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## Immune reconstitution diseases: Is it possible to establish recommendations?

**Brygida Knysz, Andrzej Gładysz**

Department of Infectious Diseases, Wrocław Medical University, Poland

### Summary

The introduction of combination antiretroviral therapy (cART) has attracted the attention of scientists and physicians all over the world to the phenomenon known as IRD, immune restoration disease. The management of IRD depends on the correct diagnosis of the syndrome, which can be difficult to establish. The atypical presentation and unpredictable course of the disease may require individual decisions regarding a delay of cART or its interruption as well as the use of corticosteroids. Thus the frequent need for individualized management of IRD can make it difficult to obtain enough results from prospective randomized trials to establish strict recommendations. However, they should be initiated as soon as possible.

**Key words:** immune reconstitution disease • immune reconstitution syndrome • HIV infection • management of IRD

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**Author's address :** Brygida Knysz MD, Ph.D, Department of Infectious Diseases, Wrocław Medical University, ul. Koszarowa 5, 51-149 Wrocław, Poland; e-mail: brygida@wroclaw.dialog.net.pl

## INTRODUCTION

The introduction of combination antiretroviral therapy (cART) has attracted the attention of scientists and physicians all over the world to the mysterious phenomenon known as IRS (immune reconstitution syndrome or immune recovery syndrome), IRIS (immune restoration inflammatory syndrome), and IRD (immune restoration disease) [6,12,32,42,44]. There are a growing number of reports concerning immune reconstitution syndromes in HIV-positive individuals commencing antiretroviral therapy. cART, by suppressing viral replication, can reverse to some extent the immune abnormalities caused by HIV infection and can improve immune function [6,28,32,42]. However, in some individuals the rate of immune restoration and, perhaps, lack of compensating immune regulatory mechanisms may lead to uncontrolled tissue damage [10,25]. The disturbed regulation of the restored immune function can promote the clinical expression and development of opportunistic infections (OIs), AIDS- and non-AIDS-related malignancies, and non-infectious complications [2,42].

The clinical manifestations of IRDs are different from those observed in the disseminated disease in that atypical symptoms and exuberant immune response are usually observed. The pathogenic mechanisms vary from one IRD to another. Many IRDs result from an enhanced antigen-specific immune response, increased production of pro-inflammatory cytokines, and genetic susceptibility [32,33,41,42]. The management of IRD depends on its correct diagnosis, which can be difficult to establish. Our understanding of IRD resulting from cART in HIV-infected patients is still evolving and the list of IRDs is not yet complete. No measurable predictors of outcome are available [6,12,18,28,32]. Data from case reports, case series, and observational studies have produced contradictory information about the optimum timing of cART's initiation and duration, and the time when corticosteroids should be used [2,3,12,17,20,35,41]. Thus the course of IRD may be unpredictable and often requires individualized management.

## DEFINITION OF IRD

Due to the complexity of IRD, a final definition of it and diagnostic methods have not yet been established. The factors that should be considered in IRD diagnostics may reflect a definition. They are [12,28,40,41,42]:

- the temporal association between initiating ART and the development IRD,
- atypical clinical presentation (opportunistic infections, tumors, autoimmune diseases) such as localized disease, exaggerated and/or atypical inflammatory reactions, or worsening of pre-existing symptoms,
- a histopathological or cytological picture of an exuberant cell-mediated immune response in tissue samples,
- a rapid fall in plasma viral load (VL) during the first three months of therapy as a result of effective ART by at least 1 log<sub>10</sub>,
- evidence of immune restoration: increasing CD4 T-cell count of at least 25/μl, although a lack of a rise in blood CD4 lymphocyte count does not indicate that there has been no immune restoration. Moreover, no correlation between systemic immunity and immunity at the site of inflammation can be observed,

- restoration of cutaneous hypersensitivity to recall antigens, increased *in vitro* T-cell proliferative responses to antigens,
- exclusion of other reasons such as drug resistance, drug toxicity (antiretroviral drugs and/or pathogen-specific drugs), drug synergistic reactions, poor adherence, and development of additional diseases (e.g. an OI).

## LABORATORY TESTS AND SYMPTOMS

Patients with CD4 T-cell counts <200 cells/μl require careful screening for subclinical infection. Routine blood test, chest radiography, USG of the abdomen, and funduscopy should be done before the initiation of ART and strictly monitored during the first year of cART [17,27,31,41,42,46]. Those with a previously documented OI readmitted to hospital because of any symptoms of an inflammatory process should be carefully assessed for IRD [17,27,31,45]. Hypercalcemia, described in MAC and TB IRD, is probably related to the overproduction of activated vitamin D by interferon-γ-activated monocytes, tissue macrophages, and granulomatous tissue. It is suggested that this parameter can have a predictive value for decreasing immune activation and TB or MAC IRD resolution [4,25].

IRD occurs frequently in HIV-1-infected patients who receive effective cART, e.g. in approximately 11–45% with tuberculosis (TB), *Mycobacterium avium* complex (MAC) infection, or cryptococcosis [20,21,31,35,38,39,41]. Other IRDs occur less frequently [16,23,36,39,41–43]. They are usually mild or moderate, but sometimes a clinically significant problem with fatal progression may occur [2,9,18,24,29,37,39,42]. The number of invasive procedures and hospitalizations in IRS patients is higher than in other HIV-positive patients. This means that preventive strategies might be cost effective [2,19,24,31,39,40].

There are two groups of patients in whom IRD may occur:

1. cART was initiated during an acute OI.
2. cART was started in a clinically asymptomatic patient with or without primary prophylaxis.

## MANAGEMENT OF IRD

There are important questions that arise in HIV-positive patients who start cART, these being the optimum timing of cART initiation in individuals with acute OI(s) and the management of cases of acute OI that develop during cART. Data from reports concerning these two problems vary [12,20,24,37,39]. The optimum time to start cART in the presence of a recently diagnosed acute OI is unknown and depends on several factors, such as the type of the disease, the specific therapy available, and advanced immune deficiency [3,19,35].

### Immediate cART

In some AIDS-defining illnesses (ADIs), no effective therapy is available. The immediate use of cART, resulting in an improvement in the immune response, can lead to the resolution of Kaposi sarcoma (KS), Castleman's disease [23], progressive multifocal leukoencephalopathy (PML) [3,29,35,39], cryptosporidiosis, and microsporidiosis [3,35].

On the other hand, IRD in KS [12], PML [29,36], and microsporidiosis were described [42]. In patients with disseminated MAC infection, the simultaneous initiation of antimycobacterial therapy and cART should be considered [3]. The immediate administration of cART in patients with CMV retinitis may be considered [3]. No clear data exist to demonstrate that the initiation of cART in these patients would have an adverse effect on retinitis, gastrointestinal disease, or pneumonitis. However, although there are also no data indicating that IRD can worsen CMV neurological disease because of the localized morbidity that might occur with such an inflammatory reaction, a brief delay in the initiation of cART until clinical improvement occurs might be considered [3,18,19]. Moreover, one should remember that the use of cART, leading to better immune function, can prevent the development of another OI [3]. The timing of cART initiation should be balanced between the risk of the development of IRS and other ADIs. No recommendations are available for patients with more ADIs occurring simultaneously, e.g. an ADI in which no effective therapy is available (immediate cART is recommended) and another in which antimicrobial therapy should be delayed. Our suggestion is that the immediate use of cART should be considered and the patient needs to be carefully monitored for the development of IRD.

### Delayed cART

The aim of delaying cART in HIV-positive individuals with an ongoing treated OI is to prevent the occurrence of IRD by decreasing the antigen burden and diminishing the expression of antigens that can initiate an exuberant immune response [4,12,32]. In order to decrease the risk of IRD, observational studies suggest that it is prudent to delay starting cART until 4-8 weeks after the initiation of the treatment of tuberculosis, cryptococcal meningitis, and *Pneumocystis carinii* (*jirovecii*) pneumonia (PCP) [3,4,35,37]. It is well known that HIV-negative patients receiving TB therapy may develop immune reconstitution syndrome. In the case of HIV-positive individuals, cART can potentiate the effect of IRD [4,10,32,37]. The delay of cART can also diminish the risk of toxicity due to drug interactions between OI therapy and cART and help to distinguish the toxicities related to the particular drugs. HIV-infected patients are more prone to develop adverse reactions to antituberculosis drugs [2,4,12,37,39]. The risk of adverse drug reactions increases with advanced immune suppression and they usually occur in the first two months of treatment [3,4,37]. This can influence the decision about delaying cART.

There are also reports [4,37] suggesting that the decision to start cART should depend on the CD4 T-cell count. In patients with CD4 T cell counts <200/ $\mu$ l, cART should be started as soon as TB therapy is tolerated. In a trial conducted by the U.S. Centers for Disease Control and Prevention, 137 HIV-positive patients with active tuberculosis who were undergoing antimycobacterial therapy began ART. Nineteen percent developed IRD, and 50% of these TB IRD cases required hospitalization. The mean duration of IRD symptoms was 64 days [5]. Shelburne et al. [38] reported that initiation of cART within 30 days after a diagnosis of disseminated *C. neoformans* infection was associated with the subsequent development of IRD. The outcome of IRD cryp-

tococcosis may often be fatal [26]. Bategay reported 3 fatal cases out of 10 with IRD cryptococcosis. In 21% of patients who started cART within 30 days of cryptococcosis diagnosis, IRD was observed [2]. Dean et al. reported the clinical deterioration of PCP after cART initiation within 15-18 days of PCP diagnosis. It led to acute respiratory failure after a mean time of 5 days [9]. Patients who have not previously been treated with cART in whom the diagnosis of disseminated MAC infection is established should have cART initiated simultaneously or within 1-2 weeks of initiation of antimycobacterial therapy [3]. As mentioned in the section concerning immediate cART, it might be prudent to delay cART for a short time until the clinical symptoms of CMV infection improve [3,13,37].

### IRD TREATMENT

Some problems should be considered in each case of IRD [3,12,13,35,39]:

1. temporary cART discontinuation until the clinical condition has improved,
2. use of non-steroidal anti-inflammatory drugs (NSAIDs) and/or systemic or topical corticosteroids and the duration of anti-inflammatory treatment,
3. pathogen-specific therapy,
4. other therapy.

### cART discontinuation

If possible, cART should not be interrupted. IRDs can recur during the re-initiation of cART even though pathogen-specific therapy is continued. cART interruption should be recommended only for patients with severe, life-threatening symptoms of the diseases until their condition is stabilized. These are: worsening respiratory function during PCP, TB, inflammatory form of PML, acute liver failure, HIV demyelinating leukoencephalopathy, focal encephalitis due to parvovirus B19 infection, tracheal mucosal edema and obstruction due to HHV-8 infection, and KS [2,3,10,36].

### NSAIDs or corticosteroids

Clinicians must consider the use of drugs which can modulate the immune response, such as NSAIDs or corticosteroids, when clinically appropriate in order to prevent irreversible inflammatory damage [10,29]. The use of NSAIDs has been recommended for the management of mild and moderate cases. The use of corticosteroids would be beneficial in individuals with severe or life-threatening disorders (especially with exacerbated inflammation), those with ongoing symptoms despite pathogen-specific therapy, and individuals who received NSAIDs and the symptoms failed to improve [3,13,35]. Corticosteroids should be considered especially in CNS IRDs because of the low tolerance to inflammatory reaction in the brain. However, they have a potential immune suppression effect and should be discontinued as soon as clinically feasible. Strict observation for the development of other OIs is necessary and they should be excluded as a cause of symptoms before corticosteroids are initiated.

There are data about the systemic use of corticosteroids in IRS, including TB [37], MAC [17], PCP [7,19], cryp-

tococcosis [14], PML [36], CMV infection [15], acute liver failure [42], inflamed warts [13], mollusca contagiosa (*Papillomavirus*) [13], tracheal mucosal edema due to KS [8], HIV demyelinating leukoencephalopathy [13,22], zoster flares [11,13], chronic erosive ulcers [11,13], sarcoidosis [27], and CNS vasculitis [43].

The exact doses and the duration of corticosteroid treatment have not yet been established and differ among the reports. The effect of corticosteroid therapy is not the same in different ADIs and sometimes they are insufficient in their management. This may depend on the type of ADI and the severity of symptoms. Generally, the initial dose of corticosteroids should be 1–2 mg/kg/day.

In a severe TB-IRS reaction, prednisone 1–2 mg/day for 1–2 weeks is recommended, after which the dose should be tapered [1]. If the symptoms persist in MAC IRD, despite NSAIDS, prednisone 0.5–1.0 mg/kg/day for 4–8 weeks should be used [1,17]. However, there are patients who require long-term specific MAC treatment as well as corticosteroids. Riddell et al. analyzed a group of 16 patients with IRS MAC diagnosis [34]. Of the 16 patients, 14 had complete resolution of symptoms after  $15.7 \pm 19$  months of specific MAC treatment. Three required adjunctive corticosteroids for a mean time of 15 months. In 2 non-responders, persistent symptoms and signs of organ inflammation despite  $42 \pm 46$  months of specific MAC treatment was observed. Most patients had a complete response to MAC IRD, often requiring at least 1 year of specific MAC treatment and prolonged steroid use. The same observation concerning long-term therapy was made by Knysz et al. [17]. The patient required anti-MAC drugs, cART, together with corticosteroids for one year.

Dean et al. described clinical deterioration of PCP in three patients treated effectively with co-trimoxazole and high doses of corticosteroids for 12–15 days [9]. Too early interruption of corticosteroids and the initiation of cART within 15–18 days of PCP diagnosis led to acute respiratory failure after a mean time of 5 days. Alternative management strategies may include delaying the introduction of ART in the early stages of PCP or prolonging steroid use if cART is commenced. To prevent paradoxical PCP worsening after introducing cART, corticosteroid adjunctive therapy probably should not be shorter than three weeks [7].

Systemic or periocular corticosteroids are preferable in CMV immune reconstitution vitritis (CMV IRV) [3,46]. About 50% responded to the therapy [1]. Topical corticosteroids are recommended if any risk of vision loss is suspected [3,46].

The restoration of the inflammatory response after cART played a role in the pathogenesis of CNS vasculitis [43]. The patient initially received 1000 mg of prednisone for 3 days and then 40 mg was reduced to zero after a period of 8 weeks. One week after stopping the prednisone, the neurological symptoms reappeared. The histopathological examination revealed lymphocytic vasculitis. The recurrence of symptoms was observed when the daily dose of prednisone was reduced to 15 mg. In PML IRD, methylprednisolone 250 mg every 12 h, dexamethasone 10 mg daily for 4 weeks were given to patients whose conditions impro-

ved only for a short time [36]. The outcome of the disease was fatal. In sarcoidosis, dramatic improvement after initiation of corticosteroid therapy (20–30 mg of prednisone daily) was observed [27].

No data are available about the use of corticosteroids in hemorrhagic cystitis due to BKV infection, parvovirus B19 focal encephalitis, *Chlamydia trachomatis* infection, Guillain-Barre syndrome (GBS), *Mycobacterium leprae* cutaneous lesions, Histoplasma lymph node granuloma, and appendicitis.

### Pathogen-specific therapy

Antimicrobial therapy should be started or continued in the case of an acute OI or unmasking an ongoing infection by a documented or suspected pathogen [12,25,38,39]. No antimicrobial therapy should be recommended if there is an exacerbated immune response to a non-replicating antigen [3]. However, in some cases it may be impossible to establish whether an acute infection is absent. On the other hand, some IRDs resolve without specific treatment. In a few cases, intensification of the pathogen-specific treatment should be considered. The decision should be made individually on the basis of the course of IRD (severe), identification of the pathogen, and the efficacy of the present therapy.

### Other therapy

IVIg is recommended in focal encephalitis (Parvovirus B19) [30] and GBS in a dose 400 mg/kg [13]. To avoid difficulties in the differential diagnosis of respiratory failure, abacavir, which was recently implicated in cases of acute respiratory distress syndrome, should be not used during PCP therapy [45].

### OTHER INTERVENTIONS

Specific management may be necessary for atypical presentation of the symptoms, such as:

1. Surgical intervention, e.g. lymph node drainage in MAC IRD, bowel perforation in TB IRD, or appendectomy because of appendicitis.
2. Dialysis in acute renal failure as a result of TB IRD.
3. Plasmapheresis in the case of GBS.
4. Liver transplantation: in the case of acute liver failure, transplantation should be considered.

### COST EFFECTIVENESS

It has been determined that individuals with IRD require more interventions to prevent morbidity and mortality. As reported by Shelburne et al, patients with IRS required in the 12 months after starting cART an increased number of invasive procedures, such as lumbar punctures, to relieve increased intracranial pressure and a high number of hospitalizations [11]. This means that preventive strategies might be cost effective.

### CONCLUSION

There are some important questions concerning immune reconstitution disease in the setting of cART. The syn-

drome is still poorly understood. The pathogenesis seems to be complex and it varies from one IRD to another. The atypical presentation and severe course may require individual decisions of the delay of cART or its interruption as well as the use of corticosteroids. The frequent need for individualized management of IRD can make it difficult to obtain enough results from prospective randomized trials

to establish strict recommendations. Case reports and case reports series are a precious source of data. Moreover, the list of IRD has not been closed yet and more interesting case reports can be expected. That is why each case report should be noted to establish a more precise list of IRDs, even though it presents only a suspected diagnosis based on the current, still imprecise definition.

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