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REVIEW

# Immune reconstitution inflammatory syndrome: immunopathogenesis, risk factors, diagnosis, treatment and prevention

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## ABSTRACT

**Immune reconstitution inflammatory syndrome (IRIS) occurs in a subpopulation of HIV-infected patients after the introduction of antiretroviral therapy (ART). The purpose of this review is to describe the immunopathogenesis, risk factors, diagnostic problems, treatment and prevention of IRIS. A literature search was performed and finally 15 recent articles were selected.**

**The immunopathogenesis of IRIS is characterised by a dysbalanced restoration of the immune system resulting in pathological inflammation. Risk factors are low baseline CD4-cell count, an excellent virological response, an increased antigenic burden of an opportunistic infection and early initiation of ART after an opportunistic infection. The differential diagnosis of IRIS is elaborate. Treatment options include discontinuation of ART, corticosteroids or pathogen-specific therapy.**

**Diagnosis can be difficult, because IRIS may manifest with a diverse range of clinical presentations. Adopting one case definition and performing more research regarding diagnosis and treatment of IRIS are important recommendations for future studies.**

## KEYWORDS

Antiretroviral treatment, HIV infection, immune reconstitution inflammatory syndrome

## INTRODUCTION

Immune reconstitution inflammatory syndrome (IRIS) is seen in a subpopulation of HIV-infected patients after the initiation of antiretroviral therapy (ART). Most HIV-infected patients improve after the introduction of ART because ART will reduce the HIV-RNA and boost up the immune system. In some patients another response is seen after starting ART. Their clinical condition worsens and they develop symptoms compatible with infectious diseases such as tuberculosis, herpes zoster, cryptococcosis, toxoplasmosis or bacterial pneumonia. This phenomenon has been termed IRIS and has been thought to be due to the restored ability to mount an inflammatory response after the initiation of ART.[1]

There are two common clinical scenarios: unmasking IRIS and paradoxical IRIS. In unmasking IRIS, the infection is newly identified after the initiation of ART, and usually the provoking pathogen is viable. In paradoxical IRIS, the infection was previously treated but worsened clinically after ART initiation and the causative pathogens can be either viable or non-viable.[1]

Studies have demonstrated that 10 to 32% of patients starting ART will develop IRIS.[2] Hospital admission is not uncommon, medical regimens have to be revised and this brings discomfort to the patient. For example, in a prospective cohort study among HIV-infected patients starting ART in Ethiopia, 76% of hospital admissions after ART introduction were because of IRIS.[3] The biggest problems are faced in the developing countries, where ART is now used on a much larger scale. Due to the high incidence of tuberculosis (TB) and the limitations in diagnostic procedures, diagnosis and treatment of IRIS can be more troublesome in these poor resource settings.[1]

In this review, we provide an overview on the pathogenesis, risk factors, diagnostic problems, treatment, and prevention of IRIS.

## LITERATURE SEARCH

To address this topic, a search was performed in the PubMed database with the following terms: immune recovery syndrome OR immune reconstitution inflammatory syndrome OR immune restoration disease (#1) and (HIV) OR (AIDS) (#2). The last-mentioned terms were added because IRIS is also seen in some autoimmune diseases and malignancies, and we wanted to limit our study to HIV/AIDS. Limitations were: published in the last ten years, humans, English, clinical trials, meta-analyses, practical guidelines, randomised controlled trials and reviews. Studies that focused too much on one particular case or type of IRIS were excluded, because the purpose of this article was to describe IRIS in its general form.
Search #1 resulted in 1753 citations and search #2 resulted in 276,626 citations. The two searches were combined with the term "AND", this yielded 950 citations (#3). After adding the limits mentioned above, a total of 192 articles remained. The titles and abstracts of these articles were reviewed and judged on relevance. Finally, 13 articles were judged as being relevant. Three more articles were retrieved by using references, 'linked articles' or suggested by one of the reviewers. Further details on the articles are addressed in *table 1*.

## IMMUNOPATHOGENESIS

When we look at IRIS, one of the most striking features is that the clinical presentation depends heavily on the type of underlying infection.[1] This suggests that an antigen-driven process is going on in which a specific immune response is generated. Furthermore, we see an inflammatory response that is exaggerated. This could be explained by the fact that mechanisms that normally limit inflammation are missing.[4]
Two types of T cells are important in this matter, the pro-inflammatory TH17 cell and the regulatory T cell (Treg). The Treg suppresses proliferation of effector cells of the immune system and their cytokine production.[4] In a normal situation, the ratio between TH17 cells and Tregs is 2:1.[5] During immune reconstitution this ratio may be disturbed. Seddiki *et al.* hypothesised that Tregs could be defective in either numbers and/or function and therefore unable to ensure the physiological equilibrium of the immune system in patients with IRIS. They examined Treg frequency and, in contrary to what they expected, found a significant expansion of Tregs in IRIS patients compared with controls. The ratio of Treg to effector cells was also increased. However, when they performed *in vitro* suppression assays with these Tregs, they detected abnormalities in their function in IRIS patients.[5] Tregs of IRIS patients are less effective in regulating homeostasis of the immune system, because they show blunted ability to suppress the release of pro-inflammatory cytokines.
IL-7 is a haematopoietic growth factor and induces differentiation of the effector cells of the immune system and IL-7 levels inversely correlate with the CD4+ T-cell count.[4] HIV-infected patients with a low CD4 cell count before starting ART normally have high levels of IL-7. Seddiki *et al.* found that despite marked CD4 reconstitution in IRIS patients following ART, high IL-7 levels persisted, in contrast to treated HIV-infected patients without IRIS, in whom plasma IL-7 levels decreased progressively after ART when their CD4 cell count increased. So in theory, IL-7 levels could be used as a diagnostic measure for IRIS in the future.
Examination of the histopathological characteristics and inflammatory cell infiltrate of affected tissues or organs has demonstrated that CD8 T cells predominate in IRIS that is provoked by viruses, such as JC virus and cytomegalovirus. In contrast, granulomatous inflammation usually predominates in IRIS that is provoked by fungi such as *Histoplasma* species and cryptococci, by protozoans such as *Leishmania* species, mycobacteria such as *M. tuberculosis, Mycobacterium leprae,* and by nontuberculous mycobacteria. This would support the idea that the immunopathogenesis of IRIS is dependent on the provoking pathogen.[1]

**Table 1.** *Overview of the included case-control studies*

| Author (reference) | Study type | Number of included patients | Number of included controls | Follow-up period | Subject covered |
|---|---|---|---|---|---|
| Klotz[3] | Prospective | 74 | 15 | 6 months | Incidence, clinical presentation, management in a resource-poor setting |
| Seddiki[4] | Cross-sectional | 8 | 6 | N/A | Immunopathogenesis |
| De Boer[5] | Retrospective | 17 | 20 | 12 months | Risk factors, clinical and immunological characteristics |
| Meintjes[6] | Prospective | 80 | 20 | Not reported | Diagnosis, management in a resource-poor setting |
| Stone[7] | Retrospective | 37 | 15 | Not reported | Immunopathogenesis |
| Manabe[8] | Prospective | 49 | 196 | 6 months | Risk factors, treatment |
| Meintjes[9] | Prospective | 129 | 0 | 2 months | Immunopathogenesis |

## RISK FACTORS

Four factors show association with an increased risk for developing IRIS.

The first one is a low baseline CD4 T-cell count. When CD4 T cells are <200 cells/μl before ART initiation, patients are more likely to develop IRIS.[4] This is due to the greater risk of an opportunistic infection, more progressive damage to the immune system and disruption of regulatory mechanisms. This risk factor has particular implications for populations in developing countries, where persons are more likely to have advanced AIDS, co-infection with opportunistic infections, and lower CD4 T-cell counts when they initiate treatment. Furthermore, in a case-control study from the Netherlands it was demonstrated that the IRIS cases had a significantly higher-fold increase in CD4 T cells compared with controls.[5]

A second risk factor is an excellent virological response. Patients with a >2 log drop in HIV-1 RNA after 90 days of ART are at higher risk for IRIS. For example, it has been shown that in ART pretreated populations, where HIV virological resistance is more common, only those patients who respond to ART are at risk for IRIS.[10]

The third risk factor is an increased antigenic burden of an opportunistic infection at the initiation of ART. In a retrospective cohort study of TB patients, those with disseminated TB or extra-pulmonary TB had a greater incidence of IRIS compared with those with a lower antigenic burden with only a pulmonary infection.[10]

Therefore, the fourth risk factor is early initiation of ART after an opportunistic infection. Persons starting ART within two months after an opportunistic infection appear to have anywhere from zero to up to ten-fold risk of IRIS.[10] It still remains unclear what the optimal timing is for starting ART in patients with recent opportunistic infections. With an early start, the risk of IRIS is greater, and with a delayed start, the risk of death and new AIDS events increases. A recent study contradicts the findings of Bonham *et al*. In this study 282 patients with opportunistic infections (excluding TB) were enrolled, and randomised to early ART initiation *vs* delayed ART initiation. They concluded that early ART does not lead to an increase in IRIS in non-TB opportunistic infections.[11] This evidence makes early initiation of ART after an opportunistic infection questionable as a risk factor for IRIS.

Current research has demonstrated that different types of IRIS are associated with different genetic profiles. Patients with cytomegalovirus-related IRIS have been found to have increased frequency of human leukocyte antigen (HLA) B44 haplotypes compared with patients who do not develop IRIS. Specific cytokine gene polymorphisms that play a key role in decreasing cytokine production have been reported to be protective against mycobacterial- and herpes virus-associated IRIS.[10]

## DIAGNOSIS

Unfortunately, there is no diagnostic test for IRIS and the differential diagnosis is complex, including treatment failure of ART, failure of treatment of an opportunistic infection, drug interactions, drug toxicity or an alternative opportunistic infection. The diagnostic problems of tuberculosis-related IRIS (TB-IRIS) have been studied the most and will give us a good insight into the problem.

In countries with high rates of TB, an emerging complication of ART is TB-IRIS. TB-IRIS manifests with new, worsening or recurrent symptoms, signs or radiological manifestations of TB after ART is initiated (*table 2*). This pattern is seen in 8 to 43% of patients who start ART while receiving TB treatment.[6]

Concurrent with the increase in prevalence of TB-IRIS, there is also an emergence of multidrug-resistant (MDR) and extensively drug-resistant TB, especially in Southern Africa where HIV infection is highly prevalent. Treatment of TB-IRIS is usually with corticosteroids and it is therefore very important to determine the cause of deterioration in patients with TB during ART. Adjunctive corticosteroid therapy may worsen an already immunosuppressed patient's condition if it is used in the presence of incompletely effective TB treatment or another opportunistic infection.

In a prospective cohort study from Cape Town, South Africa, 100 patients who were considered to be likely cases of TB-IRIS were evaluated. In this area, routine TB drug susceptibility testing is not performed for new

**Table 2.** *Case definitions for tuberculosis (TB) immune reconstitution inflammatory syndrome (IRIS)*[8]

**Criteria that must be met for the diagnosis of TB IRIS before the initiation of cART**

- Microbiological, histological, or very strong clinical evidence of TB
- Initial improvement of >1 of the following during multidrug TB treatment: symptoms, Karnofsky score, weight, fever, clinical signs, or radiographic findings
- The infecting strain of *Mycobacterium tuberculosis* is susceptible to rifampin (if this result is available)
- The patient was receiving antitubercular therapy when cART was initiated

**Criteria that must be met for the diagnosis of TB IRIS within three months after the initiation of cART**

- New or recurrent TB-related symptoms and/or
- New or worsening TB manifestations, such as >1 of the following: new or expanding lymph nodes, new or expanding tuberculous cold abscesses, new or expanding intracranial tuberculomas, new or expanding pulmonary infiltrates (radio graphically confirmed), new or recurrent tuberculous meningitis (after exclusion of bacteria and fungi), new or enlarging serous effusions (pericardial, pleural, or ascitic; radiographically confirmed), new or worsening granulomatous hepatitis, new or worsening granulomatous infiltration of bone marrow, other new or worsening tuberculous lesions

**No other opportunistic disease to explain the new or recurrent symptoms and/or new or worsening**

TB cases. The clinical case definitions that were used for TB-IRIS are listed in *table 2*. Undiagnosed drug-resistant TB was present in 10.1% of patients who presented with TB-IRIS, once those with alternative diagnoses and TB with known drug-resistance were excluded.[6] Therefore, corticosteroids should be used with caution for patients with presumed TB-IRIS until results of drug-susceptibility testing are known.

When we look from a more general perspective, it is important to note that IRIS is a *diagnosis per exclusionem* which means that first all other possible causes of clinical worsening should be ruled out before we can conclude that the patient has IRIS.

## TREATMENT AND PREVENTION

Prevention and treatment of IRIS is difficult because no prospective controlled clinical trials concerning this topic have yet been published. There is one ongoing study (www.controlled-trials.com/mrct/search.html, accessed on 1 June 2009). When it comes to prevention, initiation of ART before advanced immunosuppression would be expected to reduce the risk of IRIS because advanced immunosuppression increases the risk for opportunistic infections, which is in itself a risk factor for IRIS.[10] To prevent unmasking IRIS, a thorough screening for active opportunistic infections before ART initiation is critical, because patients with advanced immunosuppression may have atypical or minimal symptoms owing to the absence of an inflammatory response. The screening for TB is difficult because the sensitivity of chest radiography and sputum smear examination in diagnosing active TB is reduced in HIV-infected persons.[12]

Early initiation of ART after an opportunistic infection has been identified as a risk factor,[10] but recent evidence contradicts these findings, at least for cases of non-TB-IRIS. In the case of TB-IRIS, the World Health Organisation (WHO) recommends ART initiation two weeks to two months after TB treatment is started in patients with a CD4 <200 cells/µl, but delaying in patients with higher counts. For other opportunistic infections no official recommendations have been established, so the clinician has to weigh the risks that come with delaying ART and advanced immunosuppression against the risks of IRIS.

Treatment of IRIS should be started after all other alternatives are ruled out and can be categorised in four different approaches, which can be used as mono or combination therapy.[13,14] The four approaches are: temporary ART discontinuation until the clinical condition has improved, use of non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids, pathogen-specific therapy or other therapy.

ART interruption should be recommended only for patients with severe, life-threatening symptoms until their condition is stabilised. IRIS can recur during re-initiation of ART, so this has to be monitored carefully. However, stopping ART in the setting of incompletely suppressed HIV replication may be associated with an increased risk of antiretroviral resistance.[15]

The use of drugs which can modulate the immune response, such as NSAIDs or corticosteroids, has been proposed. NSAIDs are advised for the management of mild and moderate cases, and corticosteroids for the individuals with severe or life-threatening disorders.[13] On the other hand, corticosteroids have been shown to be associated with an excess of Kaposi's sarcoma and herpes virus reactivation in HIV-infected patients with low CD4 counts but not in patients with increasing CD4 counts after initiation of ART.[12] The exact doses and duration of corticosteroid treatment have not yet been established. In a report of 49 cases of IRIS related to various infections, the median duration of prednisone treatment was 138 days.[8]

Pathogen-specific therapy should be started or continued in the case of unmasking or paradoxical IRIS. Other therapy includes needle aspiration of cold abscesses in TB-IRIS, therapeutic lumbar punctures and other drainage procedures for cryptococcal meningitis-IRIS and surgery for complications such as bowel perforation.[12]

## DISCUSSION

IRIS can be seen as a condition in which the immune system improves after introduction of ART, but is exaggerated, due to lack of homeostatic regulation. Clinically, the syndrome is very diverse, but a distinction can be made between paradoxical and unmasked IRIS. The most important risk factors for IRIS are a low baseline CD4 T-cell count, an excellent virological response, an increased antigenic burden of an opportunistic infection and early initiation of ART after an opportunistic infection. Diagnosis of IRIS is difficult because it has to be differentiated from treatment failure, drug interactions, non-compliance or an alternative opportunistic infection. Treatment options include discontinuation of ART, corticosteroids or pathogen-specific therapy.

This review has some limitations. Because studies on specific cases or forms of IRIS were excluded, the results of our search give an impression of the phenomenon of IRIS as a whole, in a more general perspective. Since the clinical presentation of IRIS is so diverse and depends on the underlying condition, the results presented here may not be applicable to each individual case. Furthermore, the cohorts of IRIS patients included were small, ranging from eight[4] to 129 patients.[9] The clinical heterogeneity of the syndrome cautions against drawing conclusions from

limited numbers of patients. Secondly, the follow-up period ranged from two months[9] to six months.[8] IRIS usually occurs within three months of ART introduction, but may also occur when a failing ART regiment is switched to a virally suppressive one or when ART is resumed after a temporarily interruption.[16] It is possible that cases of IRIS were missed because of the short follow-up period, or that only the most severe cases were seen because they tend to occur early after ART initiation. Despite the limitations of these studies, we think that IRIS is a very prevalent phenomenon especially in resource-poor countries and that research for diagnostic tests (as for example IL-7) and best treatment strategies (agent choice and duration) are urgently warranted.

Seddiki's study[4] needs to be mentioned separately. In this study the central role of the regulatory T cell was demonstrated for the first time. Their data have been adopted by many other researchers in the field. But it should be noted that Sedikki used only eight IRIS patients and six controls, who were all in late stage HIV (CD4 <50 cells/µl). This makes it difficult to generalise their results to a bigger population of IRIS patients.

There is a big difference in HIV prevalence and treatment between resource-poor countries and the Western world. In the resource-poor countries, the triple coincidence of very high TB rates, an expanding HIV epidemic and the large-scale roll-out of ART has led to a large increase in the number of cases of IRIS, especially TB-IRIS.[11] HIV-infected patients in these areas usually start ART with lower CD4 cell counts and a higher burden of opportunistic infections, which makes them more susceptible to IRIS. Diagnostic tests for opportunistic infections are not always available.[2]

One of the biggest problems faced in the IRIS-research field is the fact that there is not one case definition of IRIS that is used by all researchers. The International Network for the Study of HIV-associated IRIS (INSHI), has set up a list of criteria for the diagnosis of IRIS.[15] Unfortunately, these criteria are not incorporated by the researchers in their case definitions. Rather, they use the case definitions that are proposed in the latest review. If different criteria for IRIS are used in different studies, it is not possible to combine the results and increase the evidence that is available on the subject.

Lastly, the evidence for the benefits of corticosteroids in the treatment of IRIS is very poor. At present, there is no evidence from clinical trials available to support their use. Case reports and case report series are the only source of data. As a consequence, they should be administered with caution.

In summary, it is possible to conclude that the identified literature had given us a good insight into IRIS in its general form. IRIS will have the greatest impact in resource-poor countries, where patients are often co-infected with TB and TB drug resistance is rising. To increase the evidence on this topic studies with larger cohorts of patients are needed, and all researchers should use the same diagnostic criteria. Research efforts should focus on diagnosis and treatment of IRIS.

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