Immune Reconstitution in HIV-Infected Patients

Hans H. Hirsch,[1,2] Gilbert Kaufmann,[1] Pedram Sendi,[1,3] and Manuel Battegay[1]

[1]Division of Infectious Diseases and Institutes for [2]Medical Microbiology and [3]Clinical Epidemiology, University Hospital Basel, Switzerland

The prognosis of patients infected with human immunodeficiency virus (HIV) type 1 has dramatically improved since the advent of potent antiretroviral therapies (ARTs), which have enabled sustained suppression of HIV replication and recovery of CD4 T cell counts. Knowledge of the function of CD4 T cells in immune reconstitution was derived from large clinical studies demonstrating that primary and secondary prophylaxis against infectious agents, such as *Pneumocystis jirovecii (Pneumocystis carinii), Mycobacterium avium* complex, cytomegalovirus, and other pathogens, can be discontinued safely once CD4 T cell counts have increased beyond pathogen-specific threshold levels (usually >200 CD4 T cells/mm^3) for 3–6 months. The downside of immune reconstitution is an inflammatory syndrome occurring days to months after the start of ART, with outcomes ranging from minimal morbidity to fatal progression. This syndrome can be elicited by infectious and noninfectious antigens. Microbiologically, the possible pathogenic pathways involve recognition of antigens associated with ongoing infection or recognition of persisting antigens associated with past (nonreplicating) infection. Specific antimicrobial therapy, nonsteroidal anti-inflammatory drugs, and/or steroids for managing immune reconstitution syndrome should be considered.

The hallmark of HIV disease is the continuous depletion of CD4 T cells, leading to progressive immunodeficiency, opportunistic diseases, and death [1]. Despite the fact that CD4 T cells function at a pathogen-specific level that is not yet assessable in the clinical routine, a clear inverse relationship exists between the number of CD4 T cells in the patient's peripheral blood and their risk of opportunistic infection. Thus, in asymptomatic HIV-infected patients, total CD4 T cell counts provide a major criterion for initiating primary prophylaxis against opportunist illness, such as *Pneumocystis jirovecii* (also known as *Pneumocystis carinii*) pneumonia (if the CD4 T cell count is <200 cells/mm^3) and disseminated *Mycobacterium avium* complex infection (if the CD4 T cell count is <50 cells/mm^3) [2]. Conversely, an increase in CD4 T cell count after the suppression of HIV replication by antiretroviral therapy (ART) correlates with improved T cell responses to antigens and mitogens [3, 4] and adequate protection against specific opportunistic infections, allowing discontinuation of primary and secondary prophylaxis in clinical practice [5–9]. Thus, plasma HIV load and peripheral CD4 T cell count represent surrogate markers for assessing the risk of AIDS, as well as the need for ART and/or prophylaxis [7, 10].

RECOVERY OF CD4 T CELL COUNTS

Recent studies indicate that CD4 T cell recovery is sustained for ⩾3–4 years in individuals with advanced HIV-1 infection who receive ART [11, 12]. After an initial rapid increase in CD4 T lymphocyte counts within the first 3–6 months of ART, a second phase of slower increase occurs in most patients [13]. However, considerable individual variation has been noted in this response. In fact, CD4 T cell counts may remain below the critical threshold of 200 cells/mm^3 in 10%–20% of treated individuals [12]. Several factors are associated with impaired CD4 T cell reconstitution, including older age, nonsuppressed HIV replication, and treatment interruption [7, 12]. In general, the lower the CD4 T cell count at the initiation of ART, the longer it takes to reach desired target levels [14, 15]. Certain investigations even suggest that CD4 T cell recovery may level off before the physiological range is reached, particularly in individuals who begin ART when their CD4 T cell counts are extremely low (i.e., <50 cells/mm^3) [15, 16]. Conversely, early initiation of ART during primary HIV-1 infection may not only

Received 14 August 2003; accepted 15 December 2003; electronically published 5 April 2004.

Reprints or correspondence: Dr. Manuel Battegay, Div. of Infectious Diseases, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland (mbattegay@uhbs.ch).

Clinical Infectious Diseases 2004;38:1159–66

1058-4838/2004/3808-0020$15.00

preserve but also rapidly restore memory and naive CD4 T cells, which are crucial for the rate and the range of the adaptive immune response [15]. These observations should be taken into account when counseling the patient with respect to the start of ART [17–19].

RECOVERY OF PATHOGEN-SPECIFIC CD4 T CELL FUNCTION

In the late 1990s, it became evident that ART resulted not only in a numerical increase in CD4 T cells, but also in a functional immune reconstitution [3, 4]. Qualitative and quantitative recovery of pathogen-specific cellular and humoral responses has been demonstrated for a number of agents, including mycobacteria, cytomegalovirus, Epstein-Barr virus, hepatitis B virus (HBV) and hepatitis C virus (HCV), and *Candida albicans* [3, 20–22]. Improvements in pathogen-specific immune responses to HBV and HCV are illustrated by seroconversion to anti-HCV–positive or anti-Hbe–positive states and by clearance of hepatitis [23–25]. With the possible exception of delayed-type hypersensitivity skin testing for particular antigens, the more sophisticated assays that measure cytokine concentration, lymphoproliferation, specific T cell receptors, or cytotoxicity have not yet entered clinical routine and/or are lacking clinical validation. In the clinical arena, randomized, open clinical studies, as well as prospective cohorts, have demonstrated that stopping primary prophylaxis for *P. jirovecii* is safe in patients with CD4 T cell counts that are stably reconstituted to >200 cells/mm^3 for >6 months [9, 26–31]. This same conclusion was reached for *M. avium* complex in patients with CD4 T cell counts of >100 cells/mm^3 for >3 months, according to 2 randomized, blinded trials and a cohort study in which disease occurred in only 2 of 863 patients during a follow-up period of $\geqslant$1 year [32–34].

Immunologically and clinically more challenging is the discontinuation of secondary prophylaxis, particularly when it concerns pathogens with a propensity for latent infection in vulnerable sites (e.g., cytomegalovirus or *Toxoplasma gondii,* which have a propensity for latent infection in the CNS). For *P. jirovecii,* Lopez et al. [30] demonstrated in a prospective trial involving 113 individuals with a median follow-up period of 12 months that interruption of secondary prophylaxis is safe. No case of *P. jirovecii* pneumonia was observed among the 60 patients who had CD4 T cell counts of >200 cells/mm^3 for >3 months and virus loads of <5000 copies/mL (no incidents per 100 person-years; 95% CI, 0–4.57) [30]. Similar results were obtained from a large observational study [35] that analyzed the data of 8 European HIV databases (no incidents per 100 person-years; 95% CI, 0–1.3). For *Cryptococcus neoformans*, a prospective randomized trial confirmed that discontinuation of secondary prophylaxis after adequate treatment for cryptococcal meningitis is safe in patients who had CD4 T cell counts of >100 cells/mm^3 and HIV loads of <50 copies/mL for >3 months [36].

For cytomegalovirus retinitis, observational studies and case series indicate that secondary prophylaxis can be safely discontinued provided that the disease is determined to no longer be active by repeated ophthalmologic examination and a sustained CD4 T cell increase to levels ranging from >100 cells/mm^3 to >150 cells/mm^3 for >6 months has been documented [37–43]. In these studies, the inclusion criteria regarding CD4 T cell thresholds and/or increases varied considerably, from 50–150 cells/mm^3, with nadirs ranging from 10–42 cells/mm^3. However, there were only 2 cases of cytomegalovirus disease among >200 patients studied [37–43]. In the comprehensive study by Kirk et al. [43], interruption of maintenance therapy against previous infection with 4 common HIV-associated opportunistic pathogens was investigated. In this observational study, 358 patients who were receiving ART and who had CD4 T cell counts of >50 cells/mm^3 interrupted secondary prophylaxis. A total of 379 episodes were analyzed (162 episodes of cytomegalovirus disease, 103 episodes of *M. avium* complex infection, 75 episodes of toxoplasmosis, and 39 episodes of cryptococcosis). Only 5 patients experienced a relapse during 781 person-years of follow-up; 2 patients had cytomegalovirus disease, 2 patients had *M. avium* complex infection, and 1 patient had toxoplasmosis [43]. Few of these events occurred at CD4 T cell counts greater than the respective thresholds. The overall incidence of recurrent disease was calculated per 100 person-years as follows: cytomegalovirus, 0.54 (95% CI, 0.07–1.95); *M. avium* complex, 0.90 (95% CI, 0.11–3.25); toxoplasmosis, 0.84 (95% CI, 0.02–4.68); and cryptococcosis, 0.0 (95% CI, 0.00–5.27) [43]. Discontinuation of antifungal therapy for disseminated histoplasmosis after ART was investigated in 32 patients with CD4 T cell counts of >150 cells/mm^3 (median CD4 T cell count, 289 cells/mm^3). No relapse of disseminated histoplasmosis was observed (95% CI, 4.6 incidents per 100 person years) [44], indicating that discontinuation of antifungal treatment for disseminated histoplasmosis is safe in this setting. In summary, the current recommendations for discontinuing secondary prophylaxis require completion of initial therapy, inactive disease, and stable CD4 T cell counts greater than pathogen-related thresholds. For patients with *P. jirovecii* infection and toxoplasmosis, a CD4 T cell count of >200 cells/mm^3 for $\geqslant$3 months is recommended; for patients with *M. avium* complex infection, cytomegalovirus disease, and cryptococcosis, a CD4 T cell count of >100 cells/mm^3 for $\geqslant$6 months is recommended (guidelines are available at http://www.aidsinfo.nih.gov/guidelines/). However, CD4 T cell counts have to be monitored so that prophylaxis can be reinitiated if decreasing values are noted. Although there are no data specifically addressing this issue, reinitiation of prophylaxis uses the same thresholds as primary prophylaxis. As a note of caution,

Table 1. Review of immune reconstitution syndrome, by pathogen.

Pathogen	Manifestation	Management	Reference(s)
Mycobacterium avium complex	Skin, focal lymphadenitis, pulmonary infiltrates, mediastinitis, liver granuloma, osteomyelitis, cerebritis	Continue ART; antibiotics (steroids)	[52–60]
Mycobacterium tuberculosis	Pneumonitis, adult respiratory distress syndrome, lymphadenitis, hepatitis, CNS tuberculosis, gut perforation, renal failure, epididymitis	Continue ART; antibiotics (steroids)	[61–66, 103–106]
Mycobacterium leprae	Cutaneous lesions	Continue ART; dapsone	[67]
Cryptococcus species	Meningitis, palsy, hearing loss, abscess, mediastinitis, lymphadenitis	Continue ART; steroids; antifungals	[68–73]
Pneumocystis jirovecii	Pneumonitis	Continue ART; steroids; antibiotics	[74, 75]
Histoplasma species	Lymph node granuloma	Continue ART; antifungals	[46]
Hepatitis B and C viruses	Hepatitis	Continue or discontinue ART; IFN[a]	[20]
JC virus	Contrast-enhanced CNS lesions, inflammatory infiltrates on biopsy	Continue ART; steroids; cidofovir[a]	[76–78]
BK virus	Hemorrhagic cystitis	Continue ART; symptomatic therapy	[50, 51, 79]
Herpes simplex virus	Chronic erosive ulcera, encephalomyelits	Continue ART; antivirals[a]; steroids[a]	[80]
Varicella-zoster virus	Zoster flares, sine herpete flares	Continue ART; antivirals; steroids[a]	[81]
Cytomegalovirus	Vitritis, cystoid macular edema, uveitis, vitreomacular traction	Continue ART; IVIG; steroids; vitrectomy; antivirals	[82]
Kaposi human herpes virus–8	Tracheal mucosal edema, obstruction	Discontinue ART; clear airway; steroids	[4]
Papillomavirus	Inflamed warts, mollusca contagiosa	Steroids[a]; surgical[a]	[83]
Parvovirus B19	Focal encephalitis	IVIG; discontinue ART	[76]
HIV	Demyelinating leukoencephalopathy	Steroids[a]; discontinue ART	[49]
Chlamydia trachomatis	Reiter syndrome, urethritis, balanitis circinata, arthritis, hemorrhagic conjunctivitis	Doxycyline	[84]
Unknown	Guillain-Barré syndrome	Plasmapheresis; IVIG	[85]
Unknown	Sarcoidosis	Steroids[a]	[86–89]
Unknown	Appendicitis	Surgical	[90]

NOTE. ART, antiretroviral therapy; IVIG, intravenous immunoglobulin.

[a] Indicates uncertain benefit in some of the patients with the specified complication and may require individual decisions.

CD4 T cell thresholds are not absolute, but are only intended to provide guidance. This is illustrated by data from the Swiss HIV Cohort Study of patients with toxoplasmic encephalitis. Of these patients, 7% were determined to have had CD4 T cell counts of >200 cells/mm^3 (which is the threshold recommended by the Swiss guidelines), and 19.4% were determined to have had CD4 T cell counts of >100 cells/mm^3 (which is the threshold recommended by the US guidelines) [45].

IMMUNE RECONSTITUTION SYNDROME (IRS)

IRS is recognized as a potential complication that can occur after potent ART [46]. The frequency of IRS has not been reported conclusively, but it may be estimated to occur in 10%–25% of patients who receive ART [47]. However, the first cases of *M. avium*–associated IRS were reported to have occurred after administration of zidovudine monotherapy [48]. Mycobacterial antigens are frequently implicated in IRS, and together they represent almost one-third of all reported cases [20]. Other infectious agents that are frequently associated with IRS include *C. neoformans,* cytomegalovirus, and HBV and HCV. More recently, it has been proposed that HIV-mediated IRS mediates a novel form of severe demyelinating leucoencephalopathy in the CNS [49]. Also, a role for BK virus–targeted IRS might account for cases of hemorrhagic cystitis, as discussed elsewhere [50, 51]. Table 1 summarizes manifestations associated with different microbes and the reported management of those manifestations.

The onset of IRS is characterized by paradoxical worsening of clinical or laboratory parameters despite "favorable" development of the HIV surrogate markers [63]. In the affected patients, CD4 T cell counts are often <50 cells/mm^3 at the start of ART and subsequently increase >2–4 fold during the 12 months after initiation of ART, and a significant decrease in HIV load of >2 $\log_{10}$ copies/mL is often noted [4, 20]. However, initial experience of IRS occurring after zidovudine monotherapy suggests that small breaks of HIV replication may already be sufficient for IRS to occur in response to some particular antigens [48]. The interval between the start of ART and the onset of IRS is highly variable, ranging from <1 week to several months, but the majority of events occur within the first 8 weeks after ART initiation [4, 20, 47] and occur in

Table 2. Recommended management of immune reconstitution syndrome.

Variable	Management
Differential pathogenesis	
Unmasking and/or recognition of ongoing infections	Antimicrobial therapy
Reconstituting immune reaction to nonreplicating antigens	No antimicrobial therapy
Differential diagnosis	
Drug toxicity	Stop and/or modify antiretroviral or antimicrobial therapy
Drug failure	Restart and/or adapt antimicrobial treatment
Treatment	NSAIDs, steroids (timing, dosing, duration),[a] intravenous immunoglobulins,[a] thalidomide[a]

NOTE. NSAIDs, nonsteroidal anti-inflammatory drugs.

[a] Indicates uncertain benefit in some of the patients with the specified complication and may require individual decisions.

patients with low mean CD4 T cell counts [47]. In vitro characterization suggested that reconstitution occurred earlier in response to antigens of ubiquitous or abundant exposure, compared with antigens of low exposure (such as tetanus toxoid), and that earlier reconstitution correlated with an increase in memory CD4 T cells [3, 91]. Of note, HIV-specific immunity is not adequately reconstituted in most patients [92], a fact underscored by recent reports of HIV superinfection [93–95].

IRS may arise in 2 different settings, depending on whether ART was started in a patient treated for ongoing opportunistic infection or in a clinically stable patient with or without requiring primary prophylaxis. For patients with active infection and antimicrobial treatment for *P. jirovecii* or *Mycobacterium tuberculosis*, for example, some clinicians may choose to defer ART by 1–3 weeks to avoid high pill counts, cumulating toxicity, and possibly IRS. If IRS occurs in such patients, the differential diagnosis includes failure of the antimicrobial therapy; manifestation of a new opportunistic infection; unmasking of an ongoing, previously undiagnosed infection; or manifestation of a diagnosed, ongoing infection in a previously unrecognized site of involvement. Although discontinuing ART has to be considered (table 1), most clinicians prefer to continue ART if the CD4 T cell counts are <100 cells/mm^3 or if IRS manifests months after ART has been initiated. There are no clear guidelines on when to stop ART. As gathered from anecdotal reports, ART is more readily discontinued if inflammatory responses are considered life-threatening, the responses are not amenable to steroids, and the pathogens involved are not controllable by specific antimicrobial treatments (as exemplified by IRS in response to parvovirus B19 or polyomavirus JC [78, 96]), or if ART toxicity was the main differential diagnosis (e.g., as in hepatitis).

An increase in transaminase levels after the initiation of ART is observed in 1%–5% of patients and is associated with coinfection with HBV and/or HCV [97–99]. A recent study of 915 adverse events that occurred among 755 patients who were receiving ART identified severe hepatotoxicity in 26 (3.4%) of the patients (incidence, 4.2 adverse events per 100 person-years), with risk factors being injection drug use, chronic alcohol abuse, and chronic viral hepatitis (including HBV and HCV, as confirmed by histology) [100]. The incidence of liver failure was 1.1%. Liver failure was associated with a lower CD4 T cell count at baseline (median, 94 cells/mm^3), compared with the CD4 T cell count at baseline of the 19 patients without liver failure (median, 260 cells/mm^3), suggesting a role for IRS [100]. Drug hepatotoxicity is associated with ART regimens that contain nevirapine, efavirenz, didanosine, zalcitabine, ritonavir, or saquinavir [97, 101]. However, discontinuation of ART may be associated with rebounding HBV replication in patients coinfected with HIV–HBV who are treated with lamivudine- or tenofovir-containing regimens. In these cases, continuation of monotherapy with lamivudine or tenofovir should be considered. On the other hand, persistent HBV replication and the emergence of lamivudine-resistant HBV has been observed in ~10% of patients after long-term ART with regimens containing lamivudine [102].

Specific treatments may be required for unusual manifestations of IRS (table 1), such as surgical intervention in a case of bowel perforation due to *M. tuberculosis*–mediated IRS [65]. Acute renal failure has been observed in a case of *M. tuberculosis*–associated IRS in a patient whose renal function was initially normal, but who had documented prior miliary spread and who had urine cultures positive for *M. tuberculosis* [103]. The unmasking, as a result of IRS, of previously undiagnosed ongoing infections, such as *Cryptococcus*-associated meningitis, has been previously described [68]. In fact, IRS in response to the simultaneous occurrence of 2 entities (i.e., cytomegalovirus and *Cryptococcus* species) has been reported [104].

The management of symptoms, particularly through the use of nonsteroidal anti-inflammatory drugs, has been recommended. Immune modulation is warranted, but specific drugs and protocols are lacking. Thalidomide, intravenous immunoglobulins, and steroids have been discussed [20]. Steroids represent an important, although double-edged, measure in IRS

treatment. Systemic steroids are often considered when inflammatory damage at the site of involvement severely impairs organ function (e.g., eye, liver, brain, or lungs) and becomes life-threatening. For progressive multifocal leucoencephalopathy mediated by polyomavirus JC, transient improvement of the patient's condition on administration of steroids that then showed lethal progression has been reported. The unfavorable course may be the result of several factors, including the advanced stage of the disease, the patient's inability to mount a complete immune response, and the protracted administration of steroids (which adversely affected immune effectors), in addition to the lack of effective pathogen-specific antivirals. However, judicious use of steroids and further immune reconstitution by continued ART remain the only option [77, 105].

Regarding the management of IRS, the question of whether IRS is elicited by active infection or by persisting antigens arises (table 2). If active infection is suspected, antimicrobial therapy is warranted, and modification of treatment should be considered in cases in which the patient is already receiving antimicrobials. On the other hand, reconstitution of immune reaction to persisting antigens of microbes that no longer replicate may make antimicrobial therapy unnecessary and may, in fact, add to toxicity. In clinical practice, it may be impossible to dissect these entities, and hands-on antimicrobial therapy may be administered even if an ongoing infection was not proven and if the differential diagnosis includes antimicrobial treatment failure [8].

CONCLUSIONS

Immune reconstitution, marked by an increase in CD4 T cell count, is the most crucial process that takes place in a patient after initiation of ART. Success of ART translates into a sustained recovery of CD4 T cells, which is the primary surrogate marker used in clinical praxis. Recommendations for discontinuing prophylaxis involve well-defined CD4 T cell count thresholds. Nevertheless, clinical judgment may require adaptation of these recommendations, particularly in the first phase of immune recovery. Because IRS may be more frequent in patients with advanced HIV disease who are initiating ART, this complication of immune recovery may decrease in frequency if ART is initiated in patients whose CD4 T cell counts have not already decreased to <200 cells/mm^3.

References

1. Saag MS, Holodniy M, Kuritzkes DR, et al. HIV viral load markers in clinical practice. Nat Med **1996**; 2:625–9.
2. Kaplan JE, Masur H, Holmes KK. Guidelines for preventing opportunistic infections among HIV-infected persons—2002: recommendations of the US Public Health Service and the Infectious Diseases Society of America. MMWR **2002**; 51(RR-8):1–52.
3. 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**; 277:112–6.
4. Cooney EL. Clinical indicators of immune restoration following highly active antiretroviral therapy. Clin Infect Dis **2002**; 34:224–33.
5. Egger M, Hirschel B, Francioli P, et al. Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. Swiss HIV Cohort Study. BMJ **1997**; 315: 1194–9.
6. 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**; 338:853–60.
7. Egger M, May M, Chene G, et al. Prognosis of HIV-1–infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet **2002**; 360:119–29.
8. Ledergerber B, Egger M, Erard V, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. JAMA **1999**; 282:2220–6.
9. Furrer H, Egger M, Opravil M, et al. Discontinuation of primary prophylaxis against *Pneumocystis carinii* pneumonia in HIV-1–infected adults treated with combination antiretroviral therapy. Swiss HIV Cohort Study. N Engl J Med **1999**; 340:1301–6.
10. Furrer H. Management of opportunistic infection prophylaxis in the highly active antiretroviral therapy era. Swiss Cohort Study. Curr Infect Dis Rep **2002**; 4:161–74.
11. Smith CJ, Sabin CA, Lampe FC, et al. The potential for CD4 cell increases in HIV-positive individuals who control viraemia with highly active antiretroviral therapy. AIDS **2003**; 17:963–9.
12. Kaufmann GR, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. Arch Intern Med **2003**; 163:2187–95.
13. Pakker NG, Notermans DW, de Boer RJ, et al. Biphasic kinetics of peripheral blood T cells after triple combination therapy in HIV-1 infection: a composite of redistribution and proliferation. Nat Med **1998**; 4:208–14.
14. Kaufmann GR, Bloch M, Finlayson R, et al. The extent of HIV-1–related immunodeficiency and age predict the long-term CD4 T lymphocyte response to potent antiretroviral therapy. AIDS **2002**; 16: 359–67.
15. Kaufmann GR, Bloch M, Zaunders JJ, et al. Long-term immunological response in HIV-1–infected subjects receiving potent antiretroviral therapy. AIDS **2000**; 14:959–69.
16. Tarwater PM, Margolick JB, Jin J, et al. Increase and plateau of CD4 T-cell counts in the 3 1/2 years after initiation of potent antiretroviral therapy. J Acquir Immune Defic Syndr **2001**; 27:168–75.
17. Wit FW, Reiss P. When to start antiretroviral therapy and what to start with—a European perspective. Curr Infect Dis Rep **2003**; 5: 349–57.
18. Wilkin TJ, Gulick RM. Antiretroviral therapy: when and what to start—an American perspective. Curr Infect Dis Rep **2003**; 5:339–48.
19. Dybul M, Fauci AS, Bartlett JG, et al. Guidelines for using antiretroviral agents among HIV-infected adults and adolescents: recommendations of the panel on clinical practices for treatment of HIV. Panel on Clinical Practices for the Treatment of HIV. MMWR Recomm Rep **2002**; 51(RR-7):1–55.
20. Cheng VC, Yuen KY, Chan WM, et al. Immunorestitution disease involving the innate and adaptive response. Clin Infect Dis **2000**; 30: 882–92.
21. Deayton JR, Sabin CA, Britt WB, et al. Rapid reconstitution of humoral immunity against cytomegalovirus but not HIV following highly active antiretroviral therapy. AIDS **2002**; 16:2129–35.
22. Stone SF, Price P, Tay-Kearney ML, French MA. Cytomegalovirus (CMV) retinitis immune restoration disease occurs during highly active antiretroviral therapy–induced restoration of CMV-specific im-

mune responses within a predominant Th2 cytokine environment. J Infect Dis **2002**; 185:1813–7.
23. Carr A, Cooper DA. Restoration of immunity to chronic hepatitis B infection in HIV-infected patient on protease inhibitor. Lancet **1997**; 349:995–6.
24. John M, Flexman J, French MA. Hepatitis C virus–associated hepatitis following treatment of HIV-infected patients with HIV protease inhibitors: an immune restoration disease? AIDS **1998**; 12:2289–93.
25. Rouanet I, Peyriere H, Mauboussin JM, et al. Acute clinical hepatitis by immune restoration in a human immunodeficiency virus/hepatitis B virus co-infected patient receiving antiretroviral therapy. Eur J Gastroenterol Hepatol **2003**; 15:95–7.
26. Mussini C, Pezzotti P, Govoni A, et al. Discontinuation of primary prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type 1–infected patients: the changes in opportunistic prophylaxis study. J Infect Dis **2000**; 181:1635–42.
27. Yangco BG, Von Bargen JC, Moorman AC, Holmberg SD. Discontinuation of chemoprophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection. HIV Outpatient Study (HOPS) Investigators. Ann Intern Med **2000**; 132:201–5.
28. 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**; 353:201–3.
29. Weverling GJ, Mocroft A, Ledergerber B, et al. Discontinuation of *Pneumocystis carinii* pneumonia prophylaxis after start of highly active antiretroviral therapy in HIV-1 infection. EuroSIDA Study Group. Lancet **1999**; 353:1293–8.
30. Lopez Bernaldo de Quiros JC, Miro JM, Pena JM, et al. A randomized trial of the discontinuation of primary and secondary prophylaxis against *Pneumocystis carinii* pneumonia after highly active antiretroviral therapy in patients with HIV infection. Grupo de Estudio del SIDA 04/98. N Engl J Med **2001**; 344:159–67.
31. Kirk O, Lundgren JD, Pedersen C, et al. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? AIDS **1999**; 13: 1647–51.
32. El Sadr WM, Burman WJ, Grant LB, et al. Discontinuation of prophylaxis for *Mycobacterium avium* complex disease in HIV-infected patients who have a response to antiretroviral therapy. Terry Beirn Community Programs for Clinical Research on AIDS. N Engl J Med **2000**; 342:1085–92.
33. 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.
34. Furrer H, Telenti A, Rossi M, Ledergerber B. Discontinuing or withholding primary prophylaxis against *Mycobacterium avium* in patients on successful antiretroviral combination therapy. The Swiss HIV Cohort Study. AIDS **2000**; 14:1409–12.
35. Ledergerber B, Mocroft A, Reiss P, et al. Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection who have a response to antiretroviral therapy. Eight European Study Groups. N Engl J Med **2001**; 344:168–74.
36. Vibhagool A, Sungkanuparph S, Mootsikapun P, et al. Discontinuation of secondary prophylaxis for cryptococcal meningitis in human immunodeficiency virus–infected patients treated with highly active antiretroviral therapy: a prospective, multicenter, randomized study. Clin Infect Dis **2003**; 36:1329–31.
37. Macdonald JC, Karavellas MP, Torriani FJ, et al. Highly active antiretroviral therapy–related immune recovery in AIDS patients with cytomegalovirus retinitis. Ophthalmology **2000**; 107:877–81.
38. 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**; 177:1080–3.
39. Vrabec TR, Baldassano VF, Whitcup SM. Discontinuation of maintenance therapy in patients with quiescent cytomegalovirus retinitis and elevated $CD4^+$ counts. Ophthalmology **1998**; 105:1259–64.
40. Jabs DA, Bolton SG, Dunn JP, Palestine AG. Discontinuing anticytomegalovirus therapy in patients with immune reconstitution after combination antiretroviral therapy. Am J Ophthalmol **1998**; 126: 817–22.
41. Di Perri G, Vento S, Mazzi R, et al. Recovery of long-term natural protection against reactivation of CMV retinitis in AIDS patients responding to highly active antiretroviral therapy. J Infect **1999**; 39: 193–7.
42. Whitcup SM, Fortin E, Lindblad AS, et al. Discontinuation of anticytomegalovirus therapy in patients with HIV infection and cytomegalovirus retinitis. JAMA **1999**; 282:1633–7.
43. Kirk O, Reiss P, Uberti-Foppa C, et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. Ann Intern Med **2002**; 137:239–50.
44. Goldman M, Zackin R, Fichtenbaum CJ, et al. Discontinuation of antifungal therapy for disseminated histoplasmosis (DH) following immunologic response to antiretroviral therapy (ART) is safe: AIDS Clinical Trials Group Study A5038 [abstract 1761]. In: Program and abstracts of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago. Washington, DC: American Society for Microbiology, **2003**.
45. Furrer H, Fux C. Opportunistic infections: an update. J HIV Ther **2002**; 7:2–7.
46. DeSimone JA, Pomerantz RJ, Babinchak TJ. Inflammatory reactions in HIV-1–infected persons after initiation of highly active antiretroviral therapy. Ann Intern Med **2000**; 133:447–54.
47. French MA, Lenzo N, John M, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. HIV Med **2000**; 1:107–15.
48. French MA, Mallal SA, Dawkins RL. Zidovudine-induced restoration of cell-mediated immunity to mycobacteria in immunodeficient HIV-infected patients. AIDS **1992**; 6:1293–7.
49. Langford TD, Letendre SL, Marcotte TD, et al. Severe, demyelinating leukoencephalopathy in AIDS patients on antiretroviral therapy. AIDS **2002**; 16:1019–29.
50. Barouch DH, Faquin WC, Chen Y, et al. BK virus–associated hemorrhagic cystitis in a human immunodeficiency virus–infected patient. Clin Infect Dis **2002**; 35:326–9.
51. Hirsch HH, Steiger J. Polyomavirus BK: old dog—new tricks? Lancet Infect Dis **2003**; 3:611–23.
52. Barbaro DJ, Orcutt VL, Coldiron BM. *Mycobacterium avium–Mycobacterium intracellulare* infection limited to the skin and lymph nodes in patients with AIDS. Rev Infect Dis **1989**; 11:625–8.
53. Schwietert M, Battegay M. Focal mycobacterial lymphadenitis after starting highly active antiretroviral therapy [in German]. Dtsch Med Wochenschr **1999**; 124:45–8.
54. 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: 122–8.
55. Foudraine NA, Hovenkamp E, Notermans DW, et al. Immunopathology as a result of highly active antiretroviral therapy in HIV-1–infected patients. AIDS **1999**; 13:177–84.
56. Murray R, Mallal S, Heath C, French M. Cerebral *Mycobacterium avium* infection in an HIV-infected patient following immune reconstitution and cessation of therapy for disseminated *Mycobacterium avium* complex infection. Eur J Clin Microbiol Infect Dis **2001**; 20: 199–201.
57. Cabie A, Abel S, Brebion A, et al. Mycobacterial lymphadenitis after initiation of highly active antiretroviral therapy. Eur J Clin Microbiol Infect Dis **1998**; 17:812–3.
58. Dworkin MS, Fratkin MD. *Mycobacterium avium* complex lymph

node abscess after use of highly active antiretroviral therapy in a patient with AIDS. Arch Intern Med **1998**; 158:1828.
59. Nannini EC, Okhuysen PC. HIV-1 and the gut in the era of highly active antiretroviral therapy. Curr Gastroenterol Rep **2002**; 4:392–38.
60. Aberg JA, Chin-Hong PV, McCutchan A, et al. Localized osteomyelitis due to *Mycobacterium avium* complex in patients with human immunodeficiency virus receiving highly active antiretroviral therapy. Clin Infect Dis **2002**; 35:E8–E13.
61. Chien JW, Johnson JL. Paradoxical reactions in HIV and pulmonary TB. Chest **1998**; 114:933–6.
62. Goldsack NR, Allen S, Lipman MC. Adult respiratory distress syndrome as a severe immune reconstitution disease following the commencement of highly active antiretroviral therapy. Sex Transm Infect **2003**; 79:337–8.
63. Fishman JE, Saraf-Lavi E, Narita M, et al. Pulmonary tuberculosis in AIDS patients: transient chest radiographic worsening after initiation of antiretroviral therapy. AJR Am J Roentgenol **2000**; 174:43–9.
64. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. Am J Respir Crit Care Med **1998**; 158:157–61.
65. Guex AC, Bucher HC, Demartines N, et al. Inflammatory bowel perforation during immune restoration after one year of antiretroviral and antituberculous therapy in an HIV-1–infected patient: report of a case. Dis Colon Rectum **2002**; 45:977–8.
66. Crump JA, Tyrer MJ, Lloyd-Owen SJ, et al. Military tuberculosis with paradoxical expansion of intracranial tuberculomas complicating human immunodeficiency virus infection in a patient receiving highly active antiretroviral therapy. Clin Infect Dis **1998**; 26:1008–9.
67. Lawn SD, Wood C, Lockwood DN. Borderline tuberculoid leprosy: an immune reconstitution phenomenon in a human immunodeficiency virus–infected person. Clin Infect Dis **2003**; 36:e5–e6.
68. Woods ML, MacGinley R, Eisen DP, Allworth AM. HIV combination therapy: partial immune restitution unmasking latent cryptococcal infection. AIDS **1998**; 12:1491–4.
69. Blanche P, Gombert B, Ginsburg C, et al. HIV combination therapy: immune restitution causing cryptococcal lymphadenitis dramatically improved by anti-inflammatory therapy. Scand J Infect Dis **1998**; 30: 615–6.
70. Jenny-Avital ER, Abadi M. Immune reconstitution cryptococcosis after initiation of successful highly active antiretroviral therapy. Clin Infect Dis **2002**; 35:e128–33.
71. Trevenzoli M, Cattelan AM, Rea F, et al. Mediastinitis due to cryptococcal infection: a new clinical entity in the HAART era. J Infect **2002**; 45:173–9.
72. Rambeloarisoa J, Batisse D, Thiebaut JB, et al. Intramedullary abscess resulting from disseminated cryptococcosis despite immune restoration in a patient with AIDS. J Infect **2002**; 44:185–8.
73. King MD, Perlino CA, Cinnamon J, Jernigan JA. Paradoxical recurrent meningitis following therapy of cryptococcal meningitis: an immune reconstitution syndrome after initiation of highly active antiretroviral therapy. Int J STD AIDS **2002**; 13:724–6.
74. Barry SM, Lipman MC, Deery AR, et al. Immune reconstitution pneumonitis following *Pneumocystis carinii* pneumonia in HIV-infected subjects. HIV Med **2002**; 3:207–11.
75. Koval CE, Gigliotti F, Nevins D, Demeter LM. Immune reconstitution syndrome after successful treatment of *Pneumocystis carinii* pneumonia in a man with human immunodeficiency virus type 1 infection. Clin Infect Dis **2002**; 35:491–3.
76. Hoffmann C, Horst HA, Albrecht H, Schlote W. Progressive multifocal leucoencephalopathy with unusual inflammatory response during antiretroviral treatment. J Neurol Neurosurg Psychiatry **2003**; 74:1142–4.
77. Cinque P, Bossolasco S, Brambilla AM, et al. The effect of highly active antiretroviral therapy–induced immune reconstitution on development and outcome of progressive multifocal leukoencephalopathy: study of 43 cases with review of the literature. J Neurovirol **2003**; 9:73–80.
78. 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**; 35:1250–7.
79. Gluck TA, Knowles WA, Johnson MA, et al. BK virus–associated haemorrhagic cystitis in an HIV-infected man. AIDS **1994**; 8:391–2.
80. Fox PA, Barton SE, Francis N, et al. Chronic erosive herpes simplex virus infection of the penis, a possible immune reconstitution disease. HIV Med **1999**; 1:10–8.
81. Domingo P, Torres OH, Ris J, Vazquez G. 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**; 110:605–9.
82. Johnson SC, Benson CA, Johnson DW, Weinberg A. Recurrences of cytomegalovirus retinitis in a human immunodeficiency virus–infected patient, despite potent antiretroviral therapy and apparent immune reconstitution. Clin Infect Dis **2001**; 32:815–9.
83. French M, Price P. Immune restoration disease in HIV patients: aberrant immune responses after antiretroviral therapy. J HIV Ther **2002**; 7:46–51.
84. Neumann S, Kreth F, Schubert S, et al. Reiter's syndrome as a manifestation of an immune reconstitution syndrome in an HIV-infected patient: successful treatment with doxycycline. Clin Infect Dis **2003**; 36:1628–9.
85. Piliero PJ, Fish DG, Preston S, et al. Guillain-Barre syndrome associated with immune reconstitution. Clin Infect Dis **2003**; 36:e111–4.
86. Gomez V, Smith PR, Burack J, et al. Sarcoidosis after antiretroviral therapy in a patient with acquired immunodeficiency syndrome. Clin Infect Dis **2000**; 31:1278–80.
87. Mirmirani P, Maurer TA, Herndier B, et al. Sarcoidosis in a patient with AIDS: a manifestation of immune restoration syndrome. J Am Acad Dermatol **1999**; 41:285–6.
88. Naccache JM, Antoine M, Wislez M, et al. Sarcoid-like pulmonary disorder in human immunodeficiency virus–infected patients receiving antiretroviral therapy. Am J Respir Crit Care Med **1999**; 159: 2009–13.
89. Viani RM. Sarcoidosis and interstitial nephritis in a child with acquired immunodeficiency syndrome: implications of immune reconstitution syndrome with an indinavir-based regimen. Pediatr Infect Dis J **2002**; 21:435–8.
90. Aldeen T, Horgan M, Macallan DC, et al. Is acute appendicitis another inflammatory condition associated with highly active antiretroviral therapy (HAART)? HIV Med **2000**; 1:252–5.
91. Wendland T, Furrer H, Vernazza PL, et al. HAART in HIV-infected patients: restoration of antigen-specific CD4 T-cell responses in vitro is correlated with CD4 memory T-cell reconstitution, whereas improvement in delayed type hypersensitivity is related to a decrease in viraemia. AIDS **1999**; 13:1857–62.
92. Letvin NL, Walker BD. Immunopathogenesis and immunotherapy in AIDS virus infections. Nat Med **2003**; 9:861–6.
93. Jost S, Bernard MC, Kaiser L, et al. A patient with HIV-1 superinfection. N Engl J Med **2002**; 347:731–6.
94. Altfeld M, Allen TM, Yu XG, et al. HIV-1 superinfection despite broad CD8+ T-cell responses containing replication of the primary virus. Nature **2002**;420:434–9.
95. Koelsch KK, Smith DM, Little SJ, et al. Clade B HIV-1 superinfection with wild-type virus after primary infection with drug-resistant clade B virus. AIDS **2003**; 17:F11–6.
96. Nolan RC, Chidlow G, French MA. Parvovirus B19 encephalitis presenting as immune restoration disease after highly active antiretroviral therapy for human immunodeficiency virus infection. Clin Infect Dis **2003**; 36:1191–4.
97. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. 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.
98. Saves M, Raffi F, Clevenbergh P, et al. Hepatitis B or hepatitis C virus

infection is a risk factor for severe hepatic cytolysis after initiation of a protease inhibitor–containing antiretroviral regimen in human immunodeficiency virus–infected patients. The APROCO Study Group. Antimicrob Agents Chemother **2000**; 44:3451–5.
99. Law WP, Dore GJ, Duncombe CJ, et al. Risk of severe hepatotoxicity associated with antiretroviral therapy in the HIV-NAT Cohort, Thailand, 1996–2001. AIDS **2003**; 17:2191–9.
100. 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**; 32:259–67.
101. Martinez E, Blanco JL, Arnaiz JA, et al. Hepatotoxicity in HIV-1–infected patients receiving nevirapine-containing antiretroviral therapy. AIDS **2001**; 15:1261–8.
102. Hoff J, Bani-Sadr F, Gassin M, Raffi F. Evaluation of chronic hepatitis B virus (HBV) infection in coinfected patients receiving lamivudine as a component of anti–human immunodeficiency virus regimens. Clin Infect Dis **2001**; 32:963–9.
103. Jehle AW, Khanna N, Sigle JP, et al. Acute renal failure upon immune reconstitution in an HIV-positive patients with miliary tuberculosis. Clin Infect Dis **2004**; 38:e32–5.
104. Legendre U, Battegay M, Nuttli I, et al. Simultaneous occurrence of 2 HIV-related immunereconstitution diseases after initiation of highly active antiretroviral therapy. Scand J Infect Dis **2001**; 33:388–9.
105. Furrer H, Malinverni R. Systemic inflammatory reaction after starting highly active antiretroviral therapy in AIDS patients treated for extrapulmonary tuberculosis. Am J Med **1999**; 106:371–2.
106. Du Pasquier RA, Koralnik IJ. Inflammatory reaction in progressive multifocal leukoencephalopathy: harmful or beneficial? J Neurovirol **2003**; 9(Suppl 1):25–31.