CLINICAL VIGNETTE

A Case of Mistaken Acute Retroviral Syndrome

Peter Young, MD and Joshua Khalili, MD

A 22-year-old male with no significant past medical history presented to the emergency room with one week of pharyngitis, abdominal discomfort, and diarrhea.

His symptoms began with pharyngitis one week prior to presentation, followed by periumbilical abdominal discomfort and loose brown stools. He noted generalized fatigue and low-grade fevers. He was previously healthy, with no recent travel or sick-contacts. He denied cough, rhinorrhea, or shortness of breath. His family history was unremarkable. He used daily marijuana but no other substances. He endorsed unprotected anal and oral receptive and insertive sex with several male partners, most recently two weeks before his symptoms began.

He was diagnosed with viral gastroenteritis. Sexually transmitted infection testing and stool studies were sent and he was discharged with instructions to establish with a primary care doctor.

Lab testing returned with a positive HIV-1/2 antigen-antibody immunoassay. Stool studies were negative for bacterial pathogens or leukocytes. RPR was negative, as was his urine Gonorrhea/Chlamydia PCR. He was contacted by the emergency room and instructed to start HIV treatment with tenofovir disoproxil fumarate/emtricitabine and dolutegravir.

At his initial ambulatory visit one week later, reflex testing had returned indeterminate for HIV-1 and negative for HIV-2. His symptoms had improved significantly. He had not started antiretroviral therapy due to medication cost. His vital signs were T 98.6°F, BP 153/89, HR 69, SpO2 96% and his exam was unremarkable.

Labs were notable for AST 70 and ALT 115. WBC was 8.37 x10E3/µL and 45.5% lymphocytes. Hepatitis serologies and Gonorrhea/Chlamydia PCR of his rectum and oropharynx were negative. HIV quantitative viral load was undetectable.

CMV and EBV antibody testing were added on to his bloodwork, which returned positive for CMV IgM and IgG antibodies. EBV IgG was positive, with negative EBV IgM and negative infectious mononucleosis antibody.

The patient was contacted and asked to return to repeat his HIV immunoassay, which was negative. He was diagnosed with presumed acute CMV infection with a false-positive HIV assay. He was asked to follow up in to discuss further monitoring for seroconversion and HIV Pre-Exposure Prophylaxis (PrEP) initiation, but unfortunately, was lost to follow-up.

Discussion

Acute retroviral syndrome, also known as acute HIV-1 infection, is characterized by non-specific symptoms that can easily be mistaken for mononucleosis, influenza, or other viral illnesses. Retrospective studies estimate that 40% to 90% of patients who acquire HIV-1 will experience some form of this syndrome, which includes any combination of fever, fatigue, pharyngitis, mucosal ulcers, weight loss, night sweats, lymphadenopathy, myalgias, headache, rash, arthralgias, nausea, and diarrhea.[1,2] Patients can also develop neurologic manifestations including aseptic meningitis, peripheral neuropathy, and Guillain-Barré.[3]

The rash of acute HIV-1 is most often erythematous and maculopapular, nonpruritic, and classically involving the trunk and extremities though it can occasionally involve the face, palms, and soles.[3] Laboratory abnormalities are nonspecific, including thrombocytopenia, leukopenia or lymphopenia, and mild transaminitis. Signs and symptoms of acute HIV-1 infection correlate with a burst of viremia, with HIV-1 RNA often greater than 100,000 copies/mL.[4] This high-level viremia is thought to trigger a surge of inflammatory cytokines.[5] Symptoms can appear anywhere from 2-6 weeks following HIV exposure and typically last for about 14 days.[6]

Because of the non-specific symptoms of acute HIV-1 infection, clinicians must maintain a high index of suspicion when caring for patients with these syndromes. A thorough history and physical exam is crucial, with particular attention to social history and risk factors for HIV exposure. The differential diagnosis for acute retroviral syndrome includes a myriad of diseases such as EBV mononucleosis, CMV, streptococcal pharyngitis, viral hepatitis, influenza, toxoplasmosis, syphilis, and systemic lupus erythematosus (SLE).

To understand testing for acute and chronic HIV-1 infection, it is important to appreciate the timeline at which various markers of infection can be detected in serum. HIV-1 RNA is present first, typically appearing around 10-12 days after exposure.[4] Prior to this, no available test can detect the presence of HIV; which is called the eclipse phase of infection. Two to three weeks after transmission, HIV-1 p24 antigen is present, followed by HIV-1 IgM antibodies at three to four weeks.[3]

Since 2014, the CDC-recommended HIV screening algorithm (Figure 1) has started with a combination antigen-antibody immunoassay, which detects antibodies to HIV-1, antibodies to HIV-2, and the HIV-1 p24 antigen.[7] This highly sensitive test is positive in 50% of individuals infected with HIV within 18days of exposure, and 99% at 45 days.[8] The recommended window period is 45 days.[8] When acute HIV or recent infection is suspected, a negative screening assay should always be followed by an HIV-1 nucleic acid test (NAT).

The screening assay reflexes to a confirmatory HIV-1/HIV-2 antibody differentiation immunoassay, which reports the detection of antibodies to HIV-1 and HIV-2. Results can be positive, negative, or indeterminate. A positive test confirms the diagnosis of HIV-1 or HIV-2. Indeterminate or negative results on the confirmatory test should prompt an HIV-1 NAT. This pattern can occur during acute HIV-1 infection prior to seroconversion, where HIV-1 p24 antigen is detectable but HIV-1 antibodies are negative or indeterminate. HIV-1 NAT should be positive. A negative HIV-1 NAT suggests that the initial immunoassay was a false positive.

In this patient, the initial HIV-1 screening assay was positive, followed by an indeterminate HIV-1 antibody. With his constellation of symptoms and recent high-risk exposure, suspicion for acute retroviral syndrome was high. His negative HIV-1 PCR while off any antiretroviral therapy was not consistent with acute HIV, however, suggesting an alternate diagnosis. Given his positive CMV IgM antibody, it is likely that his presentation was due to CMV infection.

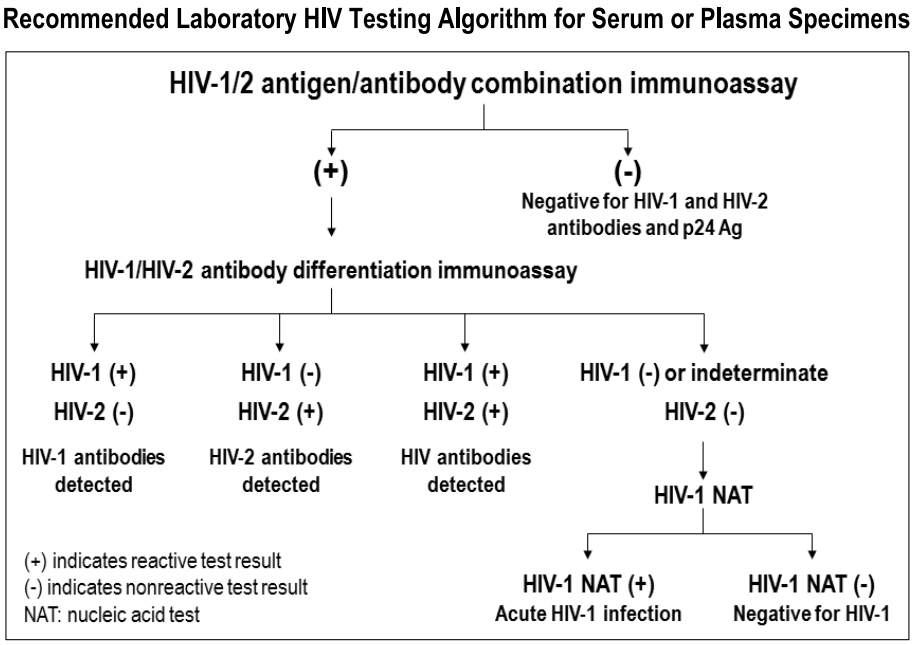
The sensitivity and specificity of the HIV combination antigen/antibody immunoassay are both reported to be greater than 99%, but must always be interpreted in the context of disease prevalence.[9] Comorbid conditions are known to cause false-positive results due to antibody cross-reactivity. The list of scenarios is comprehensive, including: rheumatologic disease, viral hepatitis, malignancy, mycobacterial infection, pregnancy, *Rickettsia* infection, EBV and other viruses, *Schistosoma* infection, toxoplasmosis, and various vaccines.[9]

A high index of suspicion for HIV infection remains crucial, but this case also demonstrates the importance of following the CDC algorithm for confirming infection and understanding the pathophysiology of acute HIV-1 infection. A negative HIV-1 PCR is not compatible with acute HIV-1 and suggests an alternate diagnosis.

REFERENCES

1. **Kahn JO, Walker BD**. Acute human immunodeficiency virus type 1 infection. *N Engl J Med*. 1998 Jul 2;339(1):33-9. doi: 10.1056/NEJM199807023390107. PMID: 9647878.
2. **Kassutto S, Rosenberg ES**. Primary HIV type 1 infection. *Clin Infect Dis*. 2004 May 15;38(10):1447-53. doi: 10.1086/420745. Epub 2004 Apr 30. PMID: 15156484.
3. **Hardy WD**. Fundamentals of HIV Medicine for the HIV Specialist. *Oxford University Press*, 2017.
4. **Fiebig EW, Wright DJ, Rawal BD, Garrett PE, Schumacher RT, Peddada L, Heldebrant C, Smith R, Conrad A, Kleinman SH, Busch MP**. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. *AIDS*. 2003 Sep 5;17(13):1871-9. doi: 10.1097/00002030-200309050-00005. PMID: 12960819.
5. **Cohen MS, Shaw GM, McMichael AJ, Haynes BF**. Acute HIV-1 Infection. *N Engl J Med*. 2011 May 19;364(20):1943-54. doi: 10.1056/NEJMra1011874. PMID: 21591946; PMCID: PMC3771113.
6. **Schacker T, Collier AC, Hughes J, Shea T, Corey L**. Clinical and epidemiologic features of primary HIV infection. *Ann Intern Med*. 1996 Aug 15;125(4):257-64. doi: 10.7326/0003-4819-125-4-199608150-00001. Erratum in: *Ann Intern Med* 1997 Jan 15;126(2):174. PMID: 8678387.
7. Centers for Disease Control and Prevention and Association of Public Health Laboratories. Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations. Published June 27, 2014.
8. **Delaney KP, Hanson DL, Masciotra S, Ethridge SF, Wesolowski L, Owen SM**. Time Until Emergence of HIV Test Reactivity Following Infection With HIV-1: Implications for Interpreting Test Results and Retesting After Exposure. *Clin Infect Dis*. 2017 Jan 1;64(1):53-59. doi: 10.1093/cid/ciw666. Epub 2016 Oct 12. PMID: 27737954.
9. **Liu P, Jackson P, Shaw N, Heysell S**. Spectrum of false positivity for the fourth generation human immunodeficiency virus diagnostic tests. *AIDS Res Ther*. 2016 Jan 5;13:1. doi: 10.1186/s12981-015-0086-3. PMID: 26734067; PMCID: PMC4700595.v

Figure 1: CDC Testing Algorithm for HIV Infection[7]



1. Laboratories should conduct initial testing for HIV with an FDA-approved antigen/antibody combination immunoassay* that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen to test for established HIV-1 or HIV-2 infection and for acute HIV-1 infection. No further testing is required for specimens that are nonreactive on the initial immunoassay.
2. Specimens with a reactive antigen/antibody combination immunoassay result (or repeatedly reactive, if repeat testing is recommended by the manufacturer or required by regulatory authorities) should be tested with an FDA-approved antibody immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies. Reactive results on the initial antigen/antibody combination immunoassay and the HIV-1/HIV-2 antibody differentiation immunoassay should be interpreted as positive for HIV-1 antibodies, HIV-2 antibodies, or HIV antibodies, undifferentiated.
3. Specimens that are reactive on the initial antigen/antibody combination immunoassay and nonreactive or indeterminate on the HIV-1/HIV-2 antibody differentiation immunoassay should be tested with an FDA-approved HIV-1 nucleic acid test (NAT).
    - A reactive HIV-1 NAT result and nonreactive HIV-1/HIV-2 antibody differentiation immunoassay result indicates laboratory evidence for acute HIV-1 infection.
    - A reactive HIV-1 NAT result and indeterminate HIV-1/HIV-2 antibody differentiation immunoassay result indicates the presence of HIV-1 infection confirmed by HIV-1 NAT.
    - A negative HIV-1 NAT result and nonreactive or indeterminate HIV-1/HIV-2 antibody differentiation immunoassay result indicates a false-positive result on the initial immunoassay.
4. Laboratories should use this same testing algorithm, beginning with an antigen/antibody combination immunoassay, with serum or plasma specimens submitted for testing after a reactive (preliminary positive) result from any rapid HIV test.

* *Exception: As of April 2014, data are insufficient to recommend use of the FDA-approved single-use rapid HIV-1/HIV-2 antigen/antibody combination immunoassay as the initial assay in the algorithm.*