Clinical Case of the Month

A 23-Year-Old Man With Fever and Malaise

Evan Atkinson, MD; Maria Miklowski, MD; Fred Lopez, MD; David Klibert, MD

Acute infection with human immunodeficiency virus (HIV) is infrequently diagnosed, owing in large part to vague or non-specific symptoms. Among the most common of these symptoms are fever, fatigue, pharyngitis, lymphadenopathy, anorexia, arthralgia, myalgia, rash, and headache. Some patients seek no medical attention for such symptoms, and others recall no symptoms whatsoever. Physicians in all healthcare environments must maintain a high index of suspicion for HIV in the setting of these symptoms. For suspected acute infection, rapid serologic tests should be supplemented with assays of p24 antigen and/or HIV RNA viral load. We report here a case of acute HIV infection in a young man who presented with a negative rapid serologic test, as well as pancytopenia and transaminitis. We also review the epidemiology, transmission, diagnosis, and management of acute HIV infection.

CASE PRESENTATION

A 23-year-old previously healthy and active man was in his usual state of health until five days prior to admission, when he developed several episodes of non-bloody, non-bilious emesis. The next day, he began to have watery bowel movements, which abated two days later. Thereafter, he noted onset of malaise, myalgia, fevers, chills, and a sore throat. He presented to a local urgent care clinic, where a complete blood count (CBC) was drawn, and he was advised to report to an emergency room for "low cell counts." He had no chronic illnesses but two weeks prior, had a thigh abscess incised and drained. He completed a five-day course of trimethoprim-sulfamethoxazole and doxycycline, with resolution of the abscess. He was also recently taking ranitidine and promethazine. He denied drug allergies and had routinely used neither prescription nor over-the-counter medications. He also denied a family history of hematologic problems. He lives with his grandmother and works as a garbage man. One month prior to presentation, he had spent less than a week in Missouri. He denied sick contacts while in Missouri but reported that his 3-year-old niece had three to four days of nausea, vomiting, and diarrhea the week prior to onset of his own symptoms. He reported a monogamous relationship with a single female beginning one year ago, with intermittent use of barrier contraception. He was treated for chlamydial urethritis one year ago but could not recall if he was tested for human immunodeficiency virus (HIV). He denied intravenous drug use, concern over accidental needle sticks while working, or having ever received a blood transfusion.

On examination, our patient was a well-developed and well-nourished black man who appeared ill but in no acute distress. He was diaphoretic and had an oral temperature of 100.9°F. His pupils were equally round and reactive to light and his extraocular movements intact. His neck was supple. His oropharynx exhibited posterior erythema but no tonsillar exudate, oral ulcers, thrush, or petechiae. His right posterior auricular lymph nodes were enlarged and mildly tender, but he had no palpable enlargement of cervical, axillary, or inguinal lymph nodes. Examination of his heart, lungs, and genitals was unremarkable. His abdomen was scaphoid, nontender, and without organomegaly. On his right posterior thigh was a well-healed scar consistent with his recently drained abscess. He exhibited no rashes, joint effusions, musculoskeletal tenderness to palpation, or neurologic deficits.

Initial laboratory studies revealed a white blood cell (WBC) count of 3.9 x 10^3 cells/µL [normal 4.5-11], hemoglobin of 16.6 g/dL [13.5-17.5], and a platelet count of 55 x 10^3 platelets/µL [130-400]. Lactate dehydrogenase (LDH) was 615 IU/L [<201]. Blood urea nitrogen was 27 mg/dL [7-25], and creatinine was 1.98 mg/dL [0.7-1.4]. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 100 U/L [<45] and 36 U/L [<46], respectively. Rapid tests for HIV and influenza were negative, as were tests for acute hepatitis and heterophile antibodies. A repeat CBC after administration of intravenous normal saline for volume depletion revealed a hemoglobin of 13 x 10^6 g/dL, haptoglobin 20 mg/dL [30-195], and reticulocyte count 0.2% [0.5-1.5%]. The peripheral blood smear was without schistocytes, spherocytes, or atypical cells. Prothrombin and

partial thromboplastin times were normal. Renal function quickly normalized with intravenous fluids. On the day after admission, we questioned our patient further about his sexual history, and he subsequently left against medical advice, despite extensive counseling.

Our patient returned to the hospital the following day (cumulative hospital day 3), with an oral temperature of 103.4°F. One of four blood cultures drawn two days prior was growing gram-positive cocci in clusters, and he was started on intravenous vancomycin. His WBC count had decreased to 1.5 x 10^3 cells/µL, with an absolute neutrophil count (ANC) of 1,000 cells/µL [1.8-8], and his platelet count had decreased to 21 x 10^3 platelets/µL. His AST and ALT had increased to 200 and 49 U/L, respectively. On day 4, his LDH was 1,379 U/L. A bone marrow aspirate performed that day was not suggestive of acute leukemia, a lymphoproliferative process, myelosuppresion, or hemolysis. In the meantime, the following labs ordered earlier in the hospitalization returned as negative or normal: antinuclear antibodies; C3, C4, and antistreptolysin O (ASO) levels; rapid plasma reagin (RPR); acute immune response titers (IgM) for Epstein-Barr virus (EBV), cytomegalovirus (CMV), and parvovirus; and bacterial throat culture. Glucose-6-phosphate dehydrogenase (G6PD) function was also normal.

The patient continued to deteriorate on appropriate antibiotics. On day 4, he required a platelet transfusion for gingival bleeding at a platelet count of 16 x 10^3 platelets/µL. By day 5, his WBC count had decreased to 0.8 x 10^3 cells/µL (ANC 300 cells/µL), necessitating the institution of neutropenic precautions and addition of cefepime for febrile neutropenia. Due to worsening right upper quadrant pain and transaminitis, he underwent a contrasted computed tomography scan of his abdomen and pelvis, which was found to be unremarkable. His lab findings subsequently began to improve. His AST peaked at 412 U/L on day 6, and his ALT and LDH peaked at 324 and 1562 U/L, respectively, on day 8. His WBC and platelet counts also began to improve. Eventually, only one of four blood cultures had grown coagulase-negative staphylococci (suggesting contamination), and therefore, all antibiotics were discontinued. His abdominal pain had also begun to remit. Throughout his hospitalization, his primary complaint was that he could neither eat nor drink secondary to severe throat pain, unrelieved by topical anesthetics. Re-inspection of his throat revealed a small, clean-based and exquisitely tender ulcer proximal to his right tonsil; viral cultures of the ulcer were negative. He was noted to have scant thrush and started on fluconazole.

An HIV viral load level was ordered and revealed greater than 10 million copies/mL of HIV RNA. Subsequent immunodeficiency panel revealed a CD4 count of 101 cells/µL [228-2,290], with a CD4 percentage of 24% [37-63]. By hospital day 9, our patient tolerated a liquid diet and was discharged. Owing to his severely depressed CD4 count, he was discharged on atovaquone for pneumocystis prophylaxis. On day 13, when contacted by phone, he reported to be "getting back to normal," with significant relief of his sore throat, improved appetite, and an energy level approaching his baseline. Outpatient labs on day 14 demonstrated continued resolution of his pancytopenia and transaminitis: WBC count 2.6 x 10^3 cells/µL (ANC 1240 cells/µL), platelet count 153 x 10^3 platelets/µL, hemoglobin 13.4 g/dL, AST 98 U/L, and ALT 136 U/L. CD4 count and percentage were 121 cells/µL and 9.4%. Repeat HIV viral load remained greater than 10 million copies/mL. HIV serology at that time was reactive, but confirmatory Western blot revealing bands for p24, p40, and p55 was interpreted as indeterminate. Upon follow-up in our HIV outpatient clinic on day 20, his symptoms had completely resolved. At that visit, he amended his sexual history, stating he met his current girlfriend via a social networking site two weeks prior to engaging in unprotected sexual intercourse with her. The initiation of sexual intercourse preceded his symptoms by approximately three weeks.

Analysis of our patient's bone marrow, including send-out testing, was completed on day 25. His marrow was hypocellular at approximately 30%, with only rare foci of erythroid precursors, but was parvovirus-negative. While it exhibited increased iron stores, hemophagocytic histiocytes were identified rarely. The marrow contained high percentages of myeloid cells, monocytes, and megakaryocytes, with atypia in all three of these cell lines. No immature blasts were found, fluorescence in-situ hybridization (FISH) testing revealed no evidence of myelodysplastic syndrome, and microbiologic testing remained unremarkable. These marrow findings were attributed to acute HIV infection.

Repeat outpatient labs on day 69 revealed complete resolution of our patient's leukopenia and anemia, but his platelets were mildly depressed at 96 x 10^3 platelets/µL. His transaminitis had resolved. HIV viral load at that time was 69,645 copies/mL, and his CD4 count and percentage were 173 cells/µL and 9.4%, respectively.

EPIDEMIOLOGY

As of 2009, there had been 60 million worldwide infections with HIV and 25 million deaths attributed to the virus.[1] While new infections have declined since peaking in 1997, due in large part to education and access to combination antiretroviral therapy (ART), HIV remains a significant health threat.[2] In the United States, there have been an estimated 1.1 million cases of acquired immunodeficiency syndrome (AIDS) diagnosed since the start of the epidemic and nearly 620,000 deaths.[3] Living with HIV in the U.S. are about 1.2 million people, one-fifth of who are unaware of their infection.[3] The southern US is disproportionately affected by AIDS, accounting for 39% of national prevalence and 45% of national incidence in 2010.[4] Louisiana has the second-highest HIV case rate, 28.5 per 100,000 persons.[4] Among all metropolitan statistical areas, Baton Rouge and New Orleans are ranked second and third, respectively, with HIV case rates of 43 and 36.9 per 100,000 persons.[4]

While the overall rate of new HIV diagnosis in the U.S. has recently been stable - 16.1 per 100,000 persons in

2010 - rates have been increasing in both adolescents and young adults.[4] Among persons aged 20-24 years, the rate of diagnosis increased from 28.3 to 36.9 per 100,000 persons, up by 30% from 2006 to 2010.[4] This trend is seen in Louisiana, with an increase among persons aged 13-24 years of 48% from 2006 to 2009.[5] Black men aged 25-34 years old remain the highest risk group in urban areas of Louisiana.[5] Regardless, HIV permeates all demographics and parishes of the state, with 8.3% of new diagnoses during 2009 made in persons aged 55 years or more and 16.7% made in rural parishes.[5] The most common transmission categories in Louisiana remain male-to-male sexual contact (48%), high-risk heterosexual contact (35%), and injection drug use (13%). However, nearly half of all persons diagnosed with HIV in Louisiana from 2000-2009 reported no risk.[5]

TRANSMISSION

HIV transmission requires inoculation of an uninfected person with body fluid from an infected person. An estimated 80% of HIV infections worldwide occur via mucosal transmission.[2] HIV virions and virion-infected cells cross epithelial barriers of the genital tract within a matter of hours, remain in the submucosa for three to six days where they may infect WBCs, then rapidly disseminate via draining lymphatics and establish CD4 T-cell viral reservoirs.[6] During this "eclipse-phase," which lasts 7-21 days (Figure 1[7]), the virus cannot be detected in plasma.[6] Immediately following this phase, patients often have peak viral loads and therefore, a high risk of transmitting the virus to others. The virus can be detected by quantitative nucleic acid amplification assays once HIV RNA reaches a level of 50 copies/mL.[6] HIV infection is characterized by six stages (I-VI), each heralded by the ability to detect a viral component or host antibody in the plasma: HIV viral RNA (stage I), p24 antigen (stage II), antibodies specific for recombinant viral proteins in which ELISA testing is positive (stage III), and antibodies binding to fixed viral proteins during which Western blot testing is expected to be positive (stages IV-VI).[6] Following the initial robust immune response, a prolonged clinical latency period is typical before onset of immune deficiency occurs and is brought to medical attention, often in the form of an opportunistic infection.

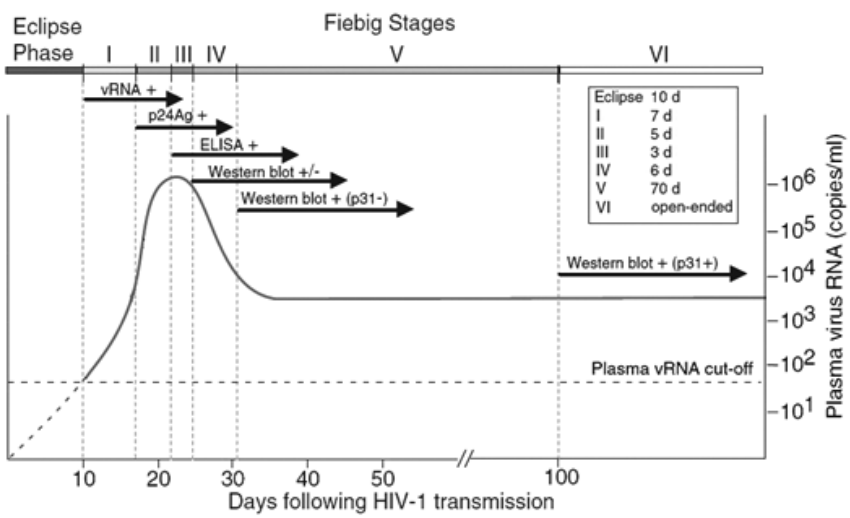

Figure 1: Fiebig stages of acute HIV infection, modified from Keele et al.[7] with publisher's permission. Reprinted courtesy of the National Academy of Sciences.

DIAGNOSIS

Seroconversion is defined as the onset of detectable antibodies in plasma generated by a host response to infection. HIV serologic tests employ enzyme-linked immunosorbent assays (ELISA) to detect antibodies against viral antigens p24, p31, gp41, and gp120/gp160. Many rapid serologic tests approved by the Food and Drug Administration (FDA) are available, offering screening in 5-20 minutes that is highly sensitive and specific.[8,9] Positive rapid tests should always be confirmed with traditional serology and Western blot because, while rapid tests typically have specificities near 100%, false positives have been reported.[10] Given its low cost, accessibility, quick turnaround, and excellent performance, rapid serologic testing is generally preferred when screening for HIV. A notable drawback of all serologic tests, however, is the inability to detect HIV prior to seroconversion, historically termed the diagnostic window period.

The diagnostic window period has been successively shortened with the development of novel serologic assays. First-generation tests relied on lysate of HIV virions to bind any anti-human IgG antibodies in the specimen, but second-generation tests developed in the late 1980s used sophisticated recombinant HIV proteins and synthetic peptides to bind the antibodies. Third-generation tests developed in the early 1990s were designed to detect IgM in addition to IgG antibodies.[11] From first to third-generation tests, the window period has narrowed from approximately eight to three weeks.[12] To further shorten the interval from HIV infection to detection, later tests have targeted HIV RNA and p24 antigen during stages I and II of acute infection, respectively.

A Baltimore study undertaken in 1989 sought to diagnose acute HIV during the window period among randomly selected emergency room patients. Of 2,300 patients, 180 were HIV-positive by Western blot. Of the 2,120 patients whose Western blot was negative or indeterminate, six (0.28%) tested positive for p24 antigen and were found by nucleic acid amplification

testing (NAAT) to have HIV viral loads of 10,000 to 100,000 copies/mL. Only three of six patients were seropositive by third-generation ELISA testing, and none were suspected of having acute HIV infection on clinical grounds.[13]

The use of NAAT from a public health perspective has been additionally investigated since the Baltimore study. A North Carolina study conducted between 2002 and 2003 investigated the utility of pooled NAAT in HIV screening. Of 109,250 patients tested at publicly funded sites, 583 were HIV-antibody positive. Of the remaining 108,667 patients, 23 were found by NAAT to be infected with HIV. The median viral load was 258,000 copies/mL and ranged from 2,609 to 4,998,000 copies/mL. As in the Baltimore study, none of these patients had been suspected to have acute HIV infection, though seven of the 23 subjects were determined retrospectively to have presented with symptoms of acute infection.[14] This and similar studies in Florida and Los Angeles demonstrated rates of antibody-negative, HIV RNA-positive results of 0.02 to 0.09%.[11] Studies within high-risk settings of Atlanta, Los Angeles, and San Francisco demonstrated higher rates of 0.2 to 1.1%.[11] A San Francisco group reporting use of pooled NAAT in an STD clinic increased its rate of detection of acute HIV by 8.1%.[15]

Assays targeting p24 antigen can detect HIV within approximately two weeks of infection.[12] Fourth-generation or "combination" ELISAs merged these antigen-based assays with existing third-generation serologic techniques. Such combined tests have been demonstrated to increase the rate of diagnosis of acute HIV infection by a factor of 1.5 when compared to third-generation tests.[11] In 2010, the ARCHITECT Ag/Ab Combo Assay became the first fourth-generation test to garner approval by the FDA.[16] Rapid fourth-generation tests are being studied but have not demonstrated improved detection of acute HIV infection compared to rapid third-generation tests.[17]

For the present time, HIV RNA viral load measurement remains the most reliable diagnostic test for acute HIV infection during the window period, due to its higher sensitivity. The sensitivities of p24 antigen and HIV RNA tests for acute HIV infection are 79-89 and 100%, respectively. Conversely, p24 antigen testing is more specific in this population, having a specificity of 99-100% compared to 95-97% for HIV RNA testing.[18,19] HIV RNA is detectable by standard clinical assays once it exceeds 50 copies/mL, approximately 10 days post-infection.[6] False positive HIV RNA results can occur due to this modality's exquisite sensitivity[20], and data suggests values below 5,000 or 10,000 be considered indeterminate and bear repeating.[18,19] Studies of pooled HIV RNA testing have shown a marked decrease in the number of false positives when calculated on a per-specimen, not per-test, basis.[14]

The Infectious Diseases Society of America (IDSA) recommends general screening via either rapid or conventional ELISA, with confirmation of positive screens via Western blot. For asymptomatic patients with high-risk behavior (see Screening) within three months, repeat serologic testing at 6, 12, and 24 weeks is advised. The IDSA cautions that the FDA has not approved quantitative plasma HIV RNA (viral load) for diagnosing HIV, advising subsequent serologic testing to document seroconversion.[21] Regardless, HIV RNA testing is very helpful in the setting of acute infection. A reasonable diagnostic approach for acute HIV infection is to begin with serologic testing, measuring p24 antigen or HIV RNA if the suspicion of HIV remains high. If traditional, non-rapid serologic testing is employed, and especially in settings of high patient attrition, it is also reasonable to send plasma for concomitant measurement of HIV RNA.

SCREENING

The Centers for Disease Control and Prevention (CDC) advocates universal voluntary screening of all patients aged 13-64 years for HIV at least once in their life,[22] and the American College of Physicians (ACP) suggests extending the age to 75 years.[23] Informed consent should include a description of HIV, the meaning of positive and negative test results, and should address patient concerns and questions. Explicit written consent for HIV testing is no longer recommended; as for other screening tests, it may be covered by a general medical consent signed by the patient upon entering into a physician's care. Additionally, it is now recommended that patients be required to opt-out of HIV testing offered by their physician, and decisions to opt-out should be recorded in the patient's chart. Louisiana law supports the CDC's revised recommendations and in addition, stipulates that anonymous testing should be available.[5,24] The U.S. Preventative Task Force (USPTF) "makes no recommendation for or against routinely screening for HIV" in persons not at increased risk for HIV (Grade C), though it strongly recommends screening all at-risk adolescents and adults, as well as all pregnant women (Grade A).[25]

Repeat screening for HIV should be performed if a patient is diagnosed with tuberculosis, seeks treatment for or is diagnosed with a sexually transmitted disease, before becoming sexually active with a new partner, if occupational exposure is suspected, during the first and possibly also third (if has high-risk behavior) trimester of pregnancy, and at least annually for all patients with high-risk behavior.[22] The IDSA enumerates high-risk behaviors as: men having sex with men, using injection drugs, having multiple sexual partners, exchanging money or drugs for sex, and having sex with an HIV-positive person or one at risk for HIV infection.[21] Screening should also be performed any time HIV is included in the differential diagnosis.

Rapid serologic testing costs $10-$25 and is the screening modality of choice,[9] with viral load measurement reserved for patients suspected of acute infection in whom rapid testing is negative. While the cost of viral load measurement, including labor and consumables, approaches $150,[26] low-cost tests developed for low-income countries cost about one-fifth of this, or $30.[27] It is thus conceivable that costs will soon decline in developed nations. Pooled HIV RNA testing, while not amenable to measuring viral loads in HIV-positive populations, has been shown to ef-

fectively diagnose HIV even in the acute stages for a mere $2 per patient.[14]

CLINICAL PRESENTATION

The acute retroviral syndrome (ARS) was first described in 1985 as a mononucleosis-like illness.[28,29] It defines the constellation of signs and symptoms with onset one to four weeks post-inoculation with HIV and lasting less than a few weeks in most cases.[30] Though two-thirds to 90% of patients acutely infected with HIV report symptoms of ARS, the vast majority are unlikely to be diagnosed at this time.[30,31] Several small cohort studies designed to identify patients with acute HIV infection report it was correctly diagnosed in 15-25% of initial patient encounters,[30,32] and in more common settings, estimates may be as low as 2%.[33] In analyses of 563 and 499 patients presenting for urgent care with reports of mononucleosis-like or "viral" symptoms, 1 to 1.2% were retrospectively found on initial presentation to have been acutely infected with HIV.[34,35] Unfortunately, because progression to AIDS and opportunistic infections often develops many years following infection, treatment and prevention of transmission are thereby delayed if the diagnosis is missed during the acute stages of HIV.

Fever is the most reliable symptom, present in more than 80% of ARS.[36] Lymphadenopathy is often present and occasionally remains beyond the acute stages of HIV infection as persistent generalized lymphadenopathy (PGL). Pharyngeal edema and erythema, when present, usually occur in the absence of tonsillar enlargement or exudates. Involvement of the gastrointestinal tract, thought to be important to the establishment of HIV in its host,[6] often manifests as anorexia, weight loss, nausea, vomiting, and diarrhea. Mucocutaneous ulceration within either the gastrointestinal or genitourinary tracts, while infrequent, can be exquisitely painful and is perhaps the most ARS-specific symptom.[12,31] Occasional dermatologic findings include candidiasis, herpes zoster, and herpes simplex. A rash appearing two days after onset of fever and lasting approximately one week may be present and is typically maculopapular, non-pruritic, and can involve any area, including palms and soles. Malaise, myalgia, arthralgia, and headache are relatively common. While some patients experience meningismus as retrobulbar headaches exacerbated by eye movement, serious CNS involvement such as encephalitis is rare. Opportunistic infections are also rare, though such infections would increase the suspicion of HIV, as would findings of other sexually transmitted diseases, including urethritis, ulcerations, and warts.

Hematologic derangements during acute HIV infection include not only leukopenia but also anemia and thrombocytopenia. The prevalence of thrombocytopenia ($< 150 \times 10^3$ platelets/μL) within a large cohort of chronic HIV patients from 1997-2006 was 14%[37]; 3.1% of patients had counts $< 50 \times 10^3$ platelets/μL and 1.7% had counts $< 30 \times 10^3$ platelets/μL. In another study of 701 chronic HIV patients, the mean platelet count was $> 200 \times 10^3$ platelets/μL.[38] Anemia was present in 38% of patients in the latter study and associated with a higher death rate: 14 versus 4 in the low CD4 count group (< 200 cells/μL), and eight deaths versus one in the higher CD4 count group (> 200 cells/μL). Data is lacking on the severity of thrombocytopenia during acute infection; the profound degree of our patient's thrombocytopenia is not well documented in the medical literature. Severe neutropenia during acute HIV infection is rare, and to the best of our knowledge, our patient is only the sixth such case reported.[39]

Hepatocellular damage in the setting of acute HIV infection is described. In a chart review from 1990-2009, 15 of 23 patients with acute HIV infection had transaminitis, with median AST and ALT levels of 112 and 146 U/L, respectively.[33] Severe elevation of transaminases has been reported in cases of co-infection with HBV and CMV.[40,41] The mechanism of hepatocellular damage in otherwise healthy HIV patients remains unclear, but virion-mediated inflammation might be responsible. A moderately strong, positive correlation between HIV viral load and serum transaminase level has been observed.[42] This association could explain the unusual degree of transaminitis in our patient, who exhibited a viral load of greater than 10 million copies/mL.

TREATMENT

Evidence-based treatment strategies for acute infection with HIV are lacking. The Department of Health and Human Services (DHHS) recommends prompt initiation of ART for all HIV-infected pregnant women (Level A1), citing a significant risk of mother-to-child transmission of HIV.[43] The initiation of ART during acute infection is otherwise a weak recommendation (Level C3), and it should be considered in conjunction with a specialist in HIV care. Reasons to elect treatment include symptomatic relief along with the theoretical benefits in long-term clinical and immunologic factors thought to derive from early treatment. Limiting the transmission of HIV is another potential benefit of starting ART at a time associated with peak viral loads. In a recent meta-analysis, the sexual transmission rate of HIV was 0.46% for those treated with ART versus 5.64% for those untreated and having higher viral loads.[44]

While there are theoretical benefits for early initiation of ART in non-pregnant patients, the risks are tangible. Further studies are needed to determine the real benefits of early therapy. Patients opting for ART might be best served by enrollment in a clinical trial via **www.clinicaltrials.gov**. We chose not to initiate ART in the hospital for our patient, but given his very low CD4 count, we discharged him with pneumocystis prophylaxis and close follow-up with the HIV outpatient clinic.

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Dr. Atkinson is a second-year Resident in the Combined Internal Medicine and Pediatrics Residency Program, Department of Medicine, Louisiana State University Health Sciences Center at New Orleans. **Dr. Miklowski** is a Clinical Assistant Professor in the Section of Hospital Medicine at LSUHSC-New Orleans. **Dr. Lopez** is the Richard Vial Professor and Vice Chair for Education at LSUHSC-New Orleans. He is also Section Editor for the *Journal of the Louisiana State Medical Society*. **Dr. Klibert** is a first-year Resident in the Internal Medicine Residency Program, Department of Medicine, LSUHSC-New Orleans.