarity between the spike proteins of HIV and SARS-CoV-2 may lead to cross-reactivity of antibodies, resulting in false-positive results on immunoassay screening tests. This hypothesis presents a serious diagnostic challenge. Patients presenting discordant COVID-19 and HIV results should undergo confirmation of the HIV chemiluminescent immunoassay due to the potential for analytical errors. It is essential to highlight the potential for false-positive HIV results related to SARS-CoV-2.

Key word: COVID-19, HIV, Serological test, Vaccine.

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Introduction

The COVID-19 pandemic has brought up several important and unresolved issues, such as the potential adverse effects of vaccination. More research is necessary to better understand these issues, including the problem of false-positive (FP) HIV tests associated with COVID-19 infections (1-10). The mechanisms behind these FP results are not yet fully understood, but research indicates that the spike proteins of SARS-CoV-2 share structural similarities with various viruses, which can lead to antibody cross-reactivity. For instance, studies suggest that HIV-1 gp41 and SARS-CoV-2 share similar structural sequences and motifs, such as the N-terminal leucine/isoleucine repeat sequence and the C-terminal leucine/isoleucine repeat motif. (1-3, 5, 6).

A look at possible causes

The helix structures of various viruses, including SARS-CoV-2 and HIV, are similar, which allows them to fuse their membranes in the same way (3,5). This structural similarity can also cause the spike protein of these viruses to cross-react with antibodies, leading to false-positive (FP) results on HIV tests. Individuals with COVID-19 infections may also show FP results on 4th generation HIV tests due to an unknown physiopathology involving the generation of broad acute polyclonal antibodies (3,6). However, the time period between the FP test and the last infection or vaccination, as well as the point at which the PCR becomes negative, have not yet been established through research. Literature indicates that COVID-19 vaccination can also cause FP results in HIV screening tests, as seen with the Australian COVID-19 vaccine that was abandoned (3,4,6,8). This paper aims to increase the interest of healthcare workers in relevant issues and briefly highlight key points from case studies related to FP results.

Alfie LG et al. conducted a study in Argentina that examined the occurrence of false-positive HIV tests in patients with a COVID-19 diagnosis and in individuals vaccinated against SARS-CoV-2 (1). The samples were evaluated using the Genscreen Ultra HIV Ag-Ab test, and positive results were further analyzed using ELISA lateral flow Determine Early Detect, RecomLine HIV-1 & HIV-2 IgG, and Abbott m2000 RealTime PCR to quantify HIV-1 viral load. The presence of anti-SARS-CoV-2 IgG antibodies was also evaluated using an ELISA COVIDAR kit (1). The study found that the false-positive HIV ELISA rate was 1.3% ($p = 0.03$), which is higher than the expected rate of 0.4%. The rate increased to 1.4% ($p = 0.02$) when only samples from individuals with a previous COVID-19 diagnosis were analyzed and to 1.8% ($p = 0.005$) when only samples from individuals with IgG SARS-CoV-2 antibodies were examined. The authors recommended that health authorities pay attention to the higher rate of false-positive HIV tests in individuals with antibodies against the Spike SARS-CoV-2 protein (1). Cipitelli

MdC et al. presented a case study of a 43-year-old asymptomatic man who underwent routine exams, including the fourth generation chemiluminescence assay Vitros HIV Combo for HIV-1 and HIV-2, which resulted in positive HIV-1 and HIV-2 antibodies and p24 antigen (2). A new sample was taken to confirm and quantify HIV-1 viral load using real-time reverse transcription PCR, and to search for antibody specific viral HIV-1 antigens (p17, p24, p31, gp41, p51, p55, p66, and gp120/160) using western blotting. Although the chemiluminescence HIV-1/HIV-2 test showed similar reactivity to the first sample, HIV infection was excluded by an undetectable viral load and negative western blotting. Cross-reactivity between HIV and SARS-CoV-2 is due to protein similarities, as both viruses share motifs in the N-terminal leucine/isoleucine zipper-like sequence and C-terminal heptad repeat located upstream of the aromatic residue-rich region. The authors emphasized that exposure to SARS-CoV-2 should be considered an additional factor when evaluating possible false-positive results in the HIV chemiluminescence assays (2). Feldman J et al. discussed the potential for the "Australian effect" to occur with other SARS-CoV-2 vaccines that contain HIV protein fragments, which can lead to false-positive HIV tests even with confirmatory exams, except for PCR-based antibody testing. The authors highlighted that false-positive tests occurred only in vaccinated individuals who were negative for the N-protein, which warrants further investigation through dedicated research. They recommended that HIV-positive individuals without risk factors should undergo confirmation testing with HIV antibody PCR at least three times per year, despite the high cost of this method (3).

In a separate study, Hakobyan N et al. reported two cases of false-positive HIV tests in COVID-19-positive patients. The patients initially tested positive for HIV with a fourth-generation test, but further evaluation revealed no viral load, and the ELISA test was negative for HIV (4). This cross-reactivity is due to the sharing of several structural sequences and motifs between HIV-1 gp41 and SARS-CoV-2, which can cause false-positive results when screening for HIV in COVID-19-positive individuals. The authors emphasized the impact of COVID-19 on diagnostic testing for other diseases and recommended performing a more specific confirmatory HIV test, such as ELISA, for patients who are infected or vaccinated against COVID-19 and present with a positive HIV screening test. Although HIV chemiluminescent immunoassays can have a specificity of over 99%, specific confirmation should be required in case of discordant COVID-19 and HIV tests.

Hayat L et al. observed a higher frequency of false-positive HIV 1/2 antibody tests among immune plasma donors compared to healthy donors during routine laboratory screening (5). Between April and July 2020, a total of 2593 donors were screened for HIV1/2 antibodies using eCLIA, and confirmation tests were performed using LIA. The immune plasma donor group consisted of individuals aged between 18 and 60 years old. The study found that the repeated reactivity rate was significantly higher in the immune plasma donor group (1.87%) than in the control group (0.13%, $p < 0.05$), but no significant difference was observed between the confirmed reactivity rates of the study group (0.03%) and the control group (0.01%). The authors concluded that false-positive results obtained from serologic HIV screening tests of convalescent plasma donors were significantly higher than those of healthy donors.

Salih RQ et al. reported the case of a 32-year-old woman with mild symptoms of COVID-19 infection who repeatedly tested false-positive for HIV screening tests due to cross-reactivity, which was confirmed by a negative result from RNA PCR performed for HIV diagnosis (6). The PCR for COVID-19 also turned negative with treatment, and the HIV immunoassay became negative. The authors emphasized that HIV and SARS-CoV-2 have a similar spike protein, which could lead to antibody cross-reactivities and false-positive screening results. They suggested keeping this possibility in mind to avoid misdiagnosis and distress to the patient (6).

Shallal et al. conducted a retrospective cross-sectional study between March 2020 and August 2021, in which they analyzed the results of SARS-CoV-2 PCR tests taken within two weeks of a diagnostic HIV 4th generation assay Elecsys HIV Duo. Additionally, they evaluated confirmatory HIV-1 and HIV-2 antibodies, as well as quantitative HIV RNA for all positive 4th generation tests (7). The positive HIV 4th generation assays were categorized into two groups: true positives (TP) and false positives (FP). The study reviewed 23,041 medical records, and the rates of COVID-19 positive tests were distributed among the groups of HIV TP, FP, and true negatives (TN). The results showed 167 cases of TP and 70 cases of FP. Notably, individuals with HIV FP tests had the highest rate of COVID-19 positive tests (22.9%) compared to those with HIV TN (10.2%) and HIV TP (7.2%). The authors highlighted that acute COVID-19 infection can cause FP 4th generation HIV tests due to the generation of broad polyclonal antibodies and cross-reactivity with the spike protein.

In a report by Tan SS et al., two cases of positive COVID-19 results on rRT-PCR were also reported to have false-positive HIV results on the Architect platform in the same month (8). The first patient was a young man in his early 20s who presented with persistent fever for two days, dry cough, and pharyngitis. The second patient was an elderly man in his early 70s, who had a wife diagnosed with COVID-19, and presented with high fever, dry cough, and pharyngitis, as well as lower left atelectasis seen on chest X-ray. Both patients had no history of blood transfusions, intravenous drug use, or drug therapies. Their serum samples were examined on different Abbott Architect platforms in separate institutions and continued to show positive reactivity on the HIV chemiluminescent immunoassay. However, both patients tested negative on the 4th-generation VIDAS HIV duo assay, an enzyme-linked fluorescent assay that combines the detection of anti-HIV-1 and anti-HIV-2 total immunoglobulins with the HIV-1 p24 antigens. Confirmatory tests using the MP Biomedicals HIV immunoblot were also negative. The authors highlighted the importance of HIV nucleic acid testing as a definitive method, in addition to investigating cross-reactivity

by studying spiked SARS-CoV-2 antigen/antibodies on healthy sera to verify the HIV chemiluminescent immunoassay (8).

Finally, it's worth mentioning two other issues related to COVID-19 and HIV. In a case report by Triebelhorn J et al., a 26-year-old man experienced fever and headache after receiving a COVID-19 vaccine, which were initially thought to be side effects of the vaccine. However, he later tested positive for HIV on a 4th-generation p24/ab-ELISA exam (9). Based on further laboratory tests, the final diagnosis was Fiebig stage II acute HIV infection, which occurred three weeks after an unprotected anal intercourse with another man. Accurate patient history enabled early diagnosis and prompt antiretroviral therapy. However, the gap between HIV infection and reactive results on 4th-generation HIV screening tests is usually 17-21 days, which highlights the importance of early diagnosis of primary HIV infection for prevention of transmission. Symptoms of acute HIV infection, which are nonspecific and include malaise, headache, fever, generalized lymphadenopathy, diarrhea, rash, and meningeal symptoms in severe cases, can be difficult to distinguish from the side effects of COVID-19 vaccination. The authors emphasized the possibility of HIV infection being mistaken for COVID-19 vaccination side-effects, leading to late diagnosis (9).

Yamaniha K et al. reported on a 39-year-old man who had one day of high fever and tested negative for COVID-19 on RT-PCR. He presented with cough, fatigue, and anorexia, and was admitted to the hospital 9 days after the onset of symptoms. The rapid antigen test (ESPLINE SARS-CoV-2) on nasopharyngeal swab was positive, but the chest CT images were normal. Despite the antigen test being repeatedly positive three times, the results of three repeated RT-PCR tests for SARS-CoV-2 on nasopharyngeal swabs were negative. Due to the patient's history of sex with men, there was suspicion of HIV infection, and the rapid antigen/antibody test (ESPLINE® HIV Ag/Ab) was negative, while the chemiluminescent immunoassay (ARCHITECT® HIV Ag/Ab) was positive. The diagnosis of acute HIV infection was confirmed by a high titer of HIV-RNA (>1.0 × 107 copies/mL) and a lack of plasma HIV-1/2 antibodies on a Western blot assay (NEW LAV BLOT 1 and 2). The authors discussed the possibility of false-positive results on SARS-CoV-2 antigen tests in patients with HIV infection (10).

Conclusion

The significant similarity between the spike proteins of HIV and SARS-CoV-2 can lead to antibody cross-reactivities, resulting in false-positive results on immunoassay screening tests for HIV. Therefore, healthcare workers should consider the possibility of HIV false-positives in patients with positive antibodies against the spike protein of SARS-CoV-2. In cases where there are discordant COVID-19 and HIV test results, confirmation may be required for the HIV chemiluminescent immunoassay, as there is a possibility of analytical error. Furthermore, the presented data suggests that false-positive HIV results may be related to COVID-19 vaccination. It is important for healthcare workers to be aware of this potential issue to avoid misdiagnosis and to provide appropriate care to patients.

Authors' Contribution

The authors confirm contribution to the paper as follows - conception and design: Vitorino Modesto dos Santos and Taciana Arruda Modesto Sugai; data collection: Vitorino Modesto dos Santos and Taciana Arruda Modesto Sugai; analysis and interpretation of results: Vitorino Modesto dos Santos and Taciana Arruda Modesto Sugai; and draft manuscript preparation: Vitorino Modesto dos Santos and Taciana Arruda Modesto Sugai. All authors reviewed the results and approved the final version of the manuscript. All authors agreed to be responsible for all aspects of the work to ensure the accuracy and integrity of the published manuscript.

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The authors declare that they have no conflict of interest.

Ethical Statement

In writing the manuscript, the authors followed the policy of the Committee on Publication Ethics (COPE).

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