Prevention and treatment of the immune reconstitution inflammatory syndrome

Graeme Meintjes[a,b] and Lut Lynen[c]

[a]Institute of Infectious Diseases and Molecular Medicine and Department of Medicine, University of Cape Town, [b]GF Jooste Hospital, Cape Town, South Africa and [c]Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium

Correspondence to Graeme Meintjes, GF Jooste Hospital, Duinefontein Road, Manenberg, 7764, South Africa
Tel: +27 21 6901000; fax: +27 21 6920289; e-mail: graemein@mweb.co.za

Current Opinion in HIV and AIDS 2008, 3:468–476

Purpose of review

The immune reconstitution inflammatory syndrome occurs in a proportion of HIV-infected patients initiated on combination antiretroviral therapy and results from dysregulated inflammatory responses driven by the recovering immune system. Infective forms may manifest as the unmasking of preexisting untreated opportunistic infections or the paradoxical clinical deterioration of appropriately treated opportunistic infections. The prevention and treatment of this condition is the focus of much research attention, which is the scope of this review.

Recent findings

Approaches to prevention are informed by studies that have reported on risk factors, particularly those that are modifiable. Two key ongoing research issues are optimal screening for opportunistic infections prior to combination antiretroviral therapy in order to prevent unmasking forms and the optimal timing of combination antiretroviral therapy in patients on treatment for an opportunistic infection, balancing the risk of paradoxical immune reconstitution inflammatory syndrome that is associated with early initiation with the risk of advancing immunosuppression associated with delaying. In most cases of immune reconstitution inflammatory syndrome combination antiretroviral therapy has been continued. A variety of additional management strategies have been used including corticosteroids, nonsteroidal anti-inflammatory drugs, drainage procedures and surgery. The advantages and disadvantages of different management strategies are discussed.

Summary

No controlled clinical trials regarding the prevention or treatment of immune reconstitution inflammatory syndrome have been completed. There is a need for such studies in order to guide clinicians in their approach to this condition.

Keywords

cART, combination antiretroviral therapy, HIV, immune reconstitution inflammatory syndrome, IRIS

Curr Opin HIV AIDS 3:468–476

1746-630X

Introduction

The immune reconstitution inflammatory syndrome (IRIS) occurs in 15–25% of HIV-infected patients experiencing immune recovery on combination antiretroviral therapy (cART) [1]. IRIS may manifest as unmasking of preexisting untreated opportunistic infections or paradoxical clinical deterioration of known and appropriately treated opportunistic infections [2]. The most frequent forms of IRIS are in association with mycobacterial infections [especially tuberculosis (TB)], cryptococcosis and skin disorders. IRIS has also been reported in association with neoplasms [3–7], auto-immune conditions [8–12], and other inflammatory conditions such as sarcoidosis [13].

As cART is rolled out in resource limited settings the challenges that IRIS poses clinically and programmatically are increasingly being recognized [14,15•,16]. Much is known about the risk factors and spectrum of manifestations of IRIS, but no prospective controlled clinical trials regarding prevention and treatment have yet been completed. Our understanding of IRIS prevention is informed by evidence regarding risk factors for the condition, particularly those that are modifiable (Table 1 [15•,17••,18–22,23•,24–27,28••,29–37]). Our approaches to treatment are informed by reports of the outcomes of various treatment strategies used. Patients often require individualized approaches to management [38]. IRIS is associated with an exacerbation of pro-inflammatory responses driven by immune recovery [2,39,40•]. Thus anti-inflammatory treatments are the focus of therapeutic investigation.

In this review, we discuss the prevention of unmasking and paradoxical IRIS. General management principles are discussed with particular attention to the advantages

Table 1 Risk factors identified for the immune reconstitution inflammatory syndrome

	Risk factor	References
Related to opportunistic infection (OI)	Disseminated infection	[17••,18–22,23•]
	Higher number of OIs prior to cART	[24]
	Higher OI antigen load	[25]
	Shorter interval between starting OI treatment and cART	[15•,17••,18,21,25–27]
Related to baseline investigations	Lower CD4 cell count	[19,21,28••,29]
	Lower haemoglobin	[24]
	Lower CD4%	[30]
	Lower CD4 : CD8 ratio	[30]
	Higher viral load	[20,25,29]
Related to cART and response to cART	Use of ritonavir-boosted protease inhibitors	[28••,31,32]
	Greater CD4 response to cART	[19,29,30,33]
	Greater viral load response to cART	[26,27,28••,34,35]
	Greater CD4 cell percentage rise and CD4 : CD8 ratio rise on cART	[20]
Other factors	Younger age	[30]
	Black race	[17••]
	Certain genetic polymorphisms	[36,37]
	cART naïve	[23•,25,27]

cART, combined antiretroviral therapy.

and disadvantages of corticosteroids. We have focused on infective forms of IRIS. Areas where further research is needed are highlighted.

Prevention

Advanced immunosuppression increases the risk for opportunistic infections and disseminated infections, predisposing to IRIS, probably due to the presence of greater amounts of infective antigen [24]. Initiation of cART prior to advanced immunosuppression would be expected to reduce the risk of IRIS and the risk of early mortality. A low CD4 count at cART initiation is associated with increased mortality [41–44]. Some of these deaths are likely to be related to IRIS. Patients switching to second-line cART because of treatment failure may also develop IRIS [45,46]. In these cases, earlier switch may prevent IRIS.

Key issues that are the focus of ongoing research are how to optimally screen patients for opportunistic infections prior to starting cART and the optimal timing of cART after an opportunistic infection diagnosis [47••,48].

Preventing unmasking immune reconstitution inflammatory syndrome

A thorough screen for active opportunistic infections before cART initiation is critical. Detailed clinical assessment should direct investigations. Patients with advanced immunosuppression may have atypical or minimal symptoms related to active opportunistic infections owing to the absence of inflammatory response. Clinicians need to be alerted by nonspecific features such as recent rapid weight loss and decline in functional status. Investigations may include sputum smear examination, abdominal ultrasound, chest radiograph and serum cryptococcal antigen test [49•] to screen for TB, *Mycobacterium avium* complex (MAC) and cryptococcosis [38,50]. Fundoscopy should be performed to screen for cytomegalovirus (CMV) retinitis, especially in patients with a CD4 count under 100 cells/μl [51].

The sensitivity of symptom screening questionnaires for TB prior to isoniazid preventive therapy has been studied [52–54], but not prior to cART initiation. Some studies have demonstrated that the presence of symptoms is a reliable screen in HIV-infected people [52,53]. Others have shown that a small proportion of HIV-infected people without symptoms of TB may have active TB when investigated (2–10%) [54–58]. Extrapulmonary TB may present with nonspecific symptoms.

The sensitivity of chest radiography and sputum smear examination in diagnosing active TB is reduced in HIV-infection. Up to 30% of HIV-infected persons with sputum culture-proven TB may have normal chest radiographs [59] and over 50% may have negative sputum smears [59–61]. TB culture is unavailable in most resource-limited settings and waiting for results may delay cART. It is a priority that more sensitive, rapid and affordable diagnostic tests for TB are developed [62].

Preventing paradoxical immune reconstitution inflammatory syndrome

Regarding the prevention of paradoxical TB-IRIS, given that a shorter interval between starting TB treatment and cART has been identified as a risk factor [15•,17••,26,27], it would be expected that delaying cART to the end of TB treatment would reduce the risk of TB-IRIS. Delaying cART, however, carries the risk of advancing immunosuppression. The mortality of patients with HIV-associated TB not started on cART is substantial [63] and therefore given that mortality from TB-IRIS is relatively uncommon it has been argued that cART should thus not be delayed to prevent TB-IRIS in those with advanced immunosuppression [48,64]. A modelling study [47••]

suggested that if the mortality attributable to TB-IRIS is less than 4.6%, early cART initiation after TB treatment is preferable. WHO recommends cART initiation 2 weeks to 2 months after TB treatment is started in patients with a CD4 under 200 cells/μl, but delaying in patients with higher counts [65]. No prospective evidence on this issue exists, but studies are underway in South East Asia and Africa [66•].

Similarly the timing of cART in patients with cryptococcal meningitis is not based on prospective evidence. An individualized approach is used [67•] and most investigators recommend waiting at least 4 weeks after initiation of cryptococcal meningitis treatment [68]. Given that antigen load has been identified as an important risk factor (Table 1), it makes sense to use initial cryptococcal meningitis treatment that more rapidly reduces viable cryptococcal burden in the cerebral spinal fluid (CSF) such as amphotericin B rather than fluconazole monotherapy [67•,69].

Favoring early cART initiation after opportunistic infection treatment generally, the ACTG A5164 study, a randomized strategy trial of immediate versus deferred cART in patients diagnosed with acute opportunistic and bacterial infections, showed less AIDS progression and death in the immediate treatment arm who started cART a median of 12 days after opportunistic infection diagnosis. Patients with TB were excluded. The most common infections in the study population were *Pneumocystis jiroveci* pneumonia (63%), cryptococcal meningitis (13%) and bacterial pneumonia (10%). There was no difference in the incidence of IRIS between the two arms [70].

Some authors have suggested that more potent cART, especially with boosted protease inhibitors, carries a higher risk for IRIS [28••,31,32]. Whether these agents should be avoided in high-risk patients remains unclear. With respect to hepatitis B IRIS, given that tenofovir, lamivudine and emtricitabine also have antihepatitis B activity, it has been advised they are used for co-infected individuals [71,72]. By rapidly reducing hepatitis B viral load this may protect against hepatitis B IRIS. This has not been proven in prospective studies.

The treatment of immune reconstitution inflammatory syndrome

It is important to exclude differential diagnoses before deciding on treatment options [73•]. The most important are an alternative infection or malignancy, drug hypersensitivity reactions, antimicrobial drug resistance [74•], poor adherence or drug malabsorption [75]. Distinguishing hepatic TB-IRIS from drug-induced hepatitis may be difficult [76].

There are many case reports and series reporting various approaches to management. Most IRIS cases are self-limiting, mortality is uncommon and corticosteroid therapy, which has been most frequently used, has potentially significant adverse effects. In some cases, IRIS has been associated with substantial morbidity [17••] and is potentially life threatening [17••,77].

Management of unmasking IRIS should be targeted at diagnosing the opportunistic infection and instituting appropriate treatment. There are few reports of the use of corticosteroids for this form of IRIS, mainly in those associated with mycobacterial infections [78,79]. In paradoxical IRIS it is important to ensure the patient is on optimal therapy for the opportunistic infection. Usually cART is continued, but some have suggested interrupting cART if IRIS is lifethreatening or unresponsive to corticosteroids [80,81] and there have been reports of response to this strategy [81–84]. cART interruption, however, places the patient at risk of other opportunistic infections and development of cART resistance. IRIS may still recur when cART is re-initiated [82,83,85]. In mild cases management is supportive: symptomatic treatment and reassurance.

Corticosteroids at a range of doses have been used, particularly in patients with severe manifestations. The risks and benefits of corticosteroids need to be weighed. Corticosteroids have been shown to be associated with an excess of Kaposi's sarcoma and herpes virus reactivations in HIV-infected patients [86,87] as well as typical steroid side-effects such as diabetes mellitus and hypertension [88]. If the diagnosis of IRIS is incorrect and the cause for deterioration is drug resistance, or an undiagnosed infection, steroids would worsen the patient's condition.

The duration of corticosteroid therapy required is variable. Some require a few weeks, whereas a subgroup of patients with mycobacterial IRIS may require prolonged courses to control symptoms [28••,89•]. In a report of 49 cases of IRIS related to various infections [28••], 32% received prednisone. This was mainly (75%) in patients with IRIS associated with mycobacterial infections. The median duration of prednisone treatment was 138 days (range 21–551 days). Four patients [two with TB and two with non-tuberculous mycobacterial (NTM) infection] required prednisone for over 6 months. This was attributed to high antigen burden resulting in prolonged stimulus for IRIS from dead organisms.

Other management strategies used are shown in Table 2 [17••,18,20–22,26,78,81,90–98]. The treatment of common forms of infective IRIS is discussed below.

Table 2 Treatment strategies that have been used for immune reconstitution inflammatory syndrome

Treatment	References[a]
No additional intervention other than continuation of cART and OI treatment	
Symptomatic treatment	
Corticosteroids	
Systemic	[18,21,78]
Local corticosteroid injections for CMV IRV	[90,91]
NSAIDs	[92]
Needle aspiration of cold abscesses	[17••,93]
Therapeutic lumbar punctures and other drainage procedures for CM-IRIS	
Surgery for cold abscess drainage and complications such as bowel perforation	[22,94]
cART interruption	[20,26,81,95]
Thalidomide	[21,96]
Pentoxyfiline	[97]
IL-2 and GM-CSF	[98]
Hydroxychloroquine	[95]

cART, combined antiretroviral therapy; CM, cryptococcal meningitis; CMV IRV, cytomegalovirus immune recovery vitritis; GM-CSF, granulocyte/macrophage colony stimulating factor; IRIS, immune reconstitution inflammatory syndrome; OI, opportunistic infection.
[a]References given are examples of studies in which these strategies have been used.

Paradoxical tuberculosis immune reconstitution inflammatory syndrome

New, recurrent or worsening TB clinical or radiological manifestations develop in 8–45% of patients started on cART while on TB treatment [15•,16,18–20,27,34,99]. Many cases are mild and self-limiting, only symptomatic treatment being required. Mortality is infrequent [15•,16,35]. In a review of 86 TB-IRIS cases, management involved corticosteroids in 26%, cART interruption in 15% and surgery in 7% [80]. Breen *et al.* [18] reported that among eight patients, treated with corticosteroids because of severe systemic manifestations or prolonged IRIS, all improved after a median of 3 days.

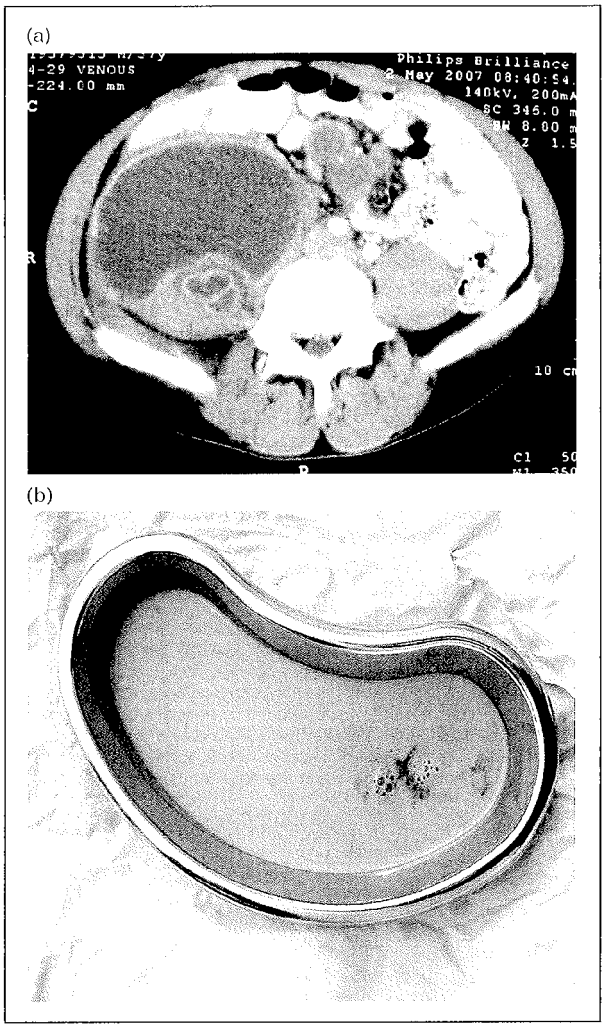
Corticosteroid use is supported by evidence for their role as adjunctive treatment for TB meningitis [100] and pericarditis [101,102] in non-IRIS settings. It is proposed that steroids blunt immunopathogenic pro-inflammatory responses in these settings and may have a similar role in TB-IRIS. Most clinicians would consider corticosteroids for patients with severe presentations such as respiratory failure, vital structure compression or central nervous system (CNS) manifestations. CNS manifestations (enlarging tuberculomata or tuberculous meningitis) likely carry the worst prognosis [103•]. Whether corticosteroids are indicated for less severe presentations remains to be determined. A randomized placebo-controlled trial of prednisone for mild and moderate TB-IRIS is underway in South Africa.

In rare cases, cART has been interrupted for severe manifestations [20]. Surgery may be required for complications such as organ rupture or for drainage procedures. Radiology-guided aspiration of cold abscesses (Fig. 1) has been reported to provide symptomatic relief [93].

Nontuberculous mycobacterial immune reconstitution inflammatory syndrome

Management principles are similar to TB-IRIS. Desimone *et al.* [104] proposed a management algorithm for MAC IRIS lymphadenitis which included appropriate MAC therapy, continuing cART, corticosteroids for painful lymphadenopathy and surgery for suppurative or nonresponsive lesions. Surgery may be complicated by chronic sinuses due to poor wound healing. In one study [78], among nine patients treated with prednisone for NTM-IRIS, eight responded. In another, among 20 cases of MAC IRIS [89•], eight patients received corticosteroids for an

Figure 1 Right psoas abscess due to tuberculosis immune reconstitution inflammatory syndrome



(a) This patient developed a right psoas abscess due to tuberculosis immune reconstitution inflammatory syndrome that was complicated by a right femoral deep vein thrombosis due to venous compression. (b) A volume of 2000 ml of caseous pus was aspirated under radiological guidance resulting in symptomatic relief.

average of 17 months. One required 48 months of corticosteroids.

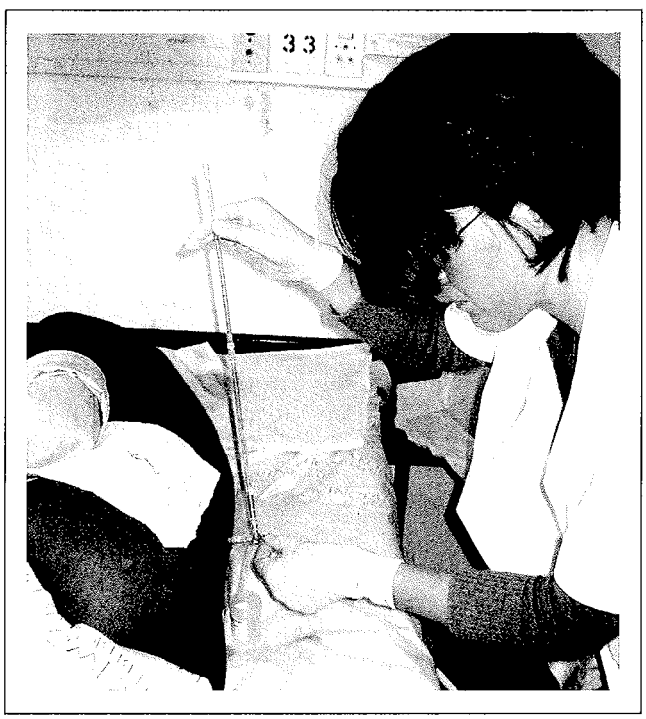
Cryptococcal immune reconstitution inflammatory syndrome

The most frequent manifestation is recurrence of meningitis in patients previously treated for cryptococcal meningitis. Typically the CSF is fungal culture negative and there may be associated raised intracranial pressure (median opening pressure 39 cm H_2O in one study [25]). Most patients have continued antifungal therapy and cART. Some patients require therapeutic lumbar punctures to control raised intracranial pressure and corticosteroids have been used for refractory cases [21,84,95]. Therapeutic lumbar punctures (Fig. 2) have been shown to reduce morbidity and mortality in those with raised intracranial pressure associated with cryptococcal meningitis generally [105]. Occasionally other drainage procedures such as lumbar drains and ventric-ular shunts are required to control raised pressures in cryptococcal meningitis [106].

Cytomegalovirus immune recovery vitritis

CMV immune recovery vitritis (IRV) mainly occurs in patients with treated CMV retinitis after cART initiation and manifests with floaters and impaired visual acuity [90,91,107]. cART and anti-CMV therapy should be continued. Most cases are mild and transient and do not require additional treatment [91]. In those with severe or persistent symptoms, particularly those with declining visual acuity or cystoid macular oedema, anti-inflammatory therapy is required. Topical corticosteroids have been used [91,107]. Henderson and Mitchell [91] reported improvement or stabilization in nine eyes with severe or persistent CMV IRV treated with orbital floor corticosteroid injections after topical therapy had failed. Periocular corticosteroid injections have not been associated with CMV retinitis reactivation [90,91]. Systemic corticosteroids [90] and acetazolamide [91] have rarely been used.

Figure 2 Cryptococcal meningitis immune reconstitution inflammatory syndrome is frequently complicated by raised intracranial pressure



In patients with cryptococcal meningitis-immune reconstitution inflammatory syndrome the cerebrospinal fluid opening pressure should be measured at lumbar puncture and if elevated serial therapeutic lumbar punctures should be performed.

Progressive multifocal leukoencephalopathy immune reconstitution inflammatory syndrome

There is no specific therapy for JC virus infection [the cause of progressive multifocal leukoencephalopathy (PML)], but prognosis is improved by cART [32,108]. A subgroup will paradoxically deteriorate after starting cART due to PML IRIS. This is characterized by features of inflammation on brain imaging and histology [109,110]. Fatalities are reported [32,111]. Some with PML IRIS have improved after initial deterioration without interruption of cART [110,112] suggesting that in these cases the inflammation was self-limiting and immune reconstitution then controlled JC virus infection [113]. It has been suggested that corticosteroids should only be used in severe inflammatory reactions with significant cerebral oedema and mass effect [110,113]. One patient had marked and sustained improvement following cART interruption for 2 weeks and treatment with dexamethasone [109]. Some patients have died after transient improvement with corticosteroids [111]. The role of corticosteroids remains controversial considering there is no specific treatment for JC virus infection and it is postulated that an inflammatory response in PML may actually prevent disease progression and improve prognosis [113].

Cutaneous manifestations of immune reconstitution inflammatory syndrome

Cutaneous forms of IRIS account for around half of cases [14,33] and usually respond to specific therapy for the associated condition [114]. Patients with herpes zoster and simplex IRIS typically respond to appropriate antivirals [29,115], but refractory cases of simplex IRIS are described [116]. Distinguishing an IRIS rash from a drug rash is important so as to avoid inappropriate treatment discontinuation [114].

Viral hepatitis immune reconstitution inflammatory syndrome

Chronic viral hepatitis may flare as a result of IRIS. When severe, cART should be interrupted because of difficulties

differentiating from drug-induced hepatitis and potential risk of hepatic failure. In less severe cases, liver enzymes should be closely monitored, but cART should not be interrupted prematurely [2]. Corticosteroids are not advised [117••].

Conclusion

While no controlled clinical trials regarding the prevention or treatment of IRIS have been completed, our approach to these issues is informed by studies reporting on risk factors and management approaches used. To prevent unmasking IRIS it is important to exclude active opportunistic infections prior to cART. Optimum strategies, particularly for excluding TB in resource-limited settings, need further study. A shorter delay between treatment for an opportunistic infection and cART is a risk factor for paradoxical IRIS. Nonetheless one recent study [70] showed that cART introduction early after opportunistic infection treatment reduced mortality and disease progression. Further prospective evidence regarding optimal timing of cART in patients with TB and cryptococcal meningitis is needed.

Mild cases can be managed without cART interruption, continuation of opportunistic infection treatment and symptomatic therapy. Severe cases may require corticosteroid treatment. cART has been interrupted in life-threatening cases. Prospective clinical trials to define the role of corticosteroids and other immunomodulatory therapy are required. Consensus case definitions for IRIS should be used to allow for comparability of results [118•].

Acknowledgements

Graeme Meintjes is funded by the Wellcome Trust, UK.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 527–528).

1 Shelburne SA, Montes M, Hamill RJ. Immune reconstitution inflammatory syndrome: more answers, more questions. J Antimicrob Chemother 2006; 57:167–170.

2 Shelburne SA 3rd, Hamill RJ. The immune reconstitution inflammatory syndrome. AIDS Rev 2003; 5:67–79.

3 Connick E, Kane MA, White IE, *et al.* Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma during potent antiretroviral therapy. Clin Infect Dis 2004; 39:1852–1855.

4 Bower M, Nelson M, Young AM, *et al.* Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma. J Clin Oncol 2005; 23:5224–5228.

5 Weir A, Wansbrough-Jones M. Mucosal Kaposi's sarcoma following protease inhibitor therapy in an HIV-infected patient. AIDS 1997; 11:1895–1896.

6 Powles T, Thirlwell C, Nelson M, Bower M. Immune reconstitution inflammatory syndrome mimicking relapse of AIDS related lymphoma in patients with HIV 1 infection. Leuk Lymphoma 2003; 44:1417–1419.

7 Knysz B, Kuliszkiewicz-Janus M, Jelen M, *et al.* Non-Hodgkin's lymphoma as a rare manifestation of immune reconstitution disease in HIV-1 positive patients. Postepy Hig Med Dosw (Online) 2006; 60:547–551.

8 French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. AIDS 2004; 18:1615–1627.

9 Crum NF, Ganesan A, Johns ST, Wallace MR. Graves disease: an increasingly recognized immune reconstitution syndrome. AIDS 2006; 20:466–469.

10 Calza L, Manfredi R, Colangeli V, *et al.* Systemic and discoid lupus erythematosus in HIV-infected patients treated with highly active antiretroviral therapy. Int J STD AIDS 2003; 14:356–359.

11 Chen F, Day SL, Metcalfe RA, *et al.* Characteristics of autoimmune thyroid disease occurring as a late complication of immune reconstitution in patients with advanced human immunodeficiency virus (HIV) disease. Medicine (Baltimore) 2005; 84:98–106.

12 Calabrese LH, Kirchner E, Shrestha R. Rheumatic complications of human immunodeficiency virus infection in the era of highly active antiretroviral therapy: emergence of a new syndrome of immune reconstitution and changing patterns of disease. Semin Arthritis Rheum 2005; 35:166–174.

13 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; 41:285–286.

14 Puthanakit T, Oberdorfer P, Akarathum N, *et al.* Immune reconstitution syndrome after highly active antiretroviral therapy in human immunodeficiency virus-infected thai children. Pediatr Infect Dis J 2006; 25:53–58.

15 • Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. AIDS 2007; 21:335–341.
This study reported the incidence and risk factors for TB IRIS in a cART cohort in South Africa.

16 Manosuthi W, Kiertiburanakul S, Phoorisri T, Sungkanuparph S. Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculous and antiretroviral therapy. J Infect 2006; 53:357–363.

17 •• Burman W, Weis S, Vernon A, *et al.* Frequency, severity and duration of immune reconstitution events in HIV-related tuberculosis. Int J Tuberc Lung Dis 2007; 11:1282–1289.
This prospective study of patients starting cART while on TB treatment, documented 25 TB-IRIS events. The need for hospitalization and therapeutic procedures was appreciable in these patients indicating that TB-IRIS may be associated with significant morbidity.

18 Breen RA, Smith CJ, Bettinson H, *et al.* Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. Thorax 2004; 59:704–707.

19 Michailidis C, Pozniak AL, Mandalia S, *et al.* Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. Antivir Ther 2005; 10:417–422.

20 Breton G, Duval X, Estellat C, *et al.* Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. Clin Infect Dis 2004; 39:1709–1712.

21 Lortholary O, Fontanet A, Memain N, *et al.* Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococcosis in France. AIDS 2005; 19:1043–1049.

22 Wendel KA, Alwood KS, Gachuhi R, *et al.* Paradoxical worsening of tuberculosis in HIV-infected persons. Chest 2001; 120:193–197.

23 • Serra FC, Hadad D, Orofino RL, *et al.* Immune reconstitution syndrome in patients treated for HIV and tuberculosis in Rio de Janeiro. Braz J Infect Dis 2007; 11:462–465.
This is the only study to report a clinical sign as a predictor of TB-IRIS: the presence of peripheral lymphadenopathy at the time of TB diagnosis strongly predicted the subsequent occurrence of IRIS (11-fold more likely).

24 Robertson J, Meier M, Wall J, *et al.* Immune reconstitution syndrome in HIV: validating a case definition and identifying clinical predictors in persons initiating antiretroviral therapy. Clin Infect Dis 2006; 42:1639–1646.

25 Shelburne SA 3rd, Darcourt J, White AC Jr, *et al.* The role of immune reconstitution inflammatory syndrome in AIDS-related Cryptococcus neoformans disease in the era of highly active antiretroviral therapy. Clin Infect Dis 2005; 40:1049–1052.

26 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.

27 Shelburne SA, Visnegarwala F, Darcourt J, *et al.* Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. AIDS 2005; 19:399–406.

28 Manabe YC, Campbell JD, Sydnor E, Moore RD. Immune reconstitution •• inflammatory syndrome: risk factors and treatment implications. J Acquir Immune Defic Syndr 2007; 46:456–462.

This case-control study in an American cART cohort provides novel insights into the risk factors associated with IRIS. Experience with the use of corticosteroids to treat IRIS is reported. Corticosteroids were predominantly used for mycobacterial IRIS and some patients required prolonged therapy.

29 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; 1:107–115.

30 Ratnam I, Chiu C, Kandala NB, Easterbrook PJ. Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1-infected cohort. Clin Infect Dis 2006; 42:418–427.

31 Vidal JE, Fink MC, Cedeno-Laurent F, *et al.* BK virus associated meningoencephalitis in an AIDS patient treated with HAART. AIDS Res Ther 2007; 4:13.

32 Cinque P, Pierotti C, Vigano MG, *et al.* The good and evil of HAART in HIV-related progressive multifocal leukoencephalopathy. J Neurovirol 2001; 7:358–363.

33 Jevtovic DJ, Salemovic D, Ranin J, *et al.* The prevalence and risk of immune restoration disease in HIV-infected patients treated with highly active antiretroviral therapy. HIV Med 2005; 6:140–143.

34 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; 158:157–161.

35 Olalla J, Pulido F, Rubio R, *et al.* Paradoxical responses in a cohort of HIV-1-infected patients with mycobacterial disease. Int J Tuberc Lung Dis 2002; 6:71–75.

36 Price P, Mathiot N, Krueger R, *et al.* Immune dysfunction and immune restoration disease in HIV patients given highly active antiretroviral therapy. J Clin Virol 2001; 22:279–287.

37 Price P, Morahan G, Huang D, *et al.* Polymorphisms in cytokine genes define subpopulations of HIV-1 patients who experienced immune restoration diseases. Aids 2002; 16:2043–2047.

38 Knysz B, Gladysz A. Immune reconstitution diseases: is it possible to establish recommendations? Postepy Hig Med Dosw (Online) 2007; 61:220–225.

39 Bourgarit A, Carcelain G, Martinez V, *et al.* Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients. Aids 2006; 20:F1–F7.

40 French MA. Disorders of immune reconstitution in patients with HIV infection • responding to antiretroviral therapy. Curr HIV/AIDS Rep 2007; 4:16–21.

An important conceptual paper that categorises the various disorders of immune reconstitution that may occur in HIV-infected patients on cART.

41 Braitstein P, Brinkhof MW, Dabis F, *et al.* Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet 2006; 367:817–824.

42 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; 360:119–129.

43 Hogg RS, Yip B, Chan KJ, *et al.* Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. JAMA 2001; 286:2568–2577.

44 Palella FJ Jr, Deloria-Knoll M, Chmiel JS, *et al.* Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata. Ann Intern Med 2003; 138:620–626.

45 Corti M, Villafane MF, Ambroggi M, *et al.* Soft tissue abscess and lymphadenitis due to Mycobacterium avium complex as an expression of immune reconstitution inflammatory syndrome after a second scheme of highly active antiretroviral therapy. Rev Inst Med Trop Sao Paulo 2007; 49:267–270.

46 Kumarasamy N, Venkatesh KK, Devaleenal B, *et al.* Opportunities and options for the use of protease inhibitors in a resource-poor setting: experiences from southern India. J Acquir Immune Defic Syndr 2007; 46:119–121.

47 Schiffer JT, Sterling TR. Timing of antiretroviral therapy initiation in tubercu- •• losis patients with AIDS: a decision analysis. J Acquir Immune Defic Syndr 2007; 44:229–234.

The first study to use a modeling approach to estimate the risks associated with early versus delayed initiation of cART in patients with TB. In the absence of clinical trials data regarding this issue, this study serves as a useful guide emphasizing the mortality benefit of not delaying cART, despite the higher risk of IRIS.

48 Lawn SD, Wood R. Optimum time to initiate antiretroviral therapy in patients with HIV-associated tuberculosis: there may be more than one right answer. J Acquir Immune Defic Syndr 2007; 46:121–123; author reply 123.

49 Micol R, Lortholary O, Sar B, *et al.* Prevalence, determinants of positivity, and • clinical utility of cryptococcal antigenemia in Cambodian HIV-infected patients. J Acquir Immune Defic Syndr 2007; 45:555–559.

Study from Cambodia which demonstrates the value of serum cryptococcal antigen testing as a screening tool to exclude cryptococcal disease before the start of cART.

50 Lynen L. Chapter 16: opportunistic infections and HAART. In: Clinical HIV/AIDS care guidelines for resource-poor settings. 2nd ed. Belgium-Luxemburg: MSF; 2006. pp. 287–308.

51 Heiden D, Ford N, Wilson D, *et al.* Cytomegalovirus retinitis: the neglected disease of the AIDS pandemic. PLoS Med 2007; 4:e334.

52 Mohammed A, Ehrlich R, Wood R, *et al.* Screening for tuberculosis in adults with advanced HIV infection prior to preventive therapy. Int J Tuberc Lung Dis 2004; 8:792–795.

53 Mosimaneotsile B, Talbot EA, Moeti TL, *et al.* Value of chest radiography in a tuberculosis prevention programme for HIV-infected people, Botswana. Lancet 2003; 362:1551–1552.

54 Day JH, Charalambous S, Fielding KL, *et al.* Screening for tuberculosis prior to isoniazid preventive therapy among HIV-infected gold miners in South Africa. Int J Tuberc Lung Dis 2006; 10:523–529.

55 Mtei L, Matee M, Herfort O, *et al.* High rates of clinical and subclinical tuberculosis among HIV-infected ambulatory subjects in Tanzania. Clin Infect Dis 2005; 40:1500–1507.

56 Wood R, Middelkoop K, Myer L, *et al.* Undiagnosed tuberculosis in a community with high HIV prevalence: implications for tuberculosis control. Am J Respir Crit Care Med 2007; 175:87–93.

57 Swaminathan S, Paramasivan CN, Kumar SR, *et al.* Unrecognised tuberculosis in HIV-infected patients: sputum culture is a useful tool. Int J Tuberc Lung Dis 2004; 8:896–898.

58 Hawken M, Nganga L, Meme H, *et al.* Is cough alone adequate to screen HIV-positive persons for tuberculosis preventive therapy in developing countries? Int J Tuberc Lung Dis 1999; 3:540–541.

59 Harries AD, Banda HT, Boeree MJ, *et al.* Management of pulmonary tuberculosis suspects with negative sputum smears and normal or minimally abnormal chest radiographs in resource-poor settings. Int J Tuberc Lung Dis 1998; 2:999–1004.

60 Colebunders R, Bastian I. A review of the diagnosis and treatment of smear-negative pulmonary tuberculosis. Int J Tuberc Lung Dis 2000; 4:97–107.

61 Siddiqi K, Lambert ML, Walley J. Clinical diagnosis of smear-negative pulmonary tuberculosis in low-income countries: the current evidence. Lancet Infect Dis 2003; 3:288–296.

62 Perkins MD, Cunningham J. Facing the crisis: improving the diagnosis of tuberculosis in the HIV era. J Infect Dis 2007; 196 (Suppl 1):S15–S27.

63 Mwaungulu FB, Floyd S, Crampin AC, *et al.* Cotrimoxazole prophylaxis reduces mortality in human immunodeficiency virus-positive tuberculosis patients in Karonga District, Malawi. Bull World Health Organ 2004; 82:354–363.

64 Lawn SD, Wood R. When should antiretroviral treatment be started in patients with HIV-associated tuberculosis in South Africa? S Afr Med J 2007; 97:412–415.

65 WHO. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public healthy approach. 2006 revision. Geneva: World Health Organisation; 2006.

66 Blanc FX, Havlir DV, Onyebujoh PC, *et al.* Treatment strategies for HIV- • infected patients with tuberculosis: ongoing and planned clinical trials. J Infect Dis 2007; 196 (Suppl 1):S46–S51.

Review that highlights the gaps that exist in the evidence base regarding the management of TB-HIV co-infection and the clinical trials that are ongoing in this regard.

67 Khawcharoenporn T, Apisarnthanarak A, Mundy LM. Treatment of crypto- • coccosis in the setting of HIV coinfection. Expert Rev Anti Infect Ther 2007; 5:1019–1030.

Review of cryptococcal meningitis management issues in the context of HIV.

68 Jarvis JN, Harrison TS. HIV-associated cryptococcal meningitis. AIDS 2007; 21:2119–2129.

69 Brouwer AE, Rajanuwong A, Chierakul W, *et al.* Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. Lancet 2004; 363:1764–1767.

70 Zolopa A, Andersen J, Komarow L, *et al.* Immediate versus deferred ART in the setting of acute AIDS-related opportunistic infection: final results of a randomized strategy trial, ACTG A5164 [abstract]. In: Programme and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections; 3–6 February 2008; Boston. Alexandria: CROI; 2008. Abstract 142.

71 Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Washington, DC: Department of Health and Human Services; 29 January 2008. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. [Accessed 2 April 2008]

72 BHIVA Coinfection Guideline Committee on behalf of the BHIVA Executive Committee. BHIVA Guidelines: HIV and Chronic Hepatitis: Co-Infection with HIV and Hepatitis B Virus Infection. London: BHIVA; 2004.

73 • Dhasmana DJ, Dheda K, Ravn P, *et al.* Immune Reconstitution Inflammatory Syndrome in HIV-Infected Patients Receiving Antiretroviral Therapy: Pathogenesis, Clinical Manifestations and Management. Drugs 2008; 68:191–208.
A review of IRIS focusing on the pathogenesis, spectrum of clinical manifestations and management.

74 • Bicanic T, Harrison T, Niepieklo A, *et al.* Symptomatic relapse of HIV-associated cryptococcal meningitis after initial fluconazole monotherapy: the role of fluconazole resistance and immune reconstitution. Clin Infect Dis 2006; 43:1069–1073.
Interesting study showing the difficulty that may arise in differentiating cryptococcal meningitis relapse due to IRIS from that due to fluconazole resistance.

75 McIlleron H, Wash P, Burger A, *et al.* Determinants of rifampin, isoniazid, pyrazinamide, and ethambutol pharmacokinetics in a cohort of tuberculosis patients. Antimicrob Agents Chemother 2006; 50:1170–1177.

76 Lawn SD, Wood R. Hepatic involvement with tuberculosis-associated immune reconstitution disease. AIDS 2007; 21:2362–2363.

77 Lawn SD, Bekker LG, Myer L, *et al.* Cryptococcocal immune reconstitution disease: a major cause of early mortality in a South African antiretroviral programme. Aids 2005; 19:2050–2052.

78 Phillips P, Bonner S, Gataric N, *et al.* Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. Clin Infect Dis 2005; 41:1483–1497.

79 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; 79:337–338.

80 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.

81 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.

82 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.

83 Foudraine NA, Hovenkamp E, Notermans DW, *et al.* Immunopathology as a result of highly active antiretroviral therapy in HIV-1-infected patients. Aids 1999; 13:177–184.

84 Shelburne SA 3rd, Hamill RJ, Rodriguez-Barradas MC, *et al.* Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. Medicine (Baltimore) 2002; 81:213–227.

85 Sotto A, Guillot B, Dandurand M, Jourdan J. Exacerbation of skin mycobacterial lesions under highly active antiretroviral therapy in an HIV-infected patient. Aids 1999; 13:1790–1791.

86 Elliott AM, Halwiindi B, Bagshawe A, *et al.* Use of prednisolone in the treatment of HIV-positive tuberculosis patients. Q J Med 1992; 85:855–860.

87 Elliott AM, Luzze H, Quigley MA, *et al.* A randomized, double-blind, placebo-controlled trial of the use of prednisolone as an adjunct to treatment in HIV-1-associated pleural tuberculosis. J Infect Dis 2004; 190:869–878.

88 Mayanja-Kizza H, Jones-Lopez E, Okwera A, *et al.* Immunoadjuvant prednisolone therapy for HIV-associated tuberculosis: a phase 2 clinical trial in Uganda. J Infect Dis 2005; 191:856–865.

89 • Riddell Jt, Kaul DR, Karakousis PC, *et al.* Mycobacterium avium complex immune reconstitution inflammatory syndrome: Long term outcomes. J Transl Med 2007; 5:50.
A case series of 20 patients with MAC-IRIS that demonstrates that this condition may run a prolonged course and be complex to manage.

90 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.

91 Henderson HW, Mitchell SM. Treatment of immune recovery vitritis with local steroids. Br J Ophthalmol 1999; 83:540–545.

92 Skiest DJ, Hester LJ, Hardy RD. Cryptococcal immune reconstitution inflammatory syndrome: report of four cases in three patients and review of the literature. J Infect 2005; 51:e289–e297.

93 Rajeswaran G, Becker JL, Michailidis C, *et al.* The radiology of IRIS (immune reconstitution inflammatory syndrome) in patients with mycobacterial tuberculosis and HIV co-infection: Appearances in 11 patients. Clin Radiol 2006; 61:833–843.

94 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; 45:977–978.

95 Boelaert JR, Goddeeris KH, Vanopdenbosch LJ, Casselman JW. Relapsing meningitis caused by persistent cryptococcal antigens and immune reconstitution after the initiation of highly active antiretroviral therapy. AIDS 2004; 18:1223–1224.

96 Fernandes GC, Vieira MA, Lourenco MC, *et al.* Inflammatory paradoxical reaction occurring in tuberculosis patients treated with HAART and rifampicin. Rev Inst Med Trop Sao Paulo 2002; 44:113–114.

97 John M, French MA. Exacerbation of the inflammatory response to Mycobacterium tuberculosis after antiretroviral therapy. Med J Aust 1998; 169:473–474.

98 Pires A, Nelson M, Pozniak AL, *et al.* Mycobacterial immune reconstitution inflammatory syndrome in HIV-1 infection after antiretroviral therapy is associated with deregulated specific T-cell responses: beneficial effect of IL-2 and GM-CSF immunotherapy. J Immune Based Ther Vaccines 2005; 3:7.

99 Kumarasamy N, Chaguturu S, Mayer KH, *et al.* Incidence of immune reconstitution syndrome in HIV/tuberculosis-coinfected patients after initiation of generic antiretroviral therapy in India. J Acquir Immune Defic Syndr 2004; 37:1574–1576.

100 Thwaites GE, Nguyen DB, Nguyen HD, *et al.* Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med 2004; 351:1741–1751.

101 Strang JI, Kakaza HH, Gibson DG, *et al.* Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. Lancet 1987; 2:1418–1422.

102 Hakim JG, Ternouth I, Mushangi E, *et al.* Double blind randomised placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. Heart 2000; 84: 183–188.

103 • Murdoch DM, Venter WD, Van Rie A, Feldman C. Immune reconstitution inflammatory syndrome (IRIS): review of common infectious manifestations and treatment options. AIDS Res Ther 2007; 4:9.
Review of IRIS that focuses on the most frequent infectious manifestations of the condition: TB, NTM, CMV, varicella zoster and cryptococcal.

104 Desimone JA Jr, Babinchak TJ, Kaulback KR, Pomerantz RJ. Treatment of Mycobacterium avium complex immune reconstitution disease in HIV-1-infected individuals. AIDS Patient Care STDS 2003; 17:617–622.

105 Graybill JR, Sobel J, Saag M, *et al.* Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups. Clin Infect Dis 2000; 30:47–54.

106 Macsween KF, Bicanic T, Brouwer AE, *et al.* Lumbar drainage for control of raised cerebrospinal fluid pressure in cryptococcal meningitis: case report and review. J Infect 2005; 51:e221–e224.

107 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.

108 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 (Suppl 1):73–80.

109 Martinez JV, Mazziotti JV, Efron ED, *et al.* Immune reconstitution inflammatory syndrome associated with PML in AIDS: a treatable disorder. Neurology 2006; 67:1692–1694.

110 Silva MT, Pacheco MC Jr, Vaz B. Inflammatory progressive multifocal leukoencephalopathy after antiretroviral treatment. AIDS 2006; 20:469–471.

111 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.

112 D'Amico R, Sarkar ,S, Yusuff J, *et al.* Immune reconstitution after potent antiretroviral therapy in AIDS patients with progressive multifocal leukoencephalopathy. Scand J Infect Dis 2007; 39:347–350.

113 Du Pasquier RA, Koralnik IJ. Inflammatory reaction in progressive multifocal leukoencephalopathy: harmful or beneficial? J Neurovirol 2003; 9 (Suppl 1): 25–31.

114 Lehloenya R, Meintjes G. Dermatologic manifestations of the immune reconstitution inflammatory syndrome. Dermatol Clin 2006; 24:549–570.

115 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.

116 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; 1:10–18.

117 •• Lesho E. Evidence base for using corticosteroids to treat HIV-associated immune reconstitution syndrome. Expert Rev Anti Infect Ther 2006; 4:469–478.

An important review of the role that corticosteroids play in the management of various forms of IRIS. The literature that has reported on the use of steroids in IRIS is reviewed in detail. The rationale, advantages and disadvantages of corticosteroids for IRIS are discussed.

118 • Colebunders R, John L, Huyst V, *et al.* Tuberculosis immune reconstitution inflammatory syndrome in countries with limited resources. Int J Tuberc Lung Dis 2006; 10:946–953.

A review on TB-IRIS that emphasizes the need for a uniform clinical case definition that can be used in resource limited settings to facilitate comparison between studies.