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Chapter 15

The Downside of an Effective cART: The Immune Restoration Disease

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Additional information is available at the end of the chapter

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1. Introduction

The prognosis of patients infected with human immunodeficiency virus (HIV) type 1 has dramatically improved since the advent of the highly active antiretroviral therapy (HAART), which have enabled sustained suppression of HIV replication and recovery of CD4+ T cells count [1-3]. However, many patients in resource-poor settings still start HAART at a late stage of HIV infection when they already have advanced immunodeficiency [4,5]. Immune reconstitution in HIV infected patients is characterized by replenishment of immune cells depleted directly or indirectly by HIV infection, by regeneration of primary and secondary lymphoid organs, by restoration of pathogen-specific T, B and NK cells and by a regulation of the reconstituted immune system [2]. It is unclear whether complete immune reconstitution ever occurs but individuals with human immunodeficiency virus infection starting antiretroviral therapy when they are very immunodeficient are susceptible to immune reconstitution disorders. This phenomenon is known as a multitude of names including "immune reconstitution inflammatory syndrome (IRIS)", "immune reconstitution or restoration disease" (IRD) or immune reconstitution syndrome" and includes various forms of a clinical deterioration as a consequence of a rapid and dysregulated restoration of antigen specific immune responses causing an exuberant inflammatory reaction and a cytokines storm [1-3]. This was first noted following the introduction of zidovudine monotherapy in the early 1990s, when localized forms of *Mycobacterium avium intracellulare* (MAI) infection where observed in association with the recovery rather than failure of cellular immune response [6]. Later, in 1992, *French MA et al* showed that the disease associated with Mycobacterium avium complex (MAC) infection occurred after nucleoside analogue therapy and correlated with restoration of delayed hypersensitivity (DTH) responses to mycobacterial antigens [7].

2. Definition and epidemiology

IRIS is a well established entity still lacking of a consistent definition due to a wide variety of pathogens and disease processes involved. It has been associated with herpetic, mycobacterial and cryptococcal infections, Kaposi's sarcoma, non – Hodgkin lymphoma and progressive multifocal leukoencephalopathy. Non AIDS defining pathologies such as sarcoidosis, Graves disease and rheumatic disease can also occur [1-3]. General case definitions have been proposed by *Shelburne et al* (2009), *French MA et al* (2004) and by *Robertson J et al* (2006) [8,9,10] but diagnostic criteria for IRIS have not been standardized except for TB-IRIS [3, 11]. This syndrome can be elicited by infectious and non infectious antigens and may arise in two different settings, depending on whether HAART was started in a patient treated for an ongoing opportunistic infection or in a clinically stable patient with or without requiring primary prophylaxis [2]. "Unsmasking IRIS" is an immune response against an infection that was subclinical before the initiation of HAART whereas "paradoxical IRIS" indicates a condition in which the opportunistic infection is present and treated at the time of initiation of HAART and worsens on therapy. Unmasking IRIS usually presents within the first three months of therapy and viable pathogens may be isolated from samples obtained from affected body sites, particularly when there is tissue necrosis. Paradoxical IRIS is common during the first three months of HAART but may present later and frequently immune response is against non viable pathogens. It occurs in 8-43% of patients with treated tuberculosis and in 4-66% of patients with treated cryptococcal infection becoming an important concern in poor resources countries [1-3]. Paradoxical IRIS is also exemplified by immune recovery, which occurs in eyes previously affected by cytomegalovirus (CMV) retinitis. Particularly in paradoxical IRIS, clinicians need to exclude alternative explanations for deterioration, such as failure to treat the opportunistic infection or failure of HAART because of poor adherence or drug resistance [3].

Some authors suggested using terms of "simultaneous IRIS" for patients who develop IRIS and a newly diagnosed opportunistic infection (OI) at the same time and "delayed IRIS" for those with an OI in which IRIS manifests sometimes thereafter [12].

However, although several case definitions for IRIS have been proposed, certain minimum criteria should be fulfilled in order to diagnose it. First of all, there must be the temporal association between initiation of HAART and subsequent development of symptoms of an inflammatory localized or systemic process, characterized by worsening of clinical or laboratory parameters despite "favorable" evolution of the HIV surrogate markers [1,2]. A rise in blood CD4 + T cells is commonly seen in IRIS but it is not an essential element for the diagnosis and is only a supportive criterion in both of the general case definitions for IRIS [9,10]. *Philips P et al* found that about 10% of patients with Mycobacterium avium complex immune restoration disease haven't an increased CD4+ T cells count [13]. Neverthless, a lack of rise in blood CD4 + T cells doesn't indicate that there has been no restoration of functional T lymphocyte response. On the other hand, IRIS has been described at higher CD4 + T cells count, suggesting that functional status of cells has a role in the pathogenesis of IRIS too. Therefore a falling plasma viral load is a more important indicator than CD4 T cells count recovery [14].

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The immune restoration outcomes range from minimal morbidity to fatal progression [15]. The immune restoration shows a biphasic pattern and is demonstrated by a decrease in plasma HIV RNA levels by more than 1 $\log_{10}$ copies/ml and an increase in CD4 + T cells count from baseline [1,2,16]. Initial recovery of the immune system consists in an increase in memory T cells followed by an increase in thymic production of naïve T cells [1,2,16-20]. In addition there is the recovery of reduced or damaged secondary lymphoid organs such as the gut and the mesentheric associated lymphoid tissue, which are often lost due to chronic HIV- mediated inflammation [21]. The initial and rapid rise of CD4 + T memory cells released from compartments into circulation can be detrimental and a mild OI can appear as an overwhelming infection because memory T cells respond to their antigens more readily than naïve T cells [2,22].

CD8 + T cells also increase during the first two months of HAART and then tend to return to baseline [18].

Differentiation between an opportunistic infection with normal presentation and a disorder with a presentation compatible with unmasking IRIS is particularly difficult and the differences between intended HAART – associated immune reconstitution and undesired manifestations of IRIS is probably a continuum [3].The damage may indicate a failure of the immune system to properly regulate the potency of the immune response [23].

The differential diagnosis includes failure of the antimicrobial therapy in patient with active infection, manifestations of a new opportunistic infection, unmasking of an ongoing, previously undiagnosed infection or manifestation of a diagnosed, ongoing infection in a previously unrecognized site of involvement [1-3,16]. Drug toxicity must be ruled out. For example, hepatitis flares in patients coinfected with hepatitis B virus or hepatitis C virus may be the result of IRIS in the liver or of HAART- associated hepatotoxicity [2, 24].In occurring IRIS, inflammation is atypical in presentation or more exaggerated than in immunodeficiency disease being characterized by pain, suppuration and necrosis and examination of affected tissue or body fluids samples reveals evidence of an immune response with scarcity of pathogens, infiltrating lymphocytes and granulomatous reaction [1-3].

IRIS may be estimated to occur in 10% to 50 % of patients starting HAART with similar percentages occurring in children and the incidence varies with the AIDS-defining illness [1-3]. Differences reported in the incidence of IRIS between opportunistic infections seem to be related to CD4+ T cells count at baseline [3]. IRIS is common in patients starting HAART with a low CD4 + T cells count and a CMV retinitis or cryptococcal meningitis whereas Kaposi's sarcoma and TB-IRIS have also been described at an high count of CD4 + T cells count [3,25].

Moreover, the variation reported in frequency is due to differences in case definitions and, above all, to differences in study populations with heterogeneous risk profiles and underlying burden of opportunistic infections [1,2]. In a recent meta-analysis and systematic review including 54 cohort studies and 13.103 patients starting HAART of whom 1699 develope IRIS, the lowest to highest incidence of IRIS by previously diagnosed opportunistic illness resulted 6,4% in patients with Kaposi's sarcoma (based on two studies), 12,2% in patients with Herpes Zoster (based on one study), 15,7% in patients with tuberculosis (based on 16 studies), 16,7% in patients with progressive multifocal leukoencephalopathy (based on two studies), 19,5% in patients with cryptococcal meningitis (based on six studies) and 37,7% in

patients with cytomegalovirus retinitis (based on ten studies). In the same review IRIS developed in 16,1% of unselected patients starting HAART and the incidence of IRIS associated with tuberculosis and cryptococcal meningitis seemed to be lower in cohorts from low and middle income countries probably due to limited diagnostic capacity in these settings. The strength of this affirmation is supported by the evidence of an high incidence of IRIS associated uveitis in all settings: inflammatory reactions, even if moderate, are more likely to be recognized in the eye than in other organs [3].

Risk factors for IRIS are difficult to establish because of the cohorts differ with regards to the study populations and the type of IRIS examined. Anyway, several risk factors for IRIS has been identified and, first of all, the presence of an opportunistic infection at the time of initiation of HAART, specially for TB and cryptococcal diseases [1,2]. *Müller M et colleagues* reported an analysis stratified by median CD4+ T cells count at the beginning of HAART showing the different incidence of IRIS [Tab. 1, 3]. Male sex and younger age have been identified as significant predictors too [15,26].

Initiation of HAART soon after treatment for an opportunistic infection is considered a risk factor too [1-3,15].

A shorter interval between the treatment of an opportunistic infection and the initiation of HAART is associated with a higher risk of IRIS in these patients [1-3,15].

3. Pathogenesis

The immunopathological process is still poorly understood but is strictly related with the provoking pathogen and with host. In fact, some people develop IRIS and others, with similar clinical status and risk factors, do not. It remains unclear if the disease mechanisms associated with IRIS are the same for each OI or if there are microbial-driven specific immune responses that result in different pathologies for each pathogen [12]. Several studies using a simian immunodeficiency virus model indicate differential expression of viral peptides by distinct MHC alleles, which could influence the aggressiveness of the immune response directed toward SIV [27].

Essentially any pathogen that can cause an opportunistic infection in patients with impaired cellular immune responses can provoke IRIS. It also appears that HIV infection itself can cause IRIS [28]. Two patients were reported with HIV encephalitis after effective HAART. Neuropathological features consisted in massive CD8+/CD4- lymphocytes brain infiltration and in a diffuse microglial hyperplasia [28].

The antigenic stimulus in infectious conditions are either intact viable organism or dead organism and their residual antigens whereas autoimmunity to innate antigens are involved in the non-infectious causes of the syndrome [1-3].

If the pathogen is viral, i.e. CMV or JC, CD8 + - T lymphocytes predominate in inflammatory cells infiltrates whereas if the pathogen is tuberculous or non tuberculous mycobacteria, a

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protozoan as Leishmania species or a fungus as Cryptococcus neoformans granulomatous CD4 + - T helper cells type 1 inflammation predominates [1-3].

Price P et al suggested a genetic predisposition and certain genes have been associated with an increased susceptibility to development of IRIS in presence of mycobacteria and herpesviruses. The TNF α-308*2 carried in linkage disequilibrium with HLA-A2,-B44,-DR4 and without BAT1 (intron 10)*2 is more common in patients with herpesvirus-associated IRIS and is not present in any patients who has experienced mycobacterial IRIS. Therefore TNF α polymorphisms should be considered in the context of the adjacent MHC alleles. The absence of C allele of IL6-174 together with TNF α - 308*1 confers an increased relative risk for mycobacterial IRIS probably due to a limited TNF-mediated bactericidal activity and to a lower TNFα production in monocytes [29]. The CMV retinitis IRD patients have over 4 years on HAART progressively increased plasma levels of bioavailable IL-6 and of soluble CD30, a type 2 (T2) immune response marker and 92% of them result homozygous for IL12B-3'UTR* 1 suggesting a dysregulation of the T1/T2 balance [30,31]. Th1 cells are characterized by the production of interferon γ and elicit proinflammatory responses. Th2 cells produce antiinflammatory and immunosuppressive cytokines (i.e. interleukin 10). [31,32]. These considerations suggest that IRIS could be sustained form several immunopathological mechanisms and that further studies need to better establish the role of cytokines in the different forms of IRIS [31].

In addition to the reconstitution of immune cell numbers and function, redistribution of lymphocytes, defects in regulatory function, changes in Th cell profile are also involved [23]. Mycobacterial IRIS usually presents with suppuration of lympho nodes or other organ affected because of an activation of Th 17 lymphocytes inducing inflammation mediated by neutrophils [33]. Production of cytokines inducing cellular proliferation is the main mechanism of IRIS-Kaposi [34]. An unbalanced immune reconstitution of effector and regulatory T cells in patients receiving HAART has been noted. In particular, two types of T cells seem to take part to the development of the disease: the proinflammatory Th 17 lymphocytse and the T regulatory cells. The latter are implied in preventing collateral damage from exuberant inflammatory responses and may be defective in number and function during IRIS [1,2,23,31]. A role has been hypotized for NK cells by killer immunoglobulin-like receptors activity. Macrophages are inappropriately activated in IRIS-TB [1].

Actually serological markers for IRIS diagnosis are lacking. Inflammatory markers, cytokines and chemokines are shown to be elevated in IRIS, specially IL 6. Paradoxical TB-IRIS has been associated with elevation of interleukin(IL) -4, IL -6, IL-7, IFN (interferon) γ and tumor necrosis factor alpha (TNF-α) and cryptococcal meningitis with increased pre-HAART levels of C reactive protein (CRP), IL-4 e IL-17 and lower levels of vascular endothelial growth factor (VEGF), granulocytes colony-stimulating factor (G-CSF) and TNF-α during clinical events [1,31,35].

To sum up, IRIS has been associated with certain human leucocyte antigen (HLA) profiles and regulatory cytokine genes polymorphisms but further research is needed to evaluate their potential role in identifying patients at risk, developing better therapeutics and monitoring response to therapy.

4. Clinical settings

Lots of clinical manifestation have been described in occurring IRIS.

Several pathogens have been associated with IRIS, including JC virus, herpes viruses, BK virus, Parvovirus B19, human T lymphotropic virus type 2, Epstein Barr virus, HHV 8, Cytomegalovirus, Cryptococcus neoformans, Toxoplasma gondii. Mycobacterium tuberculosis, Mycobacterium leprae and Mycobacterium avium complex (MAC) contribute too [1-3,15]. The antigens driving IRIS often belong to opportunistic pathogens but sometimes IRIS can be a result of HIV- specific responses [1-3,15].

TB-IRIS manifestations include worsening respiratory symptoms, fever, lymphonode enlargement and suppuration, appearance of new infiltrates and mediastinal lymphoadenopathy on chest radiograph, visceral or cutaneous abscesses, pleural and pericardial effusion and rarely intracranial tubercoloma, acute renal failure, meningitis and cognitive impairment. Moreover abdominal TB-IRIS can present with non-specific abdominal pain and obstructive jaundice. Differential diagnosis from drug-resistant tuberculosis is difficult [15,36-39]. MAC remains the most reported atypical mycobacterium and the most common manifestation in MAC-IRIS is fever with suppurative painful lymphadenitis followed by pulmonary disease but involvement of joints, spine, skin and soft tissue has also been reported. In contrast to disseminated MAC disease of advanced AIDS, MAC-IRIS usually presents as localized disease [40]. Mycobacterial IRIS has to be distinguished from sarcoidosis that can also occur in the context of IRIS [1]. Measurement of a delayed-type hypersensitivity response to tuberculin by a skin test may help to differentiate immune reconstitution-associated sarcoidosis from mycobacterial IRIS, because a response is absent in patients with sarcoidosis but is often present in patients with mycobacterial IRIS [1,2,7, 41,42].

Patients with Pneumocystis jirovecii IRIS manifest recurrence of fever, worsening hypoxia and fresh pulmonary infiltrates on chest radiograph. In addition to the general risk factors, PaO_2 < 70 mmHg and a recent completion of steroid therapy for Pneumocystis jirovecii pneumonia promote IRIS [1, 43,44].

CNS-IRIS occurs at much lower frequencies with about 0,9-1,5% of patients developing some CNS-IRIS after initiating HAART [45-47]. The heightened immune response in a relatively closed space leads to raised intracranial pressure, with potentially irreversible damage. Diagnosis of CNS-IRIS is difficult because CNS is a region of limited access and requires pathological confirmation and invasive procedures. A worsening of clinical neurological status can be accompanied by new neuroradiological findings or by deterioration of previous findings with T cell infiltrates into the CNS. Depending on the severity of CNS-IRIS it may be classified as asymptomatic, symptomatic and catastrophic. Asymptomatic CNS-IRIS consists in radiological changes only, such as increased enhancement. Symptomatic CNS-IRIS is characterized by clinical deterioration in neurological function with new changes on MRI scan of brain. In the catastrophic CNS-IRIS severe neurological deficits occur such as coma and imminent signs of cerebral herniation [12, 45-48]. JC virus is the causative agent of PML and one of the most devastating of the OIs associated with IRIS leading to a 42% mortality. Of the approximate 5% of HIV + patients who develop PML up to 19% are PML-IRIS patients. Differential diagnosis between PML and PML-IRIS can be done by MRI:

the presence of contrast enhancement suggest an inflammatory response and is indicative of PML-IRIS. The response to steroids confirms the diagnosis. The prognosis of delayed PML-IRIS is worse than the form that begins simultaneously [49,50].

A stroke occurring after initiation of HAART can be due to a vasculitis in the context of a VZV-IRIS [51]. Genital ulceration related to Herpes Simplex virus and genital warts related to human papillomavirus are frequently observed [1]. Most commonly CMV is associated with CMV-IRIS retinitis, vitreitis and uveitis with loss of visual acuity and floaters [1, 52]. CMV ventriculitis without retinal damage has been described [53].

Cryptococcus neoformans is frequently involved in IRIS development. It can provoke a CNS associated IRIS and a non-CNS IRIS: the first results in an aseptic recurrence of meningitis or rarely in a cryptococcoma; the second is more common and is a lymphoadenitis or a mediastinitis or rarely a cavitary pneumonia. In a patient with cryptococcal meningitis rapidly worsening because of headache, nausea and vomiting after HAART initiation IRIS has to be considered above all in presence of sterile inflammation of the CSF, residual cryptococcal antigens and absence of viable yeast on culture. Patients with Cryptococcus neoformans associated IRIS has usually higher opening pressure, white cell count and glucose levels than patients with Cryptococcus neoformans infection only. Neuroimaging is usually not useful in cryptococcal meningitis diagnosis but in occurring IRIS evidence of meningeal or choroid plexus enhancement or linear perivascular enhancement in the sulci at CT scan is frequent and represent a sign of inflammation [54-57]. Patients with cryptococcal meningitis particularly with IRIS are likely to develop a communicating idrocephalus due to blockage of CSF absorption at the arachnoid villi by cryptococcal antigens and by the inflammatory cells. This is a serious condition that may require drainage by repeated lumbar punctures [48].

There is only a case report of immune reconstitution syndrome occurring in a patient with Candida meningitis in the literature and a case report of visual loss and detection of EBV in CSF by PCR after initiation of HAART [12, 58]. In few cases Toxoplasma gondi is the responsible agent of CNS-IRIS [59].

Some patients may develop a severe progressive encephalitis after initiation of HAART with seizures, altered mental status, coma and death. HIV may be detectable in CSF even when results undetectable in blood. MRI can show diffuse multifocal white matter changes with associated cerebral edema [12,28].

Given the known associations of Kaposi's sarcoma with human herpesvirus 8 and non Hodgkin lymphoma with Epstein Barr virus it is not surprising to observe these cancers occurring or worsening in the context of IRIS [12,60-63]. Both clinical sudden progression of established lesions and new Kaposi sarcoma have been described after HAART initiation [12, 60-62]. HIV-infected patients starting HAART may present manifestations of autoimmune disease like most frequently sarcoidosis and Graves disease but also systemic lupus erythematosus, rheumatoid arthritis, Reiter's syndrome, polymyositis and Guillain-Barrè syndrome [1-3, 64-70]. At last, high levels of CNS inflammation have been demonstrated in the hippocampus of patients successfully treated with HAART and IRIS could contribute to pathogenetic mechanism leading to a cognitive impairment [12].

5. Treatment and prevention

Till now, on the grounds of available data, it appears prudent that HAART should be initiated before the onset of severe immunodeficiency. A detailed evaluation should be done for identification of opportunistic infections before HAART initiation. Patients with high risk features for the development of IRIS should be identified and OIs should be optimally treated if present [1-3, 71-73]. In the context of opportunistic infections, the benefit of reducing the likelihood of IRIS by deferring HAART must be balanced with the risk of delaying HAART, above all if patients are severely immunodeficient. The ACTG 5164 is a randomized trial comparing immediate versus deferred antiretroviral therapy initiation in patients presenting with acute OIs. Significant reduction in clinical progression or death among patients who received antiretroviral therapy within 14 days of presenting with acute OI versus those who deferred antiretroviral therapy until after OI had been treated was found and the incidence of immune reconstitution events resulted similar between groups [73].

To date, literature is lacking about the optimal time of HAART initiation following a treatment of opportunistic infections with exception of tuberculosis/HIV coinfection. Regarding this concern the most recent WHO and DHHS guidelines recommend the initiation of HAART between 2 and 8 weeks after starting treatment against tuberculosis for patients with a CD4 count < 200/μl [71,72].

Actually management of patients with IRIS was founded upon clinical observations and expert opinions only. In general non steroidal anti-inflammatory drugs should be reserved for milder manifestations and steroids for cases with severe inflammation. Interruption of HAART is rarely necessary but could be considered in life threatening situations or when pathogens involved are not controllable by specific antimicrobial therapy, as JC virus [15]. Stopping HAART may improve symptoms but there is no guarantee that the condition will not recur once HAART is resumed [74]. In a randomized controlled trial, *Meintjes G et al* reported the utility of prednisolone (1.5 mg/kg per day for two weeks followed by 0.75 mg/kg per day for further two weeks) in the treatment of paradoxical tuberculosis-IRIS with worsening chest radiograph, enlarging lymph node, serous effusion and cold abscess, CNS manifestations, tracheal compression due to lymphadenopathy and acute respiratory distress syndrome (ARDS). For atypical mycobacterial – IRIS treatment is similar to TB-IRIS. Surgical excision of profoundly enlarged nodes or debridement of necrotic areas is anecdotally reported [75,76]. Cryptococcal meningoencephalitis IRIS requires prompt control of raised intracranial pressure and hydrocephalus by serial lumbar punctures. Corticosteroids are indicated for cerebral oedema and ARDS in pulmonary cryptococcosis [48,77-78]. The development of PCP-IRIS after discontinuation of steroid therapy suggest a role for the reintroduction of steroids in these patients [44]. In cases of ocular CMV-IRIS systemic or periocular steroid injections have been used bur a clear benefit has not been demonstrated. The role of corticosteroids in PML-IRIS is not clear and a long term treatment may be necessary until T memory cells and a more directed immune response against JC virus predominates [50,79]. Unfortunately increased risk of progression of herpes zoster and Kaposi's sarcoma and reactivation of latent infections have also been reported with corticosteroids.

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6. Conclusions

The majority of patients with IRIS have a self-limiting disease course but associated morbidity places a considerable burden on the health care system. Morbidity and mortality rates vary according to the pathogen and organ involved. Mortality is usually uncommon with the exception of the setting of opportunistic infections involving the CNS [1]. Lethality ranges from about 3% in patients with tuberculosis to more than 20% in patients with cryptococcal meningitis, with an higher early mortality in resource-limited settings due to probable underdiagnoses [3]. The occurrence of IRIS and its contribution to mortality in a given setting is affected by the relative importance of different infections, the degree of access to facilities for diagnosis of such illnesses and the extent of screening for and treatment of opportunistic infections before starting HAART [80].Research efforts should be focused on increasing knowledge about IRIS so that diagnostic tests and prevention and treatment strategies could be improved.

	CD4 < 50 µl	CD4 > 50 µl
IRIS-TB	20,7%	17,7%
IRIS-cryptococcal meningitis	28,3%	2%
IRIS- CMV retinitis	37,7%	No studies

Table 1. Development of IRIS in analysis stratified by median CD4+ cells count at the start of HAART [3]

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