

The introduction of combination antiretroviral therapy (cART) has led to declines in AIDS-related mortality and the incidence of opportunistic infections. cART-induced viral suppression is associated with clinically significant restoration of immune function. This immune recovery is characterised by the restoration of pathogen-specific immune responses, which contribute to the resolution of opportunistic infections, and allows the safe cessation of primary and secondary opportunistic infection prophylaxis. Immune restoration may also result in the paradoxical development of inflammatory reactions to pre-existent or subclinical infections.

22.1 Immunological aspects of immune reconstitution

Total restoration of immune function following cART will require the regeneration of functionally competent, antigen-specific CD4 cell clones that are lost with progressive HIV disease. In most patients the initiation of cART results in only partial restoration of their immune systems. In a significant proportion of those treated, CD4 cell counts do not return to normal, nor does their CD4:CD8T cell ratio, the degree of immune activation or the ratio of memory and naïve T cells even after five or more years of fully suppressive therapy. The degree of normalisation of immune function correlates with the nadir CD4 cell count and sustained viral suppression.^{1,2}

cART usually restores immune function sufficiently to protect patients from many of the opportunistic infections that complicate HIV infection³ and restores CD4 cell responses to major opportunistic pathogens such as cytomegalovirus (CMV), *Mycobacterium avium* complex (MAC) and *Mycobacterium tuberculosis*.^{4,5,6,7} In some studies, restoration of antigen-specific proliferative responses which were absent at baseline was not observed, although significant increases in the magnitude of baseline proliferative responses were demonstrated.⁸ This suggests deletion of the clones mediating the response. Responses to less common pathogens, such as tetanus, are more difficult to detect. However, the demonstration of an immune response to this pathogen following re-immunisation in patients on cART indicates that complete clonal deletion has not occurred.⁹

The extent of cART related restoration of pathogen specific responses is not uniform among patients. In general, the lower the nadir CD4 cell count the less the extent of restoration. Response to vaccination is an *in vivo* measure of CD4 cell help, as antibody responses to influenza vaccination have been shown to increase in patients treated with cART when compared with untreated historical controls.¹⁰

A second factor that contributes to altered pathogen-specific immune restoration is persistent immune activation. Following

cART, there is a decline in the level of immune activation however, despite complete and prolonged suppression of plasma viral load, usually immune activation does not return to levels seen in normal healthy individuals.^{11,12} This has been thought to reflect ongoing low level viral replication. However, another possible cause of the ongoing immune activation may be translocation of microbial products from the gut because of damage to the gut associated lymphoid tissue due to the preferential infection and depletion of CD4+CCR5+ T cells that predominate in gut-associated lymphoid tissue.^{13,14}

Finally, throughout the natural history of HIV infection, there is a progressive decline in the percentage and number of naïve CD4 cells in untreated HIV disease. Following the initiation of cART, there is usually an increase in phenotypically naïve CD4 cells.¹⁵ This occurs later and more slowly than the initial rise in CD4 cell counts as these cells must arise through the thymus. Even in adults without HIV infection the thymus has limited capacity to generate naïve T cells. As HIV causes further damage to this organ, the capacity of the thymus in people with HIV infection is likely to be compromised to even a greater extent.¹⁶ The magnitude of the increase in these naïve cells is directly related to the proportion of naïve cells prior to initiation of cART.¹⁷ This may explain the variability in immune reconstitution seen at the clinical level.

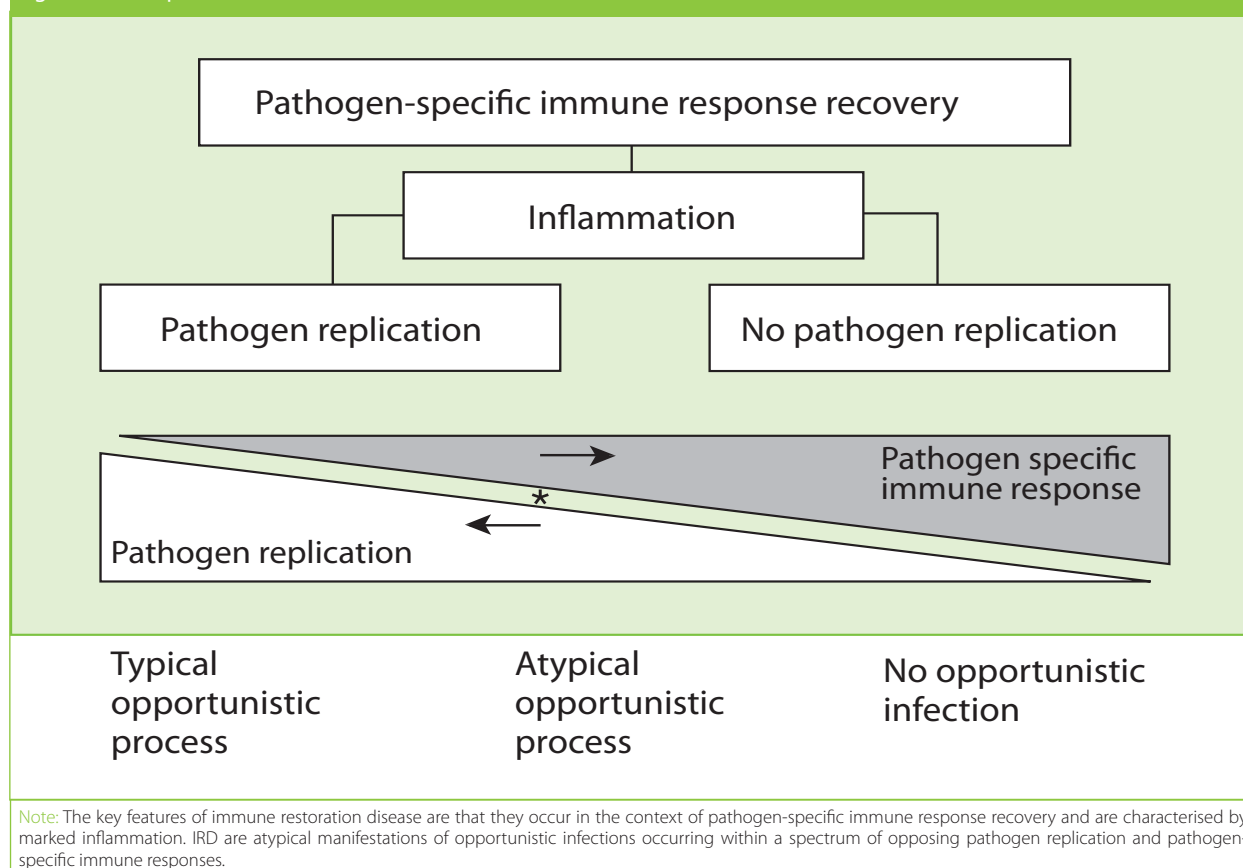
22.2 Immune restoration disease

Following the administration of cART, infectious and/or inflammatory diseases may be a manifestation of immune restoration. Collectively these conditions are referred to as immune restoration diseases (IRDs). Similar reactions have been described in patients who cease iatrogenic immunosuppression,^{18,19} and in patients who commence therapy for tuberculosis or leprosy. IRDs were first described following zidovudine monotherapy,²⁰ but have been increasingly recognised in the post-cART era.²¹ The incidence of IRD increases as the CD4 cell count prior to commencing cART decreases and is most commonly seen in people commencing cART late in the disease with CD4 cell counts <50 cells/ μ L. However, IRD must be considered as a likely differential diagnosis in any patient commencing cART with advanced HIV infection. The symptoms and signs of IRD may be misinterpreted either as an opportunistic infection resulting from persistent immunodeficiency or as an effect of drug toxicity.

22.2.1 Immunological aspects of immune restoration disease

The immunopathogenesis of IRD has not been clearly defined and it is likely that the immunopathogenesis varies for different pathogens and stages of immune restoration post-cART (Figure 22.1). Lesions associated with IRD are characterised by marked inflammation. IRD can be viewed on a spectrum with varying

Figure 22.1 Spectrum of immune restoration disease



contributions from pathogen replication and pathogen-specific immune responses. Initially, cART-induced immunological changes may promote a destructive inflammatory response, but this is balanced by an improved host immune response, which in general leads to clinical resolution of IRD.

Typically, in patients with AIDS, opportunistic infections are manifested by uncontrolled pathogen replication in the absence of pathogen-specific immune responses. In some patients, pathogen replication may be subclinical prior to cART initiation. The reconstitution of pathogen-specific immune responses may initially augment pathogen induced tissue damage or result in increased tissue destruction perhaps due to dysregulated production of pro-inflammatory cytokines.²² Typically, IRD that is associated with pathogen replication occurs within three months of cART initiation, e.g. MAC, cryptococcal meningitis, progressive multifocal leukoencephalopathy (PML), or CMV retinitis.

At the other end of the spectrum IRD may occur in the setting of brisk pathogen-specific immune responses in the presence of minimal pathogen replication. These IRD typically manifest later than IRD associated with pathogen replication. These tend to occur after the first three months of cART. The average time to onset of CMV vitritis, for example, is two to four months following initiation of cART.

IRD typically occurs before substantial true immune reconstitution (defined by the magnitude of increase in naïve CD4 cells). It may even occur in the absence of an increase in the peripheral CD4 cell count.²³ Redistribution memory cells trapped in lymph

node or the reduction of immune-activation-induced energy or altered cytokine production (shift from Th2 to Th1) may contribute to this phenomenon.²⁴ Restoration of pathogen-specific immune responses has been documented for MAC and *M. tuberculosis* IRDs. The association between restoration of mycobacterial cutaneous delayed type hypersensitivity reactions and mycobacterial IRDs suggest that mycobacterial-specific CD4 cells may play a central role.²⁵

Improvements in antigen-presenting cell function might be an additional or alternative mechanism. CD8 cells have also been implicated in IRD, particularly in those triggered by viral antigens. But the role of increased antigen specific cell function in these conditions is less clear. CD4 cell responses to CMV often take more than one year to reconstitute so it is difficult to invoke a direct role for these responses.⁵ More effective CD8 cell responses may be secondary to increases in CD8 cells or increased CD4 cell help or both. It has also been proposed that increases in CD8 cells may contribute to IRD-associated hepatitis.^{26,27} Herpes zoster IRD is predicted by higher baseline CD8 cells as well as greater post-cART increases in CD8 cells.²¹

Altered pathogen-specific inflammatory responses have also been identified in IRD. Increased interleukin-6 (IL-6) production is a feature of IRDs associated with human herpes virus infections (CMV, herpes zoster and herpes simplex) and may play a role in IRD associated with these viruses.²⁸ It has been postulated that decreases in interferon-alfa levels associated with cART may lead to an increase in hepatitis C viraemia.²⁹

Host genetics also play a role in IRD but their role is yet to be fully delineated. Not surprisingly, different genetic polymorphisms are associated with different pathogen associated IRDs. Certain HLA-Class I alleles (HLA-B44 and HLA-A2), have been associated with the development of CMV or herpes simplex virus related IRDs.³⁰ Various polymorphisms in cytokine genes such as tumour necrosis factor- α , IL-6 and IL-12 have been associated with the development of either mycobacterial or herpes virus IRDs.³¹ However, these studies have been based on small populations and require confirmation in larger prospective series. Genetic linkage between HLA alleles and certain cytokine polymorphisms make it difficult to identify the exact causative gene. At present these associations are not assessed as part of a diagnostic work up for IRD.

22.2.2 Clinical aspects of immune restoration disease

IRDs generally occur two to 12 weeks following initiation of cART and often within the first several weeks if there is a precipitous drop in viral load. The typical clinical scenario is the onset of fever and pathogen-specific symptoms in a patient with a low nadir CD4 cell count. The presentations are atypical and are altered by pathogen-specific immune responses. Having CD4 cell counts <50 CD4 cells/ μ L is a risk factor for the development of IRD.^{21,32} Nadir CD4 cell count may predict the type of pathogen-specific IRD. Herpesvirus-associated IRDs are generally seen in patients with nadir CD4 cell counts <90 cells/ μ L, whereas mycobacterial-associated IRDs can occur in patients with higher CD4 cell nadirs.²¹

Subsequent immune restoration has been variable in patients experiencing IRD. While patients with herpes virus-associated IRD had identical CD4 cell count increases as patients without IRD, patients with non-herpesvirus-associated IRD had significantly delayed increases in CD4 cell counts independent of plasma viral load. This latter finding may be explained by discontinuation of cART or the use of steroids during clinically active IRD. However, other studies have shown a survival trend in favour of those who suffered IRD early in cART therapy.³² The definitive studies analysing the long-term outcomes of this syndrome have not yet been conducted.

Mycobacterial immune restoration disease

Mycobacterial IRD was first reported with zidovudine monotherapy.²⁰ Subsequently, MAC, *M. tuberculosis* and *Bacille Calmette-Guerin* vaccination IRD were reported in the setting of dual therapy.^{33,34} However, mycobacterial IRDs have been diagnosed more frequently in the cART era and are the most frequently reported IRDs. MAC-associated IRD has been reported in up to 5% of patients who commence cART with CD4 cell counts below 100 cells/ μ L. *M. tuberculosis*-associated IRD has been reported in over one-third of patients with co-infection who commence cART.³⁵ *M. tuberculosis*-associated IRD is more likely to occur if cART is initiated close to the diagnosis of *M. tuberculosis* (and therefore early in the treatment of *M. tuberculosis*) and in those with lower CD4 cell counts.³⁶ Mycobacterial IRDs usually occur within two months of commencing cART.³²

Clinical manifestations of mycobacterial IRD are often extrapulmonary. Patients present with fever and focal lymphadenitis, involving peripheral, mediastinal or abdominal lymph nodes.^{32,37} The lymph nodes are characteristically painful and may cause abdominal symptoms. Neutrophilia

is a common feature of acute presentations of mycobacterial IRD.³⁷ Other manifestations include hepatitis, pulmonary infiltrates, intracranial tuberculoma, osteomyelitis, bursitis, cerebral tuberculoma, Addison's disease, and skin nodules.^{21,38} Fine-needle aspiration generally reveals caseating necrosis and granulomata with scanty (or absent) acid-fast bacilli. *Mycobacteria* are usually able to be cultured from tissue specimens. Delayed-type hypersensitivity (DTH) skin tests are positive for mycobacterial antigens, as are lymphoproliferative reactions to mycobacterial antigens.³⁹

Typically, CD4 cells produce large amounts of IL-2 and interferon-gamma in response to mycobacterial antigens. Late stage HIV-infection is characterised by a lack of CD4 cells with proliferative potential, negative DTH tests and an absence of Th1 cytokines. These large or even supra normal responses to mycobacterial antigens are therefore surprising at this stage of the disease as each of these tests would be expected to be negative or at best borderline positive. The exuberant nature of these responses in those suffering IRD suggests IRD is the result of an uncontrolled dysregulated immune response, and access to this type of data can be used as a diagnostic aid to differentiate the cause of the clinical picture.

Herpes virus immune restoration disease

IRDs involving herpes viruses have been commonly reported. A spectrum of ocular disease related to CMV has been documented in patients who have recently commenced cART ranging from (initial or relapsed) retinitis to vitritis/uveitis.^{40,41} The latter is reported in up to 50% of patients with prior CMV retinitis who experience immune restoration following the introduction of cART.²¹ Patients with these conditions present in a similar manner with typical visual disturbance, describing floaters and decreased visual acuity. The diagnosis is usually made by ophthalmological examination, but may require biopsy. CMV vitritis/uveitis is usually benign, but may be associated with vitreomacular traction syndrome with retinal detachment.⁴² Extraocular manifestations include viraemia, colitis, pancreatitis, and submandibular inflammation in patients with no prior history of CMV disease.⁴³ At present it is not possible to predict which patients will develop CMV IRD.

Dermatoma varicella zoster is not infrequent in patients treated with cART.⁴⁴ The mean time to development of symptomatic varicella zoster after cART is 16 weeks.⁴⁴ While typical dermatoma varicella zoster is most commonly reported, zoster sine zoster and Ramsay Hunt syndrome have also been recognised to occur in this context.²¹ Patients who develop varicella-zoster virus IRD are less immunodeficient than patients who experience other forms of IRD.²¹ Moreover, higher baseline and greater increases in CD8 cells following initiation of cART predict varicella zoster IRD.²¹

Herpes simplex virus IRD usually presents with acute or chronic anogenital ulceration. Relapse or first presentation of mucocutaneous herpes can occur within the first eight weeks of cART.²¹ Myelitis and encephalitic presentations have been reported.²¹ Apparent flares of Kaposi's sarcoma has also been reported in patients following the initiation of cART.⁴⁵

Hepatitis C virus (HCV) and hepatitis B virus (HBV) immune restoration disease

Hepatitis following initiation of cART occurs in up to 8% of patients with HCV co-infection.⁴⁶ The spectrum of clinical manifestations includes asymptomatic transaminitis, fever and jaundice. Hepatic decompensation may occur in the setting of cirrhosis. Liver biopsies demonstrate changes consistent with viral hepatitis, but not drug toxicity.²⁷

Hepatitis following initiation of cART is even more common in patients with HIV-HBV co-infected.⁴⁷ Poor outcomes have been reported in those with established cirrhosis and/ or high levels of HBV DNA prior to initiation of cART. Given that tenofovir and lamivudine have both anti-HBV and anti-HIV activity, treatment of both infections is usually initiated at the same time.⁴⁸ There are currently limited effective options available to treat HBV before treating HIV. Therefore, individuals with HIV-HBV co-infection who initiate HBV-active cART are at risk of IRD and careful clinical observation is recommended.

Finally, IRD hepatitis may have a beneficial outcome as it has been associated with clearance of HBV DNA, seroconversion to hepatitis B surface antigen or clearance of HCV RNA.^{26,27} No specific therapy other than careful observation is required as hepatic dysfunction generally resolves spontaneously on cART.^{47,49} With severe IRD hepatitis, referral to an expert with experience in this area is recommended.

Other viral immune restoration disease

PML may worsen or manifest for the first time in patients commencing cART.^{50,51} In some patients with PML, deterioration post-cART is associated with inflammatory brain lesions and a predominant CD8 cell response, suggesting an immunopathological response to John Cunningham virus.⁵²

Exacerbations of molluscum contagiosum and cutaneous and oral warts have been reported in the context of immune recovery.²¹ Other dermatological manifestations include inflammatory folliculitis.⁵³

Fungal immune restoration disease

Atypical presentations of cryptococcal meningitis have been described following the initiation of cART.⁵⁴ Characteristically, patients with baseline CD4 cell counts less than 50 cells/ μ L present with fever, headache and meningism within six weeks of commencing cART.⁵² The cerebrospinal fluid is usually culture positive and contains an unusually high white cell count but the patient may be antigenemic without recoverable viable organisms suggesting that the response is dysregulated and may be triggered by antigen rather than by viable organisms.²¹ However, *cryptococcal* IRD may also present with extra-central nervous system manifestations particularly with lymphadenitis, often with mediastinal involvement.⁵⁵

Clinical deterioration following withdrawal of steroids in a patient with *Pneumocystis jirovecii* pneumonia (PJP) who had commenced cART early after diagnosis of PJP has been reported suggesting PJP IRD may also occur.⁵⁶

Parasitic immune restoration disease

IRD associated parasitic infections including leishmaniasis, toxoplasmosis, cryptosporidiosis, schistosomiasis, strongyloidiasis have been reported from areas where these infections are endemic.

Parasitic IRD often demonstrate granulomatous inflammation.⁵⁷ However, their incidence and their effects on mortality and morbidity are still to be evaluated.

Non-infectious immune restoration disease

Sarcoid-like pulmonary lesions not associated with identifiable pathogens have been reported in patients following the commencement of cART. The differential diagnosis of *mycobacterial* IRD must always be considered in these cases. Onset of sarcoidosis like conditions have been reported following initiation of cART at higher CD4 cell counts.^{58,59}

Thyroid diseases such as Graves' disease and autoimmune thyroiditis have been reported in patients following initiation of cART. These manifestations may occur early or late.^{60,61}

22.2.3 Principles of management of immune restoration disease

While IRD may be considered an adverse reaction to cART, it is not necessarily a reason to stop effective therapy. Indeed, IRD may require specific therapy for controlling symptoms with both anti-inflammatory and antimicrobial therapy. A diagnostic dilemma is evident when a patient with a virological and immunological response to cART presents with a fever and evidence of tissue inflammation. The differential diagnostic triad includes opportunistic infection (secondary to failed cART or unrecognised prior to cART initiation), adverse effect of an antiretroviral agent, or IRD. Permanent withdrawal of antiretroviral therapy may be inappropriate if the fever and inflammation is secondary to improved immune function. Misinterpretation of IRD as an opportunistic infection may result in unnecessary administration of antimicrobial agents.

Prospective studies are required to ascertain the role of prophylactic antimicrobial agents before initiation of cART, and the role of the measurement of pathogen-specific immune responses in the diagnosis of IRD. While comparative data are lacking, in general, cART should continue in most cases of IRD. The co-administration of anti-inflammatory agents (corticosteroids, pentoxifylline and nonsteroidal anti-inflammatory agents, leukotriene inhibitors^{62,11}) and/or antimicrobial agents may result in amelioration of IRD. However, these interventions are based on anecdotal reports. cART should be temporarily ceased only when pain or organ dysfunction prevents ongoing cART. Antiretroviral therapy should then be reintroduced when the opportunistic infection has been treated. While most reactions continue for a limited period of time, cases have been reported of continuing IRD, with recurrent necrosis of lymph nodes and the formation of sterile abscess within lymph nodes that require surgical intervention.^{63,64}

Although data are currently sparse it is generally accepted in patients presenting late with CD4 cell counts <100 cells/ μ L that if an intercurrent infection is identified prior to commencing cART, then that infection should be treated first prior to commencing cART in an attempt to reduce antigen load and therefore reduce the likelihood of developing IRD. This recommendation has been formally made with regards pre-existing *M. tuberculosis* diagnosed at any CD4 cell count and has been extended in many clinical practices to other opportunistic infections such as CMV or PJP.⁶⁵ Ongoing studies are assessing the voracity of these recommendations at present

IRD may be more common in those commencing a protease containing regimen, but a definitive prospective study has not been performed. IRD has been reported in those commencing integrase inhibitor containing regimens. It is unclear whether there is an increased incidence with certain drug classes or whether the increased incidence relates to the rate of viral load reduction. Although there are theoretical reasons as to why

CCR5 inhibitors may induce less IRD, due to alterations in T cell trafficking to sites of inflammation, there are no published data to support this theory.

Although certain genetic predispositions have been described there are no data and no algorithms that identify those at higher risk of IRD. Prospective studies of the condition are required before such algorithms can be developed.

Table 22.1 Cessation of opportunistic infection prophylaxis in people with HIV infection experiencing cART-induced immune recovery

Opportunistic Infection	Criteria to cease prophylaxis				Comments
		CD4 cell count (cells/ μ L)	Duration (months)	Rating strength for supporting evidence ^(a)	
PJP	Primary	>200	\geq 3	AI	
	Secondary	>200	\geq 3	BII	If PJP occurred at CD4 cells count >200 cells μ L, then secondary prophylaxis should be continued for life.
MAC	Primary	100	\geq 3	AI	
	Secondary	>100	\geq 6	CIII	Patient should have completed 12 months of MAC therapy and remained asymptomatic. Some specialists obtain a blood culture for MAC before discontinuation of secondary prophylaxis.
CMV retinitis	Secondary	>100-150	\geq 6	BII	Decision to cease maintenance therapy should be made in consultation with an ophthalmologist. All patients ceasing maintenance therapy should undergo regular ophthalmological review. The role of CMV viral load, antigenaemia and DNA testing in predicting relapse remains to be defined.
Cryptococcal meningitis	Secondary	>100-200	\geq 6	C III	Patient should have successfully completed induction therapy and remained asymptomatic. Some specialists perform lumbar puncture to determine if CSF is culture-negative before stopping maintenance therapy.
Toxoplasmosis	Primary	>200	\geq 3	AI	
	Secondary	>200	\geq 3	C III	Some specialists obtain a cerebral MRI before discontinuation of maintenance therapy.

(a) Strength of rating used in the US Public Health Service Guidelines.

Strength of recommendation: A = Strong evidence for efficacy and substantial clinical benefit support recommendation for use. Should always be offered; B = Moderate evidence for efficacy or strong evidence for efficacy, but only limited clinical benefit. Supports recommendation for use. Should generally be offered; C = Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g. drug toxicity, drug interactions) or cost of the prophylaxis or alternative approaches. Optional. Quality of evidence supporting the recommendation; I = Evidence from at least one properly randomised, controlled trial; II = Evidence from at least one well designed clinical trial without randomisation, from cohort or case-controlled analytic studies (preferably from more than one centre), or from multiple time-series studies, or dramatic results from uncontrolled experiments; III = Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

References: Adapted from DHHS Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents, June 18, 2008, 1-302. Available at: http://aidsinfo.nih.gov/contentfiles/Adult_OI.pdf (cited February, 2009)
 Masur H, Kaplan J, Holmes K. Guidelines for preventing opportunistic infections among HIV-infected persons. *Ann Intern Med* 2002;137:435-477;
 Treating Opportunistic infections Among HIV-infected Adults and Adolescents, Benson CA, Kaplan JE, Masur H, Pau A, Holmes KK. *MMWR*, Dec 17, 2004/53 (RR15);1-112.
 Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. June 18, 2008

CMV = cytomegalovirus; CSF = cerebrospinal fluid; MAC = *Mycobacterium avium* complex; MRI = magnetic resonance imaging scan; PJP = *Pneumocystis jirovecii* pneumonia.

22.3 Ceasing prophylaxis for opportunistic infections

Most patients who respond to cART restore pathogen-specific cell-mediated immune responses. This has been demonstrated for CMV and MAC.^{66,67} Primary prophylaxis for PJP and MAC can be ceased in patients who experience CD4 cell count rises with cART. Data suggest that a sufficient number of functional T cell clones specific for the particular pathogen have to be reconstituted to protect against disease. In almost 2000 patients who ceased primary PJP prophylaxis, only one patient developed PJP. This patient, however, had a CD4 cell count below 200 cells/ μ L when PJP developed.⁶⁸ Similarly, of the almost 900 reported patients who ceased primary MAC prophylaxis, no patient has developed MAC infection during follow-up.⁶⁹ Guidelines for the cessation of opportunistic infection prophylaxis in people with HIV infection experiencing cART-induced immune recovery are outlined in Table 22.1.

Given the potential for IRD, opportunistic infection prophylaxis should be ceased only after the patient's CD4 cell count has risen above the necessary threshold for at least three months. Furthermore, it is conceivable that some patients never regain adequate levels of pathogen-specific cell-mediated immune responses. This may be secondary to either T cell clone depletion or irreversible functional changes. A documented decline in CMV-specific immune responses before the development of retinitis has been observed in patients developing recurrent CMV retinitis.^{70,71}

References

- Moore RD and Keruly JC, CD4+ Cell count 6 years after commencement of HAART in persons with sustained virologic suppression. *CID* 2007;44:441-6,
- Kaufmann GR, Furrer H, Ledergerber B, Perrin L, Opravil M, Vernazza P, et al. Characteristics, determinants, and clinical relevance of CD4+ T cell recovery to >500 cell/ μ L in HIV type 1-infected individuals receiving potent antiretroviral therapy. *CID* 2005;41:361-72
- Koletar SL, Williams PL, Wu J, McCutchan JA, Cohn SE, Murphy RL, Lederman HM, et al. Long term follow-up of HIV infected individuals who have significant increases in CD4+ Cell counts during antiretroviral therapy *CID*, 2004;39:1500-6
- Li TS, Tubiana R, Katlama C, Calvez V, Ait Mohand H, Autran B. Long-lasting recovery in CD4 T-cell function and viral-load reduction after highly active antiretroviral therapy in advanced HIV-1 disease. *Lancet* 1998;351:1682-6.
- Keane NM, Price P, Almeida CA, Stone SF, James I, MA French Restoration of CD4 T-cell responses to cytomegalovirus is short-lived in severely immunodeficient HIV-infected patients responding to HAART. *HIV Medicine* 2004;5:407-14
- Ramaswamy M, Waters A, Smith C, Hainsworth E, Hardy G, Johnson M, et al. Reconstitution of Herpes simplex virus specific T cell immunity in HIV-infected patients receiving HAART. *JID* 2007;195 410-5
- Rinaldo CR Jr, Liebmann JM, Huang XL, Fan Z, Al-Shboul Q, McMahon DK, et al. Prolonged suppression of human immunodeficiency virus type 1 viremia in persons with advanced disease results in enhancement of CD4 T cell reactivity to microbial antigens but not to HIV-1 antigens. *JID* 1999;179:129-36
- Lederman MM, Connick E, Landay A, Kuritzkes DR, Spritzler J, St Clair M, et al. Immunologic responses associated with 12 weeks of combination antiretroviral therapy consisting of zidovudine, lamivudine, and ritonavir: results of AIDS Clinical Trials Group Protocol 315. *J Infect Dis* 1998;178:70-9.
- Valdez H, Smith KY, Landay A, Connick E, Kuritzkes DR, Kessler H, et al. Response to immunization with recall and neoantigens after prolonged administration of an HIV-1 protease inhibitor-containing regimen. ACTG 375 team. *AIDS Clinical Trials Group. AIDS* 2000;14:11-21.
- Kroon FP, Rimmelzwaan GF, Roos MT, Osterhaus AD, Hamann D, Miedema F, et al. Restored humoral immune response to influenza vaccination in HIV-infected adults treated with highly active antiretroviral therapy. *AIDS* 1998;12:F217-23.
- Lesho E. Evidence base for using corticosteroids to treat HIV-associated immune reconstitution syndrome. *Expert Rev Anti-infect. Ther.* 2006;4:469-78
- Evans TG, Bonnez W, Soucier HR, Fitzgerald T, Gibbons DC, Reichman RC. Highly active antiretroviral therapy results in a decrease in CD8+ T cell activation and preferential reconstitution of the peripheral CD4+ T cell population with memory rather than naive cells. *Antiviral Res* 1998;39:163-73.
- Steel A, Cox AE, Shamji MH, John L, Nelson M, Henderson DC, et al. HIV- viral replication below 50 copies/ml in patients on anti retroviral therapy is not associated with CD8+ T cell activation. *Antiviral Therapy* 2007;12:971-5
- Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med* 2006;12:1365-71
- Autran B, Carcelain G, Li TS, Blanc C, Mathez D, Tubiana R, et al. Positive effects of combined antiretroviral therapy on CD4+ T cell homeostasis and function in advanced HIV disease. *Science* 1997;277:112-6.
- Cohen Stuart J, Hamann D, Borleffs J, Roos M, Miedema F, Boucher C, et al. Reconstitution of naive T cells during antiretroviral treatment of HIV-infected adults is dependent on age. *Aids.* 2002;16:2263-6.
- Connors M, Kovacs JA, Krevet S, Gea-Banacloche JC, Sneller MC, Flanigan M, et al. HIV infection induces changes in CD4+ T-cell phenotype and depletions within the CD4+ T-cell repertoire that are not immediately restored by antiviral or immune-based therapies. *Nat Med* 1997;3:533-40.
- Berger BB, Weinberg RS, Tessler HH, Wyhinny GJ, Vygantas CM. Bilateral cytomegalovirus panuveitis after high-dose corticosteroid therapy. *Am J Ophthalmol* 1979;88:1020-5.
- Vento S, Cainelli F, Mirandola F, Cosco L, Di Perri G, Solbiati M, et al. Fulminant hepatitis on withdrawal of chemotherapy in carriers of hepatitis C virus. *Lancet* 1996;347:92-3.
- 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.
- French MA, Lenzo N, John M, Mallal SA, McKinnon EJ, James IR, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. *HIV Med* 2000;1:107-15.
- Stone SF, Price P, Keane NM, Murray RJ, French MA, et al. Levels of IL-6 and soluble IL-6 receptor are increased in HIV patients with a history of immune restoration disease after HAART. *HIV Med* 2002; 3,:21-7
- Bower M, Nelson M, Young AM, Thirlwell C, Newsom-Davis T, Mandalia S, et al. immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma. *J Clin Oncol* 2005;23:5224-8
- Imami N, Antonopoulos C, Hardy G, Gazzard B, Gotch F. Assessment of type 1 and type 2 cytokines in HIV type-1 infected individuals: impact of highly active antiretroviral therapy. *AIDS Research and Human Retroviruses* 1999;15:1499-08.
- Dannenber AM, Jr. Delayed-type hypersensitivity and cell-mediated immunity in the pathogenesis of tuberculosis. *Immunol Today* 1991;12:228-33.
- Carr A, Cooper DA. Restoration of immunity to chronic hepatitis B infection in HIV-infected patient on protease inhibitor. *Lancet* 1997;349:995-6.
- 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.

- 28 Stone SF, Price P, Brochier J, French MA. Plasma bioavailable interleukin-6 is elevated in human immunodeficiency virus-infected patients who experience herpesvirus-associated immune restoration disease after start of highly active antiretroviral therapy. *J Infect Dis* 2001;184:1073-7.
- 29 Rutschmann OT, Negro F, Hirschel B, Hadengue A, Anwar D, Perrin LH. Impact of treatment with human immunodeficiency virus (HIV) protease inhibitors on hepatitis C viremia in patients co-infected with HIV. *J Infect Dis* 1998;177:783-5.
- 30 Price P, Keane NM, Stone SF, Cheong KY, French MA. MHC haplotypes affect the expression of opportunistic infections in HIV patients. *Hum Immunol* 2001;62:157-64.
- 31 Price P, Morahan G, Huang D, Stone E, Cheong KY, Castley A, et al. Polymorphisms in cytokine genes define subpopulations of HIV-1 patients who experienced immune restoration diseases. *AIDS* 2002;16:2043-7.
- 32 Shelburne SA, Visnegarwala F, Darcourt J, Graviss EA, Giordano TP, Clinton White A, Hamill RJ. Incidence and Risk factors for Immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. *AIDS* 2005;19:399-406
- 33 Chien JW, Johnson JL. Paradoxical reactions in HIV and pulmonary TB. *Chest* 1998;114:933-6.
- 34 Sharp MJ, Mallon DF. Regional Bacillus Calmette-Guerin lymphadenitis after initiating antiretroviral therapy in an infant with human immunodeficiency virus type 1 infection. *Pediatr Infect Dis J* 1998;17:660-2.
- 35 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.
- 36 Lawn SD, Meyer L, Beller LG, Wood R. Tuberculosis associated immune reconstitution disease: incidence, risk factors, and Impact in an antiretroviral treatment service in South Africa. *AIDS* 2007;21:335-41
- 37 Race EM, Adelson-Mitty J, Kriegel GR, Barlam TF, Reimann KA, Letvin NL, et al. Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. *Lancet* 1998;351:252-5.
- 38 del Giudice P, Durant J, Counillon E, Mondain V, Bernard E, Roger PM, et al. Mycobacterial cutaneous manifestations: a new sign of immune restoration syndrome in patients with acquired immunodeficiency syndrome. *Arch Dermatol* 1999;135:1129-30.
- 39 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.
- 40 Jacobson MA, Zegans M, Pavan PR, O'Donnell JJ, Sattler F, Rao N, et al. Cytomegalovirus retinitis after initiation of highly active antiretroviral therapy. *Lancet* 1997;349:1443-5.
- 41 Karavellas MP, Plummer DJ, Macdonald JC, Torriani FJ, Shufelt CL, Azen SP 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.
- 42 Canzano JC, Reed JB, Morse LS. Vitreomacular traction syndrome following highly active antiretroviral therapy in AIDS patients with cytomegalovirus retinitis. *Retina* 1998;18:443-7.
- 43 Gilquin J, Piketty C, Thomas V, Gonzales-Canali G, Belec L, Kazatchkine MD. 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;11:1659-60.
- 44 Aldeen T, Hay P, Davidson F, Lau R. Herpes zoster infection in HIV-seropositive patients associated with highly active antiretroviral therapy. *AIDS* 1998;12:1719-20.
- 45 Weir A, Wansbrough-Jones M. Mucosal Kaposi's sarcoma following protease inhibitor therapy in an HIV-infected patient. *AIDS* 1997;11:1895-6.
- 46 French M. Antiretroviral therapy immune restoration disease in HIV-infected patients on HAART. *AIDS Read* 1999;9:548-62
- 47 Gavazzi G, Bouchard O, Leclercq P, Morel-Baccard C, Bosserey A, et al. Change in transaminases in hepatitis C virus- and HIV-co-infected patients after highly active antiretroviral therapy: differences between complete and partial virologic responders? *AIDS Res Hum Retroviruses* 2000;16:1021-3.
- 48 Drake A, Mich A, Sasadeusz J. Immune reconstitution hepatitis in HIC and Hepatitis B co-infection despite lamivudine therapy as a part of HAART. *CID*, 2004;39:129-32.
- 49 Arribas JR, Ibáñez C, Ruiz-Antoran B, Peña JM, Esteban-Calvo C, Frías J, et al. Acute hepatitis in HIV-infected patients during ritonavir treatment. *AIDS* 1998;12:1722-4.
- 50 Mayo J, Collazos J, Martinez E. Progressive multifocal leukoencephalopathy following initiation of highly active antiretroviral therapy. *AIDS* 1998;12:1720-2.
- 51 Tantisiriwat W, Tebas P, Clifford DB, Powderly WG, Fichtenbaum CJ. Progressive multifocal leukoencephalopathy in patients with AIDS receiving highly active antiretroviral therapy. *Clin Infect Dis* 1999;28:1152-4.
- 52 Miralles P, Berenguer J, Lacruz C, Cosín J, López JC, Padilla B, et al. Inflammatory reactions in progressive multifocal leukoencephalopathy after highly active antiretroviral therapy. *AIDS* 2001;15:1900-2.
- 53 Bouscarat F, Maubec E, Matheron S, Descamps V. Immune recovery inflammatory folliculitis. *AIDS* 2000;14:617-8.
- 54 Woods ML, 2nd, MacGinley R, Eisen DP, Allworth AM. HIV combination therapy: partial immune restitution unmasking latent cryptococcal infection. *AIDS* 1998;12:1491-4.
- 55 French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS* 2004;18:1615-27.
- 56 Wislez M, Bergot E, Antoine M, Parrot A, Carette MF, Mayaud C, et al. Acute respiratory failure following HAART introduction in patients treated for *Pneumocystis carinii* pneumonia. *Am J Respir Crit Care Med* 2001;164:847-51.
- 57 Lawn SD. Immune reconstitution disease associated with Parasitic infections following initiation of anti-retroviral therapy. *Current Opinion in Infectious Diseases*. 2007;20:482-8.
- 58 Naccache JM, Antoine M, Wislez M, Fleury-Feith J, Oksenhendler E, Mayaud C, 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.
- 59 Foulon G, Wislez M, Naccache JM, Blanc FX, Rabbat A, Israël-Biet D, Valeyre D, Mayaud C, Cadranel J. Sarcoidosis in HIV-infected patients in the era of highly active antiretroviral therapy. *CID*, 2004;38:418-25.
- 60 Jubault V, Penfornis A, Schillo F, Hoen B, Izembart M, Timsit J, et al. Sequential occurrence of thyroid autoantibodies and Graves' disease after immune restoration in severely immunocompromised human immunodeficiency virus-1-infected patients. *J Clin Endocrinol Metab* 2000;85:4254-7.
- 61 Knysz B, Bolanowski M, Klimczak M, Gladysz AJ, Zwolinska K. Graves' Disease as an Immune reconstitution syndrome in a HIV-1-positive patient commencing effective antiretroviral therapy: Case report and Literature review. *Viral Immunology* 2006;19:102-7.
- 62 Hardwick C, White D, Morris E, Monteiro EF, Breen RA, Lipman M. Montelukast in the treatment of HIV associated immune reconstitution disease *Sex Transm Inf* 2006;82: 513-4.
- 63 Riddell J, Kaul DR, Karakousis PC, Gallant JE, Mitty J, Kazanjian PH. *Mycobacterium avium* complex immune reconstitution inflammatory syndrome: Long term outcomes. *J Trans Med* 2007;5:50.
- 64 Pett SL, Kelleher AD. Antiretroviral therapy-induced immune restoration in HIV-infection: a double edged sword? *Expert Rev Anti-infect. Ther.* 2004;2:335-9.
- 65 American Thoracic Society/ Centres for Disease Control and Prevention? Infectious Diseases Society of America. Treatment of Tuberculosis. *MMWR Recomm Rep* 2003. 52:1-77.

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- 66 Komanduri KV, Viswanathan MN, Wieder ED, Schmidt DK, Bredt BM, Jacobson MA, et al. Restoration of cytomegalovirus-specific CD4+ T-lymphocyte responses after ganciclovir and highly active antiretroviral therapy in individuals infected with HIV-1. *Nat Med* 1998;4:953-6.
- 67 Havlir DV, Schrier RD, Torriani FJ, Chervenak K, Hwang JY, Boom WH. Effect of potent antiretroviral therapy on immune responses to *Mycobacterium avium* in human immunodeficiency virus-infected subjects. *J Infect Dis* 2000;182:1658-63.
- 68 Kirk O, Lundgren JD, Pedersen C, Nielsen H, Gerstoft J. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? *AIDS* 1999;13:1647-51.
- 69 Cooney, EL. Clinical indicators of immune restoration following highly active antiretroviral therapy. *Clin Infect Dis* 2002;34:224-33.
- 70 Komanduri KV, Feinberg J, Hutchins RK, Frame RD, Schmidt DK, Viswanathan MN, et al. Loss of cytomegalovirus-specific CD4+ T cell responses in human immunodeficiency virus type 1-infected patients with high CD4+ T cell counts and recurrent retinitis. *J Infect Dis* 2001;183:1285-9.
- 71 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;32:815-19.