CLINICAL PROBLEM-SOLVING

A Matter of Time

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In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information by sharing relevant background and reasoning with the reader (regular type). The authors' commentary follows.*

A 29-year-old woman with active opioid, alcohol, benzodiazepine, tobacco, and cocaine use disorders and recent intravenous drug use presented with acute onset of chills and increased pain and drainage of chronic wounds in both legs. Her wounds first appeared more than a year before presentation and were attributed to xylazine exposure. She had not injected into the wounds or shared needles.

Xylazine is an α_2-agonist used as a veterinary sedative that is a common contaminant of illicit fentanyl. Its use is associated with severe wounds, sometimes distant from injection sites. The patient's increased wound drainage and chills, especially if accompanied by surrounding cellulitis or other signs of systemic inflammation, suggest the possibility of secondary purulent skin and soft-tissue infection (SSTI).

She reported that she did not have fever, sweats, rigors, rash, cough, abdominal pain, or dysuria. The wounds in her legs were purulent, erythematous, and painful (Fig. 1). She reported no additional medical history and took no medications. Her social history was notable for engaging in occasional unprotected transactional sex. The hemoglobin level was 8.7 g per deciliter with a mean corpuscular volume of 78.5 fl (both unchanged from 1 month earlier), white-cell count 4930 per cubic millimeter with 57% neutrophils and 31% lymphocytes, and platelet count 484,000 per cubic millimeter. The results of a complete metabolic panel were unremarkable. The erythrocyte sedimentation rate was 77 mm per hour, and the C-reactive protein level was 3.1 mg per deciliter. Given concern for SSTI, with possible underlying osteomyelitis, blood cultures were obtained and empirical antimicrobial therapy was initiated with vancomycin.

Her chills, elevated inflammatory markers, anemia, and thrombocytosis suggest inflammation, most likely from chronic wounds and acute SSTI. However, wounds can progress to deep-seated complications. Computed tomography (CT) is more readily attained than magnetic resonance imaging (MRI) and is highly effective at diagnosing abscesses, but MRI is superior for diagnosing osteomyelitis. Imaging is indicated if there is clinical suspicion for these complications on the basis of bedside wound examination or lack of improvement despite appropriate antibiotic therapy. Beyond SSTIs, persons who inject drugs are at high risk for other infections, including viral hepatitis, human immunodeficiency virus (HIV), syphilis, and endovascular infections such as infective endocarditis. Finally, her sexual practices place her at high risk for sexually transmitted infections.

She began to have withdrawal symptoms. These included tremors, anxiety, restlessness, nausea, abdominal pain, and diffuse body aches.

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CME

Prompt evidence-based management of her withdrawal and substance use disorders is of paramount importance. Sedative hypnotic withdrawal should be managed with benzodiazepines or barbiturates. Opioid withdrawal should be managed with symptomatic therapy and medications for opioid use disorder such as buprenorphine or methadone; short-acting opioid agonists may also be used temporarily.

Symptom-triggered benzodiazepines and a phenobarbital taper were initiated to treat her sedative hypnotic withdrawal. Methadone, clonidine, and hydromorphone were initiated to treat her opioid withdrawal and opioid use disorder. Fourth-generation HIV testing (which includes testing for the p24 antigen, an early marker of HIV infection, and for antibodies to HIV type 1 [HIV-1] and HIV type 2 [HIV-2]) was negative. Tests for hepatitis B core and surface antibodies were positive; a test for hepatitis B surface antigen was negative. A test for hepatitis C antibodies was positive, and nucleic acid testing for hepatitis C virus was negative. A test for *Treponema pallidum* chemiluminescence antibodies was negative. On further history taking, she disclosed a sexual assault approximately 7 days before presentation and vaginal discharge of recent onset. A sexual assault forensic examination was offered, which the patient declined. Given the recency of the assault, as well as plans to recommend HIV preexposure prophylaxis, nucleic acid testing for HIV was performed and was also negative.

In caring for victims of sexual assault, a trauma-informed approach to history taking, physical examination, sample collection, and procedures is critical. The reported sexual assault is outside the window for HIV postexposure prophylaxis (72 hours) or emergency contraception (5 days). Abnormal vaginal discharge is often infectious. Sexually transmitted causes include trichomoniasis, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae*. Although bacterial vaginosis is not historically classified as a sexually transmitted infection, sexual transmission is a contributing factor. Candidal vulvovaginitis is a common non–sexually transmitted infection.

Nucleic acid testing of a urine sample was positive for *Trichomonas vaginalis* and negative for *C. trachomatis*

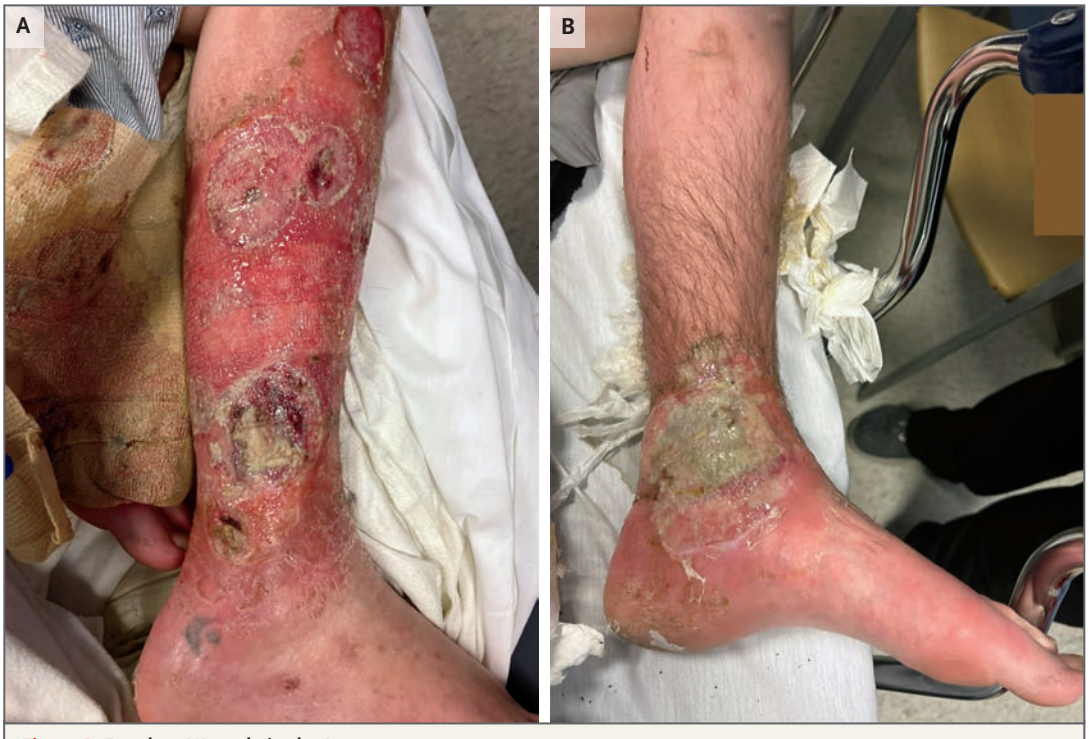

Figure 1. Purulent Wounds in the Legs.
Panel A shows the right leg, and Panel B shows the left leg.

and *N. gonorrhoeae*. Metronidazole was initiated. Blood cultures remained without growth, and the wounds in her legs showed clinical improvement. A CT scan of the legs with intravenous contrast did not identify a soft-tissue abscess but revealed a periosteal reaction of the right distal fibula that was suggestive of chronic osteomyelitis. On hospital day 9, while the patient was awaiting further MRI evaluation for osteomyelitis, drenching night sweats (without fever) developed.

New nocturnal drenching sweats suggest worsening systemic inflammation, even in the absence of fever or leukocytosis. Her withdrawal syndromes are probably not to blame, given that the sweats began well after the initiation of appropriate treatment, which is important to recognize, because patients with substance use disorders often have missed diagnoses owing to anchoring on their substance use.

Interval improvement of her skin findings suggests that the antibiotics she received were effective for the SSTI, which arouses concern that her sweats indicate inadequate source control of a more deep-seated infection such as septic arthritis, osteomyelitis, or endocarditis. The CT imaging showed no evidence of abscess. A detailed physical examination should be performed, as well as advanced imaging guided by the examination. MRI of the legs is warranted given its higher sensitivity than CT for osteomyelitis.

The negative blood cultures rule out typical pathogens that cause infective endocarditis; culture-negative infective endocarditis remains possible. Echocardiography is reasonable to assess for valvular disease and vegetations. Consideration should also be given to the possibility of atypical bacterial, viral, mycobacterial, fungal, and parasitic pathogens, as well as noninfectious causes such as cancer, autoimmune diseases, drug reactions, and hyperthyroidism.

An MRI scan of her legs showed the fibular cortical thickening previously seen on CT, but the T1-weighted bone marrow signal was normal. On review of both CT and MRI findings, the radiologist was not concerned about osteomyelitis. Two additional sets of blood cultures and nucleic acid testing for respiratory pathogens were negative, and levels of thyroid-stimulating hormone and free T4 were in the normal range. Transthoracic echocardiography showed no vegetations or valvular disease. Further history taking confirmed that she had no recent animal exposure or international travel.

The MRI findings do not suggest osteomyelitis, and laboratory values are inconsistent with hyperthyroidism. The negative blood cultures and transthoracic echocardiogram make endovascular infection less likely, but the receipt of antibiotics before repeat blood cultures limits their sensitivity. Transthoracic echocardiography may miss vegetations; transesophageal echocardiography is more sensitive. In the absence of fever, bacteremia, or embolic phenomena, alternative evaluations should be prioritized. The medical history, physical examination, and medication-administration record warrant revisiting. Further imaging should be considered to assess for occult infection or cancer.

On day 16 of hospitalization, a repeat complete blood count showed a decrease in the white-cell count to 1710 per cubic millimeter with 35% neutrophils, 48% lymphocytes, and 9% atypical lymphocytes. The absolute lymphocyte count was 970 per cubic millimeter (normal range, 1100 to 4800). The hemoglobin and platelet count were stable. CT of the chest, abdomen, and pelvis revealed enlarged bilateral axillary and right retropectoral lymph nodes, measuring up to 1.2 cm, and splenomegaly (Fig. 2).

The ongoing night sweats and newly discovered leukopenia, lymphadenopathy, and splenomegaly refine the search for the cause of her chills and sweats. The syndrome is suspicious for mononucleosis; however, it would be unusual for symptoms to manifest late in hospitalization, unless a pathogen was acquired during her stay or shortly before admission. Infectious mononucleosis and similarly presenting syndromes, most commonly caused by Epstein–Barr virus (EBV), can also be caused by cytomegalovirus (CMV), acute HIV infection, toxoplasmosis, and secondary syphilis, among others. The patient's previous negative HIV testing, which included nucleic acid testing, provides some reassurance against acute HIV infection. However, even nucleic acid testing for HIV can be falsely negative if performed within the first 10 days after HIV acquisition. As such, nucleic acid testing for HIV should be repeated to reassess for acute HIV infection.

Several other infections might alternatively ex-

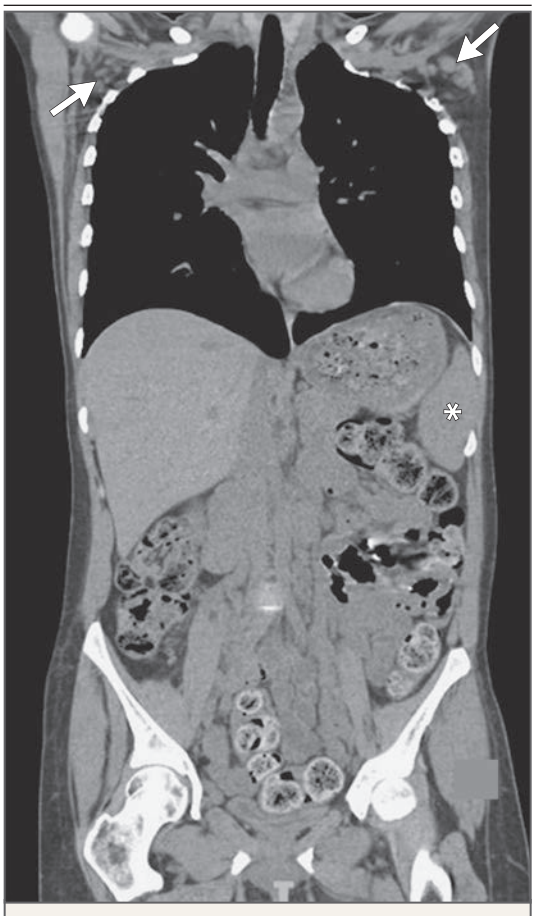

Figure 2. Coronal View of Computed Tomography (CT) of the Chest, Abdomen, and Pelvis with Intravenous Contrast.

The scan revealed bilateral axillary lymphadenopathy (arrows). Splenomegaly (asterisk) was also noted but is better visualized on other sections.

plain the patient's symptoms and signs, including (but not limited to) disseminated mycobacterial infections, endemic mycoses, and zoonoses such as bartonella, coxiella, and brucella. These diagnoses are less likely in the absence of epidemiologic risk or underlying immunodeficiency. If evaluation for infectious causes of mononucleosis-like syndromes is unrevealing, cancer (e.g., leukemia or lymphoma) must also be considered. In addition to testing for the aforementioned infections, a peripheral-blood smear should be performed; excisional lymph-node biopsy, bone marrow biopsy, or both would be next steps, as needed.

Systemic rheumatic disorders also warrant consideration as a cause of night sweats, enlarged lymph nodes, and splenic enlargement. Specifically, adult-onset Still's disease and systemic lupus erythematosus (SLE) can account for these clinical features. However, the patient does not have high spiking fever, skin rash, and arthritis, the prototypic triad of adult-onset Still's disease, and this would be a diagnosis of exclusion. In contrast, SLE induces leukopenia, and lymphopenia specifically, together with lymphadenopathy and splenomegaly.

A peripheral-blood smear showed reactive-appearing large, atypical lymphocytes; hypochromic anemia with anisocytosis; and platelets that were normal in number with frequent large forms. Mononucleosis heterophile antibody screening was negative. Antinuclear antibody screening was negative. Given the multifocal lymphadenopathy and persistent and profuse night sweats, there was increasing concern for lymphoma. Consequently, a positron-emission tomography (PET)–CT scan was ordered to further characterize the lymphadenopathy and identify a possible excisional node biopsy site. PET-CT revealed multiple prominent bilateral cervical, axillary, mediastinal, retroperitoneal, pelvic, and inguinal lymph nodes with mild-to-moderate ^{18}F-fluorodeoxyglucose (FDG) avidity, as large as 1.3 cm. The spleen was enlarged and FDG avid (Fig. 3). The radiologist's chief concern was for lymphoma.

Heterophile antibody testing has poor sensitivity, so EBV and other mononucleosis mimics remain possible. IgG and IgM testing for EBV and CMV as well as nucleic acid testing for HIV are indicated, with acute HIV infection being the "can't miss" diagnosis. Atypical lymphocytes can also be seen in leukemias, lymphomas, and severe adverse drug reactions. Although the PET-CT scan was read as concerning for lymphoma, infectious or inflammatory conditions are also often FDG avid.

An excisional lymph-node biopsy and bone marrow biopsy were planned. However, before these examinations were undertaken, repeat nucleic acid testing for HIV was positive with a viral load of 4,480,000 copies per milliliter. HIV-1 and HIV-2 antigen–antibody testing was then repeated and was also positive. HIV-1 and HIV-2 differentiation antibody testing was negative. The patient was diagnosed with acute HIV infection. Antiretroviral therapy (ART) with coformulated bictegravir, emtricitabine, and tenofovir alafenamide was initiated, and her night sweats gradually resolved. She was connected

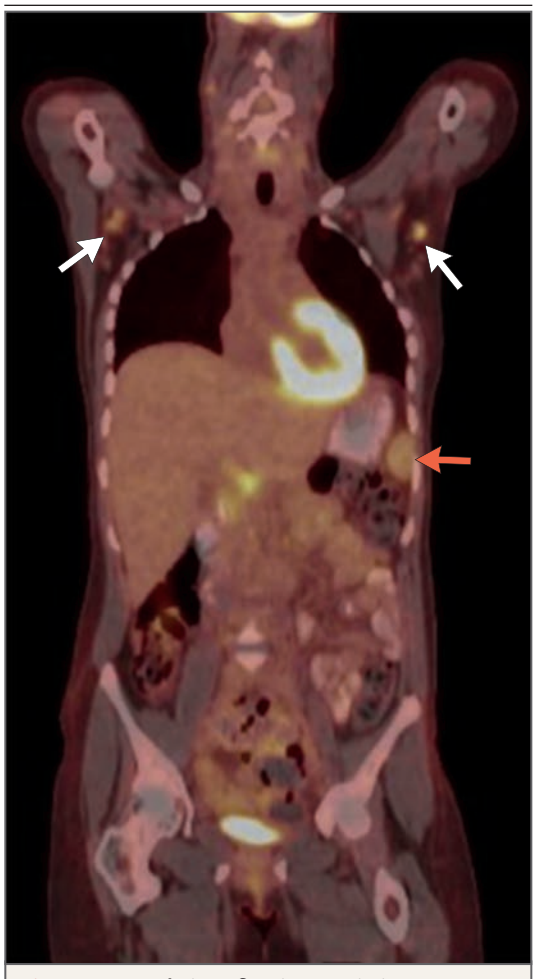

Figure 3. Coronal View of Positron-Emission Tomography–CT.

The scan revealed ^{18}F-fluorodeoxyglucose (FDG)–avid bilateral axillary lymphadenopathy (white arrows). An enlarged spleen with increased FDG intensity was partially visualized (red arrow).

with comprehensive care for HIV and substance use disorders and was discharged. She had an undetectable HIV viral load approximately 2 months later and has since maintained an undetectable HIV viral load 20 months after discharge.

COMMENTARY

A 29-year-old woman with opioid, alcohol, benzodiazepine, tobacco, and cocaine use disorders initially presented with increased pain and drainage of chronic wounds in both legs, as well as vaginal discharge after a sexual assault 1 week earlier. She was treated for cellulitis, opioid and sedative hypnotic withdrawal, and vaginal trichomoniasis. While she was hospitalized, drenching night sweats developed, followed by leukopenia and diffuse lymphadenopathy. The differential diagnosis and workup were broadened, with particular concern for an intercurrent infection or for an occult lymphoproliferative disorder. At this key juncture in her care, repeat HIV testing returned positive, resulting in a diagnosis of acute HIV infection, despite negative testing for HIV by both fourth-generation antigen–antibody testing and nucleic acid testing during the initial 24 hours of her hospitalization. This narrative highlights the importance of understanding the clinical presentation of acute HIV infection, corresponding viral dynamics, and implications for HIV testing.

Acute HIV infection, when symptomatic, most commonly manifests with a mononucleosis-like syndrome.[1] The manifestations most frequently reported in cohort studies include fever (>80 to 90% of patients), fatigue (>70 to 90%), rash (>40 to 80%; typically maculopapular), headache (32 to 70%), and lymphadenopathy (40 to 70%).[1] Approximately 50% of affected persons have night sweats, and leukopenia develops in approximately 40%, as seen in this case.[1] Many persons are asymptomatic.[1]

HIV testing is based on the interplay of several virologic and immunologic events.[2] Immediately after infection, the "eclipse period" begins, during which HIV replicates in local lymphoid tissue and is not detectable in the bloodstream by diagnostic tests.[2-4] With ongoing viral replication, the virus becomes detectable in the blood with nucleic acid testing approximately 7 to 10 days after infection.[1-3,5-7] The p24 antigen can be detected by fourth-generation testing approximately 14 to 20 days after infection.[2,8] Subsequently, IgM antibody formation increases and becomes detectable approximately 20 to 23 days after infection (ending the acute phase of infection), followed by IgG antibody formation around day 30 to 35 (Fig. 4).[2-4,8] After the IgG antibody response has matured, the viral load enters a relatively steady "set point" and becomes classified as an established infection.[2,8,9]

The Centers for Disease Control and Prevention recommends that testing for HIV begin with laboratory-based fourth-generation testing, which detects the HIV p24 antigen and HIV-1 and HIV-2 antibodies with greater than 99% sensitivity and specificity for established HIV infection.[8] If there is high suspicion for acute HIV infection and this

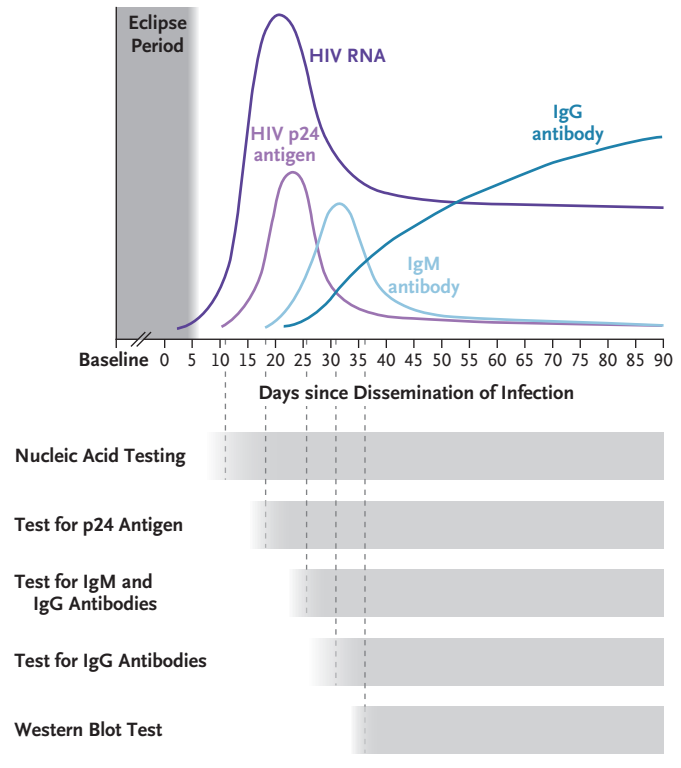

Figure 4. Viral and Immune Dynamics of Human Immunodeficiency Virus (HIV) Infection.

The time to reactivity for each diagnostic test is shown below the graph. Adapted from Saag.[4]

testing is negative, nucleic acid testing should be performed, because fourth-generation testing is only 62 to 83% sensitive for diagnosing acute HIV infection.[8] If nucleic acid testing is negative but a person is potentially in the eclipse period, repeat testing is indicated.[2,8] If a fourth-generation antigen–antibody test is positive, confirmation IgG antibody differentiation testing is performed to confirm HIV-1 or HIV-2 infection.[2,8] If antibody differentiation testing is negative, nucleic acid testing is performed.[2,8] If nucleic acid testing is positive, it confirms acute HIV infection; if this testing is negative, the fourth-generation test was falsely positive.[2,5,8]

Our patient presented approximately 7 days after a high-risk exposure, and initially, both nucleic acid testing and fourth-generation testing for HIV were negative. When symptoms subsequently developed that were compatible with acute HIV infection (night sweats, lymphadenopathy, and leukopenia), HIV testing with both nucleic acid testing and fourth-generation antigen–antibody testing was repeated and returned positive. Antibody differentiation testing was reflexively performed and was negative, which confirmed the diagnosis of acute HIV infection. The initial negative nucleic acid testing indicates that the patient presented during the eclipse period.

Prompt diagnosis and treatment of HIV infection has critical implications for not only the patient but also public health. These benefits are magnified in acute HIV infection. At the individual level, cohort studies have shown that as compared with delayed ART initiation, initiation during acute HIV infection is associated with a more robust recovery of the CD4 count and a decreased viral reservoir, which may improve long-term disease control.[10,11] Early diagnosis and treatment is also critical to reduce transmission. Although the duration of acute HIV is relatively short, the risk of transmission is disproportionately high during this period owing to high viral loads and unawareness of serostatus.[12] Modeling estimates the risk of sexual transmission to be up to 26 times as great during acute HIV infection as during chronic HIV infection, and phylogenetic data have suggested that as much as half of total HIV transmission may occur during the acute phase (although some estimates are lower).[12] Acute HIV infection also poses greater risk of mother-to-child transmission.[12] If the infection is diagnosed and treated, the risk of transmission can be promptly and profoundly mitigated by a blend of behavioral interventions (e.g., temporary abstinence, condoms, and clean needle usage), partner usage of preexposure prophylaxis, and ART.[12] When the viral load is persistently undetectable, there is zero risk of sexual transmission.[13]

In most adolescents and adults with acute HIV infection, initial recommended treatment regimens include a second-generation integrase strand-transfer inhibitor, with either bictegravir or dolutegravir, combined with two nucleoside reverse-transcriptase inhibitors, with tenofovir and either emtricitabine or lamivudine.[14,15] Treatment is continued indefinitely, and linkage to HIV care for longitudinal management — including (but not limited to) monitoring ART adherence, viral suppression, and CD4 count reconstitution — is critical.[14,15]

This case of acute HIV infection diagnosed in

an at-risk hospitalized patient underscores the value of a detailed exposure history, including the timing of exposures, and the importance of understanding acute HIV viral dynamics and their implications for HIV test performance. It also highlights the importance of reexamining the differential diagnoses when new symptoms arise despite appropriate therapy. In this patient, uncovering the correct diagnosis was a matter of time.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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