

Diagnosis and Initial Management of Acute HIV Infection

CAROLYN CHU, MD, MSc, and PETER A. SELWYN, MD, MPH, *Albert Einstein College of Medicine, Bronx, New York*

Recognition and diagnosis of acute human immunodeficiency virus (HIV) infection in the primary care setting presents an opportunity for patient education and health promotion. Symptoms of acute HIV infection are nonspecific (e.g., fever, malaise, myalgias, rash), making misdiagnosis common. Because a wide range of conditions may produce similar symptoms, the diagnosis of acute HIV infection involves a high index of suspicion, a thorough assessment of HIV exposure risk, and appropriate HIV-related laboratory tests. HIV RNA viral load testing is the most useful diagnostic test for acute HIV infection because HIV antibody testing results are generally negative or indeterminate during acute HIV infection. After the diagnosis of acute HIV infection is confirmed, physicians should discuss effective transmission risk reduction strategies with patients. The decision to initiate antiretroviral therapy should be guided by consultation with an HIV specialist. (*Am Fam Physician*. 2010;81(10):1239-1244. Copyright © 2010 American Academy of Family Physicians.)

Acute human immunodeficiency virus (HIV) infection, also known as primary HIV infection or acute retroviral syndrome, is the period just after initial HIV infection, generally before seroconversion. Although some patients remain asymptomatic, acute HIV infection often manifests with transient symptoms related to high levels of HIV viral replication and the subsequent immune response. Because symptoms of acute HIV infection (e.g., fever, rash, malaise, sore throat) mimic other, more prevalent conditions, such as influenza, misdiagnosis is common. Furthermore, patterns of care for patients seeking medical attention for acute HIV infection are largely unknown. One study based on a national probability sample of patients presenting to physician offices, emergency departments, and hospital outpatient clinics estimated rates of acute HIV infection to be 0.13 to 0.66 percent among symptomatic ambulatory patients,¹ making detection a clinical and public health challenge.

Acute HIV infection provides a unique opportunity for patient education, health promotion, and prevention; primary care physicians must be able to recognize and diagnose it. This article provides an update to previously published reviews of acute HIV syndrome.²⁻⁴

Epidemiology

In the Centers for Disease Control and Prevention's most recent HIV/AIDS surveillance report, the number of new adult and adolescent HIV infections in the United States during 2006 was estimated to be 56,300 (a rate of 22.8 per 100,000 persons).⁵ There were notable disparities and trends among certain subgroups. The incidence rate in non-Hispanic blacks versus non-Hispanic whites was 83.7 versus 11.5 per 100,000 persons. Also, persons 40 to 49 years of age accounted for 25 percent of all new infections, whereas those 50 years and older accounted for 10 percent. Persons infected through high-risk heterosexual contact represented 31 percent of new infections, compared with 12 percent for those infected through injection drug use. Although such patterns indicate that certain populations are at higher risk of infection, HIV continues to affect every ethnic, age, and risk group and every geographic area in the United States. Physicians must keep acute HIV infection in the differential diagnosis of any patient with otherwise unexplained symptoms.

Clinical Presentation

At least 50 (and up to 90) percent of patients with acute HIV infection develop symptoms consistent with acute infection,^{6,7} although timing and duration are variable.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendations	Evidence rating	References
HIV infection should be confirmed with repeat HIV enzyme-linked immunoabsorbent assay and Western blot test to document seroconversion within four to six weeks.	C	19, 20
Patients with acute HIV infection should receive education and counseling on strategies to reduce the risk of transmission.	C	23, 24
Following diagnosis of acute HIV infection, two sets of CD4 lymphocyte counts and HIV viral load levels should be checked within four to six weeks to monitor level of immune suppression and viremia.	C	27
Patients with acute HIV infection should be screened for sexually transmitted infections (e.g., chlamydia, gonorrhea, syphilis), hepatitis B and C, and tuberculosis.	C	27
An HIV genotype should be strongly considered to assess for baseline resistance mutations.	C	27, 29
Consultation with an HIV specialist should occur before initiation of antiretroviral therapy.	C	30, 31

HIV = human immunodeficiency virus.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

For most symptomatic patients, acute illness develops within one to four weeks after transmission, and symptoms usually persist for two to four weeks. Acute HIV infection is often described as mononucleosis- or influenza-like, with the most prevalent symptoms being fever, fatigue, myalgias/arthralgias, rash (typically an erythematous

maculopapular exanthem), and headache⁶⁻¹⁰ (*Tables 1*^{8,9} and *2*). Patients also may experience anorexia, pharyngitis, lymphadenopathy, mucocutaneous ulcerations, diarrhea, or a combination of these symptoms. Severe manifestations of acute HIV infection (e.g., meningoencephalitis, myelitis), although rare, have been described.¹¹ CD4 lymphocyte

Table 1. Diagnostic Value of Signs and Symptoms in Acute HIV Infection

Sign/symptom	Sensitivity* (%)	Specificity† (%)	Positive likelihood ratio‡	Negative likelihood ratio§
Mucocutaneous ulcerations	2 to 37	85 to 97	2.2	0.9
Rash	51 to 58	66 to 82	2.1	0.6
Myalgias/arthralgias	49 to 60	69 to 74	1.9	0.6
Anorexia/weight loss	32 to 54	68 to 86	1.9	0.7
Fever	80 to 88	50 to 56	1.8	0.3
Severe central nervous system manifestations	25	82	1.4	0.9
Fatigue/malaise	68 to 78	38 to 51	1.3	0.6
Headache	54 to 55	56 to 57	1.3	0.8
Lymphadenopathy	38	71	1.3	0.9
Pharyngitis	43 to 44	51 to 77	1.2	0.9
Gastrointestinal distress	12 to 49	60 to 91	1.2	0.9

NOTE: Signs and symptoms are listed in order of descending positive likelihood ratio.

HIV = human immunodeficiency virus.

*—Sign or symptom is present when patient has acute HIV infection. Signs and symptoms with high sensitivity tend to rule out acute HIV when they are absent.

†—Sign or symptom is not present when patient does not have acute HIV. Signs and symptoms with high specificity tend to rule in acute HIV when they are present.

‡—The amount the likelihood of acute HIV increases when the sign or symptom is present.

§—The amount the likelihood of acute HIV decreases when the sign or symptom is absent.

Information from references 8 and 9.

Table 2. Differential Diagnosis of Acute HIV Infection

Most common	Least common
Epstein-Barr virus	Acute cytomegalovirus infection
Influenza	Acute toxoplasmosis
Streptococcal pharyngitis	Brucellosis
Viral/noninfectious gastroenteritis	Disseminated gonococcemia
Viral upper respiratory tract infection	Measles
Less common	
Acute viral hepatitis	Meningitis/encephalitis
Drug reaction	Primary immunodeficiencies
Primary herpes simplex infection	Rubella
Secondary syphilis	Travel-related pathogens (e.g., malaria, typhoid)

HIV = human immunodeficiency virus.

counts exhibit a marked transient decrease during acute infection. There have been case reports of patients with acute infection presenting with opportunistic infections, such as esophageal candidiasis.¹² Physical examination is nondiagnostic but may be notable for hepatosplenomegaly.

Because symptoms are nonspecific, symptom-based algorithms are generally not useful in detecting acute HIV infection in the general U.S. population. However, such algorithms are being combined with clinical risk factors to develop targeted testing strategies in high-risk and high-prevalence groups, such as populations in sub-Saharan Africa.^{13,14} Physicians should be aware of current HIV transmission patterns in their communities (e.g., men who have sex with men, persons who share needles) but should retain a low threshold to consider acute infection in anyone presenting with any constellation of suggestive symptoms. Evaluation should include a thorough and accurate assessment of all activities that potentially involve HIV exposure, including heterosexual intercourse with a long-term partner.

Testing for Acute HIV Infection

With the evolution of HIV enzyme-linked immunosorbent assays (ELISA) from first to third generation tests, the window period (i.e., the time between transmission and production of HIV antibodies when an HIV ELISA test result may be falsely negative) for

confirming HIV infection through antibody testing has narrowed from approximately 56 to 21 days. However, because acute HIV infection occurs before the appearance of HIV antibodies, it can be diagnosed only by demonstrating the presence of p24 antigen or HIV viral RNA, which can be detected as early as 14 to 15 days and 11 to 12 days after infection, respectively (*Table 3*¹⁵ and *Figure 1*¹⁶).

The usefulness of p24 testing for acute HIV infection is somewhat limited because (1) HIV viral load assays are now more widely available in the United States, and (2) the level of sufficiently detectable p24 antigenemia in patients is inconsistent and short-lived (i.e., serum p24 levels typically decrease as HIV antibody titers increase and immune complexes develop). However, some new rapid HIV tests, which are generally HIV antibody-based, may also include

Table 3. Diagnostic Tests Used in Acute HIV Infection

Test	Purpose	Time from infection to detection*
HIV RNA viral load	Measures level of HIV nucleic acid/RNA using quantitative polymerase chain reaction testing, branched DNA, or nucleic acid amplification assays	11 to 12 days
p24 antigen	Measures level of HIV p24 core protein	14 to 15 days (levels fall within six to eight weeks as HIV p24 antibody increases and immune complexes form, decreasing test sensitivity)
HIV enzyme-linked immunosorbent assay	Detects presence of HIV antibody; positive test confirmed with Western blot test	Three to eight weeks (median 25 days)

HIV = human immunodeficiency virus.

*—Symptoms of acute HIV infection usually develop within one to four weeks after transmission and persist for two to four weeks.

Information from reference 15.

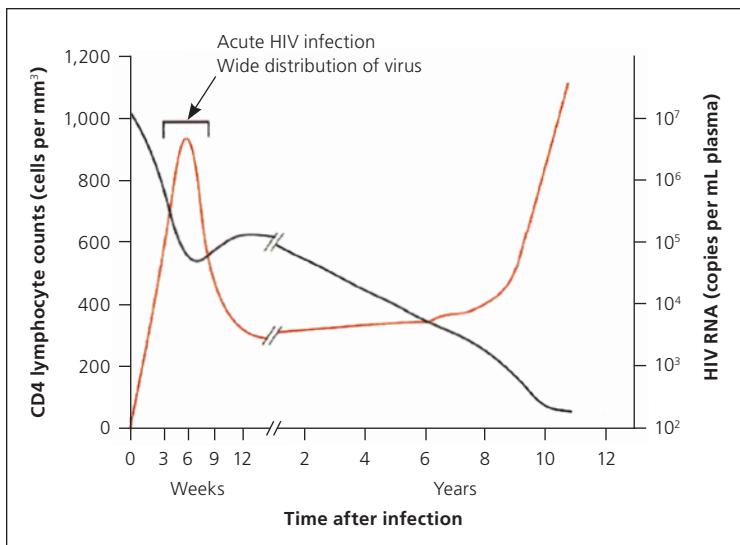


Figure 1. Human immunodeficiency virus (HIV) viremia and CD4 lymphocyte counts during acute infection.

Adapted from Pantaleo G, Graziosi C, Fauci AS. New concepts in the immunopathogenesis of human immunodeficiency virus infection. *N Engl J Med.* 1993;328(5):327-335.

p24 antigen testing. This makes them potentially valuable for point-of-care detection of acute HIV infection.¹⁷

Because of the limitations of p24 antigen testing, HIV RNA viral load is arguably the most useful diagnostic marker for acute HIV infection. It has a sensitivity close to 100 percent and a specificity from 95 to 98 percent, depending on the type of assay.⁸ In patients with acute HIV infection, RNA levels typically rise above 100,000 copies per mL. Low viral loads (particularly 1,000 RNA copies per mL or less) in a person with suspected acute HIV infection may indicate a false-positive result.¹⁸ To confirm the diagnosis of acute HIV infection (or rule out infection in patients with a low but detectable RNA level), viral load testing should be repeated with ELISA and Western blot test within four to six weeks.^{19,20}

Initial Management of Acute HIV Infection

One of the most important clinical considerations for patients with acute HIV infection is psychosocial evaluation and stabilization, including a domestic violence screen and referral to counseling or support services if available. Physicians should educate patients about their potentially heightened infectiousness,^{21,22} and discuss effective transmission risk reduction strategies.^{23,24} These include consistent and effective condom use, limiting drug and alcohol intake (which may

impair the ability to negotiate safe sex), and the incorporation of alternative sexual practices that do not involve the exchange of body fluids. Patients, particularly men who have sex with men, should be warned of the risks of serosorting, which is the identification of sex partners based on their HIV status that may lead to unprotected intercourse.²⁵ Partner notification should be discussed with all patients with acute HIV infection and carried out promptly per local health department guidelines.

Because symptoms of acute infection are usually self-limited, specific management is often supportive. Treatment may include antipyretics, nonsteroidal anti-inflammatory drugs, and close follow-up of significant laboratory abnormalities (e.g., anemia, thrombocytopenia, elevated transaminases). A proportion of patients with severe symptoms or laboratory abnormalities may require hospitalization; steroids have not been consistently effective in these patients.^{11,26}

Several additional laboratory tests should be performed once acute HIV infection is diagnosed: two sets of CD4 lymphocyte counts and HIV viral load levels within four to six weeks to monitor the level of immune suppression and viremia; screening for other sexually transmitted infections (e.g., chlamydia, gonorrhea, syphilis) and hepatitis B and C; and skin testing for tuberculosis.²⁷ Given the prevalence of primary antiretroviral drug resistance that has been described in some populations,²⁸ an HIV genotype should be strongly considered to detect transmitted mutations that may cause resistance to future antiretroviral treatment.^{27,29} A repeat HIV antibody test should also be performed within four to six weeks to document seroconversion (*Figure 2*).^{18-20,23,24,27,29-31}

There is ongoing debate about the role of combination, highly active antiretroviral therapy in acute HIV infection. The relationships between symptom severity, level of viremia, and CD8 lymphocyte activation response in acute infection are complicated. Research suggests these factors are major determinants of subsequent HIV disease progression by affecting the rate of CD4 lymphocyte loss and the viral set point

Diagnosis and Follow-up of Acute HIV Infection

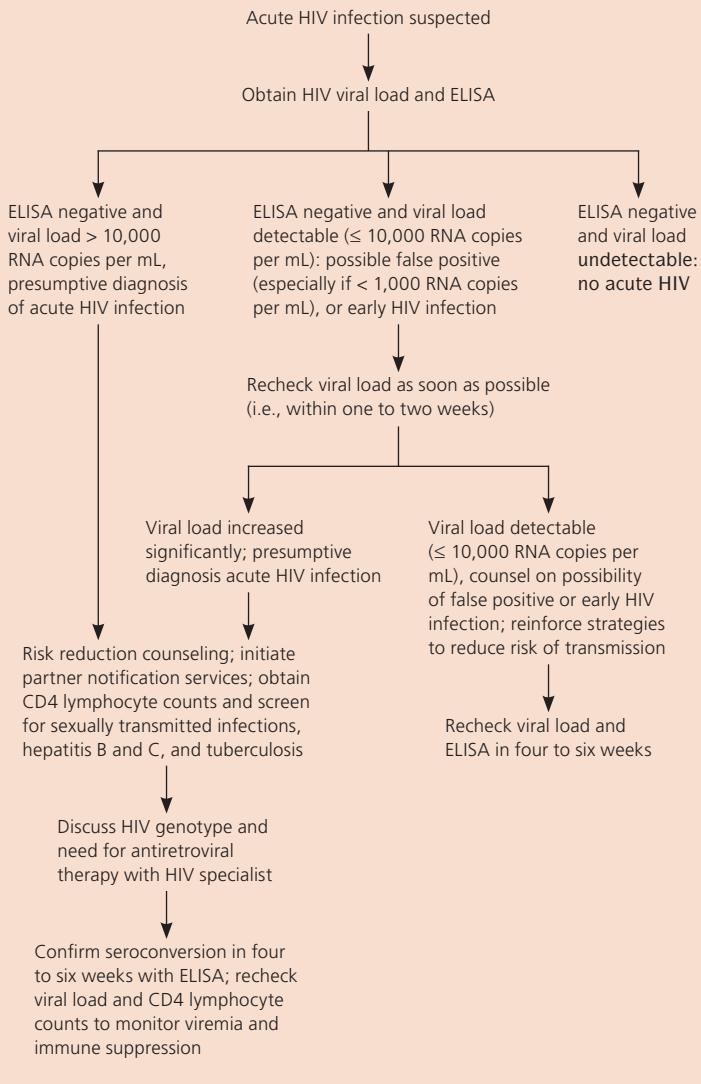


Figure 2. Suggested algorithm for the diagnosis and follow-up of acute human immunodeficiency virus (HIV) infection. (ELISA = enzyme-linked immunoabsorbent assay.)

Information from references 18 through 20, 23, 24, 27, and 29 through 31.

2. Daar ES, Pilcher CD, Hecht FM. Clinical presentation and diagnosis of primary HIV-1 infection. *Curr Opin HIV AIDS*. 2008;3(1):10-15.
3. Taiwo BO, Hicks CB. Primary human immunodeficiency virus. *South Med J*. 2002;95(11):1312-1317.
4. Perlmuter BL, Glaser JB, Oyugi SO. How to recognize and treat acute HIV syndrome [published correction appears in *Am Fam Physician*. 2000;61(2):308]. *Am Fam Physician*. 1999;60(2):535-542, 545-546.
5. Centers for Disease Control and Prevention. Cases of HIV infection and AIDS in the United States and dependent areas, 2007. HIV/AIDS surveillance report, volume 19. <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2007report/>. Accessed July 1, 2009.
6. Lavrey L, Thompson ML, Martin HL Jr, et al. Primary human immunodeficiency virus type 1 infection: clinical manifestations among women in Mombasa, Kenya. *Clin Infect Dis*. 2000;30(3):486-490.

(the rate of HIV virus replication that stabilizes and remains at a particular level after acute infection).³²⁻³⁴ It has been theorized that treatment of acute HIV infection may alter the natural course of HIV infection or delay the need for chronic antiretroviral therapy by preserving immune function.³⁵ Treatment may also have wider public health implications by reducing transmission.³⁶ Longitudinal studies have sought to identify the virologic, immunologic, and clinical benefits of antiretroviral therapy initiation during acute infection, but results from these studies have been inconclusive. Current evidence suggests there is not significant long-term or clinically meaningful improvement despite short-term viral suppression and CD4 lymphocyte restoration.³⁷⁻⁴⁰ Therefore, antiretroviral therapy for patients with acute HIV infection should be initiated only after consultation with an HIV specialist.^{30,31}

If therapy is initiated, specific guidelines for recommended antiretroviral combinations and follow-up can be found on the U.S. Department of Health and Human Services AIDSinfo Web site at <http://www.aidsinfo.nih.gov/guidelines/>. Physicians may also refer patients to clinical trials on the natural history and treatment outcomes of acute HIV infection. Information on these trials may be found on the AIDSinfo Web site at <http://www.aidsinfo.nih.gov/clinicaltrials/> or by calling 800-HIV-0440.

The Authors

CAROLYN CHU, MD, MSc, is an assistant professor of family medicine at Albert Einstein College of Medicine in the Bronx, NY.

PETER A. SELWYN, MD, MPH, is chair of the Department of Family and Social Medicine and a professor of family medicine, internal medicine, and epidemiology and population health at Albert Einstein College of Medicine.

Address correspondence to Carolyn Chu, MD, MSc, Department of Family and Social Medicine, 3544 Jerome Ave., Bronx, NY 10467 (e-mail: cchu@montefiore.org). Reprints are not available from the authors.

Author disclosure: Nothing to disclose.

REFERENCES

1. Coco A, Kleinhans E. Prevalence of primary HIV infection in symptomatic ambulatory patients. *Ann Fam Med*. 2005;3(5):400-404.

7. Schacker T, et al. Clinical and epidemiologic features of primary HIV infection [published correction appears in *Ann Intern Med.* 1997;126(2):174]. *Ann Intern Med.* 1996;125(4):257-264.
8. Hecht FM, Busch MP, Rawal B, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. *AIDS.* 2002;16(8):1119-1129.
9. Daar ES, Little S, Pitt J, et al. Diagnosis of primary HIV-1 infection. Los Angeles County Primary HIV Infection Recruitment Network. *Ann Intern Med.* 2001;134(1):25-29.
10. Vanhems P, Hughes J, Collier AC, et al. Comparison of clinical features, CD4 and CD8 responses among patients with acute HIV-1 infection from Geneva, Seattle and Sydney. *AIDS.* 2000;14(4):375-381.
11. Douvogiannis M, Litman N. Acute encephalopathy and multi-organ involvement with rhabdomyolysis during primary HIV infection. *Int J Infect Dis.* 2009;13(5):e299-e304.
12. Manata MJ, Melo AZ, Quaresma MJ. Esophageal candidiasis in acute HIV infection. Presented at: International Conference on AIDS; August 7-12, 1994; Lisbon, Portugal. Abstract PB0593.
13. Miller WC, Leone PA, McCoy S, Nguyen TQ, Williams DE, Pilcher CD. Targeted testing for acute HIV infection in North Carolina. *AIDS.* 2009;23(7):835-843.
14. Powers KA, Miller WC, Pilcher CD, et al.; Malawi UNC Project Acute HIV Study Team. Improved detection of acute HIV-1 infection in sub-Saharan Africa: development of a risk score algorithm. *AIDS.* 2007;21(16):2237-2242.
15. Busch MP, Satten GA. Time course of viremia and antibody seroconversion following human immunodeficiency virus exposure. *Am J Med.* 1997;102(5B):117-124.
16. Pantaleo G, Graziosi C, Fauci AS. New concepts in the immunopathogenesis of human immunodeficiency virus infection. *N Engl J Med.* 1993;328(5):327-335.
17. Weber B, Orazi B, Rainieri A, et al. Multicenter evaluation of a new 4th generation HIV screening assay Elecsys HIV combi. *Clin Lab.* 2006;52(9-10):463-473.
18. Rich JD, Merriman NA, Mylonakis E, et al. Misdiagnosis of HIV infection by HIV-1 plasma viral load testing: a case series. *Ann Intern Med.* 1999;130(1):37-39.
19. Chou R, Huffman LH, Fu R, Smits AK, Korthuis PT. Screening for HIV: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2005;143(1):55-73.
20. Centers for Disease Control (CDC). Update: serologic testing for HIV-1 antibody—United States, 1988 and 1989. *MMWR Morb Mortal Wkly Rep.* 1990;39(22):380-383.
21. Lee CC, Sun YJ, Barkham T, Leo YS. Primary drug resistance and transmission analysis of HIV-1 in acute and recent drug-naïve seroconverters in Singapore. *HIV Med.* 2009;10(6):370-377.
22. Brenner BG, Roger M, Routy JP, et al.; Quebec Primary HIV Infection Study Group. High rates of forward transmission events after acute/early HIV-1 infection. *J Infect Dis.* 2007;195(7):951-959.
23. Incorporating HIV prevention into the medical care of persons living with HIV. Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America [published correction appears in *MMWR Recomm Rep.* 2004;53(32):744]. *MMWR Recomm Rep.* 2003;52(RR-12):1-24.
24. Healthy Living Project Team. Effects of a behavioral intervention to reduce risk of transmission among people living with HIV: the healthy living project randomized controlled study. *J Acquir Immune Defic Syndr.* 2007;44(2):213-221.
25. Xia Q, Molitor F, Osmond DH, et al. Knowledge of sexual partner's HIV serostatus and serosorting practices in a California population-based sample of men who have sex with men. *AIDS.* 2006;20(16):2081-2089.
26. Tambussi G, Gori A, Capiluppi B, et al. Neurological symptoms during primary human immunodeficiency virus (HIV) infection correlate with high levels of HIV RNA in cerebrospinal fluid. *Clin Infect Dis.* 2000;30(6):962-965.
27. Aberg JA, Gallant JE, Anderson J, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2004;39(5):609-629.
28. Truong HM, et al. Routine surveillance for the detection of acute and recent HIV infections and transmission of antiretroviral resistance. *AIDS.* 2006;20(17):2193-2197.
29. Hirsch MS, Brun-Vézinet F, D'Aquila RT, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: recommendations of an International AIDS Society-USA Panel. *JAMA.* 2000;283(18):2417-2426.
30. Landon BE, et al. Physician specialization and the quality of care for human immunodeficiency virus infection. *Arch Intern Med.* 2005;165(10):1133-1139.
31. Landon BE, Wilson IB, Cohn SE, et al. Physician specialization and antiretroviral therapy for HIV. *J Gen Intern Med.* 2003;18(4):233-241.
32. Kelley CF, Barbour JD, Hecht FM. The relation between symptoms, viral load, and viral load set point in primary HIV infection. *J Acquir Immune Defic Syndr.* 2007;45(4):445-448.
33. Streeck H, Jolim JS, Qi Y, et al. Human immunodeficiency virus type 1-specific CD8+ T-cell responses during primary infection are major determinants of the viral set point and loss of CD4+ T cells. *J Virol.* 2009;83(15):7641-7648.
34. Burgers WA, et al.; CAPRISA 002 Acute Infection Study Team. Association of HIV-specific and total CD8+ T memory phenotypes in subtype C HIV-1 infection with viral set point. *J Immunol.* 2009;182(8):4751-4761.
35. Oxenius A, Price DA, Easterbrook PJ, et al. Early highly active antiretroviral therapy for acute HIV-1 infection preserves immune function of CD8+ and CD4+ T lymphocytes. *Proc Natl Acad Sci USA.* 2000;97(7):3382-3387.
36. Koopman JS, et al. The role of early HIV infection in the spread of HIV through populations. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1997;14(3):249-258.
37. Pantazis N, et al.; CASCADE Collaboration. The effect of antiretroviral treatment of different durations in primary HIV infection. *AIDS.* 2008;22(18):2441-2450.
38. Voirin N, et al. Effect of early initiation of highly active antiretroviral therapy on CD4 cell count and HIV-RNA viral load trends within 24 months of the onset of acute retroviral syndrome. *HIV Med.* 2008;9(6):440-444.
39. Hecht FM, Wang L, Collier A, et al.; AIEDRP Network. A multicenter observational study of the potential benefits of initiating combination antiretroviral therapy during acute HIV infection. *J Infect Dis.* 2006;194(6):725-733.
40. Smith DE, et al. Is antiretroviral treatment of primary HIV infection clinically justified on the basis of current evidence? *AIDS.* 2004;18(5):709-718.