Management of Immune Reconstitution Inflammatory Syndrome (IRIS)
Purpose of the IRIS Guideline

- Raise awareness among healthcare providers about IRIS, including its clinical presentation.
- Provide treatment recommendations for IRIS.
- Encourage clinicians to seek the assistance of an experienced HIV care provider when managing IRIS.
- Emphasize that ART should not be interrupted in patients with IRIS except in life-threatening cases.
Terminology

- **IRIS**: An undesirable disease- or pathogen-specific inflammatory response that may be triggered by ART-associated immune system recovery
- **Immune restoration disease**: Another name for IRIS
- **Paradoxical IRIS**: Refers to a worsening of a previously diagnosed disease after ART initiation
- **Unmasking IRIS**: Refers to the appearance of a previously undiagnosed disease following ART initiation
Timing ART/Preventing IRIS

RECOMMENDATIONS

Clinicians should recommend starting ART within 2 weeks of starting treatment for an OI (AIII), or as soon as the patient is clinically stable, for individuals with

- Cryptosporidiosis
- Microsporidiosis
- Progressive multifocal leukoencephalopathy (PML)
- Kaposi’s sarcoma (KS)
- *Pneumocystis jiroveci* pneumonia (formerly PCP)
- HCV or HBV infection
- Pulmonary tuberculosis (TB)
- Other serious bacterial infections
Timing ART/Preventing IRIS

✔ RECOMMENDATIONS

• For patients with HIV and HBV or HCV, clinicians should:
  o Measure transaminase levels before ART initiation, at 6 and 12 weeks after, and at least every 6 months to monitor for possible IRIS. (AIII)
  o Refer patients with elevated transaminase levels and jaundice, elevated bilirubin levels, or loss of synthetic function for evaluation by a hepatologist. (BIII)

• For patients with CD4 counts <100 cells/mm³ or known OIs who are initiating ART, clinicians should be vigilant, and educate patients to be vigilant, for the signs and symptoms of IRIS. (AIII)

• For patients with active TB meningitis, extrapulmonary TB, CMV retinitis, or cryptococcal infection, clinicians should consult with an experienced HIV provider to determine when to initiate ART. (AIII)
Patients with Pulmonary TB

✓ RECOMMENDATIONS

• Clinicians should initiate ART as follows:
  o **CD4 counts ≥50 cells/mm³**: As soon as patients are clinically stable on anti-TB therapy and no later than 12 weeks after initiating anti-TB therapy. (AI)
  o **CD4 counts <50 cells/mm³**: Within the first 2 weeks after initiating anti-TB therapy. (AI)

• For patients with pulmonary TB who are ART-naïve, have a CD4 count <100 cells/mm³, and started on anti-TB treatment within the last 30 days, clinicians should initiate prednisone 40 mg daily for 14 days, followed by 20 mg daily for 14 days at the time of ART initiation. (BI)
Patients with TB Meningitis and Extrapulmonary TB

✔ RECOMMENDATION

• Clinicians should consult with an experienced HIV care provider to determine the timing of ART initiation. (AIII)
Patients with Cryptococcal Meningitis

✔ RECOMMENDATIONS

• Clinicians should treat ART-naive patients with standard antifungal therapy and should:
  o Delay ART initiation until the patient has completed at least 2 weeks of antifungal treatment. (AIII)
  o Consult with an experienced HIV care provider to determine optimal timing for ART initiation. (AIII)

• If the patient initiates ART before completing 10 weeks of antifungal therapy, the clinician should monitor closely for intracranial pressure and other signs and symptoms of IRIS and manage intracranial pressure aggressively. (AIII)

• For patients with other types of cryptococcal infection (not meningitis), clinicians should consult with an experienced HIV care provider to determine the timing of ART initiation. (AIII)
Steroids and Cryptococcal IRIS

➔ Key Points

• Steroids should not be used routinely as induction therapy in treatment of cryptococcal IRIS.

• Steroids are not effective in reducing intracranial pressure.
Patients with CMV Retinitis

RECOMMENDATIONS

- Clinicians should ensure that patients with HIV and CD4 counts <100 cells/mm³ receive a dilated ophthalmologic exam to assess for signs of CMV before initiating ART. (AII)

- Clinicians should not initiate ART immediately in patients with CMV retinitis (AII) but should consult with an experienced HIV care provider to determine the timing. (AIII)

- Clinicians should ensure that after starting ART, patients with HIV and a history of CMV retinitis are monitored by dilated ophthalmologic exam to assess for possible IRIS as follows:
  - Every 3 months for the first year. (AIII)
  - Immediately if there is a change in visual acuity or the development of floaters. (AII)
Presentation and Diagnosis of IRIS

✔ RECOMMENDATIONS

• Clinicians should include IRIS as part of the differential diagnosis when inflammatory signs or symptoms occur following recent initiation of, re-initiation of, or a change to an ART regimen. (AIII)

• In assessing patients for IRIS, clinicians should exclude HIV disease progression, new infections, and drug reactions as underlying causes for inflammatory signs or symptoms. (AIII)
## Major Presentations of IRIS

<table>
<thead>
<tr>
<th>Underlying OI</th>
<th>IRIS Signs/Symptoms*</th>
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| Tuberculosis  | • Patients responding to TB treatment may have worsening of pulmonary symptoms, X-ray findings that suggest worsening of TB disease, enlarging lymph nodes causing airway obstruction, or meningeal symptoms  
• Enlarging tuberculoma or pericardial effusions have been described  
• TB-IRIS can also result in hepatotoxicity, which may be difficult to distinguish from medication-induced toxicity  
• TB-IRIS may occur in patients with undiagnosed multidrug-resistant TB |

*See full guideline for references*
**Major Presentations of IRIS, continued**

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<td>Mycobacterium avium complex (MAC)</td>
<td>• May present as pulmonary disease or systemic inflammation that is indistinguishable from active MAC</td>
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<td>• Atypical presentations, such as localized lymphadenitis or endobronchial mass lesions, may occur; osteomyelitis is an atypical late manifestation</td>
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<td>• Patients with MAC-IRIS may not be bacteremic and may have no known history of MAC diagnosis</td>
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| CMV retinitis      | • Presents as retinitis, vitritis, or uveitis; variable timing, with median time to immune reconstitution vitritis 20 weeks after ART initiation in one study  
  o Retinitis is inflammation that is usually at the site of previous CMV retinitis lesions  
  o 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  
• CMV-IRIS in the eye can cause rapid and permanent vision loss |

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<td>Cryptococcal meningitis</td>
<td>• Usually presents as worsening of meningitis symptoms, including possible rapid hearing and/or vision loss, ataxia, and/or elevated intracranial pressure</td>
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<td>Hepatitis B or C</td>
<td>• Transient elevations in transaminases may occur after initiation of ART with immune reconstitution and can be difficult to distinguish from drug-induced hepatitis</td>
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<td>• Hepatic flares are usually mild and self-limited but can result in decompensation in someone with pre-existing cirrhosis</td>
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<td>Progressive multifocal leukoencephalopathy (PML)</td>
<td>• PML lesions may be unmasked or worsen and could appear as new or worsening focal neurologic deficits or lesions on MRI</td>
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<td>Kaposi’s sarcoma (KS)</td>
<td>• Presents as worsening of KS</td>
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<td>• Cutaneous lesions are the most common presentation; other signs include lymphedema and oral, gastric, lung, genital, or conjunctival lesions</td>
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<td>• Fatal cases of KS-IRIS have been reported</td>
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<td>Cerebral toxoplasmosis</td>
<td>• May present as cerebral abscess (also known as toxoplasmosis encephalitis) or, rarely, diffuse encephalitis or chorioretinitis</td>
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<td>Autoimmune diseases</td>
<td>• Pre-existing sarcoidosis may be exacerbated</td>
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<td>• Late presentations of Grave’s disease have been reported 8 to 33 months after ART initiation</td>
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## Minor Presentations of IRIS

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| Herpes simplex virus (HSV); varicella zoster virus (VZV) | • HSV and VZV can reactivate after initiation of ART, even in patients without previously diagnosed disease  
• Presentations are usually similar to non-IRIS disease; however, IRIS may worsen a patient’s symptoms |
| Nonspecific dermatologic complications             | • Dermatologic manifestations, such as folliculitis and oral and genital warts, may appear or worsen during immune reconstitution |

*See full guideline for references*
Management and Treatment

✓ RECOMMENDATIONS

• Clinicians should initiate appropriate treatment of OIs and symptomatic treatment and supportive care according to the severity of IRIS. (AIII)

• Clinicians should not interrupt ART except in severe, life-threatening cases of IRIS. (AIII)
Alleviating Symptoms of Minor IRIS

In addition to standard therapy for the underlying OI to reduce pathogen load, the following treatments may alleviate inflammation in patients with mild IRIS:

- Nonsteroidal anti-inflammatory agents for discomfort associated with mild inflammation or fevers
- Drainage of abscesses
- Excision of inflamed and painful lymph nodes
- Inhaled steroids for bronchospasm or cough associated with mild pulmonary inflammation
Severe IRIS

✓ RECOMMENDATIONS

• Clinicians should consult with an experienced HIV care provider for the management of severe IRIS, including the decision of whether to interrupt ART. (AIII)

• Clinicians should treat patients with severe IRIS that is not caused by either cryptococcal meningitis or KS with 1 to 2 mg/kg prednisone, or the equivalent, for 1 to 2 weeks, followed by a tapering dose for an individualized period of time. (BIII)

• Clinicians should not use corticosteroids for management of cryptococcal meningitis or in patients with KS. (AII)

• Clinicians should closely monitor patients taking corticosteroids for the development of OIs, including CMV retinitis and TB disease. (AIII)
IRIS and ART

→ Key Points

• ART should not be interrupted in patients with IRIS except in life-threatening cases

• Life-threatening cases are usually associated with CNS-IRIS, in which corticosteroids did not result in improvement.