

# IMMUNE RESTORATION SYNDROME IN AIDS PATIENTS

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**Abstract:** Human Immunodeficiency virus infection leads to rapid depletion of CD<sub>4</sub><sup>+</sup> T-cells and makes the person vulnerable for various less virulent pathogens commonly known as opportunistic pathogens, because they rarely cause diseases in immunocompetent host. When an acute opportunistic infection is present, initiation of anti-retroviral therapy (ART) is expected to improve the CD<sub>4</sub><sup>+</sup> T-cell counts and faster resolution of the opportunistic infection. However, it has been seen that due to improvement in the host immune system after ART, rather than improvement in the general condition of the patient, there is flaring of opportunistic infection or unmasking of latent infections. This may result either severe form of the existing infection such as tuberculosis or unmasking of silent infections such as Mycobacterium avium intracellulare complex (MAC), CMV retinitis, viral hepatitis, parasitic and fungal diseases. This condition previously known as paradoxical reaction has been named as immune Reconstitutive Syndrome (IRS) or Immune Reconstitutive Disease (IRD). This paper reviews various opportunistic pathogens, their manifestations during the immune reconstitutive phase and its management. This review makes important reading to clinicians and even the AIDS activists to understand this aspect of AIDS therapy, as the patient and their relatives are often mistaken as wrong or ineffective treatment with IRS.

## INTRODUCTION

As a hallmark, all HIV infected patients face severe immune suppression leading to various opportunistic infections. When highly effective antiretrovirals are given to these patients, the main focus of the treating physician is to restore the patient's immune system rapidly. However, while effective immune restoration on one hand achieves immune recovery, it can also be detrimental and lead to worsening of some latent opportunistic infections. This syndrome is known as the immune reconstitution syndrome (IRS) or immune restoration disease (IRD)<sup>1</sup>. IRD or IRS is defined as an acute symptomatic or paradoxical deterioration of a (presumably) pre-existing infection that is temporally related to the recovery of the immune system and is due to immunopathological damage associated with the reversal of immunosuppressive processes, such as withdrawal of corticosteroids, recovery of the neutrophil count from chemotherapy, engraftment after bone marrow transplantation, or highly active antiretroviral therapy (HAART) for AIDS. The pre-existing microbial infection could be either asymptomatic or mildly symptomatic. The resulting clinical manifestations of this phenomenon are diverse and depend on the associated pathogens viz. mycobacteria, parasites, viruses, or fungi<sup>1,2</sup>.

Immune reconstitution syndrome (IRS) usually occurs in patients on HAART due to effective inflammatory response to residual pathogens. It is reported that within 4–6 weeks of initiation of HAART, the HIV-RNA load declines while CD<sub>4</sub><sup>+</sup> T-cell count starts increasing<sup>2</sup>. This leads to a paradigm shift of immune response from TH<sub>2</sub> type to TH<sub>1</sub> type. Patients with very low CD<sub>4</sub><sup>+</sup> T-cell count and high HIV viral load are more prone for IRS particularly with intracellular pathogens. IRS is now a major concern in developing countries where aggressive HAART therapy is now easily available. When an acute OI is present, initiation of ART is usually expected to improve immune function and contribute to faster resolution of the OI. Initiation of ART has been documented to be effective for OIs for which effective therapy does not exist, for example, cryptosporidiosis, microsporidiosis, and progressive multifocal leukoencephalopathy (PML)<sup>1,2</sup>. After HAART, these infection might resolve or at least stabilize. For Kaposi's sarcoma (KS), initiation of ART has been documented to lead to resolution of lesions in the

absence of specific therapy for the sarcoma. However, starting ART during an acute OI has several potential disadvantages. Severely ill patients might not absorb ART drugs, leading to subtherapeutic serum levels and the development of antiretroviral drug resistance. Renal or hepatic dysfunction during acute OIs also pose problem in estimating the correct dose of ART drugs. Finally, IRIS events can occur and cause manifestations that are difficult to distinguish from other clinical conditions.

The term IRS has been used as suffix to describe a group of clinical syndromes associated with immune reconstitution that have been observed most commonly for mycobacterial infections as TB-IRS or MAC-IRS, but also for other OIs, including Pneumocystis jirovecii pneumonia (PCP), toxoplasmosis, hepatitis B and C viruses, cytomegalovirus (CMV) infection, varicella-zoster virus (VZV) infection, cryptococcal infection, histoplasmosis, Penicillium marneffeii and PML likewise<sup>1-3</sup>. IRS manifestations are diverse and have not been defined precisely; they are usually characterized by fever and worsening of the clinical manifestations of the underlying OI. These clinical manifestations might be at the site of previously recognized opportunistic disease or might "unmask" disease at new sites not previously known to be infected by the pathogen, as described in the beginning. The majority of patients who manifest IRIS do so within the first 4-8 weeks after starting ART, and have had high viral loads and low CD<sub>4</sub><sup>+</sup> T-lymphocyte (CD<sub>4</sub><sup>+</sup>) counts.

## MYCOBACTERIUM TUBERCULOSIS INFECTION AND DISEASE

Tuberculosis continues to be a major problem in Sub-Saharan Africa and Asia, killing maximum cases by a single infectious disease. Tuberculosis is the leading cause of morbidity and mortality in patients with HIV/AIDS living in low income countries. The World Health Organization (WHO) estimates that TB is the cause of death for 13% of persons with AIDS. Usually within 2-12 weeks after infection, our immune system successfully limits multiplication of tubercle bacilli. However, viable bacilli persist for years, a condition referred to as latent TB infection (LTBI). Persons with LTBI are asymptomatic and are not infectious. TB disease can develop immediately after exposure (primary disease) or after reactivation of LTBI (reactivation

disease). Primary disease accounts for one third or more of cases of TB disease in HIV-infected populations .

The estimated annual risk for active TB among persons with LTBI in the general population is 12.9 per 1,000 person-years of observation. In contrast, rates of progression to active TB among HIV-infected persons with LTBI have ranged from 35 to 162 per 1,000 person-years of observation. Unlike other AIDS-related OIs, CD<sub>4</sub><sup>+</sup> count is not a reliable predictor of increased risk for TB disease in HIV-infected persons. In both TB-endemic and non-TB-endemic areas, patients can have relatively high CD<sub>4</sub><sup>+</sup> counts at the time HIV-related TB disease develops. As with HIV-uninfected persons, HIV-infected persons who live or work in high-risk congregate settings such as correctional facilities, health-care facilities, drug-treatment units, or homeless shelters are at increased risk for acquiring TB.

### MYCOBACTERIAL IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

A baseline evaluation and monthly follow-up consisting of clinical, bacteriologic, and periodic laboratory and radiographic evaluations are essential to ensure treatment success. Clinical history and baseline tests to evaluate hepatic function (AST, bilirubin, and alkaline phosphatase), renal function (serum creatinine), complete blood count (including platelet count), and CD<sub>4</sub><sup>+</sup> counts are recommended for all patients, even though in India it is not a routine practice due to feasibility reasons. Fever in an HIV-infected patient who has been receiving effective TB therapy for several weeks might represent drug fever, a paradoxical reaction, or IRS<sup>4,6</sup>. If superinfection or worsening TB is excluded as a potential cause, all TB drugs should be stopped. Once the fever has resolved, the general guidelines described for restarting/stopping drugs in the presence of a rash should be followed. For ART-naïve, HIV-infected persons who are diagnosed with active TB, anti-TB treatment must be started immediately. There is no standard optimal timing of initiation of ART but most clinicians feel that should be started after 2 months. Options include simultaneous TB and ART or treatment of TB first with delay of ART by several weeks to months. For patients with a CD<sub>4</sub><sup>+</sup> count <100 cells/μL, ART should be started after >2 weeks of TB treatment to reduce confusion about overlapping toxicities, drug interactions, and the occurrence of IRS. For persons with a CD<sub>4</sub><sup>+</sup> count of 100-200 cells/μL, some experts advocate to delay ART until the end of the 2-month intensive phase of anti-TB treatment. In those with a sustained CD<sub>4</sub><sup>+</sup> count >200 cells/μL, ART could be started during the anti-TB maintenance phase and for those with a CD<sub>4</sub><sup>+</sup> count >350 cells/μL, after finishing anti-TB treatment. In one study, paradoxical reactions occurred in almost all HIV-infected patients with TB and a CD<sub>4</sub><sup>+</sup> count <100 cells/μL who started ART within the first 30 days of TB therapy<sup>1</sup>.

IRIS or a paradoxical reaction occurring after the initiation of ART is thought to be the result of recovery of immune responses to previously recognized TB antigens, reconstituted by ART or by TB treatment itself. The immune response might be an exaggerated inflammatory response during TB treatment in a patient known to have TB, or might unmask previously undiagnosed TB, referred to as TB-associated IRIS<sup>7-15</sup>.

TB-associated paradoxical reactions or IRIS usually occur in the first 1-3 months after starting ART in patients receiving TB treatment. The risk for IRIS is greater when ART is started within the first 2 months of TB therapy and when the CD<sub>4</sub><sup>+</sup> count is <100 cells/μL. Signs of TB-IRIS can include, but are not limited to, high fevers, worsening respiratory status, increase in size and inflammation of

involved lymph nodes or new lymphadenopathy, breakthrough meningitis or new or expanding CNS lesions, radiologic worsening of pulmonary parenchymal infiltrations, and increasing pleural effusions. Such findings should be attributed to IRS reaction only after a thorough evaluation has excluded other possible causes, especially failure of TB therapy. IRS manifestations are usually self-limited but if symptoms are severe, supportive treatment might be required, depending on the nature of the complications.

Beside *M. tuberculosis*, *Mycobacterium avium* complex (MAC) is the leading cause of Mycobacterial IRS. Though in Indian *M. tuberculosis* is most common, in USA, *M. avium* is the etiologic agent in >95% of patients with AIDS who acquire disseminated MAC disease. In the absence of effective ART or chemoprophylaxis in those with AIDS-associated immune-suppression, the incidence of disseminated MAC disease is 20%-40%. For persons with a CD<sub>4</sub><sup>+</sup> count <100 cells/μL who are receiving effective prophylaxis or have responded to ART with a sustained increase in CD<sub>4</sub><sup>+</sup> count to levels >100—200 cells/μL, the overall incidence has been estimated at 2 cases per 100 person-years. MAC disease typically occurs among persons with CD<sub>4</sub><sup>+</sup> counts <50 cells/μL. Other factors that are associated with increased susceptibility to MAC disease are high plasma HIV RNA levels (>100,000 copies/mL), previous OIs, previous colonization of the respiratory or gastrointestinal tract with MAC, and reduced in vitro lymphoproliferative immune responses to *M. avium* antigens, possibly reflecting defects in T-cell repertoire<sup>5,6,16-18</sup>.

### FUNGAL IRS

Amongst the fungi, so far, IRS has been extensively reported with *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Pneumocystis jirovecii*, *Aspergillus* and recently with *Penicillium marneffei*<sup>1,9</sup>.

### CRYPTOCOCCOSIS

The majority of HIV-associated cryptococcal infections are caused by *Cryptococcus neoformans*; rarely, infection because of *Cryptococcus neoformans* var. *gattii* is recognized in the United States. Before the advent of potent ART, approximately 5%-8% of HIV-infected patients in developed countries acquired disseminated cryptococcosis. The incidence has declined substantially since then. The majority of cases are observed among patients who have CD<sub>4</sub><sup>+</sup> counts of <50 cells/μL.

After the initial 2 weeks of treatment, a repeat lumbar puncture should be performed to ensure the organism has been cleared from the CSF, even among those who have improved after the initial 2 weeks of treatment. Positive CSF cultures after 2 weeks of therapy are predictive of future relapse and typically less favorable clinical outcomes. If new symptoms or clinical findings occur later, a repeat lumbar puncture, with measurement of opening pressure and CSF culture, should be performed. An estimated 30% of patients with cryptococcal meningitis and HIV infection experience IRIS after initiation or reinitiation of ART. Patients who have cryptococcal IRIS are more likely to be antiretroviral naïve and have higher HIV RNA levels. Appropriate management of IRIS is to continue ART and antifungal therapy. In patients with severely symptomatic IRIS, short-course glucocorticosteroids are recommended by certain specialists. Delaying the initiation of potent ART might be prudent, at least until the completion of induction therapy (the first 2 weeks) for severe cryptococcosis, especially if patients have elevated intracranial pressure<sup>1,5,6</sup>.

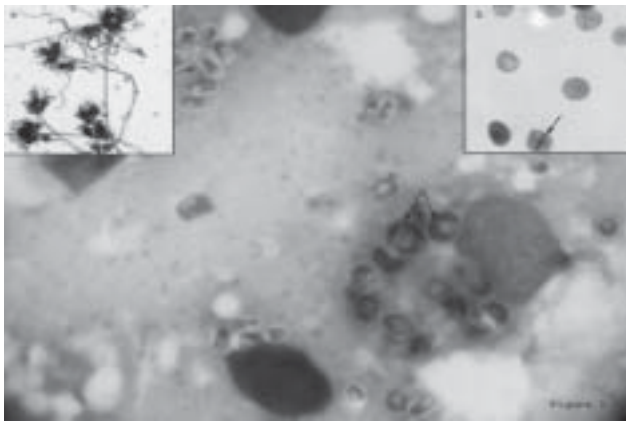
### HISTOPLASMOSIS

Histoplasmosis is caused by the dimorphic fungus *Histoplasma*

*capsulatum*. Virtually all cases of primary histoplasmosis are acquired by inhalation of microconidia from the mycelial phase of the organism. The incidence of symptomatic histoplasmosis in patients with HIV infection appears to have declined since the use of potent ART. IRIS has been reported uncommonly in patients with histoplasmosis. ART should not be withheld because of concern for the possible development of IRIS<sup>1</sup>.

## PENICILLIOSIS

*Penicilliosis marneffei* (penicilliosis) is caused by the dimorphic fungus *Penicillium marneffei*, which is endemic in Southeast Asia (especially Northern Thailand) and southern China. More recently, 50 indigenous cases of penicilliosis occurred in Manipur State, India, a new endemic area of this fungus. International travel requires increased awareness and recognition of penicilliosis and its treatment. *Penicillium marneffei* has been found to be an emerging pathogen in the Indian state of Manipur, which shares borders with Myanmar, but has never been diagnosed from north India. Recently an unique case of disseminated *Penicilliosis marneffei* and *Cytomegalo virus* manifesting as a result of immune restoration after highly active antiretroviral therapy, was reported from Delhi<sup>19</sup>. This rare case presented with fever, icterus, lymphadenopathy and hepatosplenomegaly, but no skin lesions. Differential diagnoses of disseminated tuberculosis, leishmaniasis and histoplasmosis were considered. His blood cultures were sterile and no growth of mycobacteria was seen on MGIT 960 culture. His blood was PCR negative for mycobacteria but positive for cytomegalovirus (CMV). Serology for Leishmania was also negative. However, the diagnosis of *Penicillium marneffei* was clinched on finding typical yeast cells on Giemsa stained lymph node fine-needle aspirates and typical mould forms in culture on sabouraud dextrose agar. (Figure 1) The patient was treated successfully<sup>19</sup>.



**Figure 1.** Photomicrograph of Giemsa stained lymph node aspirate showing intracellular as well as extra-cellular yeast cells. Distinctive septation was seen on Gomori's methenamine silver stain (Inset b) and also visible as negative staining on Giemsa (arrows). Lacto-phenol cotton blue preparation from growth showed typical *Penicillium* heads (Inset a).

## PARASITIC IRS

### *Pneumocystis Pneumonia*

For these reasons, no consensus has been reached concerning the optimal time to start ART in the setting of a recently diagnosed *Pneumocystis jirovecii* pneumonia (PJP). However, one recently completed randomized clinical trial has demonstrated a clinical and survival benefit of starting ART early, within the first 2 weeks, of initiation of treatment for an acute OI, excluding TB. Careful monitoring during therapy is important to

evaluate response to treatment and to detect toxicity as soon as possible. Follow-up after therapy includes assessment for early relapse, especially when therapy has been with an agent other than TMP-SMX or was shortened for toxicity. PJP prophylaxis should be initiated immediately upon completion of therapy and maintained until the CD<sub>4</sub>+ count is >200 cells/ $\mu$ L. IRIS has been reported following PCP. Most cases have occurred within weeks of the episode of PJP. Reported cases are not sufficient to provide guidance on the optimal time to start ART following a mild or severe case of PJP<sup>1</sup>.

## TOXOPLASMOSIS AND LEISHMANIASIS

Toxoplasmic encephalitis (TE) is caused by the protozoan *Toxoplasma gondii*. Disease appears to occur almost exclusively because of reactivation of latent tissue cysts. Primary infection occasionally is associated with acute cerebral or disseminated disease. Changes in antibody titers are not useful for monitoring responses to therapy. Patients with TE should be monitored routinely for adverse events and clinical and radiologic improvement. Several cases of neurologic disease have been attributed to immune reconstitution and toxoplasmosis, but more data are needed to verify that such cases are IRIS related to *T. gondii*.

Leishmaniasis among persons with HIV/AIDS has been reported primarily from Spain, Italy, France, Brazil, India and Ethiopia, but most coinfections in the developing world are never reported. In HIV-infected persons without severe immunosuppression, disease manifestations are similar to those in immunocompetent persons. Among those with advanced immunosuppression and low CD<sub>4</sub>+ counts (<200 cells/ $\mu$ L), manifestations of leishmaniasis might be both atypical and more severe, and relapse after treatment is common. There is very limited data regarding IRS-associated leishmaniasis to provide data for specific IRS management guidelines. Leishmaniasis that manifests after initiation of ART requires specific therapy consistent with guidelines for initial treatment or management of relapse<sup>1</sup>.

## CRYPTOSPORIDIOSIS

Cryptosporidiosis is caused by various species of the protozoan parasite *Cryptosporidium*, which infect the small bowel mucosa, and in immunosuppressed persons, the large bowel and extra-intestinal sites. Persons at greatest risk for disease have advanced immunosuppression, typically CD<sub>4</sub>+ counts of <100 cells/ $\mu$ L. The three most common species infecting humans are *C. hominis*, *C. parvum*, and *C. meleagridis*. Infections are usually caused by one species but might be mixed. IRIS has not been described in association with treatment of cryptosporidiosis or microsporidiosis.

## VIRAL IRS

### *Cytomegalovirus Disease*

Cytomegalovirus (CMV) is a double-stranded DNA virus in the Herpesvirus family that can cause disseminated or localized end-organ disease among patients with advanced immunosuppression. Most clinical disease occurs in previously infected (seropositive) persons and so represents either reactivation of latent infection or reinfection with a novel strain. Before potent ART, an estimated 30% of patients with AIDS experienced CMV retinitis some time between the diagnosis of AIDS and death. This incidence has declined by 75%-80% with the advent of ART and now is estimated to be <6 cases per 100 person-years.

Immune recovery uveitis (IRU) is an ocular form of IRIS caused by an immunologic reaction to CMV, characterized by inflammation in the anterior chamber or vitreous in the setting of immune recovery after initiation of ART and is usually observed among those patients with a substantial rise in CD<sub>4</sub>+ counts in the first 4-12 weeks after initiation of ART. Ocular complications of uveitis include macular edema and the

development of epiretinal membranes, which can cause loss of vision. Treatment usually requires periocular corticosteroids or short courses of systemic corticosteroids. Estimated response rates are 50%. One uncontrolled case series suggested that IRU (or CMV retinitis-associated IRIS) might respond to oral valganciclovir<sup>1,19</sup>.

## HEPATITIS B VIRUS INFECTION

Hepatitis B virus (HBV) is the leading cause of chronic liver disease worldwide, but more commonly in Asian countries. Up to 90% of HIV-infected persons have at least one serum marker of previous exposure to HBV, and approximately 10% have evidence of chronic hepatitis B.

Return of immune competence after ART can lead to reactivation of HBV-associated liver disease. Any immune reconstitution can lead to a rise in serum aminotransferases, so called "hepatitis flare", which constitutes IRIS in HIV/HBV-coinfected persons. IRIS might be manifested by dramatic increases in serum aminotransferases as CD<sub>4</sub><sup>+</sup> counts rise within the first 6-12 weeks after starting ART, with signs and symptoms characteristic of acute hepatitis. The major problem in managing adverse effects and drug-induced liver injury is determining whether the manifestations are due to medication or the hepatic flares associated with IRIS. Initiation of ART without anti-HBV therapy might lead to reactivation of HBV. A hepatic flare might also occur when patients must discontinue their ART. Elevated aminotransferases might also occur after the onset of drug resistance, which is common even and increases over time with medications such as lamivudine. Hence to confirm the hepatitis flare serum HBV DNA testing will be more appropriate<sup>1</sup>.

## HEPATITIS C VIRUS INFECTION

Hepatitis C virus (HCV) is a single-stranded RNA virus that is most efficiently spread through direct blood exposure to contaminated blood or blood products. Both HIV and HCV can be transmitted by percutaneous exposure to blood, through sexual intercourse, and from a mother to her infant. However, the relative efficiency of transmission by these routes varies. HCV is approximately 10 times more infectious than HIV through percutaneous blood exposures, but sexual transmission of HCV is inefficient compared with HIV. Transmission of HIV and HCV through contaminated blood products is now rare because of effective screening of blood and blood-derived products in the United States.

Assessment of HCV RNA level is the best measure of treatment response and should be performed at baseline and after completion of the first 12 weeks of therapy for HCV infection. In the context of treatment monitoring, relapse is defined as the absence of detectable HCV RNA at the end of treatment that is not sustained after the discontinuation of therapy. Breakthrough is the re-emergence of detectable HCV RNA following suppression below the limit of detection despite the continuation of therapy. As with HBV coinfection, in HCV-coinfected persons, IRIS might be manifested by dramatic increases in serum aminotransferases as CD<sub>4</sub><sup>+</sup> counts start rising, usually within the first 6-12 weeks. The signs and symptoms are characteristic of hepatitis flares. After introduction of ART, serum aminotransferases should be monitored closely preferably every 3 months. There is no reliable clinical or laboratory parameter to distinguish hepatotoxicity from IRIS. Prospective studies are underway at various centers to find the incidence of presumptive IRIS within the first 12 months of ART initiation<sup>1</sup>.

## OTHER OPPORTUNISTIC INFECTIONS

The reporting of IRS is not uniform and several cases go unnoticed or unreported in the literature. Ideally any OI can manifest or have unmasking if the patient is severely ill and his/ her CD<sub>4</sub><sup>+</sup> counts have gone <200 cells/ $\mu$ L. In these patients the highly active Antiretroviral Therapy (HAART), improves the CD<sub>4</sub><sup>+</sup> very quickly leading to paradoxical reactions. Reports are slowly but steadily coming involving Opportunistic infections like Parvo-B19-IRS<sup>20</sup>, *Strongyloides stercoralis* -IRS<sup>21</sup> and even worsening of Kaposi sarcoma<sup>22</sup>. Many more such IRS are expected to come to our knowledge in near future.

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### Next Issue Highlights

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