The risk for infection increased with decreasing $CD4^+$ counts, but most episodes were mild and self-limited. Anemia is common in advanced HIV infection and is an independent risk factor for mortality.[317,318] HIV-related thrombocytopenia is a result of both immune-mediated platelet destruction (as is seen in idiopathic thrombocytopenic purpura) and impaired platelet production.[319] Patients are usually asymptomatic, even with profound thrombocytopenia. The thrombocytopenia usually responds to ART; this has been best studied with zidovudine but has also been shown with ART.[320,321] Thrombotic thrombocytopenic purpura in an HIV-infected person was first described by Jokela and colleagues in 1987.[322] The classic diagnostic pentad includes thrombocytopenia, microangiopathic hemolytic anemia, renal failure, fever, and neurologic abnormalities, although not all patients have all these findings. In addition, given the high frequency of many of these findings in patients with advanced AIDS, such a diagnosis may not always be considered. The incidence of thrombotic thrombocytopenic purpura has appeared to be decreasing in the ART era.[323]

Non–AIDS-Related Cancers

Malignancies termed *AIDS-related* were those originally identified occurring as epidemics in populations in which they were usually rare (e.g., Kaposi sarcoma and non-Hodgkin lymphoma in young MSM). These conditions were included in the CDC early case definition of AIDS to ensure sensitivity of the surveillance process. Cervical cancer was added to the case definition subsequently when cases appeared out of proportion in HIV-infected women. In recent years, however, a number of cancers have been detected in populations with HIV infection in excess of what would be expected based on rates in HIV-seronegative people in the general population. Both AIDS-related and non–AIDS-related cancers remain an important cause of illness and death in people with HIV infection; in a large North American cohort between 1995 and 2009, as use of ART dramatically increased and life expectancy improved, cancers accounted for 10% of AIDS deaths.[324–326] Increases in non–AIDS-related cancers have been notable in particular for liver cancer, lung cancer, head and neck tumors, and anal cancer. The use of ART has substantially reduced the incidence of AIDS-related cancers but appears to have little effect on rates of non–AIDS-related malignancies. As the prevalence of HIV infection increases due to declining mortality and as the infected population ages, more non–AIDS-related cancers can be anticipated.

Immune Reconstitution Syndromes

ART is associated with dramatic reductions in HIV-1 RNA and increases in $CD4^+$ lymphocyte counts. In addition to decreasing HIV-related mortality and the incidence of opportunistic infections significantly (as discussed earlier), the improvement in immune function can be associated with paradoxical worsening of underlying opportunistic infections.[327,328] The clinical presentation of immune reconstitution inflammatory syndrome (IRIS) varies according to the pathogen (see later discussion). Not every patient who has immunologic improvement with ART experiences IRIS; the risk factors for the development of these syndromes are not well understood.

Tuberculosis

Paradoxical worsening of tuberculosis was initially described in HIV-seronegative patients with tuberculosis before the HIV era, but it appears to be more common in HIV-infected patients.[74] Clinical manifestations include fever, adenopathy (e.g., cervical, thoracic, intraabdominal), and worsening pulmonary infiltrates. Central nervous system tuberculomas, pleural effusions, and psoas abscesses have also been described.[73,74,329,330] Diagnoses such as lymphoma, adverse drug reaction, and tuberculosis treatment failure related to nonadherence, malabsorption, or drug resistance must be excluded before the diagnosis of tuberculosis IRIS can be established. Treatment with ART has been associated with an increased risk for IRIS in some, but not all, studies; the incidence rate ranges from 7% to 43%.[73,74,329–332] Patients who experience IRIS with ART usually do so within 2 to 3 weeks of starting therapy. Clinical management includes continuation of antituberculosis therapy and ART and the use of nonsteroidal antiinflammatory drugs for symptomatic relief. For severe manifestations such as compromise of the airways or venous return to the heart, corticosteroids (e.g., prednisone 1.5 mg/kg/day for 2 weeks followed by 0.75 mg/kg/day for 2 weeks[332a]) may be given. Unmasking of previously unrecognized tuberculosis after ART initiation has also been reported, although this may represent progression of untreated tuberculosis that is coincidental to the start of HIV therapy.[125,126]

Mycobacterium avium Complex Disease

Focal or diffuse lymphadenitis developing within 2 to 3 months of initiation of ART has been described in several patients with low baseline $CD4^+$ counts.[124,333] Mycobacteremia is generally not present, but cultures of lymph nodes usually grow *M. avium*. There have also been reports of focal osteomyelitis developing in patients who discontinue primary or secondary *M. avium* prophylaxis after sustained increases in $CD4^+$ counts during ART.[334,335] Treatment is the same as for *M. avium* infection in the absence of immune reconstitution.

Cytomegalovirus Disease

CMV retinitis in the setting of immune reconstitution (immune recovery uveitis) has been described in patients with and without a history of CMV retinitis before initiation of ART.[336–338] Development of CMV disease at extraocular sites (e.g., bloodstream, colon, pancreas) in patients without prior CMV disease has also been described.[339] Among patients with a history of CMV retinitis who subsequently initiate and respond to ART, 18% to 63% develop immune recovery uveitis.[340,341] In one study the median time of ART until development of uveitis was 43 weeks.[340] The optimal management is unclear. Oral corticosteroids with or without concomitant anti-CMV therapy are often used.

Infection With Varicella-Zoster Virus

There have been several reports of the development of herpes zoster in patients receiving ART. In two series, herpes zoster developed in 7% to 8% of patients receiving combination ART and occurred within 17 weeks of initiation of therapy.[342,343] In one report, herpes zoster was associated with an increase in $CD8^+$ lymphocytes.[342] The clinical manifestations are usually not severe and respond to acyclovir or famciclovir.

Viral Hepatitis

Patients infected with HCV can develop acute hepatitis or cirrhosis during ART.[344,345] It is difficult to discern whether elevations in hepatic aminotransferase levels are caused by toxicity of ART or immune reconstitution: there is no reliable clinical or laboratory parameter that distinguishes between these two entities. In a study of 60 patients coinfected with HIV and HCV who completed at least 16 weeks of ART, immune recovery was associated with a persistent increase in HCV RNA, particularly in patients with baseline $CD4^+$ count less than 350 cells/mm^3.[346,347] Other studies have found that hepatotoxicity in coinfected patients who respond to ART is associated with increased HCV-specific immune responses and T-cell activation.[348] This suggests that at least in some cases hepatotoxicity is associated with immune reconstitution. There have also been reports of acute hepatitis developing during ART in patients with prior HBV infection in whom increased HBV RNA levels are detected.[349] Patients with chronic HBV infection are at increased risk for hepatotoxicity from ART, and withdrawal of antiretroviral drugs that have activity against HBV such as tenofovir or lamivudine may result in worsening of hepatic function and increased aminotransferase levels, which may be caused by immune mechanisms or loss of viral suppression.[350] Management of patients with chronic hepatitis is discussed in Chapter 117.

Other Diseases

Paradoxical worsening in the setting of immune reconstitution has also been described after initiation of ART with infection with *Cryptococcus neoformans,*[351,352] *P. jirovecii* pneumonia,[353,354] progressive multifocal leukoencephalopathy,[355] and Kaposi sarcoma.[356] It has also been seen with Hodgkin and non-Hodgkin lymphoma.[357–359] Of particular concern is IRIS that involves the central nervous system because of the high associated morbidity and mortality. This has been seen with infection with *C. neoformans* and progressive multifocal leukoencephalopathy in addition to tuberculosis.

Key References

The complete reference list is available online at Expert Consult.

4. Masur H, Michelis MA, Greene JB, et al. An outbreak of community-acquired *Pneumocystis carinii* pneumonia: initial manifestation of cellular immune dysfunction. *N Engl J Med*. 1981;305:1431–1438.
6. Gottlieb MS, Schanker HM, Fan PT, et al. Pozalski I. Pneumocystis pneumonia—Los Angeles. *MMWR Morb Mortal Wkly Rep*. 1981;30:250–252.
7. Siegal FP, Lopez C, Hammer GS, et al. Severe acquired immunodeficiency in male homosexuals, manifested by chronic perianal ulcerative herpes simplex lesions. *N Engl J Med*. 1981;305:1439–1444.
10. Pape JW, Liautaud B, Thomas F, et al. Characteristics of the acquired immunodeficiency syndrome (AIDS) in Haiti. *N Engl J Med*. 1983;309:945–950.
21. Barre-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). 1983. *Rev Invest Clin*. 2004;56:126–129.
22. Gallo RC, Salahuddin SZ, Popovic M, et al. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science*. 1984;224:500–503.
34. Bacchetti P, Osmond D, Chaisson RE, et al. Survival patterns of the first 500 patients with AIDS in San Francisco. *J Infect Dis*. 1988;157:1044–1047.
48. Mellors JW, Rinaldo CR Jr, Gupta P, et al. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science*. 1996;272:1167–1170.
53. Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. 2015;373:795–807.
57. Moore RD, Chaisson RE. Natural history of opportunistic disease in an HIV-infected urban clinical cohort. *Ann Intern Med*. 1996;124:633–642.
67. Anonymous. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. Collaborative Group on AIDS Incubation and HIV Survival including the CASCADE EU Concerted Action. Concerted Action on SeroConversion to AIDS and Death in Europe. *Lancet*. 2000;355:1131–1137.
73. Lawn SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect Dis*. 2005;5:361–373.
75. Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS*. 1998;12:F51–F58.
93. Sulkowski MS, Chaisson RE, Karp CL, et al. The effect of acute infectious illnesses on plasma human immunodeficiency virus (HIV) type 1 load and the expression of serologic markers of immune activation among HIV-infected adults. *J Infect Dis*. 1998;178:1642–1648.
95. Fischl MA, Richman DD, Grieco MH, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. *N Engl J Med*. 1987;317:185–191.
104. Hammer SM, Katzenstein DA, Hughes MD, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. AIDS Clinical Trials Group Study 175 Study Team. *N Engl J Med*. 1996;335:1081–1090.
105. Pierce M, Crampton S, Henry D, et al. A randomized trial of clarithromycin as prophylaxis against disseminated *Mycobacterium avium* complex infection in patients with advanced acquired immunodeficiency syndrome. *N Engl J Med*. 1996;335:384–391.
106. Volberding PA, Lagakos SW, Koch MA, et al. Zidovudine in asymptomatic human immunodeficiency virus infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. The AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases. *N Engl J Med*. 1990;322:941–949.
112. Hogg RS, O'Shaughnessy MV, Gataric N, et al. Decline in deaths from AIDS due to new antiretrovirals. *Lancet*. 1997;349:1294.
113. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet*. 1998;352:1725–1730.
114. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338:853–860.
118. Coetzee D, Hildebrand K, Boulle A, et al. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS*. 2004;18:887–895.
121. Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996-2006: collaborative analysis of 13 HIV cohort studies. *Clin Infect Dis*. 2010;50:1387–1396.
131. Rodriguez-Guardado A, Maradona JA, Carton JA, et al. *Pneumocystis carinii* prophylaxis can be discontinued after CD4+ cell recovery over 200 x 10(6)/l. *AIDS*. 1998;12:2355–2356.
132. Schneider MM, Borleffs JC, Stolk RP, et al. Discontinuation of prophylaxis for *Pneumocystis carinii* pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. *Lancet*. 1999;353:201–203.
133. Martinez E, Miro JM, Gonzalez J, et al. Withdrawal of *Mycobacterium avium* complex suppressive therapy in HIV-1-infected patients on highly active antiretroviral therapy. *AIDS*. 1999;13:147–148.
134. Tural C, Romeu J, Sirera G, et al. Long-lasting remission of cytomegalovirus retinitis without maintenance therapy in human immunodeficiency virus-infected patients. *J Infect Dis*. 1998;177:1080–1083.
135. Cooper DA, Gold J, Maclean P, et al. Acute AIDS retrovirus infection. Definition of a clinical illness associated with seroconversion. *Lancet*. 1985;1:537–540.
136. Tindall B, Barker S, Donovan B, et al. Characterization of the acute clinical illness associated with human immunodeficiency virus infection. *Arch Intern Med*. 1988;148:945–949.
141. Anonymous. Needlestick transmission of HTLV-III from a patient infected in Africa. *Lancet*. 1984;2:1376–1377.
158. Fiebig EW, Wright DJ, Rawal BD, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. *AIDS*. 2003;17:1871–1879.
159. Ananworanich J, Fletcher JL, Pinyakorn S, et al. A novel acute HIV infection staging system based on 4th generation immunoassay. *Retrovirology*. 2013;10:56.
162. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Available at: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed August 14, 2018.
164. Finzi D, Hermankova M, Pierson T, et al. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. *Science*. 1997;278:1295–1300.
165. Persaud D, Gay H, Ziemniak C, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. *N Engl J Med*. 2013;369:1828–1835.
180. Serwadda D, Mugerwa RD, Sewankambo NK, et al. Slim disease: a new disease in Uganda and its association with HTLV-III infection. *Lancet*. 1985;2:849–852.
183. De Cock KM, Soro B, Coulibaly IM, et al. Tuberculosis and HIV infection in sub-Saharan Africa. *JAMA*. 1992;268:1581–1587.
192. Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. *Immunity*. 2013;39:633–645.
202. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS*. 2006;20:2165–2174.
252. Koehler JE, Quinn FD, Berger TG, et al. Isolation of *Rochalimaea* species from cutaneous and osseous lesions of bacillary angiomatosis. *N Engl J Med*. 1992;327:1625–1631.
253. Relman DA, Loutit JS, Schmidt TM, et al. The agent of bacillary angiomatosis. An approach to the identification of uncultured pathogens. *N Engl J Med*. 1990;323:1573–1580.
265. Sullivan RJ, Pantanowitz L, Casper C, et al. HIV/AIDS: epidemiology, pathophysiology, and treatment of Kaposi sarcoma-associated herpesvirus disease: Kaposi sarcoma, primary effusion lymphoma, and multicentric Castleman disease. *Clin Infect Dis*. 2008;47:1209–1215.
271. Boyd MA, Mocroft A, Ryom L, et al. Cardiovascular disease (CVD) and chronic kidney disease (CKD) event rates in HIV-positive persons at high predicted CVD and CKD risk: a prospective analysis of the D:A:D observational study. *PLoS Med*. 2017;14:e1002424.
275. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science*. 2010;329:841–845.
278. Cohen SD, Kopp JB, Kimmel PL. Kidney diseases associated with human immunodeficiency virus infection. *N Engl J Med*. 2018;378:1655–1656.
281. Lucas GM, Lau B, Atta MG, et al. Chronic kidney disease incidence, and progression to end-stage renal disease, in HIV-infected individuals: a tale of two races. *J Infect Dis*. 2008;197:1548–1557.
297. Gallant JE, Moore RD, Richman DD, et al. Incidence and natural history of cytomegalovirus disease in patients with advanced human immunodeficiency virus disease treated with zidovudine. The Zidovudine Epidemiology Study Group. *J Infect Dis*. 1992;166:1223–1227.
307. El-Sadr WM, Grund B, Neuhaus J, et al. Risk for opportunistic disease and death after reinitiating continuous antiretroviral therapy in patients with HIV previously receiving episodic therapy: a randomized trial. *Ann Intern Med*. 2008;149:289–299.
324. Altekruse SF, Shiels MS, Modur SP, et al. Cancer burden attributable to cigarette smoking among HIV-infected people in North America. *AIDS*. 2018;32:513–521.
325. Beachler DC, Abraham AG, Silverberg MJ, et al. Incidence and risk factors of HPV-related and HPV-unrelated head and neck squamous cell carcinoma in HIV-infected individuals. *Oral Oncol*. 2014;50:1169–1176.
326. Engels EA, Yanik EL, Wheeler W, et al. Cancer-attributable mortality among people with treated human immunodeficiency virus infection in North America. *Clin Infect Dis*. 2017;65:636–643.
332. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*. 2008;8:516–523.
346. Chung RT, Evans SR, Yang Y, et al. Immune recovery is associated with persistent rise in hepatitis C virus RNA, infrequent liver test flares, and is not impaired by hepatitis C virus in co-infected subjects. *AIDS*. 2002;16:1915–1923.
358. Jaffe HW, De Stavola BL, Carpenter LM, et al. Immune reconstitution and risk of Kaposi sarcoma and non-Hodgkin lymphoma in HIV-infected adults. *AIDS*. 2011;25:1395–1403.

References

1. Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS ONE*. 2013;8:e81355.
2. Anonymous. Kaposi's sarcoma and *Pneumocystis* pneumonia among homosexual men–New York City and California. *MMWR Morb Mortal Wkly Rep*. 1981;30:305–308.
3. Anonymous. Opportunistic infections and Kaposi's sarcoma among Haitians in the United States. *MMWR Morb Mortal Wkly Rep*. 1982;31:353–354, 360–361.
4. Masur H, Michelis MA, Greene JB, et al. An outbreak of community-acquired *Pneumocystis carinii* pneumonia: initial manifestation of cellular immune dysfunction. *N Engl J Med*. 1981;305:1431–1438.
5. Follansbee SE, Busch DF, Wofsy CB, et al. An outbreak of *Pneumocystis carinii* pneumonia in homosexual men. *Ann Intern Med*. 1982;96(6 Pt 1):705–713.
6. Gottlieb MS, Schanker HM, Fan PT, et al. *Pneumocystis* pneumonia—Los Angeles. *MMWR Morb Mortal Wkly Rep*. 1981;30:250–252.
7. Siegal FP, Lopez C, Hammer GS, et al. Severe acquired immunodeficiency in male homosexuals, manifested by chronic perianal ulcerative herpes simplex lesions. *N Engl J Med*. 1981;305:1439–1444.
8. Poon MC, Landay A, Alexander J, et al. Update on acquired immune deficiency syndrome (AIDS) among patients with hemophilia A. *MMWR Morb Mortal Wkly Rep*. 1982;31:644–646.
9. Pape JW, Liautaud B, Thomas F, et al. The acquired immunodeficiency syndrome in Haiti. *Ann Intern Med*. 1985;103:674–678.
10. Pape JW, Liautaud B, Thomas F, et al. Characteristics of the acquired immunodeficiency syndrome (AIDS) in Haiti. *N Engl J Med*. 1983;309:945–950.
11. Ehrenkranz NJ, Rubini J, Horsburgh CR, et al. *Pneumocystis carinii* pneumonia among persons with hemophilia A. *MMWR Morb Mortal Wkly Rep*. 1982;31:365–367.
12. Centers for Disease Control and Prevention. Update on acquired immune deficiency syndrome (AIDS)–United States. *MMWR Morb Mortal Wkly Rep*. 1982;31: 507–508.
13. Ammann A, Cowan M, Wara D, et al. Possible transfusion-associated acquired immune deficiency syndrome (AIDS)–California. *MMWR Morb Mortal Wkly Rep*. 1982;31:652–654.
14. Malebranche R, Arnoux E, Guerin JM, et al. Acquired immunodeficiency syndrome with severe gastrointestinal manifestations in Haiti. *Lancet*. 1983;2:873–878.
15. Abrams DI, Lewis BJ, Beckstead JH, et al. Persistent diffuse lymphadenopathy in homosexual men: endpoint or prodrome? *Ann Intern Med*. 1984;100:801–808.
16. Abrams DI, Volberding PA, Linker CA. Immune thrombocytopenic purpura in homosexual men: clinical manifestations and treatment results. *Blood*. 1983; 62(suppl):108a.
17. Metroka CE, Cunningham-Rundles S, Pollack MS, et al. Generalized lymphadenopathy in homosexual men. *Ann Intern Med*. 1983;99:585–591.
18. Walsh CM, Nardi MA, Karpatkin S. On the mechanism of thrombocytopenic purpura in sexually active homosexual men. *N Engl J Med*. 1984;311:635–639.
19. Abrams DI. AIDS-related conditions. In: Pinching AJ, ed. *AIDS and HIV Infection. Clin Immunol Allergy*. Vol. 6. Eastbourne, UK: WB Saunders Co.; 1986:581–599.
20. Harris C, Small CB, Klein RS, et al. Immunodeficiency in female sexual partners of men with the acquired immunodeficiency syndrome. *N Engl J Med*. 1983;308:1181–1184.
21. Barre-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). 1983. *Rev Invest Clin*. 2004;56:126–129.
22. Gallo RC, Salahuddin SZ, Popovic M, et al. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science*. 1984;224:500–503.
23. Levy JA, Hoffman AD, Kramer SM, et al. Isolation of lymphocytopathic retroviruses from San Francisco patients with AIDS. *Science*. 1984;225:840–842.
24. Havlir DV, Richman DD. Viral dynamics of HIV: implications for drug development and therapeutic strategies. *Ann Intern Med*. 1996;124:984–994.
25. Henrard DR, Phillips JF, Muenz LR, et al. Natural history of HIV-1 cell-free viremia. *JAMA*. 1995;274:554–558.
26. Phair J, Jacobson L, Detels R, et al. Acquired immune deficiency syndrome occurring within 5 years of infection with human immunodeficiency virus type-1: the Multicenter AIDS Cohort Study. *J Acquir Immune Defic Syndr*. 1992;5:490–496.
27. Sheppard HW, Lang W, Ascher MS, et al. The characterization of non-progressors: long-term HIV-1 infection with stable CD4+ T-cell levels. *AIDS*. 1993;7:1159–1166.
28. Pereyra F, Addo MM, Kaufmann DE, et al. Genetic and immunologic heterogeneity among persons who control HIV infection in the absence of therapy. *J Infect Dis*. 2008;197:563–571.
29. Chun TW, Shawn Justement J, Murray D, et al. Effect of antiretroviral therapy on HIV reservoirs in elite controllers. *J Infect Dis*. 2013;208:1443–1447.
30. Crowell TA, Gebo KA, Blankson JN, et al. Hospitalization rates and reasons among HIV Elite controllers and persons with medically controlled HIV infection. *J Infect Dis*. 2015;211:1692–1702.
31. Krishnan S, Wilson EM, Sheikh V, et al. Evidence for innate immune system activation in HIV type 1-infected elite controllers. *J Infect Dis*. 2014;209:931–939.
32. Bacchetti P, Moss AR. Incubation period of AIDS in San Francisco. *Nature*. 1989;338:251–253.
33. Alcabes P, Munoz A, Vlahov D, et al. Incubation period of human immunodeficiency virus. *Epidemiol Rev*. 1993;15:303–318.
34. Bacchetti P, Osmond D, Chaisson RE, et al. Survival patterns of the first 500 patients with AIDS in San Francisco. *J Infect Dis*. 1988;157:1044–1047.
35. Rothenberg R, Woelfel M, Stoneburner R, et al. Survival with the acquired immunodeficiency syndrome. Experience with 5833 cases in New York City. *N Engl J Med*. 1987;317:1297–1302.
36. Mocroft A, Johnson MA, Phillips AN. Factors affecting survival in patients with the acquired immunodeficiency syndrome. *AIDS*. 1996;10:1057–1065.
37. Osmond D, Charlebois E, Lang W, et al. Changes in AIDS survival time in two San Francisco cohorts of homosexual men, 1983 to 1993. *JAMA*. 1994;271:1083–1087.
38. Saravolatz L, Neaton JD, Sacks L, et al. CD4+ T lymphocyte counts and patterns of mortality among patients infected with human immunodeficiency virus who were enrolled in community programs for clinical research on AIDS. *Clin Infect Dis*. 1996;22:513–520.
39. Fahey JL, Taylor JM, Detels R, et al. The prognostic value of cellular and serologic markers in infection with human immunodeficiency virus type 1. *N Engl J Med*. 1990;322:166–172.
40. Goedert JJ, Biggar RJ, Melbye M, et al. Effect of T4 count and cofactors on the incidence of AIDS in homosexual men infected with human immunodeficiency virus. *JAMA*. 1987;257:331–334.
41. Moss AR, Bacchetti P, Osmond D, et al. Seropositivity for HIV and the development of AIDS or AIDS related condition: three year follow up of the San Francisco General Hospital cohort. *Br Med J (Clin Res Ed)*. 1988;296:745–750.
42. Munoz A, Schrager LK, Bacellar H, et al. Trends in the incidence of outcomes defining acquired immunodeficiency syndrome (AIDS) in the Multicenter AIDS Cohort Study: 1985-1991. *Am J Epidemiol*. 1993;137:423–438.
43. Polk BF, Fox R, Brookmeyer R, et al. Predictors of the acquired immunodeficiency syndrome developing in a cohort of seropositive homosexual men. *N Engl J Med*. 1987;316:61–66.
44. Coombs RW, Welles SL, Hooper C, et al. Association of plasma human immunodeficiency virus type 1 RNA level with risk of clinical progression in patients with advanced infection. AIDS Clinical Trials Group (ACTG) 116B/117 Study Team. ACTG Virology Committee Resistance and HIV-1 RNA Working Groups. *J Infect Dis*. 1996;174: 704–712.
45. Lefrere JJ, Roudot-Thoraval F, Mariotti M, et al. The risk of disease progression is determined during the first year of human immunodeficiency virus type 1 infection. *J Infect Dis*. 1998;177:1541–1548.
46. Mellors JW, Kingsley LA, Rinaldo CR Jr, et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. *Ann Intern Med*. 1995;122:573–579.
47. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med*. 1997;126:946–954.
48. Mellors JW, Rinaldo CR Jr, Gupta P, et al. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science*. 1996;272:1167–1170.
49. O'Brien TR, Blattner WA, Waters D, et al. Serum HIV-1 RNA levels and time to development of AIDS in the Multicenter Hemophilia Cohort Study. *JAMA*. 1996;276:105–110.
50. Staszewski S, DeMasi R, Hill AM, et al. HIV-1 RNA, CD4 cell count and the risk of progression to AIDS and death during treatment with HIV-1 reverse transcriptase inhibitors. *AIDS*. 1998;12:1991–1997.
51. Welles SL, Jackson JB, Yen-Lieberman B, et al. Prognostic value of plasma human immunodeficiency virus type 1 (HIV-1) RNA levels in patients with advanced HIV-1 disease and with little or no prior zidovudine therapy. AIDS Clinical Trials Group Protocol 116A/116B/117 Team. *J Infect Dis*. 1996;174:696–703.
52. Yerly S, Perneger TV, Hirschel B, et al. A critical assessment of the prognostic value of HIV-1 RNA levels and CD4+ cell counts in HIV-infected patients. The Swiss HIV Cohort Study. *Arch Intern Med*. 1998;158:247–252.
53. Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. 2015;373:795–807.
54. Ehmann WC, Eyster ME, Wilson SE, et al. Relationship of CD4 lymphocyte counts to survival in a cohort of hemophiliacs infected with HIV. Multicenter Hemophilia Cohort Study. *J Acquir Immune Defic Syndr*. 1994;7:1095–1098.
55. Eyster ME, Gail MH, Ballard JO, et al. Natural history of human immunodeficiency virus infections in hemophiliacs: effects of T-cell subsets, platelet counts, and age. *Ann Intern Med*. 1987;107:1–6.
56. Mariotto AB, Mariotti S, Pezzotti P, et al. Estimation of the acquired immunodeficiency syndrome incubation period in intravenous drug users: a comparison with male homosexuals. *Am J Epidemiol*. 1992;135:428–437.
57. Moore RD, Chaisson RE. Natural history of opportunistic disease in an HIV-infected urban clinical cohort. *Ann Intern Med*. 1996;124:633–642.
58. Operskalski EA, Stram DO, Lee H, et al. Human immunodeficiency virus type 1 infection: relationship of risk group and age to rate of progression to AIDS. Transfusion Safety Study Group. *J Infect Dis*. 1995;172:648–655.
59. Pedersen C, Katzenstein T, Nielsen C, et al. Prognostic value of serum HIV-RNA levels at virologic steady state after seroconversion: relation to CD4 cell count and clinical course of primary infection. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997;16:93–99.
60. Gandhi M, Bacchetti P, Miotti P, et al. Does patient sex affect human immunodeficiency virus levels? *Clin Infect Dis*. 2002;35:313–322.
61. Hubert JB, Rouzioux C, Boufassa F, et al Gender, disease progression and response to HAART [Abstract 1448]. Presented at the 14th International AIDS Conference. Barcelona, Spain, July 7-12. 2002.
62. Sterling TR, Lyles CM, Vlahov D, et al. Sex differences in longitudinal human immunodeficiency virus type 1 RNA levels among seroconverters. *J Infect Dis*. 1999;180:666–672.
63. Anastos K, Kalish LA, Hessol N, et al. The relative value of CD4 cell count and quantitative HIV-1 RNA in predicting survival in HIV-1-infected women: results of the women's interagency HIV study. *AIDS*. 1999;13:1717–1726.
64. Sterling TR, Vlahov D, Astemborski J, et al. Initial plasma HIV-1 RNA levels and progression to AIDS in women and men. *N Engl J Med*. 2001;344:720–725.
65. Chaisson RE, Keruly JC, Moore RD. Race, sex, drug use, and progression of human immunodeficiency virus disease. *N Engl J Med*. 1995;333:751–756.
66. Melnick SL, Sherer R, Louis TA, et al. Survival and disease progression according to gender of patients with HIV infection. The Terry Beirn Community Programs for Clinical Research on AIDS. *JAMA*. 1994;272:1915–1921.
67. Anonymous. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. Collaborative Group on AIDS Incubation and HIV Survival including the CASCADE EU Concerted Action. Concerted Action on SeroConversion to AIDS and Death in Europe. *Lancet*. 2000;355:1131–1137.
68. Brown AE, Malone JD, Zhou SY, et al. Human immunodeficiency virus RNA levels in US adults: a comparison based upon race and ethnicity. *J Infect Dis*. 1997;176:794–797.
69. Pezzotti P, Galai N, Vlahov D, et al. Direct comparison of time to AIDS and infectious disease death between HIV seroconverter injection drug users in Italy and the United States: results from the ALIVE and ISS studies. AIDS Link to Intravenous Experiences. Italian Seroconversion Study. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1999;20:275–282.
70. Boyle DS, Hawkins KR, Steele MS, et al. Emerging technologies for point-of-care CD4 T-lymphocyte counting. *Trends Biotechnol*. 2012;30:45–54.
71. Selik RM, Buehler JW, Karon JM, et al. Impact of the 1987 revision of the case definition of acquired immune deficiency syndrome in the United States. *J Acquir Immune Defic Syndr*. 1990;3:73–82.
72. Lohse N, Hansen AB, Pedersen G, et al. Survival of persons with and without HIV infection in Denmark, 1995-2005. *Ann Intern Med*. 2007;146:87–95.

73. Lawn SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect Dis*. 2005;5:361–373.
74. Narita M, Ashkin D, Hollender ES, et al. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med*. 1998;158:157–161.
75. Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS*. 1998;12:F51–F58.
76. Kotler DP. HIV and antiretroviral therapy: lipid abnormalities and associated cardiovascular risk in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2008;49(suppl 2):S79–S85.
77. World Health Organization. Global tuberculosis report 2017. http://www.who.int/tb/publications/global_report/en/. Accessed February 15, 2018.
78. Corbett EL, Steketee RW, ter Kuile FO, et al. HIV-1/AIDS and the control of other infectious diseases in Africa. *Lancet*. 2002;359:2177–2187.
79. Grant AD, Sidibe K, Domoua K, et al. Spectrum of disease among HIV-infected adults hospitalised in a respiratory medicine unit in Abidjan, Cote d'Ivoire. *Int J Tuberc Lung Dis*. 1998;2:926–934.
80. Gallant JE, Moore RD, Chaisson RE. Prophylaxis for opportunistic infections in patients with HIV infection. *Ann Intern Med*. 1994;120:932–944.
81. Moore RD, Keruly J, Richman DD, et al. Natural history of advanced HIV disease in patients treated with zidovudine. The Zidovudine Epidemiology Study Group. *AIDS*. 1992;6:671–677.
82. Forrest DM, Seminari E, Hogg RS, et al. The incidence and spectrum of AIDS-defining illnesses in persons treated with antiretroviral drugs. *Clin Infect Dis*. 1998;27:1379–1385.
83. Corbett EL, Churchyard GJ, Charalambos S, et al. Morbidity and mortality in South African gold miners: impact of untreated disease due to human immunodeficiency virus. *Clin Infect Dis*. 2002;34:1251–1258.
84. Carne CA, Weller IV, Loveday C, et al. From persistent generalised lymphadenopathy to AIDS: who will progress? *Br Med J (Clin Res Ed)*. 1987;294:868–869.
85. Greenspan D, Greenspan JS, Hearst NG, et al. Relation of oral hairy leukoplakia to infection with the human immunodeficiency virus and the risk of developing AIDS. *J Infect Dis*. 1987;155:475–481.
86. Murray HW, Godbold JH, Jurica KB, et al. Progression to AIDS in patients with lymphadenopathy or AIDS-related complex: reappraisal of risk and predictive factors. *Am J Med*. 1989;86:533–538.
87. Chaisson RE, Gallant JE, Keruly JC, et al. Impact of opportunistic disease on survival in patients with HIV infection. *AIDS*. 1998;12:29–33.
88. Petruckevitch A, Del Amo J, Phillips AN, et al. Disease progression and survival following specific AIDS-defining conditions: a retrospective cohort study of 2048 HIV-infected persons in London. *AIDS*. 1998;12:1007–1013.
89. Pettit AC, Giganti MJ, Ingle SM, et al. Increased non-AIDS mortality among persons with AIDS-defining events after antiretroviral therapy initiation. *J Int AIDS Soc*. 2018;21.
90. Bush CE, Donovan RM, Markowitz NP, et al. A study of HIV RNA viral load in AIDS patients with bacterial pneumonia. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1996;13:23–26.
91. Donovan RM, Bush CE, Markowitz NP, et al. Changes in virus load markers during AIDS-associated opportunistic diseases in human immunodeficiency virus-infected persons. *J Infect Dis*. 1996;174:401–403.
92. Goletti D, Weissman D, Jackson RW, et al. Effect of *Mycobacterium tuberculosis* on HIV replication. Role of immune activation. *J Immunol*. 1996;157:1271–1278.
93. Sulkowski MS, Chaisson RE, Karp CL, et al. The effect of acute infectious illnesses on plasma human immunodeficiency virus (HIV) type 1 load and the expression of serologic markers of immune activation among HIV-infected adults. *J Infect Dis*. 1998;178:1642–1648.
94. Chaisson RE, Keruly J, Richman DD, et al. *Pneumocystis* prophylaxis and survival in patients with advanced human immunodeficiency virus infection treated with zidovudine. The Zidovudine Epidemiology Group. *Arch Intern Med*. 1992;152:2009–2013.
95. Fischl MA, Richman DD, Grieco MH, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. *N Engl J Med*. 1987;317:185–191.
96. Harris JE. Improved short-term survival of AIDS patients initially diagnosed with *Pneumocystis carinii* pneumonia, 1984 through 1987. *JAMA*. 1990;263:397–401.
97. Lemp GF, Payne SF, Neal D, et al. Survival trends for patients with AIDS. *JAMA*. 1990;263:402–406.
98. Moore RD, Hidalgo J, Sugland BW, et al. Zidovudine and the natural history of the acquired immunodeficiency syndrome. *N Engl J Med*. 1991;324:1412–1416.
99. Delta Coordinating Committee. Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet*. 1996;348:283–291.
100. Enger C, Graham N, Peng Y, et al. Survival from early, intermediate, and late stages of HIV infection. *JAMA*. 1996;275:1329–1334.
101. Fischl MA, Dickinson GM, La Voie L. Safety and efficacy of sulfamethoxazole and trimethoprim chemoprophylaxis for *Pneumocystis carinii* pneumonia in AIDS. *JAMA*. 1988;259:1185–1189.
102. Graham NM, Zeger SL, Park LP, et al. Effect of zidovudine and *Pneumocystis carinii* pneumonia prophylaxis on progression of HIV-1 infection to AIDS. The Multicenter AIDS Cohort Study. *Lancet*. 1991;338:265–269.
103. Graham NM, Zeger SL, Park LP, et al. The effects on survival of early treatment of human immunodeficiency virus infection. *N Engl J Med*. 1992;326:1037–1042.
104. Hammer SM, Katzenstein DA, Hughes MD, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. AIDS clinical Trials Group Study 175 Study Team. *N Engl J Med*. 1996;335:1081–1090.
105. Pierce M, Crampton S, Henry D, et al. A randomized trial of clarithromycin as prophylaxis against disseminated *Mycobacterium avium* complex infection in patients with advanced acquired immunodeficiency syndrome. *N Engl J Med*. 1996;335:384–391.
106. Volberding PA, Lagakos SW, Koch MA, et al. Zidovudine in asymptomatic human immunodeficiency virus infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. The AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases. *N Engl J Med*. 1990;322:941–949.
107. Chene G, Sterne JA, May M, et al. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. *Lancet*. 2003;362:679–686.
108. Delta Coordinating Committee and Delta Virology Committee. HIV-1 RNA response to antiretroviral treatment in 1280 participants in the Delta Trial: an extended virology study. *AIDS*. 1999;13:57–65.
109. O'Brien WA, Hartigan PM, Martin D, et al. Changes in plasma HIV-1 RNA and CD4+ lymphocyte counts and the risk of progression to AIDS. Veterans Affairs Cooperative Study Group on AIDS. *N Engl J Med*. 1996;334:426–431.
110. Brodt HR, Kamps BS, Gute P, et al. Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy. *AIDS*. 1997;11:1731–1738.
111. Centers for Disease Control and Prevention. Update: trends in AIDS incidence–United States, 1996. *MMWR Morb Mortal Wkly Rep*. 1997;46:861–867.
112. Hogg RS, O'Shaughnessy MV, Gataric N, et al. Decline in deaths from AIDS due to new antiretrovirals. *Lancet*. 1997;349:1294.
113. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet*. 1998;352:1725–1730.
114. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338:853–860.
115. Torres RA, Barr M. Impact of combination therapy for HIV infection on inpatient census. *N Engl J Med*. 1997;336:1531–1532.
116. Centers for Disease Control and Prevention. HIV in the United States: At a glance. https://www.cdc.gov/hiv/statistics/overview/ataglance.html. Accessed December 28, 2017.
117. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet*. 2003;362:22–29.
118. Coetzee D, Hildebrand K, Boulle A, et al. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS*. 2004;18:887–895.
119. Joint United Nations Programme on HIV/AIDS. Ending AIDS. Progress towards the 90-90-90 targets. http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf. Accessed July 11, 2018.
120. Severe P, Leger P, Charles M, et al. Antiretroviral therapy in a thousand patients with AIDS in Haiti. *N Engl J Med*. 2005;353:2325–2334.
121. Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996-2006: collaborative analysis of 13 HIV cohort studies. *Clin Infect Dis*. 2010;50:1387–1396.
122. Smith CJ, Ryom L, Weber R, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet*. 2014;384:241–248.
123. Sepkowitz KA. Effect of HAART on natural history of AIDS-related opportunistic disorders. *Lancet*. 1998;351:228–230.
124. Race EM, Adelson-Mitty J, Kriegel GR, et al. Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. *Lancet*. 1998;351:252–255.
125. Lawn SD, Wilkinson RJ, Lipman MC, et al. Immune reconstitution and "unmasking" of tuberculosis during antiretroviral therapy. *Am J Respir Crit Care Med*. 2008;177:680–685.
126. Manabe YC, Breen R, Perti T, et al. Unmasked tuberculosis and tuberculosis immune reconstitution inflammatory disease: a disease spectrum after initiation of antiretroviral therapy. *J Infect Dis*. 2009;199:437–444.
127. Autran B, Carcelain G, Li TS, et al. Positive effects of combined antiretroviral therapy on CD4+ T cell homeostasis and function in advanced HIV disease. *Science*. 1997;277:112–116.
128. Bisset LR, Cone RW, Huber W, et al. Highly active antiretroviral therapy during early HIV infection reverses T-cell activation and maturation abnormalities. Swiss HIV Cohort Study. *AIDS*. 1998;12:2115–2123.
129. Pakker NG, Kroon ED, Roos MT, et al. Immune restoration does not invariably occur following long-term HIV-1 suppression during antiretroviral therapy. INCAS Study Group. *AIDS*. 1999;13:203–212.
130. Powderly WG, Landay A, Lederman MM. Recovery of the immune system with antiretroviral therapy: the end of opportunism? *JAMA*. 1998;280:72–77.
131. Rodriguez-Guardado A, Maradona JA, Carton JA, et al. *Pneumocystis carinii* prophylaxis can be discontinued after CD4+ cell recovery over 200 x 10(6)/l. *AIDS*. 1998;12:2355–2356.
132. Schneider MM, Borleffs JC, Stolk RP, et al. Discontinuation of prophylaxis for *Pneumocystis carinii* pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. *Lancet*. 1999;353:201–203.
133. Martinez E, Miro JM, Gonzalez J, et al. Withdrawal of *Mycobacterium avium* complex suppressive therapy in HIV-1-infected patients on highly active antiretroviral therapy. *AIDS*. 1999;13:147–148.
134. Tural C, Romeu J, Sirera G, et al. Long-lasting remission of cytomegalovirus retinitis without maintenance therapy in human immunodeficiency virus-infected patients. *J Infect Dis*. 1998;177:1080–1083.
135. Cooper DA, Gold J, Maclean P, et al. Acute AIDS retrovirus infection. Definition of a clinical illness associated with seroconversion. *Lancet*. 1985;1:537–540.
136. Tindall B, Barker S, Donovan B, et al. Characterization of the acute clinical illness associated with human immunodeficiency virus infection. *Arch Intern Med*. 1988;148:945–949.
137. Fox R, Eldred LJ, Fuchs EJ, et al. Clinical manifestations of acute infection with human immunodeficiency virus in a cohort of gay men. *AIDS*. 1987;1:35–38.
138. Jaffe HW, Hardy AM, Morgan WM, et al. The acquired immunodeficiency syndrome in gay men. *Ann Intern Med*. 1985;103:662–664.
139. Moss AR, Osmond D, Bacchetti P, et al. Risk factors for AIDS and HIV seropositivity in homosexual men. *Am J Epidemiol*. 1987;125:1035–1047.
140. Vanhems P, Routy JP, Hirschel B, et al. Clinical features of acute retroviral syndrome differ by route of infection but not by gender and age. *J Acquir Immune Defic Syndr*. 2002;31:318–321.
141. Anonymous. Needlestick transmission of HTLV-III from a patient infected in Africa. *Lancet*. 1984;2:1376–1377.
142. Tokars JI, Marcus R, Culver DH, et al. Surveillance of HIV infection and zidovudine use among health care workers after occupational exposure to HIV-infected blood. The CDC Cooperative Needlestick Surveillance Group. *Ann Intern Med*. 1993;118:913–919.
143. Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. *N Engl J Med*. 1998;339:33–39.
144. Quinn TC. Acute primary HIV infection. *JAMA*. 1997;278:58–62.
145. Zetola NM, Pilcher CD. Diagnosis and management of acute HIV infection. *Infect Dis Clin North Am*. 2007;21:19–48, vii.

146. Niu MT, Stein DS, Schnittman SM. Primary human immunodeficiency virus type 1 infection: review of pathogenesis and early treatment intervention in humans and animal retrovirus infections. *J Infect Dis*. 1993;168:1490–1501.
147. Carne CA, Tedder RS, Smith A, et al. Acute encephalopathy coincident with seroconversion for anti-HTLV-III. *Lancet*. 1985;2:1206–1208.
148. Clark SJ, Saag MS, Decker WD, et al. High titers of cytopathic virus in plasma of patients with symptomatic primary HIV-1 infection. *N Engl J Med*. 1991;324: 954–960.
149. Cooper DA, Imrie AA, Penny R. Antibody response to human immunodeficiency virus after primary infection. *J Infect Dis*. 1987;155:1113–1118.
150. Denning DW, Anderson J, Rudge P, et al. Acute myelopathy associated with primary infection with human immunodeficiency virus. *Br Med J (Clin Res Ed)*. 1987;294:143–144.
151. Elder G, Dalakas M, Pezeshkpour G, et al. Ataxic neuropathy due to ganglioneuronitis after probable acute human immunodeficiency virus infection. *Lancet*. 1986;2:1275–1276.
152. Ho DD, Sarngadharan MG, Resnick L, et al. Primary human T-lymphotropic virus type III infection. *Ann Intern Med*. 1985;103(6 Pt 1):880–883.
153. Rustin MH, Ridley CM, Smith MD, et al. The acute exanthem associated with seroconversion to human T-cell lymphotropic virus III in a homosexual man. *J Infect*. 1986;12:161–163.
154. Balslev E, Thomsen HK, Weismann K. Histopathology of acute human immunodeficiency virus exanthema. *J Clin Pathol*. 1990;43:201–202.
155. del Saz SV, Sued O, Falco V, et al. Acute meningoencephalitis due to human immunodeficiency virus type 1 infection in 13 patients: clinical description and follow-up. *J Neurovirol*. 2008;14:474–479.
156. Cooper DA, Tindall B, Wilson EJ, et al. Characterization of T lymphocyte responses during primary infection with human immunodeficiency virus. *J Infect Dis*. 1988;157: 889–896.
157. Goudsmit J, de Wolf F, Paul DA, et al. Expression of human immunodeficiency virus antigen (HIV-Ag) in serum and cerebrospinal fluid during acute and chronic infection. *Lancet*. 1986;2:177–180.
158. Fiebig EW, Wright DJ, Rawal BD, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. *AIDS*. 2003;17:1871–1879.
159. Ananworanich J, Fletcher JL, Pinyakorn S, et al. A novel acute HIV infection staging system based on 4th generation immunoassay. *Retrovirology*. 2013;10:56.
160. Henrard DR, Phillips J, Windsor I, et al. Detection of human immunodeficiency virus type 1 p24 antigen and plasma RNA: relevance to indeterminate serologic tests. *Transfusion*. 1994;34:376–380.
161. Crowell TA, Colby DJ, Pinyakorn S, et al. Acute retroviral syndrome is associated with high viral burden, CD4 depletion, and immune activation in systemic and tissue compartments. *Clin Infect Dis*. 2018;66:1540–1549.
162. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Available at: https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Accessed August 14, 2018.
163. Rosenberg ES, Billingsley JM, Caliendo AM, et al. Vigorous HIV-1-specific CD4+ T cell responses associated with control of viremia. *Science*. 1997;278:1447–1450.
164. Finzi D, Hermankova M, Pierson T, et al. Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy. *Science*. 1997;278:1295–1300.
165. Persaud D, Gay H, Ziemniak C, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. *N Engl J Med*. 2013;369:1828–1835.
166. Luzuriaga K, Gay H, Ziemniak C, et al. Viremic relapse after HIV-1 remission in a perinatally infected child. *N Engl J Med*. 2015;372:786–788.
167. Koenig SP, Dorvil N, Devieux JG, et al. Same-day HIV testing with initiation of antiretroviral therapy versus standard care for persons living with HIV: a randomized unblinded trial. *PLoS Med*. 2017;14:e1002357.
168. Rosen S, Maskew M, Fox MP, et al. Initiating antiretroviral therapy for HIV at a patient's first clinic visit: the RapIT randomized controlled trial. *PLoS Med*. 2016;13:e1002015.
169. United States Department of Helath and Human Services. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Available at: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0. Accessed February 15, 2018.
170. Boritz EA, Darko S, Swaszek L, et al. Multiple origins of virus persistence during natural control of HIV infection. *Cell*. 2016;166:1004–1015.
171. Brenchley JM, Schacker TW, Ruff LE, et al. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. *J Exp Med*. 2004;200:749–759.
172. Osmond D, Chaisson R, Moss A, et al. Lymphadenopathy in asymptomatic patients seropositive for HIV. *N Engl J Med*. 1987;317:246.
173. Bottles K, McPhaul LW, Volberding P. Fine-needle aspiration biopsy of patients with acquired immunodeficiency syndrome (AIDS): experience in an outpatient clinic. *Ann Intern Med*. 1988;108:42–45.
174. Oksenhendler E, Duarte M, Soulier J, et al. Multicentric Castleman's disease in HIV infection: a clinical and pathological study of 20 patients. *AIDS*. 1996;10:61–67.
175. Stebbing J, Pantanowitz L, Dayyani F, et al. HIV-associated multicentric Castleman's disease. *Am J Hematol*. 2008;83:498–503.
176. Grandadam M, Dupin N, Calvez V, et al. Exacerbations of clinical symptoms in human immunodeficiency virus type 1-infected patients with multicentric Castleman's disease are associated with a high increase in Kaposi's sarcoma herpesvirus DNA load in peripheral blood mononuclear cells. *J Infect Dis*. 1997;175:1198–1201.
177. Hengge UR, Ruzicka T, Tyring SK, et al. Update on Kaposi's sarcoma and other HHV8 associated diseases. Part 2: pathogenesis, Castleman's disease, and pleural effusion lymphoma. *Lancet Infect Dis*. 2002;2:344–352.
178. Bower M, Powles T, Williams S, et al. Brief communication: rituximab in HIV-associated multicentric Castleman disease. *Ann Intern Med*. 2007;147:836–839.
179. Lurain K, Yarchoan R, Uldrick TS. Treatment of Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. *Hematol Oncol Clin North Am*. 2018;32:75–88.
180. Serwadda D, Mugerwa RD, Sewankambo NK, et al. Slim disease: a new disease in Uganda and its association with HTLV-III infection. *Lancet*. 1985;2:849–852.
181. Chintu C, Dupont HL, Kaile T, et al. Human immunodeficiency virus-associated diarrhea and wasting in Zambia: selected risk factors and clinical associations. *Am J Trop Med Hyg*. 1998;59:38–41.
182. Sewankambo N, Mugerwa RD, Goodgame R, et al. Enteropathic AIDS in Uganda. An endoscopic, histological and microbiological study. *AIDS*. 1987;1:9–13.
183. De Cock KM, Soro B, Coulibaly IM, et al. Tuberculosis and HIV infection in sub-Saharan Africa. *JAMA*. 1992;268:1581–1587.
184. Lucas SB, De Cock KM, Hounnou A, et al. Contribution of tuberculosis to slim disease in Africa. *BMJ*. 1994;308:1531–1533.
185. Sepkowitz KA, Telzak EE, Carrow M, et al. Fever among outpatients with advanced human immunodeficiency virus infection. *Arch Intern Med*. 1993;153:1909–1912.
186. Angelino AF, Treisman GJ. Management of psychiatric disorders in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 2001;33:847–856.
187. Chuang HT, Devins GM, Hunsley J, et al. Psychosocial distress and well-being among gay and bisexual men with human immunodeficiency virus infection. *Am J Psychiatry*. 1989;146:876–880.
188. Miller EN, Selnes OA, McArthur JC, et al. Neuropsychological performance in HIV-1-infected homosexual men: the Multicenter AIDS Cohort Study (MACS). *Neurology*. 1990;40:197–203.
189. Dobs AS, Dempsey MA, Ladenson PW, et al. Endocrine disorders in men infected with human immunodeficiency virus. *Am J Med*. 1988;84(3 Pt 2):611–616.
190. Grinspoon SK, Bilezikian JP. HIV disease and the endocrine system. *N Engl J Med*. 1992;327:1360–1365.
191. Grunfeld C, Feingold KR. Metabolic disturbances and wasting in the acquired immunodeficiency syndrome. *N Engl J Med*. 1992;327:329–337.
192. Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. *Immunity*. 2013;39:633–645.
193. Mylonakis E, Koutkia P, Grinspoon S. Diagnosis and treatment of androgen deficiency in human immunodeficiency virus-infected men and women. *Clin Infect Dis*. 2001;33:857–864.
194. Sattler F, Briggs W, Antonipillai I, et al. Low dihydrotestosterone and weight loss in the AIDS wasting syndrome. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;18:246–251.
195. Gonzalez-Cadavid NF, Taylor WE, Yarasheski K, et al. Organization of the human myostatin gene and expression in healthy men and HIV-infected men with muscle wasting. *Proc Natl Acad Sci USA*. 1998;95: 14938–14943.
196. Beaugerie L, Carbonnel F, Carrat F, et al. Factors of weight loss in patients with HIV and chronic diarrhea. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;19:34–39.
197. Grinspoon S, Mulligan K. Weight loss and wasting in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 2003;36(suppl 2):S69–S78.
198. Macallan DC, Noble C, Baldwin C, et al. Energy expenditure and wasting in human immunodeficiency virus infection. *N Engl J Med*. 1995;333:83–88.
199. Strawford A, Hellerstein M. The etiology of wasting in the human immunodeficiency virus and acquired immunodeficiency syndrome. *Semin Oncol*. 1998;25(2 suppl 6):76–81.
200. Kotler DP. Wasting syndrome: nutritional support in HIV infection. *AIDS Res Hum Retroviruses*. 1994;10:931–934.
201. Tang AM, Forrester J, Spiegelman D, et al. Weight loss and survival in HIV-positive patients in the era of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2002;31:230–236.
202. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS*. 2006;20:2165–2174.
203. McComsey GA, Tebas P, Shane E, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. *Clin Infect Dis*. 2010;51:937–946.
204. Wohl DA, McComsey G, Tebas P, et al. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clin Infect Dis*. 2006;43:645–653.
205. Fong PS, Flynn DM, Evans CD, et al. Integrase strand transfer inhibitor-associated diabetes mellitus: a case report. *Int J STD AIDS*. 2017;28:626–628.
206. Norwood J, Turner M, Bofill C, et al. Brief Report: weight gain in persons with HIV switched from efavirenz-based to integrase strand transfer inhibitor-based regimens. *J Acquir Immune Defic Syndr*. 2017;76:527–531.
207. Friis-Moller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007;356:1723–1735.
208. Elion RA, Althoff KN, Zhang J, et al. Recent abacavir use increases risk of type 1 and type 2 myocardial infarctions among adults with HIV. *J Acquir Immune Defic Syndr*. 2018;78:62–72.
209. Lake JE, Li X, Palella FJ Jr, et al. Metabolic health across the BMI spectrum in HIV-infected and HIV-uninfected men. *AIDS*. 2018;32:49–57.
210. Greenspan D, Greenspan JS. HIV-related oral disease. *Lancet*. 1996;348:729–733.
211. Reznik DA. Oral manifestations of HIV disease. *Top HIV Med*. 2005;13:143–148.
212. Weinert M, Grimes RM, Lynch DP. Oral manifestations of HIV infection. *Ann Intern Med*. 1996;125:485–496.
213. Feigal DW, Katz MH, Greenspan D, et al. The prevalence of oral lesions in HIV-infected homosexual and bisexual men: three San Francisco epidemiological cohorts. *AIDS*. 1991;5:519–525.
214. Klein RS, Harris CA, Small CB, et al. Oral candidiasis in high-risk patients as the initial manifestation of the acquired immunodeficiency syndrome. *N Engl J Med*. 1984;311:354–358.
215. Royce RA, Luckmann RS, Fusaro RE, et al. The natural history of HIV-1 infection: staging classifications of disease. *AIDS*. 1991;5:355–364.
216. Lifson AR, Hilton JF, Westenhouse JL, et al. Time from HIV seroconversion to oral candidiasis or hairy leukoplakia among homosexual and bisexual men enrolled in three prospective cohorts. *AIDS*. 1994;8:73–79.
217. Greenspan D, Greenspan JS, Conant M, et al. Oral "hairy" leucoplakia in male homosexuals: evidence of association with both papillomavirus and a herpes-group virus. *Lancet*. 1984;2:831–834.
218. Greenspan JS, Greenspan D, Lennette ET, et al. Replication of Epstein-Barr virus within the epithelial cells of oral "hairy" leukoplakia, an AIDS-associated lesion. *N Engl J Med*. 1985;313:1564–1571.
219. Rowland RW, Escobar MR, Friedman RB, et al. Painful gingivitis may be an early sign of infection with the human immunodeficiency virus. *Clin Infect Dis*. 1993;16:233–236.
220. MacPhail LA, Greenspan D, Greenspan JS. Recurrent aphthous ulcers in association with HIV infection. Diagnosis and treatment. *Oral Surg Oral Med Oral Pathol*. 1992;73:283–288.
221. Jacobson JM, Greenspan JS, Spritzler J, et al. Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency virus infection. National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group. *N Engl J Med*. 1997;336: 1487–1493.
222. Paterson DL, Georghiou PR, Allworth AM, et al. Thalidomide as treatment of refractory aphthous

ulceration related to human immunodeficiency virus infection. *Clin Infect Dis*. 1995;20:250–254.

223. Ramirez-Amador VA, Esquivel-Pedraza L, Ponce-de-Leon S, et al. Thalidomide as therapy for human immunodeficiency virus-related oral ulcers: a double-blind placebo-controlled clinical trial. *Clin Infect Dis*. 1999;28:892–894.
224. Craven DE, Duncan RA, Stram JR, et al. Response of lymphoepithelial parotid cysts to antiretroviral treatment in HIV-infected adults. *Ann Intern Med*. 1998;128:455–459.
225. Dalakas MC, Pezeshkpour GH, Gravell M, et al. Polymyositis associated with AIDS retrovirus. *JAMA*. 1986;256:2381–2383.
226. Kaye BR. Rheumatologic manifestations of infection with human immunodeficiency virus (HIV). *Ann Intern Med*. 1989;111:158–167.
227. Dalakas MC, Pezeshkpour GH. Neuromuscular diseases associated with human immunodeficiency virus infection. *Ann Neurol*. 1988;23(suppl):S38–S48.
228. Johnson RW, Williams FM, Kazi S, et al. Human immunodeficiency virus-associated polymyositis: a longitudinal study of outcome. *Arthritis Rheum*. 2003;49:172–178.
229. Dalakas MC, Illa I, Pezeshkpour GH, et al. Mitochondrial myopathy caused by long-term zidovudine therapy. *N Engl J Med*. 1990;322:1098–1105.
230. Margolis AM, Heverling H, Pham PA, et al. A review of the toxicity of HIV medications. *J Med Toxicol*. 2014;10:26–39.
231. Schwartzman WA, Lambertus MW, Kennedy CA, et al. Staphylococcal pyomyositis in patients infected by the human immunodeficiency virus. *Am J Med*. 1991;90:595–600.
232. Widrow CA, Kellie SM, Saltzman BR, et al. Pyomyositis in patients with the human immunodeficiency virus: an unusual form of disseminated bacterial infection. *Am J Med*. 1991;91:129–136.
233. Amorosa V, Tebas P. Bone disease and HIV infection. *Clin Infect Dis*. 2006;42:108–114.
234. Brown P, Crane L. Avascular necrosis of bone in patients with human immunodeficiency virus infection: report of 6 cases and review of the literature. *Clin Infect Dis*. 2001;32:1221–1226.
235. Miller KD, Masur H, Jones EC, et al. High prevalence of osteonecrosis of the femoral head in HIV-infected adults. *Ann Intern Med*. 2002;137:17–25.
236. Keruly JC, Chaisson RE, Moore RD. Increasing incidence of avascular necrosis of the hip in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2001;28:101–102.
237. Monier P, McKown K, Bronze MS. Osteonecrosis complicating highly active antiretroviral therapy in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 2000;31:1488–1492.
238. Glesby MJ, Moore RD, Chaisson RE. Herpes zoster in patients with advanced human immunodeficiency virus infection treated with zidovudine. Zidovudine Epidemiology Study Group. *J Infect Dis*. 1993;168:1264–1268.
239. Garman ME, Tyring SK. The cutaneous manifestations of HIV infection. *Dermatol Clin*. 2002;20:193–208.
240. Porras B, Costner M, Friedman-Kien AE, et al. Update on cutaneous manifestations of HIV infection. *Med Clin North Am*. 1998;82:1033–1080, v.
241. Bollinger RC, Brookmeyer RS, Mehendale SM, et al. Risk factors and clinical presentation of acute primary HIV infection in India. *JAMA*. 1997;278:2085–2089.
242. Schacker T, Collier AC, Hughes J, et al. Clinical and epidemiologic features of primary HIV infection. *Ann Intern Med*. 1996;125:257–264.
243. Quinnan GV Jr, Masur H, Rook AH, et al. Herpesvirus infections in the acquired immune deficiency syndrome. *JAMA*. 1984;252:72–77.
244. Friedman-Kien AE, Lafleur FL, Gendler E, et al. Herpes zoster: a possible early clinical sign for development of acquired immunodeficiency syndrome in high-risk individuals. *J Am Acad Dermatol*. 1986;14:1023–1028.
245. Aldeen T, Hay P, Davidson F, et al. Herpes zoster infection in HIV-seropositive patients associated with highly active antiretroviral therapy. *AIDS*. 1998;12:1719–1720.
246. Buchbinder SP, Katz MH, Hessol NA, et al. Herpes zoster and human immunodeficiency virus infection. *J Infect Dis*. 1992;166:1153–1156.
247. Cohen PR, Beltrani VP, Grossman ME. Disseminated herpes zoster in patients with human immunodeficiency virus infection. *Am J Med*. 1988;84:1076–1080.
248. Grossman MC, Grossman ME. Chronic hyperkeratotic herpes zoster and human immunodeficiency virus infection. *J Am Acad Dermatol*. 1993;28(2 Pt 2):306–308.
249. Melbye M, Grossman RJ, Goedert JJ, et al. Risk of AIDS after herpes zoster. *Lancet*. 1987;1:728–731.
250. Gilson IH, Barnett JH, Conant MA, et al. Disseminated ecthymatous herpes varicella-zoster virus infection in patients with acquired immunodeficiency syndrome. *J Am Acad Dermatol*. 1989;20:637–642.
251. Horn CK, Scott GR, Benton EC. Resolution of severe molluscum contagiosum on effective antiretroviral therapy. *Br J Dermatol*. 1998;138:715–717.
252. Koehler JE, Quinn FD, Berger TG, et al. Isolation of *Rochalimaea* species from cutaneous and osseous lesions of bacillary angiomatosis. *N Engl J Med*. 1992;327:1625–1631.
253. Relman DA, Loutit JS, Schmidt TM, et al. The agent of bacillary angiomatosis. An approach to the identification of uncultured pathogens. *N Engl J Med*. 1990;323:1573–1580.
254. Slater LN, Welch DF, Min KW. Rochalimaea henselae causes bacillary angiomatosis and peliosis hepatis. *Arch Intern Med*. 1992;152:602–606.
255. Stoler MH, Bonfiglio TA, Steigbigel RT, et al. An atypical subcutaneous infection associated with acquired immune deficiency syndrome. *Am J Clin Pathol*. 1983;80:714–718.
256. Tappero JW, Mohle-Boetani J, Koehler JE, et al. The epidemiology of bacillary angiomatosis and bacillary peliosis. *JAMA*. 1993;269:770–775.
257. Koehler JE, Sanchez MA, Garrido CS, et al. Molecular epidemiology of bartonella infections in patients with bacillary angiomatosis-peliosis. *N Engl J Med*. 1997;337:1876–1883.
258. Koehler JE, LeBoit PE, Egbert BM, et al. Cutaneous vascular lesions and disseminated cat-scratch disease in patients with the acquired immunodeficiency syndrome (AIDS) and AIDS-related complex. *Ann Intern Med*. 1988;109:449–455.
259. Koehler JE, Tappero JW. Bacillary angiomatosis and bacillary peliosis in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1993;17:612–624.
260. Mohle-Boetani JC, Koehler JE, Berger TG, et al. Bacillary angiomatosis and bacillary peliosis in patients infected with human immunodeficiency virus: clinical characteristics in a case-control study. *Clin Infect Dis*. 1996;22:794–800.
261. Agan BK, Dolan MJ. Laboratory diagnosis of *Bartonella* infections. *Clin Lab Med*. 2002;22:937–962.
262. Antman K, Chang Y. Kaposi's sarcoma. *N Engl J Med*. 2000;342:1027–1038.
263. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science*. 1994;266:1865–1869.
264. Martin JN, Ganem DE, Osmond DH, et al. Sexual transmission and the natural history of human herpesvirus 8 infection. *N Engl J Med*. 1998;338:948–954.
265. Sullivan RJ, Pantanowitz L, Casper C, et al. HIV/AIDS: epidemiology, pathophysiology, and treatment of Kaposi sarcoma-associated herpesvirus disease: Kaposi sarcoma, primary effusion lymphoma, and multicentric Castleman disease. *Clin Infect Dis*. 2008;47:1209–1215.
266. Beral V, Peterman TA, Berkelman RL, et al. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? *Lancet*. 1990;335:123–128.
267. Lee NE, Taylor MM, Bancroft E, et al. Risk factors for community-associated methicillin-resistant *Staphylococcus aureus* skin infections among HIV-positive men who have sex with men. *Clin Infect Dis*. 2005;40:1529–1534.
268. Supparatpinyo K, Khamwan C, Baosoung V, et al. Disseminated *Penicillium marneffei* infection in southeast Asia. *Lancet*. 1994;344:110–113.
269. Schlesinger I, Oelrich DM, Tyring SK. Crusted (Norwegian) scabies in patients with AIDS: the range of clinical presentations. *South Med J*. 1994;87:352–356.
270. Meinking TL, Taplin D, Hermida JL, et al. The treatment of scabies with ivermectin. *N Engl J Med*. 1995;333:26–30.
271. Boyd MA, Mocroft A, Ryom L, et al. Cardiovascular disease (CVD) and chronic kidney disease (CKD) event rates in HIV-positive persons at high predicted CVD and CKD risk: a prospective analysis of the D:A:D observational study. *PLoS Med*. 2017;14:e1002424.
272. Kelleher P, Severn A, Tomson C, et al. The haemolytic uraemic syndrome in patients with AIDS. *Genitourin Med*. 1996;72:172–175.
273. Stokes MB, Chawla H, Brody RI, et al. Immune complex glomerulonephritis in patients coinfected with human immunodeficiency virus and hepatitis C virus. *Am J Kidney Dis*. 1997;29:514–525.
274. Roe J, Campbell LJ, Ibrahim F, et al. HIV care and the incidence of acute renal failure. *Clin Infect Dis*. 2008;47:242–249.
275. Genovese G, Friedman DJ, Ross MD, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science*. 2010;329:841–845.
276. Papeta N, Kiryluk K, Patel A, et al. APOL1 variants increase risk for FSGS and HIVAN but not IgA nephropathy. *J Am Soc Nephrol*. 2011;22:1991–1996.
277. Dummer PD, Limou S, Rosenberg AZ, et al. APOL1 kidney disease risk variants: an evolving landscape. *Semin Nephrol*. 2015;35:222–236.
278. Cohen SD, Kopp JB, Kimmel PL. Kidney diseases associated with human immunodeficiency virus infection. *N Engl J Med*. 2018;378:1655–1656.
279. Rao TK, Friedman EA, Nicastri AD. The types of renal disease in the acquired immunodeficiency syndrome. *N Engl J Med*. 1987;316:1062–1068.
280. Fine DM, Wasser WG, Estrella MM, et al. APOL1 risk variants predict histopathology and progression to ESRD in HIV-related kidney disease. *J Am Soc Nephrol*. 2012;23:343–350.
281. Lucas GM, Lau B, Atta MG, et al. Chronic kidney disease incidence, and progression to end-stage renal disease, in HIV-infected individuals: a tale of two races. *J Infect Dis*. 2008;197:1548–1557.
282. Kimmel PL, Barisoni L, Kopp JB. Pathogenesis and treatment of HIV-associated renal diseases: lessons from clinical and animal studies, molecular pathologic correlations, and genetic investigations. *Ann Intern Med*. 2003;139:214–226.
283. Atta MG, Estrella MM, Kuperman M, et al. HIV-associated nephropathy patients with and without apolipoprotein L1 gene variants have similar clinical and pathological characteristics. *Kidney Int*. 2012;82:338–343.
284. Ortiz C, Meneses R, Jaffe D, et al. Outcome of patients with human immunodeficiency virus on maintenance hemodialysis. *Kidney Int*. 1988;34:248–253.
285. Post FA, Campbell LJ, Hamzah L, et al. Predictors of renal outcome in HIV-associated nephropathy. *Clin Infect Dis*. 2008;46:1282–1289.
286. Szczech LA, Edwards LJ, Sanders LL, et al. Protease inhibitors are associated with a slowed progression of HIV-related renal diseases. *Clin Nephrol*. 2002;57:336–341.
287. Smith MC, Austen JL, Carey JT, et al. Prednisone improves renal function and proteinuria in human immunodeficiency virus-associated nephropathy. *Am J Med*. 1996;101:41–48.
288. Burns GC, Paul SK, Toth IR, et al. Effect of angiotensin-converting enzyme inhibition in HIV-associated nephropathy. *J Am Soc Nephrol*. 1997;8:1140–1146.
289. Ingulli E, Tejani A, Fikrig S, et al. Pomrantz A. Nephrotic syndrome associated with acquired immunodeficiency syndrome in children. *J Pediatr*. 1991;119:710–716.
290. Abraham AG, Althoff KN, Jing Y, et al. End-stage renal disease among HIV-infected adults in North America. *Clin Infect Dis*. 2015;60:941–949.
291. Muller E, Barday Z, Mendelson M, et al. HIV-positive-to-HIV-positive kidney transplantation–results at 3 to 5 years. *N Engl J Med*. 2015;372:613–620.
292. Waheed S, Sakr A, Chheda ND, et al. Outcomes of renal transplantation in HIV-1 associated nephropathy. *PLoS ONE*. 2015;10:e0129702.
293. Cunningham ET Jr, Margolis TP. Ocular manifestations of HIV infection. *N Engl J Med*. 1998;339:236–244.
294. Jabs DA. Ocular manifestations of HIV infection. *Trans Am Ophthalmol Soc*. 1995;93:623–683.
295. Sarraf D, Ernest JT. AIDS and the eyes. *Lancet*. 1996;348:525–528.
296. Spector SA, Wong R, Hsia K, et al. Plasma cytomegalovirus (CMV) DNA load predicts CMV disease and survival in AIDS patients. *J Clin Invest*. 1998;101:497–502.
297. Gallant JE, Moore RD, Richman DD, et al. Incidence and natural history of cytomegalovirus disease in patients with advanced human immunodeficiency virus disease treated with zidovudine. The Zidovudine Epidemiology Study Group. *J Infect Dis*. 1992;166:1223–1227.
298. United States Department of Helath and Human Services. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Available at: https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0. Accessed March 1, 2018.
299. Whitcup SM, Fortin E, Nussenblatt RB, et al. Therapeutic effect of combination antiretroviral therapy on cytomegalovirus retinitis. *JAMA*. 1997;277:1519–1520.
300. Margolis TP, Lowder CY, Holland GN, et al. Varicella-zoster virus retinitis in patients with the acquired immunodeficiency syndrome. *Am J Ophthalmol*. 1991;112:119–131.
301. Batisse D, Eliaszewicz M, Zazoun L, et al. Acute retinal necrosis in the course of AIDS: study of 26 cases. *AIDS*. 1996;10:55–60.
302. Wasserman L, Haghighi P. Otic and ophthalmic pneumocystosis in acquired immunodeficiency

syndrome. Report of a case and review of the literature. *Arch Pathol Lab Med*. 1992;116:500–503.
303. Barbarinia G, Barbaro G. Incidence of the involvement of the cardiovascular system in HIV infection. *AIDS*. 2003;17(suppl 1):S46–S50.
304. Rerkpattanapipat P, Wongpraparut N, Jacobs LE, et al. Cardiac manifestations of acquired immunodeficiency syndrome. *Arch Intern Med*. 2000;160:602–608.
305. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med*. 2013;173:614–622.
306. Post W, Jacobson L, Li X Age and noncalcified coronary plaque in the Multicenter AIDS Cohort Study [abstract 62]. Presented at the 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, Georgia: March 3–6. 2013.
307. El-Sadr WM, Grund B, Neuhaus J, et al. Risk for opportunistic disease and death after reinitiating continuous antiretroviral therapy in patients with HIV previously receiving episodic therapy: a randomized trial. *Ann Intern Med*. 2008;149:289–299.
308. Hofman P, Drici MD, Gibelin P, et al. Prevalence of toxoplasma myocarditis in patients with the acquired immunodeficiency syndrome. *Br Heart J*. 1993;70:376–381.
309. Herskowitz A, Wu TC, Willoughby SB, et al. Myocarditis and cardiotropic viral infection associated with severe left ventricular dysfunction in late-stage infection with human immunodeficiency virus. *J Am Coll Cardiol*. 1994;24:1025–1032.
310. Barbaro G, Di Lorenzo G, Grisorio B, et al. Incidence of dilated cardiomyopathy and detection of HIV in myocardial cells of HIV-positive patients. Gruppo Italiano per lo Studio Cardiologico dei Pazienti Affetti da AIDS. *N Engl J Med*. 1998;339:1093–1099.
311. Herskowitz A, Vlahov D, Willoughby S, et al. Prevalence and incidence of left ventricular dysfunction in patients with human immunodeficiency virus infection. *Am J Cardiol*. 1993;71:955–958.
312. Currie PF, Jacob AJ, Foreman AR, et al. Heart muscle disease related to HIV infection: prognostic implications. *BMJ*. 1994;309:1605–1607.
313. Silva-Cardoso J, Moura B, Martins L, et al. Pericardial involvement in human immunodeficiency virus infection. *Chest*. 1999;115:418–422.
314. Chen Y, Brennessel D, Walters J, et al. Human immunodeficiency virus-associated pericardial effusion: report of 40 cases and review of the literature. *Am Heart J*. 1999;137:516–521.
315. Moore RD, Keruly JC, Chaisson RE. Neutropenia and bacterial infection in acquired immunodeficiency syndrome. *Arch Intern Med*. 1995;155:1965–1970.
316. Moore DA, Benepal T, Portsmouth S, et al. Etiology and natural history of neutropenia in human immunodeficiency virus disease: a prospective study. *Clin Infect Dis*. 2001;32:469–475.
317. Mocroft A, Kirk O, Barton SE, et al. Anaemia is an independent predictive marker for clinical prognosis in HIV-infected patients from across Europe. EuroSIDA study group. *AIDS*. 1999;13:943–950.
318. Moore RD, Keruly JC, Chaisson RE. Anemia and survival in HIV infection. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;19:29–33.
319. Scaradavou A. HIV-related thrombocytopenia. *Blood Rev*. 2002;16:73–76.
320. Hymes KB, Greene JB, Karpatkin S. The effect of azidothymidine on HIV-related thrombocytopenia. *N Engl J Med*. 1988;318:516–517.
321. Arranz Caso JA, Sanchez Mingo C, Garcia Tena J. Effect of highly active antiretroviral therapy on thrombocytopenia in patients with HIV infection. *N Engl J Med*. 1999;341:1239–1240.
322. Jokela J, Flynn T, Henry K. Thrombotic thrombocytopenic purpura in a human immunodeficiency virus (HIV)-seropositive homosexual man. *Am J Hematol*. 1987;25:341–343.
323. Gervasoni C, Ridolfo AL, Vaccarezza M, et al. Thrombotic microangiopathy in patients with acquired immunodeficiency syndrome before and during the era of introduction of highly active antiretroviral therapy. *Clin Infect Dis*. 2002;35:1534–1540.
324. Altekruse SF, Shiels MS, Modur SP, et al. Cancer burden attributable to cigarette smoking among HIV-infected people in North America. *AIDS*. 2018;32:513–521.
325. Beachler DC, Abraham AG, Silverberg MJ, et al. Incidence and risk factors of HPV-related and HPV-unrelated head and neck squamous cell carcinoma in HIV-infected individuals. *Oral Oncol*. 2014;50:1169–1176.
326. Engels EA, Yanik EL, Wheeler W, et al. Cancer-attributable mortality among people with treated human immunodeficiency virus infection in North America. *Clin Infect Dis*. 2017;65:636–643.
327. DeSimone JA, Pomerantz RJ, Babinchak TJ. Inflammatory reactions in HIV-1-infected persons after initiation of highly active antiretroviral therapy. *Ann Intern Med*. 2000;133:447–454.
328. French MA. HIV/AIDS: immune reconstitution inflammatory syndrome: a reappraisal. *Clin Infect Dis*. 2009;48:101–107.
329. Navas E, Martin-Davila P, Moreno L, et al. Paradoxical reactions of tuberculosis in patients with the acquired immunodeficiency syndrome who are treated with highly active antiretroviral therapy. *Arch Intern Med*. 2002;162:97–99.
330. Wendel KA, Alwood KS, Gachuhi R, et al. Paradoxical worsening of tuberculosis in HIV-infected persons. *Chest*. 2001;120:193–197.
331. Luetkemeyer AF, Kendall MA, Nyirenda M, et al. Tuberculosis immune reconstitution inflammatory syndrome in A5221 STRIDE: timing, severity, and implications for HIV-TB programs. *J Acquir Immune Defic Syndr*. 2014;65:423–428.
332. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*. 2008;8:516–523.
332a. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*. 2010;24:2381–2390.
333. Phillips P, Kwiatkowski MB, Copland M, et al. Mycobacterial lymphadenitis associated with the initiation of combination antiretroviral therapy. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1999;20:122–128.
334. Aberg JA, Williams PL, Liu T, et al. A study of discontinuing maintenance therapy in human immunodeficiency virus-infected subjects with disseminated *Mycobacterium avium* complex: AIDS Clinical Trial Group 393 Study Team. *J Infect Dis*. 2003;187:1046–1052.
335. Currier JS, Williams PL, Koletar SL, et al. Discontinuation of *Mycobacterium avium* complex prophylaxis in patients with antiretroviral therapy-induced increases in CD4+ cell count. A randomized, double-blind, placebo-controlled trial. AIDS Clinical Trials Group 362 Study Team. *Ann Intern Med*. 2000;133:493–503.
336. Jacobson MA, Zegans M, Pavan PR, et al. Cytomegalovirus retinitis after initiation of highly active antiretroviral therapy. *Lancet*. 1997;349:1443–1445.
337. Karavellas MP, Lowder CY, Macdonald C, et al. Immune recovery vitritis associated with inactive cytomegalovirus retinitis: a new syndrome. *Arch Ophthalmol*. 1998;116:169–175.
338. Zegans ME, Walton RC, Holland GN, et al. Transient vitreous inflammatory reactions associated with combination antiretroviral therapy in patients with AIDS and cytomegalovirus retinitis. *Am J Ophthalmol*. 1998;125:292–300.
339. Gilquin J, Piketty C, Thomas V, et al. Acute cytomegalovirus infection in AIDS patients with CD4 counts above 100 x 10(6) cells/l following combination antiretroviral therapy including protease inhibitors. *AIDS*. 1997;11:1659–1660.
340. Karavellas MP, Plummer DJ, Macdonald JC, et al. Incidence of immune recovery vitritis in cytomegalovirus retinitis patients following institution of successful highly active antiretroviral therapy. *J Infect Dis*. 1999;179:697–700.
341. Nguyen QD, Kempen JH, Bolton SG, et al. Immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis after highly active antiretroviral therapy. *Am J Ophthalmol*. 2000;129:634–639.
342. Domingo P, Torres OH, Ris J, et al. Herpes zoster as an immune reconstitution disease after initiation of combination antiretroviral therapy in patients with human immunodeficiency virus type-1 infection. *Am J Med*. 2001;110:605–609.
343. Martinez E, Gatell J, Moran Y, et al. High incidence of herpes zoster in patients with AIDS soon after therapy with protease inhibitors. *Clin Infect Dis*. 1998;27:1510–1513.
344. Puoti M, Torti C, Ripamonti D, et al. Severe hepatotoxicity during combination antiretroviral treatment: incidence, liver histology, and outcome. *J Acquir Immune Defic Syndr*. 2003;32:259–267.
345. Zylberberg H, Pialoux G, Carnot F, et al. Rapidly evolving hepatitis C virus-related cirrhosis in a human immunodeficiency virus-infected patient receiving triple antiretroviral therapy. *Clin Infect Dis*. 1998;27:1255–1258.
346. Chung RT, Evans SR, Yang Y, et al. Immune recovery is associated with persistent rise in hepatitis C virus RNA, infrequent liver test flares, and is not impaired by hepatitis C virus in co-infected subjects. *AIDS*. 2002;16:1915–1923.
347. Puoti M, Gargiulo F, Quiros Roldan E, et al. Liver damage and kinetics of hepatitis C virus and human immunodeficiency virus replication during the early phases of combination antiretroviral treatment. *J Infect Dis*. 2000;181:2033–2036.
348. Stone SF, Lee S, Keane NM, et al. Association of increased hepatitis C virus (HCV)-specific IgG and soluble CD26 dipeptidyl peptidase IV enzyme activity with hepatotoxicity after highly active antiretroviral therapy in human immunodeficiency virus-HCV-coinfected patients. *J Infect Dis*. 2002;186:1498–1502.
349. Carr A, Cooper DA. Restoration of immunity to chronic hepatitis B infection in HIV-infected patient on protease inhibitor. *Lancet*. 1997;349:995–996.
350. Hoffmann CJ, Charalambous S, Martin DJ, et al. Hepatitis B virus infection and response to antiretroviral therapy (ART) in a South African ART program. *Clin Infect Dis*. 2008;47:1479–1485.
351. Sungkanuparph S, Filler SG, Chetchotisakd P, et al. Cryptococcal immune reconstitution inflammatory syndrome after antiretroviral therapy in AIDS patients with cryptococcal meningitis: a prospective multicenter study. *Clin Infect Dis*. 2009;49:931–934.
352. Woods ML 2nd, MacGinley R, Eisen DP, et al. HIV combination therapy: partial immune restitution unmasking latent cryptococcal infection. *AIDS*. 1998;12:1491–1494.
353. Koval CE, Gigliotti F, Nevins D, et al. Immune reconstitution syndrome after successful treatment of *Pneumocystis carinii* pneumonia in a man with human immunodeficiency virus type 1 infection. *Clin Infect Dis*. 2002;35:491–493.
354. Wislez M, Bergot E, Antoine M, et al. Acute respiratory failure following HAART introduction in patients treated for *Pneumocystis carinii* pneumonia. *Am J Respir Crit Care Med*. 2001;164:847–851.
355. Safdar A, Rubocki RJ, Horvath JA, et al. Fatal immune restoration disease in human immunodeficiency virus type 1-infected patients with progressive multifocal leukoencephalopathy: impact of antiretroviral therapy-associated immune reconstitution. *Clin Infect Dis*. 2002;35:1250–1257.
356. Bower M, Nelson M, Young AM, et al. Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma. *J Clin Oncol*. 2005;23:5224–5228.
357. Gopal S, Patel MR, Achenbach CJ, et al. Lymphoma immune reconstitution inflammatory syndrome in the center for AIDS research network of integrated clinical systems cohort. *Clin Infect Dis*. 2014;59:279–286.
358. Jaffe HW, De Stavola BL, Carpenter LM, et al. Immune reconstitution and risk of Kaposi sarcoma and non-Hodgkin lymphoma in HIV-infected adults. *AIDS*. 2011;25:1395–1403.
359. Kowalkowski MA, Mims MP, Amiran ES, et al. Effect of immune reconstitution on the incidence of HIV-related Hodgkin lymphoma. *PLoS ONE*. 2013;8:e77409.

123 Pulmonary Manifestations of Human Immunodeficiency Virus Infection

Paul E. Sax and Kevin L. Ard

SHORT VIEW SUMMARY

EPIDEMIOLOGY

- Human immunodeficiency virus (HIV) infection increases the risk of infectious and noninfectious respiratory conditions.
- Most complications occur in those not receiving antiretroviral therapy.
- Effective antiretroviral therapy has reduced, but not eliminated, the excess risk of pulmonary infections such as *Pneumocystis jirovecii* pneumonia (PCP) and to a lesser extent bacterial pneumonia.
- Noninfectious conditions, such as chronic obstructive pulmonary disease and lung cancer, are assuming greater importance as HIV-infected individuals live longer.

APPROACH TO THE PATIENT

- The differential diagnosis is influenced by the stage of immunosuppression, antiretroviral therapy, prophylaxis for opportunistic infections, and the local epidemiology of conditions such as tuberculosis and endemic fungal infections.
- Lower CD4 cell counts increase the risk of all pulmonary infections, including those that also occur at higher CD4 cell counts.
- Findings on chest radiography can help guide the differential diagnosis (see Table 123.2).

PNEUMOCYSTIS JIROVECII PNEUMONIA

- Most cases of PCP occur at CD4 cell counts of fewer than 200 cells/mm^3 in patients not receiving antiretroviral therapy.
- Patients with PCP typically report cough and fever of at least several weeks' duration.
- Radiographic findings include diffuse interstitial infiltrates most commonly, but cavities, pneumothoraces, pleural effusions, and normal radiographs can occur.
- Diagnosis relies on identification of the organism in respiratory secretions, often through induced sputum or bronchoalveolar lavage, which is more sensitive.
- Serum (1→3)-β-d-glucan is also highly sensitive for the diagnosis of PCP.

BACTERIAL PNEUMONIA

- *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most commonly isolated pathogens.
- With worsening immunosuppression, pneumonias due to *Staphylococcus aureus, Pseudomonas aeruginosa* (especially in the setting of neutropenia), *Nocardia* spp., and *Rhodococcus equi* can occur.

MYCOBACTERIAL PNEUMONIA

- The features of *Mycobacterium tuberculosis* pulmonary infection vary based on the degree of immunosuppression.
- HIV-infected patients with respiratory symptoms who are from tuberculosis-endemic areas or have other risk factors for tuberculosis, who have a positive test for latent tuberculosis without a history of prophylactic therapy, or who have a personal history of tuberculosis without documentation of appropriate treatment should be placed in negative air pressure rooms until the diagnosis of pulmonary tuberculosis is excluded.
- Sputum nucleic acid amplification tests can hasten diagnosis, particularly in smear-negative cases.

FUNGAL PNEUMONIA

- Fungal pneumonia tends to occur with CD4 cell counts <100 cells/mm^3, often as a component of disseminated fungal infection (cryptococcosis, histoplasmosis, coccidioidomycosis, blastomycosis).
- Histoplasmosis and coccidioidomycosis are important causes of pneumonia in those who have resided in or traveled to endemic areas; *Blastomyces* rarely causes pulmonary infection in patients with HIV.
- Pulmonary aspergillosis usually occurs in severely immunocompromised individuals with neutropenia or corticosteroid use.

VIRAL PNEUMONIA

- During the influenza season, influenza is the most common diagnosis in HIV-infected patients with fever and respiratory symptoms, although adenovirus, respiratory syncytial virus, and parainfluenza virus can cause a similar presentation.

NONINFECTIOUS RESPIRATORY DISORDERS

- Pulmonary Kaposi sarcoma usually occurs with cutaneous or mucosal disease.
- Pulmonary lymphoma causes nodules, masses, or pleural effusions and is usually diagnosed via video-assisted thoracoscopic surgery (VATS).
- Lymphocytic interstitial pneumonitis, a rare cause of interstitial infiltrates, is typically diagnosed on biopsy. It primarily occurs in children but may develop in adults, particularly those with higher CD4 counts than are seen with many opportunistic infections.

Respiratory complications of human immunodeficiency virus (HIV) infection remain a significant source of morbidity and mortality, even after the introduction of combination antiretroviral therapy in 1996.[1] Although the incidence rate of these complications has since declined, they are frequently the sentinel event that brings a person with unknown HIV status to medical attention. They also commonly occur in patients with poor adherence to their HIV treatment.

EPIDEMIOLOGY

The Pulmonary Complications of HIV Infection Study followed 1100 patients with HIV from 1988 to 1994.[2] The study also included 167 control subjects who were negative for HIV. The study preceded the availability of protease inhibitors and the widespread use of combination antiretroviral therapy, but it provided the most accurate data regarding the incidence of specific pulmonary infections among individuals with HIV. Importantly, the study included the era after which prophylaxis against *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*) pneumonia (PCP) became the standard of care. During the 5 years of follow-up, acute bronchitis was the most common lower airway infection; it occurred twice as often in those with HIV infection as in controls. By far, the two most common acquired immunodeficiency syndrome (AIDS)–defining complications were bacterial pneumonia and PCP. These occurred with approximately equal frequency, and follow-up showed higher rates of pneumonia with declining CD4 cell counts. Other specific causes of opportunistic infections occurred relatively infrequently and included infection with cytomegalovirus (CMV), *Aspergillus*, cryptococci, and herpes simplex virus.

The use of combination antiretroviral therapy has dramatically diminished the incidence of all of these complications, with some evidence of a greater decline in PCP than in bacterial pneumonia.[1,3] For the former, this decline occurred independently of PCP prophylaxis.[4] However, even among individuals with normal or near-normal CD4 cell counts who are undergoing antiretroviral therapy, the rate of bacterial pneumonia is significantly higher among those infected with HIV than

in uninfected control subjects.[5,6] Long-term administration of anti-*Pneumocystis* prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) in particular and *Mycobacterium avium* complex prophylaxis with macrolide antibiotics likely reduces the incidence of bacterial pneumonia.[7–10] Treatment with TMP-SMX, however, has been shown to increase the rate of colonization with resistant bacteria, especially pneumococci.[11]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a person with HIV infection with respiratory symptoms is exceedingly broad and includes infectious, neoplastic, and cardiovascular etiologies (Table 123.1). However, as noted previously, certain conditions (in particular, PCP and bacterial pneumonia) occur far more commonly than others; hence, the diagnostic evaluation and initial empirical therapy should be focused toward these diagnoses.

Certain historic, clinical, and radiographic clues help determine the likelihood of specific opportunistic infections and are discussed in the following sections.

TABLE 123.1 Causes of Pulmonary Disease Associated With HIV Infection

Most Common
Bacterial
No organism identified, but responsive to antibacterial therapy
Streptococcus pneumoniae
Haemophilus influenzae
Mycobacterial
Mycobacterium tuberculosis[b]
Fungal
Pneumocystis jirovecii
Less Common but Clinically Important in Some Settings
Bacterial
Pseudomonas aeruginosa
Staphylococcus aureus
Enterobacteriaceae
Legionella spp.
Nocardia spp.
Rhodococcus equi
Mycobacterial
Mycobacterium kansasii
Mycobacterium avium complex
Fungal
Cryptococcus neoformans
Histoplasma capsulatum
Coccidioides spp.
Aspergillus spp.
Blastomyces dermatitidis
Talaromyces marneffei
Viral
Influenza
Cytomegalovirus
Herpes simplex virus
Adenovirus
Respiratory syncytial virus
Parainfluenza virus
Parasitic
Toxoplasma gondii
Strongyloides stercoralis
Microsporidia spp.
Cryptosporidium parvum
Noninfectious
Chronic obstructive pulmonary disease
Lung cancer
Kaposi sarcoma
Non-Hodgkin lymphoma
Primary pulmonary hypertension
Congestive heart failure
Lymphocytic (or lymphoid) interstitial pneumonitis
Abacavir hypersensitivity

[a]Causes are listed within categories in approximate order of frequency.
[b]Frequency of *M. tuberculosis* infection is highly dependent on local rates of tuberculosis and the patient's exposure history.

Clinical or Laboratory Stage of Immunosuppression

The majority of cases of PCP occur in individuals with CD4 cell counts of fewer than 200 cells/mm.[3,12–14] If the CD4 cell count is unavailable, helpful clinical correlates are the presence of oral candidiasis, which is known to correlate with advanced HIV-related immunosuppression and the risk of PCP, and other clinical markers of advanced HIV disease, such as weight loss. Progressive immunosuppression increases the risk of all pulmonary infectious processes, including those that may occur with relatively preserved CD4 cell counts, such as bacterial pneumonia and tuberculosis (TB).

Tempo of the Illness

Individuals with HIV with bacterial pneumonia typically present in much the same way as those without HIV infection: with a relatively acute illness (measured in days) characterized by fever and chills and sometimes accompanied by pleuritic pain and sputum production.[15] PCP, in contrast, typically manifests as a subacute to chronic illness of several weeks' duration, with the most prominent symptoms being fever and shortness of breath. Other helpful clues to PCP include chest tightness (specifically a sense of difficulty in taking a full breath) and a report that a typical day's activities (climbing stairs, conversing on the telephone) are now associated with dyspnea.

Receipt and Type of *Pneumocystis* Prophylaxis

Patients receiving TMP-SMX for *Pneumocystis* prophylaxis rarely have breakthroughs of PCP if they are compliant with therapy. In contrast, second-line prophylaxis, such as atovaquone, dapsone, and aerosolized pentamidine, is associated with small but significant rates of treatment failure.[7,16–18] As noted previously, TMP-SMX reduces the risk of bacterial infections, including pneumonia. However, given the high rates of pneumococcal infection among patients with HIV, as well as the concurrently high rate of pneumococcal resistance to TMP-SMX and macrolides, receipt of these drugs for prophylaxis is partially protective at most.

Receipt of Antiretroviral Therapy

In addition to its obvious beneficial effect on HIV RNA levels and CD4 cell counts, patients who receive continuous antiretroviral therapy have a lower rate of pneumonia than a comparable group undergoing intermittent therapy. This was demonstrated in a randomized, controlled trial comparing immediate to deferred antiretroviral therapy in patients with CD4 cell counts greater than 500 cells/mm.[19] The favorable effect of HIV treatment on reducing pneumonia incidence may be in part the result of a reduction in pulmonary viral replication and improvement in lung CD4 cell function and number.[20]

History of Opportunistic Processes

Some patients with HIV appear to have prominent B-cell dysfunction and thus are at a much greater risk for the development of encapsulated bacterial infections, in particular those from *Streptococcus pneumoniae* and *Haemophilus influenzae*. Such individuals frequently have a history of multiple visits or hospitalizations for bacterial pneumonia,[10] as well as episodes of otitis media, bronchitis, and other bacterial respiratory infections. In addition, persons with a history of *Pneumocystis* infection are at greater risk for relapse, in particular if they are not receiving antiretroviral therapy or PCP prophylaxis with TMP-SMX.[7]

Injection Drug Use and Smoking

Persons with HIV who are active users of intravenous drugs are more likely to have invasive bacterial infections, including pneumonia, compared with individuals with HIV acquired from other routes.[6] As with other populations, smoking increases the risk of pneumonia

regardless of whether the patient is receiving antiretroviral therapy or not.[19] Chronic obstructive pulmonary disease (COPD) is an independent risk factor for community-acquired pneumonia, pulmonary TB, and PCP in persons living with HIV; HIV infection is an independent risk factor for acute exacerbations of COPD.[21–23]

Local Epidemiology or Past Residence

The incidence of TB as a complication of HIV infection varies markedly depending on local rates of TB and the patient's exposure history. In the United States, a majority of TB cases occur in people who have emigrated from TB-endemic areas; many of these areas (such as sub-Saharan Africa and parts of the Caribbean) also have high background rates of HIV infection. In addition, homelessness and incarceration both increase the risk of TB exposure and subsequent disease. A person's past residence or travel history may elicit potential exposure not only to TB but also to diseases caused by endemic fungi, such as histoplasmosis, coccidioidomycosis, and blastomycosis.

Characteristic Radiographic Findings

Although no radiographic finding is pathognomonic for a specific microbiologic diagnosis, certain patterns suggest various diagnoses (Table 123.2). Patients with bacterial pneumonia are more likely to have a focal infiltrate on chest radiography, whereas those with PCP typically show diffuse interstitial infiltrates.[15,24] Importantly, many exceptions to these generalizations exist, including the presence of a normal chest radiograph in up to 10% of those with PCP or TB and the occasional occurrence of diffuse interstitial infiltrates in persons with bacterial pneumonia, in particular that caused by *H. influenzae*.[25–27] In fact, given the wide range of radiographic findings that potentially result from PCP (including cavities, pneumatoceles, pleural effusions, nodules, and pneumothoraces), no radiographic appearance can entirely rule out the diagnosis of PCP in an HIV-infected host with advanced immunosuppression.[28]

TABLE 123.2 Radiographic Appearance of Pulmonary Diseases in HIV Infection

Diffuse Interstitial Infiltrates
Pneumocystis jirovecii
Mycobacterium tuberculosis, especially with advanced HIV disease
Histoplasma capsulatum
Coccidioides spp.
Cryptococcus neoformans
Toxoplasma gondii
Cytomegalovirus
Influenza
Lymphocytic interstitial pneumonitis
Abacavir hypersensitivity
Focal Consolidation
Pyogenic bacterial pneumonia from *Streptococcus pneumoniae, Haemophilus influenzae*
M. tuberculosis
Legionella spp.
Rhodococcus equi
Hilar Adenopathy
M. tuberculosis
H. capsulatum
Coccidioides spp.
Non-Hodgkin or Hodgkin lymphoma
Mycobacterium avium complex
Cavitary Disease
Pyogenic bacterial pneumonia from *Pseudomonas aeruginosa, Staphylococcus aureus,* Enterobacteriaceae
M. tuberculosis
C. neoformans
R. equi
Aspergillus spp.
Nocardia spp.
M. avium complex
P. jirovecii
Nodules or Masses
M. tuberculosis
C. neoformans
Aspergillus spp.
H. capsulatum
Nocardia spp.
Non-Hodgkin lymphoma
Kaposi sarcoma
Lung cancer
Normal Radiograph
P. jirovecii
M. tuberculosis

TRIAGE OF PATIENTS: INFECTION CONTROL ISSUES

Appropriate triage of patients with HIV-related respiratory infections is a frequently encountered dilemma because of the higher rates of TB in this context and the often atypical presentation of the disease. Because no clinical or radiographic presentation can entirely exclude TB, practitioners must have a high degree of suspicion and a low threshold to admit such patients to negative airflow rooms until TB has been ruled out or an alternative diagnosis has been established.[29]

Patients with HIV and respiratory disease are admitted to negative airflow rooms if any of the following conditions are present:

1. Any clinical presentation highly consistent with TB (cavitary lung disease, subacute course, weight loss)
2. Prior residence in a highly TB-endemic area
3. Other risk factors for TB exposure, such as contact with an active case, homelessness, or incarceration
4. History of positive tuberculin skin test or interferon-γ release assay results without preventive therapy
5. History of TB without documentation that appropriate treatment has been completed

The use of these criteria minimizes, but does not eliminate, the chance that a person with HIV is a source of a nosocomial exposure to TB.

DIAGNOSTIC TESTS

Diagnostic tests should begin with noninvasive studies, usually while empirical therapy for the most likely diagnoses (bacterial pneumonia and, if suspected, PCP) is started. These tests include a complete blood count with differential, a lactate dehydrogenase (LDH) test, two sets of blood cultures, a sputum Gram stain and culture, a serum cryptococcal antigen test, and a chest radiograph. If TB is being considered, a sputum acid-fast smear and culture should also be obtained and processed at a laboratory that is experienced in TB diagnostics and can provide results of acid-fast staining promptly (in 24–48 hours). Nucleic acid amplification tests can also aid rapid diagnosis with sputum (see Chapter 16) and hasten the time to discontinue respiratory precautions in patients with possible TB. The purpose of the blood cultures is to facilitate diagnosis of bacterial pneumonia, most notably from *S. pneumoniae,* with which bacteremia in patients with HIV occurs in up to 60% of cases.[30] Although not universally available, urinary pneumococcal antigen testing may provide a more rapid diagnosis of pneumococcal pneumonia than that provided by cultures. The reported sensitivity and specificity of this test are 81% and 98%, respectively.[31] Given the low specificity of sputum Gram stain and the low sensitivity of sputum culture, a positive blood culture or urinary antigen assay is often the only method for a specific etiologic diagnosis in a patient with bacterial pneumonia.

As noted in Chapter 269, LDH levels are generally elevated in patients with PCP, especially when the disease is severe enough to necessitate hospitalization. A normal level suggests an alternative diagnosis, and, conversely, the level of elevation correlates with the severity of the disease. Because many conditions cause an increase in LDH, the test has a low specificity for PCP but is a helpful diagnostic clue pending more definitive tests.[30] In many centers, an induced sputum sample (with hypertonic saline solution to induce cough) is the initial test of choice for diagnosis of PCP and sometimes TB. The sensitivity of this test for PCP varies widely in published reports, with a summary of several analyses citing an overall sensitivity of 55%.[32] Factors that may account for the varying sensitivity include patient cooperation with the test, persistence of the respiratory therapist in obtaining the

sample, and experience of the diagnostic laboratory in identifying the organism. Centers that use immunofluorescence staining for diagnosis likely have a higher sensitivity than those that use alternative staining methods (Giemsa, toluidine blue).[32,33]

If no definitive diagnosis has been identified, the decision to proceed with other diagnostic tests, both noninvasive and invasive, depends on whether the patient has responded to initial therapy. In clinical practice, a prompt clinical response to empirical antibiotic therapy directed at the most common pathogens in HIV-related pneumonia (*S. pneumoniae* and *H. influenzae*) serves as indirect evidence that alternative processes have not been overlooked.[30] For patients without clinical improvement and for a still unknown diagnosis, expedited referral for fiberoptic bronchoscopy with bronchoalveolar lavage (BAL), with or without a transbronchial biopsy, is recommended. Because BAL alone is highly sensitive for the diagnosis of PCP and because biopsy carries a risk of pneumothorax and pulmonary hemorrhage, many bronchoscopists prefer to perform BAL alone initially, reserving biopsy for a repeat procedure if still indicated. The main indication to proceed with a biopsy at the initial procedure is a high likelihood of an alternative diagnosis to PCP; this situation arises when a patient is taking TMP-SMX for PCP prophylaxis and has a relatively high CD4 cell count or an atypical-appearing chest radiograph, or if a diagnosis requiring biopsy for identification is highly suspected. Examples of such conditions include CMV or *Aspergillus* infection, lymphocytic interstitial pneumonitis, and malignant diseases other than Kaposi sarcoma (KS). Additional diagnostic studies depend on the degree of patient immunosuppression, epidemiologic risk factors, clinical course, and radiographic appearance. For example, a patient from a histoplasmosis-endemic area with chest imaging that shows hilar adenopathy along with diffuse infiltrates should undergo testing for histoplasmosis urinary antigen. Alternatively, someone with a history of neutropenia and receipt of corticosteroids who presents with pleuritic pain and pulmonary nodules may ultimately need video-assisted thoracoscopic surgery (VATS) for diagnosis of pulmonary aspergillosis. The various diagnostic strategies for patients with HIV-related pulmonary disease are summarized in Table 123.3.

TABLE 123.3 Diagnostic Tests Used in Patients With HIV Infection and Pulmonary Disease

TEST	COMMENT
Indicated in All Patients	
Complete blood count with differential	If neutropenia is present, empiric therapy covering *Pseudomonas aeruginosa* is indicated
Lactate dehydrogenase	Elevated in most patients with PCP; nonspecific
Blood cultures	Helpful for diagnosis of bacterial pneumonia, in particular from *Streptococcus pneumoniae*
Expectorated sputum	Often not available; Gram stain and culture have low sensitivity and specificity, especially after antibiotics have been started
Induced sputum for PCP stain, acid-fast bacilli stain, and culture	Initial test of choice in most centers for diagnosis of *Pneumocystis jirovecii,* although sensitivity varies widely
Indicated for Selected Patients Not Responding to Initial Empirical Therapy	
Fiberoptic bronchoscopy with BAL ± transbronchial biopsy	BAL highly sensitive for diagnosis of PCP; Kaposi sarcoma often diagnosed with visualization of characteristic purple endotracheal or endobronchial plaques, with no biopsy because of risk of bleeding Biopsy often necessary to establish alternative diagnoses such as cytomegalovirus, *Aspergillus,* or lymphocytic interstitial pneumonitis.
Video-assisted thoracoscopic biopsy	Useful in diagnosis of peripheral nodules, masses not reachable with bronchoscopic biopsy
Serum cryptococcal antigen	Nearly 100% sensitive for diagnosis of disseminated disease in patients with HIV infection; if positive, cerebrospinal fluid examination is mandatory to exclude meningitis
Serum (1→3)-β-D-glucan	Component of many fungal cell walls, including *P. jirovecii*; elevated in many patients with HIV-related PCP, including some with negative induced sputum examinations
Urinary histoplasmosis antigen	Indicated in patients residing in or from histoplasmosis-endemic areas, in particular if imaging shows diffuse or reticulonodular infiltrates and hilar adenopathy
High-resolution computed tomography scan	May help identify abnormalities not evident on chest radiography; normal study makes PCP highly unlikely
Gallium scan	Negative study rules out PCP; however, positive results are nonspecific, and other tests (high-resolution computed tomography scan, sputum induction) provide more useful information with greater rapidity

BAL, Bronchoalveolar lavage; *HIV,* human immunodeficiency virus; *PCP, Pneumocystis jirovecii* pneumonia.

SPECIFIC PATHOGENS

Pneumocystis Jirovecii Pneumonia

Early in the HIV epidemic, the principal risk factor for development of HIV-related PCP was determined to be a reduced CD4 cell count. Data from the Multicenter AIDS Cohort Study showed that the risk of PCP was markedly increased in patients with CD4 cell counts of fewer than 200 cells/mm^3; thrush and fever were other independent predictors.[12] In the postprophylaxis era, patients with PCP usually have advanced immunosuppression and CD4 counts below 100 cells/mm^3.[1] In one series of patients receiving care at an urban hospital, the median CD4 cell count for a first-time case of PCP was 36 cells/mm^3; for a recurrent case, it was 10 cells/mm^3.[34]

Care providers need to be aware that PCP remains a frequent sentinel opportunistic infection for patients who are not aware they are HIV positive and that this is also a risk factor for severe disease. In one retrospective series from Baltimore, 77% of patients with diagnosed PCP were not receiving prophylaxis and 33% were not previously known to have HIV infection. Patients not undergoing preventive therapy accounted for 100% of the deaths, 85% of the hospital days, and 100% of the cases admitted to the intensive care unit.[35] In large part because of this phenomenon and the advanced immunosuppression associated with the disease, short-term mortality from PCP remains significant despite the declining incidence of PCP that began in the early 1990s and has continued after the introduction of potent therapy in 1996.[36,37]

Risk factors for a poor clinical outcome in PCP include hypoxemia, extensive bilateral pulmonary involvement, other concurrent pulmonary infections, recurrent rather than primary disease, elevated LDH levels, and an alveolar-arterial gradient of greater than 30 mm Hg.[38–40] Because of the tendency for PCP to worsen after initiation of therapy (postulated as the result of an enhanced inflammatory response to dying organisms), adjunctive corticosteroids are indicated for partial pressure of oxygen less than 70 mm Hg or an alveolar-arterial gradient of greater than 35 mm Hg, because this intervention has been shown to reduce the risk of respiratory failure and death.[41,42] A Cochrane review concluded that the evidence supported the use of adjunctive corticosteroids to treat HIV-infected patients with PCP and substantial hypoxemia, although the number of appropriately conducted trials was small.[43] Although concern exists that use of adjunctive corticosteroids could worsen concomitant opportunistic infections (in particular, TB and CMV infections), these complications of steroid therapy in this context have been rare.[44] It is not essential to rule out concurrent infections before the use of steroids for PCP, although one should remain vigilant for such processes in a patient at risk.

Since the introduction of combination antiretroviral therapy, studies have identified additional risk factors for poor outcome, including older age, use of treatments other than TMP-SMX, concurrent culture of CMV from BAL fluid, and a CD4 cell count less than 50 cells/mm^3.[38,45] One retrospective study suggested that when controlling for other factors, receipt of combination antiretroviral therapy at the time of treatment for PCP is associated with improved survival.[46] Supporting this finding were the results of a controlled clinical trial that compared early versus delayed antiretroviral therapy in the setting of acute opportunistic infections, the bulk of which were PCP; the results showed that early

therapy was associated with a significantly reduced risk of HIV disease progression or death.[47]

Because culture of the organism in clinical laboratories is not practical, definitive diagnosis relies on visualization of cysts in respiratory secretions. As discussed previously, induced sputum is often the first diagnostic procedure, followed by BAL obtained with bronchoscopy, which has a sensitivity of 95% to 100%. Identification of cysts on appropriate stains is diagnostic of PCP because an asymptomatic carrier state does not appear to exist in HIV-infected individuals; however, persistence of organisms through and even after therapy is common and does not reflect failure of treatment.[48] A newer diagnostic technique is polymerase chain reaction (PCR) of respiratory secretions; however, this technique has been studied primarily in HIV-negative patients.[49] Serum (1→3)-β-D-glucan (β-glucan) is a component of the fungal wall of many fungi, including *P. jirovecii.* Measurement of serum β-glucan is a reliable serologic marker for PCP, particularly when respiratory symptoms are present.[50–53] In addition, the test may support the diagnosis of PCP when the clinical presentation is suggestive but sputum results are negative.[54]

Bacterial Pneumonia

Although impairment of cell-mediated immunity is the most notable HIV-related immune deficit, abnormalities in both humoral immunity and, in the late stages of disease, neutrophil function, occur.[55–57] As a result, bacterial infections, and particularly bacterial respiratory infections, frequently complicate HIV disease. In a study done after the availability of effective HIV therapy, the rate of bacterial pneumonia among patients with HIV was still over 10-fold higher than that in HIV-negative control subjects.[58] Because the encapsulated bacteria (in particular, *S. pneumoniae*) are more intrinsically virulent than the opportunistic infections of advanced HIV disease, these infections may occur at any stage of HIV disease and may be the sentinel opportunistic process in a person otherwise unaware of HIV infection. Among those with HIV infection, risk factors for the development of bacterial pneumonia are progressive immunodeficiency (as measured by the absolute CD4 cell count), cigarette smoking, and injection drug use.[59] Neither the use of TMP-SMX for PCP prophylaxis nor a history of immunization against *S. pneumoniae* is sufficiently protective against bacterial pneumonia to warrant a change in empirical therapy in consideration of this diagnosis.[60] Mortality from bacterial pneumonia is higher in patients with HIV who have a CD4 cell count of less than 100 cells/mm^3, radiographic progression of disease on therapy, and shock.[61] As with other opportunistic infections, use of antiretroviral therapy decreases the risk of bacterial pneumonia, but not to the rate of individuals who are HIV negative, even when the CD4 cell count normalizes.[3,6] Most patients with HIV-related community-acquired bacterial pneumonia respond promptly to empirical therapy. One study suggested that the prognosis is similar to that in patients without HIV infection, despite increased susceptibility to the disease.[62]

The most commonly identified pathogen in HIV-related bacterial pneumonia is *S. pneumoniae,* generally followed by *H. influenzae.*[63,64] Although both typically cause an acute illness and focal consolidation on chest radiography, *H. influenzae* may rarely cause a more subacute illness with diffuse interstitial infiltrates, suggestive of PCP. Gram-negative bacilli and *Staphylococcus aureus* (including methicillin-resistant strains) assume increasing importance as immunosuppression worsens, presumably from both neutrophil dysfunction and selective pressure of other antimicrobials. *Pseudomonas aeruginosa* infection has been associated with neutropenia, prior treatment with cephalosporins, and CD4 cell counts of less than 50 cells/mm^3. Another important feature of pseudomonal respiratory infections in patients with HIV is their predilection for relapse; chronic colonization typically ensues, with relapse rates after therapy between 25% and 86%.[65–67] Although pathogens of atypical pneumonia have been identified in HIV-infected hosts, in most published series they occur relatively infrequently, if at all.[63] *Nocardia* spp. are an important cause of pulmonary disease in immunocompromised hosts, including those with HIV infection.[68] The relative rarity of nocardiosis compared with other opportunistic processes may be due to the use of TMP-SMX for PCP prophylaxis, although TMP-SMX does not completely prevent *Nocardia* infection. The disease is usually subacute to chronic and limited to the lung, where cavitation may occur; it therefore may appear similar to TB.[69] Dissemination with positive blood cultures is also possible, especially in patients with advanced immunosuppression.

FIG. 123.1 Chest computed tomography in patient with human immunodeficiency virus with pulmonary and disseminated infection from *Rhodococcus equi,* showing a consolidation with cavitation in the lingula. Sputum and blood cultures were both positive for the organism, which was visualized on both Gram and acid-fast staining of respiratory secretions.

Rhodococcus equi can cause both localized pulmonary and disseminated disease in HIV-infected hosts, who appear to be particularly susceptible to this pathogen. A gram-positive coccobacillus, *R. equi* can be mistaken for routine oral flora on sputum smears; a clinical clue is that the organism also is weakly acid fast. The typical presentation is one of a chronic pneumonia (with cough, sputum production, and sometimes hemoptysis) with radiographs that show cavitary disease and often pleural effusions (Fig. 123.1); however, diverse radiographic findings have been reported.[70] Bacteremia commonly accompanies *Rhodococcus* pneumonia and may be the most reliable way to make the diagnosis.[71] Because treatment necessitates prolonged therapy with multiple agents, persistence or recurrence of symptomatic infection is common unless the immune status can be improved with antiretroviral therapy.[70]

Mycobacterial Pneumonia

HIV infection markedly increases the risk of the development of TB, as either progression of primary disease or reactivation. As noted previously, the likelihood of a pulmonary process being the result of TB is strongly influenced by the exposure history, which is related to the patient's current or past residence and the presence of other known risk factors, such as homelessness or incarceration. A majority of TB cases in the United States occur in foreign-born individuals, and rates are particularly high in immigrants from highly TB-endemic regions.[72]

The clinical presentation of TB in patients with HIV depends on the degree of immunosuppression.[25,29,73,74] Those with higher CD4 cell counts (>400 cells/mm^3) present similarly to those without HIV, with upper lobe cavitary disease and a low risk of extrapulmonary dissemination; the presence of constitutional symptoms is variable. At more advanced stages of immunosuppression, patients are more likely to have disseminated disease accompanied by prominent constitutional symptoms and unusual pulmonary manifestations such as mediastinal-hilar adenopathy, focal lower lobe or diffuse interstitial infiltrates, and pleural effusions. In these cases, sputum acid-fast smears are less likely to be positive than in those with cavitary disease, and diagnosis may ultimately be made with alternative methods such as isolator blood cultures (positive in one-fourth to one-half of patients) or tissue biopsy of an involved site (lymph node, bone marrow, or liver). Nonetheless, even with negative acid-fast bacillus smears on respiratory secretions, sputum or BAL cultures may ultimately be positive even with relatively subtle parenchymal abnormalities. Sputum nucleic acid amplification tests, some of which simultaneously assess for rifampin resistance, can hasten diagnosis, particularly for smear-negative cases.[75]

With respect to atypical mycobacteria, the respiratory tract may act as a portal of entry for *M. avium* complex, but it is rarely a primary cause of respiratory symptoms.[76,77] As a result, recovery of the organism from respiratory secretions may be a marker of colonization and a harbinger of disseminated disease but is not diagnostic of pulmonary infection and does not necessarily warrant treatment. Among the non-TB mycobacteria, *Mycobacterium kansasii* is the most likely to cause pulmonary disease in persons with HIV. It occurs uncommonly, mostly during advanced HIV disease, and has been associated with a subacute to chronic course that includes constitutional symptoms and cough; radiographic abnormalities include cavities, nodules, or infiltrates.[78–80] Isolation of the organism from sputum or BAL specimens generally warrants therapy because asymptomatic colonization is unusual.

Fungal Pneumonia

A variety of fungi other than *P. jirovecii* may cause pneumonia in patients with HIV. The most common are *Cryptococcus neoformans;* the endemic fungi *Coccidioides* species, *Histoplasma capsulatum,* and *Blastomyces dermatitidis;* and the mold *Aspergillus fumigatus.* These organisms tend to cause pneumonia only in the setting of severe immunosuppression (CD4 cell count <100 cells/mm^3). Although the lungs act as a portal of entry and may be the initial site of symptoms, hematogenous dissemination commonly occurs in the setting of advanced HIV.

Cryptococcal pneumonia typically has few symptoms; most patients present with meningitis and then are found to have a pulmonary infiltrate. However, some may have fever and cough; other findings may include dyspnea, chest pain, and hemoptysis.[81–83] Nonpulmonary symptoms depend on whether dissemination has occurred, most commonly to the central nervous system, where basilar meningitis can lead to headache, cranial neuropathies, and, in more severe cases, depressed consciousness. On occasion, physical examination reveals white papular lesions on the skin that mimic molluscum contagiosum. A wide range of radiographic abnormalities may occur, including diffuse interstitial infiltrates, focal consolidation, cavitary disease, nodules, adenopathy, and pleural effusions, with more extensive disease seen in those with lower CD4 cell counts. BAL cultures are usually positive, as is the serum cryptococcal antigen; antibody testing has no significant role. Even in the absence of central nervous system symptoms, a cerebrospinal fluid examination is mandatory in patients with AIDS who have cryptococcal pneumonia and a positive serum cryptococcal antigen because meningitis may be chronic or subacute and produce minimal symptoms. Not surprisingly, patients with HIV with higher CD4 cell counts and lower serum cryptococcal antigen titers are more likely to have localized pulmonary disease.[81]

Pulmonary histoplasmosis, coccidioidomycosis, and blastomycosis are generally limited to the geographic regions where these fungi are endemic, although, rarely, these infections may reactivate many years after travel or residence in one of these areas.[84] *Histoplasma capsulatum* is found worldwide, most notably in the Mississippi, Ohio, and St. Lawrence River valleys; the Caribbean; southern Mexico; and Central America. In patients with AIDS, pulmonary histoplasmosis is most commonly seen as a disseminated disease in an individual with a CD4 cell count of less than 100 cells/mm^3, with fever, wasting, adenopathy, diarrhea, and mucosal lesions accompanying the pulmonary process.[85,86] Cough and dyspnea are the most common pulmonary symptoms; typical radiographic findings are diffuse interstitial or reticulonodular infiltrates. The presence of hilar or mediastinal adenopathy may help distinguish histoplasmosis from *P. jirovecii,* but the clinical presentations in susceptible hosts overlap significantly. The diagnostic test of choice for histoplasmosis is detection of polysaccharide antigen in urine or blood; in disseminated histoplasmosis, these tests have reported sensitivities of 92% and 100%, respectively.[87] The antigen test does not distinguish between histoplasmosis and blastomycosis, but the latter rarely occurs in HIV-positive patients. These tests have supplanted antibody and skin testing. Blood cultures that use the lysis-centrifugation method and BAL fluid cultures are also often positive for histoplasmosis in patients with HIV. Because the organism grows slowly, results of histoplasmosis antigen testing are often available before the cultures turn positive.

Coccidioides spp. are endemic to the southwestern United States, northern Mexico, and parts of South and Central America. In endemic areas, they may cause pulmonary disease in individuals with HIV, usually affecting those with severe immunosuppression (CD4 cell counts <200 cells/mm^3).[88,89] As with histoplasmosis, pulmonary findings are often accompanied by clinical evidence of dissemination, including involvement of the skin, lymph nodes, bone, and meninges. Chest radiographic abnormalities are diverse and may include alveolar infiltrates, nodules, adenopathy, cavities, and pleural effusions. Isolation of the organism in respiratory secretions, usually through bronchoscopy, is generally necessary for the diagnosis. A positive isolator blood culture confirms the presence of disseminated disease. Presumptive diagnosis of coccidioidomycosis can also be made via urinary antigen testing, which has a sensitivity of 71% in patients with severe forms of the disease.[90] Although 80% of patients with HIV with pulmonary coccidioidomycosis have positive serology results, these titers have more of a role in monitoring response to therapy than in establishing the diagnosis. Skin testing with coccidioidal antigen has no useful role diagnostically and is no longer commercially available.

Of the endemic fungi, *B. dermatitidis* is the least likely to act as an opportunistic pathogen in patients with HIV.[91] The organism is found in the midwestern and south central United States. In a case series of blastomycosis in 15 patients with HIV, 12 had evidence of pulmonary involvement and 5 also had disseminated disease at the time of diagnosis. The predominant signs at presentation were fever, weight loss, and cough.[92]

Pulmonary aspergillosis in patients with HIV infection occurs almost exclusively in those with advanced HIV-related immunosuppression (CD4 cell count <50/mm^3). Frequently, other risk factors for aspergillosis are present as well, such as receipt of corticosteroids or neutropenia.[93–96] The specific organism is usually *A. fumigatus* or *Aspergillus flavus.* Respiratory tract disease is the most common manifestation; despite the predilection for the organism to invade blood vessel walls and disseminate, focal central nervous system disease from *Aspergillus* in patients with AIDS appears to occur more commonly from contiguous spread from the sinuses, orbits, and ears.[97]

Two types of *Aspergillus* respiratory disease have been described: invasive pseudomembranous tracheitis and invasive pneumonitis. In the former, fever, cough, dyspnea, and wheezing are common signs; the diagnosis is established when endoscopic examination reveals an exudative pseudomembrane adherent to the tracheal wall. In invasive pneumonitis, fever and cough may be accompanied by pleuritic pain and hemoptysis. Radiographic abnormalities in both of these forms overlap and can show diffuse infiltrates, cavities, and focal wedge-shaped abnormalities that reflect pulmonary infarction. A definitive diagnosis requires identification of fungal organisms consistent with *Aspergillus* on a biopsy specimen in a patient with the appropriate clinical syndrome. Not uncommonly, a presumptive diagnosis of pulmonary disease is made when *Aspergillus* spp. are cultured from respiratory secretions in a patient with fever, cough, infiltrates, and severe immunosuppression.

Viral Pneumonia

Although patients with HIV infection are at risk for viral pneumonitis, these conditions are rarely diagnosed in clinical practice, though the introduction of multiplex PCR diagnostic assays may increase the likelihood of diagnosis, at least of common respiratory viral pathogens. Cytomegalovirus presents a clinical quandary in patients with advanced HIV disease. Isolation of CMV from BAL specimens is relatively common, yet most patients with positive BAL cultures have an alternative diagnosis (especially PCP or bacterial pneumonia) and may have improvement without specific therapy directed at CMV.[98–100] Nonetheless, in a patient with advanced HIV disease (CD4 cell count <50 cells/mm^3), interstitial infiltrates on chest radiography, and no alternative diagnosis established, CMV may be the sole responsible pathogen. This diagnosis is confirmed when histopathology (samples are usually obtained via transbronchial biopsy or VATS) shows intracellular inclusions typical of CMV; cultures are confirmatory rather than diagnostic, and noninvasive blood testing (antibody or PCR) cannot provide definitive evidence of CMV pulmonary disease. Ganciclovir or valganciclovir therapy is indicated for cases confirmed with histopathology or with sufficient evidence to suggest that CMV may be acting as a copathogen when treatment of another diagnosis is associated with a suboptimal response.

During influenza season, patients with HIV may present with typical symptoms of influenza, consisting of an acute febrile illness associated with cough, myalgias, sore throat, and rigors. One prospective study found that during the winter, even when extensive testing for other respiratory viruses was done, influenza was the most common specific diagnosis among outpatients with HIV who presented with fever and respiratory symptoms.[101] Overall disease severity was mild. However, pulmonary complications from influenza and death can occur in HIV-infected individuals.[102] Although influenza vaccine is indicated for all individuals with HIV, not all patients receive the vaccine, and they may mount a suboptimal response to the vaccine with progressive immunodeficiency.[103] Chest radiographs are often negative, which suggests that, as with patients without HIV, primary influenza pneumonia is unusual[104,105]; major complications ensue with bacterial superinfection. The diagnosis of influenza is established either on clinical grounds during high influenza prevalence or with use of a reverse-transcriptase PCR influenza diagnostic test on respiratory secretions.

As with other populations with immunosuppression, pneumonitis in patients with HIV has been reported as a result of herpes simplex virus, adenovirus, respiratory syncytial virus, and parainfluenza virus. These causes of pneumonia are rare in patients with HIV but should be considered when clinicians cannot identify an alternative diagnosis. For herpes simplex virus, viral isolation in respiratory secretions usually indicates evidence of reactivation in the upper oropharynx rather than primary pneumonitis, but pulmonary or tracheal infection may occur, especially in the context of endotracheal or nasogastric intubation.

Parasitic Pneumonia

Among the various parasitic infections that occur in patients with HIV, none primarily affects the respiratory tract. However, rarely, they can lead to pulmonary disease as part of generalized dissemination or from focal lung involvement. Pulmonary toxoplasmosis is a rare form of severe pneumonia that occurs predominantly in patients with markedly depressed immune function (CD4 cell count <50 cells/mm^3).[106]

The clinical presentation of pulmonary toxoplasmosis is similar to that of PCP but, unlike PCP, it may be accompanied by a sepsis-like syndrome with hypotension. Radiographic abnormalities are diverse and consist most commonly of interstitial infiltrates but also potentially of nodules, effusions, or a mass lesion; as with PCP, an elevated LDH is a commonly reported laboratory finding.[107] Diagnosis is established with identification of *Toxoplasma* tachyzoites on Giemsa stain of BAL fluid or tissue obtained on biopsy; alternative techniques such as PCR or tissue culture are available in commercial laboratories and research settings.

Despite its association with defects in cell-mediated immunity, disseminated infection to the lung of *Strongyloides stercoralis* is surprisingly rare in individuals with HIV, even in areas highly endemic for both HIV and *Strongyloides*. Indeed, many patients with HIV with *Strongyloides* superinfection syndrome have other classic risk factors, including receipt of corticosteroids, severe wasting, or human T-cell lymphotropic virus type 1 coinfection. Clinicians should consider this diagnosis in a patient with HIV, especially with the previously mentioned risk factors, who presents with pneumonitis, gram-negative sepsis, and sometimes meningitis.[108,109] Identification of *Strongyloides* larvae on a centrifuged BAL specimen is diagnostic; eosinophilia is variably present, and its absence does not exclude the diagnosis.

Although cryptosporidiosis and microsporidiosis predominantly involve the gastrointestinal tract, both can, rarely, colonize the lung and lead to pulmonary disease.[110,111] Diagnosis is made through direct visualization of the organism on respiratory secretions or histopathology, with appropriate stains: modified acid-fast stain for cryptosporidiosis and the modified trichrome stain for microsporidiosis. Because antimicrobial treatment for these conditions is suboptimal, improvement of immune function with antiretroviral therapy is the preferred treatment.

Neoplastic and Other Noninfectious Pulmonary Complications of HIV Infection

The two neoplasms of the lung that are considered AIDS-defining conditions are pulmonary KS and non-Hodgkin lymphoma. Patients

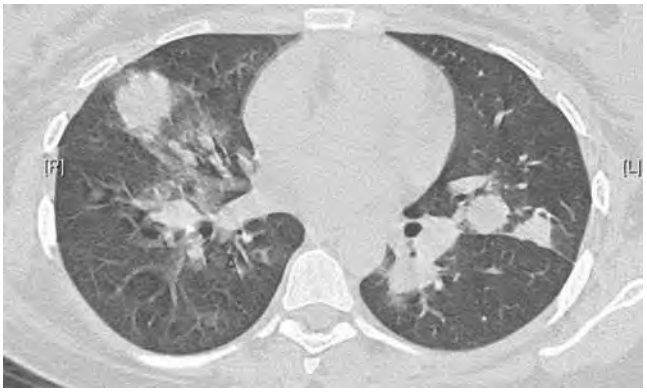

FIG. 123.2 Chest computed tomography in patient with human immunodeficiency virus with biopsy-confirmed pulmonary Kaposi sarcoma. Despite the extensive bilateral lung nodules seen on this study, the patient's only respiratory symptom was a mild cough. Nearly complete clearance was achieved with chemotherapy and combination antiretroviral therapy.

with pulmonary KS usually have evidence of cutaneous or mucosal disease; in one series, only 16% had disease limited to the lungs.[112,113] The disease may be asymptomatic even with extensive abnormalities on chest radiograph (Fig. 123.2); these abnormalities are typically nodular infiltrates with or without pulmonary effusions, with chest computed tomography showing a peribronchovascular distribution of infiltrates. Diagnosis is generally made through direct visualization of characteristic purplish plaques on bronchoscopy; because these lesions are highly vascular and quite typical, biopsy is often avoided due to the risk of hemorrhage. Treatment with chemotherapy is indicated for symptomatic pulmonary disease. However, as with cutaneous KS, antiretroviral therapy can induce significant improvement in pulmonary KS and sustained remissions; in some cases, antiretroviral therapy can even obviate the need for chemotherapy.[114,115] Conversely, HIV treatment has also rarely been associated with inflammatory worsening of KS, as a form of the immune reconstitution inflammatory syndrome.[116] Such cases should be managed with continued antiretroviral therapy combined with chemotherapy to control flares of the disease.

The radiographic findings in pulmonary lymphoma are diverse and may consist of nodules, masses, and pleural effusions.[117] Although the diagnosis can sometimes be established through BAL with cytology, transbronchial biopsy, or thoracentesis, these procedures have a low yield, and VATS is often necessary.[118] Nonspecific findings that suggest lymphoma are elevations in LDH and a positive positron emission tomography scan corresponding to the area of abnormality on chest imaging. Pleural effusion lymphocytes contain human herpesvirus 8 proteins in both KS and primary effusion lymphoma, but the cytology in the latter is distinctive.

In many centers, the most common pulmonary neoplasm encountered in patients with HIV is lung cancer.[119] Risk factors for the development of lung cancer are similar to those in non–HIV-infected populations, with smokers having the greatest risk.[120] HIV-infected patients who smoke now lose more years of life from smoking than from HIV.[121] Unlike the AIDS-defining cancers, KS and lymphoma, the incidence of lung cancer in HIV patients is likely to increase because of the prolonged survival associated with antiretroviral therapy. As with other non–AIDS-related malignant diseases, the risk appears to be greatest for those with lower nadir CD4 cell counts.[122]

Although lymphocytic interstitial pneumonitis is seen more commonly in children with HIV, this complication may, rarely, develop in adults as well.[123] The presentation is similar to a related condition, nonspecific interstitial pneumonitis, with cough, shortness of breath, and constitutional symptoms. Diffuse reticulonodular or interstitial infiltrates are seen on chest imaging, which makes differentiation from PCP difficult. However, compared with patients in whom HIV-related opportunistic infections develop, those with lymphocytic interstitial pneumonitis usually have a relatively preserved or even normal CD4 cell count.

Because diagnosis is made through histopathology and exclusion of infectious etiologies, transbronchial or VATS biopsy is indicated. Several case reports have shown that antiretroviral therapy may lead to substantial improvement in lymphocytic interstitial pneumonitis.[124,125] For unresponsive cases, corticosteroids may be effective.[123]

HIV infection is a risk factor for the development of pulmonary hypertension.[126,127] It occurs at all stages of HIV disease, with variable CD4 cell counts and HIV RNA levels at the time of presentation. In some series, women represent a disproportionate number of the cases.[128] The predominant symptom is exertional dyspnea; cough, fatigue, and chest pain may also be present. The key to the diagnosis is recognition that the symptoms are not related to a primary pulmonary infectious process; physical examination signs consistent with right ventricular hypertrophy or failure are helpful but often not present initially. An echocardiogram shows evidence of right atrial hypertrophy and elevated pulmonary pressures; this is then confirmed with right heart catheterization. Management of pulmonary hypertension is the same as for HIV-negative hosts, with prostaglandin agonists (epoprostenol), endothelin receptor antagonists (bosentan, ambrisentan), diuretics, and anticoagulation therapy; sildenafil may also have a role, but clinicians should be cautious about drug interactions with some antiretroviral agents. Studies have not consistently shown a beneficial response to antiretroviral therapy.[129,130]

Patients with HIV are at greater risk for the development of COPD, particularly emphysema, than are HIV-negative subjects.[131] Some observational studies suggest that antiretroviral therapy may decrease the likelihood of developing this condition.[5,132] Cigarette smoking is highly prevalent among patients with HIV but is an area of prevention that is often overlooked by providers.

Abacavir is a nucleoside reverse transcriptase inhibitor that causes a systemic reaction in approximately 5% of individuals, usually within 1 to 6 weeks of starting the drug[133] (see Chapter 128). As part of this multisystem reaction, cough and dyspnea may occur, along with fever, rash, fatigue, malaise, gastrointestinal symptoms, and arthralgias.[134] Clinicians who evaluate patients who have recently been started on abacavir must be aware that this nucleoside reverse transcriptase inhibitor can cause a systemic hypersensitivity reaction because continued abacavir treatment in the face of this reaction can be fatal. Symptoms generally resolve slowly after cessation of the drug. Abacavir should never be resumed in such circumstances because rechallenge can lead to an immediate and life-threatening recurrence of the hypersensitivity reaction. Because abacavir hypersensitivity can mimic other processes, in particular influenza, helpful clinical clues that make recognizing hypersensitivity more likely are worsening of symptoms after each dose, gastrointestinal symptoms, and rash.[135] A strong association is seen between the presence of the human leukocyte antigen (HLA)-B*5701 allele and the risk of development of abacavir hypersensitivity[136]; therefore patients must be tested for HLA-B*5701 before initiation of abacavir, and the drug is contraindicated in those who are positive. Such a strategy markedly reduces the risk of severe hypersensitivity.

TREATMENT

Treatment of opportunistic infections of the lung and other sites is discussed in Chapter 129.

Key References

The complete reference list is available online at Expert Consult.

1. Wolff AJ, O'Donnell AE. Pulmonary manifestations of HIV infection in the era of highly active antiretroviral therapy. *Chest*. 2001;120:1888–1893.
2. Wallace JM, Hansen NI, Lavange L, et al. Respiratory disease trends in the Pulmonary Complications of HIV Infection Study cohort. Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med*. 1997;155:72–80.
5. Gingo MR, Balasubramani GK, Kingsley L, et al. The impact of HAART on the respiratory complications of HIV infection: longitudinal trends in the MACS and WIHS cohorts. *PLoS ONE*. 2013;8:e58812.
6. Sogaard OS, Lohse N, Gerstoft J, et al. Hospitalization for pneumonia among individuals with and without HIV infection, 1995-2007: a Danish population-based, nationwide cohort study. *Clin Infect Dis*. 2008;47:1345.
12. Phair J, Munoz A, Detels R, et al. The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. *N Engl J Med*. 1990;322:161–165.
15. Selwyn PA, Pumerantz AS, Durante A, et al. Clinical predictors of *Pneumocystis carinii* pneumonia, bacterial pneumonia and tuberculosis in HIV-infected patients. *AIDS*. 1998;12:885–893.
17. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. *N Engl J Med*. 1995;332:693–699.
21. Attia EF, McGinnis KA, Feemster LC, et al. Association of COPD with risk for pulmonary infections requiring hospitalization in HIV-infected veterans. *J Acquir Immune Defic Syndr*. 2015;70:280–288.
22. Lambert AA, Kirk GD, Astemborski J, et al. HIV infection is associated with increased risk for acute exacerbation of COPD. *J Acquir Immune Defic Syndr*. 2015;69:68–74.
23. Depp TB, McGinnis KA, Kraemer K, et al. Risk factors associated with acute exacerbation of chronic obstructive pulmonary disease in HIV-infected and uninfected patients. *AIDS*. 2016;30:455–463.
25. Perlman DC, el-Sadr WM, Nelson ET, et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). *Clin Infect Dis*. 1997;25:242–246.
26. Baril L, Astagneau P, Nguyen J, et al. Pyogenic bacterial pneumonia in human immunodeficiency virus-infected inpatients: a clinical, radiological, microbiological, and epidemiological study. *Clin Infect Dis*. 1998;26:964–971.
28. DeLorenzo LJ, Huang CT, Maguire GP, et al. Roentgenographic patterns of *Pneumocystis carinii* pneumonia in 104 patients with AIDS. *Chest*. 1987;91:323–327.
29. Greenberg SD, Frager D, Suster B, et al. Active pulmonary tuberculosis in patients with AIDS: spectrum of radiographic findings (including a normal appearance). *Radiology*. 1994;193:115–119.
30. Janoff EN, Breiman RF, Daley CL, et al. Pneumococcal disease during HIV infection. Epidemiologic, clinical, and immunologic perspectives. *Ann Intern Med*. 1992;117:314–324.
34. Moore RD, Chaisson RE. Natural history of opportunistic disease in an HIV-infected urban clinical cohort. *Ann Intern Med*. 1996;124:633–642.
38. Benfield TL, Helweg-Larsen J, Bang D, et al. Prognostic markers of short-term mortality in AIDS-associated *Pneumocystis carinii* pneumonia. *Chest*. 2001;119:844–851.
39. Brenner M, Ognibene FP, Lack EE, et al. Prognostic factors and life expectancy of patients with acquired immunodeficiency syndrome and *Pneumocystis carinii* pneumonia. *Am Rev Respir Dis*. 1987;136:1199–1206.
41. Bozzette SA, Sattler FR, Chiu J, et al. A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. *N Engl J Med*. 1990;323:1451–1457.
42. Gagnon S, Boota AM, Fischl MA, et al. Corticosteroids as adjunctive therapy for severe *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A double-blind, placebo-controlled trial. *N Engl J Med*. 1990;323:1444–1450.
43. Ewald H, Raatz H, Boscacci R, et al. Adjunctive corticosteroids for *Pneumocystis jiroveci* pneumonia in patients with HIV infection. *Cochrane Database Syst Rev*. 2015;(4):CD006150.
47. Zolopa AR, Andersen J, Komarow L, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS ONE*. 2009;4:e5575.
52. Sax PE, Komarow L, Finkelman MA. Blood (1->3)-beta-D-glucan as a diagnostic test for HIV-related *Pneumocystis jirovecii* pneumonia. *Clin Infect Dis*. 2011;53:197–202.
56. Lane HC, Masur H, Edgar LC, et al. Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1983;309:453–458.
60. French N, Nakiyingi J, Carpenter LM, et al. 23-Valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet*. 2000;355:2106–2111.
62. Malinis M, Myers J, Bordon J, et al. Clinical outcomes of HIV-infected patients hospitalized with bacterial community-acquired pneumonia. *Int J Infect Dis*. 2010;14:e22–e27.
64. Rimland D, Navin TR, Lennox JL, et al. Prospective study of etiologic agents of community-acquired pneumonia in patients with HIV infection. *AIDS*. 2002;16:85–95.
65. Fichtenbaum CJ, Woeltje KF, Powderly WG. Serious *Pseudomonas aeruginosa* infections in patients infected with human immunodeficiency virus: a case-control study. *Clin Infect Dis*. 1994;19:417–422.
69. Uttamchandani RB, Daikos GL, Reyes RR, et al. Nocardiosis in 30 patients with advanced human immunodeficiency virus infection: clinical features and outcome. *Clin Infect Dis*. 1994;18:348–353.
70. Torres-Tortosa M, Arrizabalaga J, Villanueva JL, et al. Prognosis and clinical evaluation of infection caused by *Rhodococcus equi* in HIV-infected patients: a multicenter study of 67 cases. *Chest*. 2003;123:1970–1976.
79. Canueto-Quintero J, Caballero-Granado FJ, Herrero-Romero M, et al. Epidemiological, clinical, and prognostic differences between the diseases caused by *Mycobacterium kansasii* and *Mycobacterium tuberculosis* in patients infected with human immunodeficiency virus: a multicenter study. *Clin Infect Dis*. 2003;37:584–590.
81. Meyohas MC, Roux P, Bollens D, et al. Pulmonary cryptococcosis: localized and disseminated infections in 27 patients with AIDS. *Clin Infect Dis*. 1995;21:628–633.
86. Wheat LJ, Connolly-Stringfield PA, Baker RL, et al. Disseminated histoplasmosis in the acquired immune deficiency syndrome: clinical findings, diagnosis and treatment, and review of the literature. *Medicine (Baltimore)*. 1990;69:361–374.
89. Masannat FY, Ampel NM. Coccidioidomyocis in patients with HIV-1 infection in the era of potent antiretroviral therapy. *Clin Infect Dis*. 2010;50:1–7.
92. Pappas PG, Pottage JC, Powderly WG, et al. Blastomycosis in patients with the acquired immunodeficiency syndrome. *Ann Intern Med*. 1992;116:847–853.
95. Denning DW, Follansbee SE, Scolaro M, et al. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. *N Engl J Med*. 1991;324:654–662.
96. Mylonakis E, Barlam TF, Flanigan T, et al. Pulmonary aspergillosis and invasive disease in AIDS: review of 342 cases. *Chest*. 1998;114:251–262.
101. Klein MB, Lu Y, DelBalso L, et al. Influenzavirus infection is a primary cause of febrile respiratory illness in HIV-infected adults, despite vaccination. *Clin Infect Dis*. 2007;45:234–240.
102. Tempia S, Walaza S, Viboud C, et al. Deaths associated with respiratory syncytial and influenza viruses among

persons ≥5 years of age in HIV-prevalent area, South Africa, 1998-2009(1). *Emerg Infect Dis*. 2015;21:600–608.
105. Skiest DJ, Kaplan P, Machala T, et al. Clinical manifestations of influenza in HIV-infected individuals. *Int J STD AIDS*. 2001;12:646–650.
106. Rabaud C, May T, Lucet JC, et al. Pulmonary toxoplasmosis in patients infected with human immunodeficiency virus: a French National Survey. *Clin Infect Dis*. 1996;23:1249–1254.
113. Aboulafia DM. The epidemiologic, pathologic, and clinical features of AIDS-associated pulmonary Kaposi's sarcoma. *Chest*. 2000;117:1128–1145.
115. Holkova B, Takeshita K, Cheng DM, et al. Effect of highly active antiretroviral therapy on survival in patients with AIDS-associated pulmonary Kaposi's sarcoma treated with chemotherapy. *J Clin Oncol*. 2001;19:3848–3851.
119. Silverberg MJ, Lau B, Achenbach CJ, et al. Cumulative incidence of cancer among persons with HIV in North America: a cohort study. *Ann Intern Med*. 2015;163:507–518.
121. Helleberg M, May MT, Ingle SM, et al. Smoking and life expectancy among HIV-infected individuals on antiretroviral therapy in Europe and North America. *AIDS*. 2015;29:221–229.
122. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. *Ann Intern Med*. 2008;148:728–736.
123. Das S, Miller RF. Lymphocytic interstitial pneumonitis in HIV infected adults. *Sex Transm Infect*. 2003;79: 88–93.
126. Mehta NJ, Khan IA, Mehta RN, et al. HIV-related pulmonary hypertension: analytic review of 131 cases. *Chest*. 2000;118:1133–1141.
128. Opravil M, Pechere M, Speich R, et al. HIV-associated primary pulmonary hypertension. A case control study. Swiss HIV Cohort Study. *Am J Respir Crit Care Med*. 1997;155:990–995.
129. Sitbon O, Lascoux-Combe C, Sereni D, et al. Prevalence of pulmonary arterial hypertension in HIV-positive outpatients in the highly active antiretroviral therapy era. *Am J Respir Crit Care Med*. 2008;177:108–113.
130. Zuber JP, Calmy A, Evison JM, et al. Pulmonary arterial hypertension related to HIV infection: improved hemodynamics and survival associated with antiretroviral therapy. *Clin Infect Dis*. 2004;38:1178–1185.
133. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet*. 2002;359:727–732.
136. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358:568–579.

References

1. Wolff AJ, O'Donnell AE. Pulmonary manifestations of HIV infection in the era of highly active antiretroviral therapy. *Chest*. 2001;120:1888–1893.
2. Wallace JM, Hansen NI, Lavange L, et al. Respiratory disease trends in the Pulmonary Complications of HIV Infection Study cohort. Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med*. 1997;155:72–80.
3. Sullivan JH, Moore RD, Keruly JC, et al. Effect of antiretroviral therapy on the incidence of bacterial pneumonia in patients with advanced HIV infection. *Am J Respir Crit Care Med*. 2000;162:64–67.
4. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338:853–860.
5. Gingo MR, Balasubramani GK, Kingsley L, et al. The impact of HAART on the respiratory complications of HIV infection: longitudinal trends in the MACS and WIHS cohorts. *PLoS ONE*. 2013;8:e58812.
6. Sogaard OS, Lohse N, Gerstoft J, et al. Hospitalization for pneumonia among individuals with and without HIV infection, 1995-2007: a Danish population-based, nationwide cohort study. *Clin Infect Dis*. 2008;47:1345.
7. Hardy WD, Feinberg J, Finkelstein DM, et al. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trials Group Protocol 021. *N Engl J Med*. 1992;327:1842–1848.
8. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary complications of HIV Infection Study Group. *N Engl J Med*. 1995;333:845–851.
9. Mayer HB, Rose DN, Cohen S, et al. The effect of *Pneumocystis carinii* pneumonia prophylaxis regimens on the incidence of bacterial infections in HIV-infected patients. *AIDS*. 1993;7:1687–1689.
10. Navin TR, Rimland D, Lennox JL, et al. Risk factors for community-acquired pneumonia among persons infected with human immunodeficiency virus. *J Infect Dis*. 2000;181:158–164.
11. Rodriguez-Barradas MC, Tharapel RA, Groover JE, et al. Colonization by *Streptococcus pneumoniae* among human immunodeficiency virus-infected adults: prevalence of antibiotic resistance, impact of immunization, and characterization by polymerase chain reaction with BOX primers of isolates from persistent *S. pneumoniae* carriers. *J Infect Dis*. 1997;175:590–597.
12. Phair J, Munoz A, Detels R, et al. The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. *N Engl J Med*. 1990;322:161–165.
13. Hoover DR, Saah AJ, Bacellar H, et al. Clinical manifestations of AIDS in the era of *Pneumocystis* prophylaxis. Multicenter AIDS Cohort Study. *N Engl J Med*. 1993;329:1922–1926.
14. Stansell JD, Osmond DH, Charlebois E, et al. Predictors of *Pneumocystis carinii* pneumonia in HIV-infected persons. Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med*. 1997;155:60–66.
15. Selwyn PA, Pumerantz AS, Durante A, et al. Clinical predictors of *Pneumocystis carinii* pneumonia, bacterial pneumonia and tuberculosis in HIV-infected patients. *AIDS*. 1998;12:885–893.
16. Chan C, Montaner J, Lefebvre EA, et al. Atovaquone suspension compared with aerosolized pentamidine for prevention of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected subjects intolerant of trimethoprim or sulfonamides. *J Infect Dis*. 1999;180:369–376.
17. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. *N Engl J Med*. 1995;332:693–699.
18. Torres RA, Barr M, Thorn M, et al. Randomized trial of dapsone and aerosolized pentamidine for the prophylaxis of *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis. *Am J Med*. 1993;95:573–583.
19. The INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. 2015;373:795–807.
20. Twigg HL III, Weiden M, Valentine F, et al. Effect of highly active antiretroviral therapy on viral burden in the lungs of HIV-infected subjects. *J Infect Dis*. 2008;197:109–116.
21. Attia EF, McGinnis KA, Feemster LC, et al. Association of COPD with risk for pulmonary infections requiring hospitalization in HIV-infected veterans. *J Acquir Immune Defic Syndr*. 2015;70:280–288.
22. Lambert AA, Kirk GD, Astemborski J, et al. HIV infection is associated with increased risk for acute exacerbation of COPD. *J Acquir Immune Defic Syndr*. 2015;69:68–74.
23. Depp TB, McGinnis KA, Kraemer K, et al. Risk factors associated with acute exacerbation of chronic obstructive pulmonary disease in HIV-infected and uninfected patients. *AIDS*. 2016;30:455–463.
24. Crans CA Jr, Boiselle PM. Imaging features of *Pneumocystis carinii* pneumonia. *Crit Rev Diagn Imaging*. 1999;40:251–284.
25. Perlman DC, el-Sadr WM, Nelson ET, et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). *Clin Infect Dis*. 1997;25:242–246.
26. Baril L, Astagneau P, Nguyen J, et al. Pyogenic bacterial pneumonia in human immunodeficiency virus-infected inpatients: a clinical, radiological, microbiological, and epidemiological study. *Clin Infect Dis*. 1998;26:964–971.
27. Cordero E, Pachon J, Rivero A, et al. *Haemophilus influenzae* pneumonia in human immunodeficiency virus-infected patients. The Grupo Andaluz para el Estudio de las Enfermedades Infecciosas. *Clin Infect Dis*. 2000;30:461–465.
28. DeLorenzo LJ, Huang CT, Maguire GP, et al. Roentgenographic patterns of *Pneumocystis carinii* pneumonia in 104 patients with AIDS. *Chest*. 1987;91:323–327.
29. Greenberg SD, Frager D, Suster B, et al. Active pulmonary tuberculosis in patients with AIDS: spectrum of radiographic findings (including a normal appearance). *Radiology*. 1994;193:115–119.
30. Janoff EN, Breiman RF, Daley CL, et al. Pneumococcal disease during HIV infection. Epidemiologic, clinical, and immunologic perspectives. *Ann Intern Med*. 1992;117:314–324.
31. Boulware DR, Daley CL, Merrifield C, et al. Rapid diagnosis of pneumococcal pneumonia among HIV-infected adults with urine antigen detection. *J Infect*. 2007;55:300–309.
32. Cruciani M, Marcati P, Malena M, et al. Meta-analysis of diagnostic procedures for *Pneumocystis carinii* pneumonia in HIV-1-infected patients. *Eur Respir J*. 2002;20:982–989.
33. Kovacs JA, Ng VL, Masur H, et al. Diagnosis of *Pneumocystis carinii* pneumonia: improved detection in sputum with use of monoclonal antibodies. *N Engl J Med*. 1988;318:589–593.
34. Moore RD, Chaisson RE. Natural history of opportunistic disease in an HIV-infected urban clinical cohort. *Ann Intern Med*. 1996;124:633–642.
35. Gallant JE, McAvinue SM, Moore RD, et al. The impact of prophylaxis on outcome and resource utilization in *Pneumocystis carinii* pneumonia. *Chest*. 1995;107:1018–1023.
36. Azoulay E, Parrot A, Flahault A, et al. AIDS-related *Pneumocystis carinii* pneumonia in the era of adjunctive steroids: implication of BAL neutrophilia. *Am J Respir Crit Care Med*. 1999;160:493–499.
37. Walzer PD, Evans HER, Copas AJ, et al. Early predictors of mortality from *Pneumocystis jirovecii* pneumonia in HIV-infected patients: 1985-2006. *Clin Infect Dis*. 2008;46:634–636.
38. Benfield TL, Helweg-Larsen J, Bang D, et al. Prognostic markers of short-term mortality in AIDS-associated *Pneumocystis carinii* pneumonia. *Chest*. 2001;119:844–851.
39. Brenner M, Ognibene FP, Lack EE, et al. Prognostic factors and life expectancy of patients with acquired immunodeficiency syndrome and *Pneumocystis carinii* pneumonia. *Am Rev Respir Dis*. 1987;136:1199–1206.
40. Zaman MK, White DA. Serum lactate dehydrogenase levels and *Pneumocystis carinii* pneumonia. Diagnostic and prognostic significance. *Am Rev Respir Dis*. 1988;137:796–800.
41. Bozzette SA, Sattler FR, Chiu J, et al. A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. *N Engl J Med*. 1990;323:1451–1457.
42. Gagnon S, Boota AM, Fischl MA, et al. Corticosteroids as adjunctive therapy for severe *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A double-blind, placebo-controlled trial. *N Engl J Med*. 1990;323:1444–1450.
43. Ewald H, Raatz H, Boscacci R, et al. Adjunctive corticosteroids for *Pneumocystis jiroveci* pneumonia in patients with HIV infection. *Cochrane Database Syst Rev*. 2015;(4):CD006150.
44. Gallant JE, Chaisson RE, Moore RD. The effect of adjunctive corticosteroids for the treatment of *Pneumocystis carinii* pneumonia on mortality and subsequent complications. *Chest*. 1998;114:1258–1263.
45. Dworkin MS, Hanson DL, Navin TR. Survival of patients with AIDS, after diagnosis of *Pneumocystis carinii* pneumonia, in the United States. *J Infect Dis*. 2001;183:1409–1412.
46. Morris A, Wachter RM, Luce J, et al. Improved survival with highly active antiretroviral therapy in HIV-infected patients with severe *Pneumocystis carinii* pneumonia. *AIDS*. 2003;17:73–80.
47. Zolopa AR, Andersen J, Komarow L, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS ONE*. 2009;4:e5575.
48. O'Donnell WJ, Pieciak W, Chertow GM, et al. Clearance of *Pneumocystis carinii* cysts in acute *P. carinii* pneumonia: assessment by serial sputum induction. *Chest*. 1998;114:1264–1268.
49. Doyle L, Vogel S, Procop GW. *Pneumocystis* PCR: it is time to make PCR the test of choice. *Open Forum Infect Dis*. 2017;4:ofx193.
50. Fujii T, Nakamura T, Iwamoto A. *Pneumocystis* pneumonia in patients with HIV infection: clinical manifestations, laboratory findings, and radiological features. *J Infect Chemother*. 2007;13:1–7.
51. Marty FM, Koo S, Bryar J, et al. 1 → 3)β-D-glucan assay positivity in patients with *Pneumocystis (carinii) jiroveci* pneumonia. *Ann Intern Med*. 2007;147:70–72.
52. Sax PE, Komarow L, Finkelman MA. Blood (1->3)-beta-D-glucan as a diagnostic test for HIV-related *Pneumocystis jirovecii* pneumonia. *Clin Infect Dis*. 2011;53:197–202.
53. Wood BR, Komarow L, Zolopa AR, et al. Test performance of blood beta-glucan for *Pneumocystis jirovecii* pneumonia in patients with AIDS and respiratory symptoms. *AIDS*. 2013;27:967–972.
54. Pisculli ML, Sax PE. Use of a serum β-glucan assay for diagnosis of HIV-related *Pneumocystis jiroveci* pneumonia in patients with negative microscopic examination results. *Clin Infect Dis*. 2008;46:1928–1930.
55. Parkin JM, Helbert M, Hughes CL, et al. Immunoglobulin G subclass deficiency and susceptibility to pyogenic infections in patients with AIDS-related complex and AIDS. *AIDS*. 1989;3:37–39.
56. Lane HC, Masur H, Edgar LC, et al. Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1983;309:453–458.
57. Ellis M, Gupta S, Galant S, et al. Impaired neutrophil function in patients with AIDS or AIDS-related complex: a comprehensive evaluation. *J Infect Dis*. 1988;158:1268–1276.
58. Kohli R, Lo Y, Flanigan TP, et al. Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV epidemiologic research (HER) study. *Clin Infect Dis*. 2006;43:90–98.
59. Afessa B, Green B. Clinical course, prognostic factors, and outcome prediction for HIV patients in the ICU. The PIP (pulmonary complications, ICU support, and prognostic factors in hospitalized patients with HIV) study. *Chest*. 2000;118:138–145.
60. French N, Nakiyingi J, Carpenter LM, et al. 23-Valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet*. 2000;355:2106–2111.
61. Cordero E, Pachon J, Rivero A, et al. Community-acquired bacterial pneumonia in human immunodeficiency virus-infected patients: validation of severity criteria. The Grupo Andaluz para el Estudio de las Enfermedades Infecciosas. *Am J Respir Crit Care Med*. 2000;162:2063–2068.
62. Malinis M, Myers J, Bordon J, et al. Clinical outcomes of HIV-infected patients hospitalized with bacterial community-acquired pneumonia. *Int J Infect Dis*. 2010;14:e22–e27.
63. Bartlett JG. Pneumonia in the patient with HIV infection. *Infect Dis Clin North Am*. 1998;12:807–820, xi.
64. Rimland D, Navin TR, Lennox JL, et al. Prospective study of etiologic agents of community-acquired pneumonia in patients with HIV infection. *AIDS*. 2002;16:85–95.
65. Fichtenbaum CJ, Woeltje KF, Powderly WG. Serious *Pseudomonas aeruginosa* infections in patients infected with human immunodeficiency virus: a case-control study. *Clin Infect Dis*. 1994;19:417–422.
66. Asboe D, Gant V, Aucken HM, et al. Persistence of *Pseudomonas aeruginosa* strains in respiratory infection in AIDS patients. *AIDS*. 1998;12:1771–1775.

67. Sorvillo F, Beall G, Turner PA, et al. Incidence and determinants of *Pseudomonas aeruginosa* infection among persons with HIV: association with hospital exposure. *Am J Infect Control*. 2001;29:79–84.
68. Pintado V, Gomez-Mampaso E, Fortun J, et al. Infection with *Nocardia* species: clinical spectrum of disease and species distribution in Madrid, Spain, 1978-2001. *Infection*. 2002;30:338–340.
69. Uttamchandani RB, Daikos GL, Reyes RR, et al. Nocardiosis in 30 patients with advanced human immunodeficiency virus infection: clinical features and outcome. *Clin Infect Dis*. 1994;18:348–353.
70. Torres-Tortosa M, Arrizabalaga J, Villanueva JL, et al. Prognosis and clinical evaluation of infection caused by *Rhodococcus equi* in HIV-infected patients: a multicenter study of 67 cases. *Chest*. 2003;123:1970–1976.
71. Donisi A, Suardi MG, Casari S, et al. *Rhodococcus equi* infection in HIV-infected patients. *AIDS*. 1996;10:359–362.
72. Schmit KM, et al. Tuberculosis – United States, 2016. *MMWR*. 2017;66:289–294.
73. Havlir DV, Barnes PF. Tuberculosis in patients with human immunodeficiency virus infection. *N Engl J Med*. 1999;340:367–373.
74. Jones BE, Young SM, Antoniskis D, et al. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *Am Rev Respir Dis*. 1993;148:1292–1297.
75. O'Grady J, Bates M, Chilukutu L, et al. Evaluation of the Xpert MTB/RIF assay at a tertiary care hospital in a setting where tuberculosis and TB are highly endemic. *Clin Infect Dis*. 2012;55:1171–1178.
76. Chin DP, Hopewell PC, Yajko DM, et al. *Mycobacterium avium* complex in the respiratory or gastrointestinal tract and the risk of *M. avium* complex bacteremia in patients with human immunodeficiency virus infection. *J Infect Dis*. 1994;169:289–295.
77. Kalayjian RC, Toossi Z, Tomashefski JF Jr, et al. Pulmonary disease due to infection by *Mycobacterium avium* complex in patients with AIDS. *Clin Infect Dis*. 1995;20:1186–1194.
78. Campo RE, Campo CE. *Mycobacterium kansasii* disease in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1997;24:1233–1238.
79. Canueto-Quintero J, Caballero-Granado FJ, Herrero-Romero M, et al. Epidemiological, clinical, and prognostic differences between the diseases caused by *Mycobacterium kansasii* and *Mycobacterium tuberculosis* in patients infected with human immunodeficiency virus: a multicenter study. *Clin Infect Dis*. 2003;37:584–590.
80. Cattamanchi A, Nahid P, Marras TK, et al. Detailed analysis of the radiographic presentation of *Mycobacterium kansasii* lung disease in patients with HIV infection. *Chest*. 2008;133:875–880.
81. Meyohas MC, Roux P, Bollens D, et al. Pulmonary cryptococcosis: localized and disseminated infections in 27 patients with AIDS. *Clin Infect Dis*. 1995;21:628–633.
82. Wasser L, Talavera W. Pulmonary cryptococcosis in AIDS. *Chest*. 1987;92:692–695.
83. Cameron ML, Bartlett JA, Gallis HA, et al. Manifestations of pulmonary cryptococcosis in patients with acquired immunodeficiency syndrome. *Rev Infect Dis*. 1991;13:64–67.
84. Salzman SH, Smith RL, Aranda CP. Histoplasmosis in patients at risk for the acquired immunodeficiency syndrome in a non-endemic setting. *Chest*. 1988;93:916–921.
85. Nightingale SD, Parks JM, Pounders SM, et al. Disseminated histoplasmosis in patients with AIDS. *South Med J*. 1990;83:624–630.
86. Wheat LJ, Connolly-Stringfield PA, Baker RL, et al. Disseminated histoplasmosis in the acquired immune deficiency syndrome: clinical findings, diagnosis and treatment, and review of the literature. *Medicine (Baltimore)*. 1990;69:361–374.
87. Hage CA, Ribes JA, Wengenack NL, et al. A multicenter evaluation of tests for diagnosis of histoplasmosis. *Clin Infect Dis*. 2011;53:448–454.
88. Ampel NM. Coccidioidomycosis among persons with human immunodeficiency virus infection in the era of highly active antiretroviral therapy (HAART). *Semin Respir Infect*. 2001;16:257–262.
89. Masannat FY, Ampel NM. Coccidioidomyocis in patients with HIV-1 infection in the era of potent antiretroviral therapy. *Clin Infect Dis*. 2010;50:1–7.
90. Durkin M, Connolly P, Kuberski T, et al. Diagnosis of coccidioidomycosis with use of the *Coccidioides* antigen enzyme immunoassay. *Clin Infect Dis*. 2008;47:e69–e73.
91. Sarosi GA, Davies SF. Endemic mycosis complicating human immunodeficiency virus infection. *West J Med*. 1996;164:335–340.
92. Pappas PG, Pottage JC, Powderly WG, et al. Blastomycosis in patients with the acquired immunodeficiency syndrome. *Ann Intern Med*. 1992;116:847–853.
93. Pursell KJ, Telzak EE, Armstrong D. *Aspergillus* species colonization and invasive disease in patients with AIDS. *Clin Infect Dis*. 1992;14:141–148.
94. Minamoto GY, Barlam TF, Vander Els NJ. Invasive aspergillosis in patients with AIDS. *Clin Infect Dis*. 1992;14:66–74.
95. Denning DW, Follansbee SE, Scolaro M, et al. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. *N Engl J Med*. 1991;324:654–662.
96. Mylonakis E, Barlam TF, Flanigan T, et al. Pulmonary aspergillosis and invasive disease in AIDS: review of 342 cases. *Chest*. 1998;114:251–262.
97. Mylonakis E, Paliou M, Sax PE, et al. Central nervous system aspergillosis in patients with human immunodeficiency virus infection. Report of 6 cases and review. *Medicine (Baltimore)*. 2000;79:269–280.
98. Mann M, Shelhamer JH, Masur H, et al. Lack of clinical utility of bronchoalveolar lavage cultures for cytomegalovirus in HIV infection. *Am J Respir Crit Care Med*. 1997;155:1723–1728.
99. Miles PR, Baughman RP, Linnemann CC Jr. Cytomegalovirus in the bronchoalveolar lavage fluid of patients with AIDS. *Chest*. 1990;97:1072–1076.
100. Millar AB, Patou G, Miller RF, et al. Cytomegalovirus in the lungs of patients with AIDS. Respiratory pathogen or passenger? *Am Rev Respir Dis*. 1990;141:1474–1477.
101. Klein MB, Lu Y, DelBalso L, et al. Influenzavirus infection is a primary cause of febrile respiratory illness in HIV-infected adults, despite vaccination. *Clin Infect Dis*. 2007;45:234–240.
102. Tempia S, Walaza S, Viboud C, et al. Deaths associated with respiratory syncytial and influenza viruses among persons ≥5 years of age in HIV-prevalent area, South Africa, 1998-2009(1). *Emerg Infect Dis*. 2015;21:600–608.
103. Kroon FP, van Dissel JT, de Jong JC, et al. Antibody response to influenza, tetanus and pneumococcal vaccines in HIV seropositive individuals in relation to the number of CD4+ lymphocytes. *AIDS*. 1994;8:469–476.
104. Fine AD, Bridges CB, De Guzman AM, et al. Influenza A among patients with human immunodeficiency virus: an outbreak of infection at a residential facility in New York City. *Clin Infect Dis*. 2001;32:1784–1791.
105. Skiest DJ, Kaplan P, Machala T, et al. Clinical manifestations of influenza in HIV-infected individuals. *Int J STD AIDS*. 2001;12:646–650.
106. Rabaud C, May T, Lucet JC, et al. Pulmonary toxoplasmosis in patients infected with human immunodeficiency virus: a French National Survey. *Clin Infect Dis*. 1996;23:1249–1254.
107. Butt AA, Michaels S, Kissinger P. The association of serum lactate dehydrogenase level with selected opportunistic infections and HIV progression. *Int J Infect Dis*. 2002;6:178–181.
108. Celedon JC, Mathur-Wagh U, Fox J, et al. Systemic strongyloidiasis in patients infected with the human immunodeficiency virus. A report of 3 cases and review of the literature. *Medicine (Baltimore)*. 1994;73:256–263.
109. Lessnau KD, Can S, Talavera W. Disseminated *Strongyloides stercoralis* in human immunodeficiency virus-infected patients. Treatment failure and a review of the literature. *Chest*. 1993;104:119–122.
110. Kotler DP, Orenstein JM. Clinical syndromes associated with microsporidiosis. *Adv Parasitol*. 1998;40:321–349.
111. Meynard JL, Meyohas MC, Binet D, et al. Pulmonary cryptosporidiosis in the acquired immunodeficiency syndrome. *Infection*. 1996;24:328–331.
112. Huang L, Schnapp LM, Gruden JF, et al. Presentation of AIDS-related pulmonary Kaposi's sarcoma diagnosed by bronchoscopy. *Am J Respir Crit Care Med*. 1996;153:1385–1390.
113. Aboulafia DM. The epidemiologic, pathologic, and clinical features of AIDS-associated pulmonary Kaposi's sarcoma. *Chest*. 2000;117:1128–1145.
114. Aboulafia DM. Regression of acquired immunodeficiency syndrome-related pulmonary Kaposi's sarcoma after highly active antiretroviral therapy. *Mayo Clin Proc*. 1998;73:439–443.
115. Holkova B, Takeshita K, Cheng DM, et al. Effect of highly active antiretroviral therapy on survival in patients with AIDS-associated pulmonary Kaposi's sarcoma treated with chemotherapy. *J Clin Oncol*. 2001;19:3848–3851.
116. Bower M, Nelson M, Young AM, et al. Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma. *J Clin Oncol*. 2005;23:5224–5228.
117. Bazot M, Cadranel J, Benayoun S, et al. Primary pulmonary AIDS-related lymphoma: radiographic and CT findings. *Chest*. 1999;116:1282–1286.
118. Eisner MD, Kaplan LD, Herndier B, et al. The pulmonary manifestations of AIDS-related non-Hodgkin's lymphoma. *Chest*. 1996;110:729–736.
119. Silverberg MJ, Lau B, Achenbach CJ, et al. Cumulative incidence of cancer among persons with HIV in North America: a cohort study. *Ann Intern Med*. 2015;163:507–518.
120. Kirk GD, Merlo C, O'Driscoll P, et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis*. 2007;45:103–110.
121. Helleberg M, May MT, Ingle SM, et al. Smoking and life expectancy among HIV-infected individuals on antiretroviral therapy in Europe and North America. *AIDS*. 2015;29:221–229.
122. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. *Ann Intern Med*. 2008;148:728–736.
123. Das S, Miller RF. Lymphocytic interstitial pneumonitis in HIV infected adults. *Sex Transm Infect*. 2003;79:88–93.
124. Dufour V, Wislez M, Bergot E, et al. Improvement of symptomatic human immunodeficiency virus-related lymphoid interstitial pneumonia in patients receiving highly active antiretroviral therapy. *Clin Infect Dis*. 2003;36:127–130.
125. Ripamonti D, Rizzi M, Maggiolo F, et al. Resolution of lymphocytic interstitial pneumonia in a human immunodeficiency virus-infected adult following the start of highly active antiretroviral therapy. *Scand J Infect Dis*. 2003;35:348–351.
126. Mehta NJ, Khan IA, Mehta RN, et al. HIV-related pulmonary hypertension: analytic review of 131 cases. *Chest*. 2000;118:1133–1141.
127. Barnett CF, Hsue PY, Machado RF. Pulmonary hypertension: an increasingly recognized complication of hereditary hemolytic anemias and HIV infection. *JAMA*. 2008;299:324–331.
128. Opravil M, Pechere M, Speich R, et al. HIV-associated primary pulmonary hypertension. A case control study. Swiss HIV Cohort Study. *Am J Respir Crit Care Med*. 1997;155:990–995.
129. Sitbon O, Lascoux-Combe C, Sereni D, et al. Prevalence of pulmonary arterial hypertension in HIV-positive outpatients in the highly active antiretroviral therapy era. *Am J Respir Crit Care Med*. 2008;177:108–113.
130. Zuber JP, Calmy A, Evison JM, et al. Pulmonary arterial hypertension related to HIV infection: improved hemodynamics and survival associated with antiretroviral therapy. *Clin Infect Dis*. 2004;38:1178–1185.
131. Diaz PT, King ER, Wewers MD, et al. HIV infection increases susceptibility to smoking-induced emphysema. *Chest*. 2000;117:285S.
132. Crothers K, Huang I, Goulet JI, et al. HIV infection and risks for incident pulmonary diseases in the combination antiretroviral therapy era. *Am J Respir Crit Care Med*. 2011;183:388–395.
133. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet*. 2002;359:727–732.
134. No authors listed. Abacavir warning: certain respiratory symptoms can indicate hypersensitivity reaction. *AIDS Treat News*. 2000;7–8.
135. Keiser P, Nassar N, Skiest D, et al. Comparison of symptoms of influenza A with abacavir-associated hypersensitivity reaction. *Int J STD AIDS*. 2003;14:478–481.
136. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358:568–579.

124 Gastrointestinal, Hepatobiliary, and Pancreatic Manifestations of Human Immunodeficiency Virus Infection

Saleh A. Alqahtani and Mark S. Sulkowski

SHORT VIEW SUMMARY

Definition
- Gastrointestinal and hepatobiliary diseases are a common cause of morbidity in persons with human immunodeficiency virus (HIV) infection and often the result of both host factors and exposures.

Disorders of the Esophagus
- Disorders of the esophagus typically manifest as dysphagia or odynophagia and affect up to one-third of patients with acquired immunodeficiency syndrome (AIDS).
- Infectious causes include *Candida,* cytomegalovirus (CMV), herpes simplex virus, varicella-zoster virus, mycobacteria, *Histoplasma,* and *Pneumocystis jirovecii.*
- Noninfectious causes include reflux esophagitis and pill esophagitis.
- Malignant causes include esophageal carcinoma, lymphoma, and Kaposi sarcoma.
- Presumptive diagnoses can often be made with a careful history and physical examination.
- Upper endoscopy with biopsy of lesions is highly sensitive in many cases.

Disorders of the Stomach
- Gastric disorders can result from opportunistic infections but more commonly are not related to HIV-induced immunosuppression.
- *Helicobacter pylori,* CMV, and Kaposi sarcoma are common causes of gastric disorders.
- Upper endoscopy and gastric biopsies are often needed for definitive diagnosis.

Disorders of the Liver
- Because of shared modes of transmission, hepatitis caused by acute or chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) is common.
- Anti-HCV and anti-HBV treatment with oral antivirals is recommended for all persons with HIV and viral hepatitis coinfection (see Chapters 117, 145, and 154).
- Drug-induced liver injury has been observed with some antiretroviral agents and other drugs used in persons with HIV infection.

Disorders of the Biliary Tree, Gallbladder, and Pancreas
- Acalculous cholecystitis and cholangitis are found primarily in advanced AIDS and may involve the pancreas.
- CMV, *Cryptosporidium, Cystoisospora,* and microsporidia are most commonly implicated in cases of cholangitis.
- AIDS-related acalculous cholecystitis and cholangitis are rare in settings where antiretroviral therapy (ART) is widely used, and non–AIDS-related gallbladder and biliary diseases may be more common in such settings.
- Endoscopic retrograde cholangiopancreatography can be used for both diagnosis and treatment.
- Didanosine and systemic pentamidine can cause pancreatitis.
- Pancreatic infections with mycobacteria, *Cryptococcus, Toxoplasma gondii, P. jirovecii,* and CMV have been described, often in disseminated disease.

Disorders of the Small and Large Intestine
- Causes of enterocolitis include bacterial, protozoal, and viral pathogens (see Table 124.3).
- *Clostridioides difficile* (formerly *Clostridium difficile*) is the most common cause of diarrhea in persons with HIV infection.
- CMV, *Cryptosporidium,* and *Mycobacterium avium-intracellulare* complex infections are more common in the setting of severe immunodeficiency.
- HIV-associated enteropathy causes culture-negative diarrhea and may improve with ART.
- Anal cancer and high-grade anal dysplasia due to human papillomavirus are common in persons with HIV infection; screening is recommended for persons at risk.

Diseases of the gastrointestinal system frequently complicate human immunodeficiency virus (HIV) infection and mark its progression to acquired immunodeficiency syndrome (AIDS). Many HIV-related gastrointestinal diseases, such as *Candida* esophagitis, biliary cryptosporidiosis, and cytomegalovirus (CMV) colitis, represent opportunistic infections that are the result of advanced immunosuppression, whereas other gastrointestinal processes such as hepatitis B virus (HBV) or hepatitis C virus (HCV) infection may occur at any stage of HIV disease. The likelihood and nature of gastrointestinal manifestations of HIV depend on both host and environmental factors; infectious complications are typically a product of both exposure to potential pathogens and immunocompetence. With the advent of potent antiretroviral therapy (ART), the incidence and spectrum of HIV-related gastrointestinal manifestations have changed dramatically.[1] However, in the setting of severe immunodeficiency the broad range of diagnostic considerations mandates the systematic evaluation of gastrointestinal signs and symptoms. Conversely, persons with effectively treated HIV infection are highly unlikely to experience gastrointestinal manifestations of opportunistic pathogens.

DISORDERS OF THE ESOPHAGUS

Esophageal diseases occur commonly, affecting up to one-third of patients with AIDS and typically produce symptoms of dysphagia and odynophagia, which may be the result of esophageal ulceration caused by infectious pathogens or noninfectious processes.[2] Infectious esophagitis is most often due to infection with *Candida albicans* but may also be caused by viruses such as herpes simplex virus (HSV), CMV, and varicella-zoster virus (VZV), and less commonly by other infectious agents including primary HIV infection. Noninfectious processes such as reflux esophagitis, pill esophagitis (doxycycline), and malignancies (esophageal carcinoma, lymphoma, and Kaposi sarcoma) may be clinically indistinguishable from infectious esophagitis. Furthermore the risk of esophageal (and gastric) carcinoma may be higher in patients with AIDS compared with the general population.[3] Esophageal ulcerations are often caused by CMV (≈45%), idiopathic ulcers (≈40%), and HSV (≈5%), and may involve symptoms of localized pain.[4] In the era of effective ART, the clinical spectrum of esophageal disease has changed substantially; the occurrence of infectious and idiopathic esophageal ulceration has decreased significantly, whereas noninfectious esophageal diseases, such as gastroesophageal reflux disease and dysmotility disorders, may account for an increasing proportion of esophageal symptoms.

Regardless of etiology, most esophageal processes are associated with dysphagia or odynophagia, and persistent or intermittent retrosternal pain, nausea, anorexia, and weight loss may occur. The onset of symptoms may be acute but more typically follows an indolent course. Nonesophageal manifestations of disease may be found in patients with odynophagia;

for example, oral candidiasis frequently accompanies *Candida* esophagitis, and active CMV infection may be found in other anatomic sites such as the retina or colon.[5] However, among patients with advanced immunodeficiency, the broad range of disease processes and the possibility of multiple etiologies mandate a methodical approach to evaluation and management of esophageal symptoms.

Patients with high $CD4^+$ cell counts (>350 cells/mm^3) who present with typical symptoms of gastroesophageal reflux disease may be empirically treated with medications to reduce gastric acid secretion. However, because the absorption of some antiretroviral drugs (e.g., atazanavir) may be reduced in the setting of acid suppression, clinicians should be cognizant of concurrent medications. Patients with more advanced HIV disease, with or without the presence of oral candidiasis, should be empirically treated for esophageal candidiasis with antifungal therapy (e.g., fluconazole, 100–200 mg/day).[6,7] Presumptive oral antifungal therapy is highly effective and is usually preferable to initial diagnostic upper endoscopy.[8] If esophageal symptoms resolve with oral antifungals, the diagnosis of candidiasis can be established empirically. However, failure of symptoms to respond to empirical antifungal therapy within 14 to 21 days indicates a need for further evaluation. Most patients with advanced HIV disease (up to 77%) who do not respond to antifungal therapy have esophageal ulceration rather than evidence of persistent esophageal candidiasis.[9] Upper endoscopy with biopsy is a highly sensitive procedure for establishing a specific diagnosis and is the preferred approach to evaluation of patients with odynophagia or dysphagia who do not respond to empirical antifungal therapy. Upper gastrointestinal contrast radiography may reveal characteristic abnormalities, but these findings are relatively insensitive and nonspecific, whereas upper endoscopy may yield a treatable pathologic diagnosis in most patients.

The endoscopic appearance of esophageal candidiasis resembles cheesy friable plaques that may involve the entire esophagus, whereas viral esophagitis is usually associated with diffuse erythematous ulceration of the mucosa. CMV esophagitis frequently causes numerous large shallow ulcerations, whereas HSV esophagitis is typically seen as superficial confluent ulcers in the distal esophagus and may be associated with concurrent nonesophageal lesions. Idiopathic or aphthous ulcers may have an endoscopic appearance similar to that of CMV ulcers and represent a diagnosis of exclusion. Noninfectious processes such as drug-induced ulcers and malignant diseases may affect the esophagus, with the most common tumors being Kaposi sarcoma, primary lymphoma, and adenocarcinoma. Persons with HIV infection may also have conventional esophageal pathology such as reflux esophagitis.

For lesions visualized with endoscopy, a biopsy should be performed and tissue sections prepared for histopathologic stains to identify viral inclusion bodies (CMV), multinucleated giant cells (HSV), and direct evidence of HSV or CMV or invasive fungi. Immunohistochemical stains for CMV and HSV are helpful. In some settings, polymerase chain reaction (PCR) assay has been used to detect organisms from nondiagnostic ulcer biopsy specimens; however, contamination with oral secretions limits its clinical utility.[10] Cultures for fungi and viruses may be helpful, although positive results for *C. albicans* may not indicate esophagitis. Antifungal drug sensitivity testing may be useful if azole-resistant candidiasis is suspected.[11] The yield of endoscopy with biopsy and culture is high, and more than one pathologic process may be found. However, multiple biopsies (more than three) may be needed to exclude the diagnosis of viral esophagitis. Lesions that do not respond to appropriate therapy should be reevaluated with endoscopy with biopsy and culture to confirm the diagnosis and, if indicated, with drug sensitivity testing.

DISORDERS OF THE STOMACH

Gastric disorders in persons with HIV infection may be the result of opportunistic infections but are often unrelated to immunodeficiency, even among patients with advanced HIV disease. Patients with gastric disease may present with protean symptoms such as nausea, vomiting, early satiety, and anorexia; abdominal pain and hematemesis may also be present. Some disease processes, such as CMV gastritis and gastrointestinal Kaposi sarcoma, may be associated with extragastric involvement.

Gastritis and gastroduodenal ulcers may be found in persons living with HIV (PLWH) with upper gastrointestinal symptoms and may be the result of *Helicobacter pylori* infection. In some studies, the prevalence of *H. pylori* has been lower in PLWH compared with HIV-negative individuals.[12] In sub-Saharan Africa, *H. pylori* was detected in 88% of HIV-negative individuals and 51% of PLWH, among whom the prevalence decreased in persons with lower $CD4^+$ cell counts.[13] *H. pylori* infection may be detected with serology, urea breath testing, histologic evaluations, and stool *H. pylori* antigen testing, which has emerged as the preferred test for diagnosis and treatment efficacy.[14] PLWH may also have altered gastric function including decreased secretion of gastric acid and intrinsic factor. Hypochlorhydria may impair the absorption of some medications such as ketoconazole, itraconazole, and atazanavir, and may also permit bacterial overgrowth.[15]

CMV may cause gastric inflammation or ulceration alone or in association with esophageal ulceration. The appearance of gastric CMV may be diverse and includes thickened edematous gastric folds, erosive gastritis, and superficial or deep ulcerations. The radiographic features may be nonspecific and may even be masslike, suggestive of malignant disease. Other gastric infections have been reported including infection with *Cryptosporidium, Mycobacterium avium-intracellulare* complex, histoplasmosis, leishmaniasis, and syphilis. Malignant lesions that involve the stomach may also be associated with upper gastrointestinal symptoms. Gastrointestinal Kaposi sarcoma, associated with human herpesvirus type 8 infection, complicates cutaneous disease in 50% of patients and most commonly involves the stomach.[16] Gastric Kaposi sarcoma lesions may be asymptomatic but can also cause nausea, abdominal pain, and, rarely, severe hemorrhage. AIDS-related lymphomas may also involve the gastrointestinal tract; these lesions tend to be multifocal but may rarely be gastric mucosa–associated lymphoid tissue lymphomas associated with *H. pylori.*[17] Although the incidence of AIDS-related lymphoma has decreased in the era of ART, the risk of gastric carcinoma is elevated (up to 44% higher) in PLWH compared with the general population.[3] In light of these diverse diagnostic considerations, patients with persistent upper gastrointestinal symptoms, particularly patients with low $CD4^+$ cell counts, should be evaluated for opportunistic infection and malignancy disease. The definitive diagnosis of upper gastrointestinal pathology often requires endoscopic evaluation with biopsy and cultures. Kaposi sarcoma lesions typically appear as a violet-blue submucosal mass without ulceration or bleeding but may appear as linitis plastica. Biopsies of these lesions may fail to confirm Kaposi sarcoma in up to two-thirds of cases. However, when cutaneous Kaposi sarcoma has been histologically confirmed, the endoscopic appearance of the lesion may be sufficient to establish the diagnosis. Biopsies of gastroduodenal ulcerations should be performed and specimens sent for viral culture and histologic staining for evidence of viral inclusions, fungi, and *H. pylori* infection. Multiple biopsies may be needed to exclude viral pathogens, and additional stains and cultures may be helpful in diagnosing specific infections, such as acid-fast stains and culture for *M. avium-intracellulare* complex.

DISORDERS OF THE BILIARY TREE AND GALLBLADDER

Diseases of the gallbladder and biliary tree that affect PLWH include common, non–AIDS-associated conditions such as cholelithiasis and AIDS-associated conditions such as acalculous cholecystitis and cholangiopathy. Patients typically present with postprandial pain, fever, right upper quadrant tenderness, and an elevated serum alkaline phosphatase level. Ultrasound or computed tomography may reveal evidence of acute cholecystitis or cholangitis related to cholelithiasis; in patients with AIDS, these studies may suggest acalculous cholecystitis or AIDS-associated cholangitis.[18] During acute or chronic acalculous cholecystitis, the gallbladder generally appears thickened and edematous, with obliteration of the gallbladder lumen without evidence of gallstones. Nonvisualization of the gallbladder with radionuclide hepatobiliary scintigraphy is also suggestive. If a cholecystectomy is performed, operative specimens should be sent for microbiologic and histopathologic evaluation because before the advent of potent ART, opportunistic pathogens were identified in more than 50% of cases.[19] CMV, *Cryptosporidium,* and microsporidia are the pathogens most commonly associated with acalculous cholecystitis; however, multiple organisms may be recovered, and often no etiologic agent is identified after extensive microbiologic evaluation. Although the exclusion of opportunistic

infection is critical in the evaluation of patients with HIV with signs and symptoms of acute cholecystitis, the incidence of AIDS cholangiopathy is very low in settings where ART is widely used and should be primarily considered in patients with a $CD4^+$ cell count less than 50 cells/mm^3. Although rare, the HIV-1 protease inhibitor atazanavir may lead to the development of biliary stones containing significant concentrations of the actual drug; thus patients treated with atazanavir who present with symptomatic cholelithiasis warrant consideration of a change to another antiretroviral agent.[20]

If noninvasive radiographic imaging indicates intrahepatic or extrahepatic biliary ductal dilation, endoscopic retrograde cholangiopancreatography may be necessary for diagnosis and management of AIDS-associated cholangiopathy. Four common patterns of cholangiographic abnormalities are revealed with endoscopic retrograde cholangiopancreatography: stenosis of the papilla of Vater with dilated extrahepatic biliary tract, sclerosing cholangitis, a combination of sclerosing cholangitis and papillary stenosis, and choledochal long stenosis or strictures. Endoscopic collection of bile from the common bile duct and duodenal or papillary biopsy may identify an opportunistic pathogen or malignancy. Similar to acalculous cholecystitis, cholangitis is associated with opportunistic infections by CMV, *Cryptosporidium,* or microsporidia in more than half of cases. For example, among 82 patients with HIV in whom cryptosporidiosis developed during a waterborne outbreak, 24 (29%) had evidence of biliary involvement that was associated with $CD4^+$ cell counts less than 50 cells/mm^3.[4,21] If papillary stenosis is present, endoscopic sphincterotomy may produce relief of symptoms and biochemical resolution of cholestasis, although in some case series the clinical effectiveness of this procedure has been disappointing.[22]

DISORDERS OF THE LIVER

Hepatic abnormalities are common in PLWH and are often associated with elevated serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase levels. Liver disease may result from acute or chronic viral hepatitis, HIV-related opportunistic infections, or noninfectious processes such as drug-induced liver injury (DILI), alcohol, nonalcoholic fatty liver disease, or malignancy (Table 124.1). Because of shared routes of transmission, chronic infection with HBV or HCV or both frequently complicates HIV disease,[23] and liver disease caused by these pathogens in an important cause of morbidity and mortality in the era of effective ART.[24–26]

Compared with only 5% of adults without HIV infection, approximately 20% of PLWH who acquire acute HBV infection after childhood will develop chronic HBV infection, characterized by hepatitis B surface antigenemia (HBsAg) and active viral replication.[27] In addition, spontaneous HBV reactivation has been reported in anti–hepatitis B surface antibody-positive patients with severe immunosuppression.[28] Although chronic HBV infection does not appear to adversely impact the natural history of HIV disease, patients with HIV and HBV coinfection are at increased risk of liver-related morbidity and mortality compared with patients with HBV infection alone.[29] For example, among men with and without HIV infection followed longitudinally in the Multicenter AIDS Cohort Study (MACS), Thio and colleagues[29] reported that men with HIV and HBV coinfection were approximately 19 times more likely to die of liver disease compared with men infected with HBV alone. These and other data support the recommendation that all PLWH should be screened for evidence of resolved or active HBV infection.[30] Testing for HBsAg, hepatitis B surface antibody, and anti–hepatitis B core antibody (anti-HBc total) is recommended before the initiation of ART because some reverse transcriptase inhibitors used to treat HIV drugs are also active against HBV. Individuals found to be susceptible to HBV infection should undergo vaccination. Patients with chronic HBV (defined as persistent HBsAg >6 months) should undergo further evaluation to determine HBV replication status (e.g., hepatitis B e antigen and serum HBV DNA) and liver disease activity (e.g., serum ALT level or other serum markers of liver damage, liver biopsy, or transient elastography).

Patients with HIV and chronic HBV infection characterized by active HBV replication (e.g., detectable HBV DNA) are at increased risk for the development of cirrhosis, end-stage liver disease (ESLD), and hepatocellular carcinoma (HCC), and should be monitored for the development of cancer with liver ultrasound every 6 to 12 months.[31] Treatment for both HBV and HIV is recommended for all coinfected patients, regardless of serum ALT or HBV DNA level.[32] The goal of HBV therapy in coinfected patients is the prevention of liver disease, which may be achieved through sustained suppression of HBV replication and in some cases seroclearance of hepatitis virus e antigen or hepatitis virus s antigen or both. Four antiretroviral drugs approved by the US Food and Drug Administration for treatment of HIV (lamivudine, emtricitabine, tenofovir disoproxil fumarate, tenofovir alafenamide) also suppress HBV replication by inhibition of HBV DNA polymerase.[31] Similarly, entecavir, a guanosine analogue approved for treatment of chronic HBV infection, also inhibits HIV reverse transcriptase and, when used in the absence of HIV suppression with antiretrovirals, can lead to emergence of HIV-resistance mutations (M184V) that confer decreased susceptibility to lamivudine and emtricitabine.[33] To prevent the development of resistance, these dually active drugs must be used only as part of an effective antiretroviral combination therapy regimen. Oral adefovir and telbivudine are also approved for treatment of chronic HBV infection but are not recommended as first-line therapies. Peginterferon-alfa administered by weekly subcutaneous injection may also be effective in treatment of chronic HBV; however, few data exist regarding the effectiveness and tolerability in patients with HIV and HBV coinfection.[34] Treatment guidelines recommend that all HIV-infected patients with chronic HBV infection be treated for both infections with combination ART that includes tenofovir plus emtricitabine or lamivudine. Treatment of one viral infection but not the other is not recommended (see Chapter 145).

HCV coinfection is also common. Globally, HCV prevalence in PLWH is approximately 6.2%, which is about sixfold greater than the prevalence in HIV-negative populations. Among PLWH, HCV prevalence varies according to HIV risk group: 82.4% of persons who inject drugs, 6.4% of men who have sex with men (MSM), and 4.0% of heterosexually

TABLE 124.1 Selected Causes of Hepatic Disease in Persons With HIV

Viruses
Hepatitis A
Hepatitis B
Hepatitis C
Hepatitis D
Hepatitis E
Epstein-Barr
Cytomegalovirus
Herpes simplex
Adenovirus
Varicella-zoster
Fungi
Histoplasma capsulatum
Cryptococcus neoformans
Coccidioides immitis
Candida albicans
Pneumocystis jirovecii
Talaromyces marneffei
Protozoa
Toxoplasma gondii
Cryptosporidium parvum
Microsporidia
Schistosoma
Bacteria
Mycobacteria
Mycobacterium avium-intracellulare complex
Mycobacterium tuberculosis
Bartonella henselae (peliosis hepatis)
Malignant Disease
Kaposi sarcoma (HHV-8)
Non-Hodgkin lymphoma
Hepatocellular carcinoma

HHV-8, Human herpesvirus 8; *HIV,* human immunodeficiency virus.

exposed persons.[35] Heterosexual HCV transmission is uncommon but may be more likely in persons with partners who have HIV and HCV coinfection. Likewise, HCV transmission between HIV-infected MSM is relatively common, particularly among men who engage in unprotected anal receptive intercourse in the setting of noninjection drug use, and HCV sexual transmission networks have been observed.[36] Acute HCV infection may be clinically silent and detected by asymptomatic elevations in serum ALT levels. Although some PLWH may spontaneously clear acute HCV, most will progress to chronic HCV infection, which is often characterized by asymptomatic elevations in serum ALT and AST levels, but leads to progressive hepatic fibrosis that may lead to cirrhosis that may be followed by hepatic decompensation or HCC or death.[37] Patients with ESLD are profoundly symptomatic with manifestations of portal hypertension including ascites, esophageal varices, and splenomegaly; decreased hepatic synthetic function including hypoalbuminemia, thrombocytopenia, and coagulopathy; and hepatic encephalopathy. Liver transplantation is an option for management of PLWH who present with ESLD or HCC.[38] Extrahepatic manifestations of HCV infection such as membranous glomerulonephritis, porphyria cutanea tarda, and cryoglobulinemia with or without vasculitis may also occur.

On one hand, HIV coinfection adversely affects the natural history of HCV disease, with enhanced HCV replication and accelerated hepatic fibrosis progression, presumably because of HIV-related immunosuppression. On the other hand, conflicting reports exist regarding the impact of HCV infection on the natural history of HIV disease, and for most persons, HCV does not adversely affect HIV disease or its treatment with ART.[39] In the era of effective ART, HCV infection is an important cause of morbidity and mortality in PLWH.[4] As such, current management guidelines recommend that all HIV-infected patients be screened for HCV infection with an assay to detect anti-HCV. Negative anti-HCV results may be observed in PLWH who have advanced immunodeficiency (e.g., $CD4^+$ cell count <100 cells/mm^3) or in PLWH with early, acute HCV infection; in such cases, blood HCV RNA should be assessed when HCV infection is suspected in persons with negative anti-HCV results (e.g., elevated ALT levels). Patients with positive HCV antibody results should have further HCV RNA testing to confirm active HCV replication. Patients should be counseled to prevent liver damage and HCV transmission, evaluated for the presence of chronic liver disease, and offered curative HCV treatment.[2] Because alcohol ingestion accelerates the progression of liver disease, patients should be advised to abstain from alcohol. Assessments of disease severity should include a history and physical examination for signs and symptoms of chronic liver disease and measurement of blood albumin, creatinine, sodium, prothrombin time, total and direct bilirubin, and platelet count. The magnitude of HCV RNA in the blood provides only limited information regarding disease severity. Noninvasive radiographic imaging may reveal hepatic parenchymal abnormalities; mass lesions; or evidence of ascites, splenomegaly, or varices. However, imaging studies cannot reliably exclude the presence of significant liver fibrosis. Specific liver disease staging is recommended for all coinfected patients by using either noninvasive serum markers (e.g., AST-to-platelet ratio index, fibrosis-4 index), liver stiffness measurement by elastography, or liver biopsy.[40,41] In addition to hepatic fibrosis staging, histologic evaluation may be useful to exclude other causes of hepatic disease such as nonalcoholic liver fatty liver disease or DILI.

All PLWH with active HCV infection should be considered for HCV treatment with direct-acting antivirals. In clinical trials and real-world studies, approximately 95% of PLWH have achieved sustained virologic response (HCV cure) following treatment with oral HCV direct-acting antiviral regimens including the agents listed in Table 124.2. The observed sustained virologic response rates in PLWH are similar to rates observed in HIV-negative individuals; accordingly the American Association for the Study of Liver Diseases and Infectious Diseases Society of America guidance states that "HIV/HCV-coinfected persons should be treated and re-treated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications."[42,43] For example, because of inhibition or induction of cytochrome P-450 3A/4, the HCV nonstructural 3/4A protease inhibitors (grazoprevir, glecaprevir, and voxilaprevir) may be combined only with selected antiretroviral agents. Details of recommended HCV treatments and drug interactions can be found at www.hcvguidelines.org and www.hep-druginteractions.org, respectively (see Chapters 117 and 154).

Other infectious processes may also involve the liver. Viral pathogens such as CMV, Epstein-Barr virus, HSV, and adenovirus can cause hepatocellular damage, usually in the setting of disseminated disease. Other infectious pathogens such as mycobacterial and fungal agents may lead to granulomatous inflammation, characterized by elevated alkaline phosphatase levels and nonspecific hepatic granuloma. *M. avium-intracellulare* complex is the most common opportunistic pathogen that affects the liver and is associated with manifestations of systemic disease including fever, abdominal pain, and wasting.[44] Extrapulmonary *Mycobacterium tuberculosis* infection may be associated with hepatic involvement in 5% to 10% of HIV-related cases. Disseminated fungal infections with organisms including *Cryptococcus neoformans, Histoplasma capsulatum, Coccidioides immitis, Penicillium marneffei,* and *C. albicans* may produce a granulomatous response in liver.

Pneumocystis jirovecii hepatic infection may occur rarely, particularly during aerosolized pentamidine prophylactic therapy. *Bartonella henselae* can cause peliosis hepatis, a vascular proliferative liver infection, in the absence of cutaneous lesions. Peliosis hepatis occurs in patients with AIDS, who may present with fever, weight loss, and hepatosplenomegaly with an elevated serum alkaline phosphatase level. The diagnosis of bartonellosis can be made with Warthin-Starry silver staining of biopsy specimens, culture of the blood or tissue plated on heart infusion agar with 5% rabbit blood, and PCR assay.[45] Blood culture for acid-fast bacilli is usually sufficient to establish the diagnosis of disseminated mycobacterial infection. *C. neoformans* and *H. capsulatum* may be rapidly detected with evidence of antigenemia. The evaluation of other potential causes may require liver biopsy, which can yield a treatable diagnosis in approximately 60% of patients with HIV with unexplained fever and liver abnormalities. Hepatic tissue should be sent for microbiologic evaluation and culture and for routine and specific histologic staining

TABLE 124.2 Clinical Trials of Direct-Acting Antiviral Therapies in Patients With Hepatitis C Virus/HIV Coinfection

TRIAL	TOTAL NO. HIV/HCV COINFECTION PATIENTS	HCV REGIMEN	TREATMENT DURATION (weeks)	SVR (%)
ION-4	335	Sofosbuvir/ledipasvir	12	96
ERADICATE	50	Sofosbuvir/ledipasvir	12	98
C-EDGE	218	Grazoprevir/elbasvir	12	96
ALLY-2	203	Sofosbuvir + daclatasvir	8–12	76–97
TURQUOISE-1	63	Paritaprevir/ritonavir/ombitasvir + dasabuvir ± ribavirin	12–24	92
C-WORTHY	59	Grazoprevir/elbasvir ± ribavirin	12	92
ASTRAL-5	106	Sofosbuvir/velpatasvir	12	95
EXPEDITION-2	153	Glecaprevir/pibrentasvir	8–12	98

HCV, Hepatitis C virus; *HIV,* human immunodeficiency virus; *SVR,* sustained virologic response.

for acid-fast bacilli and fungal pathogens. Hepatic mass lesions are commonly the result of malignant disease, although infectious processes may resemble mass lesions radiographically. Before potent ART, the most common hepatic malignant disease was Kaposi sarcoma in the setting of cutaneous disease. Abdominal imaging with contrast-enhanced computed tomography may reveal enhanced lesions located in the capsular, hilar, and portal areas, with invasion into the liver parenchyma. The definitive diagnosis of hepatic Kaposi sarcoma requires biopsy with histologic examination; however, the risk of hemorrhage after a biopsy may be increased because of the vascular nature of the Kaposi sarcoma lesion. Non-Hodgkin lymphomas may involve the liver, usually in association with lymph node or visceral involvement or both, although primary hepatic lymphoma has been reported. Patients may present with weight loss, fever, night sweats, and abdominal pain (termed *B symptoms*); jaundice may occur with intrahepatic or extrahepatic bile duct obstruction. Radiographic imaging typically reveals solitary or multiple hepatic mass lesions and involvement of abdominal lymph nodes. Biopsy of the hepatic lesion or involved lymph nodes is needed to confirm the diagnosis of lymphoma. With effective ART, the incidence of Kaposi sarcoma and lymphoma involving the liver has declined, but HCC related to HBV or HCV has been increasingly recognized in patients with HIV, particularly patients with cirrhosis; such patients may have evidence of advanced liver disease, elevated serum α-fetoprotein level, and radiographic evidence of a mass lesion.[46]

Among noninfectious liver diseases, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis are common in PLWH. In a meta-analysis of 10 studies, the prevalence of NAFLD in PLWH evaluated by liver imaging was 35%, and the prevalence of nonalcoholic steatohepatitis in PLWH evaluated by liver biopsy was 42%.[47] Risk factors for NAFLD in PLWH are similar to risk factors reported for HIV-negative persons including high body mass index, high waist circumference, type 2 diabetes, hypertriglyceridemia, and hypertension. In addition, older nucleoside reverse transcriptase inhibitors including stavudine and didanosine were associated with hepatic steatosis; in more recent analyses, the association of HIV disease and its treatment with NAFLD is less clear.[48–50] PLWH with evidence of hepatic steatosis and abnormal liver enzymes require further evaluation for severity of liver damage including assessment of degree of fibrosis with liver biopsy or transient elastography with controlled attenuation parameters. NAFLD treatment is usually directed at control of metabolic disease including weight loss and diabetes. Although specific NAFLD treatments are under investigation, these have not been approved by the US Food and Drug Administration or investigated in PLWH.

DILI is a common cause of liver abnormalities in PLWH, and infection with HIV or HCV or both may enhance the toxicity of some medications such as antituberculosis drugs.[51] Patients typically present with elevated serum ALT and AST levels, although some drugs such as macrolide antibiotics (e.g., azithromycin) and trimethoprim-sulfamethoxazole induce a cholestatic or mixed liver injury pattern. DILI is often asymptomatic and detected through routine monitoring of serum liver enzymes. HIV-1 protease inhibitors, particularly tipranavir/ritonavir, and nonnucleoside reverse-transcriptase inhibitors, particularly nevirapine, have been associated with severe DILI after the initiation of therapy, which may be more common in the setting of chronic HBV or HCV infection.[51–55] In addition to elevations of serum ALT and AST levels, nucleoside analogue reverse-transcriptase inhibitors such as zidovudine and stavudine have been associated with mitochondrial toxicity, which leads in some cases to fatal hepatomegaly with severe steatosis and lactic acidosis.[56–58] Antiretroviral medications, particularly didanosine, have also been associated with noncirrhotic portal hypertension and nodular regenerative hyperplasia; however, the incidence of this condition is extremely low.[59–61]

DISORDERS OF THE PANCREAS

Diseases that involve the pancreas may be caused by processes unrelated to HIV infection such as alcohol, cholelithiasis, and hyperlipidemia or may be caused by HIV-related opportunistic infections or medication toxicity.[62] AIDS cholangiopathy caused by CMV, *Cryptosporidium,* or microsporidia may involve the juxtaampullary portion of the pancreatic duct. Mycobacterial infections of the pancreas have been described including pancreatic abscess related to *M. tuberculosis* and disseminated *M. avium-intracellulare* complex. Fungal pathogens such as *C. neoformans* and *Candida* spp., *Toxoplasma gondii, P. jirovecii,* and protozoal pathogens may involve the pancreas, typically in the setting of disseminated disease. Pancreatic CMV inclusions are frequently observed in autopsy specimens from patients with disseminated CMV disease, although clinical pancreatitis is infrequently recognized before death.[63] Infection with mumps may also cause pancreatitis.

Drug-induced pancreatic inflammation and dysfunction may also occur in patients with HIV disease. Didanosine may frequently cause asymptomatic hyperamylasemia; clinical pancreatitis has been observed in 1.2% to 6.7% of didanosine recipients, and fulminant pancreatic toxicity has been reported.[64] Systemic pentamidine therapy for *P. jirovecii* pneumonia is toxic to pancreatic beta-islet cells and can cause pancreatitis and symptomatic hyperglycemia or hypoglycemia; in contrast, prophylaxis with aerosolized pentamidine rarely leads to pancreatic dysfunction.[65] The risk of pancreatitis in patients receiving intravenous pentamidine is dose related, with most cases occurring after 2 weeks of therapy. Overall the incidence rate of acute pancreatitis has been low (1.27 cases per 1000 person-years) in some settings.[66]

DISORDERS OF THE SMALL AND LARGE INTESTINE

Symptomatic disease of the small intestine and colon remains common among patients with AIDS and may be caused by a diverse range of infectious agents; however, among PLWH treated with ART, the incidence of acute enterocolitis has declined substantially. Small bowel diseases generally produce bloating, nausea, cramping, and profuse diarrhea and may be associated with malabsorption and weight loss. In contrast, colitis may produce lower abdominal discomfort and cramping, urgency, and tenesmus and typically causes frequent small-volume diarrhea. Medication-related diarrhea may be observed at any stage of HIV disease, and gastrointestinal adverse effects may lead to discontinuation of antiretroviral medications.[67] Furthermore, with prolonged life expectancy the finding of colorectal malignant diseases such as adenocarcinoma is expected to increase, and recommendations for routine screening colonoscopy should be followed.[68] Inflammatory bowel diseases (e.g., ulcerative colitis, Crohn disease) have been reported in patients with HIV with diarrhea.

The differential diagnosis for enterocolitis in a severely immunocompromised patient is extensive and includes bacterial, protozoal, and viral pathogens (Table 124.3). Bacteria that are more common in patients with HIV infection include *Salmonella* spp., *Shigella, Campylobacter jejuni, Escherichia coli* (enterotoxigenic, enteroadherent, and enteroaggregative), and *Listeria monocytogenes.* Furthermore, among MSM, shigellosis is predominantly a sexually transmitted pathogen, particularly among men with HIV.[69] Nontyphoidal salmonellosis is associated with bacteremia in one-half of infections and may be recurrent in PLWH.[70] Less commonly, bacteremia may occur with *Shigella* and *Campylobacter* infection. *C. difficile* infection may also be more common among patients with HIV disease, particularly among hospitalized patients, patients who have recently undergone antibiotic therapy, and patients with advanced AIDS.[71] Small bowel overgrowth can occur and has been associated with hypochlorhydria and wasting. Other, less common bacterial causes of enterocolitis include *Aeromonas, Plesiomonas, Yersinia,* and *Vibrio* spp. Mycobacterial infections of the small bowel are usually associated with late-stage HIV disease and disseminated *M. avium-intracellulare* complex, although enteritis caused by *M. tuberculosis* has been reported. Parasites and fungi that infect the small and large bowel include spore-forming protozoa, *Cryptosporidium,* microsporidia such as *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*, *Cystoisospora, Cyclospora, Entamoeba histolytica,* and *Giardia lamblia.* Amebic infection and giardiasis may occur at any stage of HIV disease and are commonly associated with conventional risk factors, such as sexual practices and travel-related exposures. Disease caused by *Cryptosporidium* is more common and severe in patients with HIV with advanced immunosuppression and leads to persistent infection (60%), biliary disease (29%), and even fulminant disease (8%).[72] Similarly, microsporidiosis causes diarrhea in patients with advanced HIV disease ($CD4^+$ cell count <50 cells/mm^3) and may be associated with cholangiopathy. Less commonly,

TABLE 124.3 Causes of Lower Gastrointestinal Tract Disease in Persons With HIV

Causes of Enterocolitis
Bacteria
Campylobacter jejuni and other spp.
Salmonella spp.
Shigella flexneri
Aeromonas hydrophila
Plesiomonas shigelloides
Yersinia enterocolitica
Vibrio spp.
Mycobacterium avium-intracellulare complex
Mycobacterium tuberculosis
Escherichia coli (enterotoxigenic, enteroadherent)
Bacterial overgrowth
Clostridioides difficile (formerly *Clostridium difficile*) (toxin)
Parasites
Cryptosporidium parvum
Microsporidia *(Enterocytozoon bieneusi, Septata intestinalis)*
Cystoisospora belli
Entamoeba histolytica
Giardia lamblia
Cyclospora cayetanensis
Viruses
Cytomegalovirus
Adenovirus
Calicivirus
Astrovirus
Picobirnavirus
HIV
Fungi
Histoplasma capsulatum
Causes of Proctitis
Bacteria
Chlamydia trachomatis
Neisseria gonorrhoeae
Treponema pallidum
Viruses
Herpes simplex
Cytomegalovirus

HIV, Human immunodeficiency virus.

diarrhea caused by *Cystoisospora* and *Cyclospora* has been reported in patients with advanced immunosuppression.[1]

CMV is the most significant viral cause of enterocolitis and leads to fever, abdominal pain and tenderness, bloody diarrhea, and, rarely, intestinal perforation or toxic megacolon. As with its appearance in the esophagus, CMV enterocolitis occurs with severe immunodeficiency and produces mucosal inflammation with superficial ulceration.[73] Proctitis in patients with HIV disease typically reflects sexually transmitted infections such as HSV infection, *Chlamydia trachomatis* infection, syphilis, and gonorrhea, particularly among MSM. CMV proctitis is less common but may occur in the setting of extensive CMV colitis. The incidence of human papillomavirus–associated anal dysplasia and cancer is high in PWLH, particularly MSM; anal cancer screening is recommended for individuals at risk.[74,75]

Patients with HIV with diarrhea or other symptoms of enterocolitis should be carefully evaluated for identification of treatable conditions. History should focus on the nature and duration of symptoms; concomitant medications; travel; and other exposures such as food, water, or sexual contact. The standard diagnostic evaluation should include stool leukocyte examination for identification of inflammatory causes of diarrhea such as bacterial pathogens and CMV and for guiding empirical therapy; other infectious agents such as protozoa and *M. avium-intracellulare* complex are typically not associated with the finding of fecal leukocytes. Stool should be cultured for enteric bacterial pathogens, assayed for *C. difficile* toxin, and examined for ova and parasites. Stool specimens should be examined on at least three occasions with modified acid-fast stain to identify *Cryptosporidium, Cyclospora,* and *Cystoisospora.* Special trichrome staining may be useful for the identification of microsporidia. PCR multiplex panels for gastrointestinal pathogens may be useful.

If noninvasive stool studies are not diagnostic and symptoms persist, endoscopic evaluation with biopsy may prove helpful, particularly in patients with chronic diarrhea and severe immunodeficiency ($CD4^+$ cells count <100 cells/mm^3).[76] Patients with signs and symptoms suggestive of large bowel involvement should undergo colonoscopy and biopsy. The sensitivity of endoscopic biopsy for the diagnosis of CMV disease is high, and colonoscopy may be used to identify disease limited to the right side of the colon, which may be missed during flexible sigmoidoscopy. Upper endoscopy with duodenal biopsy is useful for patients with symptoms of small bowel disease or patients with persistent symptoms and negative evaluation of the lower gastrointestinal tract. In addition to hematoxylin and eosin staining, duodenal histologic specimens should be stained with fungal stains and modified acid-fast stain for *Cryptosporidium* and should undergo electron microscopy for microsporidia. PCR assay of biopsy specimens may also prove valuable in the diagnosis of some pathogens such as microsporidia. Small bowel aspirates are generally not useful in the evaluation of unexplained diarrhea.

Approximately 20% to 50% of patients with chronic diarrhea have a negative gastrointestinal tract evaluation. Patients without an identifiable cause of diarrhea may have HIV-associated enteropathy, the pathology of which is not fully understood but likely involves depletion of gut-associated $CD4^+$ cells.[77,78] Histologic evaluation of small bowel biopsy specimens may reveal a decrease in villous surface area and crypt cell proliferation in the absence of inflammation. For many pathogens, few specific therapies are available, but potent ART may effectively control diarrhea in patients with HIV enteropathy and in patients with microsporidiosis and cryptosporidiosis.

Key References

The complete reference list is available online at Expert Consult.

7. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62:e1–e50.
23. Koziel MJ, Peters MG. Viral hepatitis in HIV infection. *N Engl J Med*. 2007;356:1445–1454.
26. Smith CJ, Ryom L, Weber R, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet*. 2014;384:241–248.
29. Thio CL, Seaberg EC, Skolasky RL, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter AIDS Cohort Study (MACS). *Lancet*. 2002;360:1921–1926.
30. Günthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society-USA Panel. *JAMA*. 2016;316:191–210.
31. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol*. 2017;67:370–398.
32. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67:1560–1599.
43. Graham CS. Hepatitis C and HIV co-infection: closing the gaps. *JAMA*. 2015;313:1217–1218.

References

1. Wilcox CM, Saag MS. Gastrointestinal complications of HIV infection: changing priorities in the HAART era. *Gut*. 2008;57:861–870.
2. Connolly GM, Hawkins D, Harcourt-Webster JN, et al. Oesophageal symptoms, their causes, treatment, and prognosis in patients with the acquired immunodeficiency syndrome. *Gut*. 1989;30:1033–1039.
3. Persson EC, Shiels MS, Dawsey SM, et al. Increased risk of stomach and esophageal malignancies in people with AIDS. *Gastroenterology*. 2012;143:943–950.
4. Wilcox CM, Schwartz DA, Clark WS. Esophageal ulceration in human immunodeficiency virus infection. Causes, response to therapy, and long-term outcome. *Ann Intern Med*. 1995;123:143–149.
5. Tavitian A, Raufman JP, Rosenthal LE. Oral candidiasis as a marker for esophageal candidiasis in the acquired immunodeficiency syndrome. *Ann Intern Med*. 1986;104:54–55.
6. Laine L, Dretler RH, Conteas CN, et al. Fluconazole compared with ketoconazole for the treatment of *Candida* esophagitis in AIDS. A randomized trial. *Ann Intern Med*. 1992;117:655–660.
7. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62:e1–e50.
8. Wilcox CM, Alexander LN, Clark WS, et al. Fluconazole compared with endoscopy for human immunodeficiency virus-infected patients with esophageal symptoms. *Gastroenterology*. 1996;110:1803–1809.
9. Wilcox CM, Straub RF, Alexander LN, et al. Etiology of esophageal disease in human immunodeficiency virus-infected patients who fail antifungal therapy. *Am J Med*. 1996;101:599–604.
10. Borges MC, Colares JK, Lima DM, et al. Advantages and pitfalls of the polymerase chain reaction in the diagnosis of esophageal ulcers in AIDS patients. *Dig Dis Sci*. 2009;54:1933–1939.
11. Maenza JR, Keruly JC, Moore RD, et al. Risk factors for fluconazole-resistant candidiasis in human immunodeficiency virus-infected patients. *J Infect Dis*. 1996;173:219–225.
12. Varsky CG, Correa MC, Sarmiento N, et al. Prevalence and etiology of gastroduodenal ulcer in HIV-positive patients: a comparative study of 497 symptomatic subjects evaluated by endoscopy. *Am J Gastroenterol*. 1998;93:935–940.
13. Sarfo FS, Eberhardt KA, Dompreh A, et al. *Helicobacter pylori* infection is associated with higher CD4 T cell counts and lower HIV-1 viral loads in ART-naïve HIV-positive patients in Ghana. *PLoS ONE*. 2015;10:e0143388.
14. Gisbert JP, Pajares JM. Diagnosis of *Helicobacter pylori* infection by stool antigen determination: a systematic review. *Am J Gastroenterol*. 2001;96:2829–2838.
15. Belitsos PC, Greenson JK, Yardley JH, et al. Association of gastric hypoacidity with opportunistic enteric infections in patients with AIDS. *J Infect Dis*. 1992;166:277–284.
16. Friedman SL, Wright TL, Altman DF. Gastrointestinal Kaposi's sarcoma in patients with acquired immunodeficiency syndrome. Endoscopic and autopsy findings. *Gastroenterology*. 1985;89:102–108.
17. Cappell MS, Botros N. Predominantly gastrointestinal symptoms and signs in 11 consecutive AIDS patients with gastrointestinal lymphoma: a multicenter, multiyear study including 763 HIV-seropositive patients. *Am J Gastroenterol*. 1994;89:545–549.
18. Bonacini M. Hepatobiliary complications in patients with human immunodeficiency virus infection. *Am J Med*. 1992;92:404–411.
19. French AL, Beaudet LM, Benator DA, et al. Cholecystectomy in patients with AIDS: clinicopathologic correlations in 107 cases. *Clin Infect Dis*. 1995;21:852–858.
20. Rakotondravelo S, Poinsignon Y, Borsa-Lebas F, et al. Complicated atazanavir-associated cholelithiasis: a report of 14 cases. *Clin Infect Dis*. 2012;55:1270–1272.
21. Vakil NB, Schwartz SM, Buggy BP, et al. Biliary cryptosporidiosis in HIV-infected people after the waterborne outbreak of cryptosporidiosis in Milwaukee. *N Engl J Med*. 1996;334:19–23.
22. Cello JP, Chan MF. Long-term follow-up of endoscopic retrograde cholangiopancreatography sphincterotomy for patients with acquired immune deficiency syndrome papillary stenosis. *Am J Med*. 1995;99:600–603.
23. Koziel MJ, Peters MG. Viral hepatitis in HIV infection. *N Engl J Med*. 2007;356:1445–1454.
24. Rosenthal E, Salmon-Ceron D, Lewden C, et al. Liver-related deaths in HIV-infected patients between 1995 and 2005 in the French GERMIVIC Joint Study Group Network (Mortavic 2005 study in collaboration with the Mortalité 2005 survey, ANRS EN19). *HIV Med*. 2009;10:282–289.
25. Falade-Nwulia O, Seaberg EC, Rinaldo CR, et al. Comparative risk of liver-related mortality from chronic hepatitis B versus chronic hepatitis C virus infection. *Clin Infect Dis*. 2012;55:507–513.
26. Smith CJ, Ryom L, Weber R, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet*. 2014;384:241–248.
27. Kellerman SE, Hanson DL, McNaghten AD, et al. Prevalence of chronic hepatitis B and incidence of acute hepatitis B infection in human immunodeficiency virus-infected subjects. *J Infect Dis*. 2003;188:571–577.
28. Vento S, Di Perri G, Garofano T, et al. Reactivation of hepatitis B in AIDS. *Lancet*. 1989;2:108–109.
29. Thio CL, Seaberg EC, Skolasky RL, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter AIDS Cohort Study (MACS). *Lancet*. 2002;360:1921–1926.
30. Günthard HF, Saag MS, Benson CA, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society-USA panel. *JAMA*. 2016;316:191–210.
31. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol*. 2017;67:370–398.
32. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67:1560–1599.
33. McMahon MA, Jilek BL, Brennan TP, et al. The HBV drug entecavir—effects on HIV-1 replication and resistance. *N Engl J Med*. 2007;356:2614–2621.
34. Leemans WF, Flink HJ, Janssen HL, et al. The effect of pegylated interferon-alpha on the treatment of lamivudine resistant chronic HBeAg positive hepatitis B virus infection. *J Hepatol*. 2006;44:507–511.
35. Platt L, Easterbrook P, Gower E, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. *Lancet Infect Dis*. 2016;16:797–808.
36. van de Laar TJ, Matthews GV, Prins M, et al. Acute hepatitis C in HIV-infected men who have sex with men: an emerging sexually transmitted infection. *AIDS*. 2010;24:1799–1812.
37. Limketkai BN, Mehta SH, Sutcliffe CG, et al. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfected with HIV/HCV. *JAMA*. 2012;308:370–378.
38. Terrault NA, Roland ME, Schiano T, et al. Outcomes of liver transplantation in HCV-HIV coinfected recipients. *Liver Transpl*. 2012;18:716–726.
39. Sulkowski MS, Moore RD, Mehta SH, et al. Hepatitis C and progression of HIV disease. *JAMA*. 2002;288:199–206.
40. Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. *Ann Intern Med*. 2013;158:807–820.
41. Klibansky DA, Mehta SH, Curry M, et al. Transient elastography for predicting clinical outcomes in patients with chronic liver disease. *J Viral Hepat*. 2012;19:e184–e193.
42. American Association for the Study of Liver Disease, Infectious Diseases Society of America, International Antiviral Society-USA. Unique Patient Populations with HIV/HCV Coinfection. http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-hivhcv-coinfection. Accessed July 17, 2018.
43. Graham CS. Hepatitis C and HIV co-infection: closing the gaps. *JAMA*. 2015;313:1217–1218.
44. Poles MA, Dieterich DT, Schwarz ED, et al. Liver biopsy findings in 501 patients infected with human immunodeficiency virus (HIV). *J Acquir Immune Defic Syndr Hum Retrovirol*. 1996;11:170–177.
45. Koehler JE, Sanchez MA, Garrido CS, et al. Molecular epidemiology of *Bartonella* infections in patients with bacillary angiomatosis-peliosis. *N Engl J Med*. 1997;337:1876–1883.
46. Brau N, Fox RK, Xiao P, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a U.S.-Canadian multicenter study. *J Hepatol*. 2007;47:527–537.
47. Maurice JB, Patel A, Scott AJ, et al. Prevalence and risk factors of nonalcoholic fatty liver disease in HIV-monoinfection. *AIDS*. 2017;31:1621–1632.
48. Gaslightwala I, Bini EJ. Impact of human immunodeficiency virus infection on the prevalence and severity of steatosis in patients with chronic hepatitis C virus infection. *J Hepatol*. 2006;44:1026–1032.
49. Morse CG, McLaughlin M, Proschan M, et al. Transient elastography for the detection of hepatic fibrosis in HIV-monoinfected adults with elevated aminotransferases on antiretroviral therapy. *AIDS*. 2015;29:2297–2302.
50. Vuille-Lessard É, Lebouché B, Lennox L, et al. Nonalcoholic fatty liver disease diagnosed by transient elastography with controlled attenuation parameter in unselected HIV monoinfected patients. *AIDS*. 2016;30:2635–2643.
51. Sulkowski MS, Thomas DL, Chaisson RE, et al. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA*. 2000;283:74–80.
52. Cahn P, Villacian J, Lazzarin A, et al. Ritonavir-boosted tipranavir demonstrates superior efficacy to ritonavir-boosted protease inhibitors in treatment-experienced HIV-infected patients: 24-week results of the RESIST-2 trial. *Clin Infect Dis*. 2006;43:1347–1356.
53. Sulkowski MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology*. 2002;35:182–189.
54. Wit FW, Weverling GJ, Weel J, et al. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. *J Infect Dis*. 2002;186:23–31.
55. den Brinker M, Wit FW, Wertheim-van Dillen PM, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS*. 2000;14:2895–2902.
56. Freiman JP, Helfert KE, Hamrell MR, et al. Hepatomegaly with severe steatosis in HIV-seropositive patients. *AIDS*. 1993;7:379–385.
57. Miller KD, Cameron M, Wood LV, et al. Lactic acidosis and hepatic steatosis associated with use of stavudine: report of four cases. *Ann Intern Med*. 2000;133:192–196.
58. Ogedegbe AE, Thomas DL, Diehl AM. Hyperlactataemia syndromes associated with HIV therapy. *Lancet Infect Dis*. 2003;3:329–337.
59. Saifee S, Joelson D, Braude J, et al. Noncirrhotic portal hypertension in patients with human immunodeficiency virus-1 infection. *Clin Gastroenterol Hepatol*. 2008;6:1167–1169.
60. Mallet V, Blanchard P, Verkarre V, et al. Nodular regenerative hyperplasia is a new cause of chronic liver disease in HIV-infected patients. *AIDS*. 2007;21:187–192.
61. Carr A, Morey A, Mallon P, et al. Fatal portal hypertension, liver failure, and mitochondrial dysfunction after HIV-1 nucleoside analogue-induced hepatitis and lactic acidaemia. *Lancet*. 2001;357:1412–1414.
62. Dutta SK, Ting CD, Lai LL. Study of prevalence, severity, and etiological factors associated with acute pancreatitis in patients infected with human immunodeficiency virus. *Am J Gastroenterol*. 1997;92:2044–2048.
63. Wilcox CM, Forsmark CE, Grendell JH, et al. Cytomegalovirus-associated acute pancreatic disease in patients with acquired immunodeficiency syndrome. Report of two patients. *Gastroenterology*. 1990;99:263–267.
64. Moore RD, Keruly JC, Chaisson RE. Incidence of pancreatitis in HIV-infected patients receiving nucleoside reverse transcriptase inhibitor drugs. *AIDS*. 2001;15:617–620.
65. Assan R, Perronne C, Assan D, et al. Pentamidine-induced derangements of glucose homeostasis. Determinant roles of renal failure and drug accumulation. A study of 128 patients. *Diabetes Care*. 1995;18:47–55.
66. Smith CJ, Olsen CH, Mocroft A, et al. The role of antiretroviral therapy in the incidence of pancreatitis in HIV-positive individuals in the EuroSIDA study. *AIDS*. 2008;22:47–56.
67. Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. *Ann Intern Med*. 1999;131:81–87.
68. Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. *J Natl Cancer Inst*. 2011;103:753–762.
69. Aragon TJ, Vugia DJ, Shallow S, et al. Case-control study of shigellosis in San Francisco: the role of sexual transmission and HIV infection. *Clin Infect Dis*. 2007;44:327–334.
70. Reddy EA, Shaw AV, Crump JA. Community-acquired bloodstream infections in Africa: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10:417–432.
71. Collini PJ, Kuijper E, Dockrell DH. *Clostridium difficile* infection in patients with HIV/AIDS. *Curr HIV/AIDS Rep*. 2013;10:273–282.

72. Manabe YC, Clark DP, Moore RD, et al. Cryptosporidiosis in patients with AIDS: correlates of disease and survival. *Clin Infect Dis*. 1998;27:536–542.
73. Dieterich DT. Rahmin M. Cytomegalovirus colitis in AIDS: presentation in 44 patients and a review of the literature. *J Acquir Immune Defic Syndr*. 1991;4(suppl 1):S29–S35.
74. Chin-Hong PV, Berry JM, Cheng SC, et al. Comparison of patient- and clinician-collected anal cytology samples to screen for human papillomavirus-associated anal intraepithelial neoplasia in men who have sex with men. *Ann Intern Med*. 2008;149:300–306.
75. Piketty C, Selinger-Leneman H, Grabar S, et al. Marked increase in the incidence of invasive anal cancer among HIV-infected patients despite treatment with combination antiretroviral therapy. *AIDS*. 2008;22:1203–1211.
76. Wilcox CM, Schwartz DA, Cotsonis G, et al. Chronic unexplained diarrhea in human immunodeficiency virus infection: determination of the best diagnostic approach. *Gastroenterology*. 1996;110:30–37.
77. Kewenig S, Schneider T, Hohloch K, et al. Rapid mucosal CD4(+) T-cell depletion and enteropathy in simian immunodeficiency virus-infected rhesus macaques. *Gastroenterology*. 1999;116:1115–1123.
78. Kotler DP. HIV infection and the gastrointestinal tract. *AIDS*. 2005;19:107–117.

125 Neurologic Diseases Caused by Human Immunodeficiency Virus Type 1 and Opportunistic Infections

Omar K. Siddiqi, Shruti Agnihotri, and Igor J. Koralnik

SHORT VIEW SUMMARY

Definition
- Human immunodeficiency virus (HIV) and associated infections can adversely affect any aspect of the central and peripheral nervous system.

Epidemiology
- Ten percent of HIV-positive patients initially present with neurologic disease.
- Thirty percent to 50% of HIV-positive patients have neurologic complications.
- Eighty percent of HIV-positive patients have nervous system involvement at autopsy.

Cognitive Manifestations
- HIV-associated neurocognitive disorder (HAND) occurs in 15% of patients with acquired immunodeficiency syndrome (AIDS) and can be the first manifestation of disease in 3% to 10% of patients.
- Detailed neurocognitive testing may be required to diagnose HAND.

Central Nervous System (CNS) Mass Lesions
- Toxoplasmosis is the most frequent cerebral mass lesion. Incidence depends on the seropositivity of the population. Empirical treatment with pyrimethamine and sulfadiazine is useful when clinical and radiologic findings are consistent with the diagnosis.
- Primary CNS lymphoma is the most common HIV-associated brain malignancy and is associated with Epstein-Barr virus infection.
- Progressive multifocal leukoencephalopathy is caused by JC polyomavirus, which induces lytic infection of oligodendrocytes, causing multifocal CNS demyelination.

Spinal Cord
- Vacuolar myelopathy is present at autopsy in 17% to 46% of patients with AIDS.
- Presenting symptoms are gait disturbance, weakness, sensory changes, and urinary dysfunction.
- Diagnosis is one of exclusion.
- Etiology is unclear.

Peripheral Nervous System
- HIV-associated distal sensory polyneuropathy is the most common peripheral neuropathy seen in HIV. Symmetrical paresthesia, numbness, and painful dysesthesia of the lower extremities can occur.
- Nucleoside neuropathy, mononeuritis multiplex, demyelinating neuropathies, and diffuse infiltrative lymphocytosis syndrome–associated neuropathy are other types of neuropathies seen in HIV patients.
- Clinical presentation, electrophysiologic studies and nerve biopsy help differentiate these entities.

Neurologic manifestations are frequent in human immunodeficiency virus type 1 (HIV-1) infection. In the era before combined antiretroviral therapy (ART) or in settings where antiretroviral drugs are not available, neurologic disease constituted the initial presentation in 10% of patients, and neurologic complications developed in 30% to 50% during the course of the disease.[1,2] Autopsies have shown involvement of the nervous system in up to 80% of cases.[3,4] With the advent of ART, the overall incidence of the most frequent human immunodeficiency virus (HIV)–associated neurologic diseases has decreased. The most consistent impact has been a decreased incidence of acquired immunodeficiency syndrome (AIDS)–associated dementia, but decreases in HIV-associated polyneuropathy and central nervous system (CNS) opportunistic infections have also been observed.[5,6,7,8,9]

Diagnosis of neurologic complications in patients with HIV-1 infection poses a particular challenge for clinicians. Indeed, HIV-infected individuals are often severely debilitated and present with multiple constitutional symptoms related to systemic infections or tumors that might overshadow or mimic a primary neurologic condition. In addition, HIV-infected individuals are usually treated with a combination of prophylactic drugs and a rapidly growing number of antiretroviral medications. Drug interactions and neurologic side effects of these medications are common, which adds another level of complexity for care providers. However, certain rules can be applied to facilitate the understanding of these challenging cases:

1. The spectrum of neurologic manifestations in HIV-1–infected individuals depends on their degree of immunosuppression, reflected by $CD4^+$ T-lymphocyte counts, and the speed of disease progression, as estimated by measurement of plasma HIV-1 viral load.
2. Multiple pathologies may coexist in the context of immunosuppression. The peripheral nervous system and CNS are frequently affected concomitantly in HIV-1–infected individuals, and opportunistic infections of the brain may be superimposed on primary HIV-1–associated neurologic disorders.
3. Antiretroviral medications and prophylactic drugs taken by HIV-infected individuals often cause neurologic side effects, which must be included in the differential diagnosis of these patients.
4. Immune recovery associated with ART may be associated with an inflammatory reaction within the CNS.

PRINCIPAL NEUROLOGIC MANIFESTATIONS OF HIV TYPE 1 INFECTION

Meningeal Syndrome

Patient Otherwise Asymptomatic, $CD4^+$ T-Lymphocyte Counts >200 Cells/μL: Aseptic Meningitis

Clinical presentation. Headache, stiff neck, and fever, associated with nausea and vomiting, can be the first manifestations of HIV-1 infection. It is a self-limited illness that subsides spontaneously after several weeks. In some cases, transient cranial neuropathies may develop, affecting mostly the fifth, seventh, and eighth cranial nerves.[10]

In addition, patients may present with symptoms of encephalopathy, and postmortem examination of individuals who died of unrelated causes in this early stage showed mild meningeal inflammation, focal cerebral white matter myelin damage, and perivascular inflammatory infiltrates and gliosis.[11,12]

Laboratory investigations. Cerebrospinal fluid (CSF) analysis shows a moderate lymphocytic pleocytosis (10–100 cells/μL), which is typical of viral meningitis.[13] This aseptic meningitis can occur as soon as 1 week after the primary infection, when HIV-1 conventional serology

is still negative. HIV-1 RNA, however, should be detectable in blood and CSF, and the HIV-1 p24 antigen might be detected in the blood. Repeat serology testing after 6 weeks usually helps to clarify this situation.

Treatment. Interestingly, early onset of aseptic meningitis has not been associated with late neurologic manifestations in HIV-1 infection, and patients may remain asymptomatic for many years before developing other symptoms of HIV-1 infection. If not properly diagnosed at the time of their acute illness, these patients may therefore unwittingly infect a number of sexual partners. It is therefore crucial to include HIV-1 in the differential diagnosis of aseptic meningitis. This condition might recur at any time throughout the course of the disease, although CSF pleocytosis becomes less common with advanced immunosuppression. Treatment is symptomatic. The decision to start on antiretroviral medications should be based on current guidelines that generally recommend treatment of initial HIV-1 infection (see Chapter 119).

Patient at Any Stage of HIV-1 Infection and CD4$^+$ T-Lymphocyte Counts at Any Level: Syphilitic Meningitis

Clinical presentation. In the United States, up to 6% of HIV-infected individuals have a history of syphilis. *Treponema pallidum* infection can also occur at any time during HIV-1 infection and mimics neurologic complications of AIDS. Indeed, both conditions may cause acute or chronic meningitis, myelopathy, cranial or peripheral neuropathies, cerebrovascular disease, and dementia. Therefore it is paramount to distinguish neurosyphilis from latent disease with positive serology and normal physical examination in HIV-infected patients because it has a direct impact on treatment. Neurosyphilis can occur as early as 1 year or as late as 30 years after initial infection. In this chapter, we discuss only syphilitic meningitis; other neurologic complications of this disease are covered in Chapter 237.

Laboratory investigations. Elevation of protein concentration and leukocyte counts can be found in the CSF of approximately 15% of patients with primary syphilis and up to 40% of patients with secondary syphilis. Some of these patients eventually experience spontaneous cure of this earlier CNS infection, but the persistence of asymptomatic CSF abnormalities for more than 5 years in the untreated patient is highly predictive of the development of clinical neurosyphilis.

Persistent mononuclear pleocytosis and elevated protein concentration can be found in the CSF of HIV-1–infected patients with neurosyphilis,[14] as well as an elevated immunoglobulin G synthesis rate and oligoclonal bands. This is of no help in establishing the diagnosis of neurosyphilis in the context of HIV-1 infection because these findings occur as well in asymptomatic HIV-1 seropositive patients, especially when they have detectable HIV-1 RNA in their CSF. Using either the criterion of elevated CSF protein of greater than 50 mg/dL or white blood cell counts greater than 10 cells/μL in HIV-positive patients with reactive rapid plasma reagin may lead to overdiagnosis of neurosyphilis in the absence of clinical symptoms. Follow-up lumbar puncture after 12 months showed persistence of CSF abnormalities in 62% of cases.[15] A positive CSF Venereal Disease Research Laboratory (VDRL) test result establishes the diagnosis of neurosyphilis if the spinal tap is not bloody. However, this test may be negative in HIV-1 infection.[16,17] A reactive CSF fluorescent treponemal antibody absorbed test increases the likelihood of *T. pallidum* infection but is less specific because it can result from treated neurosyphilis or from contamination of the CSF with small amounts of blood containing antibody at the time of the lumbar puncture.

Acute symptomatic syphilitic meningitis is usually the earliest clinical manifestation of neurosyphilis, which occurs within the first year of infection and can be associated with cranial nerve palsies, including isolated eighth nerve palsy, and signs and symptoms of hydrocephalus. CSF abnormalities are similar to those of asymptomatic neurosyphilis, except that the CSF VDRL test result is nearly always positive (also see Chapter 237).

Treatment. HIV-1–infected individuals with a positive serum rapid plasma reagin test result, unexplained CSF pleocytosis, and elevated protein concentration, as well as symptoms consistent with neurosyphilis, should be treated with intravenous penicillin even in the absence of a positive VDRL test result in the CSF. Treatment consists of intravenous penicillin G (3–4 million units IV every 4 hours for 10–14 days). In case of allergy to penicillin, ceftriaxone (2 g IM or IV once daily for 10–14 days) is another option. A careful follow-up of these patients is necessary, and a repeat spinal tap 1 month after onset of treatment should show a normalization of the CSF cellularity and protein concentration. Normalization of serum rapid plasma reagin predicted normalization of CSF and clinical abnormalities 13 months after treatment in more than 90% of a cohort composed mostly of HIV-infected men. This was more frequent in those receiving ART than in untreated patients.[18] Some patients have a transient increase in CSF HIV-1 viral load to more than 100,000 copies/mL associated with neurosyphilis, which subsides after antibiotic treatment. Neurosyphilis may amplify intrathecal HIV replication, possibly through immune activation that persists even after syphilis treatment.[19] As is the case with other opportunistic infections of the brain, this viral burden is likely carried by activated circulating lymphocytes and monocytes coming to combat the CNS infection and should not be interpreted as a manifestation of HIV-1 encephalitis.

Patient With AIDS, CD4$^+$ T-Lymphocyte Counts of <200 Cells/μL: Cryptococcal Meningitis

Clinical presentation. This is the most common opportunistic meningitis in AIDS, which affected 10% of patients before the ART era[20] but has decreased in incidence since then (also see Chapter 262).[21] Cryptococcal meningitis differs from aseptic meningitis in that meningismus is present in fewer than 40% of cases, and patients may present with only fever and headache, which become progressively more debilitating. Confusion, blindness, or altered state of consciousness occurs in severe cases.

Laboratory investigations. The detection of *Cryptococcus neoformans* antigen titers by enzyme immunoassay, latex agglutination, or lateral flow assay in the CSF provides a rapid diagnosis, which is confirmed subsequently by CSF culture. Because false-positive results occur with all the antigen tests, confirmation by culture is essential to establish the diagnosis of cryptococcal meningitis. Other CSF findings include markedly elevated opening pressure, mononuclear pleocytosis, elevated protein and decreased glucose concentration in 50% of the cases, and direct detection of the organism by India ink staining in 80% of the cases. Serum cryptococcal antigen is usually detected in cryptococcal meningitis in AIDS patients, and blood and urine cultures may also be positive.

Brain imaging is usually negative. The most common finding on magnetic resonance imaging (MRI) is dilated Virchow-Robin spaces, but findings can also include pseudocysts, cryptococcomas, and hydrocephalus.[22] Poor prognosis factors include altered mental status, absence of CSF pleocytosis, CSF antigen titer greater than 1:1024, a positive blood culture, and hyponatremia.

Treatment. Treatment should begin with amphotericin B (0.7–1.0 mg/kg) with flucytosine (100 mg/kg PO in four divided doses per day) until the patient is clearly responding and for not less than 2 weeks, which is associated with significantly increased rates of yeast clearance from CSF and decreased mortality compared with amphotericin B alone. Combination of fluconazole with amphotericin B showed no survival benefit.[23] Use of fluconazole alone as initial therapy is associated with much slower culture conversion and is not recommended.[24] Consolidation therapy then consists of fluconazole (400 mg PO daily) administered for 8 weeks or until CSF cultures are sterile. Lipid formulations of amphotericin B may be used for patients with renal insufficiency, and itraconazole may be substituted for fluconazole if patients can tolerate fluconazole but is clearly inferior to the latter. Lifelong maintenance therapy using fluconazole (200 mg/day) has been previously recommended to prevent relapses.[25] Updated recommendations state that maintenance therapy can be discontinued in HIV-negative patients if they have received 6–12 months of maintenance therapy. In HIV-positive patients, maintenance therapy can be discontinued if CD4$^+$ counts reach greater than 100 cells/μL, and there is a sustained undetectable or very low HIV RNA level for 3 or more months.[26]

The outcome is generally favorable within 2 weeks, but early mortality still reaches 6%.[27] In a large multicountry study of HIV-associated

cryptococcal meningitis predominantly in resource-limited settings, 2-week mortality was 17% and 1-year mortality was 41%.[28] In Botswana, the in-hospital mortality was significantly lower among those patients who were on ART at the time of diagnosis of cryptococcal meningitis compared with untreated patients (8% vs. 21%).[29] Complications such as increased intracranial pressure greater than 200 mm H_2O occur in nearly all patients. Such a complication should be recognized and treated aggressively with mechanical drainage, including repeat lumbar punctures, temporary external lumbar drainage, or intraventricular shunts.[30,31] Corticosteroids, acetazolamide, and mannitol have not been shown to be effective. Neurologic deterioration after commencing ART occurs in 26% of patients and is caused by cryptococcosis-associated immune reconstitution inflammatory syndrome (IRIS).[32] It is more frequent if ART is given 7 days after compared with 28 days after onset of antifungal therapy.[33] ART should be deferred until 5 weeks after diagnosis and treatment of cryptococcal meningitis because ART commenced within 1 to 2 weeks is associated with higher mortality.[26,34] Persistent CSF cryptococcal growth at ART initiation and poor $CD4^+$ T-cell increases on ART are strong predictors of cryptococcosis-associated IRIS.[32] Management of cryptococcosis-associated IRIS includes continuation of ART, antifungal therapy, and a course of corticosteroids.[35]

Differential Diagnosis of Meningitis

Other CNS infections in AIDS include tuberculosis, histoplasmosis, aspergillosis, coccidioidomycosis, and infections with *Acanthamoeba, Candida albicans, Trypanosoma cruzii,* herpes simplex and herpes zoster viruses, and *Nocardia asteroides.* Geographic differences account for variations in local prevalence. Estimates indicate that more than 1 million people worldwide have tuberculosis and HIV coinfection, with the highest number of individuals in sub-Saharan Africa. CNS tuberculosis can present in numerous ways, including as a tuberculoma, an abscess, a spinal cord lesion, and most commonly as tuberculous meningitis (TBM). TBM is a highly treatable condition in resources-limited settings (RLS) because its presentation is commonly subacute and antituberculosis treatment is widely available. However, TBM diagnosis remains a challenge throughout the world. Acid-fast bacilli staining on CSF has a sensitivity of 10% to 20% that varies greatly on the basis of technical expertise.[36] CSF culture has a sensitivity of approximately 50% and can take as long as 6 weeks to become positive.[37] The Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, CA) is a molecular diagnostic test that showed 95% sensitivity for the diagnosis of TBM on CSF in a small study in Uganda. As a result, the World Health Organization has endorsed it as the test of choice for the diagnosis of TBM, when available.[38] In RLS, treatment is often initiated empirically with minimal objective testing for guidance except for hypoglycorrhachia and high CSF total protein, for which biochemical tests are available.

Bacterial meningitis is more commonly a problem for HIV-infected patients in RLS compared with resource-rich settings.[39,40] HIV-infected patients are at risk for pneumococcal infection,[41] and pneumococcal meningitis usually arises from spread of an untreated primary infection. These cases are more likely in RLS where patients present at later stages of disease and have limited access to health services.

COGNITIVE AND MOTOR SYNDROMES

HIV Type 1–Associated Neurocognitive Disorder

Clinical presentation. This common CNS complication of HIV-1 infection occurs in 15% of patients with AIDS and can be the first manifestation of the disease in 3% to 10%.[42] In the past, this condition has also been named AIDS dementia complex, HIV-1 encephalopathy, or HIV-associated major cognitive disorder. A less severe entity named HIV-1–associated mild neurocognitive disorder occurs in an additional 20% to 25%, and asymptomatic neurocognitive impairment (ANI) is used to categorize individuals with subclinical impairment.[43,44] Risk factors in uncontrolled HIV infection include an AIDS-defining illness, increased age and survival duration, lower nadir of $CD4^+$ T-cell counts, and higher baseline HIV viral loads.[45] Risk factors for neurocognitive decline in well-controlled HIV-infected individuals include glomerular filtration rate 50 mL/min or less, HIV infection for 15 years or longer, education level 12 years or less, and cerebrospinal fluid protein greater than 45 mg/dL.[46]

The clinical characteristics of this disorder can be subdivided into three main categories: cognitive, behavioral, and motor (Table 125.1).

Initial symptoms are usually subtle and include difficulty with memory, slowness of thought, and trouble concentrating. Complex mental activities become more time consuming and difficult to perform. A loss of interest in social and professional activities soon follows, and such apathy and social withdrawal may be mistaken for depression. Although cognitive and behavioral symptoms are prominent in most patients, some mainly present with motor dysfunction, which includes decreased coordination, altered handwriting, loss of balance, and gait instability.

The mental status examination reveals minor psychomotor slowing, inattention, decreased short-term memory, inability to perform simple calculations, and frontal release signs. Ocular movement testing shows saccadic pursuit. Other frequent findings are brisk reflexes, mild postural tremor, slowing of rapid alternating movements, and gait instability when performing half-turns. If untreated, dementia becomes more global, profoundly impairing orientation, memory, and cognition. Confusional or psychotic episodes have been reported, but seizures are a rare occurrence. Despite the extent of the cerebral involvement, there is usually no aphasia, apraxia, or other signs of discrete cortical dysfunction, except in terminal stages. Therefore this syndrome has been classified as a frontal-subcortical dementia. A rapid bedside evaluation can be performed with the Montreal Cognitive Assessment (MoCA) or the Ascertain Dementia 8-Item Informant Questionnaire (AD8).[47,48] However, these screening tests are not as sensitive as a detailed neuropsychological evaluation, which should include tests of attention, memory, and psychomotor speed such as digit span and verbal fluency tests and the Trail Making Test, the Grooved Pegboard Test, the Symbol Digit Modalities Test, and the Rey Auditory Verbal Learning Test.[49] The International HIV Dementia Scale can be used to identify individuals at risk of HIV-associated dementia despite language barriers.[50,51]

Unfortunately, cognitive dysfunction persists despite ART. A cross-sectional study of 1555 HIV-infected adults in the United States showed neuropsychological impairment in 52%. Prevalence estimates for specific HIV-associated neurocognitive disorder (HAND) diagnoses were 33% for ANI, 12% for mild neurocognitive disorder, and 2% for HIV-associated dementia.[52] In recent longitudinal studies that followed patients with HAND for 3 to 4 years, neurocognitive status remained stable in approximately 61% to 77% of patients, declined in 13% to 23%, and improved in 10% to 16%.[53,54] Patients with ANI developed symptomatic neurocognitive decline earlier than those with normal cognitive function.[55]

Laboratory investigations. Numerous groups have detected early neurologic dysfunction in HIV-1–infected asymptomatic individuals.[56,57,58] Subtle electrophysiologic abnormalities can be found in early HIV-1 infection (on electroencephalography, evoked potentials, and nerve conduction studies), but they do not seem to have a predictive value for the later onset of AIDS dementia, which occurs generally when the $CD4^+$ T-lymphocyte counts are less than 200 cells/μL. CSF analysis shows mild lymphocytic pleocytosis in 25% of patients and elevated protein in 55%,[59] which can also be found in nondemented patients. Increased CSF levels of neurofilament light protein and neopterin have been reported in HAND, but their use in patients' management is limited because these markers are also elevated during opportunistic infections

TABLE 125.1 Clinical Triad in Human Immunodeficiency Virus Type 1–Associated Neurocognitive Disorder

COGNITIVE	BEHAVIORAL	MOTOR
Forgetfulness	Apathy	Gait instability
Mental slowing	Social withdrawal	Poor coordination
Decreased concentration	Lack of spontaneity	Leg weakness

of the CNS and because these assays are not readily available in the clinical setting.[60,61]

Measurement of the HIV-1 CSF viral load has been evaluated as a surrogate marker in HIV-1–infected individuals with cognitive dysfunction. A wide overlap was found between CSF HIV-1 viral load values of demented and nondemented individuals, and concomitant opportunistic infections of the CNS must be ruled out because they also contribute to transient elevation of HIV-1 viral burden in the CSF.[62] These findings suggest that there may be two phases of HIV-1 infection in the CSF. First, a transitory infection of the CNS may occur early in the disease via trafficking lymphocytes. These viral strains have a lymphotropic phenotype (using CXCR4 coreceptor) and may respond to therapy in parallel to plasma virus load. Second, a more autonomous infection of CNS monocytes/macrophages may take place at a later stage, with macrophage tropic strains (using CCR5 coreceptor).[63] Such patients may need higher drug penetration in the CNS. Whether measurement of the HIV-1 CSF viral load provides an accurate representation of the viral replication occurring in the CNS is unclear. However, subsets of patients with higher CSF than plasma viral loads, known as CSF escape, have been recognized, in whom intrathecal viral replication correlates with neurologic deficits. Because HIV-1–associated dementia complex is a diagnosis of exclusion, CSF examination is indicated for bacterial, fungal, and acid-fast bacteria cultures; cryptococcal antigen; VDRL test; and cytology. In addition, performing CSF polymerase chain reaction (PCR) for JC virus (JCV), the agent of progressive multifocal leukoencephalopathy (PML), is indicated because this condition is often difficult to distinguish from HIV-1 encephalopathy on brain imaging studies (see "Progressive Multifocal Leukoencephalopathy" later; also see Chapter 144).

Imaging studies. Computed tomography (CT) and MRI may show greater subcortical atrophy than cortical atrophy, which is not proportional to the degree of dementia. The progression of brain atrophy is worse in older individuals with HIV than normal controls despite viral suppression.[64] MRI may also demonstrate multiple hyperintense signals in T2-weighted images, which are nonenhancing, poorly demarcated, and localized bilaterally in the subcortical white matter (Fig. 125.1). MRI is superior to CT for distinguishing these abnormalities from confounding illnesses such as PML. Unlike lesions of PML, there is no associated hypointensity in T1-weighted images. The severity of global brain atrophy and signal changes in basal ganglia correlates with cognitive impairment.[65]

Brain biopsy and histologic analysis. There is no indication to perform a brain biopsy in patients with HAND, unless imaging studies suggest the presence of another process. Postmortem examination reveals encephalitis with multinucleated giant cells and microglial nodules, as well as astrocytosis and perivascular mononuclear cell infiltrates. HIV-1 has been found in microglial nodules, perivascular macrophages, and multinucleated giant cells. The latter are the result of the fusion of infected macrophages. The virus can also infect astrocytes.[66] HIV-1 has also been found in endothelial cells,[67] and abnormalities of the cerebral microcirculation are characterized by increased cellularity and pleomorphism of endothelial cells, as well as prominent perivascular aggregates of HIV-infected macrophages. These findings are sometimes related to microinfarcts and are postulated to give rise to increased vascular permeability.[68] Indeed, early enhancement has been detected in the basal ganglia of patients with HAND, suggesting a disruption of the blood-brain barrier (BBB) in these regions.[69] HIV-1 does not infect glial cells in adults, whereas a limited expression of viral regulatory gene products has been demonstrated in glial cells from children with AIDS.[70] White matter pallor involving primarily the centrum semiovale is a hallmark of HIV-1 encephalopathy in adults, which may be caused by seepage of macromolecules and edema fluid in the brain parenchyma through the permeable BBB and may cause injury to the myelinated fibers. Finally, HIV-1 does not infect neurons. Therefore quantitative neuronal loss, decrease in cell size, or dendritic injury found in the cortex of demented patients[71] may only be secondary to infection of other cells and associated immune activation.[72]

Treatment. Although the pathophysiology of HAND is not entirely elucidated, HIV-1 remains the main triggering factor, and it is therefore reasonable to prevent viral replication in the CNS. However, antiretroviral drugs have variable penetration through the BBB, and evaluation of CNS concentration and pharmacokinetics of these medications is incomplete. On the basis of available pharmacologic data, antiretrovirals can be classified according to their penetration through the BBB. A CNS penetration effectiveness (CPE) score[73] is given to each medication going from 1 (low) up to 4 (high) (Table 125.2). The CPE score of an ART regimen is calculated by summing the score of each individual antiretroviral. Drugs with high CNS penetration include zidovudine, nevirapine, and ritonavir-boosted indinavir.

Since 1996, the availability of protease inhibitors (PIs) and the use of three or more drugs in ART regimens have made a major impact on the incidence of neurologic disease in HIV-1–infected patients.[74,75,76] This is somewhat surprising; PIs in general have a very low CSF-to-plasma ratio because they are highly protein bound. Nevertheless, the incidence of HAND, which was estimated at 6.49 per 1000 person-years pre-1997, decreased to 0.66 by 2003–2006, an approximately 10-fold decrease.[74,77] Although ART is now the treatment of choice for

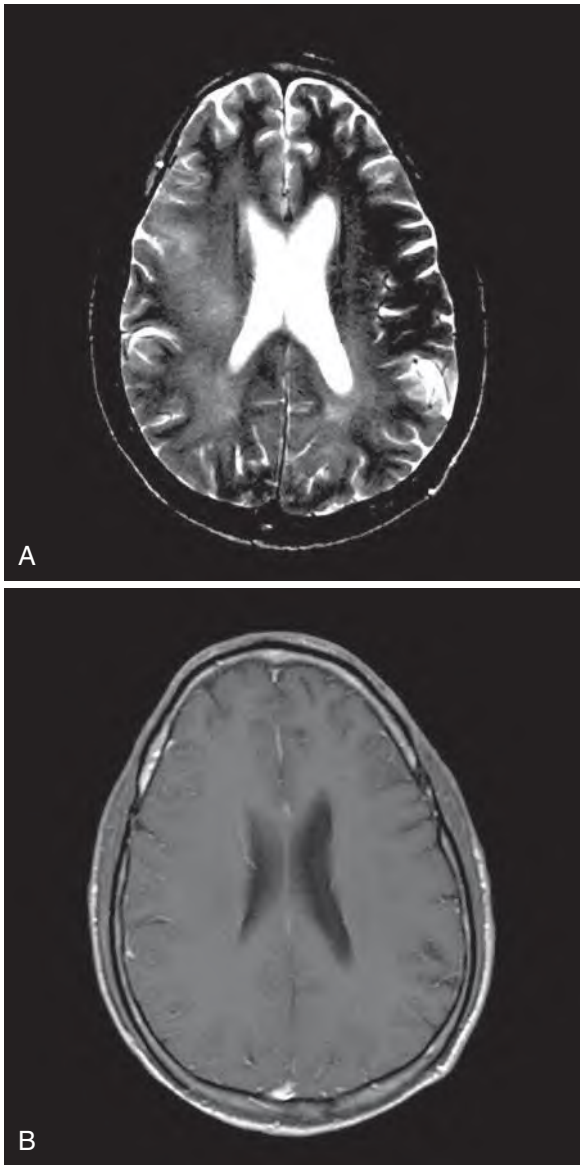

FIG. 125.1 Brain magnetic resonance images of a 42-year-old man with human immunodeficiency virus–associated neurocognitive disorder. The T2-weighted image (A) shows bilateral, ill-defined hyperintense signal in the periventricular white matter and centrum semiovale, which does not enhance with gadolinium injection on the T1-weighted image (B). The ventricles are slightly enlarged, consistent with subcortical atrophy.

TABLE 125.2 Central Nervous System Penetration Effectiveness Score for Antiretroviral Drugs

	4	3	2	1
Nucleoside reverse-transcriptase inhibitors	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir
Nonnucleoside reverse-transcriptase inhibitors	Nevirapine	Delavirdine Efavirenz	Etravirine	
Protease inhibitors	Indinavir-r	Darunavir-r Fosamprenavir-r Indinavir Lopinavir-r	Atazanavir-r Atazanavir Fosamprenavir	Nelfinavir Ritonavir Saquinavir-r Saquinavir Tipranavir
Fusion/entry inhibitors		Maraviroc		Enfuvirtide
Integrase inhibitors		Raltegravir		

[a]Numerical score of 4 is highest and 1 is lowest by method of Letendre et al.[73]
-r, Ritonavir-boosted.

advanced HIV-1 disease, the optimal drug combination for HAND has not been established. Whether regimens containing several drugs with good penetration through the BBB were advantageous has been investigated. In ART-experienced patients with $CD4^+$ T-cell counts of less than 200 cells/μL, those who received multiple CNS penetrating agents had a greater reduction of CSF HIV-1 RNA.[78,79,80] These results have been confirmed in recent studies, showing that higher CPE scores of long-term ART are associated with better viral suppression in CSF[72,73,74] and decreased risk of cognitive impairment.[81,82,83,84] However, a recent randomized trial of ART with high CNS penetration did not show any benefit in HAND; this could possibly be due to the short duration of the study and unbalanced randomization.[85] One study also showed that regimens with higher CPE scores may be associated with increased risk of HIV dementia.[86] Other studies have shown that discontinuation of efavirenz was associated with cognitive improvement in scheduled treatment interruption regimens[87] and in otherwise asymptomatic HIV-infected individuals,[88] suggesting that some antiretrovirals might have neurotoxic properties, which was also demonstrated in vitro.[89] The possible neurotoxic effects of efavirenz were also highlighted by a study that found worse neurocognitive function in patients on long-term efavirenz compared with those taking lopinovir-ritonavir.[90]

The hypothesis that discordant mutations are present in blood and CSF has been confirmed by the analysis of HIV-1 genotypes in paired samples. Mutations of the reverse-transcriptase and protease genes of CSF strains, but not in the corresponding blood isolates, were detected in 10 of 23 subjects (43%). Interestingly, mutations conferring resistance to low or high CSF-penetrating agents occurred at similar frequencies.[91] Reverse-transcriptase mutation patterns differed in 14 of 21 (67%) paired samples from plasma and CSF in one study, and HIV RNA responses and reverse-transcriptase genotypes were discordant between CSF and plasma in some subjects.[92,93] A recent study suggests a role of M184V/I mutations in influencing CNS reservoirs of HIV and CSF escape.[94] In a study of HIV-infected children starting ART, 8 of 11 had identical resistance patterns in both CSF and plasma at baseline, whereas at week 48 of treatment, only 1 of 9 children had similar genotypes, suggesting discordant viral evolution in these two compartments.[95] CSF viral escape with progressive neurologic dysfunction despite well-controlled plasma viral load and good immunologic response on ART is now well recognized.[94] In general, these patients had a higher CSF viral load compared with plasma. Clinical characteristics of patients differed based on plasma HIV RNA levels preceding the CSF escape, with low-level viremia or suppressed patients being more symptomatic.[94] These patients have CSF pleocytosis and elevated protein concentration, MRI abnormalities, and unique CSF resistance mutations compared with plasma. They have clinical and radiologic improvement after optimization of ART.[96] Failure to recognize the occurrence of different genotypic resistance patterns in plasma and CSF may lead to uncontrolled viral replication in the CNS and worsening neurologic symptoms despite evidence of viral clearance in the periphery. These resistant isolates may, in turn, spill back into the circulation and contribute to the progression of HIV-1 disease. Therefore genotypic analysis of CSF HIV-1 strains is indicated in patients with cognitive dysfunction who have good virologic response to ART in the plasma but persistence of an elevated HIV-1 CSF viral load.

In addition to antiretroviral treatment, other experimental compounds have been tested for the treatment of HAND, but without evidence of clear benefit so far. These include a calcium channel blocker (nimodipine), antioxidants (vitamin E, thioctic acid, CPI-1189), a tumor necrosis factor-α antagonist (pentoxifylline, CPI-1189), a noncompetitive *N*-methyl-D-aspartate inhibitor (memantine), peptide T, rivastigmine, selegiline, minocycline, and a combination of paroxetine and fluconazole.[97,98] Use of computerized cognitive training as in other neurodegenerative disorders is being tried for HIV patients as well.[99]

CENTRAL NERVOUS SYSTEM MASS LESIONS

In patients with AIDS presenting with change in mental status or abnormal neurologic examination results, brain lesions are frequently revealed on CT or MRI. These can be quite extensive and may represent life-threatening emergencies.

Toxoplasma Encephalitis

At the beginning of the AIDS epidemic, *Toxoplasma* encephalitis (TE) was the most common cerebral mass lesion in patients with AIDS. TE is caused by a reactivation of latent infection by the protozoan *Toxoplasma gondii* as a result of progressive loss of cellular immunity. The incidence of TE depends on the seropositivity for *T. gondii* in a specific population. Seroprevalence can vary widely between countries and even within a country depending on factors such as country of birth, climate, and socioeconomic status. The seroprevalence of toxoplasmosis in the United States for individuals ages 12 to 49 years decreased from 14.1% in the 1980s to 6.7% in 2009–2010. The reason for this decrease in seroprevalence is unclear but may be due to improved soil/cat feces–related hygiene as well as food storage.[100] The incidence of TE has decreased thanks to widespread prophylaxis for *Pneumocystis jirovecii* pneumonia using trimethoprim-sulfamethoxazole, which also prevents CNS toxoplasmosis.[101] Since the era of ART, there has been a further trend for a decreased incidence of this condition,[21] and it accounted for only 28% of focal brain lesions occurring in patients with AIDS in 1998[102] and for 26% of patients with neurologic disorders in 2004.[103] Nevertheless, TE continues to be a severe health problem. Patients who develop TE nowadays either did not receive or had not taken ART adequately.[104]

Clinical presentation. Almost 90% of patients with TE have $CD4^+$ T-lymphocyte counts less than 200 cells/μL, and 75% have $CD4^+$ counts less than 100 cells/μL at the time of clinical presentation. The most common symptoms include headache, confusion, fever, and lethargy. Cases may also occur with a strokelike presentation.[105] Seizures develop in up to 30% of patients.[106] Seventy percent of patients have focal signs

on the neurologic examination, such as hemiparesis, cranial nerve palsies, ataxia, and sensory deficits. The clinical presentation is usually subacute, ranging from a few days to a month (see Chapter 278).

Laboratory investigations. As is the case in the general population, serum anti-*Toxoplasma* immunoglobulin G antibodies can be detected in patients with TE, whereas immunoglobulin M antibodies are less commonly found, supporting the notion that most cases represent a reactivation of latent infection. Measurement of antibody titers is not helpful to establish the diagnosis. On enzyme-linked immunosorbent assay, only 7% of patients known to be seropositive for *T. gondii* had lost their antibodies at the time of presentation.[107] Therefore, a negative serology orients toward another entity, whereas a positive serology is not diagnostic (see Chapter 278).

A slight increase in CSF protein concentration and a moderate mononucleated pleocytosis (<60 cells/μL) are common but nonspecific, and may be due to the underlying HIV-1 infection. A slight decrease in the CSF glucose has been reported but is not a constant finding. The PCR technique has been less useful for detection of *T. gondii* DNA in the CSF compared with other pathogens, with a sensitivity of only 44% to 65% and a specificity of 100%.[108] However, this low sensitivity may be improved by the use of stage-specific PCR primers.[109] CSF analysis is therefore more useful to rule out other infectious processes than to confirm the diagnosis of TE.

Imaging studies. Neuroimaging with head CT or MRI demonstrates CNS lesions in almost all cases, with the exception of the rare diffuse encephalitic form of toxoplasmosis. Lesions are multiple in two-thirds of the cases, and 90% of them display ring enhancement after administration of contrast material. MRI is more sensitive than CT in detecting multiple lesions. These are generally localized at the corticomedullary junction, in the white matter, or in the basal ganglia; are surrounded by edema; and induce mass effect on surrounding structures (Fig. 125.2). Unfortunately, the neuroradiologic characteristics of TE are not pathognomonic and may be observed in other conditions such as primary CNS lymphoma (PCNSL) (see "Primary Central Nervous System Lymphoma" later).

Brain biopsy. Because of the good response to therapy, histologic examination is not required for the diagnosis of TE, and an empirical therapeutic trial is recommended when the clinical and radiologic

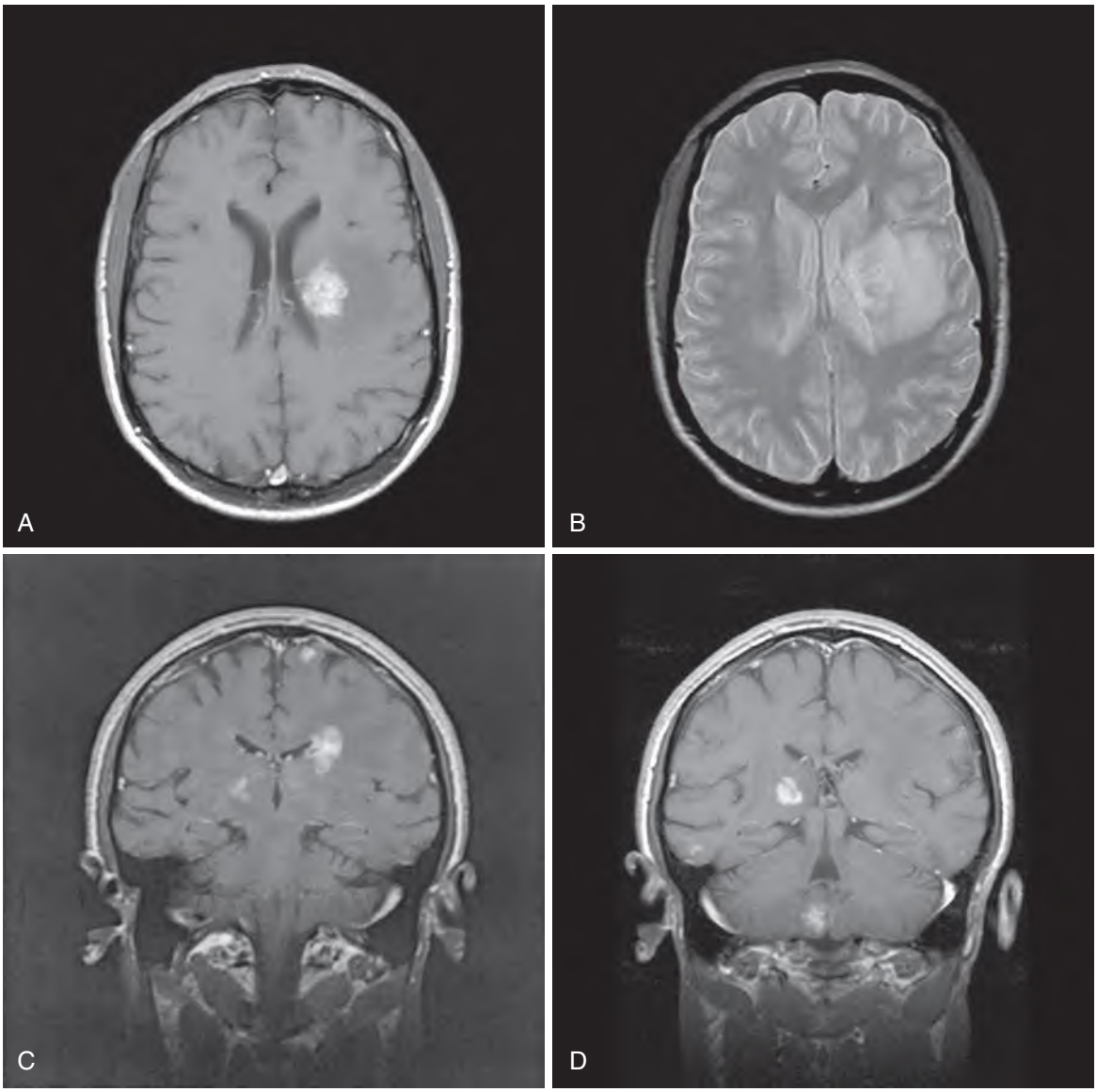

FIG. 125.2 Brain magnetic resonance images of a 38-year-old man with acquired immunodeficiency syndrome and *Toxoplasma* encephalitis. The T1-weighted image after gadolinium injection shows a large enhancing lesion in the left frontal lobe (A), surrounded by edema, as demonstrated on the T2-weighted image (B). Additional smaller enhancing lesions can be seen on coronal cuts in the right thalamus and at the left convexity (C) and in the right cerebellum and right temporal lobe (D).

findings are consistent with this diagnosis. Histologic examination shows mainly necrotic abscesses with blood vessel thrombosis and necrosis. Cysts containing bradyzoites, the dormant form of *T. gondii,* coexist with numerous active tachyzoites.

Treatment. Treatment consists of a combination of pyrimethamine and sulfadiazine, which cause a synergistic and sequential block on the folic acid metabolism necessary for the development of the parasite. Standard acute therapy consists of pyrimethamine (200 mg PO the first day of treatment, followed by 50–75 mg/day PO), sulfadiazine (1000–1500 mg PO in four divided doses), and folinic acid (10–25 mg/day PO for 6 weeks).

Clindamycin (600 mg IV or 450 mg PO four times daily) is an adequate alternative to sulfadiazine in the previous regimen for patients allergic to sulfonamides. Side effects, which consist of cytopenia, rashes, diarrhea, and increased liver enzymes, have been reported in 40% to 70% of patients receiving pyrimethamine and sulfadiazine and in 36% of those receiving pyrimethamine and clindamycin. These can cause early discontinuation of therapy. Atovaquone (1500 mg PO two times daily) can also be combined with pyrimethamine and folinic acid. Although corticosteroids are frequently prescribed to diminish cerebral edema, their use has been shown to be neither beneficial nor harmful in TE.[110] Because high doses of steroids also decrease the size of CNS lymphoma lesions, they should be administered only in cases with impending cerebral herniation during the initial medical treatment of presumed TE so as not to cloud the diagnosis. Neurologic improvement is clinically apparent in more than half the cases by day 3 of therapy and in most cases by day 7. Nevertheless, the death rate at 1 year varies from 10% to 60%.[103,111] Persistent neurologic sequelae remained in 37% of survivors.[112] A failure to improve or a worsening of the symptoms should prompt repeat imaging studies by days 10 to 14 to determine the need for a brain biopsy. TE-associated IRIS presenting simultaneously with initiation of ART has been reported in six patients, including five who were supposed to take effective prophylaxis. Brain biopsy showed intense angiocentric infiltrate consisting predominantly of $CD8^+$ T lymphocytes in two of them.[113]

Secondary prophylaxis. *Toxoplasma gondii* is sensitive to treatment only when in tachyzoite form. Because dormant cystic forms may rupture and reinitiate the infectious process at any time, maintenance therapy is necessary to prevent a relapse, which is likely to occur after a delay of 6 to 8 weeks of interruption of treatment. Standard maintenance therapy consists of pyrimethamine (25–50 mg/day) with folinic acid (10–25 mg/day) and either sulfadiazine (2–4 g/day in four divided doses) or clindamycin (450 mg PO four times daily). Patients with sustained $CD4^+$ T-cell counts higher than 200 cells/μL for more than 3 months can discontinue their secondary prophylaxis.[114] Relapse occurred in only 1 of 22 (5%) patients.[115]

If the diagnosis is made in a timely fashion and the patient does not become intolerant to the treatment, TE is currently an opportunistic infection with a relatively high therapeutic success rate, and death is usually caused by other complications of AIDS.

Primary Central Nervous System Lymphoma

This condition, which affected 2% of patients with AIDS at the beginning of the epidemic, has seen its incidence decrease considerably in the ART era.[21] In 1998, it accounted for only 12% of AIDS-related focal brain lesions.[102] Its radiographic appearance makes it the principal differential diagnosis of TE.

Clinical presentation. The onset of symptoms is generally subacute, lasting weeks to months. Confusion, lethargy, and memory loss are the most frequent symptoms. As the disease progresses, hemiparesis, aphasia, seizures, and cranial nerve palsies occur.[116] Fever, headaches, and constitutional symptoms are generally absent, which helps distinguish PCNSL from TE. At the time of diagnosis, the average $CD4^+$ T-lymphocyte counts are usually very low (≈50 cells/μL).

Laboratory investigations. A mild mononuclear pleocytosis (<30 cells/μL) and an increase in the protein concentration in the CSF are common findings in patients with PCNSL but are nonspecific and may be due to the underlying HIV-1 infection. High protein levels (≤590 mg/dL) have been reported in patients with extensive lymphomatous infiltration of both cerebral hemispheres. Hypoglycorrhachia is a rare finding.

It is important to perform cytologic analysis of the CSF because the presence of atypical or malignant lymphomatous cells can establish the diagnosis. Flow cytometry immunophenotyping has at least 25% higher sensitivity than conventional cytomorphologic methods for the detection of malignant cells.[117] Systemic extracerebral lymphomas, which have an increased incidence in AIDS patients, can also cause lymphomatous meningitis but do not generally spread to the brain itself. Similarly, PCNSL does not metastasize systemically. The Epstein-Barr virus (EBV) genome can be detected in tumor cells of nearly all PCNSLs, but only in some systemic lymphomas of AIDS patients, and rarely in primary brain lymphoma tissue from patients without immunodeficiency.[118] When testing is performed in a research setting, detection of EBV DNA by PCR in the CSF has a reported sensitivity of 80% to 90% and a specificity of 87% to 98% for the diagnosis of PCNSL. Measurement of the EBV CSF viral load by quantified PCR in the CSF may improve the sensitivity of this test[119] and may be clinically useful in monitoring responses to treatment.[120] However, other groups have found EBV DNA in the CSF of patients who did not have PCNSL, which raises doubts regarding the true predictive value of this test when performed in the clinical setting.[121,122]

Imaging studies. Head CT or MRI usually shows findings consistent with a CNS tumor. Solitary mass lesions are as frequent as multiple lesions.[116] Most lesions display some degree of enhancement, which is usually nodular or patchy. Ring enhancement, identical to that commonly seen in TE, can occur and correlate with central tumor necrosis. Subependymal enhancement seems more specific of CNS lymphoma, but this is a rare feature. Lesions are frequently located in the corpus callosum, the periventricular white matter, or the cortex. Involvement of the posterior fossa occurs only in 10% of cases.[123] Lesions can be surrounded by edema, which may induce variable mass effect on neighboring structures (Fig. 125.3).[124] Magnetic resonance imaging is more sensitive than CT in revealing multiple lesions, which can be useful if a biopsy is being considered. Thallium-201 single-photon emission CT shows an accumulation of isotope in the tumor due to increased metabolic activity.[125] In one series comparing enhancing brain lesions caused by toxoplasmosis and lymphoma, the thallium index of each lesion, measured as the ratio of the mean uptake in the lesion to that of the corresponding contralateral side, was increased and a significant predictor of lymphoma only in lesions 2 cm or larger, yielding 100% sensitivity and 89% specificity.[126] However, the usefulness of this method in differentiating CNS lymphoma from opportunistic infections may depend heavily on the resolution of the images, and appropriate technology may not be available in every center. Fluorodeoxyglucose–positron emission tomography scan has also shown utility in differentiating PCNSL from nonmalignant disease in a small series.[127]

Brain biopsy. If the CSF cytology fails to reveal lymphomatous cells and if EBV PCR is negative in the CSF, an image-guided stereotactic brain biopsy using CT or MRI is the only way to ascertain the diagnosis. The macroscopic appearance of these tumors is generally that of a multifocal, diffusely infiltrating, and expanding nonhemorrhagic mass, without well-demarcated borders, simulating the appearance of an infiltrating glioma. However, well-circumscribed, largely necrotic masses can also resemble abscesses. Microscopic analysis reveals a variety of patterns, including large cells, small noncleaved cells, and immunoblastic or mixed cellular components. These are generally of B-lymphocyte lineage. EBV is present in tumor cells, suggesting that this virus may have a role in tumorigenesis,[128] as is the case in Burkitt lymphoma and in nasopharyngeal carcinoma.

Treatment. The response to steroids seen in lymphomas of non-AIDS patients is not always seen in AIDS patients. In patients with altered mental status, debilitating focal symptoms, or impending herniation, dexamethasone (10 mg IV or PO, followed by 4 mg IV or PO every 6 hours) can provide temporary improvement. Current treatment guidelines recommend the use of high-dose methotrexate in combination with ART. A study of 51 patients treated with this regimen demonstrated a median overall survival of 5.7 years, with 5- and 10-year rates of 48% and 41%, respectively.[129] In the past, treatment of CNS lymphoma in AIDS consisted of whole-brain radiation therapy with a total of 3000

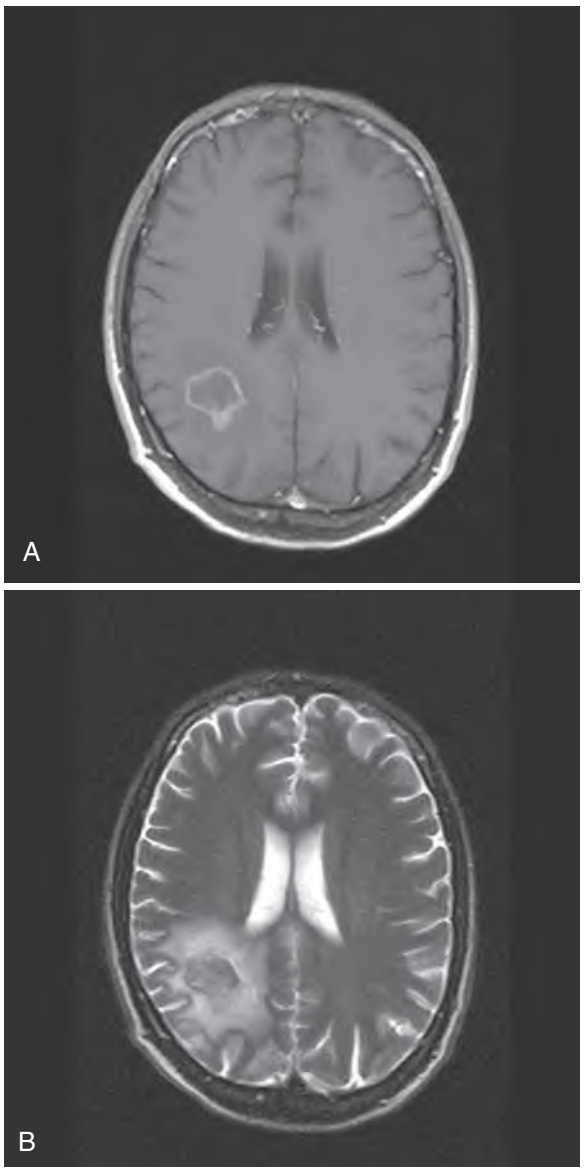

FIG. 125.3 Brain magnetic resonance images of a 50-year-old man with primary central nervous system lymphoma. (A) A 2-cm ring-enhancing lesion is present in the right parietal lobe, surrounded by edema. (B) The T2-weighted image shows low signal intensity centrally, which is more consistent with cellular proliferation than with an infectious process.

cGy over a 3-week period. Steroids were added to decrease peritumoral edema and mass effect.[123] The palliative response rate before the ART era was 53%.[130] In a series of 25 patients in the United States seen between 1995 and 2001, the median survival was 87 days. However, patients who received ART after diagnosis had a longer survival; 6 of 7 patients receiving ART were alive compared with 0 of 18 untreated patients at a median follow-up time of 1.8 years. Furthermore, the median survival was only 29 days for 11 patients who received neither radiation therapy nor ART.[131] The estimated 3-year overall survival rate of HIV-associated PCNSL after whole-brain radiation therapy was 64%. Results were influenced by the performance status at presentation, with patients with good performance status having a 100% 3-year overall survival versus 38% in those with poor performance status.[132] However, combination treatment including radiation therapy and chemotherapy is difficult to tolerate because of high toxicity. Additionally, whole-brain radiation therapy is associated with worsened cognitive function and white matter disease.[133] Immune recovery induced by an effective ART leads to dramatic improvement in survival of patients with AIDS-associated PCNSL.[134]

Progressive Multifocal Leukoencephalopathy

Before the AIDS era, PML was a rare disease affecting mainly patients with chronic lymphocytic leukemia, those with non-Hodgkin lymphoma, or organ transplant recipients.[135] At the beginning of the AIDS epidemic, up to 5% of patients developed PML.[136] Despite the availability of ART, up to 28% of focal brain lesions in AIDS patients were attributed to PML in 1998,[102] which equals the number of TE cases. The incidence of PML in ART-treated patients is 0.6 to 1.3/1000 person-years.[137,138] PML is caused by the polyomavirus JCV. This double-stranded DNA virus infects 90% of the normal adult population worldwide and remains quiescent in the kidneys without causing any disease. In the setting of immunosuppression, JCV is reactivated and induces a lytic infection of oligodendrocytes, causing multifocal demyelination of the CNS (see Chapter 144).[139]

Clinical presentation. Classic PML usually develops when $CD4^+$ T-lymphocyte counts decrease to fewer than 200 cells/μL.[136] The most common presenting symptoms are limb weakness (hemiparesis or monoparesis), altered mental status, gait ataxia, and visual symptoms, including hemianopsia, diplopia, and third nerve palsy. Approximately 80% of patients have focal neurologic findings.[140] However, PML lesions can occur anywhere in the CNS white matter, particularly at the subcortical level, although the optic nerves and the spinal cord are rarely involved.[141] Because subcortical lesions prevent the transmission of information to and from the cortical areas, presentation implying cerebral cortical dysfunction, such as aphasia, apraxia, memory loss, and visual agnosia, does not rule out this diagnosis. In fact, seizures, which are usually considered to be of cortical origin, occur in up to 44% of PML patients.[142] Some symptoms can also be attributed to HAND, which is often superimposed on other CNS pathologies in the end stages of AIDS.

Laboratory investigations. Laboratory analyses are necessary to establish the diagnosis of PML.[143] Conventional CSF analysis is normal or shows a moderate increase in protein concentration and a mild mononucleated pleocytosis (<25 cells/μL), which is nonspecific in the context of HIV-1 infection. Before the ART era, detection of JCV DNA in the CSF by PCR had a sensitivity of 74% to 92% and a specificity of 92% to 96% for the diagnosis of PML.[144,145] In patients receiving ART, the sensitivity of this test has decreased to 58%, probably because of decreased JCV replication in the context of a recovering immune system.[146] Nevertheless, measurement of JC viral load in the CSF appears to be of value as a correlate of PML disease activity and survival.[145,147,148]

Imaging studies. The hallmark of PML is patchy or confluent areas of low attenuation on CT or hyperintensity on fluid-attenuated inversion recovery or T2-weighted and hypointensity on T1-weighted MRI (Fig. 125.4). MRI is twice as sensitive as CT in distinguishing multiple lesions. These generally do not enhance after administration of contrast material, and they are not surrounded by edema, and, hence, substantial mass effect on surrounding structures is absent. However, 8% of lesions can show faint, peripheral, and irregular enhancement. Lesions are usually bilateral, asymmetrical, well demarcated, and localized preferentially in the periventricular areas and the subcortical white matter.[149] Involvement of the deep gray matter structures, including the basal ganglia and thalamus, can nevertheless be found in up to 17% of cases. In addition, a hyperintense cortical signal can be seen adjacent to PML lesions in the underlying white matter,[150] and is associated with a risk of seizures. Normal findings on CT or MRI do not rule out PML because microscopic lesions might be smaller than the resolution power of these tests. One such case showed multiple small foci of demyelination disseminated among the cortical U fibers at autopsy.[151]

HIV-1 encephalopathy can be easily mistaken for PML on brain imaging studies. As in PML, white matter lesions without mass effect or contrast enhancement are the radiologic hallmarks of this disease. However, HIV-1 encephalopathy lesions tend to be symmetrical and less clearly demarcated than the lesions of PML and are not associated with focal neurologic deficits. Proton magnetic resonance spectroscopy and magnetization transfer studies have shown promising potential in differentiating PML lesions from HIV-1 encephalopathy.[152] The typical proton magnetic resonance spectroscopy pattern in PML lesions includes a decreased *N*-acetylaspartate–to-creatine ratio, consistent with axonal

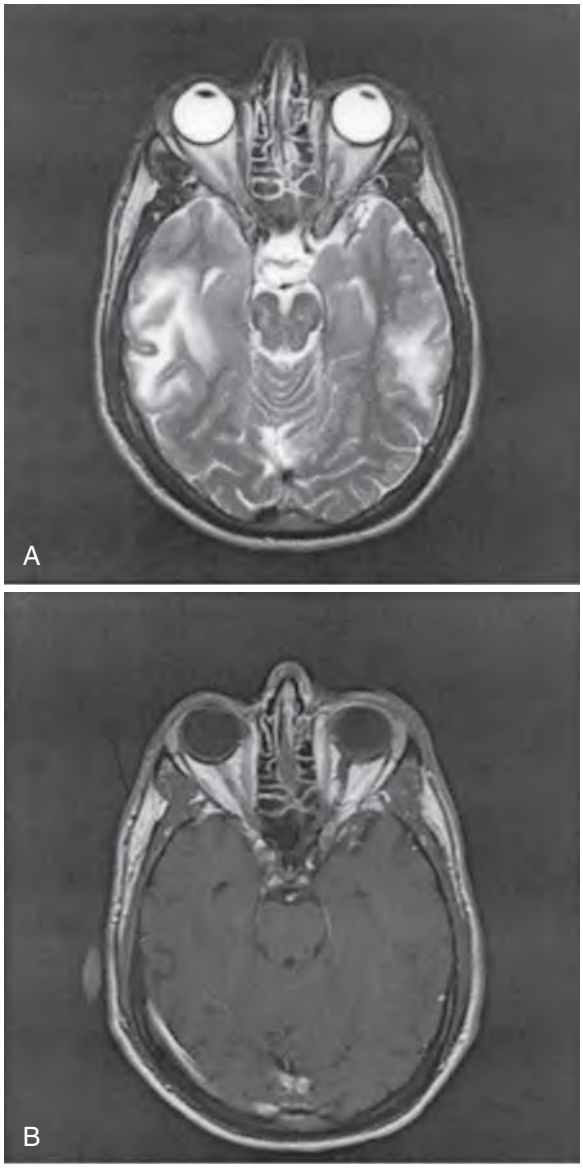

FIG. 125.4 Brain magnetic resonance images of a 43-year-old man with progressive multifocal leukoencephalopathy. (A) Prominent areas of high signal intensity are present in the subcortical white matter of both temporoparietal lobes on T2-weighted images. (B) The affected areas are hypointense on T1-weighted images, do not enhance with gadolinium, and are not associated with mass effect or edema.

compromise; increased choline/creatine ratio, indicating cell membrane breakdown and turnover; and an occasional increase in lipid/lactate and *myo*-inositol levels.[153,154,155] In one study, patients who had the longest survival had the highest *myo*-inositol level, consistent with glial activity and inflammation in PML lesions.[153] Metabolic alterations consistent with inflammation detected on proton magnetic resonance spectroscopy in PML lesions are associated with a cellular immune response against JCV. This inflammatory reaction, occurring early after disease onset, appears to be instrumental in the containment of PML.[156]

Brain biopsy. When the JC viral load is too low to be detected by PCR in the CSF, a brain biopsy may be necessary to establish the diagnosis of PML.[157] Such cases have become more frequent in the era of ART.[102] Histologic examination shows areas of demyelination in subcortical white matter or at the gray-white junction, as well as large, hyperchromatic oligodendrocytic nuclei that stain positively for JCV by immunohistochemistry and contain large amounts of JC virions detectable by electron microscopy. Other histologic features of PML include large, bizarre astrocytes with lobulated nuclei and lipid-laden macrophages engaged in removing myelin breakdown products. Demyelinating lesions may be entirely circumscribed within the cortical gray matter.[139]

Treatment. There is no specific treatment for PML. Numerous therapeutic attempts in HIV-infected patients have included cytosine arabinoside,[158] interferon-α,[159] topotecan,[160] cidofovir,[161,162] mirtazapine, and mefloquine,[163] but none showed any benefit compared with antiretroviral treatment alone. Serotonin receptors are used by JCV to enter astroglial cells in vitro.[164] Therefore serotonin receptor blockers such as mirtazapine, which downregulate receptors on the cell surface, have been used empirically with variable success.[165]

It is important to realize that there is a large diversity in the natural evolution of PML. In patients with AIDS who are profoundly immunosuppressed, the course of the disease used to be rapidly progressive, leading to death within 2 to 4 months from the time of symptom presentation. However, approximately 10% of patients had a protracted course and survived more than a year. Since the ART era, median survival has increased to 10.5 months,[166] and 40% to 50% of the patients survive PML, although some have devastating neurologic sequelae.[167] Predictive factors for longer survival include $CD4^+$ T-lymphocyte counts greater than 300 cells/μL at disease onset, as well as absence of hyperperfusion in PML lesions as measured by arterial spin labeling.[168] Study of the cellular immune response against JCV showed that detection of JCV-specific cytotoxic T lymphocytes in the peripheral blood mononuclear cells of HIV-infected patients with PML was associated with long-term survival, whereas those with undetectable cellular immune responses against the virus had a progressive neurologic disease and a fatal outcome.[169,170,171,172] Strategies aimed at boosting this immune response may prove useful for preventing uncontrolled replication of JCV and the spread of PML.[173] For the time being, optimization of ART and avoidance of immunosuppression remain the best available therapeutic option for patients with PML.

Inflammatory Progressive Multifocal Leukoencephalopathy

Inflammatory forms of PML occur frequently in the setting of IRIS in patients taking ART. This appears to be related to infiltration of cytotoxic $CD8^+$ T-cells that engage JCV-infected oligodendrocytes.[174] PML-associated IRIS is characterized by contrast-enhancing lesions and even swelling on neuroimaging studies or inflammatory infiltrates on a brain biopsy specimen,[175] or both, and their outcome is usually favorable,[176] but fatal cases have been reported.[177] PML-associated IRIS often causes a paradoxical worsening of neurologic symptoms and can be distinguished from the natural evolution of PML by magnetic resonance spectroscopy.[178] Clinicians should not disregard the diagnosis of PML in the presence of contrast-enhancing brain lesions and should use caution before treating these immunosuppressed individuals with steroids.

Cytomegalovirus Encephalitis

Cytomegalovirus (CMV) may cause necrotizing focal encephalitis and ventriculoencephalitis.[179] It occurs in patients with $CD4^+$ counts of fewer than 50 cells/μL and is often concomitant with CMV infection of other organs, including retinitis, adrenalitis, and pneumonitis (see Chapter 137). The incidence of CMV disease, including CMV encephalitis (CMVE), has decreased considerably since the availability of ART.[180]

Clinical presentation. Patients with CMVE show features similar to those with AIDS dementia but tend to have a more acute onset and more prominent confusion/disorientation or apathy/withdrawal. Hyponatremia and cranial nerve involvement, which are usually not present in AIDS dementia, are also helpful for establishing the diagnosis.[181]

Laboratory investigations. The conventional CSF examination is generally nonspecific because it is either normal or shows a slight protein increase and mononucleated pleocytosis. CMV culture often remains negative. However, the detection of CMV DNA by PCR in the CSF is both sensitive and specific.[182]

Imaging studies. Focal necrotizing lesions associated with periventricular and meningeal enhancement or hydrocephalus may be seen on brain imaging studies.[183] Although MRI has better resolution than CT, it often lacks sensitivity for diagnosing CMVE.[184]

Brain biopsy. Microglial nodule encephalitis with CMV inclusions can be readily diagnosed by histologic examination. Interestingly, similar findings can be found at autopsy in 6% to 40% of patients with AIDS and dementia.[179] However, autopsy findings of CMV infection of the brain do not always correlate with the presence of cognitive dysfunction.

Treatment. The management of CMVE is difficult.[185] In one autopsy-confirmed series, half of the patients were taking maintenance doses of ganciclovir for the treatment of CMV retinitis. CMVE developed in others during first full-dose inductions with ganciclovir or foscarnet for retinitis.[183] The possibility of viral resistance to antivirals should be considered if treatment failure occurs.

The treatment for CMVE is induction therapy with ganciclovir at 5 mg/kg/day IV every 12 hours and foscarnet 60 mg/kg every 8 hours or 90 mg/kg IV every 12 hours for 14 to 21 days. Maintenance therapy can include a low dose combination of ganciclovir and foscarnet, foscarnet monotherapy, ganciclovir monotherapy, and valganciclovir monotherapy. The duration may be indefinite or until CD4 count is greater than 100 cells/mm^3. If ganciclovir resistance is suspected, foscarnet should be used, with foscarnet induction at 90 mg/kg IV every 12 hours for 14 to 21 days, followed by maintenance 90 to 120 mg/kg/day indefinitely. Blood levels of oral valganciclovir at a dose of 900 mg are equivalent to those of intravenous ganciclovir at a dose of 5 mg/kg. The prognosis is usually poor, with median survival not exceeding 5 weeks. Cidofovir may be used in patients in whom ganciclovir or foscarnet has failed or who have become intolerant to these drugs. The cidofovir dose is 5 mg/kg/wk for 2 weeks, followed by 5 mg/kg every 2 weeks. This drug is nephrotoxic and should be given with intravenous hydration and high doses of probenecid before and after cidofovir injection (see Chapter 137).

Miscellaneous Mass Lesions and Rationale for Brain Biopsy

Brain biopsy used to be considered the gold standard for the diagnosis of CNS mass lesions in AIDS. The biopsy is the most specific, but not always the most sensitive, test. Indeed, sensitivities of 64% to 96% have been reported in AIDS patients. In addition, this procedure is not without significant risks in this patient population. Brain biopsy has a mortality rate of 0% to 3%, a major morbidity rate of 0.5% to 9%, and a minor morbidity rate of 2% to 4%.[186,187,188,189]

Brain biopsy is often impractical because of the location of the lesion. In addition, several disease processes can coincide in patients with multiple lesions, and multiple biopsies are rarely performed. Finally, change of therapy indicated by the result of the biopsy is not always possible in patients with advanced AIDS, and overall survival was improved by only a couple of months before the era of ART.[187,189]

The availability of molecular diagnosis by PCR in the CSF has considerably changed the management of these patients. A decision analysis was performed on 136 consecutive HIV-1 patients presenting with mass lesions between 1991 and 1995.[188] After 3 weeks of empirical therapy for TE, patients with progressive disease underwent a brain biopsy. CSF PCR amplification for *T. gondii,* EBV, and JCV DNA was performed in 66 patients. The presence or absence of mass effect surrounding the brain lesions, knowledge of the patient's serologic status for *T. gondii,* and a prophylactic regimen with trimethoprim-sulfamethoxazole, as well as PCR results, were used in this analysis. The probability of TE was 0.87 in *Toxoplasma*-seropositive patients with mass effect who were not receiving trimethoprim-sulfamethoxazole, but only 0.59 for those receiving prophylaxis. For *Toxoplasma*-seropositive patients receiving trimethoprim-sulfamethoxazole, the probability of PCNSL was 0.36. Conversely, in *Toxoplasma*-seronegative patients with mass effect, the likelihood of PCNSL was 0.74, which increased to 0.96 if the EBV PCR result was positive in the CSF. Among focal brain lesions without mass effect, the probability of PML was 0.81, which increased to 0.99 if JCV DNA was detected in the CSF.

Therefore brain biopsy is not necessary to confirm a diagnosis of PML, and JCV PCR in the CSF is now being used as a diagnostic test and for inclusion of patients in treatment studies.[190] Bypassing the need for tissue diagnosis is more controversial in patients with suspicion of PCNSL who have a positive result on EBV PCR in the CSF. Because treatment consists of whole-brain radiation, the risk of a false-positive PCR result has to be balanced with the risks of brain biopsy and by the fact that this technique does not always yield a definitive diagnosis.

An algorithm for the management of HIV-1–infected patients with CNS mass lesions is shown in Fig. 125.5.

SPINAL SYNDROME

Myelopathy is a frequent finding at autopsy in patients with AIDS and is probably underrecognized clinically. It can be primarily HIV-1–associated or caused by other opportunistic infections or tumors.

Vacuolar Myelopathy

Vacuolar myelopathy (VM) is present at autopsy in 17% to 46% of patients with AIDS.[191,192,193] This disorder occurs with advanced

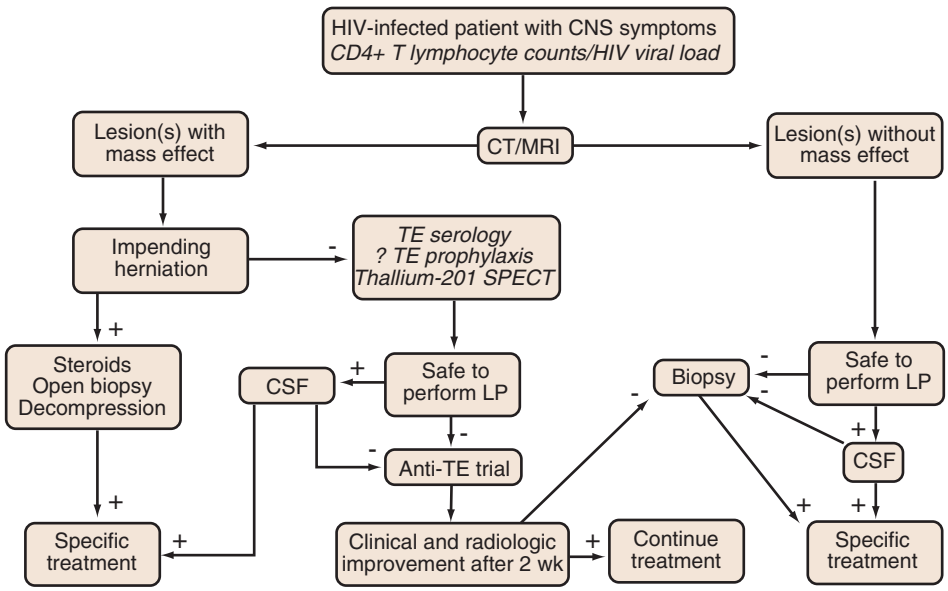

FIG. 125.5 Management of the human immunodeficiency virus (HIV) type 1–infected patient with central nervous system (CNS) mass lesions. The elements in italics represent data that contribute to the decision-making process (see text for details). *CSF,* Cerebrospinal fluid; *CT,* computed tomography; *LP,* lumbar puncture; *MRI,* magnetic resonance imaging; *SPECT,* single-photon emission computed tomography; *TE, Toxoplasma* encephalitis.

immunosuppression, and the symptoms are often overlooked or attributed to debilitation.

Clinical presentation. Symptoms are often overshadowed by coexisting central or peripheral nervous system impairment, such as AIDS dementia, which occurs late in the course of the disease.[191] Usually, patients report progressive, painless gait disturbance; weakness and sensory disturbances in the legs; impotence in men; and urinary frequency and urgency. The evolution is usually progressive and leads to severe paralysis of the legs and loss of sphincter control. Neurologic signs include spastic paraparesis, hyperreflexia, extensor plantar responses, and mild sensory impairment, with vibratory and position sense being disproportionately affected. There is usually no associated sensory level.

Laboratory investigations. CSF analysis either is normal or demonstrates a slight increase in protein and lymphocytosis frequently seen in HIV-1 infection. Opposite to what is observed in AIDS dementia, the CSF HIV-1 viral load is not increased in patients with VM.[194] However, CSF examination is a useful test to rule out other treatable infections (see "Histologic Studies" later).

Imaging studies. Findings on MRI of the spinal cord are usually normal in patients with VM. However, this examination is useful to rule out an extradural or intradural mass lesion or an epidural abscess.[195]

Histologic studies. Because an anatomic diagnosis is not possible, VM remains a clinical diagnosis of exclusion. At autopsy, discrete or coalescent 10- to 100-µm vacuoles containing cellular debris or macrophages and, rarely, axonal swelling can be seen in the white matter of the spinal cord, involving principally the posterior or lateral columns, or both. These lesions are usually symmetrical and more frequent at the middle to lower thoracic levels. Vacuoles appear to be the result of focal swelling within the myelin sheath. Ultrastructural studies indicate both axonal and myelin injury,[196] although axonal destruction is seen only in areas of intense vacuolation. The etiology of VM is still unknown. Consistent with the absence of an increased HIV-1 CSF viral load, immunohistochemistry studies did not demonstrate an association between HIV-1 antigens and VM.[192,197] Therefore the role of HIV-1 may only be indirect. Because histologic findings are similar to those of subacute combined degeneration of the spinal cord and because patients with VM usually have normal serum levels of vitamin B_{12} and folic acid, it was suggested that abnormal metabolism of the vitamin B_{12}–dependent transmethylation pathway may be important in the pathogenesis of VM. Indeed, *S*-adenosylmethionine and methionine were decreased in the CSF and serum of patients with VM, respectively.[198] The underlying cause of this metabolic disorder is unclear. Macrophage activation might generate substrates that are metabolized by methylation and therefore trigger a local deficit of methyl group donors in the spinal cord, leading to myelin vacuolization.

Treatment. An open-label pilot clinical trial suggested that patients with VM may benefit from supplements of L-methionine, but a double-blind placebo controlled trial demonstrated no benefit.[199,199a] However, there are also reports indicating a role for ART in the treatment of myelopathy in an antiretroviral-naïve HIV-infected patient[200] and for the combination of lopinavir-ritonavir in an ART-experienced patient.[201] Because there is no way to confirm the diagnosis of VM outside of a postmortem examination, it is possible that the patients who responded to various ART formulations were instead affected by HIV-1 myelitis,[202] which has the same histologic features as HIV-1 encephalitis, and therefore may benefit from antiretroviral treatment.

Differential Diagnosis of a Noncompressive Myelopathy

Other etiologies of noncompressive myelopathy in patients with advanced HIV-1 infection include other viral infections such as CMV, varicella-zoster virus, and herpes simplex virus types 1 and 2, as well as human T-cell lymphotropic virus type 1. Human T-cell lymphotropic virus type 1 is also transmitted sexually or through transfusion of cellular blood products and is the agent of a chronic spastic paraparesis called human T-cell lymphotropic virus type 1–associated myelopathy (see Chapter 168).[203] Syphilitic meningomyelitis and rare fungal or parasitic infections are diagnosed by appropriate serologies and cultures.[204]

PERIPHERAL NERVOUS SYSTEM SYNDROMES

Peripheral neuropathies have become the most common neurologic complication of HIV infection. Neuropathies include several entities that are thought to be directly associated with HIV and occur at different stages of immunosuppression. Other forms are caused by opportunistic pathogens, such as CMV. Finally, the peripheral nervous system can also be affected by antiretroviral treatment toxicities.

HIV-Associated Neuropathies

Inflammatory Demyelinating Polyneuropathies

These entities can occur at the time of seroconversion but are generally diagnosed in seropositive patients who are otherwise asymptomatic and not yet profoundly immunosuppressed, although some cases have also been reported in late stages of the disease.[205] Acute inflammatory demyelinating polyneuropathy (AIDP) has clinical features similar to those of Guillain-Barré syndrome. Sensory symptoms such as paresthesias may precede an acute, progressive weakness of distal and proximal muscles of two or more limbs, associated with areflexia. Respiratory muscles may be involved, and patients sometimes require assisted ventilation.[206] Sensory signs are usually mild, even in the setting of severe weakness. The maximal weakness is usually reached within the first 4 weeks. Patients with a more protracted course are affected by the chronic form of inflammatory demyelinating polyneuropathy (CIDP), which may be monophasic or relapsing.[207,208] In regions with a high prevalence of HIV, CIDP is commonly associated with HIV infection. At a single hospital in Johannesburg, South Africa, 43% of all CIDP cases over a 2-year period occurred in HIV-infected individuals.[209] A severe case of AIDP was observed in a patient with advanced AIDS 4 weeks after starting on ART, concomitant with immune reconstitution.[210] AIDP should therefore be included in the growing number of ART-induced IRISs in HIV-infected individuals.

Laboratory investigations. The CSF analysis often differs from that of HIV-1–seronegative patients with Guillain-Barré syndrome by the presence of a mononuclear pleocytosis of 20 to 50 cells/µL. The CSF protein concentration is usually elevated to levels as high as 250 mg/dL, and a polyclonal gammaglobulinemia can be detected.

Electrophysiologic studies. Demyelination is demonstrated by decreased motor nerve conduction velocities or prolonged distal latencies and minimum F-wave latencies in two or more nerves. Conduction block is often prominent.

Nerve biopsy. Sural nerve biopsy generally demonstrates the presence of a perivascular and endoneural mononuclear cell infiltrate with macrophage-mediated segmental demyelination. In severe cases, wallerian-like degeneration of axons can be seen. Similar to Guillain-Barré syndrome occurring in immunocompetent individuals, the etiology of AIDP in HIV-infected patients is thought to be autoimmune. Anti–peripheral nerve myelin antibodies have been found in HIV-1–positive patients with AIDP, as well as increased levels of soluble CD8 and neopterin in the CSF, indicating an abnormal immune activation. CMV was found at autopsy in the peripheral nerves of one patient with AIDS who presented with AIDP.[211]

Treatment. Spontaneous recovery is usually the outcome of AIDP, although HIV-1–infected patients tend to have a more severe course with a slower recovery than immunocompetent individuals with Guillain-Barré syndrome. Plasmapheresis is indicated if the illness is sufficiently severe to warrant treatment. Patients with CIDP benefit from treatment with prednisone or plasmapheresis.[212,213] However, prednisone should be used with great caution in patients with immunosuppression. Other treatments such as intravenous immunoglobulin have also been used successfully in HIV-1–positive patients with inflammatory demyelinating polyneuropathy, sometimes in combination with plasmapheresis.[214] In cases of AIDP occurring in late stages of the disease, a trial of ganciclovir may be warranted if other treatments are not efficient.[211]

Distal Sensory Polyneuropathy

Distal sensory polyneuropathy (DSPN) is the most common cause of peripheral neuropathy in HIV-1 infection, which is symptomatic in 38% of patients and asymptomatic in an additional 20%.[214,215] Moreover,

histologic abnormalities can be detected at autopsy in most patients dying of AIDS.[216] Distal sensory polyneuropathy occurs despite ART; 87% of affected individuals have an HIV-1 virus load less than 400 cps/mL, and 70% have $CD4^+$ T-cell counts greater than 350/μL.[217] DSPN is associated with older age, low CD4 nadir, diabetes, and past nucleoside analogue reverse-transcriptase inhibitor (NRTI) exposure. In the United States, HIV-positive African-American women had a higher incidence of DSPN (41.3%) compared with whites (34.8%) and Hispanics (24.7%).[218] Older age, taller height, PI use, and female sex have been identified as risk factors for development of DSPN.[219] Depression, prior opioid use, and certain iron regulatory gene polymorphisms have been identified as additional risk factors for distal neuropathic pain.[220,221]

Clinical presentation. DSPN is characterized by the progressive onset of symmetrical paresthesia, numbness, and painful dysesthesia of the lower extremities. The pain is often described as an aching or burning sensation and is worse on the soles of the feet. Some patients have a lower pain threshold (hyperalgesia) or pain induced by nonnoxious stimuli (allodynia), such as the contact with bed covers at night. Symptoms may remain stable or progress over months and ascend in a length-dependent fashion up the legs. Fingertips may become affected when symptoms reach the knees. Although wearing shoes and walking may exacerbate the pain for some patients, others report maximal discomfort when they are barefoot in bed. Therefore DSPN may have a major negative impact on patients' ability to ambulate and the quality of their sleep. Perception of noxious stimuli, temperature, and vibrations is usually more affected than light touch and proprioception. DSPN may even have several forms because some patients only have decreased sensation for noxious stimuli and temperature, indicating dysfunction of small unmyelinated sensory fibers; some only have decreased vibration sense and proprioception, consistent with dysfunction of large myelinated fibers; and others have decreased sensation for all modalities. Hyporeflexia of the lower extremities is a common finding, and gait ataxia with a positive Romberg sign is present in severe cases. Weakness is rarely found on the examination or is confined to the intrinsic foot muscles. Autonomic dysfunction is increasingly recognized and can be present in up to 90% of patients with severe DSPN and in 30% of patients with mild to no DSPN.[222]

Laboratory investigations. CSF analysis shows only nonspecific findings with mild elevation of protein concentration and mononucleated pleocytosis, which is common in HIV-1 infection.

Electrophysiologic studies. Nerve conduction studies show low-amplitude or absent sural nerve action potentials. Sensory and motor nerve conduction velocities are normal or only mildly reduced. Electromyographic studies demonstrate acute denervation and chronic reinnervation in distal leg muscles. These findings are consistent with an axonal distal symmetrical, predominantly sensory, polyneuropathy.

Nerve and skin biopsy. Sural nerve biopsy confirms the diagnosis of axonal degeneration of myelinated and unmyelinated axons. Punch skin biopsies show evidence of decreased epidermal nerve fiber density in the distal leg. In patients with advanced HIV infection, epidermal nerve fiber density correlated with the clinical and electrophysiologic severity of DSPN.[223] A modest dorsal root ganglion (DRG) neuronal loss has also been demonstrated in DSPN,[224] as well as selective degeneration of the axons and myelin sheaths in the cervical and upper thoracic levels of the gracile tracts. This process therefore represents the degeneration of the centrally directed extension of the sensory neurons.[225]

Inflammatory infiltrates around peripheral nerve fibers and in DRGs consist of activated macrophages, with local release of cytokines such as tumor necrosis factor-α, interferon-γ, and interleukin-6.[216] As is the case in VM and, to some extent, in HIV encephalitis, productive HIV-1 replication in the peripheral nerves and DRGs is sparse and limited to monocyte/macrophages. Therefore the presence of activated macrophages secreting inflammatory cytokines, rather than the virus itself, seems to account for most of the peripheral nerve damage.[226] How activated macrophages penetrate DRGs and peripheral nerve fibers is unclear, and it has been hypothesized that the blood-nerve barrier, like the BBB, may be affected in HIV-infected patients.[216] Finally, experimental models in animals suggest that it is still possible that HIV, or HIV-1 proteins, may have a direct toxic effect on the neuropathic pain of DSPN.[227]

Because a similar type of polyneuropathy is common in the HIV-1–seronegative population, other etiologies such as vitamin B_{12} deficiency, neurotoxic medications, alcoholism, and diabetes mellitus should be ruled out.

Treatment. There is no available therapy that leads to the regeneration of nerve fibers and DRGs and reversal of symptoms. Suppression of viral replication with ART is unfortunately not associated with clinical improvement in DSPN. Therefore treatment of neuropathic pain in DSPN is purely symptomatic and is aimed primarily at attenuating the painful dysesthesia and improving the quality of life of these patients. Treatment should not be administered if numbness and decreased sensation for noxious stimuli and temperature are the only symptoms because they do not improve.

Nucleoside Neuropathy

Clinical presentation. Dose-dependent neurotoxicity of the NRTIs didanosine and stavudine (d4T) has been detected in approximately 30% of patients taking these medications.[228] The risk is increased in patients on regimens containing a combination of didanosine and d4T.[229] The clinical presentation and electrophysiologic study results were indistinguishable from those of DSPN, and the diagnosis can be established only by a temporal association between initiation of a dideoxynucleoside NRTI and the onset of the symptoms, which can occur as early as 1 week. Discontinuation of the offending medication may lead to symptomatic improvement over several weeks in two-thirds of patients, although it is often preceded by a transient worsening of symptoms known as "coasting."[230]

Laboratory investigations. The pathogenetic mechanism of nucleoside neuropathy appears to be most likely related to nucleoside-induced mitochondrial dysfunction. Indeed, NRTIs inhibit mitochondrial polymerase in vitro, resulting in tissue-specific injury. Zidovudine toxicity affects mainly skeletal muscle (see "Muscular Complications From Therapies in HIV" later), whereas didanosine and d4T cause pancreatitis in addition to neuropathy. Nucleoside neuropathy occurs more frequently in individuals with preexisting DSPN, and administration of NRTIs to healthy animals does not result in neuropathy.[216] These data suggest that NRTIs may only exacerbate an inflammatory process triggered by activated macrophages in peripheral nerve fibers or DRGs of HIV-infected individuals. Clinicians should therefore use caution before removing didanosine or d4T from successful ART regimens, unless there is a clear temporal association between the administration of these medications and the onset of the symptoms or an elevated serum lactate level.[231] A list of neurotoxic medications that have been associated with DSPN in HIV-infected patients is shown in Table 125.3.

Treatment. First-line therapies include nonsteroidal antiinflammatory drugs and acetaminophen, as well as topical application of capsaicin[232,233] or 5% lidocaine gel.[234] Anticonvulsant medications are the second line of treatment. Medications such as carbamazepine and phenytoin that are commonly used in other forms of painful neuropathies are contraindicated because both are metabolized by the liver, which may cause unwanted interactions in patients taking PIs. Gabapentin is metabolized by the kidneys and is usually well tolerated by HIV-infected individuals.[235] Treatment starts using 300 mg PO at bedtime and is increased to 300 mg PO three times daily over 1 week. The extent of symptomatic relief is variable, and some patients may need doses as high as 1200 mg three times daily for a significant reduction in their discomfort. Fatigue and sleepiness are infrequent but may be limiting in some patients. Pregabalin, which is similar to gabapentin, is used as well, although studies have failed to show any benefit over placebo.[236] Another anticonvulsant, lamotrigine, showed substantial pain reduction in a subgroup of patients receiving neurotoxic NRTIs but no difference compared with placebo in patients with DSPN who were not receiving nucleosides.[237]

Amitriptyline, which is commonly used for the treatment of diabetic neuropathy, is not superior to placebo in HIV-infected patients with DSPN.[238] However, adjunction of tricyclics with lower anticholinergic side effects, such as nortriptyline, may benefit patients who remain symptomatic on adequate doses of anticonvulsants. In refractory cases, a combination of anticonvulsant, tricyclic, nonsteroidal antiinflammatory, and topical medications may be necessary to achieve significant relief.

TABLE 125.3 Neurotoxic Medications Used in Human Immunodeficiency Virus-1 Infection

NAME	CLINICAL PRESENTATION
Nucleoside Reverse-Transcriptase Inhibitors	
Zidovudine	Myopathy
Didanosine	DSPN
Stavudine	DSPN
Nonnucleoside Reverse-Transcriptase Inhibitors	
Efavirenz	Vivid dreams
Antiviral Agent	
Foscarnet	Seizures
Antibacterial Agents	
Isoniazid	DSPN
Dapsone	DSMP
Metronidazole[a]	DSPN
Antineoplastic Agents	
Vincristine	DSMP, CN
Cisplatin	DSPN

[a]High doses only.
CN, Cranial neuropathy; *DSMP,* distal sensory motor polyneuropathy; *DSPN,* distal sensory polyneuropathy.

Narcotic analgesics should be used as the last resort because of their addictive potential in the context of a chronic pain syndrome. Tramadol shares properties with opioid analgesics but is less likely to cause dependence and lead to abuse.[239] Long-acting opioid agonists such as fentanyl patches should be preferred to short-acting agents. Smoked cannabis may be as efficient as oral drugs for treatment of neuropathic pain.[240,241] Numerous experimental drugs and therapies have been disappointing in the treatment of DSPN, including mexiletine, memantine, prosaptide, peptide T, recombinant human nerve growth factor, plasmapheresis, and acupuncture (for reviews, see Simpson[242] and Gonzalez-Duarte and colleagues[243]). Depletion of acetylcarnitine, a substrate in the production of energy during β-oxidation of free fatty acids, was implicated in the pathogenesis of DSPN,[244] but this was not confirmed in a larger sample of patients.[245]

Mononeuritis Multiplex

Patients with previously asymptomatic HIV-1 infection and $CD4^+$ T-lymphocyte counts greater than 200 cells/μL, as well as patients with AIDS and profound immunosuppression, can be affected by mononeuritis multiplex.

Clinical presentation. Patients present with acute onset of sensory or motor deficit limited to one or more peripheral nerves. Involvement of a facial or laryngeal nerve has also been reported. The asymmetrical nature of this disorder and the prominent weakness differentiate it from other HIV-associated neuropathies. The course can be self-limited in early HIV-1 infection[246] or more severe in patients with advanced disease.

Laboratory investigations. CSF analysis is nonspecific and shows only a mild elevation of protein concentration and a mononuclear pleocytosis. Cryoglobulinemia was reported in one case.[247]

Electrophysiologic studies. Nerve conduction studies reveal a reduction of the amplitude of sensory nerve action potentials and compound muscle action potentials, as well as a mild reduction in nerve conduction velocities in the distribution of single nerves. The electromyographic examination is also consistent with focal or asymmetrical multifocal axonal degeneration, although considerable overlap may exist with DSPN and inflammatory demyelinating polyneuropathy.

Nerve biopsy. Similar to its clinical presentation, the nerve biopsy specimen of patients with mononeuritis multiplex shows a spectrum of pathologies rather than a single pattern. Axonal degeneration and perivascular inflammatory infiltrates are found in patients with early HIV-1 infection and limited clinical involvement. Patients with AIDS and CMV infection usually have mixed axonal and demyelinating lesions with inflammatory infiltrates also containing polymorphonuclear cells, as well as, sometimes, characteristic cytomegalic inclusion bodies.[248] The most aggressive form consists of a necrotizing arteritis with necrosis of endoneurial or epineurial vessels and might be caused by circulating immune complexes.

Treatment. Mild forms of mononeuritis multiplex developing in patients who are otherwise asymptomatic might improve without specific treatment. Others might benefit from therapies such as plasmapheresis[247] or intravenous immunoglobulin.[249] Corticosteroids and cyclophosphamide should be reserved for aggressive cases of mononeuritis multiplex with vasculitis proved by nerve biopsy. In late HIV-1 infection, especially in patients with concurrent systemic CMV infection, empirical therapy with ganciclovir for CMV should be considered.[250]

Progressive Polyradiculopathy

Because it occurs late in the course of HIV-1 infection, in patients with low $CD4^+$ T-lymphocyte counts and concurrent systemic illnesses, progressive polyradiculopathy is often underrecognized.

Clinical presentation. Initially patients report lower extremity and sacral paresthesia and, sometimes, radicular pain in the cauda equina distribution. These symptoms are followed by a rapidly progressive areflexive paraparesis and ascending sensory loss, often accompanied by urine retention. The upper extremities are relatively spared. A thoracic sensory level, if present, indicates concomitant medullary involvement, but other features indicating upper motor neuron damage, such as spasticity and hyperreflexia, are usually absent. A prominent infection with CMV, mainly retinitis, esophagitis, or colitis, is conspicuously present in a majority of cases.

Laboratory investigations. In contrast to other peripheral nervous system diseases associated with HIV-1 infection, the CSF analysis is useful in establishing the diagnosis. A marked polymorphonuclear cell pleocytosis, elevated protein concentration, and hypoglycorrhachia are the hallmarks of this syndrome.[251] CSF cultures demonstrate the presence of CMV in 60% of the cases.[252] Cultures may take as long as 2 weeks to grow, and CSF samples must be kept on ice immediately after the lumbar puncture. As is the case with CMVE,[182] CMV DNA may be detectable in the CSF by PCR. Because of the frequent concomitant systemic infection with CMV, blood culture may also be positive for this virus. Urine culture is nonspecific because many AIDS patients shed CMV in the urine asymptomatically. Cytologic studies can reveal cytomegalic cells with intranuclear and intracytoplasmic CMV inclusions.

Electrophysiologic studies. Electromyographic examination is useful to differentiate this syndrome from AIDP. Severe and widespread proximal axonal damage in lumbar nerve root distribution is correlated by fibrillation potentials, complex repetitive discharges, and motor unit recruitment patterns in lower extremity muscles. Motor nerve conduction velocities are minimally altered, but affected muscles display prolonged or absent F waves. These findings are consistent with extensive denervation of the lower extremity muscles, which is characteristic in this syndrome.

Nerve biopsy. Because of the radicular localization of the lesions, a nerve biopsy is not helpful for diagnosis. Autopsy studies reveal a severe inflammation associated with necrosis of the ventral and dorsal nerve roots. Cytomegalic inclusions can be detected within the nucleus and cytoplasm of Schwann, ependymal, and endothelial cells, which are also positive for CMV by in situ hybridization studies. Similar findings have been reported in cranial nerves at the site of exit from the brainstem.

Despite the strong association of polyradiculopathy and CMV in patients with AIDS, other possibilities include neurosyphilis and lymphomatous meningitis, which should be ruled out by the CSF analysis.

Treatment. The treatment of CMV-associated progressive polyradiculopathy is similar to that of CMVE (see earlier). It consists of intravenous ganciclovir or foscarnet, or both.[253] Newer anti-CMV medication such as valganciclovir and cidofovir have not been evaluated for progressive polyradiculopathy. Phenotypic and genotypic characterization of viral

isolates should be considered in case of resistance to treatment.[254] The clinical response is variable but usually best if therapy is started within days after the onset of symptoms.

Because the results of PCR for CMV DNA in the CSF can take 1 to 2 weeks to obtain, empirical treatment can be justified in this entity, especially if the workup reveals a polymorphonuclear pleocytosis in the CSF or widespread systemic infection with this virus. The rationale is to prevent irreversible necrosis of the nerve roots. In patients who are already paraplegic several weeks after the onset of their symptoms, treatment can achieve stabilization, but no real improvement should be expected. Neutropenia is the most common dose-limiting toxicity of ganciclovir and may preclude concomitant use of other myelotoxic drugs such as zidovudine. Concomitant treatment with granulocyte colony-stimulating factor may become necessary in that setting.

Diffuse Infiltrative Lymphocytosis Syndrome–Associated Neuropathy

A small subset of HIV-infected patients develops persistent CD8 hyperlymphocytosis and a Sjögren syndrome–like illness associated with multivisceral CD8 T-cell infiltration, known as *diffuse infiltrative lymphocytosis syndrome*. These individuals usually have parotid enlargement and generally have higher $CD4^+$ T-lymphocyte counts, fewer opportunistic infections, and longer survival times than do other HIV-infected patients.[255] Some of these patients may develop a primary B-cell lymphoma.

Clinical presentation. Some of these patients present with an acute or subacute sensorimotor distal symmetrical neuropathy, which is always painful.[256]

Electrophysiologic studies. Electromyographic and nerve conduction study results are consistent with axonal neuropathy.

Nerve biopsy. A nerve biopsy specimen shows marked angiocentric $CD8^+$ infiltrates without mural necrosis and abundant expression of HIV-1 p24 protein in macrophages. The lymphocytic infiltrate is polyclonal in most patients. The HIV-1 proviral load in peripheral nerve is much higher than in other types of HIV-associated neuropathy.[257]

Treatment. Zidovudine and steroid therapy were associated with improvement in a small group of patients.[256] The prevalence of diffuse infiltrative lymphocytosis syndrome has significantly decreased in the ART era, suggesting that this condition is an antigen-driven response against HIV and should be treated with anti-HIV therapy.[258]

Amyotrophic Lateral Sclerosis–Like Syndrome

During the past 20 years, at least 19 cases of amyotrophic lateral sclerosis (ALS) or ALS-like syndromes have been reported in HIV-infected individuals.[259,260,261] These cases differed from classic ALS because they occurred in younger patients, were unusually rapidly progressive, and improved after the institution of ART. Case studies at autopsy exhibited pathology outside the motor neuron pool. The etiology of this syndrome is unclear because HIV-1 does not infect neurons. It has also been suggested that ALS is caused by another, yet unidentified, retrovirus, and the retroviral enzyme reverse transcriptase has been found in 50% to 56% of sera from HIV-1–negative ALS patients, but not in CSF, at levels comparable to those of HIV reverse transcriptase, compared with 7% to 19% of controls.[262,263] However, this causality is not proven, and there is no indication for administering antiretroviral treatment to HIV-1–negative patients with ALS. ALS and HIV-1 infection can also be coincidental,[264] and these data indicate that HIV-1 should be included in the differential diagnosis of ALS.[265]

MUSCULOSKELETAL SYNDROMES

Muscular disorders have been described in HIV-1–infected individuals and can occur at any stage of the disease.

HIV-Associated Myopathies

HIV-associated polymyositis occurs in 0.22% of HIV-infected patients.[266] Patients report mainly lower extremity weakness, characterized by difficulty in rising from a chair or climbing stairs, as well as fatigue. Myalgias are present in as many as half of the cases, and the neurologic examination reveals proximal symmetrical lower extremity weakness.[267] Cutaneous rash or involvement of the extraocular and facial muscles is absent. There is a mild elevation of creatine phosphokinase in the serum (median, ≅500 IU/L), although creatine phosphokinase can be as high as 7500 IU/L in some cases.[266] This may be an incidental finding that orients toward a diagnosis in cases in which muscle strength is still intact. The creatine phosphokinase level correlates with the degree of myonecrosis seen on a muscle biopsy specimen, but not with the weakness. Electromyographic testing may reveal polyphasic small motor unit potentials, fibrillations, and increased insertional irritability, but it can also be normal in 30% of the cases.[266] Muscle biopsy is the most definitive test and shows endomysial lymphocytic infiltrates without rimmed vacuoles or chronic myopathic features similar to those seen in idiopathic polymyositis.[268] Infiltrating cells are predominantly $CD8^+$ T cells and macrophages.[269] Interestingly, almost one-half of patients with HIV-1 polymyositis also had diffuse infiltrative lymphocytosis syndrome. Because both conditions are extremely rare, their association is not likely to be coincidental.[266] Similar to idiopathic polymyositis, patients with HIV-1 polymyositis have had a favorable response with corticosteroids (prednisone 1 mg/kg/day) for an average of 9 months. However, the risk of long-term immunosuppressive therapy should be carefully considered in this population of patients. Other immunologically based therapies such as azathioprine, methotrexate, or intravenous immunoglobulin have also been successful.[266]

Inclusion body myositis seen in HIV-infected patients is similar to sporadic inclusion body myositis except that it has younger age of onset and can sometimes respond to immunosuppressive therapies. A recent study showed significant overlap between HIV-associated polymyositis and inclusion body myositis, with all patients eventually developing finger and wrist flexor weakness, rimmed vacuoles on biopsy, or anti-NT5C1A autoantibodies—features most consistent with inclusion body myositis.[270]

Rare cases of nemaline rod myopathy as well as muscle involvement with diffuse infiltrative lymphocytosis syndrome have also been reported in HIV-infected individuals.[255] All these syndromes must be differentiated from HIV-1 wasting syndrome and may easily be overlooked in a population of debilitated patients who often present with generalized weakness. In addition, it may occur simultaneously with CNS or peripheral nervous system complications of HIV-1 infection.

Muscular Complications From Therapies in HIV

Myopathy occurs in 17% of patients treated with zidovudine for periods longer than 270 days.[271] The clinical presentation is indistinguishable from HIV-associated myositis.[267] In zidovudine myopathy, biopsy results reveal numerous ragged red fibers and abnormal mitochondria.[272] Zidovudine-induced mitochondrial toxicity is mediated through the inhibition of the enzyme γ-DNA polymerase, which is responsible for the replication of mitochondrial DNA. This induces an energy shortage within the muscle, which results in overt myopathy over time.

In zidovudine-induced myopathy, treatment consists of zidovudine withdrawal. Objective improvement in muscle strength is expected to occur in most patients after 8 weeks.[273]

More worrisome is the prospect of statin-associated rhabdomyolysis.[274] Indeed, increased cholesterol and triglyceride values are frequent in HIV-infected patients on ART, requiring therapy with statins with the aim of preventing cardiovascular complications. Most statins are metabolized by the liver cytochrome P-450 isoenzyme 3A4. Similarly, PIs are both substrates for and inhibitors of cytochrome P-450 isoenzyme 3A4 and substrates for P-glycoprotein, a bidirectional drug transporter that is also inhibited by statins to varying degrees. Pharmacokinetic studies have shown that PIs may greatly increase statin concentrations. Statin-associated rhabdomyolysis occurs within weeks from onset of treatment and may be fatal.[275]

HIV-associated lipodystrophy syndrome is increasingly recognized in patients treated with ART. Increased lipid content in muscles has been seen in imaging studies as well as muscle biopsies of such patients.[276] HIV-infected patients on ART often complain of arthralgias, and cases of frozen shoulder, tendonitis, and temporomandibular joint dysfunction have been described within a year of starting on indinavir. A survey using an anonymous questionnaire answered by 292 HIV-infected

TABLE 125.4 Neuromuscular Syndromes in Human Immunodeficiency Virus Type 1 (HIV-1) Infection

DIAGNOSIS	DISEASE STAGE	CLINICAL FEATURES	DIAGNOSTIC STUDIES	TREATMENT
AIDP	Early > late	Weakness more than sensory loss	CSF: ↑ WBCs	Early: IVIG, steroids, plasmapheresis
CIDP			↑↑ Protein NCSs: demyelination	Late: consider ganciclovir/foscarnet
MM	Early or late	Multiple painful mononeuropathies	NCSs: multifocal axonal neuropathy Biopsy: inflammation/vasculitis CMV	Early: none Late: steroids/cyclophosphamide Ganciclovir/foscarnet
Nucleoside	Any stage	Distal sensory loss	NCSs: distal axonopathy	Nucleoside withdrawal
Neuropathy		Neuropathic pain	Increased serum lactate	
DSPN	Late	Distal sensory loss Neuropathic pain	NCSs: distal axonopathy	NSAIDs, capsaicin AED, tricyclics
PP	Late	Progressive flaccid paraparesis, urinary dysfunction, LS pain	CSF: increased WBCs (PMNs), CMV PCR+	Ganciclovir/foscarnet Cidofovir
DILS	Late	Sjögren syndrome, distal motor and sensory loss, pain	NCSs: axonal neuropathy Biopsy: $CD8^+$ T cells, HIV-1	Zidovudine/ART Steroids
Zidovudine	Any stage	Proximal weakness	EMG: ± irritative	Zidovudine withdrawal
Myopathy		Myalgias	Biopsy: ragged red fibers	
Polymyositis	Any stage	Proximal weakness Myalgias	EMG: ± irritative Biopsy: inflammatory infiltrates	Steroids, IVIG Immunosuppressants
ALS-like	Late	Weakness, dysphagia	EMG: neurogenic	ART

AED, Antiepileptic drug; *AIDP,* acute inflammatory demyelinating polyneuropathy; *ALS,* amyotrophic lateral sclerosis; *ART,* antiretroviral therapy; *CIDP,* chronic inflammatory demyelinating polyneuropathy; *CMV,* cytomegalovirus; *CSF,* cerebrospinal fluid; *DILS,* diffuse infiltrative lymphocytosis syndrome; *DSPN,* distal sensory polyneuropathy; *EMG,* electromyography; *IVIG,* intravenous immunoglobulin; *LS,* lumbosacral; *MM,* mononeuritis multiplex; *NCS,* nerve conduction studies; *NSAID,* nonsteroidal anti-inflammatory drug; *PCR,* polymerase chain reaction; *PMNs,* polymorphonuclear leukocytes; *PP,* progressive polyradiculopathy; *WBCs,* white blood cells.

patients in Europe indicated that arthralgias were more frequent in patients taking PIs, especially indinavir (40.6%) or ritonavir plus saquinavir (41.9%), compared with nonnucleoside reverse-transcriptase inhibitors (NNRTIs) (26.5%) or NRTIs (25.3%).[277] Indinavir causes urolithiasis by crystallizing in the urinary tract, and indinavir crystals have been found in the joint fluid of patients with frozen shoulder. Temporary interruption of the PI or replacement with an NNRTI should be considered on the basis of the patient's discomfort, ART history, and HIV-1 genotype studies.

Opportunistic Infections and Tumor Infiltrations

Opportunistic agents causing pyomyositis include *Mycobacterium tuberculosis, Mycobacterium avium intracellulare,* CMV, and *T. gondii.* Muscle involvement can occur with Kaposi sarcoma and non-Hodgkin lymphoma.[255]

SEIZURES

HIV-positive patients have an increased risk to develop seizure activity due to HIV-associated brain lesions and metabolic disturbances. The incidence of seizures depends on the degree of immunosuppression.

CNS mass lesions and meningitis are the major causes of seizures, but no identifiable cause other than HIV-1 infection can be detected in up to 25% of cases.[278] Unless a reversible cause can be readily identified and treated, anticonvulsant therapy should be initiated after the first seizure.

Antiepileptic drugs (AEDs) and antiretrovirals can adversely affect each other when coadministered. The adverse effects can include breakthrough seizures, virologic failure, or drug toxicity. One of the recommendations is that it may be important to avoid cytochrome P-450 enzyme-inducing AEDs in people on antiretroviral regimens that include PIs or NNRTIs because pharmacokinetic interactions may result in virologic failure.[279] This particularly applies to the older generation AEDs—primidone, phenytoin, phenobarbital, and carbamazepine.

In addition, protein binding must be considered. Most AEDs and PIs are highly protein bound, as are other medications taken by HIV-infected patients, such as trimethoprim-sulfamethoxazole. This may result in competition for available protein binding sites. Valproic acid and phenytoin commonly displace other drugs from albumin, which may result in increased free drug levels, side effects, and toxicity. Conversely, PIs may also displace AEDs such as carbamazepine from protein binding sites and result in toxicity. There have been no studies of the outcome of seizure management in HIV-infected patients on ART. Until these data are available, clinicians should favor the use of AEDs that have no effect on the cytochrome P-450 system and have limited protein binding, such as levetiracetam, lacosamide, gabapentin, and pregabalin.[280] The choice of the AED or combination thereof depends on the type of seizure presented by the patient. In the case of status epilepticus or emergencies in which intravenous treatment is indicated, traditional AEDs such as phenytoin or phenobarbital should be used temporarily in the acute phase and should then be replaced by medications that have lower interaction potential with PIs once seizure control has been achieved.

The principal neuromuscular syndromes found in HIV-1 infection are listed in Table 125.4. A summary of the principal neurologic complications of HIV infection is provided in Fig. 125.6.

TEMPORAL TRENDS AND AGING IN NEUROLOGIC MANIFESTATIONS OF HIV INFECTION

The spectrum of CNS complications of HIV-1 diseases is constantly evolving, and both quantitative and qualitative changes have been noted in recent years.[76,281] Patients are living longer with ART, but they may become resistant to antiretrovirals. The clinical presentation of known diseases such as PML may be altered by ART-induced immune reconstitution,[176] and new entities, such as severe HIV-associated leukoencephalopathy, have been described in ART-experienced individuals.[281,282] Expanded tropism of JCV to cerebellar neurons has been demonstrated, which may have implications in the pathogenesis of cerebellar atrophy occurring in HIV-infected individuals.[283] In addition, PIs are associated with a marked increase in serum cholesterol and triglycerides. Therefore long-term HIV-1–infected individuals are at increased risk of developing cerebrovascular events.[283,284] Stroke usually occurs in younger patients infected with HIV-1 compared with HIV-negative individuals, and, in some cases, it may be caused by a vasculopathy.[285]

The number of people living with HIV who are 55 years of age and older is expected to more than double between 2013 and 2045.[286] As this population becomes older, age-related entities such as Alzheimer dementia are expected to overlap with HIV-associated neurologic

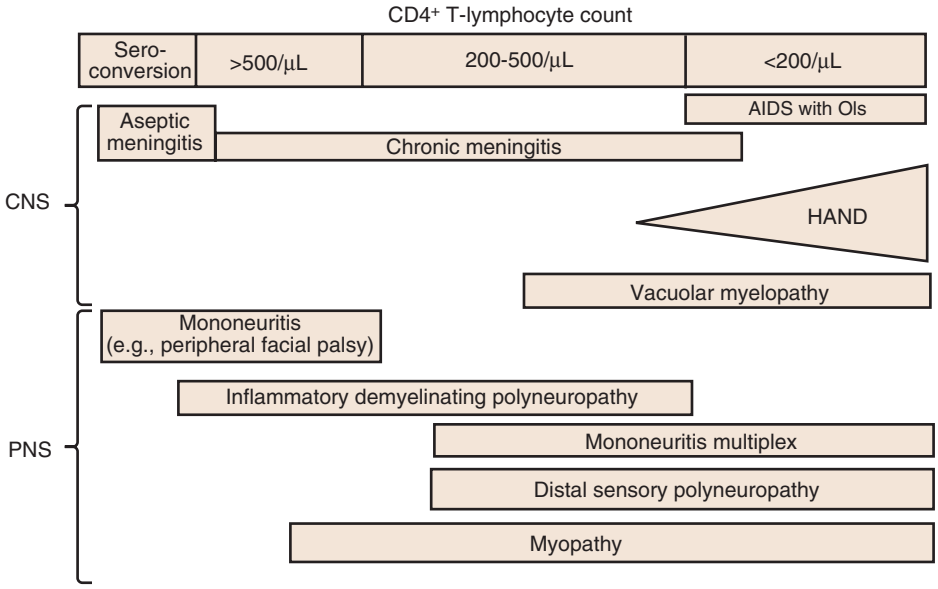

FIG. 125.6 Occurrence of the principal neurologic complications of human immunodeficiency virus (HIV) type 1 infection according to the degree of immunosuppression as measured by CD4⁺ T-lymphocyte counts (see text for details). *AIDS,* Acquired immunodeficiency virus; *CNS,* central nervous system; *HAND,* HIV-associated neurocognitive disorder; *OIs,* opportunistic infections; *PNS,* peripheral nervous system.

conditions and add another layer of complexity to management of these patients.[287,288,289] Not surprisingly, older age and diabetes were associated with increased frequency of dementia in HIV-infected patients.[290,291] In addition, cerebral small vessel ischemic vascular disease may cause white matter lesions and cortical atrophy, thus compounding the effect of HIV on the CNS of older patients.[292] Because of these trends and the fact that new clinical entities may potentially warrant different treatments, a brain biopsy should be considered in cases in which molecular diagnosis cannot be obtained, and postmortem analysis should be sought for all patients who did not respond to treatment.

Key References

The complete reference list is available online at Expert Consult.

5. d'Arminio Monforte A, Duca PG, Vago L. Decreasing incidence of CNS AIDS-defining events associated with antiretroviral therapy. *Neurology*. 2000;54:1856–1859.
6. Maschke M, Kastrup O, Esser S, et al. Incidence and prevalence of neurological disorders associated with HIV since the introduction of highly active antiretroviral therapy (HAART). *J Neurol Neurosurg Psychiatry*. 2000;69:376–380.
9. Etherton MR, Lyons JL, Ard KL, et al. HIV-associated neurocognitive disorders and antiretroviral therapy: current concepts and controversies. *Curr Infect Dis Rep*. 2015;17:485.
15. Ghanem KG, Moore RD, Rompalo AM, et al. Neurosyphilis in a clinical cohort of HIV-1-infected patients. *AIDS*. 2008;22:1145–1151.
21. Sacktor N. The epidemiology of human immunodeficiency virus-associated neurological disease in the era of highly active antiretroviral therapy. *J Neurovirol*. 2002;8:115–121.
24. Bicanic T, Wood R, Meintjes G, et al. High-dose amphotericin B with flucytosine for the treatment of cryptococcal meningitis in HIV-infected patients: a randomized trial. *Clin Infect Dis*. 2008;47:123–130.
26. Perfect JR, Dismukes WE, Dromer F, et al. Practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50:291–322.
31. Manosuthi W, Sungkanuparph S, Chottanapund S, et al. Temporary external lumbar drainage for reducing elevated intracranial pressure in HIV-infected patients with cryptococcal meningitis. *Int J STD AIDS*. 2008;19:268–271.
44. McArthur JC, Steiner J, Sacktor N, et al. Human immunodeficiency virus-associated neurocognitive disorders: mind the gap. *Ann Neurol*. 2010;67:699–714.
47. Sakamoto M, Marcotte TD, Umlauf A, et al. Concurrent classification accuracy of the HIV dementia scale for HIV-associated neurocognitive disorders in the CHARTER cohort. *J Acquir Immune Defic Syndr*. 2013;62:36–42.
49. Valcour V, Paul R, Chiao S, et al. Screening for cognitive impairment in human immunodeficiency virus. *Clin Infect Dis*. 2011;53:836–842.
50. Sacktor NC, Wong M, Nakasujja N, et al. The international HIV dementia scale: a new rapid screening test for HIV dementia. *AIDS*. 2005;19:1367–1374.
53. Heaton RK, Franklin DR Jr, Deutsch R, et al. Neurocognitive change in the era of HIV combination antiretroviral therapy: the longitudinal CHARTER study. *Clin Infect Dis*. 2015;60:473–480.
54. Sacktor N, Skolasky RL, Seaberg E, et al. Prevalence of HIV-associated neurocognitive disorders in the multicenter AIDS cohort study. *Neurology*. 2016;86:334–340.
60. Spudich SS, Ances BM. Central nervous system complications of HIV infection. *Top Antivir Med*. 2011;19:48–57.
62. Ellis RJ, Moore DJ, Childers ME, et al. Progression to neuropsychological impairment in human immunodeficiency virus infection predicted by elevated cerebrospinal fluid levels of human immunodeficiency virus RNA. *Arch Neurol*. 2002;59:923–928.
66. Churchill MJ, Wesselingh SL, Cowley D, et al. Extensive astrocyte infection is prominent in human immunodeficiency virus-associated dementia. *Ann Neurol*. 2009;66:253–258.
72. Spudich S, Gisslen M, Hagberg L, et al. Central nervous system immune activation characterizes primary human immunodeficiency virus 1 infection even in participants with minimal cerebrospinal fluid viral burden. *J Infect Dis*. 2011;204:753–760.
73. Letendre SL, Marquie-Beck J, Capparelli E, et al. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol*. 2008;65:65–70.
76. Gray F, Chretien F, Vallat-Decouvelaere AV, et al. The changing pattern of HIV neuropathology in the HAART era. *J Neuropathol Exp Neurol*. 2003;62:429–440.
82. Ciccarelli N, Fabbiani M, Colafigli M, et al. Revised central nervous system neuropenetration-effectiveness score is associated with cognitive disorders in HIV-infected patients with controlled plasma viraemia. *Antivir Ther*. 2013;18:153–160.
90. Ma Q, Vaida F, Wong J, et al. Long-term efavirenz use is associated with worse neurocognitive functioning in HIV-infected patients. *J Neurovirol*. 2016;22:170–178.
96. Peluso MJ, Ferretti F, Peterson J, et al. Cerebrospinal fluid HIV escape associated with progressive neurologic dysfunction in patients on antiretroviral therapy with well controlled plasma viral load. *AIDS*. 2012;26:1765–1774.
101. Masur H, Kaplan JE, Holmes KK. Guidelines for preventing opportunistic infections among HIV-infected persons–2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *Ann Intern Med*. 2002;137:435–478.
105. Philip-Ephraim EE, Charidimou A, Williams E, et al. Stroke-like presentation of cerebral toxoplasmosis: two HIV-infected cases. *Cerebrovasc Dis Extra*. 2015;5:28–30.
115. Bertschy S, Opravil M, Cavassini M, et al. Discontinuation of maintenance therapy against toxoplasma encephalitis in AIDS patients with sustained response to anti-retroviral therapy. *Clin Microbiol Infect*. 2006;12:666–671.
122. Corcoran C, Rebe K, van der Plas H, et al. The predictive value of cerebrospinal fluid Epstein-Barr viral load as a marker of primary central nervous system lymphoma in HIV-infected persons. *J Clin Virol*. 2008;42:433–436.
131. Skiest DJ, Crosby C. Survival is prolonged by highly active antiretroviral therapy in AIDS patients with primary central nervous system lymphoma. *AIDS*. 2003;17:1787–1793.
134. Hoffmann C, Tabrizian S, Wolf E, et al. Survival of AIDS patients with primary central nervous system lymphoma is dramatically improved by HAART-induced immune recovery. *AIDS*. 2001;15:2119–2127.
137. Khanna N, Elzi L, Mueller NJ, et al. Incidence and outcome of progressive multifocal leukoencephalopathy over 20 years of the Swiss HIV cohort study. *Clin Infect Dis*. 2009;48:1459–1466.
139. Gheuens S, Wuthrich C, Koralnik IJ. Progressive multifocal leukoencephalopathy: why gray and white matter. *Ann Rev Pathol*. 2013;8:189–215.
188. Antinori A, Ammassari A, De Luca A, et al. Diagnosis of AIDS-related focal brain lesions: a decision-making analysis based on clinical and neuroradiologic characteristics combined with polymerase chain reaction assays in CSF. *Neurology*. 1997;48:687–694.
190. Marra CM, Lockhart D, Zunt JR, et al. Changes in CSF and plasma HIV-1 RNA and cognition after starting potent antiretroviral therapy. *Neurology*. 2003;60:1388–1390.
191. Petito CK, Navia BA, Cho ES, et al. Vacuolar myelopathy pathologically resembling subacute combined

degeneration in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1985;312:874–879.
192. Henin D, Smith TW, De Girolami U, et al. Neuropathology of the spinal cord in the acquired immunodeficiency syndrome. *Hum Pathol*. 1992;23:1106–1114.
200. Staudinger R, Henry K. Remission of HIV myelopathy after highly active antiretroviral therapy. *Neurology*. 2000;54:267–268.
204. Berger JR, Sabet A. Infectious myelopathies. *Semin Neurol*. 2002;22:133–142.
205. Brannagan TH 3rd, Zhou Y. HIV-associated Guillain-Barre syndrome. *J Neurol Sci*. 2003;208:39–42.
208. Afzal A, Benjamin M, Gummelt KL, et al. Ascending paralysis associated with HIV infection. *Proc (Bayl Univ Med Cent)*. 2015;28:25–28.
209. Mochan A, Anderson D, Modi G. CIDP in a HIV endemic population: a prospective case series from Johannesburg, South Africa. *J Neurol Sci*. 2016;363:39–42.
214. Schifitto G, McDermott MP, McArthur JC, et al. Incidence of and risk factors for HIV-associated distal sensory polyneuropathy. *Neurology*. 2002;58:1764–1768.
216. Keswani SC, Pardo CA, Cherry CL, et al. HIV-associated sensory neuropathies. *AIDS*. 2002;16:2105–2117.
217. Evans SR, Ellis RJ, Chen H, et al. Peripheral neuropathy in HIV: prevalence and risk factors. *AIDS*. 2011;25:919–928.
227. Herzberg U, Sagen J. Peripheral nerve exposure to HIV viral envelope protein gp120 induces neuropathic pain and spinal gliosis. *J Neuroimmunol*. 2001;116:29–39.
243. Gonzalez-Duarte A, Robinson-Papp J, Simpson DM. Diagnosis and management of HIV-associated neuropathy. *Neurol Clin*. 2008;26:821–832.
250. Kolson DL, Gonzalez-Scarano F. HIV-associated neuropathies: role of HIV-1, CMV, and other viruses. *J Peripher Nerv Syst*. 2001;6:2–7.
261. Verma A, Berger JR. ALS syndrome in patients with HIV-1 infection. *J Neurol Sci*. 2006;240:59–64.
279. Birbeck GL, French JA, Perucca E, et al. Evidence-based guideline: antiepileptic drug selection for people with HIV/AIDS: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy. *Neurology*. 2012;78:139–145.
281. Langford TD, Letendre SL, Larrea GJ, et al. Changing patterns in the neuropathogenesis of HIV during the HAART era. *Brain Pathol*. 2003;13:195–210.
284. Vinikoor MJ, Napravnik S, Floris-Moore M, et al. Incidence and clinical features of cerebrovascular disease among HIV-infected adults in the southeastern United States. *AIDS Res Human Retroviruses*. 2013;29:1068–1074.
288. Goodkin K, Wilkie FL, Concha M, et al. Aging and neuro-AIDS conditions and the changing spectrum of HIV-1–associated morbidity and mortality. *J Clin Epidemiol*. 2001;54:S35–S43.
292. McMurtray A, Nakamoto B, Shikuma C, et al. Cortical atrophy and white matter hyperintensities in HIV: the Hawaii Aging with HIV Cohort Study. *J Stroke Cerebrovasc Dis*. 2008;17:212–217.

References

1. Snider WD, Simpson DM, Nielsen S, et al. Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. *Ann Neurol*. 1983;14:403–418.
2. Levy RM, Bredesen DE, Rosenblum ML. Neurological manifestations of the acquired immunodeficiency syndrome (AIDS): experience at UCSF and review of the literature. *J Neurosurg*. 1985;62:475–495.
3. Petito CK. Review of central nervous system pathology in human immunodeficiency virus infection. *Ann Neurol*. 1988;23:S54–S57.
4. De Girolami U, Smith TW, Henin D, et al. Neuropathology of the acquired immunodeficiency syndrome. *Arch Pathol Lab Med*. 1990;114:643–655.
5. d'Arminio Monforte A, Duca PG, Vago L. Decreasing incidence of CNS AIDS-defining events associated with antiretroviral therapy. *Neurology*. 2000;54:1856–1859.
6. Maschke M, Kastrup O, Esser S, et al. Incidence and prevalence of neurological disorders associated with HIV since the introduction of highly active antiretroviral therapy (HAART). *J Neurol Neurosurg Psychiatry*. 2000;69:376–380.
7. Sacktor N, Lyles RH, Skolasky R, et al. HIV-associated neurologic disease incidence changes: multicenter AIDS cohort study, 1990-1998. *Neurology*. 2001;56:257–260.
8. d'Arminio Monforte A, Cinque P, Mocroft A, et al. Changing incidence of central nervous system diseases in the EuroSIDA cohort. *Ann Neurol*. 2004;55:320–328.
9. Etherton MR, Lyons JL, Ard KL, et al. HIV-associated neurocognitive disorders and antiretroviral therapy: current concepts and controversies. *Curr Infect Dis Rep*. 2015;17:485.
10. Serrano P, Hernandez N, Arroyo JA, et al. Bilateral bell palsy and acute HIV type 1 infection: report of 2 cases and review. *Clin Infect Dis*. 2007;44:e57–e61.
11. Gray F, Lescs MC, Keohane C, et al. Early brain changes in HIV infection: neuropathological study of 11 HIV seropositive, non-AIDS cases. *J Neuropathol Exp Neurol*. 1992;51:177–185.
12. Gray F, Scaravilli F, Everall I, et al. Neuropathology of early HIV-1 infection. *Brain Pathol*. 1996;6:1–15.
13. Hollander H, McGuire D, Burack JH. Diagnostic lumbar puncture in HIV-infected patients: analysis of 138 cases. *Am J Med*. 1994;96:223–228.
14. Johns DR, Tierney M, Felsenstein D. Alteration in the natural history of neurosyphilis by concurrent infection with the human immunodeficiency virus. *N Engl J Med*. 1987;316:1569–1572.
15. Ghanem KG, Moore RD, Rompalo AM, et al. Neurosyphilis in a clinical cohort of HIV-1-infected patients. *AIDS*. 2008;22:1145–1151.
16. Musher DM, Hamill RJ, Baughn RE. Effect of human immunodeficiency virus (HIV) infection on the course of syphilis and on the response to treatment. *Ann Intern Med*. 1990;113:872–881.
17. Feraru ER, Aronow HA, Lipton RB. Neurosyphilis in AIDS patients: initial CSF VDRL may be negative. *Neurology*. 1990;40:541–543.
18. Marra C, Maxwell CL, Tantalo LC, et al. Normalization of serum rapid plasma reagin titer predicts normalization of cerebrospinal fluid and clinical abnormalities after treatment of neurosyphilis. *Clin Infect Dis*. 2008;47:893–899.
19. de Almeida SM, Bhatt A, Riggs PK, et al. Cerebrospinal fluid human immunodeficiency virus viral load in patients with neurosyphilis. *J Neurovirol*. 2010;16:6–12.
20. Powderly WG. Cryptococcal meningitis and AIDS. *Clin Infect Dis*. 1993;17:837–842.
21. Sacktor N. The epidemiology of human immunodeficiency virus-associated neurological disease in the era of highly active antiretroviral therapy. *J Neurovirol*. 2002;8:115–121.
22. Loyse A, Moodley A, Rich P, et al. Neurological, visual, and MRI brain scan findings in 87 South African patients with HIV-associated cryptococcal meningoencephalitis. *J Infect*. 2015;70:668–675.
23. Day JN, Chau TT, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. *N Engl J Med*. 2013;368:1291–1302.
24. Bicanic T, Wood R, Meintjes G, et al. High-dose amphotericin B with flucytosine for the treatment of cryptococcal meningitis in HIV-infected patients: a randomized trial. *Clin Infect Dis*. 2008;47:123–130.
25. Saag MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the management of cryptococcal disease. *Clin Infect Dis*. 2000;30:710–718.
26. Perfect JR, Dismukes WE, Dromer F, et al. Practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50:291–322.
27. van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. *N Engl J Med*. 1997;337:15–21.
28. Arvis JN, Bicanic T, Loyse A, et al. Determinants of mortality in a combined cohort of 501 patients with HIV-associated cryptococcal meningitis: implications for improving outcomes. *Clin Infect Dis*. 2014;58:736–745.
29. Bisson GP, Nthobatsong R, Thakur R, et al. The use of HAART is associated with decreased risk of death during initial treatment of cryptococcal meningitis in adults in Botswana. *J Acquir Immune Defic Syndr*. 2008;49:227–229.
30. Johnston SR, Corbett EL, Foster O, et al. Raised intracranial pressure and visual complications in AIDS patients with cryptococcal meningitis. *J Infect*. 1992;24:185–189.
31. Manosuthi W, Sungkanuparph S, Chottanapund S, et al. Temporary external lumbar drainage for reducing elevated intracranial pressure in HIV-infected patients with cryptococcal meningitis. *Int J STD AIDS*. 2008;19:268–271.
32. Chang CC, Dorasamy AA, Gosnell BI, et al. Clinical and mycological predictors of cryptococcosis-associated immune reconstitution inflammatory syndrome (C-IRIS). *AIDS*. 2013.
33. Bisson GP, Molefi M, Bellamy S, et al. Early versus delayed antiretroviral therapy and cerebrospinal fluid fungal clearance in adults with HIV and cryptococcal meningitis. *Clin Infect Dis*. 2013;56:1165–1173.
34. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med*. 2014;370:2487–2498.
35. Tan IL, Smith BR, von Geldern G, et al. HIV-associated opportunistic infections of the CNS. *Lancet Neurol*. 2012;11:605–617.
36. Clarridge JE 3rd, Shawar RM, Shinnick TM, et al. Large-scale use of polymerase chain reaction for detection of mycobacterium tuberculosis in a routine mycobacteriology laboratory. *J Clin Microbiol*. 1993;31:2049–2056.
37. Garg RK. Tuberculosis of the central nervous system. *Postgrad Med J*. 1999;75:133–140.
38. Bahr NC, Nuwagira E, Evans EE, et al. Diagnostic accuracy of Xpert MTB/RIF ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. *Lancet Infect Dis*. 2017.
39. Tan K, Patel S, Gandhi N, et al. Burden of neuroinfectious diseases on the neurology service in a tertiary care center. *Neurology*. 2008;71:1160–1166.
40. Hakim JG, Gangaidzo IT, Heyderman RS, et al. Impact of HIV infection on meningitis in Harare, Zimbabwe: a prospective study of 406 predominantly adult patients. *AIDS*. 2000;14:1401–1407.
41. Janoff EN, Breiman RF, Daley CL, et al. Pneumococcal disease during HIV infection. Epidemiologic, clinical, and immunologic perspectives. *Ann Intern Med*. 1992;117:314–324.
42. McArthur JC, Hoover DR, Bacellar H, et al. Dementia in AIDS patients: incidence and risk factors. Multicenter AIDS cohort study. *Neurology*. 1993;43:2245–2252.
43. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007;69:1789–1799.
44. McArthur JC, Steiner J, Sacktor N, et al. Human immunodeficiency virus-associated neurocognitive disorders: mind the gap. *Ann Neurol*. 2010;67:699–714.
45. McCombe JA, Vivithanaporn P, Gill MJ, et al. Predictors of symptomatic HIV-associated neurocognitive disorders in universal health care. *HIV Med*. 2013;14:99–107.
46. Yuen T, Brouillette MJ, Fellows LK, et al. CHARTER group,. Personalized risk index for neurocognitive decline among people with well-controlled HIV infection. *J Acquir Immune Defic Syndr*. 2017;76:48–54.
47. Sakamoto M, Marcotte TD, Umlauf A, et al. Concurrent classification accuracy of the HIV dementia scale for HIV-associated neurocognitive disorders in the CHARTER cohort. *J Acquir Immune Defic Syndr*. 2013;62:36–42.
48. Overton ET, Azad TD, Parker N, et al. The Alzheimer's disease-8 and montreal cognitive assessment as screening tools for neurocognitive impairment in HIV-infected persons. *J Neurovirol*. 2013;19:109–116.
49. Valcour V, Paul R, Chiao S, et al. Screening for cognitive impairment in human immunodeficiency virus. *Clin Infect Dis*. 2011;53:836–842.
50. Sacktor NC, Wong M, Nakasujja N, et al. The international HIV dementia scale: a new rapid screening test for HIV dementia. *AIDS*. 2005;19:1367–1374.
51. Haddow LJ, Floyd S, Copas A, et al. A systematic review of the screening accuracy of the HIV dementia scale and international HIV dementia scale. *PLoS ONE*. 2013;8:e61826.
52. Heaton RK, Clifford DB, Franklin DR Jr, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER study. *Neurology*. 2010;75:2087–2096.
53. Heaton RK, Franklin DR Jr, Deutsch R, et al. Neurocognitive change in the era of HIV combination antiretroviral therapy: the longitudinal CHARTER study. *Clin Infect Dis*. 2015;60:473–480.
54. Sacktor N, Skolasky RL, Seaberg E, et al. Prevalence of HIV-associated neurocognitive disorders in the multicenter AIDS cohort study. *Neurology*. 2016;86:334–340.
55. Grant I, Franklin DR Jr, Deutsch R, et al; CHARTER group. Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. *Neurology*. 2014;82:2055–2062.
56. Smith T, Jakobsen J, Gaub J, et al. Clinical and electrophysiological studies of human immunodeficiency virus-seropositive men without AIDS. *Ann Neurol*. 1988;23:295–297.
57. Rosenhall U, Hakansson C, Lowhagen GB, et al. Otoneurological abnormalities in asymptomatic HIV-seropositive patients. *Acta Neurol Scand*. 1989;79:140–145.
58. Koralnik IJ, Beaumanoir A, Hausler R, et al. A controlled study of early neurologic abnormalities in men with Asymptomatic human immunodeficiency virus infection. *N Engl J Med*. 1990;323:864–870.
59. Portegies P, Enting RH, de Gans J, et al. Presentation and course of AIDS dementia complex: 10 years of follow-up in Amsterdam, the Netherlands. *AIDS*. 1993;7:669–675.
60. Spudich SS, Ances BM. Central nervous system complications of HIV infection. *Top Antivir Med*. 2011;19:48–57.
61. Edén A, Marcotte TD, Heaton RK, et al. Increased intrathecal immune activation in virally suppressed HIV-1 infected patients with neurocognitive impairment. *PLoS ONE*. 2016;11:e0157160.
62. Ellis RJ, Moore DJ, Childers ME, et al. Progression to neuropsychological impairment in human immunodeficiency virus infection predicted by elevated cerebrospinal fluid levels of human immunodeficiency virus RNA. *Arch Neurol*. 2002;59:923–928.
63. Price RW. The two faces of HIV infection of cerebrospinal fluid. *Trends Microbiol*. 2000;8:387–391.
64. Clifford KM, Samboju V, Cobigo Y, et al. Progressive brain atrophy despite persistent viral suppression in HIV over age 60. *J Acquir Immune Defic Syndr*. 2017.
65. Steinbrink F, Evers S, Buerke B, et al. Cognitive impairment in HIV infection is associated with MRI and CSF pattern of neurodegeneration. *Eur J Neurol*. 2013;20:420–428.
66. Churchill MJ, Wesselingh SL, Cowley D, et al. Extensive astrocyte infection is prominent in human immunodeficiency virus-associated dementia. *Ann Neurol*. 2009;66:253–258.
67. An SF, Groves M, Gray F, et al. Early entry and widespread cellular involvement of HIV-1 DNA in brains of HIV-1 positive asymptomatic individuals. *J Neuropathol Exp Neurol*. 1999;58:1156–1162.
68. Smith TW, DeGirolami U, Henin D, et al. Human immunodeficiency virus (HIV) leukoencephalopathy and the microcirculation. *J Neuropathol Exp Neurol*. 1990;49:357–370.
69. Berger JR, Nath A, Greenberg RN, et al. Cerebrovascular changes in the basal ganglia with HIV dementia. *Neurology*. 2000;54:921–926.
70. Tornatore C, Chandra R, Berger JR, et al. HIV-1 infection of subcortical astrocytes in the pediatric central nervous system. *Neurology*. 1994;44:481–487.
71. Everall IP, Heaton RK, Marcotte TD, et al. Cortical synaptic density is reduced in mild to moderate human immunodeficiency virus neurocognitive disorder. HNRC group. HIV neurobehavioral research center. *Brain Pathol*. 1999;9:209–217.
72. Spudich S, Gisslen M, Hagberg L, et al. Central nervous system immune activation characterizes primary human immunodeficiency virus 1 infection even in participants with minimal cerebrospinal fluid viral burden. *J Infect Dis*. 2011;204:753–760.
73. Letendre SL, Marquie-Beck J, Capparelli E, et al. Validation of the CNS penetration-effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol*. 2008;65:65–70.
74. Giancola ML, Lorenzini P, Cingolani A, et al. Virological response in cerebrospinal fluid to antiretroviral therapy in a large Italian cohort of HIV-infected patients with neurological disorders. *AIDS Res Treat*. 2012;2012:708456.

75. Vago L, Bonetto S, Nebuloni M, et al. Pathological findings in the central nervous system of AIDS patients on assumed antiretroviral therapeutic regimens: retrospective study of 1597 autopsies. *AIDS*. 2002;16:1925–1928.
76. Gray F, Chretien F, Vallat-Decouvelaere AV, et al. The changing pattern of HIV neuropathology in the HAART era. *J Neuropathol Exp Neurol*. 2003;62:429–440.
77. Bhaskaran K, Mussini C, Antinori A, et al. Changes in the incidence and predictors of human immunodeficiency virus-associated dementia in the era of highly active antiretroviral therapy. *Ann Neurol*. 2008;63:213–221.
78. Antinori A, Giancola ML, Grisetti S, et al. Factors influencing virological response to antiretroviral drugs in cerebrospinal fluid of advanced HIV-1-infected patients. *AIDS*. 2002;16:1867–1876.
79. De Luca A, Ciancio BC, Larussa D, et al. Correlates of independent HIV-1 replication in the CNS and of its control by antiretrovirals. *Neurology*. 2002;59:342–347.
80. Anderson AM, Muñoz-Moreno JA, McClernon DR, et al; CHARTER group. Prevalence and correlates of persistent HIV-1 RNA in cerebrospinal fluid during antiretroviral therapy. *J Infect Dis*. 2017;215:105–113.
81. Letendre SL, McCutchan JA, Childers ME, et al. Enhancing antiretroviral therapy for human immunodeficiency virus cognitive disorders. *Ann Neurol*. 2004;56:416–423.
82. Ciccarelli N, Fabbiani M, Colafigli M, et al. Revised central nervous system neuropenetration-effectiveness score is associated with cognitive disorders in HIV-infected patients with controlled plasma viraemia. *Antivir Ther*. 2013;18:153–160.
83. Carvalhal A, Gill MJ, Letendre SL, et al. Centre for brain health in HIV/AIDS. Central nervous system penetration effectiveness of antiretroviral drugs and neuropsychological impairment in the Ontario HIV treatment network cohort study. *J Neurovirol*. 2016;22:349–357.
84. Vassallo M, Durant J, Biscay V, et al. Can high central nervous system penetrating antiretroviral regimens protect against the onset of HIV-associated neurocognitive disorders? *AIDS*. 2014;28:493–501.
85. Ellis RJ, Letendre S, Vaida F, et al. Randomized trial of central nervous system-targeted antiretrovirals for HIV-associated neurocognitive disorder. *Clin Infect Dis*. 2014;58:1015–1022.
86. Caniglia EC, Cain LE, Justice A, et al; HIV-CAUSAL collaboration. Antiretroviral penetration into the CNS and incidence of AIDS-defining neurologic conditions. *Neurology*. 2014;83:134–141.
87. Robertson KR, Su Z, Margolis DM, et al. Neurocognitive effects of treatment interruption in stable HIV-positive patients in an observational cohort. *Neurology*. 2010;74:1260–1266.
88. Ciccarelli N, Fabbiani M, Di Giambenedetto S, et al. Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. *Neurology*. 2011;76:1403–1409.
89. Robertson K, Liner J, Meeker RB. Antiretroviral neurotoxicity. *J Neurovirol*. 2012;18:388–399.
90. Ma Q, Vaida F, Wong J, et al. Long-term efavirenz use is associated with worse neurocognitive functioning in HIV-infected patients. *J Neurovirol*. 2016;22:170–178.
91. Stingele K, Haas J, Zimmermann T, et al. Independent HIV replication in paired CSF and blood viral isolates during antiretroviral therapy. *Neurology*. 2001;56:355–361.
92. Lanier ER, Sturge G, McClernon D, et al. HIV-1 reverse transcriptase sequence in plasma and cerebrospinal fluid of patients with AIDS dementia complex treated with abacavir. *AIDS*. 2001;15:747–751.
93. Cinque P, Presi S, Bestetti A, et al. Effect of genotypic resistance on the virological response to highly active antiretroviral therapy in cerebrospinal fluid. *AIDS Res Hum Retroviruses*. 2001;17:377–383.
94. Mukerji SS, Misra V, Lorenz D, et al. Temporal patterns and drug resistance in CSF viral escape among ART-experienced HIV-1 infected adults. *J Acquir Immune Defic Syndr*. 2017;75:246–255.
95. McCoig C, Castrejon MM, Castano E, et al. Effect of combination antiretroviral therapy on cerebrospinal fluid HIV RNA, HIV resistance, and clinical manifestations of encephalopathy. *J Pediatr*. 2002;141:36–44.
96. Peluso MJ, Ferretti F, Peterson J, et al. Cerebrospinal fluid HIV escape associated with progressive neurologic dysfunction in patients on antiretroviral therapy with well controlled plasma viral load. *AIDS*. 2012;26:1765–1774.
97. Nakasujja N, Miyahara S, Evans S, et al. Randomized trial of minocycline in the treatment of HIV-associated cognitive impairment. *Neurology*. 2013;80:196–202.
98. Sacktor N, Skolasky RL, Moxley R, et al. Paroxetine and fluconazole therapy for HIV-associated neurocognitive impairment: results from a double-blind, placebo-controlled trial. *J Neurovirol*. 2018;24:16–27.
99. Hossain S, Fazeli PL, Tende F, et al. The potential of computerized cognitive training on HIV-associated neurocognitive disorder: A case comparison study. *J Assoc Nurses AIDS Care*. 2017.
100. Jones JL, Kruszon-Moran D, Rivera HN, et al. Toxoplasma gondii seroprevalence in the United States 2009-2010 and comparison with the past two decades. *Am J Trop Med Hyg*. 2014;90:1135–1139.
101. Masur H, Kaplan JE, Holmes KK. Guidelines for preventing opportunistic infections among HIV-infected persons–2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *Ann Intern Med*. 2002;137:435–478.
102. Ammassari A, Cingolani A, Pezzotti P, et al. AIDS-related focal brain lesions in the era of highly active antiretroviral therapy. *Neurology*. 2000;55:1194–1200.
103. Antinori A, Antinori A, Larussa D, et al. Italian registry investigative NeuroAIDS. Prevalence, associated factors, and prognostic determinants of AIDS-related toxoplasmic encephalitis in the era of advanced highly active antiretroviral therapy. *Clin Infect Dis*. 2004;39:1681–1691.
104. Kiderlen TR, Liesenfeld O, Schurmann D, et al. Toxoplasmic encephalitis in AIDS-patients before and after the introduction of highly active antiretroviral therapy (HAART). *Eur Clin Microbiol Infect Dis*. 2011;30:1521–1525.
105. Philip-Ephraim EE, Charidimou A, Williams E, et al. Stroke-like presentation of cerebral toxoplasmosis: two HIV-infected cases. *Cerebrovasc Dis Extra*. 2015;5:28–30.
106. Renold C, Sugar A, Chave JP, et al. Toxoplasma encephalitis in patients with the acquired immunodeficiency syndrome. *Medicine (Baltimore)*. 1992;71:224–239.
107. Luft BJ, Hafner R, Korzun AH, et al. Toxoplasmic encephalitis in patients with the acquired immunodeficiency syndrome. Members of the ACTG 077p/ANRS 009 study team. *N Engl J Med*. 1993;329:995–1000.
108. Schoondermark-van de Ven E, Galama J, Kraaijeveld C, et al. Value of the polymerase chain reaction for the detection of toxoplasma gondii in cerebrospinal fluid from patients with AIDS. *Clin Infect Dis*. 1993;16:661–666.
109. Contini C, Cultrera R, Seraceni S, et al. The role of stage-specific oligonucleotide primers in providing effective laboratory support for the molecular diagnosis of reactivated toxoplasma gondii encephalitis in patients with AIDS. *J Med Microbiol*. 2002;51:879–890.
110. Haverkos HW. Assessment of therapy for toxoplasma encephalitis. The TE study group. *Am J Med*. 1987;82:907–914.
111. Mayor AM, Fernandez Santos DM, Dworkin MS, et al. Toxoplasmic encephalitis in an AIDS cohort at Puerto Rico before and after highly active antiretroviral therapy (HAART). *Am J Trop Med Hygiene*. 2011;84:838–841.
112. Hoffmann C, Ernst M, Meyer P, et al. Evolving characteristics of toxoplasmosis in patients infected with human immunodeficiency virus-1: clinical course and toxoplasma gondii-specific immune responses. *Clin Microbiol Infect*. 2007;13:510–515.
113. Martin-Blondel G, Alvarez M, Delobel P, et al. Toxoplasmic encephalitis IRIS in HIV-infected patients: a case series and review of the literature. *J Neurol Neurosurg Psychiatry*. 2011;82:691–693.
114. Kaplan JE, Masur H, Holmes KK. Guidelines for preventing opportunistic infections among HIV-infected persons–2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2002;51:1–52.
115. Bertschy S, Opravil M, Cavassini M, et al. Discontinuation of maintenance therapy against toxoplasma encephalitis in AIDS patients with sustained response to anti-retroviral therapy. *Clin Microbiol Infect*. 2006;12:666–671.
116. So YT, Beckstead JH, Davis RL. Primary central nervous system lymphoma in acquired immune deficiency syndrome: a clinical and pathological study. *Ann Neurol*. 1986;20:566–572.
117. Subirá D, Górgolas M, Castañón S, et al. Advantages of flow cytometry immunophenotyping for the diagnosis of central nervous system non-hodgkin's lymphoma in AIDS patients. *HIV Med*. 2005;6:21–26.
118. MacMahon EM, Glass JD, Hayward SD, et al. Association of Epstein-Barr virus with primary central nervous system lymphoma in AIDS. *AIDS Res Hum Retroviruses*. 1992;8:740–742.
119. Yanagisawa K, Tanuma J, Hagiwara S, et al. Epstein-Barr viral load in cerebrospinal fluid as a diagnostic marker of central nervous system involvement of AIDS-related lymphoma. *Intern Med*. 2013;52:955–959.
120. Bossolasco S, Cinque P, Ponzoni M, et al. Epstein-Barr virus DNA load in cerebrospinal fluid and plasma of patients with AIDS-related lymphoma. *J Neurovirol*. 2002;8:432–438.
121. Ivers LC, Kim AY, Sax PE. Predictive value of polymerase chain reaction of cerebrospinal fluid for detection of Epstein-Barr virus to establish the diagnosis of HIV-related primary central nervous system lymphoma. *Clin Infect Dis*. 2004;38:1629–1632.
122. Corcoran C, Rebe K, van der Plas H, et al. The predictive value of cerebrospinal fluid Epstein-Barr viral load as a marker of primary central nervous system lymphoma in HIV-infected persons. *J Clin Virol*. 2008;42:433–436.
123. Forsyth PA, DeAngelis LM. Biology and management of AIDS-associated primary CNS lymphomas. *Hematol Oncol Clin North Am*. 1996;10:1125–1134.
124. Thurnher MM, Thurnher SA, Schindler E. CNS involvement in AIDS: spectrum of CT and MR findings. *Eur Radiol*. 1997;7:1091–1097.
125. Antinori A, De Rossi G, Ammassari A, et al. Value of combined approach with thallium-201 single-photon emission computed tomography and Epstein-Barr virus DNA polymerase chain reaction in CSF for the diagnosis of AIDS-related primary CNS lymphoma. *J Clin Oncol*. 1999;17:554–560.
126. Young RJ, Ghesani MV, Kagetsu NJ, et al. Lesion size determines accuracy of thallium-201 brain single-photon emission tomography in differentiating between intracranial malignancy and infection in AIDS patients. *AJNR Am J Neuroradiol*. 2005;26:1973–1979.
127. Westwood TD, Hogan C, Julyan PJ, et al. Utility of FDG-PETCT and magnetic resonance spectroscopy in differentiating between cerebral lymphoma and non-malignant CNS lesions in HIV-infected patients. *Eur J Radiol*. 2013;82:e374–e379.
128. Knowles DM. Etiology and pathogenesis of AIDS-related non-hodgkin's lymphoma. *Hematol Oncol Clin North Am*. 2003;17:785–820.
129. Moulignier A, Lamirel C, Picard H, et al. Long-term AIDS-related PCNSL outcomes with HD-MTX and combined antiretroviral therapy. *Neurology*. 2017;89:796–804.
130. Corn BW, Donahue BR, Rosenstock JG, et al. Performance status and age as independent predictors of survival among AIDS patients with primary CNS lymphoma: a multivariate analysis of a multi-institutional experience. *Cancer J Sci Am*. 1997;3:52–56.
131. Skiest DJ, Crosby C. Survival is prolonged by highly active antiretroviral therapy in AIDS patients with primary central nervous system lymphoma. *AIDS*. 2003;17:1787–1793.
132. Nagai H, Odawara T, Ajisawa A, et al. Whole brain radiation alone produces favourable outcomes for AIDS-related primary central nervous system lymphoma in the HAART era. *Eur J Haematol*. 2010;84:499–505.
133. Omuro AM, Ben-Porat LS, Panageas KS, et al. Delayed neurotoxicity in primary central nervous system lymphoma. *Arch Neurol*. 2005;62:1595.
134. Hoffmann C, Tabrizian S, Wolf E, et al. Survival of AIDS patients with primary central nervous system lymphoma is dramatically improved by HAART-induced immune recovery. *AIDS*. 2001;15:2119–2127.
135. Koralnik IJ, Schellingerhavt D, Frosch MP. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises: a 66-year-old man with progressive neurologic deficits. *N Engl J Med*. 2004;350:1882–1893.
136. Berger JR, Kaszovitz B, Post MJ, et al. Progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection: a review of the literature with a report of sixteen cases. *Ann Intern Med*. 1987;107:78–87.
137. Khanna N, Elzi L, Mueller NJ, et al. Incidence and outcome of progressive multifocal leukoencephalopathy over 20 years of the Swiss HIV cohort study. *Clin Infect Dis*. 2009;48:1459–1466.
138. Engsig FN, Hansen AB, Omland LH, et al. Incidence, clinical presentation, and outcome of progressive multifocal leukoencephalopathy in HIV-infected patients during the highly active antiretroviral therapy era: a nationwide cohort study. *J Infect Dis*. 2009;199:77–83.
139. Gheuens S, Wuthrich C, Koralnik IJ. Progressive multifocal leukoencephalopathy: why gray and white matter. *Ann Rev Pathol*. 2013;8:189–215.
140. Fong IW, Toma E. The natural history of progressive multifocal leukoencephalopathy in patients with AIDS. Canadian PML study group. *Clin Infect Dis*. 1995;20:1305–1310.

141. Bernal-Cano F, Joseph JT, Koralnik IJ. Spinal cord lesions of progressive multifocal leukoencephalopathy in an acquired immunodeficiency syndrome patient. *J Neurovirol*. 2007;13:474–476.
142. Miskin DP, Herman ST, Ngo LH, et al. Predictors and characteristics of seizures in survivors of progressive multifocal leukoencephalopathy. *J Neurovirol*. 2016;22:464–471.
143. Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN neuroinfectious disease section. *Neurology*. 2013;80:1430–1438.
144. McGuire D, Barhite S, Hollander H, et al. JC virus DNA in cerebrospinal fluid of human immunodeficiency virus-infected patients: predictive value for progressive multifocal leukoencephalopathy [published erratum appears in *Ann Neurol*. 1995;37:687]. *Ann Neurol*. 1995;37:395–399.
145. Koralnik IJ, Boden D, Mai VX, et al. JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy. *Neurology*. 1999;52:253–260.
146. Marzocchetti A, Di Giambenedetto S, Cingolani A, et al. Reduced rate of diagnostic positive detection of JC virus DNA in cerebrospinal fluid in cases of suspected progressive multifocal leukoencephalopathy in the era of potent antiretroviral therapy. *J Clin Microbiol*. 2005;43:4175–4177.
147. Taoufik Y, Gasnault J, Karaterki A, et al. Prognostic value of JC virus load in cerebrospinal fluid of patients with progressive multifocal leukoencephalopathy. *J Infect Dis*. 1998;178:1816–1820.
148. Yiannoutsos CT, Major EO, Curfman B, et al. Relation of JC virus DNA in the cerebrospinal fluid to survival in acquired immunodeficiency syndrome patients with biopsy-proven progressive multifocal leukoencephalopathy. *Ann Neurol*. 1999;45: 816–821.
149. Whiteman ML, Post MJ, Berger JR, et al. Progressive multifocal leukoencephalopathy in 47 HIV-seropositive patients: neuroimaging with clinical and pathologic correlation. *Radiology*. 1993;187:233–240.
150. Khoury MN, Alsop DC, Agnihotri SP, et al. Hyperintense cortical signal on magnetic resonance imaging reflects focal leukocortical encephalitis and seizure risk in progressive multifocal leukoencephalopathy. *Ann Neurol*. 2014;75:659–669.
151. Gray F, Geny C, Lescs MC, et al. AIDS-related progressive multifocal leukoencephalopathy limited to U fibers, responsible for subacute encephalopathy with normal CT scan findings. *Arch Anat Cytol Pathol*. 1992;40:132–137.
152. Chang L, Ernst T, Tornatore C, et al. Metabolite abnormalities in progressive multifocal leukoencephalopathy by proton magnetic resonance spectroscopy. *Neurology*. 1997;48:836–845.
153. Chang L, Miller BL, McBride D, et al. Brain lesions in patients with AIDS: h-1 MR spectroscopy. *Radiology*. 1995;197:525–531.
154. Simone IL, Federico F, Tortorella C, et al. Localised 1h-MR spectroscopy for metabolic characterisation of diffuse and focal brain lesions in patients infected with HIV. *J Neurol Neurosurg Psychiatry*. 1998;64: 516–523.
155. Iranzo A, Moreno A, Pujol J, et al. Proton magnetic resonance spectroscopy pattern of progressive multifocal leukoencephalopathy in AIDS. *J Neurol Neurosurg Psychiatry*. 1999;66:520–523.
156. Katz-Brull R, Lenkinski RE, Du Pasquier RA, et al. Elevation of myo-inositol is associated with disease containment in PML. *Neurology*. 2004;63:897–900.
157. Cinque P, Koralnik IJ, Clifford D. The evolving face of progressive multifocal leukoencephalopathy: towards the definition of a consensus terminology. *J Neurovirol*. 2003;9:88–92.
158. Hall CD, Dafni U, Simpson D, et al. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. AIDS clinical trials group 243 team. *N Engl J Med*. 1998;338: 1345–1351.
159. Geschwind MD, Skolasky RI, Royal WS, et al. The relative contributions of HAART and alpha-interferon for therapy of progressive multifocal leukoencephalopathy in AIDS. *J Neurovirol*. 2001;7:353–357.
160. Royal W 3rd, Dupont B, McGuire D, et al. Topotecan in the treatment of acquired immunodeficiency syndrome-related progressive multifocal leukoencephalopathy. *J Neurovirol*. 2003;9:411–419.
161. Marra CM, Rajicic N, Barker DE, et al. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. *AIDS*. 2002;16:1791–1797.
162. De Luca A, Ammassari A, Pezzotti P, et al. Gesida 9/99, IRINA, ACTG 363 study groups. Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated progressive multifocal leukoencephalopathy: a multicohort analysis. *AIDS*. 2008;22:1759–1767.
163. Clifford DB, Nath A, Cinque P, et al. A study of mefloquine treatment for progressive multifocal leukoencephalopathy: results and exploration of predictors of PML outcomes. *J Neurovirol*. 2013;19: 351–358.
164. Elphick GF, Querbes W, Jordan JA, et al. The human polyomavirus, JCV, uses serotonin receptors to infect cells. *Science*. 2004;306:1380–1383.
165. Verma S, Cikurel K, Koralnik IJ, et al. Mirtazapine in progressive multifocal leukoencephalopathy associated with polycythemia vera. *J Infect Dis*. 2007;196: 709–711.
166. Tantisiriwat W, Tebas P, Clifford DB, et al. Progressive multifocal leukoencephalopathy in patients with AIDS receiving highly active antiretroviral therapy. *Clin Infect Dis*. 1999;28:1152–1154.
167. Marzocchetti A, Tompkins T, Clifford DB, et al. Determinants of survival in progressive multifocal leukoencephalopathy. *Neurology*. 2009;73:1551–1558.
168. Khoury MN, Gheuens S, Ngo L, et al. Hyperperfusion in progressive multifocal leukoencephalopathy is associated with disease progression and absence of immune reconstitution inflammatory syndrome. *Brain*. 2013;136(Pt 11):3441–3450.
169. Du Pasquier RA, Clark KW, Smith PS, et al. JCV-specific cellular immune response correlates with a favorable clinical outcome in HIV-infected individuals with progressive multifocal leukoencephalopathy. *J Neurovirol*. 2001;7:318–322.
170. Koralnik IJ, Du Pasquier RA, Kuroda MJ, et al. Association of prolonged survival in HLA-a2+ progressive multifocal leukoencephalopathy patients with a CTL response specific for a commonly recognized JC virus epitope. *J Immunol*. 2002;168:499–504.
171. Du Pasquier RA, Kuroda MJ, Schmitz JE, et al. Low frequency of cytotoxic T lymphocytes against the novel HLA-A*0201-restricted JC virus epitope VP1p36 in patients with proven or possible progressive multifocal leukoencephalopathy. *J Virol*. 2003;77:11918–11926.
172. Gheuens S, Bord E, Kesari S, et al. Role of CD4+ and CD8+ T-cell responses against JC virus in the outcome of patients with progressive multifocal leukoencephalopathy (PML) and PML with immune reconstitution inflammatory syndrome. *J Virol*. 2011;85:7256–7263.
173. Marzocchetti A, Lima M, Tompkins T, et al. Efficient in vitro expansion of JC virus-specific CD4+ T cell responses by JCV peptide-stimulated dendritic cells from patients with progressive multifocal leukoencephalopathy. *Virology*. 2009;383:173–177.
174. Martin-Blondel G, Bauer J, Cuvinciuc V, et al. In situ evidence of JC virus control by CD8+ T cells in PML-IRIS during HIV infection. *Neurology*. 2013;81.
175. Falcó V, Olmo M, del Saz SV, et al. Influence of HAART on the clinical course of HIV-1-infected patients with progressive multifocal leukoencephalopathy: results of an observational multicenter study. *J Acquir Immune Defic Syndr*. 2008;49:26–31.
176. Du Pasquier RA, Koralnik IJ. Inflammatory reaction in progressive multifocal leukoencephalopathy: harmful or beneficial? *J Neurovirol*. 2003;9:25–31.
177. Vendrely A, Bienvenu B, Gasnault J, et al. Fulminant inflammatory leukoencephalopathy associated with HAART-induced immune restoration in AIDS-related progressive multifocal leukoencephalopathy. *Acta Neuropathol*. 2005;109:449–455.
178. Gheuens S, Ngo L, Wang X, et al. Metabolic profile of PML lesions in patients with and without IRIS: an observational study. *Neurology*. 2012;79:1041–1048.
179. Morgello S, Cho ES, Nielsen S, et al. Cytomegalovirus encephalitis in patients with acquired immunodeficiency syndrome: an autopsy study of 30 cases and a review of the literature. *Hum Pathol*. 1987;18:289–297.
180. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS clinical trials group 320 study team. *N Engl J Med*. 1997;337:725–733.
181. Arribas JR, Storch GA, Clifford DB, et al. Cytomegalovirus encephalitis. *Ann Intern Med*. 1996;125:577–587.
182. Cinque P, Vago L, Brytting M, et al. Cytomegalovirus infection of the central nervous system in patients with AIDS: diagnosis by DNA amplification from cerebrospinal fluid. *J Infect Dis*. 1992;166:1408–1411.
183. Holland NR, Power C, Mathews VP, et al. Cytomegalovirus encephalitis in acquired immunodeficiency syndrome (AIDS). *Neurology*. 1994;44:507–514.
184. Clifford DB, Arribas JR, Storch GA, et al. Magnetic resonance brain imaging lacks sensitivity for AIDS associated cytomegalovirus encephalitis. *J Neurovirol*. 1996;2:397–403.
185. Whitley RJ, Jacobson MA, Friedberg DN, et al. Guidelines for the treatment of cytomegalovirus diseases in patients with AIDS in the era of potent antiretroviral therapy: recommendations of an international panel. International AIDS Society—USA. *Arch Intern Med*. 1998;158:957–969.
186. Levy RM, Russell E, Yungbluth M, et al. The efficacy of image-guided stereotactic brain biopsy in neurologically symptomatic acquired immunodeficiency syndrome patients. *Neurosurgery*. 1992;30:186–190.
187. Holloway RG, Mushlin AI. Intracranial mass lesions in acquired immunodeficiency syndrome: using decision analysis to determine the effectiveness of stereotactic brain biopsy. *Neurology*. 1996;46:1010–1015.
188. Antinori A, Ammassari A, De Luca A, et al. Diagnosis of AIDS-related focal brain lesions: a decision-making analysis based on clinical and neuroradiologic characteristics combined with polymerase chain reaction assays in CSF. *Neurology*. 1997;48:687–694.
189. Antinori A, Ammassari A, Luzzati R, et al. Role of brain biopsy in the management of focal brain lesions in HIV-infected patients. Gruppo italiano cooperativo AIDS & tumori. *Neurology*. 2000;54:993–997.
190. Marra CM, Lockhart D, Zunt JR, et al. Changes in CSF and plasma HIV-1 RNA and cognition after starting potent antiretroviral therapy. *Neurology*. 2003;60: 1388–1390.
191. Petito CK, Navia BA, Cho ES, et al. Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1985;312: 874–879.
192. Henin D, Smith TW, De Girolami U, et al. Neuropathology of the spinal cord in the acquired immunodeficiency syndrome. *Hum Pathol*. 1992;23:1106–1114.
193. Dal Pan GJ, Glass JD, McArthur JC. Clinicopathologic correlations of HIV-1-associated vacuolar myelopathy: an autopsy-based case-control study. *Neurology*. 1994;44:2159–2164.
194. Geraci A, Di Rocco A, Liu M, et al. AIDS myelopathy is not associated with elevated HIV viral load in cerebrospinal fluid. *Neurology*. 2000;55:440–442.
195. Thurnher MM, Post MJ, Jinkins JR. MRI of infections and neoplasms of the spine and spinal cord in 55 patients with AIDS. *Neuroradiology*. 2000;42:551–563.
196. Rottnek M, Di Rocco A, Laudier D, et al. Axonal damage is a late component of vacuolar myelopathy. *Neurology*. 2002;58:479–481.
197. Shepherd EJ, Brettle RP, Liberski PP, et al. Spinal cord pathology and viral burden in homosexuals and drug users with AIDS. *Neuropathol Appl Neurobiol*. 1999;25:2–10.
198. Di Rocco A, Bottiglieri T, Werner P, et al. Abnormal cobalamin-dependent transmethylation in AIDS-associated myelopathy. *Neurology*. 2002;58:730–735.
199. Di Rocco A, Tagliati M, Danisi F, et al. A pilot study of L-methionine for the treatment of AIDS-associated myelopathy. *Neurology*. 1998;51:266–268.
199a. Di Rocco A, Werner P, Bottiglieri T, et al. Treatment of AIDS-associated myelopathy with L-methionine: a placebo-controlled study. *Neurology*. 2004;63: 1270–1275.
200. Staudinger R, Henry K. Remission of HIV myelopathy after highly active antiretroviral therapy. *Neurology*. 2000;54:267–268.
201. Eyer-Silva WA, Couto-Fernandez JC, Caetano MR, et al. Remission of HIV-associated myelopathy after initiation of lopinavir in a patient with extensive previous exposure to highly active antiretroviral therapy. *AIDS*. 2002;16: 2367–2369.
202. Feki I, Belahsen F, Ben Jemaa M, et al. Subacute myelitis revealed by human immunodeficiency virus infection. *Rev Neurol (Paris)*. 2003;159:577–580.
203. Gessain A, Gout O. Chronic myelopathy associated with human T-lymphotropic virus type I (HTLV-I). *Ann Intern Med*. 1992;117:933–946.
204. Berger JR, Sabet A. Infectious myelopathies. *Semin Neurol*. 2002;22:133–142.
205. Brannagan TH 3rd, Zhou Y. HIV-associated Guillain-Barre syndrome. *J Neurol Sci*. 2003;208:39–42.
206. Cornblath DR, McArthur JC, Kennedy PG, et al. Inflammatory demyelinating peripheral neuropathies associated with human T-cell lymphotropic virus type III infection. *Ann Neurol*. 1987;21:32–40.
207. Miller RG, Parry GJ, Pfaeffl W, et al. The spectrum of peripheral neuropathy associated with ARC and AIDS. *Muscle Nerve*. 1988;11:857–863.
208. Afzal A, Benjamin M, Gummelt KL, et al. Ascending paralysis associated with HIV infection. *Proc (Bayl Univ Med Cent)*. 2015;28:25–28.

209. Mochan A, Anderson D, Modi G. CIDP in a HIV endemic population: a prospective case series from Johannesburg, South Africa. *J Neurol Sci*. 2016;363: 39–42.
210. Piliero PJ, Fish DG, Preston S, et al. Guillain-Barre syndrome associated with immune reconstitution. *Clin Infect Dis*. 2003;36:111–114.
211. Morgello S, Simpson DM. Multifocal cytomegalovirus demyelinative polyneuropathy associated with AIDS. *Muscle Nerve*. 1994;17:176–182.
212. Leger JM, Bouche P, Bolgert F, et al. The spectrum of polyneuropathies in patients infected with HIV. *J Neurol Neurosurg Psychiatry*. 1989;52:1369–1374.
213. Kiprov D, Pfaeffl W, Parry G, et al. Antibody-mediated peripheral neuropathies associated with ARC and AIDS: successful treatment with plasmapheresis. *J Clin Apheresis*. 1988;4:3–7.
214. Schifitto G, McDermott MP, McArthur JC, et al. Incidence of and risk factors for HIV-associated distal sensory polyneuropathy. *Neurology*. 2002;58: 1764–1768.
215. Ellis RJ, Rosario D, Clifford DB, et al. Continued high prevalence and adverse clinical impact of human immunodeficiency virus-associated sensory neuropathy in the era of combination antiretroviral therapy: the CHARTER study. *Arch Neurol*. 2010;67:552–558.
216. Keswani SC, Pardo CA, Cherry CL, et al. HIV-associated sensory neuropathies. *AIDS*. 2002;16:2105–2117.
217. Evans SR, Ellis RJ, Chen H, et al. Peripheral neuropathy in HIV: prevalence and risk factors. *AIDS*. 2011;25:919–928.
218. Anziska Y, Helzner EP, Crystal H, et al. The relationship between race and HIV-distal sensory polyneuropathy in a large cohort of US women. *J Neurol Sci*. 2012;315:129–132.
219. Chen H, Clifford DB, Deng L, et al. Peripheral neuropathy in ART-experienced patients: prevalence and risk factors. *J Neurovirol*. 2013;19:557–564.
220. Malvar J, Vaida F, Sanders CF, et al; CHARTER group. Predictors of new-onset distal neuropathic pain in HIV-infected individuals in the era of combination antiretroviral therapy. *Pain*. 2015;156:731–739.
221. Kallianpur AR, Jia P, Ellis RJ, et al; CHARTER study group. Genetic variation in iron metabolism is associated with neuropathic pain and pain severity in HIV-infected patients on antiretroviral therapy. *PLoS ONE*. 2014;9:e103123.
222. Robinson-Papp J, Sharma S, Simpson DM, et al. Autonomic dysfunction is common in HIV and associated with distal symmetric polyneuropathy. *J Neurovirol*. 2013;19:172–180.
223. Zhou L, Kitch DW, Evans SR, et al. Correlates of epidermal nerve fiber densities in HIV-associated distal sensory polyneuropathy. *Neurology*. 2007;68:2113–2119.
224. Bradley WG, Shapshak P, Delgado S, et al. Morphometric analysis of the peripheral neuropathy of AIDS. *Muscle Nerve*. 1998;21:1188–1195.
225. Rance NE, McArthur JC, Cornblath DR, et al. Gracile tract degeneration in patients with sensory neuropathy and AIDS. *Neurology*. 1988;38:265–271.
226. Tyor WR, Wesselingh SL, Griffin JW, et al. Unifying hypothesis for the pathogenesis of HIV-associated dementia complex, vacuolar myelopathy, and sensory neuropathy. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1995;9:379–388.
227. Herzberg U, Sagen J. Peripheral nerve exposure to HIV viral envelope protein gp120 induces neuropathic pain and spinal gliosis. *J Neuroimmunol*. 2001;116: 29–39.
228. Browne MJ, Mayer KH, Chafee SB, et al. 2',3'-didehydro-3'-deoxythymidine (d4T) in patients with AIDS or AIDS-related complex: a phase I trial. *J Infect Dis*. 1993;167:21–29.
229. Pollard RB, Peterson D, Hardy D, et al. Safety and antiretroviral effects of combined didanosine and stavudine therapy in HIV-infected individuals with CD4 counts of 200 to 500 cells/mm3. *J Acquir Immune Defic Syndr*. 1999;22:39–48.
230. Berger AR, Arezzo JC, Schaumburg HH, et al. 2',3'-dideoxycytidine (ddC) toxic neuropathy: a study of 52 patients. *Neurology*. 1993;43:358–362.
231. Brew BJ, Tisch S, Law M. Lactate concentrations distinguish between nucleoside neuropathy and HIV neuropathy. *AIDS*. 2003;17:1094–1096.
232. Paice JA, Ferrans CE, Lashley FR, et al. Topical capsaicin in the management of HIV-associated peripheral neuropathy. *J Pain Symptom Manage*. 2000;19:45–52.
233. Simpson DM, Brown S, Tobias J, et al. Controlled trial of high-concentration capsaicin patch for treatment of painful HIV neuropathy. *Neurology*. 2008;70: 2305–2313.
234. Dorfman D, Dalton A, Khan A, et al. Treatment of painful distal sensory polyneuropathy in HIV-infected patients with a topical agent: results of an open-label trial of 5% lidocaine gel. *AIDS*. 1999;13: 1589–1590.
235. La Spina I, Porazzi D, Maggiolo F, et al. Gabapentin in painful HIV-related neuropathy: a report of 19 patients, preliminary observations. *Eur J Neurol*. 2001;8:71–75.
236. Simpson DM, Rice AS, Emir B, et al. A randomized, double-blind, placebo-controlled trial and open-label extension study to evaluate the efficacy and safety of pregabalin in the treatment of neuropathic pain associated with human immunodeficiency virus neuropathy. *Pain*. 2014;155:1943–1954.
237. Simpson DM, McArthur JC, Olney R, et al. Lamotrigine for HIV-associated painful sensory neuropathies: a placebo-controlled trial. *Neurology*. 2003;60:1508–1514.
238. Kieburtz K, Simpson D, Yiannoutsos C, et al. A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. *Neurology*. 1998;51:1682–1688.
239. Mendell JR, Sahenk Z. Clinical practice: painful sensory neuropathy. *N Engl J Med*. 2003;348:1243–1255.
240. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology*. 2007;68: 515–521.
241. Phillips TJ, Cherry CL, Cox S, et al. Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. *PLoS ONE*. 2010;5:e14433.
242. Simpson DM. Selected peripheral neuropathies associated with human immunodeficiency virus infection and antiretroviral therapy. *J Neurovirol*. 2002;8:33–41.
243. Gonzalez-Duarte A, Robinson-Papp J, Simpson DM. Diagnosis and management of HIV-associated neuropathy. *Neurol Clin*. 2008;26:821–832.
244. Famularo G, Moretti S, Marcellini S, et al. Acetyl-carnitine deficiency in AIDS patients with neurotoxicity on treatment with antiretroviral nucleoside analogues. *AIDS*. 1997;11:185–190.
245. Simpson DM, Katzenstein D, Haidich B, et al. Plasma carnitine in HIV-associated neuropathy. *AIDS*. 2001;15:2207–2208.
246. Simpson DM, Olney RK. Peripheral neuropathies associated with human immunodeficiency virus infection. *Neurol Clin*. 1992;10:685–711.
247. Stricker RB, Sanders KA, Owen WF, et al. Mononeuritis multiplex associated with cryoglobulinemia in HIV infection. *Neurology*. 1992;42:2103–2105.
248. Said G, Lacroix C, Chemouilli P, et al. Cytomegalovirus neuropathy in acquired immunodeficiency syndrome: a clinical and pathological study. *Ann Neurol*. 1991;29:139–146.
249. Schifitto G, Barbano RL, Kieburtz KD, et al. HIV related vasculitic mononeuropathy multiplex: a role for IVIg? *J Neurol Neurosurg Psychiatry*. 1997;63: 255–256.
250. Kolson DL, Gonzalez-Scarano F. HIV-associated neuropathies: role of HIV-1, CMV, and other viruses. *J Peripher Nerv Syst*. 2001;6:2–7.
251. So YT, Olney RK. Acute lumbosacral polyradiculopathy in acquired immunodeficiency syndrome: experience in 23 patients. *Ann Neurol*. 1994;35:53–58.
252. de Gans J, Portegies P, Tiessens G, et al. Therapy for cytomegalovirus polyradiculomyelitis in patients with AIDS: treatment with ganciclovir. *AIDS*. 1990;4: 421–425.
253. McCutchan JA. Cytomegalovirus infections of the nervous system in patients with AIDS. *Clin Infect Dis*. 1995;20:747–754.
254. Smith IL, Shinkai M, Freeman WR, et al. Polyradiculopathy associated with ganciclovir-resistant cytomegalovirus in an AIDS patient: phenotypic and genotypic characterization of sequential virus isolates. *J Infect Dis*. 1996;173:1481–1484.
255. Authier FJ, Gheradi RK. Peripheral neuropathies in HIV-infected patients in the era of HAART. *Brain Pathol*. 2003;13:223–228.
256. Moulignier A, Authier FJ, Baudrimont M, et al. Peripheral neuropathy in human immunodeficiency virus-infected patients with the diffuse infiltrative lymphocytosis syndrome. *Ann Neurol*. 1997;41: 438–445.
257. Gherardi RK, Chretien F, Delfau-Larue MH, et al. Neuropathy in diffuse infiltrative lymphocytosis syndrome: an HIV neuropathy, not a lymphoma. *Neurology*. 1998;50:1041–1044.
258. Basu D, Williams FM, Ahn CW, et al. Changing spectrum of the diffuse infiltrative lymphocytosis syndrome. *Arthritis Rheum*. 2006;55:466–472.
259. Moulignier A, Moulonguet A, Pialoux G, et al. Reversible ALS-like disorder in HIV infection. *Neurology*. 2001;57:995–1001.
260. MacGowan DJ, Scelsa SN, Waldron M, et al. Like syndrome with new HIV infection and complete response to antiretroviral therapy. *Neurology*. 2001;57: 1094–1097.
261. Verma A, Berger JR. ALS syndrome in patients with HIV-1 infection. *J Neurol Sci*. 2006;240: 59–64.
262. MacGowan DJ, Scelsa SN, Imperato TE, et al. A controlled study of reverse transcriptase in serum and CSF of HIV-negative patients with ALS. *Neurology*. 2007;68:1944–1946.
263. McCormick AL, Brown RH Jr, Cudkowicz ME, et al. Quantification of reverse transcriptase in ALS and elimination of a novel retroviral candidate. *Neurology*. 2008;70:278–283.
264. Zoccolella S, Carbonara S, Minerva D, et al. A case of concomitant amyotrophic lateral sclerosis and HIV infection. *Eur J Neurol*. 2002;9:180–182.
265. Jubelt B, Berger JR. Does viral disease underlie ALS? Lessons from the AIDS pandemic. *Neurology*. 2001;57:945–946.
266. Johnson RW, Williams FM, Kazi S, et al. Human immunodeficiency virus-associated polymyositis: a longitudinal study of outcome. *Arthritis Rheum*. 2003;49:172–178.
267. Simpson DM, Citak KA, Godfrey E, et al. Myopathies associated with human immunodeficiency virus and zidovudine: can their effects be distinguished? *Neurology*. 1993;43:971–976.
268. Hiniker A, Daniels BH, Margeta M. T-cell-mediated inflammatory myopathies in HIV-positive individuals: A histologic study of 19 cases. *J Neuropathol Exp Neurol*. 2016;75:239–245.
269. Illa I, Nath A, Dalakas M. Immunocytochemical and virological characteristics of HIV-associated inflammatory myopathies: similarities with seronegative polymyositis. *Ann Neurol*. 1991;29:474–481.
270. Lloyd TE, Pinal-Fernandez I, Michelle EH, et al. Overlapping features of polymyositis and inclusion body myositis in HIV-infected patients. *Neurology*. 2017;88:1454–1460.
271. Peters BS, Winer J, Landon DN, et al. Mitochondrial myopathy associated with chronic zidovudine therapy in AIDS. *Q J Med*. 1993;86:5–15.
272. Dalakas MC, Illa I, Pezeshkpour GH, et al. Mitochondrial myopathy caused by long-term zidovudine therapy. *N Engl J Med*. 1990;322:1098–1105.
273. Grau JM, Masanes F, Pedrol E, et al. Human immunodeficiency virus type 1 infection and myopathy: clinical relevance of zidovudine therapy. *Ann Neurol*. 1993;34:206–211.
274. Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother*. 2002;36:288–295.
275. Hare CB, Vu MP, Grunfeld C, et al. Simvastatin-nelfinavir interaction implicated in rhabdomyolysis and death. *Clin Infect Dis*. 2002;35:e111–e112.
276. Torriani M, Hadigan C, Jensen ME, et al. Psoas muscle attenuation measurement with computed tomography indicates intramuscular fat accumulation in patients with the HIV-lipodystrophy syndrome. *J Appl Physiol*. 2003;95:1005–1010.
277. Florence E, Schrooten W, Verdonck K, et al. Rheumatological complications associated with the use of indinavir and other protease inhibitors. *Ann Rheum Dis*. 2002;61:82–84.
278. Modi G, Modi M, Martinus I, et al. New-onset seizures associated with HIV infection. *Neurology*. 2000;55: 1558–1561.
279. Birbeck GL, French JA, Perucca E, et al. Evidence-based guideline: antiepileptic drug selection for people with HIV/AIDS: report of the quality standards subcommittee of the American Academy of Neurology and the Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy. *Neurology*. 2012;78:139–145.
280. Siddiqi O, Birbeck GL. Safe treatment of seizures in the setting of HIV/AIDS. *Curr Treat Options Neurol*. 2013;15:529–543.
281. Langford TD, Letendre SL, Larrea GJ, et al. Changing patterns in the neuropathogenesis of HIV during the HAART era. *Brain Pathol*. 2003;13:195–210.
282. Langford TD, Letendre SL, Marcotte TD, et al. Severe, demyelinating leukoencephalopathy in AIDS patients on antiretroviral therapy. *AIDS*. 2002;16: 1019–1029.
283. Du Pasquier RA, Corey S, Margolin DH, et al. Productive infection of cerebellar granule cell neurons by JC virus in an HIV+ individual. *Neurology*. 2003;61: 775–782.
284. Vinikoor MJ, Napravnik S, Floris-Moore M, et al. Incidence and clinical features of cerebrovascular disease among HIV-infected adults in the southeastern

United States. *AIDS Res Human Retroviruses*. 2013;29:1068–1074.
285. Tipping B, de Villiers L, Wainwright H, et al. Stroke in patients with human immunodeficiency virus infection. *J Neurol Neurosurg Psychiatry*. 2007;78:1320–1324.
286. Hood JE, Golden MR, Hughes JP, et al. Projected demographic composition of the United States population of people living with diagnosed HIV. *AIDS Care*. 2017;29:1543–1550.
287. Morgello S, Mahboob R, Yakoushina T, et al. Autopsy findings in a human immunodeficiency virus-infected population over 2 decades: influences of gender, ethnicity, risk factors, and time. *Arch Pathol Lab Med*. 2002;126:182–190.
288. Goodkin K, Wilkie FL, Concha M, et al. Aging and neuro-AIDS conditions and the changing spectrum of HIV-1–associated morbidity and mortality. *J Clin Epidemiol*. 2001;54:S35–S43.
289. Milanini B, Valcour V. Differentiating HIV-associated neurocognitive disorders from Alzheimer's disease: an emerging issue in geriatric neuroHIV. *Curr HIV/AIDS Rep*. 2017;14:123–132.
290. Valcour V, Shikuma C, Shiramizu B, et al. Higher frequency of dementia in older HIV-1 individuals: the Hawaii Aging with HIV-1 Cohort. *Neurology*. 2004;63:822–827.
291. Valcour VG, Shikuma CM, Shiramizu BT, et al. Diabetes, insulin resistance, and dementia among HIV-1-infected patients. *J Acquir Immune Defic Syndr*. 2005;38:31–36.
292. McMurtray A, Nakamoto B, Shikuma C, et al. Cortical atrophy and white matter hyperintensities in HIV: the Hawaii Aging with HIV Cohort Study. *J Stroke Cerebrovasc Dis*. 2008;17:212–217.

126 Human Immunodeficiency Virus Infection in Women

Susan E. Cohn, Catherine A. Chappell, and Monica Gandhi

Human immunodeficiency virus (HIV) infection has had a profound impact on the health of women worldwide. By the end of 2016, 52% of the more than 36.7 million people living with HIV infection were women.[1] HIV infection and resultant acquired immunodeficiency syndrome (AIDS) are the leading causes of death among women in their reproductive years (ages 15–49).[2] Sub-Saharan Africa remains the most severely affected region, with nearly 1 in 20 adults (4.9%) living with HIV infection (more than half of whom are women) and accounting for 69% of all people living with HIV infection worldwide.[2] In the United States, 7% of all cases of AIDS reported as of 1985 occurred in women; this proportion increased to 26% of all AIDS cases newly diagnosed in 2001; by 2015, 19% of all new HIV diagnoses were among women.[3]

With the advent of increasing access to potent HIV antiretroviral therapy (ART) worldwide, new HIV infection rates have decreased overall and by 50% or more in many countries including in sub-Saharan Africa.[2] However, there were profound differences in infection rates among young men and women in 2016; new infections among women ages 15 to 24 years were 44% higher than rates among men in the same age group.[2] Although all people infected with HIV continue to face stigma, discrimination, and injustice, factors such as gender inequity, differential access to health service, and sexual violence are particularly prominent hardships among women.[2] This chapter discusses the epidemiology of HIV infection in women, transmission of HIV to women, prevention of heterosexual HIV transmission, pregnancy and risk for perinatal transmission, and clinical manifestations and management issues for women infected with HIV.

EPIDEMIOLOGY

Epidemiology in the United States

Risk Factors for and Changing Patterns of Transmission

When AIDS was first recognized in 1981,[4] it was considered to be a disease of men who have sex with men (MSM) and of injection drug users. However, with the rapid increase in the number of women infected with HIV in the United States and globally, heterosexual transmission of HIV has emerged as the most common risk factor for HIV infection worldwide. By 2001, women accounted for 26% of new AIDS diagnoses (11,164 of 43,158 cases), 18% of the 816,149 cumulative AIDS cases, and 32% of newly reported HIV diagnoses (11,394 of 35,575 cases) in the United States. Since then, annual HIV diagnoses have declined 20% among women from 2010 to 2014; in 2015 women made up 19% (7402) of the 39,513 new HIV diagnoses.[5] Overall, per the Centers for Disease Control and Prevention (CDC), women represented 20% (248,270) of the 1,216,917 cumulative AIDS diagnoses in the United States from the beginning of the epidemic through the end of 2015.[3]

Heterosexual contact has become the predominant mode of exposure for women in the United States, accounting for 86% of new HIV infections among women in the United States in 2015.[5] Cases associated with injection drug use among women have declined since 1992, with 13% of cases now attributed to injection drug use. However, there are racial and ethnic disparities in types of transmission risk among women throughout the United States, with overall higher rates of transmission due to injection drug use in 2015 among white women (32%).[3] Most new HIV infections in the United States continue to occur through male-to-male sexual contact (70% in 2016), but increases in HIV incidence among young African-American and Hispanic gay and bisexual men may be helping to drive the ongoing epidemic in women.[5] For instance, in a large study of African-American men who have sex with men and women in three cities (Chicago, Philadelphia, Los Angeles), 39% of the sample (584 men) were HIV-positive.[6] Of men who were HIV-positive, 46% reported sex without condoms with HIV-negative or unknown male partners and 45% with HIV-negative or unknown female partners.

Bisexual activity in men who do not identify as gay or disclose their bisexual activities has been labeled as "on the down low" activity.[7] Another study among men who have sex with men and women (MSMW) found differences in sexual behaviors compared with men who have sex with men only (MSMO).[8] This study was conducted among MSM who participated in the National HIV Behavioral Surveillance study and included 2042 (11.9%) participants who identified as MSMW. Compared with MSMO, MSMW had higher numbers of sexual partners, higher numbers of casual partners, higher rates of sex without condoms, and higher rates of sexually transmitted infections (STIs) and were more likely to engage in transactional sex for either money or drugs. Therefore tailored interventions to reduce HIV risk behavior among MSMW may have implications for reducing HIV transmission rates among women.[3]

Female-to-female sexual transmission of HIV remains exceedingly rare.[9] In populations of women with HIV infection who report having sexual contact only with women, most have had a secondary risk factor such as injection drug use.[9] In a study published in 1995 of 498 lesbian and bisexual women frequenting public venues in San Francisco and Berkeley, California, 6 (1.2%) were HIV infected.[10] This population showed high rates of high-risk behaviors (10% reported injection drug use, and 40% reported unprotected sex with men, some of whom were bisexual men and male injection drug users), and no evidence of sexual transmission between women was found. These data and other more recent studies suggest that the frequency of female-to-female HIV transmission remains very low.[9]

The epidemic of drug use continues to influence HIV risk among women in the United States, despite the fact that injection drug use plays a less prominent role in the spread of infection now than in the past. In 1996, after exclusion of the 24% of women whose initial mode of transmission was not reported, 45% of women with AIDS reported injection drug use or heterosexual contact with an injection drug user (18%).[11] By 2001, after excluding the 42% of women without a reported risk behavior, only one-third of women with newly diagnosed AIDS reported injection drug use, and 14% reported heterosexual contact with an injection drug user.[12] By 2015, the percentage of HIV infections attributed to injection drug use was highest among white women (32%), but the overall rates of transmission among women due to injection drugs are now at an all-time low at 13%.[13]

Needle exchange programs have long been known to decrease spread of HIV among intravenous drug users and are a powerful tool to combat new infections in the context of the recently declared opioid epidemic in the United States.[13] In 2015, in Austin, Indiana, a rural town of about 4000 residents with an historically very low prevalence of HIV infection, almost 200 individuals were found to be newly infected with HIV as a result of injection of oxymorphone.[14] A public health emergency was declared, and following national media exposure and a CDC-led investigation,[15] the state expanded free HIV and hepatitis C virus testing and partner services, established local HIV treatment services, and provided immediate access to health insurance. Through an executive