I. INTRODUCTION

The goal of ARV therapy in immunocompromised HIV-infected individuals is immune reconstitution. However, an aberrant manifestation of this effect sometimes occurs. Immune reconstitution inflammatory syndrome (IRIS), also known as immune restoration disease, refers to a disease- or pathogen-specific inflammatory response in HIV-infected patients that may be triggered after:

- Initiation or re-initiation of ARV therapy
- Change to more active ARV therapy

IRIS is usually accompanied by an increase in CD4 cell count and/or a rapid decrease in viral load. Although most cases of IRIS occur in patients who have low CD4 counts and high viral load levels at the time ARV therapy is initiated, IRIS can occur at any CD4 count. The time of presentation is usually within the first 4 to 8 weeks after initiation of ARV therapy; however, IRIS has occurred many weeks after initiation and in sequestered sites, such as bone.1

After immune reconstitution, inflammatory reactions to many pathogens have been described, including mycobacterium, fungi, virus, and bacteria (see Table 1). IRIS that involves worsening of some malignancies, including Kaposi’s sarcoma,2 and autoimmune phenomena have also been documented.

Epidemiologic data regarding IRIS are variable and depend largely on the incidence and types of infections that patients have at the time of initiation of ARV therapy. In the United States, retrospective studies have reported IRIS in 63% of HIV-infected patients who had inactive CMV retinitis at the time of initiation of ARV therapy3 and 30% to 34% of those with inactive cryptococcus.4,5 Similar rates have been found retrospectively in 30% and 31% of HIV-infected patients with Mycobacterium tuberculosis and M. avium complex (MAC), respectively.5 However, retrospective studies may overestimate the incidence of IRIS. A prospective ACTG study, ACTG A5164, reported a rate of 7.6%;6 however, this rate may have been low because most of the reported opportunistic infections (OIs) were PCP. Steroid treatment for PCP may have mitigated IRIS-related symptoms and reduced the number of IRIS diagnoses in the study.

Caution and clinical judgment are required when implementing these guidelines because no prospective or randomized trials of treatments for IRIS exist; therefore, the recommendations here are based on small case series and expert opinion.

For further OI-specific guidance on management of IRIS, see Guidelines for Prevention and Treatment of Opportunistic Infections Guidelines issued by the NIH, CDC, and HIVMA/IDSA.1
II. PATHOGENESIS

The pathogenesis of IRIS is largely speculative. Although one common aspect to IRIS cases is a significant increase in CD4 cells after initiation of ARV therapy in patients who had low CD4 cells prior to treatment, the pathogenesis of the inflammatory response may not be the CD4 cell increase. Instead, patients who develop IRIS may have preexisting perturbations in their T-regulatory cell profile and proinflammatory and regulatory responses, such as cytokine imbalances, that may significantly contribute to onset of the syndrome after initiation of an ARV regimen that is highly active against HIV in a given patient. IRIS may also be more severe in patients with a higher burden of organism, which also suggests that antigen load may play a role.

III. DECIDING WHEN TO INITIATE ARV THERAPY IN PATIENTS WITH RECENT OIs

RECOMMENDATION:
Clinicians should strongly recommend that patients recovering from acute OIs initiate ARV therapy as soon as tolerability has been established and the potential for drug-drug interactions has been minimized (see Antiretroviral Therapy).

No consensus has been reached concerning the optimal time to initiate ARV therapy in patients with a recently diagnosed OI. In some cases, determination of the optimal timing for initiating therapy in these patients is complex and may require consultation with an experienced HIV provider.

The ACTG A5164 study suggests that benefits from immediate initiation of ARV therapy, particularly in the setting of PCP, outweigh the risks for IRIS. Accordingly, clinicians should strongly recommend that patients recovering from acute OIs, such as those resulting from cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy (PML), Kaposi’s sarcoma, PCP, and serious bacterial infections, initiate ARV therapy as soon as tolerability has been established and the potential for drug-drug interactions has been minimized.

Increasing the length of time between treatment of known TB and MAC and initiation of ARV therapy by 60 days has been shown to decrease the incidence of IRIS in those diseases. However, the benefits of early initiation of ARV therapy in patients with active TB and very low CD4 counts (<50 cells/mm³) likely outweigh the risks for morbidity associated with TB-IRIS. Careful monitoring for IRIS, and timely treatment if it occurs (see Section V: Prevention of Complications of IRIS and Section VI: Management and Treatment), may significantly reduce morbidity associated with mycobacterium-related IRIS while also ensuring that other risks associated with severe immunosuppression are managed effectively with ARV therapy.
**Key Point:**
Although the risk for TB-IRIS may be as high as 32% in severely immunocompromised patients, the overall mortality associated with delayed initiation of ARV therapy in these patients is greater than any potential risk of death resulting from IRIS.13

**IV. PRESENTATION AND DIAGNOSIS**

**RECOMMENDATION:**
Clinicians should consider IRIS when inflammatory signs or symptoms occur after recent initiation, re-initiation, or change to a more effective combination ARV therapy with associated increase in CD4 cell count and/or decrease in viral load and the following have been excluded:

- Worsening of known infections due to inadequate or inappropriate therapy (AIII)
- New infections not known to be associated with IRIS (e.g., bacterial sepsis) (AIII)
- Medication reaction (AIII)

Proposed case definitions do not provide clear consensus on the many manifestations of IRIS.5,14-16 However, some well-established clinical syndromes exist, including fever and/or unmasking or worsening of previously quiescent or mild underlying disease symptoms. If the pathogen or condition provoking the inflammatory response was previously undiagnosed, the IRIS response is termed *unmasking*. Exacerbation or recurrence of symptoms from a previously known or treated disease is termed *paradoxical worsening*.

IRIS symptoms range from mild to severe but do not appear to have favorable or unfavorable implications for patient survival, with the exception of IRIS associated with cryptococcal meningitis.1,17 The majority of IRIS cases occur within 4 to 8 weeks after initiation of or change in ARV therapy. However, the time until presentation can vary, with cases reported as few as 3 days and as many as several years after ARV therapy initiation. Late manifestations of IRIS (>7 months) may demonstrate atypical manifestations, such as osteomyelitis resulting from MAC.18 The presentation of IRIS will vary depending on the underlying OI or illness. Table 1 describes major and minor presentations of IRIS.

The spectrum of signs and symptoms of IRIS often poses a challenge to diagnosis. The diagnosis of IRIS is based on clinical judgment, and multiple diagnoses can be present. The somewhat characteristic presentations of many OIs may aid in the diagnosis of IRIS (see Table 1).
<table>
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<th>Major Presentations</th>
<th>Minor Presentations</th>
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| **Tuberculosis**                                                                   | • Patients responding to TB treatment may have worsening of pulmonary symptoms or X-ray findings that indicate worsening of TB disease, enlarging lymph nodes, or meningeal symptoms^4
| • TB-IRIS can also result in hepatotoxicity, which may be difficult to distinguish from medication-induced toxicity^19
| • Multidrug-resistant TB may increase the risk for IRIS^20                           | • Presentations are usually similar to non-IRIS disease; however, IRIS may worsen a patient’s symptoms
| **Mycobacterium avium complex**                                                    | • Some patients become aware of their HSV infection only after the presentation of IRIS
| • May present as localized lymphadenitis, pulmonary disease, or systemic inflammation that are indistinguishable from active MAC
| • Patients with MAC-IRIS are not bacteremic^21                                      | • Presents as worsening of Kaposi’s sarcoma^2
| **Cryptococcus**                                                                  | • Fatal IRIS has occurred in patients with preexisting Kaposi’s sarcoma and multicentric Castleman disease after initiating ARV therapy^1
| • Usually presents as worsening of meningitis symptoms^4,17,22-24                    | • The frequency of human herpesvirus-8-associated IRIS is not known^1
| **Cytomegalovirus**                                                                | **Autoimmune diseases**                                                            |
| • Presents as retinitis, vitritis, or uveitis:                                       | • Presentations are usually similar to non-IRIS disease; however, IRIS may worsen a patient’s symptoms
|   • **Retinitis** is inflammation that is usually at the site of previous CMV retinitis lesions
|   • **Uveitis** and **vitritis** are the presence of inflammatory cells in the eye as a result of IRIS and may help to distinguish IRIS from active CMV retinitis^3
| • IRIS due to CMV in the eye can cause rapid and permanent vision loss
| • The time to IRIS is variable; in one study, the median time to immune reconstitution vitritis was 20 weeks after initiation of ARV therapy^3 | • Preexisting autoimmune disorders such as sarcoidosis or Grave’s disease may be exacerbated
| **Hepatitis B or C**                                                               | **Herpes simplex virus and varicella zoster virus**                                 |
| • Transient elevations in transaminases may occur after initiation of ARV therapy with immune reconstitution and can be difficult to distinguish from drug-induced hepatitis
| • Hepatic flares are usually mild and self-limited but can result in decompensation in someone with preexisting cirrhosis | • HSV and VZV can reactivate after initiation of ARV therapy
| **Progressive multifocal leukoencephalopathy**                                    | • Presentations are usually similar to non-IRIS disease; however, IRIS may worsen a patient’s symptoms
| • PML lesions may be unmasked or worsen and could appear as new or worsening focal neurologic deficits or lesions on MRI scans^24-26 | • Some patients become aware of their HSV infection only after the presentation of IRIS
| **Kaposi’s sarcoma**                                                              | **Nonspecific dermatologic complications**                                         |
| • Presents as worsening of Kaposi’s sarcoma^2                                       | • A number of dermatologic manifestations, such as folliculitis and oral and genital warts, may appear or worsen during immune reconstitution
| • Fatal IRIS has occurred in patients with preexisting Kaposi’s sarcoma and multicentric Castleman disease after initiating ARV therapy^1
| • The frequency of human herpesvirus-8-associated IRIS is not known^1                |
V. PREVENTION OF COMPLICATIONS OF IRIS

RECOMMENDATIONS:
Clinicians should be alert to the possibility of IRIS as CD4 cell counts are restored after initiation of ARV therapy. (AIII)

After initiation of ARV therapy, HIV-infected patients with a history of CMV retinitis should be monitored for possible IRIS by dilated ophthalmologic examination:
- Every 3 months for the first year after initiation of ARV therapy (AIII)
- Immediately if there is a change in visual acuity or development of floaters (AIII)

For HIV-infected patients who are co-infected with hepatitis B or C, clinicians should measure transaminase levels:
- Before initiation of ARV therapy (AI)
- Monthly for the first 3 months after initiation of ARV therapy to monitor for possible immune reconstitution inflammatory syndrome (AIII)

Prevention of complications associated with IRIS involves careful monitoring, particularly in patients with low CD4 counts and a past or current history of co-infections. After initiating ARV therapy, clinicians should be alert to the possibility of IRIS as CD4 cell counts are restored.

A high index of suspicion for ophthalmologic manifestations of IRIS after initiation of ARV therapy, particularly among patients with low CD4 counts at the start of therapy, is warranted to avoid complications resulting from CMV. Patients with a history of CMV retinitis, even if receiving treatment, should receive a dilated ophthalmologic examination every 3 months for the first year after initiation of ARV therapy and immediately if there is a change in visual acuity or development of floaters. Cases of CMV-IRIS myelopathy that respond to steroids have been reported, as have cases of CMV-IRIS colitis.27,28 Refer to Ophthalmologic Complications of HIV Infection.

For patients with hepatitis B or C, transaminases should be measured prior to initiation of ARV therapy and monitored monthly for the first 3 months after initiation of ARV therapy in HIV/HBV or HIV/HCV co-infected patients. Any transaminase elevation that is associated with jaundice or elevated bilirubin levels or loss of synthetic function in these patients (e.g., elevated PT/INR or decreased albumin) should be evaluated in conjunction with a hepatologist (see Hepatitis B Virus and Hepatitis C Virus).
VI. MANAGEMENT AND TREATMENT

RECOMMENDATIONS:
Clinicians should initiate symptomatic treatment and supportive care for patients with IRIS. In severe cases, clinicians should consider prescribing prednisone 1-2 mg/kg or equivalent for 1-2 weeks, followed by a taper. (AIII)

Clinicians should closely monitor patients receiving corticosteroids for the development of opportunistic infections, including CMV retinitis and TB disease. (AIII)

Except in severe cases, ARV therapy should not be interrupted in patients with IRIS. (AIII)

Whenever IRIS is suspected, initial efforts should be focused on diagnosing and appropriately treating the OI, either previously known or unmasked by IRIS. IRIS resolves over time in most patients, and if not severe, symptomatic treatment and supportive care is often sufficient.

A. Management and Treatment of Mild IRIS
When minor IRIS presentations occur, clinicians can reassure patients that these are an indication of immune reconstitution rather than progression of HIV disease and will resolve with standard treatment. In addition to standard therapy for the offending OI, the following treatments may alleviate inflammation in patients with mild IRIS:

- Nonsteroidal anti-inflammatory agents can be used for cases in which mild inflammation or fevers cause patients discomfort
- Abscesses may be drained
- Inflamed and painful lymph nodes may be excised
- Inhaled steroids may alleviate mild pulmonary inflammation that cause bronchospasm or cough

B. Management and Treatment of Severe IRIS
Severe IRIS may threaten a patient’s functional status or may cause permanent disability. Examples of this are a decline in pulmonary capacity from TB or MAC, neurologic complications from cryptococcus, or vision loss from CMV.

Corticosteroid therapy to suppress inflammatory response is the most commonly used intervention in cases of severe IRIS. In a series of eight patients with severe TB-IRIS who were treated with 10 to 80 mg of prednisone daily, all patients improved. The median time to improvement was 3 days.\(^{29}\) In nine patients with MAC-IRIS, eight responded to prednisone.\(^{30}\) No trials on which to base a recommended dose of corticosteroids have been conducted, but some experts recommend 1-2 mg/kg prednisone, or the equivalent, for 1-2 weeks, then taper.
The risks of corticosteroid therapy should be weighed against the severity of the IRIS manifestations and the potential benefits, particularly given the high prevalence of diabetes mellitus, hypertension, and mental health disorders among HIV-infected patients. Risks of corticosteroid therapy include:

- Hyperglycemia
- Hypertension
- Mental status changes
- Worsening of an existing infection
- Predisposition to a new infection

Improvement in life-threatening cases of IRIS after combination ARV therapy is discontinued has been reported; however, except in severe cases, ARV therapy should not be interrupted in patients with IRIS. Risks of stopping combination ARV therapy include HIV resistance, acquisition of new OIs, and recurrence of IRIS when therapy is later restarted.

In cases of cryptococcal-IRIS with worsening meningitis symptoms, therapeutic lumbar puncture to lower intracranial pressure, much like in acute cryptococcal meningitis, has been used.

Treatment of CMV vitritis with intraocular steroids has been described but has not been useful in uveitis.
REFERENCES


**FURTHER READING**


