Original Article

Immune Reconstitution Inflammatory Syndrome (IRIS): An Update on Aetiopathogenesis

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ABSTRACT

Immune reconstitution inflammatory syndrome (IRIS), an overwhelming inflammatory response to antigens in patients with rapidly recovering immune system is a life-threatening medical condition. Literature search for this topic was done on Google Scholar Database using terms such as: immune reconstitution inflammatory syndrome, immune restoration inflammatory syndrome, immune recovery syndrome OR immune restoration disease (#1) and HIV/AIDS (#2), TB (#3) OR Cryptococcus (#4). Articles published in the last twenty years in human studies with infectious causes linked to the developing IRIS were selected while those older than twenty years or which neither involve humans nor had non-infectious causes were excluded. A total of 51 papers were therefore reviewed and findings showed that essentially, viruses (HIV, JC, cytomegalovirus), fungi (Histoplasma species and Cryptococci), protozoans (Leishmania species) and mycobacteria (M. tuberculosis, Mycobacterium leprae) are the pathogens which cause most forms of antigens-specific IRIS. There was no common pathophysiological explanation for all forms of IRIS but the syndrome is largely driven by cytokine production leading to an unbalanced immune reconstitution of effector and regulatory T cells in patients undergoing rapid immune reconstitution. Understanding of possible risk factors for the development of IRIS as well as its pathogenesis and presentation is key to its management and prevention.

Keywords: Immune, Inflammatory, Reconstitution, Syndrome.

INTRODUCTION

Immune reconstitution inflammatory syndrome (IRIS) is an overwhelming inflammatory response to a viable, dormant, or nonviable antigen in patients with rapidly recovering immune system. The recovering immune status can be driven by the introduction of ART in HIV patients, neutrophil recovery after chemotherapy and/or stem cell transplant, inadequate balancing of immunosuppressive therapy after solid organ transplantation.[1,2] and even by post-partum immunological changes after pregnancy.[3]

IRIS has been known and described in literature for man-y decades using various terminologies such as *immune restoration illness*, *immune reconstitution syndrome*, and *immune recovery disease*. However, the term *immune reconstitution inflammatory syndrome* is the most recognized and widely used, probably because of how it reflects the characteristic nature of the condition.

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The syndrome manifests in either of these two patterns: 'unmasking IRIS' or 'paradoxical IRIS." However, before any of these assessment is made, other factors such as the failure to treat opportunistic infection, drug resistance or treatment failure due to poor adherence to therapy must be excluded.

EPIDEMIOLOGY

The incidence of IRIS is difficult to measure given the wide range of possible disease presentations, local incidence of opportunistic infection and variations in local diagnostic capacity.[4] However, IRIS has been reported by many investigators to have an overall incidence of between 25%–35% and

Table 1: Incidence of IRIS in different regions of the world

Country	Over all incidence %	**IRIS-associated condition/opportunistic infection, proportion of total IRIS cases, %**	Citation
USA	11 (paradoxical IRIS only	KS, 57 TB, 19 PCP, 14 Disseminated Cryptococcosis, 5 MAI, 5	Achenbach *et al.* (2012) [6]
USA	10.6 (unmasking IRIS only)	Candidiasis, 23 Folliculitis, 13.8 HSV, 12.4 Warts, 12.2 Tinea, 11.1	Novak *et al.* (2012) [7]
Mexico	27	VZV, 32 TB, 11 MAI, 9 PCP, 6 *Cryptococcus neoformans* , 5	Hoyo-Ulloa *et al.* (2011) [8]
India	35	Mucocutaneous (combined), 35.2 TB, 29.4 PCP, 17.6 CMV retinitis, 5.9 CM, 5.9 MAI, 5.9	Kumar *et al.* (2012) [9]
Mozambique	26.5	Tinea, 25 KS, 22.2 TB, 16.7 PCP/pneumonitis, 8.3 HSV, 8.3	Letang *et al.* (2011) [10]
South Africa	22.9	Folliculitis, 27.3 TB, 24.4 HSV, 9.4 VZV, 6.5 Warts, 7.2	Haddow *et al.* (2012) [11]

Key: CM= cryptococcal meningitis; CMV= Cytomegalovirus; HSV= herpes simplex virus; IRIS= immune reconstitution inflammatory syndrome; KS= Kaposi's sarcoma; MAI= *Mycobacterium avium-intracellulare*; PCP= *Pneumocystis jirovecii*pneumonia; TB= tuberculosis; VZV= Varicella zoster virus

Risk Factors

Risk factors for IRIS can be classified into: Host-related, Pathogen-related and Treatment-related risk factors[12] which generally include the following:

1. **HAART-naïve patient**— This allows for a more intense inflammatory response to develop.[13]
2. **Severe immunocompromise at the initiation of ART**— very low CD4 counts <50 cells per cubic millimetre.[14,15]
3. **High pre-HAART HIV-1 RNA levels**
4. **Falling HIV-1 RNA levels in response to HAART initiation,** especially when this fall occurs rapidly within 90 days of the introduction of HAART and results in significant level reductions.[13,16,17]
5. **Rising CD4 counts after initiation of HAART,** especially later in the course of

therapy after falling HIV-1 RNA levels have resulted in an initial redistribution of memory CD4 lymphocytes. [13, 17] In general, any rapid immune recovery can lead to IRIS, driven by multifactorial factors such as: patient response to drugs (ART, antifungals, etc), host immune genetics, and the microbial strain.

6. **Opportunistic Infections (OIs) or the patient been on treatment for OIs when HAART is initiated,** especially within a month of the OI diagnosis, because the increased antigenic burden evokes a more robust inflammatory response.[13,18]
7. **Resumption of HAART after an interruption**
8. **Genetic factors** that alter the clearance of the pathogen (such as with *herpesviruses* or mycobacteria) or enhance the immune response to it via polymorphisms in cytokine genes.[17,19]
9. **Solid organ transplantation:** Cryptococcosis, *Cytomegalovirus* disease, and tuberculosis are the most common infections associated with IRIS in solid organ transplant recipients.[20]
10. **Postpartum**: Immediate postpartum period (3 to 6 weeks) has an increased risk of IRIS, most commonly with Cryptococcosis, herpes virus infection, human papillomavirus reactivation, leprosy, tuberculosis, viral hepatitis, and a flare-up of autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis.[20]
11. **Neutropenia**: Patients with an absolute neutrophil count (ANC) below 500 per microliter are at increased risk of fungal and viral opportunistic infections (*Aspergillus* infections, CMV)[20]
12. **Patients on TNF antagonists:** use of TNF antagonists can significantly impair the host response against infections such as TB. These TB infections can be latent while using TNF antagonists, but once these medications are discontinued, there will be a subsequent macrophage activation, leading to IRIS associated with TB.[20]

CLASSIFICATION OF IRIS

The presentations of IRIS which define its clinical forms involves the unmasking of covert infections due to a viable pathogen or the worsening of overt conditions due to a persistent antigen; but it can also develop as progression of proliferative disease in patients with cancers.[21] Based on this, IRIS has been classified into two forms: Paradoxical IRIS and Unmasking IRIS

- **Paradoxical IRIS** also called the **Delayed type**, is a worsening of clinical symptoms as a result of immune response to persistent antigens in a patient with previously treated infection while
- **Unmasking IRIS** also called **the Simultaneous type** is a flaring up of clinical symptoms as a result of immune response to a previously undiagnosed /occult infection following rapid immune restoration.[15,22]

METHODOLOGY

Literature search for this topic was done on google scholar database using the following terms: immune reconstitution inflammatory syndrome OR immune restoration inflammatory syndrome OR immune recovery syndrome OR immune restoration disease (#1) and HIV/AIDS (#2) OR TB (#3) OR Cryptococcus (#4). These last disease entities were added to the parent search terms because IRIS is also seen in some autoimmune diseases and malignancies, but we wanted to limit our study to infectious causes only.

Selection criteria was based on articles that involve clinical trials, meta-analyses, randomised controlled trials and reviews of human studies published in the last twenty years. Studies which were older than twenty years or which did not involve humans were excluded.

In this review, we summarized current knowledge on the immunopathogenesis of IRIS as well as risk

factors with clinical / biological manifestations and diagnostic approaches from 51 articles in order to bring together expert knowledge on the subject besides highlighting more research priorities.

AETIOLOGY

The aetiology of IRIS can be broadly classified into 2

1. Infectious causes
2. Non –infectious causes

Table 2: aetiological factors for IRIS

A. Infectious causes[20]	
1. Mycobacteria :	**2. Viruses** :
Mycobacterium tuberculosis	HIV
Mycobacterium avium complex	Herpes simplex virus
Mycobacterium leprae	Herpes zoster virus
Bacille -Calmette -Guerin	Cytomegalovirus
	JC virus
3. Fungal infections :	HIV encephalitis
Cryptococcus species	Hepatitis B and C virus
Pneumocystis jiroveci	Parvovirus B19
Histoplasma species	Molluscum contagiosum
Candida	**5. Bacteria** :
4. Protozoa :	Bartonella
Toxoplasma	**6. Helminth** :
Microsporidia	Schistosoma
Leishmania	Strongyloides
Cryptosporidia	
B. Non-infectious causes	
1. Autoimmune diseases :	**2. Inflammatory conditions**
Systemic lupus erythematosus (SLE)	Sarcoidosis
Lupus -like disease	Lymphoid interstitial pneumonitis
Thyroid disease	Folliculitis
Rheumatoid arthritis	
Guillain -Barre syndrome	**1. Malignancies:**
Reiter's syndrome	Kaposi's sarcoma
Polymyositis	Lymphoma

IMMUNOPATHOGENESIS

Finding a common pathophysiological explanation for all forms of IRIS is a bit challenging because of the diverse aetiological factors and immunological mechanisms involved as well as their clinical presentations.[23] Though the immune pathophysiology of IRIS appears to vary as stated, the syndrome is largely due to an unbalanced immune reconstitution of effector and regulatory T cells in patients undergoing rapid immune reconstitution.[23,24] Understanding of these mechanisms is important for the development of immunomodulatory pharmacological interventions for treatment and prevention of the condition.

Common factors known to influence immunosuppression in the host include HIV infection, pregnancy, and chemotherapy amongst others.[25] HIV appears to drive the depletion of all Th cell subsets by depleting the total pool of CD4+ T-cells including Th0 cells. This way, HIV induces preferential death of Th1 cells as well as the preferential differentiation of the remaining Th0 cells into Th2 cells through a critical change in cytokine balance thereby favouring an anti-inflammatory state.[25,26] However, 4–6 weeks following introduction of ART, the production of naive CD4+ T-cells and memory T-cells occurs, a condition that is known to coincide with the mean onset of paradoxical IRIS.[24,27-29]

During pregnancy, mechanisms of foetal tolerance lead to downregulation of the Th1/Th17 axis. For example, pregnancy hormones inhibit the differentiation of naive Th0 cells into Th1 cells, thus promoting a Th2 state that is anti-inflammatory in nature.[30,31] However, a shift in cytokine pattern is observed during the post-partum period that may be associated with pathological inflammatory syndrome and has been documented 3–6 weeks after delivery.[3,31,32]

It has also been observed that following solid organ transplantation, graft survival relies on the inhibition of allo-reactive Th1/Th17 responses by immunosuppressive drugs through different mechanisms. Calcineurin inhibitors such as tacrolimus strongly suppress the Th1 response while rapamycin promotes Treg survival and function and suppresses the differentiation of Th17 cells. Corticosteroids on the other hand decrease Th1 responses but also expand Th2 cells and Tregs.[2] Post-transplant IRIS is subsequent to a decrease in immunosuppression due to drug–drug interactions or an intentional modification in drug dosage in the context of an ongoing infection, therefore increasing Th1/Th17 responses.[33]

In general, following immune recovery after a state of immunosuppression, precursor T helper cells

(Th0) differentiate into Th1, Th17 or Th2 cells and Tregs depending on the cytokines produced in the surrounding environment through induction of specific transcription factor expression such as: FOXP3/STAT-5, GATA-3/STAT-6, T-bet/STAT-4, and rROR-t/STAT-3 for Treg, Th2, Th1, and Th17, respectively.[34,35] The differentiated Th1 and Th17 cells been pro-inflammatory cells produce IFN which drive macrophage differentiation into M1 macrophages. M1 macrophages activation favours the secretion of large amounts of pro-inflammatory cytokines, such as IL-1, TNF, IL-12, IL-18, and IL-23, which in turn drive Th1/Th17 cell inflammatory response.[36] This promotes granuloma formation and subsequently produce more IFN, thus creating an amplification loop leading to an inflammation burst.[23] An inadequate balance between pro-inflammatory Th1/Th17 response and anti-inflammatory Th2/Treg axes is commonly admitted to be the origin of IRIS.[23]

Histologic examinations of tissues or organs with inflammatory cell infiltrates by various studies have demonstrated that CD8+ T cells predominate in IRIS provoked by viruses such as JC virus, HIV and cytomegalovirus[37,38] while granulomatous inflammation usually predominates in IRIS provoked by fungi such as *Histoplasma* species and Cryptococci; protozoans such as *Leishmania* species and by mycobacteria such as *M. tuberculosis, Mycobacterium leprae* and nontuberculous mycobacteria.[39-42] Granulomas may display very distinct features, may be activated or latent, and their cell-type composition may vary according to the situation and pathogen.[43] Furthermore, mycobacterial IRIS may also present with suppuration of lymph nodes or other affected organs. Though the immunopathology in such cases is still unclear at the moment, it is postulated that the tissue suppuration is a reflection of Th17 response against mycobacterial antigens, because Th17 responses induce inflammation that is often mediated by neutrophils.[21,44-45]

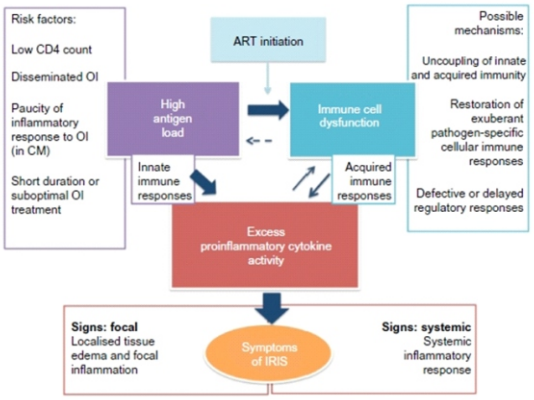

Fig 1: Diagram illustrating the pathophysiology of IRIS[15]

Note: A conceptual model of immune reconstitution inflammatory syndrome (IRIS) pathophysiology with three key features represented in central rectangles.

Excess antigen is a feature of tuberculosis (TB) IRIS, cryptococcal IRIS and Kaposi's sarcoma IRIS. This may result from extreme immunosuppression prior to antiretroviral therapy (ART) initiation, which increases the risk of opportunistic infection (OI) dissemination (in TB), and is associated with paucity of inflammation in cryptococcal meningitis (CM), especially in those patients who go on to develop IRIS. Antigen is likely to be more abundant if the OI is untreated, or if treatment has recently started. Immune cell dysfunction following ART has been described in IRIS, although the mechanism of this is incompletely understood but is thought to involve uncoupling of innate and acquired immune responses, restoration of exuberant pathogen-specific cellular responses, and defective or delayed regulatory responses. An excess of pro-inflammatory cytokines has been associated with TB-IRIS, and cryptococcal IRIS, in blood and cerebrospinal fluid. Possible relationships between the three key components are depicted by differentially weighted arrows. However, the direction of causality is not clear. It is probable that the presence of high antigen in IRIS drives pro-inflammatory cytokine responses directly through stimulation of innate immune responses and indirectly when adaptive immunity recovers. Further studies are required to improve understanding of these interactions.

Table 3: How diverse forms of IRIS share common features leading to the manifestation of disease.[46]

Form of IRIS	Progression of events leading to IRIS					
	Infection or iatrogenic immunosuppression	Immune defect	High microbial load without normal inflammation	Clinical intervention	Full inflammation restored	Pathology
HIV-associated	HIV	↓ $CD4^+$ T cells	Many, including mycobacteria and cryptococci	ART	↑ $CD4^+$ T cells	Many manifestations
Exacerbation of TB after withdrawal of TNF blockade	TNF blockade	↓ TNF	*M. tuberculosis*	Stop TNF blockade	↑ TNF	Lung pathology, lymphadenitis
PML-associated	α4 integrin blockade	↓ Immune cell migration into CNS	JC polyoma virus	Stop α4 integrin blockade	↑ Immune cell migration into CNS	Leukoencephalopathy
Organ transplant-associated	Anti-graft rejection treatment	Broad immunosuppression	*C. neoformans*	Decrease immunosuppressive treatment	Many factors?	Meningitis
Mouse model	TCRαKO or scid mice	T cell deficiency	*M. avium* or *P. carinii*	Inject $CD4^+$ T cells	↑ $CD4^+$ T cells	Wasting, lung pathology

Key: ART, antiretroviral therapy; *C. neoformans*, *Cryptococcus neoformans*; CNS, central nervous system; IRIS, immune reconstitution inflammatory syndrome; *M. avium*, *Mycobacterium avium*; *M. tuberculosis*, *Mycobacterium tuberculosis*; *P. carinii*, *Pneumocystis carinii*; PML, progressive multifocal leukoencephalopathy; *scid*, severe combined immunodeficient; TB, tuberculosis; TCRαKO, T cell receptor-α knockout; TNF, tumour necrosis factor.

CLINICAL MANIFESTATIONS

Although presentation varies by associated pathogen, a common feature is that onset is usually acute and there are features of inflammation, which may be generalized (eg, fever, tachycardia) or localized (eg, lymphadenitis).[12] In paradoxical IRIS, symptoms of the previously diagnosed opportunistic infection may recur or worsen, but a clear improvement is usually reported after the start of opportunistic infection treatment prior to starting ART.

Clinical features associated with different forms of IRIS are as seen in the table below:

Table 3: Pathogens and key clinical features of associated IRIS.[12]

	Pathogen associated	Features of IRIS
1	*Mycobacterium tuberculosis*	Fever, lymphadenitis, new/ worsening pulmonary infiltrates, pleural effusions, hepatomegaly, paradoxical or unmasking TBM/ tuberculoma
2	Nontuberculous mycobacteria(NTM)	Fever, lymphadenitis (painful/suppurative), pulmonary infiltrates and cavitation, inflammatory masses
3	Cytomegalovirus	Immune recovery uveitis (usually following previous history of retinitis), retinitis (typically unmasking)
4	Varicella zoster virus	Dermatologic reactivation (shingles), encephalitis, transverse myelitis, stromal keratitis
5	Human herpes virus-8 (Kaposi's sarcoma virus)	Kaposi's sarcoma- IRIS, multicentric Castleman's disease
6	*Cryptococcus neoformans*	Meeningitis with raised intracranial pressure, lymphadenitis, pneumonitis, ocular and soft tissue inflammation
7	*Pneumocystis jirovecii*	Unmasking PCP, paradoxical deterioration during or shortly after treatment with worsening hypoxia and new pulmonary infiltrates, organizing pneumonia (rare)

KEY: ART, anti-retroviral therapy; PCP, *Pneumocystis jirovecii*pneumonia; TBM, tuberculosis meningitis;

DIAGNOSIS

There is no single test currently available for the diagnosis of IRIS. Therefore, information regarding history, diagnosis, treatment and response to treatment of opportunistic infections before the commencement of ART is crucial to the diagnosis of "paradoxical" IRIS. However, diagnosis is further complicated in patients with "unmasking" IRIS as it is difficult to prove that the previous existence of a hidden opportunistic infection or the observed increase in inflammation is due to immune recovery. IRIS therefore is oftentimes a diagnosis of exclusion.[17] Because of the dilemma involved in making the diagnosis of IRIS, general case definitions have been proposed to enable clinicians consider the diagnosis of IRIS in their patients especially in resource-constrained settings. However, they lack specificity and do not discriminate between the different forms of IRIS.[13,47,48] Furthermore, diagnosis can be supported by the detection of atypical imaging findings such as new imaging patterns, kidney function tests, liver function tests, clotting profile/coagulation studies, serological tests and microbiological cultures that might detect viable organisms. Pathologically, T-cell infiltration confirms the diagnosis.[22]

CASE DEFINITIONS OF IRIS

Common case definitions used for IRIS are based on the major aetiological causes of IRIS, namely: HIV and Tuberculosis[49,50] proposed the HIV associated case definitions while[47] and INSHI (International Network for the Study of HIV-associated IRIS) proposed TB associated IRIS case definitions in use today.

IRIS case definition proposed by French *et al.* (2004)[49]

Diagnosis requires two major criteria (A+B) or one major criterion (A) plus two minor criteria:

Major criteria:

A. Atypical presentation of opportunistic infections or tumours in patients responding to ART, manifested by any of the following:

- Localized disease
- Exaggerated inflammatory reaction
- Atypical inflammatory response in affected tissues
- Progression of organ dysfunction or enlargement of pre-existing lesions after definite clinical improvement with pathogen-specific therapy prior to ART and exclusion of treatment toxicity and new diagnoses

B. Decrease in plasma HIV RNA level >1 $\log_{10}$ copies/ml

Minor criteria:

- Increase in CD4 count after ART\
- Increase in an immune response specific to the relevant pathogen
- Spontaneous resolution of disease with continuation of ART

IRIS case definition proposed by Robertson *et al.* (2006)[50]

Required criterion

– Worsening symptoms of inflammation/infection

– Temporal relationship with starting antiretroviral treatment

– Symptoms not explained by newly acquired infection or disease or the usual course of a previously acquired disease

– >1 $\log_{10}$ decrease in plasma HIV load

Supportive criterion

– Increase in CD4+ cell count of ≥25 cells/μl

– Biopsy demonstrating well-formed granulomatous inflammation or unusually exuberant inflammatory response.

Case definition for tuberculosis-associated IRIS by Colebunders*et al.* (2006)[47]

Suspected case(must meet the following three criteria)

– An initial clinical response to tuberculosis treatment

– New persistent fevers without another identifiable cause and/or one or more of the following:

worsening or emergence of dyspnoea, stridor, an increase in lymph node size, development of abscesses, development of abdominal pain with ultrasound evidence of abdominal adenopathies, unexplained CNS symptoms

- Adequate adherence to ART and tuberculosis treatment

Confirmed case(must meet the following three criteria)

- New/worsening radiological signs
- A good virological response and/or increase in CD4+ lymphocyte count, and/or conversion of tuberculin skin test from negative to positive, and/or adequate adherence to ART and tuberculosis treatment
- Exclusion of treatment failure or other concomitant infections, tumours, or allergic reactions.

INSHI case definition for paradoxical TB-IRIS[48]

(A) Antecedent requirements (both criteria must be met)

- Diagnosis of tuberculosis: the diagnosis of tuberculosis made before starting ART (WHO criteria).
- Initial response to tuberculosis treatment: initial improvement or stabilisation on appropriate anti-TB treatment before ART initiation (however, in patients starting ART within 2wk of starting tuberculosis treatment, insufficient time may have elapsed for a clinical response to be reported).

(B) Clinical criteria (one major criterion or two minor clinical criteria are required)

The onset of TB-IRIS manifestations within 3 months of ART initiation, re-initiation, or regimen change.

Major criteria:

- New or enlarging lymph nodes, cold abscesses, or other focal tissue involvement
- New or worsening serositis
- New or worsening CNS tuberculosis
- New or worsening radiological features of tuberculosis

Minor criteria

- New or worsening constitutional symptoms
- New or worsening respiratory symptoms
- New or worsening abdominal pain accompanied by peritonitis, hepatomegaly, splenomegaly, or abdominal adenopathy

(C) Alternative explanations must be excluded if possible

- Tuberculosis drug resistance, poor adherence to treatment, drug toxicity, and another opportunistic infection.

BIOMARKERS FOR THE DIAGNOSIS OF IRIS

Studies have shown that there are some biomarkers associated with specific forms of IRIS. For instance, paradoxical TB-IRIS is shown to be associated with elevated interleukin (IL)-4, IL-6, IL-7, interferon gamma (IFN- γ) and tumour necrosis factor alpha (TNF-α) during clinical events.[24,51] Some of such biomarkers include: C-reactive protein (CRP), interferon (INF)-γ, interleukin (IL)-2,6,7,12,13,17,18, tumour necrosis factor (TNF)-α, INF- γ inducible protein-10 (IP-10) or D-dimer.[24,51]

However, as at the moment, none of these markers are consensual and more studies are needed for proper cut-offs before they could be included in standard patient care guidelines for screening/diagnostic tests to identify patients at risk, develop better therapeutics and monitor response to therapy. A selection of a few of these markers, based on ease of use in the laboratory, reproducibility, price, and effectiveness to predict IRIS should

provide a strong algorithm and robust tool for stratifying patients with high, moderate, and low risk to develop IRIS.[20,23]

CONCLUSION

From the various studies, our review has been able to largely highlight the fact that there's no common pathophysiological explanation for all forms of IRIS, the syndrome is largely due to an unbalanced immune reconstitution of effector and regulatory T cells in patients undergoing rapid immune reconstitution. It is found out from histologic examinations of tissues or organs with inflammatory cell infiltrates by various studies that T cells cytotoxicity predominate in IRIS provoked by viruses while granulomatous inflammation predominates in IRIS provoked by fungi, protozoans and mycobacteria. However, more research is needed to delineate the specific antigens/cytokines that directly provoke IRIS in various settings of immune recovery, understanding of which is important for the development of immunomodulatory pharmacological interventions for the treatment and prevention of this life-threatening condition.

Keywords: Cytokine-storm, HIV-IRIS, immune, IRIS, reconstitution, recovery, TB-IRIS

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