

Advance for Nurse Practitioners

Acute HIV Infection in Primary Care. Don't Miss the Signs and Symptoms

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Casey is a 34-year-old woman who presents to you, her primary care provider, with a 2-week history of pharyngitis, cervical lymphadenopathy and generalized myalgias. A week earlier, she sought evaluation of the same symptoms at the emergency department, where the staff performed rapid streptococcal antigen testing and point-of-care testing for infectious mononucleosis; both tests produced negative results. Casey's symptoms have persisted, and she now has a painful genital ulcer that emerged 3 days ago.

During the sexual history, Casey reveals that she has a new sexual partner who does not use condoms. They have been together for 1 month and have had repeated episodes of unprotected vaginal, anal and oral intercourse.

Casey would like to be tested for "everything" at her visit today, meaning all sexually transmitted infections. You mention that you will include a screen for human immunodeficiency virus (HIV) in her workup, and she does not object.

A week later, Casey returns to discuss her test results. The results of the screening tests are negative for chlamydia, gonorrhea and syphilis. Wet mount does not reveal trichomonas. Herpes simplex culture is negative. The HIV screen is nonreactive, and the throat culture did not grow infectious organisms.

Casey is reassured by these results, but you are not convinced that her workup is complete. How do you proceed? What may have been missed? How might you counsel her about follow-up testing, given her history and constellation of symptoms?

The HIV Landscape

The Centers for Disease Control and Prevention (CDC) estimates that 54,230 new HIV infections were diagnosed in the United States in 2006.¹This is a higher estimate than those made in previous years and reinforces the need to keep HIV prevention at the top of the public health agenda.

Detecting HIV is a primary step in preventing the spread of this virus. The CDC now recommends opt-out HIV testing for all patients in all healthcare settings, including pregnant women (Table 1).²This is a major change from previous guidelines, which encouraged opt-in testing and suggested that providers consider HIV prevalence and individual risk factors when choosing to recommend HIV testing to patients.³The newer testing guidelines are aimed at improving access to HIV testing across the United States and increasing the number of people getting tested each year. Up to 25% of people infected with HIV are unaware of their status, and universal HIV testing may identify more of them.⁴

While universal testing for HIV remains fundamental to the fight against HIV, standard HIV screening misses an important group of people: those most recently infected. Screening tests for HIV detect antibodies to the virus, but the body may not develop HIV-specific antibodies for weeks to months. Therefore, HIV-infected patients who are in the "window period" between infection and seroconversion may have negative results on an HIV screen.

Acute HIV infection, also called acute retroviral syndrome or primary HIV infection, describes the period immediately following HIV acquisition when the body has not yet mounted an antibody response but the virus is actively replicating, typically at high rates. This state may induce physical symptoms that can be recognized in the clinical setting. Nurse practitioners in primary care and emergency department settings are often the first to encounter patients experiencing acute HIV symptoms, which may present like the flu or infectious mononucleosis. With understanding of the presentation and diagnosis of this infection, nurse practitioners can help identify and counsel patients in this early stage and prevent the onward transmission of HIV.

Presentation

Acute HIV was first described by DA Cooper, an Australian physician, in 1985. Cooper looked back at the clinical notes for 12 patients who had seroconverted to what he called the AIDS-associated retrovirus and found that 11 of the 12 had experienced an illness resembling infectious mononucleosis prior to HIV diagnosis. The onset of symptoms was sudden, and symptoms lasted 3 to 14 days.⁵Seroconversion occurred 6 to 56 days after the onset of symptoms, which included fever, pharyngitis, sweats, malaise, lethargy and rash.

Today, we know that 40% to 90% of people infected with HIV may experience symptoms consistent with acute HIV.^{6,7}Symptoms typically emerge about 2 weeks after infection, but they have been reported a few days to a few weeks after infection.⁸Patients experiencing symptomatic acute HIV may complain of fever, pharyngitis (without exudate), lymphadenopathy, rash, headache, myalgias, arthralgias or mucocutaneous ulcers (Table 2).

Rash associated with acute HIV is typically generalized and maculopapular and occurs more commonly on the trunk or face than on the extremities. The rash is not typically pruritic. Mucocutaneous ulcers may occur in the mouth or anogenital area. Lesions may be painful, shallow and sharply demarcated.⁹All symptoms tend to resolve spontaneously within 2 weeks of onset, but lymphadenopathy may persist past that point.

The nonspecific symptoms of acute HIV may be mistaken for many other illnesses. The list of differential diagnoses for acute HIV is broad and may include influenza, viral upper respiratory illnesses, acute pharyngitis, secondary syphilis, herpes simplex virus, drug eruption rash and others.

Like Cooper, many healthcare providers and researchers have likened acute HIV to infectious mononucleosis in its presentation. In one study performed in Boston, researchers retrospectively performed HIV-RNA tests on serum collected for routine Epstein-Barr virus (EBV) heterophile antibody testing. HIV-RNA, also known as viral load testing, is a way to detect and quantify viral genetic material in the blood. Of the 563 EBV-negative serum samples that underwent HIV-RNA testing, 11 tested positive for HIV-RNA.¹⁰Seven of these were believed to represent acute HIV infections.¹⁰

While this represents a small percentage of the study samples, it reinforces that acute HIV may be confused with other illnesses, particularly infectious mononucleosis. Healthcare providers in primary care and emergency department settings should consider acute HIV in patients who present with symptoms suggestive of mononucleosis and who also have risk factors for HIV. Factors that may differentiate mononucleosis from acute HIV infection are a lack of mucocutaneous ulcers or rash (unless the patient is taking ampicillin) and presence of exudative pharyngitis.

Lab abnormalities may also be present in the setting of acute HIV infection. Most common are leucopenia, mild anemia, thrombocytopenia and elevation of transaminases (Table 2).

All healthcare providers should become comfortable performing routine HIV risk assessments on all patients. Understanding sexual and substance abuse risk behaviors is the foundation for identifying patients who have acute HIV as well as patients who need further HIV prevention counseling. Initially, patients may not be forthcoming about their behaviors, particularly if they feel shameful or fear "disappointing" their healthcare provider.

To combat this, ask about risk behaviors using open-ended questions in everyday language that makes the patient feel comfortable. It is often helpful to begin a risk history with a statement such as, "I ask all my patients about their experiences with drugs and alcohol. Responses are always confidential. How would you describe your experience with these substances?" This approach helps normalize the subject matter. More information and training materials are available at www.aidset.org and www.cdc.gov.

Pathogenesis

In the years since acute HIV infection was first described, researchers have identified the cellular mechanisms that accompany its clinical presentation. HIV most commonly enters the host through percutaneous or genital routes. Once the virus has penetrated the mucosal epithelium, it infects

macrophages, CD4+ T cells and dendritic cells with subsequent spread to systemic lymph nodes within 2 days after infection. Within another 3 days, it is detectable in the plasma.¹¹ Plasma viremia then results in dissemination to body organs, including the brain and spleen.

Interestingly, due to its high volume of CD4+ T cells, the gastrointestinal tract undergoes massive immune destruction in the first few weeks after infection. Up to 60% of CD4+ T cells in the lamina propria of the lower GI tract may be lost in the first 2 to 4 weeks of infection.¹² This early destruction of systemic CD4+ T cells results in an initial decline in absolute CD4+ T cells and a subsequent explosion in viremia, because HIV uses infected CD4+ T cells to replicate at high frequencies. Thus, within the first weeks of infection, numbers of CD4+ T cells are at their lowest, and viremia is at its highest.

Diagnostic Challenges

The laboratory testing involved in diagnosing acute HIV infection may be the first reason why acute HIV infection is often missed in clinical practice. The test used for HIV screening in 2009 is the standard enzyme-linked immunoassay (ELISA), which determines the presence of HIV antibodies. Standard ELISA testing has sensitivity greater than 99.5% in patients with established HIV disease (more than 3 months posttransmission). But because the body may not develop antibodies to HIV for 10 days to 4 weeks, it misses patients in the window period between infection and seroconversion. This is the reason why repeat HIV testing is recommended 3 to 6 months after a negative test result.

All positive ELISA screening tests undergo an additional serologic test called a Western blot. The Western blot is the gold standard for diagnosing HIV infection and detects antibodies to specific HIV proteins, such as core and envelope proteins. Indeterminate Western blot testing is common in acute HIV infection, because some, but not all, protein-specific antibodies may develop early in the course of disease.

Because standard screening tests alone are incapable of identifying acute HIV infection, HIV-RNA testing is an option. HIV-RNA is commonly used to monitor disease progression and response to antiretroviral therapy in people with established HIV infection, but it can also be used to help identify patients with acute HIV. Patients with acute HIV typically have extremely high levels of circulating virus, up to 1 million copies per milliliter, making HIV-RNA easy to detect, even with less sensitive assays.

In one study of the usefulness of HIV-RNA testing for acute HIV, all patients with confirmed acute HIV had viral loads of more than 100,000 copies/mL. The few patients who had false-positive viral load results had HIV-RNA levels of less than 2,000 copies/mL.¹³ The authors suggested that in the setting of negative or indeterminate serologic testing, suspect a false-positive viral load when levels are below 5,000 to 10,000 copies/mL.^{7,13}

The diagnosis of acute HIV is based on the combination of two particular laboratory findings: documented evidence of detectable HIV-RNA or DNA and documented negative or indeterminate HIV antibody test results (Table 3). These lab findings must be from specimens collected on the same day.¹⁴ The p54 antigen assay is another way to detect early infection in the absence of an antibody response, but this assay is less sensitive than HIV nucleic acid testing and is not as commonly used to identify acute HIV infection.

¹³Several newer assays have been developed to assist in detecting recent HIV infections, but many are available only in research settings. The Serologic Testing Algorithm for Recent HIV Seroconversion (STARHS) is one such test. Also called a "detuned ELISA," the STARHS is less sensitive than the standard ELISA test used for HIV screening. It has a 4- to 6-month delay in sensitivity compared with standard ELISA. Because patients in early stages of infection have HIV antibody titers that are rising over time, a positive ELISA that is negative using the detuned assay indicates a recently acquired infection. The STARHS assay recognizes infections that have been acquired in the previous 170 days. Although this does not necessarily detect acute HIV, it provides a way to improve incidence reporting, and it is used in research settings to do just that.

Challenges in Recognition

Another reason that acute HIV is often missed in clinical practice is because many providers are untrained in recognizing the symptoms and may lack knowledge about it. Researchers examined the charts of 29 acutely infected patients to retrospectively analyze them and track the path of their diagnoses.⁷

Of the 29 who displayed symptoms of acute HIV, 45% presented to the emergency department, 28% presented to a primary care provider, and another 28% presented to an acute care clinic. Only five of these patients were diagnosed with acute HIV infection as a result of their first visit. One had a known high-risk sexual contact, which placed HIV infection higher on the differential diagnosis list. The other four were admitted to the hospital from the emergency department for "febrile illness," and the diagnosis of acute HIV was made while they were hospitalized, most of the time by the infectious disease service. Interestingly, for the patients who presented to an emergency department, acute HIV infection was never considered in the initial differential diagnosis.

Patients with symptoms of acute HIV infection do not always present to a healthcare provider for assessment and diagnosis. A British study found that only 70% of patients diagnosed with acute HIV infection were symptomatic.⁶Of those with symptoms, only 53% sought care from a healthcare provider, and most diagnoses were missed by primary care providers.

Public Health Benefits

The public health benefits of identifying acute HIV infection are numerous. Perhaps the greatest benefit is preventing the transmission of HIV to sexual and drug partners. HIV levels in the blood are exceptionally high during the acute phase of infection – perhaps the highest of anytime during the course of disease. The amount of virus in genital secretions is also believed to be high during this time. In fact, the risk of transmission from a person with acute HIV infection may be 20 times higher than the risk from someone with chronic infection.¹⁵Mathematical models show that early infections may be responsible for a major proportion of onward infections because of this.¹⁶Counseling patients with acute HIV about transmission risks may improve condom use and decrease the number of sexual partners, therefore decreasing transmission.

An equally important public health benefit of detecting acute HIV is preventing mother-to-child transmission of HIV. Acute HIV is particularly concerning in pregnancy because high amounts of virus increase the risk of mother-to-child transmission. Also, if acute HIV infection is missed, an infected mother cannot benefit from receiving prenatal antiretroviral therapy, which is known to decrease the risk of mother-to-child transmission.¹⁷Mother-to-child transmission rates are much higher for women with acute infection compared with women with chronic infection.

For example, between 2002 and 2004, 31 cases of acute HIV were detected in pregnant women in New York state. Of these 31 women with acute HIV, 12 transmitted HIV to their babies.¹⁸This rate of transmission (38.7%) is much higher than the transmission rates for chronically infected women.

Guidelines for detecting acute HIV infection in pregnancy recommend immediate testing using an HIV antibody test and, if acute HIV is possible, HIV-RNA testing.¹⁸CDC guidelines recommend repeat third-trimester HIV testing at 36 to 38 weeks' gestation if a woman had a negative HIV test earlier in pregnancy.²Repeat testing will help identify women who have been infected with HIV during pregnancy; women infected during pregnancy have rates of mother-to-child transmission.

Management

The decision to provide antiretroviral therapy to patients during the acute phase of HIV infection is both complex and controversial. Supporters of treatment cite immunologic benefits as rationale for early antiretroviral therapy. Slowing or stopping rapid HIV replication by initiating antiretroviral therapy during acute HIV may limit the HIV reservoir that results from viral seeding early in infection. Another rationale for treating during acute HIV infection is to decrease the viral load in the blood and genital tract, thus making transmission to partners less likely.

Opponents of treatment are concerned about the challenges associated with antiretroviral therapy, a regimen that is likely to be lifelong. The Strategies for Management of Antiretroviral Therapy (SMART) study showed that intermittent antiretroviral therapy may be associated with more heart, kidney and liver disease than uninterrupted therapy.¹⁹Thus, starting someone on antiretroviral medication during acute HIV may mean indefinite continuation of therapy. In addition, antiretroviral toxicities are burdensome. They may include hyperlipidemia, peripheral neuropathy, fat redistribution, cardiac dysfunction and many

others. Further, adherence to antiretrovirals may be difficult in the emotional and physical upheaval that is common right after diagnosis. Suboptimal adherence to antiretrovirals increases the risk of viral resistance and antiretroviral failure.

Current guidelines do not recommend antiretroviral therapy during acute HIV, mostly due to the uncertainty of its benefit. Exceptions may be made if a patient experiences an opportunistic infection or experiences a CD4 count below 200 for 3 months after acute HIV is detected. Discuss with affected patients the risks and benefits of providing antiretrovirals during acute HIV. If a patient feels strongly about starting medications, his or her wishes should be considered.

Fortunately, several randomized, controlled trials are under way to assess the benefits of antiretroviral treatment during acute HIV infection.

Putting It Into Practice

Awareness of the signs and symptoms of acute HIV is a powerful strategy for HIV prevention. Essential to this task are taking a comprehensive sexual and drug history and keeping acute HIV on the radar when patients present with flu-like or mononucleosis-like symptoms.

Because patients often present to primary care providers first, nurse practitioners are on the front line of acute HIV detection and can play an influential role in stopping the spread of this devastating virus.

Returning to the case example, given Casey's history and exam findings, you are concerned that she is experiencing symptoms of acute HIV infection. You discuss this with her and outline her options: return for repeat HIV screening when she is outside the window period or undergo HIV-RNA testing today. Unfortunately, Casey's insurance carrier does not pay for HIV-RNA testing without confirmed infection, but she pays out of pocket.

One week later, Casey is feeling much better. All but the fatigue and lymphadenopathy have resolved. You discuss her test results, which reveal an HIV viral load of 1.3 million copies. Repeat ELISA was reactive, with an indeterminate Western Blot. You explain that it is highly likely that she has HIV infection, and that she was probably infected quite recently. She tells you that her partner tested positive at the health department this week.

You explain that a final repeat ELISA with reactive Western Blot is necessary to confirm the diagnosis and refer Casey to a colleague who specializes in HIV. The two of you will collaborate on Casey's care.

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