Immune reconstitution inflammatory syndrome after highly active antiretroviral therapy: a review

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Summary

The use of highly active antiretroviral therapy (HAART) in the management of human immunodeficiency virus (HIV) restores immune responses against pathogens and has greatly decreased mortality. However, in about 25% to 35% of patients receiving HAART, the reconstituted immune system leads to a pathological inflammatory response, commonly known as immune reconstitution inflammatory syndrome (IRIS), which causes substantial short-term morbidity, or even mortality. Although we have gleaned some knowledge on IRIS in the past few years, a number of unanswered questions remain. In this review, we discuss the definition, diagnostic criteria, pathogenesis, risk factors, clinical spectrum including oral manifestations, and management of IRIS.

Introduction

Since the introduction of highly active antiretroviral therapy (HAART) in 1995, the incidence of opportunistic infections, incidence of acquired immunodeficiency syndrome (AIDS), and overall mortality of human immunodeficiency virus (HIV)-infected individuals have all markedly decreased (Mocroft *et al*., 2003). It is becoming clear, however, that some patients receiving HAART show clinical deterioration despite increased CD4+ T-cell counts and decreased plasma HIV viral loads (French *et al*., 2000). This phenomenon has been termed immune restoration disease, immune reconstitution syndrome, or paradoxical reactions, because of clinical deterioration during the apparent recovery of the immune system. Immune reconstitution inflammatory syndrome (IRIS) is another widely used and accepted term because of the role of the host inflammatory response (Shelburne *et al*., 2002). The latter term will be used throughout this review.

According to the available literature, about 25% to 35% of HIV-infected patients responding to HAART develop IRIS, with the majority of cases occurring within the first 60 days of initiating HAART (French *et al*., 2000; Narita *et al*., 1998). The clinical manifestations of IRIS are diverse and depend on the infectious or noninfectious agents involved. However, lack of consensus on the definition of IRIS and on standardization in clinical and laboratory diagnosis may result in the labeling of any condition after initiation of HAART that is atypical or difficult to classify as being IRIS (Reddy and Luzzi, 2005).

Whether oral diseases play a role in IRIS is unclear. Recognition of this entity is crucial, for successful treatment relies on alleviation of the patient's symptoms without compromising antiretroviral or antimicrobial therapy. To date, only a few studies have reported oral lesions in association with IRIS. Hence, the aim of this review is to provide an update on IRIS and its clinical manifestations, with special attention to oral disease. Citations were searched systematically by two independent reviewers using the NCBI PubMed database with the search terms of "immune reconstitution inflammatory syndrome", "immune restoration disease", or "immune reconstitution syndrome", in combination with "HIV" and subsequently "oral". Further articles in reference lists of key articles were also searched.

Definitions

Immune reconstitution is defined as a CD4+ count of > 200 cells/mm^3 and an increase of $>$ or $= 100$ cells over baseline any time since starting HAART (Arici *et al*., 2001). According to IRIS definitions proposed by different investigators (Table 1), IRIS is basically an "unmasking" or paradoxical worsening of a pre-existing infection following the initiation of HAART, in the presence of improved immune response and a decreasing viral load. Features are consistent with an inflammatory process. The lack of consensus on the definition means that diagnosis of IRIS depends heavily on exclusion and on case definitions incorporating clinical and laboratory data.

Diagnostic criteria

The main challenge in diagnosis is to distinguish IRIS from recurrence or relapse of an infection. A few key workers have presented case definitions of IRIS (Tables 2 and 3) (French *et al*., 2004; Shelburne *et al*., 2006). These case definitions include five fundamental criteria: (1) confirmed case of HIV, (2) temporal association between development of IRIS and initiation of HAART, (3) specific host responses to HAART, such as increase in CD4+ cell count and decrease in HIV viral load, (4) clinical deterioration characterized by an inflammatory process, and (5) exclusion of other causes that may lead to similar clinical presentation. Other causes include drug resistance or toxicity, drug malabsorption, patient non-adherence to regimen, super-infection by other pathogens, delayed recovery of immune function after the initiation of HAART, inadequate antimicrobial therapy of the pre-existing infection, and development of non-infectious complications (Cheng *et al*., 2000; French, 1999; French *et al*., 2001; Michelet *et al*., 1998; Lawn *et al*., 2005).

Problems still exist with these current diagnostic criteria, however (Lipman and Breen, 2006). Firstly, they are not clear-cut enough and also do not recognize the time lag between commencement of HAART and appearance of IRIS, which has been reported to vary from a few weeks to 4 years (Wright *et al*., 2003). Secondly, in some cases, there are no significant differences in the extent of elevation in CD4+ cell count and reduction in plasma HIV RNA load among HIV-infected patients who develop IRIS and those who do not (French *et al*., 2000; Jevtovic *et al*., 2005). Thirdly, most studies on IRIS to date are retrospective, and detailed data on the changes that occur in host immune responses in cases of IRIS are not clearly documented. Fourthly, there are no specific biomarkers for IRIS and a wide range of markers has been used by different laboratories to diagnose different pathogens (French *et al*., 2004).

In addition, immune responses in IRIS can sometimes exhibit "compartmentalization". For example, in a patient with IRIS who had multilevel transverse myelitis associated with infection with varicella zoster virus, activated lymphocytes were found in the cerebrospinal fluid but not in the blood (Clark *et al*., 2004). Numbers of circulating CD4+ and CD8+ cells and their functional competence do not correspond to those in infected or inflamed tissues (Lawn *et al*., 2005). Therefore, measurements from blood samples may not accurately reflect the actual concentration of the markers at the affected site (Barry *et al*., 2003; Wilkinson *et al*., 2005).

Pathogenesis

In theory, any pathogen that can cause an opportunistic infection (OI) because of impaired cellular immune response may imitate the development of IRIS in immune-reconstituted patients (French, 2009). The mechanism of IRIS is still largely speculative and may consist of a combination of three aspects—namely, the degree of immune restoration following HAART, underlying antigenic burden, and host genetic susceptibility.

Degree of immune restoration

The potent effect of HAART on suppressing HIV and increasing the level of CD4+ T-cells is mainly due to a redistribution of cells with a memory (CD45RO) phenotype from lymphoid tissue (Carcelain *et al*., 2001). If viral replication can be maintained at a low level, production of naive lymphocytes (CD45RA) will increase owing to the

restoration of thymic activity. A rapid change in the CD4+ T-cell count is associated with IRIS, with IRIS occurring more frequently among patients who have faster and a more marked rise in the CD4+ T-cell count than among others (Michailidis *et al*., 2005). Studies on patients presenting with CMV uveitis, *Cryptococcus* meningitis, and tuberculosis show that IRIS is more common when there is extensive disease present (Breen *et al*., 2004; Shelburne *et al*., 2005a; Karavellas *et al*., 2001; Jenny-Avital *et al*., 2002). These observations may be explained by the exaggerated immune response that is triggered by abundant microbial antigens and mediated by a sudden increase in antigenic-specific cells (Lipman and Breen, 2006).

Underlying antigenic burden

In patients who develop an OI while initiating HAART, IRIS may appear as a paradoxical relapse of the infection. However, pathogens from samples collected at the affected sites may not be cultivable; hence in such cases, the immune response appears to be directed toward the antigens of non-viable pathogens. This problem is commonly seen in cases of *Mycobacterium tuberculosis* or cryptococcal infection in which IRIS may present months to years after HAART initiation (Breton *et al*., 2004; Burman *et al*., 2007; Shelburne *et al*., 2005a; Lortholary *et al*., 2005a). On the other hand, viable pathogens may be isolated from affected sites in patients with subclinical infections in whom the infection will be unmasked by immune reconstitution after the initiation of HAART.

Autoimmunity to innate antigens may play a role in non-infectious cases of IRIS. Although there are uncertainties whether autoimmune diseases are related to IRIS, evidence so far shows that at least Graves' disease may be a complication of HAART-induced immune reconstitution (Crum *et al*., 2006; Knysz *et al*., 2006; Vos *et al*., 2006). Others reports indicate that rheumatoid arthritis and related autoimmune diseases can also be causes of IRIS (Bell *et al*., 2002).

The immunopathology of IRIS is currently believed to be determined mainly by the provoking pathogens. In IRIS associated with viruses such as John Cunningham virus (JCV is a type of human polyomavirus that is associated with progressive multifocal leukoencephalopathy in people with immunodeficiency, such as AIDS), HIV, and cytomegalovirus, CD8+ T-cells are found to be the predominate cell type (Gray *et al*., 2005; Miller *et al*., 2004; Mutimer *et al*., 2002). In contrast, in IRIS associated with fungi such as *Cryptoccocus* and *Histoplasma* (Lortholary *et al*., 2005a; Breton *et al*., 2006), protozoans such as *Leishmania* (Blanche *et al*., 2002), or mycobacteria, granulomatous inflammatory reactions can be triggered (Batista *et al*., 2008; Couppié *et al*., 2004; Philips *et al*., 2005). Furthermore, there is an increase in circulating T-cells that produce IFN-γ in patients with IRIS involving *M. tuberculosis* or *Cryptococcus* (Bourgarit *et al*., 2006; Tan *et al*., 2008). Suppuration of lymph nodes or other organs in mycobacterial IRIS (Philips *et al*., 2005; Burman *et al*., 2007; Puthanakit *et al*., 2005; Meintjes *et al*., 2008) is thought to be the result of the Th17 response, which is often mediated by neutrophils (Scriba *et al*., 2008; Matsuzaki *et al*., 2007).

Cellular proliferative disease such as Kaposi's sarcoma may be a consequence of production of cytokines that induce cellular proliferation. Tamburini *et al*. (2007) found raised IL-6 and tumor necrosis factor alpha levels in two patients with IRIS associated with Kaposi's sarcoma. Because vascular endothelial growth factor decreased dramatically with the onset of Kaposi's sarcoma, the authors surmised that IRIS could be due to reduced production of vascular endothelial growth factor in response to the extensive Kaposi's sarcoma.

Host genetic susceptibility

Another possible mechanism for IRIS could be the host's genetic susceptibility to effects of the exuberant immune response to antigens during immune reconstitution. Human leukocyte antigen and cytokine gene polymorphisms have been reported in IRIS secondary to herpesviruses and mycobacterial infections (Price *et al*., 2002). These polymorphisms are responsible for different aspects of the host response and may thus explain in part why patients with similar antigenic burden and immunological responses to HAART have different IRIS responses (Price *et al*., 2001; Price *et al*., 2002).

Risk factors

CD4+ T-cell count

The evidence on CD4+ T-cell count as a risk factor for IRIS is mixed. Patients with relatively high CD4+ T-cell counts, of > 350 cells/µL, when they start HAART rarely develop IRIS (Srikantiah *et al*., 2007). Conversely, patients with low baseline counts

seem to have an increased risk of developing IRIS (French *et al*., 2000; Shelburne *et al*., 2005b; Michailidis *et al*., 2005). Ratnam *et al*. (2006) found that patients with baseline CD4+ T-cell percentage of < 10% had a three-fold increased risk of IRIS. Nevertheless, no significant association between the magnitude of increase in CD4+ T-cell count and incidence of IRIS was found in that study or in three others (French *et al*., 2000; Jevtovic *et al*., 2005; Manabe *et al*., 2007).

Two other studies showed that IRIS is associated with an increased CD4+ cell percentage or ratio of CD4+ to CD8+ T-cells. During the first 30 days of HAART, an increase of ≥ 12% in the CD4 percentage had the highest positive predictive value of IRIS (Breton et al., 2004), and an increase of > 0.33 in the CD4+ to CD8+ ratio was strongly correlated with IRIS (Barry *et al*., 2002; Breton *et al*., 2004). Bower *et al*. (2005) found that the only variables to be associated with the development of IRIS were a higher CD4+ cell count at the time of diagnosis of Kaposi's sarcoma and the presence of edema linked to Kaposi's sarcoma.

HIV-1 RNA level

A rapid initial fall in HIV-1 RNA level within 90 days of starting HAART has been proposed as a risk factor for IRIS (Shelburne *et al*., 2005b). The increased risk may be related to the redistribution of memory CD4 lymphocytes as a response to HAART-induced reduction in HIV-1 RNA levels (Bucy *et al*., 1999).

Opportunistic infections

Evidence that the risk of IRIS is increased by concomitant OIs comes from a report in which the incidence of IRIS among a group of patients with disseminated cryptococcal fungemia was approximately six times that of patients who had cryptococcal infection without cryptococcemia (Lortholary *et al*., 2005a). Similarly, patients with disseminated tuberculosis or extrapulmonary tuberculosis had a higher risk of IRIS than did patients with only pulmonary infection (Burman *et al*., 2007). In analyses of timing of HAART administration, the risk of IRIS for patients initiating HAART within 2 months of OI diagnosis was 10 times that for other patients (Shelburne *et al*., 2005b; Lawn *et al*., 2005; Lawn *et al*., 2007), leading Shelburne *et al*. (2005b) to speculate that OI pretreatment reduces antigenic burden and lessens the extent of the immune response triggered by HAART.

Susceptibility to OIs has also been implicated as a possible risk factor. Some patients with CMV retinitis were found to be co-infected with other herpesviruses, indicating a genetic susceptibility to an immunopathological response against herpesviruses. Genetic studies have shown that herpesvirus IRIS I associated with HLA-B44 and major histocompatibility complex ancestral haplotypes HLA-A2, -B44, and -DR4 (Price *et al*., 2001), as well as allele 1 at a single nucleotide polymorphism in the 39UTR of the IL12B gene encoding IL-12 p40 (Price *et al*., 2002). In contrast, alleles of other cytokine genes (TNFA-308*2 and IL6-174*G) were associated with mycobacterial IRIS but not herpesvirus IRIS (French *et al*., 2000).

Age and gender

Age has not been identified to be a risk factor for the development of IRIS in general (French *et al*., 2004; Shelburne *et al*., 2005b; Breton *et al*., 2004). However, younger age at initiation of HAART is a strong predictor (Ratnam *et al*., 2006). Younger age groups will have more pronounced immune restoration and hence an increased risk of developing IRIS (Florence *et al*., 2003; Douek *et al*., 1998).

Bonham *et al*. (2008) commented that gender is unlikely to be an independent risk factor for IRIS. No association between gender and IRIS was found in several prospective studies (Burman *et al*., 2007; Kambugu *et al*., 2008; Murdoch *et al*., 2008). By contrast, some retrospective studies reported a two- to three-fold higher risk of IRIS among men (Olalla *et al*., 2002; Lortholary *et al*., 2005a; Shelburne *et al*., 2005b).

HAART regimen

Whether the use of protease inhibitors in HAART is a risk factor is unclear. Some studies have found no association (Shelburne *et al*., 2005b; Burman *et al*., 2007), but some have. A regimen containing both a protease inhibitor and a non-nucleoside reverse transcriptase inhibitor was associated with the development of IRIS, perhaps because of the increased potency of the HAART regimen versus other regimens using a single protease inhibitor or non-nucleoside reverse transcriptase inhibitor (Bower *et al*., 2005). Similar results were obtained in another study (Manabe *et al*., 2007), in which multivariate analysis revealed an independent association between boosted protease inhibitor use and a decline in viral load.

Antiretroviral regimens before therapy may also influence treatment success or IRIS development, as demonstrated in a study in which patients who were antiretroviral therapy-naive had a more robust virological and immunological response to therapy than patients who were heavily pretreated with antiretroviral drugs (Palella *et al*., 2002).

Caveats on identifying risk factors

Although the mentioned risk factors may be predictive for IRIS in specific study populations, the results should not be extrapolated for individuals. Moreover, risk factors may be specific to IRIS scenarios with specific pathogens. Therefore, generalizations about risk across all IRIS conditions may be inappropriate (Bonham *et al*., 2008).

Clinical spectrum

There are basically two major clinical scenarios of IRIS. The first one is paradoxical IRIS in which a previously treated infection shows a symptomatic relapse. The second is unmasked IRIS, which is an accelerated presentation of a new OI that is occult or latent when HAART is started.

In principle, every OI can cause IRIS as immune status improves. In most cases, fever is a frequent symptom and the majority of clinical manifestations resemble the

original disease. Diagnosing and distinguishing IRIS from the primary disease can hence be a challenge to clinicians. Other conditions that are reported to be associated with IRIS are reactivation of autoimmune diseases such as Graves' disease (Crum *et al*., 2006; Knysz *et al*., 2006; Vos *et al*., 2006) and systemic lupus erythematosus, and other non-infectious conditions such as sarcoidosis (Lenner *et al*., 2001; Li *et al*., 2002).

Common pathogens in cases of IRIS are *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, *Mycobacterium avium-complex*, cytomegalovirus, hepatitis B, *Pneumocystis jirovecci*, JC virus, and herpesvirus. Commonly reported clinical manifestations include tuberculosis, *Mycobacterium avium intracellulare* infection, CMV-associated immune recovery vitritis, immune recovery uveitis, Kaposi's sarcoma, leishmaniasis, cerebral toxoplasmosis, *Pneumocystis* pneumonia, JC virus-induced progressive multifocal leukoencephalopathy, and herpes simplex infections (Barry *et al*., 2002; Ratnam *et al*., 2006; Manabe *et al*., 2007). Uncommon manifestations that have been reported have been summarized by French *et al*. (2004) (Table 4).

Oral manifestations

In theory, any pathogen that can cause an OI could cause IRIS in immune-reconstituted patients, and there is no reason to believe the oral cavity would be spared. Unfortunately, there are limited studies on the oral manifestations of IRIS. The most commonly reported oral diseases associated with IRIS follow.

Kaposi's sarcoma

Rapid clinical progression of Kaposi's sarcoma was found in 6.6% of 150 HIV-infected patients with Kaposi's sarcoma after commencing HAART (Bower *et al*., 2005); three of the 10 patients with IRIS had extensive oral involvement. Feller *et al*. (2008) reported a case of IRIS-associated Kaposi's sarcoma that was a temporary immunoinflammatory reaction brought about by HAART and which was controlled effectively by limited systemic cytotoxic chemotherapy.

Oral candidiasis

A retrospective study in France reviewed the incidence of mucosal candidiasis in association with IRIS in 474 patients over a period of 10 years (Nacher *et al*., 2007). There was a significant increase in the incidence of oral and vaginal candidiasis in the first 2 months after HAART initiation (13.1/100 and 14.1/100 person-years, respectively). However, because only the CD4+ count and a very few other clinical or laboratory data were available, the authors could not conclude that the observed candidiasis was a definite form of IRIS.

In a retrospective study of 389 patients treated with HAART, Jevtovic *et al*. (2005) demonstrated that in 65 OI episodes that fulfilled the criteria for the clinical OI to be defined as IRIS, three patients had *C. albicans* angular cheilitis. In contrast, Gaitan Cepeda *et al*. (2008) found a relatively high prevalence of oral candidiasis (30%) among patients with quantitative evidence of immune reconstitution. Erythematous candidiasis was the most common oral lesion detected. Other oral lesions were

pseudomembranous candidiasis, angular cheilitis, hairy leukoplakia, and herpes labialis. The authors argued that the relatively higher prevalence of oral candidiasis could be due to a longer observation period, and a time-analysis confirmed that mycotic lesions occurred in later stages of disease.

Oral warts

King *et al*. (2002) reported an increased incidence of oral warts (1.6%) in a cohort of HIV-infected patients, suggesting that the development of the warts could be partly related to immune reconstitution. Although they found no association between changes in CD4+ counts and the risk of oral warts, the authors pointed out that IRIS has been described previously in patients in the absence of a significant increase in CD4+ cell count (Race *et al*., 1998). Other authors have also reported an increased prevalence of oral warts in HIV-infected patients receiving HAART (Patton *et al*., 2000; Greenspan *et al*., 2001; Greenwood *et al*., 2002). Schmidt-Westhausen *et al*. (2000) found that among 61 of 103 HIV-infected patients who were available for examination after 6 months of HAART initiation, the number of oral lesions was significantly lower than other patients not receiving HAART. Only five (8.2%) patients had oral manifestations, four of whom had condylomata acuminata. The authors surmised that this could be due to the less immunocompetent cells produced during the initial phase of HAART. However, a close examination of the immunological findings showed that the CD4+ count increased while the HIV viral load decreased significantly after HAART initiation. Therefore, cases of human papillomavirus infection could well be oral manifestations of IRIS.

Salivary gland disease

Ortega *et al*. (2008a) found that parotid enlargement was the most common oral manifestation (57.14%) among HIV-infected patients receiving HAART who showed immune reconstitution. An earlier retrospective study of HIV-infected patients receiving HAART also showed an increased incidence of salivary gland disease, as well as a six-fold increase in the incidence of oral warts (Greenspan *et al*., 2001). The authors commented that the increase in salivary gland disease was not unexpected, and considered this change to be part of CD8+ cell diffuse infiltrative lymphocytosis syndrome, which has previously been associated with improved prognosis. Whether these HIV-related salivary gland diseases represent IRIS-associated diffuse infiltrative lymphocytosis syndrome remains to be verified.

Herpes zoster

A sizeable proportion (7%-12%) of OIs associated with IRIS involved mucocutaneous herpes zoster infection (Dunic *et al*., 2005; French *et al*., 2000; Domingo *et al*., 2001; Martinez *et al*., 1998). The incidence of herpes zoster infections in patients receiving HAART was three to five times higher than that in non-HAART patients (Martinez *et al*., 1998; Domingo *et al*., 2001). CD8+ proportion at baseline was significantly higher in patients with herpes zoster-associated IRIS than in those without IRIS. The rise in CD8+ proportion 1 month after initiation of HAART was also significantly higher (Martinez *et al*., 1998). Most of the patients had typical or atypical dermatomal manifestations, although other complications, such as acute retinal necrosis, peripheral nerve palsy, myelitis, or encephalitis, have also been reported (Martinez *et al*., 1998; Domingo *et al*., 2001; Glesby *et al*., 1995).

Other oral symptoms

Ramírez-Amador *et al*. (2009) followed a group of HIV-infected individuals receiving HAART for up to 12 weeks. In eight patients who fulfilled strict IRIS criteria, two developed clinical signs of oral candidosis, two had oral ulcers, one had Kaposi's sarcoma, and three had hairy leukoplakia. These findings illustrate the diversity possible in clinical manifestation of IRIS.

In a case described by Ortega *et al*. (2008b), a 41-year-old HIV-infected white male with a history of genital syphilis, condyloma acuminatum, lung tuberculosis, hepatitis B and C, and anemia complained of pain and mobility in a premolar. A diagnosis of osteonecrosis was made. On the basis of the clinical and laboratory evidence, the authors concluded that a relationship between osteonecrosis and IRIS was possible. This case again shows the wide clinical spectrum that can be observed in patients with IRIS.

Management

Favorable viral suppression and immune reconstitution have been observed in patients with IRIS after 24 months of HAART (Shelburne *et al*., 2005b). The long-term outcome of these patients appears to be comparatively better than that of patients without the syndrome. The main role of the clinician is thus to provide reassurance to patients. Nevertheless, patients who develop IRIS often require significant interventions to minimize short-term morbidity.

There are to date no controlled prospective studies from which to formulate treatment guidelines for IRIS. The prevention of IRIS depends largely on optimal screening for OIs before commencing HAART in order to prevent unmasking and to optimally time HAART in patients who are receiving treatment for an OI. It is particularly important for clinicians to include IRIS in the differential diagnosis of a patient who presents with an inflammatory process after initiation of HAART.

There are different ways to prevent the development of IRIS. Since a low CD4+ T-cell count is a risk factor for development, some authors have suggested starting HAART early before the CD4+ cell count drops to below 100 cells/µL (Jevtovic *et al*., 2005). Others suggest delaying HAART for 4 to 8 weeks until the co-existing infection resolves (Lortholary *et al*., 2005b; Blumberg *et al*., 2003). Given that IRIS occurs more frequently if HAART is initiated early when antigens are abundant, or if there is more advanced immunosuppression, delaying HAART until the antigen load is reduced by antimicrobials will, in theory, reduce the risk of IRIS. Nevertheless, patients will be at risk of other AIDS events if HAART is delayed (Dean *et al*., 2002; Dheda *et al*., 2004). Starting HAART immediately and using prophylaxis against any suspected asymptomatic infection could be another option (French, 1999).

When IRIS is diagnosed, treatment options depend on the potential hazards and the extent of discomfort for the patient (Goebel, 2005). If IRIS may cause severe irreversible damage, such as liver failure or CMV retinitis, HAART may have to be stopped until the IRIS infection is checked (Drake *et al*., 2004). In many cases, IRIS is self-limiting and only symptomatic treatment is needed, besides treating the IRIS

infection. HAART can be continued if the scenario is not life-threatening. Treatment should aim at targeting the infectious agents and monitoring for complications secondary to the inflammatory process. Empirical treatment of symptomatic IRIS using non-steroidal anti-inflammatory drugs has been reported in a number of case reports (Blanche *et al*., 1998; Lortholary *et al*., 2005a; Breton *et al*., 2006). If a corticosteroid is used, the risk-benefit should be carefully assessed, particularly for patients with mycobacterial disease. Affected patients are capable of generating an inflammatory response, so many of them ultimately discontinue secondary prophylaxis against the offending pathogen (Bower *et al*., 2005).

Conclusions

In the absence of large prospective clinical trials, little is known about IRIS. In the next decade, IRIS is likely to become a serious problem, especially when HAART becomes more accessible to HIV-infected patients in resource-limited countries. Many of these patients will have a high antigenic burden and low CD4+ cell counts when starting HAART. Future studies should aim at decreasing the rate of IRIS in high-risk groups. The pathophysiology of IRIS is still poorly understood, and biomarkers for diagnosis and prediction of IRIS remain to be identified. Pathogen-specific laboratory studies to validate and refine diagnostic criteria are therefore urgently needed. Oral manifestations of IRIS also remain illusive and are another field that warrants further clinical research.

Author contributions

CSP Tsang is responsible for the literature search, manuscript writing, and he is the corresponding author. LP Samaranayake is responsible for the literature search, and advised on data analysis, interpretation and manuscript preparation.

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Table 1. Definitions of immune reconstitution inflammatory syndrome.

Authors	Year	Definition
Shelburne *et al.*	2002	Immune reconstitution inflammatory syndrome is defined as a paradoxical deterioration in clinical status attributable to the recovery of the immune system during HAART.
Bower *et al.*	2005	Immune reconstitution inflammatory syndrome may be defined as a progressive deterioration in clinical status as a result of recovery of the immune system, leading to worsening infection despite improvements in surrogate markers of HIV.
Goebel	2005	Immune reconstitution inflammatory syndrome describes a collection of different inflammatory disorders which are associated with paradoxical deterioration of various preexisting infectious processes following commencement of HAART in HIV-infected patients.
Lawn *et al.*	2005	"Immune restoration disease" could be defined as the presentation or clinical deterioration of opportunistic infections in HIV-infected patients as a direct result of the enhancement of immune responses to those pathogens during HAART.
Ratnam *et al.*	2006	On patients with previous history of infection, recurrent disease was defined as an immune reconstitution inflammatory syndrome event only if there was documented evidence of a significant increased frequency, severity, and/or poor treatment response in the six months after initiation of HAART.

Table 2. Proposed criteria for diagnosis of immune reconstitution inflammatory syndrome in HIV patients on antiretroviral therapy* (French *et al.*, 2004).

Major criteria

A. Atypical presentation of "opportunistic infections or tumors" in patients responding to antiretroviral therapy (ART).
- Localized disease, e.g. lymph nodes, liver, spleen
- Exaggerated inflammatory reaction, e.g.
  - Severe fever, with exclusion of other causes
  - Painful lesions
- Atypical inflammatory response in affected tissues, e.g.
  - Granulomas, suppuration, necrosis
  - Perivascular lymphocytic inflammatory cell infiltrate
- Progression of organ dysfunction or enlargement of pre-existing lesions after definite clinical improvement with pathogen-specific therapy prior to the commencement of ART and exclusion of treatment toxicity and new diagnoses, e.g.
  - Development or enlargement of cerebral space occupying lesions after treatment for cerebral cryptococcosis or toxoplasmosis
  - Progressive pneumonitis or the development of organizing pneumonia after treatment for pulmonary *Mycobacterium tuberculosis* or *Pneumocystis carinii* pneumonitis
  - New onset or worsening of uveitis/vitritis after the resolution of CMV retinitis
  - Fever and cytopenia after treatment for disseminated *Mycobacterium avium* complex
  - Enlargement of Kaposi's sarcoma lesions and subsequent resolution or partial regression without commencement of radiotherapy, systemic chemotherapy or intralesional therapy

B. Decrease in plasma HIV RNA level by >1 log10 copies/mL

Minor criteria

- Increased blood CD4+ T-cell count after ART.
- Increase in an immune response specific to the relevant pathogen, e.g. DTH response to mycobacterial antigens
- Spontaneous resolution of disease without specific antimicrobial therapy or tumor chemotherapy with continuation of anti-retroviral therapy

* A diagnosis requires both major criteria, or criterion A and two minor criteria.

Table 3. Proposed criteria for diagnosis of immune reconstitution inflammatory syndrome in HIV patients receiving antiretroviral therapy (Shelburne *et al*., 2006).

- HIV-positive

- Receiving HAART
    - Decrease in HIV-1 RNA level from baseline
    - Increase in CD4+ cells from baseline (may lag HIV-1 RNA decrease)

- Clinical symptoms consistent with inflammatory process

- Clinical course not consistent with:
    - Expected course of previously diagnosed opportunistic infection
    - Expected course of newly diagnosed opportunistic infection
    - Drug toxicity

Table 4. Uncommon clinical manifestations of immune reconstitution inflammatory syndrome (French *et al*., 2004).

Pathogen	Disease	Reference
Parvovirus B19	Encephalitis	Nolan *et al*., 2003
Skin yeasts	Folliculitis	Bouscarat *et al*., 2000
Leishmania major	Uveitis	Blanche *et al*., 2002
Leishmania infantum	Post-kala-azar dermal leishmaniasis	Ridolfo *et al*., 2000
Bartonella henselae	Granulomatous splenitis	Abino *et al*., 2002
Microsporidia	Keratoconjunctivitis	Gajdatsy and Tay-Kearney, 2001
Chlamydia trachomatis	Reiter's syndrome	Neumann *et al*., 2003