



CLINICAL GUIDELINES PROGRAM

NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV • HCV • STIs • SUBSTANCE USE • LGBTQ+ HEALTH

Management of Immune Reconstitution Inflammatory Syndrome (IRIS)

Updates, Authorship, and Related Resources

Date of current publication	March 7, 2024
Highlights of changes, additions, and updates in the March 7, 2024 edition	<ul style="list-style-type: none">• Histoplasmosis and mpox added to Table 2: Major and Minor Presentations of IRIS.• Citations and references updated throughout the guideline.
Intended users	Clinicians in New York State who are managing ART in patients with HIV and monitoring for and managing IRIS when indicated
Lead author	James C. M. Brust, MD
Writing group	Joseph P. McGowan, MD, FACP, FIDSA; Steven M. Fine, MD, PhD; Samuel T. Merrick, MD; Asa E. Radix, MD, MPH, PhD, FACP, AAHIVS; Rona M. Vail, MD; Brianna Norton, DO, MPH; Charles J. Gonzalez, MD; Christopher J. Hoffmann, MD, MPH
Author and writing group conflict of interest disclosures	There are no author or writing group conflict of interest disclosures.
Date of original publication	June 30, 2017
Committee	Medical Care Criteria Committee
Developer and funder	New York State Department of Health AIDS Institute (NYSDOH AI)
Development process	See Supplement: Guideline Development and Recommendation Ratings
Related NYSDOH AI resources	Guidelines <ul style="list-style-type: none">• Rapid ART Initiation• Selecting an Initial ART Regimen Podcast <ul style="list-style-type: none">• Viremic—Cases in HIV

Management of Immune Reconstitution Inflammatory Syndrome (IRIS)

Date of current publication: March 7, 2024

Lead author: James C. M. Brust, MD

Writing group: Joseph P. McGowan, MD, FACP, FIDSA; Steven M. Fine, MD, PhD; Samuel T. Merrick, MD; Asa E. Radix, MD, MPH, PhD, FACP, AAHIVS; Rona M. Vail, MD; Brianna Norton, DO, MPH; Charles J. Gonzalez, MD; Christopher J. Hoffmann, MD, MPH

Committee: [Medical Care Criteria Committee](#)

Date of original publication: June 30, 2017

Contents

Purpose of This Guideline	2
Manifestations of IRIS	3
Development and Pathogenesis of IRIS	3
Paradoxical IRIS	4
Unmasking IRIS	4
Mortality	5
Timing of ART Initiation in Patients with Recent OIs and Prevention of IRIS	5
Initiating ART	6
Pulmonary TB	7
TB Meningitis and Extrapulmonary TB	8
Cryptococcal Meningitis	8
CMV Retinitis	9
Presentation and Diagnosis of IRIS	9
Management and Treatment of IRIS	12
Mild IRIS	12
Severe IRIS	12
All Recommendations	14
References	15
Supplement: Guideline Development and Recommendation Ratings	21

Purpose of This Guideline

This guideline was developed by the New York State Department of Health AIDS Institute (NYSDOH AI) for primary care providers and other practitioners who manage immune reconstitution inflammatory syndrome (IRIS) in patients with HIV. The guideline aims to achieve the following goals:

- 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 antiretroviral therapy (ART) should not be interrupted in patients with IRIS except in life-threatening cases.

The NYSDOH AI is publishing this guideline at a critical time: 1) Initiation of ART is now recommended for all patients diagnosed with HIV; 2) Identifying and linking patients with HIV infection to care and treatment that achieves optimal virologic suppression are crucial to the success of New York State’s [Ending the Epidemic](#) initiative; and 3) The ability of

primary care providers and other clinicians in New York State to manage IRIS is key to the successful treatment of patients with HIV.

Although ART dramatically reduces HIV-associated mortality and improves patient outcomes, initiation of or a change in ART introduces the potential for IRIS. This early complication is seen most often within the first 8 weeks of therapy in patients with advanced HIV disease. Mild IRIS resolves over time in most patients, and symptomatic treatment is often sufficient. Severe IRIS may threaten a patient’s functional status or cause permanent disability or death. But interrupting combination ART in a patient with IRIS may lead to acquisition of new opportunistic infections, recurrence of IRIS when therapy is later restarted, and possible HIV-drug resistance.

This guideline, therefore, addresses management of IRIS to avoid ART interruption except in life-threatening cases. Key recommendations cover the following:

- Timing of ART initiation relative to timing of treatment for opportunistic infections
- When to consult an experienced HIV care provider
- Diagnosis of IRIS
- Management and treatment of mild and severe IRIS

Note on “experienced” HIV care providers: The NYSDOH AI Clinical Guidelines Program defines an “experienced HIV care provider” as a practitioner who has been accorded HIV Specialist status by the [American Academy of HIV Medicine](#). Nurse practitioners (NPs) and licensed midwives who provide clinical care to individuals with HIV in collaboration with a physician may be considered experienced HIV care providers if all other practice agreements are met; NPs with more than 3,600 hours of qualifying experience do not require collaboration with a physician (8 NYCRR 79-5:1; 10 NYCRR 85.36; 8 NYCRR 139-6900). Physician assistants who provide clinical care to individuals with HIV under the supervision of an HIV Specialist physician may also be considered experienced HIV care providers (10 NYCRR 94.2).

Manifestations of IRIS

The goal of antiretroviral therapy (ART) in individuals with HIV is immune reconstitution, which may also produce the manifestation of immune reconstitution inflammatory syndrome (IRIS). IRIS, which is also known as immune restoration disease, refers to a disease- or pathogen-specific inflammatory response that may be triggered after ART initiation in treatment-naïve patients, after re-initiation of ART, or after a change to a more effective ART regimen in patients who fail to achieve viral suppression. After a patient starts ART, IRIS may manifest as a worsening of previously diagnosed disease, termed *paradoxical IRIS*, or as the appearance of a previously undiagnosed disease, termed *unmasking IRIS*.

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 the worsening of a previously diagnosed disease after ART initiation.
- **Unmasking IRIS:** Refers to the appearance of a previously undiagnosed disease following ART initiation.

IRIS is usually accompanied by an increase in CD4 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 loads at the time of ART initiation, IRIS can occur at any CD4 count [Novak, et al. 2012; Müller, et al. 2010; Shelburne(a), et al. 2005; Shelburne(b), et al. 2005; Breton, et al. 2004]. It usually presents within the first 4 to 8 weeks after ART initiation but has occurred many weeks later and in sequestered sites, such as bone [McComsey, et al. 2012].

Development and Pathogenesis of IRIS

IRIS often presents within the first 4 to 8 weeks after initiation of or a change in ART as mild to moderate disease or symptoms; life-threatening cases are rare [Müller, et al. 2010]. Although most cases of IRIS occur in patients who, at the time of ART initiation, have a low CD4 count, particularly below 50 cells/mm³, and a high viral load (>100,000 copies/mL) [Novak, et al. 2012; Müller, et al. 2010; Shelburne(a), et al. 2005; Shelburne(b), et al. 2005; Breton, et al. 2004], specific changes in

these markers are not required for the diagnosis of IRIS. For example, IRIS may occur without a significant increase in the absolute CD4 count, suggesting that measurements obtained from the peripheral blood may not reflect the number of CD4 cells present at the site of an opportunistic infection (OI) [Sereti, et al. 2020; Haddow(b), et al. 2010]. Some studies have found a higher incidence of IRIS in patients treated with regimens containing integrase strand transfer inhibitors (INSTIs), which was hypothesized to be related to the rapid drop in viral load associated with INSTI treatment [Wijting, et al. 2019; Dutertre, et al. 2017; Psychogiou, et al. 2017]. A meta-analysis of 14 randomized controlled trials including more than 8,500 participants did not, however, find any difference in risk of IRIS between those receiving versus not receiving integrase inhibitors [Zhao, et al. 2022].

Although understanding of the pathogenesis of IRIS, including the inflammatory role of T-regulatory cells and cytokine imbalances [Boulware(a), et al. 2010; Haddow(a), et al. 2010; Shankar, et al. 2008], remains largely speculative, inflammatory reactions to many pathogens have been described, including mycobacteria, fungi, viruses, and bacteria (see [Table 2: Major and Minor Presentations of IRIS](#)). IRIS that involves worsening symptoms of some malignancies, including Kaposi's sarcoma (KS) [Feller, et al. 2008], and autoimmune phenomena, such as sarcoid [Foulon, et al. 2004], also have been documented. IRIS may be more severe in patients with a higher burden of an OI organism, suggesting that antigen load may play a role in pathogenesis [Shelburne(b), et al. 2005].

Paradoxical IRIS

“Paradoxical IRIS” describes the worsening of previously diagnosed disease after ART is initiated. Epidemiologic data regarding paradoxical IRIS are variable and depend largely on the CD4 count and the prevalence and types of OI present at the time of ART initiation. A review and meta-analysis of 54 cohort studies from 22 countries that included 13,903 patients initiating ART found that, overall, 13% of patients developed IRIS [Müller, et al. 2010]. In 22 studies (41%) that reported participants' CD4 counts at the start of therapy, CD4 counts were low overall, with a median of 57 cells/mm³ (range, 17 to 174 cells/mm³), and occurrences of IRIS were significantly higher among patients with CD4 counts <50 cells/mm³. Though rates of IRIS were highest in patients with cytomegalovirus (CMV) retinitis (37.7%), it was also observed in patients with cryptococcal meningitis (19.5%), progressive multifocal leukoencephalopathy (16.7%), tuberculosis (TB) (15.7%), herpes zoster (12.2%), and KS (6.4%). As noted in the analysis, the higher occurrences of IRIS associated with CMV retinitis, in particular, were not surprising because this condition most often occurs at CD4 counts <50 cells/mm³. Significant heterogeneity between studies was also noted, in part, because of non-standardized diagnostic criteria and difficulty in distinguishing IRIS from the progression of OIs.

In the United States, the prospective AIDS Clinical Trials Group study A5164 reported IRIS in 7.6% of patients [Grant, et al. 2010], and another large multisite U.S. prospective cohort reported an occurrence of 10.6% [Novak, et al. 2012].

However, concurrent steroid treatment in some individuals and the studies' inclusion of low numbers of patients with the OIs that are most commonly associated with IRIS may obscure the true incidence. Retrospective studies have reported a higher occurrence, with IRIS reported in 63% of patients with a history of CMV retinitis [Karavellas, et al. 1999] and in 30% to 34% of those with previously diagnosed cryptococcal infection [Shelburne(a), et al. 2005; Shelburne(b), et al. 2005]. Other retrospective studies have reported IRIS in 30% and 31% of patients with TB and *Mycobacterium avium* complex (MAC), respectively [Shelburne(a), et al. 2005]. However, the studies were conducted in the era before early treatment, when ART was more often initiated in patients with low CD4 counts, and, as retrospective studies, are more likely to overestimate the incidence of IRIS.

Unmasking IRIS

“Unmasking IRIS” describes the appearance of previously undiagnosed disease after ART is initiated. Data on unmasking IRIS are limited primarily to case reports. A re-analysis of cohort data from 6 European countries and the United States found a significantly increased risk of MAC-IRIS up to 3 months after ART initiation. A slight but statistically nonsignificant increase of IRIS-associated TB, CMV retinitis, herpes simplex virus, KS, and non-Hodgkin lymphoma was reported among patients without HIV who had a median CD4 count of 279 cells/mm³ at the time of ART initiation. The epidemiologic patterns for MAC and TB were most consistent with unmasking IRIS [Lodi, et al. 2014]. In a French study of 47 patients taking ART at the time of TB diagnosis, 11 patients were diagnosed with unmasking TB-IRIS; identified risk factors for unmasking TB-IRIS included African origin, higher baseline RNA, and a strong response to ART [Valin, et al. 2010].

Mortality

IRIS is associated with an increased risk of death, with a reported overall mortality rate of 4.5% [Novak, et al. 2012; Müller, et al. 2010]. However, mortality rates depend on the associated OI, access to treatment, diagnostic criteria, degree of immunosuppression, and geography. In general, the highest mortality rates (13% to 75%) have been reported among patients with IRIS affecting the central nervous system [Bahr, et al. 2013; Müller, et al. 2010].

Timing of ART Initiation in Patients with Recent OIs and Prevention of IRIS

RECOMMENDATIONS

Initiating ART

- Clinicians should recommend that patients initiate ART within 2 weeks of beginning treatment for active OIs, with exceptions to this recommendation noted below. (A1)
- Clinicians should consult with a care provider experienced in managing HIV in patients with active OIs to determine when to initiate ART in patients with TB meningitis, extrapulmonary TB, CMV retinitis, or cryptococcal infection. (A3)
- For patients with CD4 counts <100 cells/mm³ or known concomitant OIs who are initiating ART, clinicians should be vigilant for the signs and symptoms of IRIS and should educate patients about the risk of developing IRIS. (A3)
- For patients with HIV who have HBV or HCV co-infection, clinicians should:
 - Measure transaminase levels before initiation of ART, at 6 and 12 weeks after initiation, and at least every 6 months thereafter to monitor for possible IRIS. (A3)
 - Refer patients with elevated transaminase levels in conjunction with jaundice, elevated bilirubin levels, or loss of synthetic function for evaluation by a hepatologist. (B3)

Pulmonary TB

- For patients with pulmonary TB, clinicians should initiate ART as follows:
 - **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. (A1)
 - **CD4 counts < 50 cells/mm³**: Within the first 2 weeks after initiating anti-TB therapy. (A1)
- For patients with pulmonary TB who are ART-naïve, who have a CD4 count <100 cells/mm³, and who 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. (B1)

TB Meningitis or Extrapulmonary TB

- For patients with TB meningitis or extrapulmonary TB, clinicians should consult with an experienced HIV care provider to determine the timing of ART initiation. (A3)

Cryptococcal Meningitis

- Clinicians should treat ART-naïve patients diagnosed with cryptococcal meningitis with standard antifungal therapy and should:
 - Delay ART initiation until the patient has completed at least 2 weeks of antifungal treatment. (A1)
 - Consult with an experienced HIV care provider to determine optimal timing for ART initiation. (A3)
- If the patient initiates ART before completing 10 weeks of antifungal therapy, the clinician should monitor closely for increased intracranial pressure and other signs and symptoms of IRIS and manage intracranial pressure aggressively. (A2)
- 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. (A3)

RECOMMENDATIONS

CMV Retinitis

- Clinicians should not initiate ART immediately in patients with known or strongly suspected CMV retinitis (A2) but should consult with an experienced HIV care provider to determine the timing of ART initiation. (A3)
- Clinicians should refer patients with HIV who have CD4 counts <100 cells/mm³ but without known or suspected CMV for a dilated ophthalmologic examination as soon as possible after initiating ART to assess for signs of CMV. (A2) If the dilated exam shows signs of CMV, clinicians should consult with an experienced HIV care provider.
- Clinicians should ensure that after initiating ART, patients with a history of CMV retinitis are monitored by dilated ophthalmologic examination to assess for possible IRIS as follows:
 - Every 3 months for the first year after initiation of ART. (A3)
 - Immediately if there is a change in visual acuity or development of floaters. (A2)

Abbreviations: ART, antiretroviral therapy; CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; IRIS, immune reconstitution inflammatory syndrome; OI, opportunistic infection; TB, tuberculosis.

Initiating ART

Because ART is key to the recovery of immune function, the benefits of early ART initiation outweigh the risks of IRIS under most circumstances [Ford, et al. 2018; Lodi, et al. 2014; Grant, et al. 2010]. Clinicians should strongly recommend that patients being treated for any of the following active infections initiate ART within 2 weeks of starting OI treatment or as soon as the patient is clinically stable on OI therapy and the potential for drug-drug interactions has been minimized:

- Cryptosporidiosis
- Microsporidiosis
- Progressive multifocal leukoencephalopathy
- Kaposi’s sarcoma (KS)
- Pneumocystis jiroveci pneumonia—formerly known as Pneumocystis carinii
- HBV infection
- HCV infection
- Any other serious bacterial infection

The optimal timing for ART initiation is not well established for other OIs, including TB meningitis, extrapulmonary TB, CMV retinitis, and cryptococcal meningitis, as described below. Clinicians should consult with a care provider experienced in the management of ART in patients with these infections.

→ KEY POINTS

- Clinicians should strongly recommend that patients being treated for infections other than TB meningitis, cryptococcal disease, and CMV retinitis initiate ART within 2 weeks of starting OI treatment or as soon as the patient is clinically stable on OI therapy and the potential for drug-drug interactions has been minimized.
- Before initiating ART in patients who have TB meningitis, extrapulmonary TB, CMV retinitis, or cryptococcal infection, clinicians should consult with a care provider who is experienced in managing the care of patients with HIV in patients with active OIs.
- The [Clinical Education Initiative \(CEI\) Line](#), which is available through the [New York State Department of Health CEI](#), provides access to care providers with experience in managing all aspects of HIV infection: 866-637-2342.

Table 1: Summary of Recommendations Regarding Timing of ART Initiation	
Opportunistic Infection	Timing of ART Initiation After Starting OI Treatments
<ul style="list-style-type: none"> • Cryptosporidiosis • Microsporidiosis • Progressive multifocal leukoencephalopathy • Kaposi’s sarcoma • Pneumocystis jiroveci pneumonia (formerly PCP) • Hepatitis B virus infection • Hepatitis C virus infection • Pulmonary TB • Other serious bacterial infections 	<p>Within 2 weeks of starting treatment for an OI or as soon as the patient is clinically stable.</p>
Pulmonary TB	<ul style="list-style-type: none"> • CD4 count >50 cells/mm³: Initiate ART as soon as the patient is clinically stable after initiating TB therapy, but no more than 12 weeks later. • CD4 count <50 cells/mm³: Initiate ART within the first 2 weeks after initiating TB therapy.
Extrapulmonary TB	Optimal timing has not been established; consult with an experienced HIV care provider.
TB meningitis	Optimal timing has not been established; consult with an experienced HIV care provider.
Cryptococcal meningitis	<ul style="list-style-type: none"> • Delay 2 to 10 weeks after starting antifungal therapy. • Optimal timing has not been established; consult with an experienced HIV care provider.
Cryptococcal infection other than meningitis	<ul style="list-style-type: none"> • Delay at least 2 weeks after starting antifungal therapy. • Optimal timing has not been established; consult with an experienced HIV care provider.
Cytomegalovirus retinitis	<ul style="list-style-type: none"> • Immediate ART is not recommended. • Optimal timing has not been established; consult with an experienced HIV care provider.
Abbreviations: ART, antiretroviral therapy; OI, opportunistic infection; TB, tuberculosis.	

Prevention of complications associated with IRIS involves careful monitoring, particularly in patients with low CD4 counts and past or current history of co-infections. After initiating ART in patients at the highest risk for IRIS, including those with CD4 counts <100 cells/mm³ or known concomitant OIs, clinicians should be vigilant for signs and symptoms of IRIS, which are described in more detail in the guideline section [Presentation and Diagnosis of IRIS](#). These patients should be counseled about the risk of developing IRIS at the time of ART initiation. To promote trust in the treatment plan and adherence to ART, patients should be informed that starting ART could lead to an initial worsening of OI symptoms or the appearance of a previously undiagnosed OI (e.g., herpes zoster).

Pulmonary TB

IRIS has been described in 8% to 51% of patients with HIV and TB after initiation of ART [Narendran, et al. 2013; Haddow(b), et al. 2010; Meintjes, et al. 2008] with a reported overall mortality rate of 2% [Namale, et al. 2015]. In determining the timing of ART initiation in patients with HIV/TB co-infection, the risk of TB-IRIS and the overlapping toxicity, potential drug-drug interactions, and adherence challenges of multidrug therapy for HIV and TB warrant careful consideration.

Several studies have assessed the optimal timing of ART initiation during treatment for pulmonary TB [Amogne, et al. 2015; Mfinanga, et al. 2014; Manosuthi, et al. 2012; Sinha, et al. 2012; Blanc, et al. 2011; Havlir, et al. 2011; Abdool Karim, et al. 2010]. Two separate meta-analyses compared ART initiation at 1 to 4 weeks after starting TB treatment with ART initiation at >4 weeks after starting TB treatment. Both studies found a statistically significant decrease in mortality with early ART

initiation only in the subgroup of patients with CD4 counts <50 cells/mm³. Early ART reduced the incidence of AIDS-defining events but nearly doubled the incidence of TB-IRIS irrespective of CD4 count [Burke, et al. 2021; Uthman, et al. 2015]. The authors concluded that although early ART improves survival for patients with low CD4 counts, not enough evidence is available to support or refute a survival benefit from early ART in patients with pulmonary TB who have CD4 counts >50 cells/mm³ [Uthman, et al. 2015]. Further studies are needed to more definitively determine the CD4 count threshold below which the mortality benefit supports early initiation of ART.

Two trials compared ART initiation during TB treatment with deferral until after completion of TB treatment. The SAPIT trial ($n = 642$) in South Africa [Abdool Karim, et al. 2010], which evaluated patients with smear-positive TB, was stopped early because the mortality rate in the group that initiated ART during TB treatment was 56% lower than in the deferred group. The survival benefit of initiating ART before completing TB treatment was observed in all ranges of CD4 counts but was highest in patients with CD4 counts <50 cells/mm³. Although the incidence of IRIS was much higher in patients who initiated ART early, it was mostly mild and was outweighed by the other benefits of early treatment. The subsequent TB- HAART trial ($n = 1,675$), conducted in South Africa, Tanzania, Uganda, and Zambia [Mfinanga, et al. 2014], compared initiation of ART after 2 weeks of TB treatment with ART initiation deferred until after completion of 6 months of TB treatment in patients with CD4 counts >220 cells/mm³. More grade 3 and 4 adverse events were reported among those with early ART initiation, with no difference in mortality or IRIS incidence between early and deferred ART.

Although early ART increases the risk of TB-associated IRIS, this risk should be weighed against the survival benefit of early HIV treatment given a patient's CD4 count. The benefits of early ART initiation in patients with active TB and very low CD4 counts (<50 cells/mm³) likely outweigh the risks for morbidity associated with TB-IRIS [Battegay, et al. 2008; Lawn, et al. 2007]. To decrease the risk of IRIS, initiation of ART may be safely delayed up to 12 weeks after starting TB therapy in patients with CD4 counts of ≥ 50 cells/mm³. Careful monitoring for IRIS, and timely treatment if it occurs, may significantly reduce morbidity associated with TB-IRIS; it may also ensure that other risks associated with severe immunosuppression (CD4 counts <50 cells/mm³) are managed effectively with ART.

A study of 240 patients enrolled in the PredART trial demonstrated that prednisone initiated around the time of ART initiation reduced the risk of IRIS in patients receiving TB treatment [Meintjes, et al. 2018]. ART-naïve adults with HIV infection, CD4 counts <100 cells/mm³, who were on confirmed treatment for TB were randomized to receive either 40 mg per day of prednisone for 2 weeks followed by 20 mg per day of prednisone for 2 weeks or placebo. The prednisone and ART were initiated on the same day and were initiated within 30 days of the start of TB treatment. Use of corticosteroids was allowed to treat IRIS if it developed. Patients with rifampin resistance, central nervous system (CNS) TB, KS, HBVsAg+, or poor adherence were excluded from the study. In patients receiving prednisone, TB-IRIS was reduced by 30% (47% vs 33%; RR 0.7, $p 0.03$) and subsequent use of corticosteroids to treat IRIS was reduced by 53% (28% vs 13%; RR 0.47). Grade 3 adverse events were reduced from 45% to 28% ($p 0.01$), and fewer hospitalizations occurred in patients who received prednisone. The prednisone was well tolerated, and there were no additional infections or malignancies in patients receiving prednisone compared with those receiving placebo.

TB Meningitis and Extrapulmonary TB

Compared with non-CNS-related diseases, IRIS-associated TB meningitis has a higher mortality rate [Marais, et al. 2013]. The optimal timing of ART initiation in patients treated for TB meningitis or extrapulmonary TB remains unclear. In a randomized controlled trial, initiation of ART within 7 days was not associated with increased survival for patients with TB meningitis compared with delaying treatment for 2 months. Although the incidence of severe (grade 3 and 4) adverse events was similar in the 2 groups, early initiation of ART was associated with a higher incidence of the most severe (grade 4) adverse events [Török, et al. 2011]. A 2- to 9-fold increased risk of development of IRIS has been described for patients with extrapulmonary TB after ART initiation [Namale, et al. 2015]; however, insufficient data are available to guide timing of ART initiation.

Cryptococcal Meningitis

With rapid immune reconstitution in patients with cryptococcal meningitis, there is a risk of increased inflammatory response in the meninges that can lead to paradoxical worsening of the symptoms and, sometimes, death. Paradoxical IRIS was noted in 6% to 45% of patients with cryptococcal meningitis following ART initiation [Longley, et al. 2013]. Most cases occurred within the first 1 to 2 months, but some occurred 6 to 9 months later. The presentation of cryptococcal IRIS may mimic aseptic meningitis and can be difficult to distinguish from progression of cryptococcal disease associated with treatment failure [Boulware(b), et al. 2010; Haddow(a), et al. 2010; Bicanic, et al. 2009].

→ KEY POINTS

- Steroids should not be used routinely as induction therapy in treatment of cryptococcal IRIS.
- Steroids are not effective in reducing intracranial pressure.

The optimal timing of ART initiation in patients with cryptococcal meningitis is controversial, with inconclusive study results among the 4 trials conducted to date. In 2 studies (each with fewer than 40 participants with cryptococcal meningitis), initiation of ART within 2 weeks of diagnosis was observed to be safe but without significant improvement in survival [Bisson, et al. 2013; Zolopa, et al. 2009]. In contrast, 2 clinical trials were stopped early because of a high mortality rate in the early ART arm [Boulware, et al. 2014; Makadzange, et al. 2010]. In a study from Zimbabwe of 54 patients with cryptococcal meningitis, administration of ART within 72 hours of diagnosis resulted in higher mortality than when ART was deferred for 10 or more weeks [Makadzange, et al. 2010]. The more recent and larger COAT trial involving 177 ART-naive patients with HIV and cryptococcal meningitis in Uganda and South Africa was also stopped early because of a 15% higher mortality in the group randomized to ART initiation within 2 weeks compared with delaying treatment by at least 5 weeks [Boulware, et al. 2014]. However, interpretation of results is limited because neither trial included flucytosine in the cryptococcal treatment regimen [Scriven, et al. 2015].

Until further studies are available to definitively determine the optimal time for ART initiation for patients with cryptococcal meningitis, treatment should be delayed for at least 2 weeks (after completion of antifungal therapy induction phase) and possibly for up to 10 weeks (after completion of both induction and consolidation phases of antifungal therapy), particularly in those with increased intracranial pressure or low cerebral spinal fluid white blood cell counts. If ART is started before 10 weeks, clinicians should be vigilant for signs and symptoms of IRIS and aggressively manage any complications. The optimal timing for initiation of ART for other forms of cryptococcosis is also unclear; it is recommended to delay ART initiation for at least 2 weeks after starting antifungal therapy [DHHS 2021].

CMV Retinitis

Immediate initiation of ART is not recommended based on the results of a controlled study that reported a lower prevalence and severity of immune recovery uveitis in patients with deferred initiation of ART [Ortega-Larrocea, et al. 2005]. The optimal timing for initiation of ART in patients treated for CMV retinitis has not been definitively established. The overall incidence of CMV-IRIS has declined to an estimated 2.7 to 3.6 per 100 person-years in recent years [Jabs, et al. 2015; Jabs, et al. 2010], and the risk of IRIS should be weighed against the risk of developing other OIs due to delay in ART initiation.

To avoid the possible devastating effects of CMV-IRIS, ART should not be started immediately in patients with known or strongly suspected CMV. All patients with HIV who have CD4 counts <100 cells/mm³ who do not have known or strongly suspected CMV should be screened for signs of CMV by dilated ophthalmologic examination as soon as possible after initiation of ART. If signs of CMV are seen on dilated exam, clinicians should consult with an experienced HIV care provider to determine if ART must be temporarily paused. In mild cases, it may be appropriate to continue ART while treating the CMV, but such patients must be followed closely by an ophthalmologist with experience in managing CMV retinitis.

Even if receiving treatment, patients with a history of CMV retinitis should receive a dilated ophthalmologic examination every 3 months for the first year after initiation of ART 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 [Acosta, et al. 2008; von Both, et al. 2008]. For more information, see DHHS [Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV > Cytomegalovirus Disease](#).

Presentation and Diagnosis of IRIS

☑ RECOMMENDATIONS

Diagnosing IRIS

- 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. (A3)

RECOMMENDATIONS

- In assessing patients for IRIS, clinicians should exclude HIV disease progression, new infections, and drug reactions as underlying causes for inflammatory signs or symptoms. (A3)

Abbreviations: ART, antiretroviral therapy; IRIS, immune reconstitution inflammatory syndrome.

Table 2, below, describes major and minor clinical presentations of IRIS. Proposed case definitions do not provide clear consensus on the many manifestations of IRIS [Haddow(a), et al. 2010; Haddow(b), et al. 2010; Bicanic, et al. 2009; Meintjes, et al. 2008; Robertson, et al. 2006; Shelburne, et al. 2006; French, et al. 2004]. Common features are clinical deterioration after ART initiation and localized tissue inflammation, with or without a systemic inflammatory response [Walker, et al. 2015], but the presentation of IRIS varies depending on the underlying opportunistic infection (OI) or illness. The majority of IRIS cases occur within 4 to 8 weeks after initiation of or a change in ART [Novak, et al. 2012; Shelburne(b), et al. 2005; Breton, et al. 2004]. However, cases have been reported as early as 3 days or as late as several months, or, rarely, several years, after ART initiation [Letang, et al. 2013; Novak, et al. 2012; Haddow(b), et al. 2010; Valin, et al. 2010; Lortholary, et al. 2005; Shelburne(a), et al. 2005; Rambeloarisoa, et al. 2002]. Late manifestations of IRIS (>7 months) may be atypical, such as osteomyelitis resulting from *Mycobacterium avium* complex [Aberg, et al. 2002].

A definitive diagnostic test is not available for IRIS; therefore, diagnosis is based largely on clinical judgment, which may be challenged by the broad array of IRIS signs and symptoms and the presence of multiple OIs. A rise in CD4 count is often present in IRIS cases but is not a required criterion for diagnosis [Sereti, et al. 2020; Walker, et al. 2015; Haddow(a), et al. 2010; Haddow(b), et al. 2010; Meintjes, et al. 2008; Robertson, et al. 2006]; therefore, absence of an increase in absolute CD4 count should not exclude the possibility of IRIS during a paradoxical response to treatment of an OI.

In patients who were responding favorably to OI treatment prior to ART initiation, but who worsen after, the differential diagnosis includes paradoxical IRIS, OI treatment toxicity, OI drug resistance, poor OI treatment adherence, or development of a new OI. Development of a new OI after ART initiation of ART may be attributable to unmasking IRIS or to the effects of persistent immune compromise [Walker, et al. 2015].

Table 2: Major and Minor Presentations of IRIS	
Underlying Opportunistic Infection	IRIS Signs/Symptoms
<i>Major Presentations</i>	
Tuberculosis (TB)	<ul style="list-style-type: none"> • 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 [Meintjes, et al. 2008]. • TB-IRIS can also result in acute hepatitis, which may be difficult to distinguish from medication-induced toxicity [Lawn and Wood 2007]. • Undiagnosed multidrug-resistant TB can mimic TB-IRIS and should be ruled out in patients whose symptoms worsen while receiving first-line TB treatment [Meintjes, et al. 2009].
<i>Mycobacterium avium</i> complex (MAC)	<ul style="list-style-type: none"> • May present as pulmonary disease or systemic inflammation that is indistinguishable from active MAC. • Atypical presentations, such as localized lymphadenitis or endobronchial mass lesions, may occur [Lawn(b), et al. 2005]; osteomyelitis is an atypical late manifestation [Aberg, et al. 2002]. • Patients with MAC-IRIS may not be bacteremic and may have no known history of a MAC diagnosis [Lawn(b), et al. 2005].
Cryptococcal meningitis	Usually presents as worsening of meningitis symptoms [Kambugu, et al. 2008; Gray, et al. 2005; Lawn(a), et al. 2005; Lortholary, et al. 2005; Shelburne(b), et al. 2005; Rambeloarisoa, et al. 2002], including possible rapid hearing and/or vision loss, ataxia, and/or elevated intracranial pressure.

Table 2: Major and Minor Presentations of IRIS	
Underlying Opportunistic Infection	IRIS Signs/Symptoms
Cytomegalovirus (CMV) retinitis	<ul style="list-style-type: none"> • Presents as retinitis, vitritis, or uveitis (variable timing, with median time to immune reconstitution vitritis 20 weeks after ART initiation in one study) [Karavellas, et al. 1999]: <ul style="list-style-type: none"> – 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 [Karavellas, et al. 1999]. • CMV-IRIS in the eye can cause rapid and permanent vision loss.
Hepatitis B or C virus	<ul style="list-style-type: none"> • Transient elevations in transaminases may occur after initiation of ART with immune reconstitution and can be difficult to distinguish from drug-induced hepatitis [Anderson, et al. 2010; Crane, et al. 2009; Perrella, et al. 2006; Konopnicki, et al. 2005; Drake, et al. 2004]. • Hepatic flares are usually mild and self-limited but can result in decompensation in someone with pre-existing cirrhosis [Anderson, et al. 2010; Crane, et al. 2009; Perrella, et al. 2006; Konopnicki, et al. 2005; Drake, et al. 2004].
Progressive multifocal leukoencephalopathy (PML)	PML lesions may be unmasked or worsen and could appear as new or worsening focal neurologic deficits or lesions on MRI [Summers, et al. 2019; Tan, et al. 2009; Gray, et al. 2005; Safdar, et al. 2002].
Kaposi’s sarcoma (KS)	<ul style="list-style-type: none"> • Presents as worsening of KS. • Cutaneous lesions are the most common presentation; other signs include lymphedema and oral, gastric, lung, genital, or conjunctival lesions [Volkow, et al. 2017; Bower, et al. 2005; Leidner and Aboulafia 2005]. • Fatal cases of KS-IRIS have been reported [Odongo 2013; Stover, et al. 2012].
Cerebral toxoplasmosis	May present as a cerebral abscess (also known as toxoplasmosis encephalitis) or, rarely, diffuse encephalitis or chorioretinitis [Bowen, et al. 2016].
Histoplasmosis	May present as mucocutaneous lesions, disseminated disease, or fever without localizing symptoms [Melzani, et al. 2020].
Autoimmune diseases	<ul style="list-style-type: none"> • Pre-existing sarcoidosis may be exacerbated [Foulon, et al. 2004]. • Late presentations of Grave’s disease have been reported 8 to 33 months after ART initiation [Rasul, et al. 2011].
<i>Minor Presentations</i>	
Herpes simplex virus (HSV) and varicella zoster virus (VZV)	<ul style="list-style-type: none"> • 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.
Mpox	Several case reports have described worsening of previously crusted lesions, the appearance of new lesions, and necrosis after ART initiation [Martinez, et al. 2023; Rajme-López, et al. 2023; Warner, et al. 2023].
Nonspecific dermatologic complications	A number of dermatologic manifestations, such as folliculitis and oral and genital warts, may appear or worsen during immune reconstitution.
Abbreviations: ART, antiretroviral therapy; IRIS, immune reconstitution inflammatory syndrome; MRI, magnetic resonance imaging.	

Management and Treatment of IRIS

RECOMMENDATIONS

Management and Treatment

- Clinicians should initiate appropriate treatment of OIs, as well as symptomatic treatment and supportive care according to the severity of IRIS. (A3)
- Clinicians should not interrupt ART except in severe, life-threatening cases of IRIS. (A3)
- Clinicians should not use prednisone to prevent IRIS in patients with low CD4 counts who do not have active TB. (A3)

Severe IRIS

- Clinicians should consult with an experienced HIV care provider for the management of severe IRIS, including the decision of whether to interrupt ART if IRIS is severe. (A3)
- 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 period of tapering dose that is individualized. (B3)
- Clinicians should not use corticosteroids for management of cryptococcal meningitis or in patients with KS. (A2)
- Clinicians should closely monitor patients receiving corticosteroids for the development of OIs, including CMV retinitis and TB disease. (A3)

Abbreviations: ART, antiretroviral therapy; CMV, cytomegalovirus; IRIS, immune reconstitution inflammatory syndrome; KS, Kaposi’s sarcoma; OI, opportunistic infection; TB, tuberculosis.

Whenever IRIS is suspected, initial efforts should focus on diagnosing and treating the underlying OI. IRIS resolves over time in most patients, and if not severe, symptomatic treatment is often sufficient.

Mild IRIS

When minor IRIS presentations occur, clinicians can reassure patients that symptoms 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 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

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 *Mycobacterium avium* complex (MAC) infection, neurologic complications from cryptococcal infection, or vision loss from CMV retinitis infection.

Corticosteroid therapy to suppress inflammatory response is the most commonly used intervention in cases of severe IRIS. Studies to determine the effectiveness of corticosteroid treatment are limited. A randomized, placebo-controlled trial demonstrated benefits of corticosteroids for paradoxical TB-IRIS [Meintjes, et al. 2010], and a study of patients with MAC-IRIS ($n = 9$) demonstrated clinical response to prednisone [Phillips, et al. 2005]. No trials have compared different dosing regimens of corticosteroids, but this Committee recommends 1 to 2 mg/kg prednisone, or the equivalent, for 1 to 2 weeks, followed by a period of tapering dose that is individualized. If a flare of symptoms occurs during or at the end of the steroid taper, the dose may be increased and the taper slowed, and the patient should be assessed for possible disease progression due to failure of treatment.

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 type 2 diabetes, hypertension, and mental health disorders among patients with HIV. Risks of corticosteroid therapy include the following:

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

Except in the most severe cases, ART should not be interrupted in patients with IRIS. Discontinuation of ART can be considered in life-threatening cases in which corticosteroids did not result in improvement, usually associated with central nervous system (CNS)-IRIS. Risks of stopping combination ART include acquisition of new OIs and recurrence of IRIS when therapy is later restarted. HIV drug resistance may also be a theoretical concern. The decision to stop ART should be made in consultation with an experienced HIV care provider if possible.

→ **KEY POINT**

- ART should not be interrupted in patients with IRIS except in life-threatening cases, usually associated with CNS-IRIS, in which corticosteroids did not result in improvement.

In cases of cryptococcal-IRIS with worsening meningitis symptoms, including cranial nerve defects, hearing, or vision changes, therapeutic lumbar puncture can be used to lower intracranial pressure. Corticosteroids are not recommended for treatment of cryptococcal meningitis in patients with HIV. A trial of treatment of HIV-associated cryptococcal meningitis with dexamethasone was stopped because of the high incidence of adverse events and disability observed in the treatment arm compared with placebo [Beardsley, et al. 2016].

Corticosteroids are associated with increased risk of development of new KS or worsening of pre-existing disease among patients with HIV [Volkow, et al. 2008; Elliott, et al. 2004; Gill, et al. 1989]. Treatment of CMV vitritis with intraocular steroids has been described [Schrier, et al. 2006] but has not been useful in uveitis.

There are limited case reports of improvement in clinical symptoms following treatment with thalidomide and other immunomodulators (pentoxifylline, chloroquine, TNF- α inhibitors, leukotriene antagonists) in patients with severe disease [Armange, et al. 2023; Fourcade, et al. 2014; Brunel, et al. 2012; Meintjes, et al. 2012; Marais, et al. 2009; Hardwick, et al. 2006]. However, data are insufficient to recommend the use of these alternative therapies.

The CCR5 inhibitor maraviroc has been used for treatment of progressive multifocal leukoencephalopathy-associated IRIS because direct treatment for JC virus is not available to lower the pathogen burden and treatment with corticosteroids may dampen the immune response. However, case reports indicate mixed success [Giacomini, et al. 2014; Rodríguez, et al. 2014; Martin-Blondel, et al. 2009], and a recent randomized, placebo-controlled trial found that maraviroc was not effective for prevention of IRIS in patients starting ART with CD4 count <100 cells/mm³ and HIV RNA $>1,000$ copies/mL [Sierra-Madero, et al. 2014].

For further OI-specific guidance on management of IRIS, see DHHS [Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV](#).

All Recommendations

☑ ALL RECOMMENDATIONS: MANAGEMENT OF IRIS

Initiating ART

- Clinicians should recommend that patients initiate ART within 2 weeks of beginning treatment for active OIs, with exceptions to this recommendation noted below. (A1)
- Clinicians should consult with a care provider experienced in managing HIV in patients with active OIs to determine when to initiate ART in patients with TB meningitis, extrapulmonary TB, CMV retinitis, or cryptococcal infection. (A3)
- For patients with CD4 counts <100 cells/mm³ or known concomitant OIs who are initiating ART, clinicians should be vigilant for the signs and symptoms of IRIS and should educate patients about the risk of developing IRIS. (A3)
- For patients with HIV who have HBV or HCV co-infection, clinicians should:
 - Measure transaminase levels before initiation of ART, at 6 and 12 weeks after initiation, and at least every 6 months thereafter to monitor for possible IRIS. (A3)
 - Refer patients with elevated transaminase levels in conjunction with jaundice, elevated bilirubin levels, or loss of synthetic function for evaluation by a hepatologist. (B3)

Pulmonary TB

- For patients with pulmonary TB, clinicians should initiate ART as follows:
 - **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. (A1)
 - **CD4 counts < 50 cells/mm³:** Within the first 2 weeks after initiating anti-TB therapy. (A1)
- For patients with pulmonary TB who are ART-naïve, who have a CD4 count <100 cells/mm³, and who 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. (B1)

TB Meningitis or Extrapulmonary TB

- For patients with TB meningitis or extrapulmonary TB, clinicians should consult with an experienced HIV care provider to determine the timing of ART initiation. (A3)

Cryptococcal Meningitis

- Clinicians should treat ART-naïve patients diagnosed with cryptococcal meningitis with standard antifungal therapy and should:
 - Delay ART initiation until the patient has completed at least 2 weeks of antifungal treatment. (A1)
 - Consult with an experienced HIV care provider to determine optimal timing for ART initiation. (A3)
- If the patient initiates ART before completing 10 weeks of antifungal therapy, the clinician should monitor closely for increased intracranial pressure and other signs and symptoms of IRIS and manage intracranial pressure aggressively. (A2)
- 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. (A3)

CMV Retinitis

- Clinicians should not initiate ART immediately in patients with known or strongly suspected CMV retinitis (A2) but should consult with an experienced HIV care provider to determine the timing of ART initiation. (A3)
- Clinicians should refer patients with HIV who have CD4 counts <100 cells/mm³ but without known or suspected CMV for a dilated ophthalmologic examination as soon as possible after initiating ART to assess for signs of CMV. (A2) If the dilated exam shows signs of CMV, clinicians should consult with an experienced HIV care provider.
- Clinicians should ensure that after initiating ART, patients with a history of CMV retinitis are monitored by dilated ophthalmologic examination to assess for possible IRIS as follows:
 - Every 3 months for the first year after initiation of ART. (A3)
 - Immediately if there is a change in visual acuity or development of floaters. (A2)

ALL RECOMMENDATIONS: MANAGEMENT OF IRIS

Diagnosing IRIS

- 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. (A3)
- In assessing patients for IRIS, clinicians should exclude HIV disease progression, new infections, and drug reactions as underlying causes for inflammatory signs or symptoms. (A3)

Management and Treatment

- Clinicians should initiate appropriate treatment of OIs, as well as symptomatic treatment and supportive care according to the severity of IRIS. (A3)
- Clinicians should not interrupt ART except in severe, life-threatening cases of IRIS. (A3)
- Clinicians should not use prednisone to prevent IRIS in patients with low CD4 counts who do not have active TB. (A3)

Severe IRIS

- Clinicians should consult with an experienced HIV care provider for the management of severe IRIS, including the decision of whether to interrupt ART if IRIS is severe. (A3)
- 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 period of tapering dose that is individualized. (B3)
- Clinicians should not use corticosteroids for management of cryptococcal meningitis or in patients with KS. (A2)
- Clinicians should closely monitor patients receiving corticosteroids for the development of OIs, including CMV retinitis and TB disease. (A3)

Abbreviations: ART, antiretroviral therapy; CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; IRIS, immune reconstitution inflammatory syndrome; KS, Kaposi’s sarcoma; OI, opportunistic infection; TB, tuberculosis.

References

Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med* 2010;362(8):697–706. [PMID: 20181971] <https://pubmed.ncbi.nlm.nih.gov/20181971>

Aberg JA, Chin-Hong PV, McCutchan A, et al. Localized osteomyelitis due to mycobacterium avium complex in patients with human immunodeficiency virus receiving highly active antiretroviral therapy. *Clin Infect Dis* 2002;35(1):E8–13. [PMID: 12060894] <https://pubmed.ncbi.nlm.nih.gov/12060894>

Acosta RD, Mays BC, Wong RK. Electronic clinical challenges and images in GI. CMV colitis with immune reconstitution syndrome. *Gastroenterology* 2008;134(2):e1–2. [PMID: 18242197] <https://pubmed.ncbi.nlm.nih.gov/18242197>

Amogne W, Aderaye G, Habtewold A, et al. Efficacy and safety of antiretroviral therapy initiated one week after tuberculosis therapy in patients with CD4 counts < 200 cells/μL: TB-HAART Study, a randomized clinical trial. *PLoS One* 2015;10(5):e0122587. [PMID: 25966339] <https://pubmed.ncbi.nlm.nih.gov/25966339>

Anderson AM, Mosunjac MB, Palmore MP, et al. Development of fatal acute liver failure in HIV-HBV coinfecting patients. *World J Gastroenterol* 2010;16(32):4107–11. [PMID: 20731028] <https://pubmed.ncbi.nlm.nih.gov/20731028>

Armenge L, Lacroix A, Petitgas P, et al. The use of TNF-α antagonists in tuberculosis to control severe paradoxical reaction or immune reconstitution inflammatory syndrome: a case series and literature review. *Eur J Clin Microbiol Infect Dis* 2023;42(4):413–22. [PMID: 36795280] <https://pubmed.ncbi.nlm.nih.gov/36795280>

Bahr N, Boulware DR, Marais S, et al. Central nervous system immune reconstitution inflammatory syndrome. *Curr Infect Dis Rep* 2013;15(6):583–93. [PMID: 24173584] <https://pubmed.ncbi.nlm.nih.gov/24173584>

Battegay M, Fehr J, Flückiger U, et al. Antiretroviral therapy of late presenters with advanced HIV disease. *J Antimicrob Chemother* 2008;62(1):41–44. [PMID: 18408235] <https://pubmed.ncbi.nlm.nih.gov/18408235>

Beardsley J, Wolbers M, Kibengo FM, et al. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. *N Engl J Med* 2016;374(6):542–54. [PMID: 26863355] <https://pubmed.ncbi.nlm.nih.gov/26863355>

- Bicanic T, Meintjes G, Rebe K, et al. Immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis: a prospective study. *J Acquir Immune Defic Syndr* 2009;51(2):130–34. [PMID: 19365271] <https://pubmed.ncbi.nlm.nih.gov/19365271>
- Bisson GP, Molefi M, Bellamy S, et al. Early versus delayed antiretroviral therapy and cerebrospinal fluid fungal clearance in adults with HIV and cryptococcal meningitis. *Clin Infect Dis* 2013;56(8):1165–73. [PMID: 23362285] <https://pubmed.ncbi.nlm.nih.gov/23362285>
- Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med* 2011;365(16):1471–81. [PMID: 22010913] <https://pubmed.ncbi.nlm.nih.gov/22010913>
- Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med* 2014;370(26):2487–98. [PMID: 24963568] <https://pubmed.ncbi.nlm.nih.gov/24963568>
- Boulware(a) DR, Meya DB, Bergemann TL, et al. Clinical features and serum biomarkers in HIV immune reconstitution inflammatory syndrome after cryptococcal meningitis: a prospective cohort study. *PLoS Med* 2010;7(12):e1000384. [PMID: 21253011] <https://pubmed.ncbi.nlm.nih.gov/21253011>
- Boulware(b) DR, Bonham SC, Meya DB, et al. Paucity of initial cerebrospinal fluid inflammation in cryptococcal meningitis is associated with subsequent immune reconstitution inflammatory syndrome. *J Infect Dis* 2010;202(6):962–70. [PMID: 20677939] <https://pubmed.ncbi.nlm.nih.gov/20677939>
- Bowen LN, Smith B, Reich D, et al. HIV-associated opportunistic CNS infections: pathophysiology, diagnosis and treatment. *Nat Rev Neurol* 2016;12(11):662–74. [PMID: 27786246] <https://pubmed.ncbi.nlm.nih.gov/27786246>
- Bower M, Nelson M, Young AM, et al. Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma. *J Clin Oncol* 2005;23(22):5224–28. [PMID: 16051964] <https://pubmed.ncbi.nlm.nih.gov/16051964>
- Breton G, Duval X, Estellat C, et al. Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. *Clin Infect Dis* 2004;39(11):1709–12. [PMID: 15578375] <https://pubmed.ncbi.nlm.nih.gov/15578375>
- Brunel AS, Reynes J, Tuaille E, et al. Thalidomide for steroid-dependent immune reconstitution inflammatory syndromes during AIDS. *AIDS* 2012;26(16):2110–12. [PMID: 22874513] <https://pubmed.ncbi.nlm.nih.gov/22874513>
- Burke RM, Rickman HM, Singh V, et al. What is the optimum time to start antiretroviral therapy in people with HIV and tuberculosis coinfection? A systematic review and meta-analysis. *J Int AIDS Soc* 2021;24(7):e25772. [PMID: 34289243] <https://pubmed.ncbi.nlm.nih.gov/34289243>
- Crane M, Oliver B, Matthews G, et al. Immunopathogenesis of hepatic flare in HIV/hepatitis B virus (HBV)-coinfected individuals after the initiation of HBV-active antiretroviral therapy. *J Infect Dis* 2009;199(7):974–81. [PMID: 19231993] <https://pubmed.ncbi.nlm.nih.gov/19231993>
- DHHS. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: cryptococcosis. 2021 Jul 1. <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/cryptococcosis?view=full> [accessed 2021 Mar 8]
- Drake A, Mijch A, Sasadeusz J. Immune reconstitution hepatitis in HIV and hepatitis B coinfection, despite lamivudine therapy as part of HAART. *Clin Infect Dis* 2004;39(1):129–32. [PMID: 15206064] <https://pubmed.ncbi.nlm.nih.gov/15206064>
- Dutertre M, Cuzin L, Demonchy E, et al. Initiation of antiretroviral therapy containing integrase inhibitors increases the risk of IRIS requiring hospitalization. *J Acquir Immune Defic Syndr* 2017;76(1):e23–26. [PMID: 28418992] <https://pubmed.ncbi.nlm.nih.gov/28418992>
- Elliott AM, Luzze H, Quigley MA, et al. A randomized, double-blind, placebo-controlled trial of the use of prednisolone as an adjunct to treatment in HIV-1-associated pleural tuberculosis. *J Infect Dis* 2004;190(5):869–78. [PMID: 15295690] <https://pubmed.ncbi.nlm.nih.gov/15295690>
- Feller L, Anagnostopoulos C, Wood NH, et al. Human immunodeficiency virus-associated Kaposi sarcoma as an immune reconstitution inflammatory syndrome: a literature review and case report. *J Periodontol* 2008;79(2):362–68. [PMID: 18251652] <https://pubmed.ncbi.nlm.nih.gov/18251652>
- Ford N, Migone C, Calmy A, et al. Benefits and risks of rapid initiation of antiretroviral therapy. *AIDS* 2018;32(1):17–23. [PMID: 29112073] <https://pubmed.ncbi.nlm.nih.gov/29112073>
- Foulon G, Wislez M, Naccache JM, et al. Sarcoidosis in HIV-infected patients in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2004;38(3):418–25. [PMID: 14727215] <https://pubmed.ncbi.nlm.nih.gov/14727215>
- Fourcade C, Mauboussin JM, Lechiche C, et al. Thalidomide in the treatment of immune reconstitution inflammatory syndrome in HIV patients with neurological tuberculosis. *AIDS Patient Care STDS* 2014;28(11):567–69. [PMID: 25285462] <https://pubmed.ncbi.nlm.nih.gov/25285462>

- French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS* 2004;18(12):1615–27. [PMID: 15280772] <https://pubmed.ncbi.nlm.nih.gov/15280772>
- Giacomini PS, Rozenberg A, Metz I, et al. Maraviroc and JC virus-associated immune reconstitution inflammatory syndrome. *N Engl J Med* 2014;370(5):486–88. [PMID: 24476450] <https://pubmed.ncbi.nlm.nih.gov/24476450>
- Gill PS, Loureiro C, Bernstein-Singer M, et al. Clinical effect of glucocorticoids on Kaposi sarcoma related to the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1989;110(11):937–40. [PMID: 2719427] <https://pubmed.ncbi.nlm.nih.gov/2719427>
- Grant PM, Komarow L, Andersen J, et al. Risk factor analyses for immune reconstitution inflammatory syndrome in a randomized study of early vs. deferred ART during an opportunistic infection. *PLoS One* 2010;5(7):e11416. [PMID: 20617176] <https://pubmed.ncbi.nlm.nih.gov/20617176>
- Gray F, Bazille C, Adle-Biassette H, et al. Central nervous system immune reconstitution disease in acquired immunodeficiency syndrome patients receiving highly active antiretroviral treatment. *J Neurovirol* 2005;11 Suppl 3:16–22. [PMID: 16540449] <https://pubmed.ncbi.nlm.nih.gov/16540449>
- Haddow(a) LJ, Colebunders R, Meintjes G, et al. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. *Lancet Infect Dis* 2010;10(11):791–802. [PMID: 21029993] <https://pubmed.ncbi.nlm.nih.gov/21029993>
- Haddow(b) LJ, Moosa MY, Easterbrook PJ. Validation of a published case definition for tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS* 2010;24(1):103–8. [PMID: 19926965] <https://pubmed.ncbi.nlm.nih.gov/19926965>
- Hardwick C, White D, Morris E, et al. Montelukast in the treatment of HIV associated immune reconstitution disease. *Sex Transm Infect* 2006;82(6):513–14. [PMID: 17151039] <https://pubmed.ncbi.nlm.nih.gov/17151039>
- Havliv DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med* 2011;365(16):1482–91. [PMID: 22010914] <https://pubmed.ncbi.nlm.nih.gov/22010914>
- Jabs DA, Ahuja A, Van Natta M, et al. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: five-year outcomes. *Ophthalmology* 2010;117(11):2152–61.e1–2. [PMID: 20673591] <https://pubmed.ncbi.nlm.nih.gov/20673591>
- Jabs DA, Ahuja A, Van Natta ML, et al. Long-term outcomes of cytomegalovirus retinitis in the era of modern antiretroviral therapy: results from a United States cohort. *Ophthalmology* 2015;122(7):1452–63. [PMID: 25892019] <https://pubmed.ncbi.nlm.nih.gov/25892019>
- Kambugu A, Meya DB, Rhein J, et al. Outcomes of cryptococcal meningitis in Uganda before and after the availability of highly active antiretroviral therapy. *Clin Infect Dis* 2008;46(11):1694–1701. [PMID: 18433339] <https://pubmed.ncbi.nlm.nih.gov/18433339>
- Karavellas MP, Plummer DJ, Macdonald JC, et al. Incidence of immune recovery vitritis in cytomegalovirus retinitis patients following institution of successful highly active antiretroviral therapy. *J Infect Dis* 1999;179(3):697–700. [PMID: 9952380] <https://pubmed.ncbi.nlm.nih.gov/9952380>
- Konopnicki D, Mocroft A, de Wit S, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS* 2005;19(6):593–601. [PMID: 15802978] <https://pubmed.ncbi.nlm.nih.gov/15802978>
- Lawn SD, Myer L, Bekker LG, et al. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS* 2007;21(3):335–41. [PMID: 17255740] <https://pubmed.ncbi.nlm.nih.gov/17255740>
- Lawn SD, Wood R. Hepatic involvement with tuberculosis-associated immune reconstitution disease. *AIDS* 2007;21(17):2362–63. [PMID: 18090294] <https://pubmed.ncbi.nlm.nih.gov/18090294>
- Lawn(a) SD, Bekker LG, Myer L, et al. Cryptococcal immune reconstitution disease: a major cause of early mortality in a South African antiretroviral programme. *AIDS* 2005;19(17):2050–52. [PMID: 16260920] <https://pubmed.ncbi.nlm.nih.gov/16260920>
- Lawn(b) SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect Dis* 2005;5(6):361–73. [PMID: 15919622] <https://pubmed.ncbi.nlm.nih.gov/15919622>
- Leidner RS, Aboulaflia DM. Recrudescence Kaposi's sarcoma after initiation of HAART: a manifestation of immune reconstitution syndrome. *AIDS Patient Care STDS* 2005;19(10):635–44. [PMID: 16232048] <https://pubmed.ncbi.nlm.nih.gov/16232048>

- Letang E, Lewis JJ, Bower M, et al. Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma: higher incidence and mortality in Africa than in the UK. *AIDS* 2013;27(10):1603–13. [PMID: 23462220] <https://pubmed.ncbi.nlm.nih.gov/23462220>
- Lodi S, del Amo J, Moreno S, et al. Opportunistic infections and AIDS malignancies early after initiating combination antiretroviral therapy in high-income countries. *AIDS* 2014;28(16):2461–73. [PMID: 25265230] <https://pubmed.ncbi.nlm.nih.gov/25265230>
- Longley N, Harrison TS, Jarvis JN. Cryptococcal immune reconstitution inflammatory syndrome. *Curr Opin Infect Dis* 2013;26(1):26–34. [PMID: 23242412] <https://pubmed.ncbi.nlm.nih.gov/23242412>
- Lortholary O, Fontanet A, Mémain N, et al. Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococcosis in France. *AIDS* 2005;19(10):1043–49. [PMID: 15958835] <https://pubmed.ncbi.nlm.nih.gov/15958835>
- Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. *Clin Infect Dis* 2010;50(11):1532–38. [PMID: 20415574] <https://pubmed.ncbi.nlm.nih.gov/20415574>
- Manosuthi W, Mankatitham W, Lueangniyomkul A, et al. Time to initiate antiretroviral therapy between 4 weeks and 12 weeks of tuberculosis treatment in HIV-infected patients: results from the TIME study. *J Acquir Immune Defic Syndr* 2012;60(4):377–83. [PMID: 22592586] <https://pubmed.ncbi.nlm.nih.gov/22592586>
- Marais S, Meintjes G, Pepper DJ, et al. Frequency, severity, and prediction of tuberculous meningitis immune reconstitution inflammatory syndrome. *Clin Infect Dis* 2013;56(3):450–60. [PMID: 23097584] <https://pubmed.ncbi.nlm.nih.gov/23097584>
- Marais S, Wilkinson RJ, Pepper DJ, et al. Management of patients with the immune reconstitution inflammatory syndrome. *Curr HIV/AIDS Rep* 2009;6(3):162–71. [PMID: 19589302] <https://pubmed.ncbi.nlm.nih.gov/19589302>
- Martin-Blondel G, Cuzin L, Delobel P, et al. Is maraviroc beneficial in paradoxical progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome management? *AIDS* 2009;23(18):2545–46. [PMID: 19907215] <https://pubmed.ncbi.nlm.nih.gov/19907215>
- Martinez AE, Frattaroli P, Vu CA, et al. Successful outcome after treatment with cidofovir, vaccinia, and extended course of tecovirimat in a newly-diagnosed HIV patient with severe mpox: a case report. *Vaccines (Basel)* 2023;11(3):650. [PMID: 36992234] <https://pubmed.ncbi.nlm.nih.gov/36992234>
- McComsey GA, Kitch D, Daar ES, et al. Inflammation markers after randomization to abacavir/lamivudine or tenofovir/emtricitabine with efavirenz or atazanavir/ritonavir. *AIDS* 2012;26(11):1371–85. [PMID: 22546988] <https://pubmed.ncbi.nlm.nih.gov/22546988>
- Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis* 2008;8(8):516–23. [PMID: 18652998] <https://pubmed.ncbi.nlm.nih.gov/18652998>
- Meintjes G, Rangaka MX, Maartens G, et al. Novel relationship between tuberculosis immune reconstitution inflammatory syndrome and antitubercular drug resistance. *Clin Infect Dis* 2009;48(5):667–76. [PMID: 19191655] <https://pubmed.ncbi.nlm.nih.gov/19191655>
- Meintjes G, Scriven J, Marais S. Management of the immune reconstitution inflammatory syndrome. *Curr HIV/AIDS Rep* 2012;9(3):238–50. [PMID: 22752438] <https://pubmed.ncbi.nlm.nih.gov/22752438>
- Meintjes G, Stek C, Blumenthal L, et al. Prednisone for the prevention of paradoxical tuberculosis-associated IRIS. *N Engl J Med* 2018;379(20):1915–25. [PMID: 30428290] <https://pubmed.ncbi.nlm.nih.gov/30428290>
- Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS* 2010;24(15):2381–90. [PMID: 20808204] <https://pubmed.ncbi.nlm.nih.gov/20808204>
- Melzani A, de Reynal de Saint Michel R, Ntab B, et al. Incidence and trends in immune reconstitution inflammatory syndrome associated with histoplasma capsulatum among people living with human immunodeficiency virus: a 20-year case series and literature review. *Clin Infect Dis* 2020;70(4):643–52. [PMID: 30921453] <https://pubmed.ncbi.nlm.nih.gov/30921453>
- Mfinanga SG, Kirenga BJ, Chanda DM, et al. Early versus delayed initiation of highly active antiretroviral therapy for HIV-positive adults with newly diagnosed pulmonary tuberculosis (TB-HAART): a prospective, international, randomised, placebo-controlled trial. *Lancet Infect Dis* 2014;14(7):563–71. [PMID: 24810491] <https://pubmed.ncbi.nlm.nih.gov/24810491>
- Müller M, Wandel S, Colebunders R, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2010;10(4):251–61. [PMID: 20334848] <https://pubmed.ncbi.nlm.nih.gov/20334848>

- Namale PE, Abdullahi LH, Fine S, et al. Paradoxical TB-IRIS in HIV-infected adults: a systematic review and meta-analysis. *Future Microbiol* 2015;10(6):1077–99. [PMID: 26059627] <https://pubmed.ncbi.nlm.nih.gov/26059627>
- Narendran G, Andrade BB, Porter BO, et al. Paradoxical tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) in HIV patients with culture confirmed pulmonary tuberculosis in India and the potential role of IL-6 in prediction. *PLoS One* 2013;8(5):e63541. [PMID: 23691062] <https://pubmed.ncbi.nlm.nih.gov/23691062>
- Novak RM, Richardson JT, Buchacz K, et al. Immune reconstitution inflammatory syndrome: incidence and implications for mortality. *AIDS* 2012;26(6):721–30. [PMID: 22233655] <https://pubmed.ncbi.nlm.nih.gov/22233655>
- Odongo FC. Fatal disseminated Kaposi's sarcoma due to immune reconstitution inflammatory syndrome following HAART initiation. *Case Rep Infect Dis* 2013;2013:546578. [PMID: 23936695] <https://pubmed.ncbi.nlm.nih.gov/23936695>
- Ortega-Larrocea G, Espinosa E, Reyes-Terán G. Lower incidence and severity of cytomegalovirus-associated immune recovery uveitis in HIV-infected patients with delayed highly active antiretroviral therapy. *AIDS* 2005;19(7):735–38. [PMID: 15821403] <https://pubmed.ncbi.nlm.nih.gov/15821403>
- Perrella O, Sbreglia C, De Sena R, et al. Immune reconstitution: bad or good factor in hepatitis B virus and HIV co-infection? *AIDS* 2006;20(5):790–91. [PMID: 16514319] <https://pubmed.ncbi.nlm.nih.gov/16514319>
- Phillips P, Bonner S, Gataric N, et al. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. *Clin Infect Dis* 2005;41(10):1483–97. [PMID: 16231262] <https://pubmed.ncbi.nlm.nih.gov/16231262>
- Psichogiou M, Basoulis D, Tsikala-Vafea M, et al. Integrase strand transfer inhibitors and the emergence of immune reconstitution inflammatory syndrome (IRIS). *Curr HIV Res* 2017;15(6):405–10. [PMID: 29173177] <https://pubmed.ncbi.nlm.nih.gov/29173177>
- Rajme-López S, Corral-Herrera EA, Tello-Mercado AC, et al. Clinical, molecular, and histological characteristics of severely necrotic and fatal mpox in HIV-infected patients. *AIDS Res Ther* 2023;20(1):85. [PMID: 38012656] <https://pubmed.ncbi.nlm.nih.gov/38012656>
- Rambeloarisoa J, Batisse D, Thiebaut JB, et al. Intramedullary abscess resulting from disseminated cryptococcosis despite immune restoration in a patient with AIDS. *J Infect* 2002;44(3):185–88. [PMID: 12099747] <https://pubmed.ncbi.nlm.nih.gov/12099747>
- Rasul S, Delapenha R, Farhat F, et al. Graves' disease as a manifestation of immune reconstitution in HIV-infected individuals after initiation of highly active antiretroviral therapy. *AIDS Res Treat* 2011;2011:743597. [PMID: 21804938] <https://pubmed.ncbi.nlm.nih.gov/21804938>
- Robertson J, Meier M, Wall J, et al. Immune reconstitution syndrome in HIV: validating a case definition and identifying clinical predictors in persons initiating antiretroviral therapy. *Clin Infect Dis* 2006;42(11):1639–46. [PMID: 16652323] <https://pubmed.ncbi.nlm.nih.gov/16652323>
- Rodríguez M, Silva-Sánchez FA, Luna-Rivero C, et al. Maraviroc failed to control progressive multifocal leukoencephalopathy-associated IRIS in a patient with advanced HIV infection. *Case Rep Med* 2014;2014:381480. [PMID: 25587282] <https://pubmed.ncbi.nlm.nih.gov/25587282>
- Safdar A, Rubocki RJ, Horvath JA, et al. Fatal immune restoration disease in human immunodeficiency virus type 1-infected patients with progressive multifocal leukoencephalopathy: impact of antiretroviral therapy-associated immune reconstitution. *Clin Infect Dis* 2002;35(10):1250–57. [PMID: 12410486] <https://pubmed.ncbi.nlm.nih.gov/12410486>
- Schrier RD, Song MK, Smith IL, et al. Intraocular viral and immune pathogenesis of immune recovery uveitis in patients with healed cytomegalovirus retinitis. *Retina* 2006;26(2):165–69. [PMID: 16467672] <https://pubmed.ncbi.nlm.nih.gov/16467672>
- Scriven JE, Rhein J, Hullsiek KH, et al. Early ART after cryptococcal meningitis is associated with cerebrospinal fluid pleocytosis and macrophage activation in a multisite randomized trial. *J Infect Dis* 2015;212(5):769–78. [PMID: 25651842] <https://pubmed.ncbi.nlm.nih.gov/25651842>
- Sereti I, Sheikh V, Shaffer D, et al. Prospective international study of incidence and predictors of immune reconstitution inflammatory syndrome and death in people living with human immunodeficiency virus and severe lymphopenia. *Clin Infect Dis* 2020;71(3):652–60. [PMID: 31504347] <https://pubmed.ncbi.nlm.nih.gov/31504347>
- Shankar EM, Vignesh R, Velu V, et al. Does CD4+CD25+foxp3+ cell (Treg) and IL-10 profile determine susceptibility to immune reconstitution inflammatory syndrome (IRIS) in HIV disease? *J Inflamm (Lond)* 2008;5:2. [PMID: 18282273] <https://pubmed.ncbi.nlm.nih.gov/18282273>
- Shelburne SA, Montes M, Hamill RJ. Immune reconstitution inflammatory syndrome: more answers, more questions. *J Antimicrob Chemother* 2006;57(2):167–70. [PMID: 16354748] <https://pubmed.ncbi.nlm.nih.gov/16354748>

- Shelburne(a) SA, Visnegarwala F, Darcourt J, et al. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. *AIDS* 2005;19(4):399–406. [PMID: 15750393] <https://pubmed.ncbi.nlm.nih.gov/15750393>
- Shelburne(b) SA, Darcourt J, White AC, Jr., et al. The role of immune reconstitution inflammatory syndrome in AIDS-related cryptococcus neoformans disease in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2005;40(7):1049–52. [PMID: 15825000] <https://pubmed.ncbi.nlm.nih.gov/15825000>
- Sierra-Madero JG, Ellenberg SS, Rassool MS, et al. Effect of the CCR5 antagonist maraviroc on the occurrence of immune reconstitution inflammatory syndrome in HIV (CADIRIS): a double-blind, randomised, placebo-controlled trial. *Lancet HIV* 2014;1(2):e60–67. [PMID: 26423989] <https://pubmed.ncbi.nlm.nih.gov/26423989>
- Sinha S, Shekhar RC, Singh G, et al. Early versus delayed initiation of antiretroviral therapy for Indian HIV-Infected individuals with tuberculosis on antituberculosis treatment. *BMC Infect Dis* 2012;12:168. [PMID: 22846195] <https://pubmed.ncbi.nlm.nih.gov/22846195>
- Stover KR, Molitorisz S, Swiatlo E, et al. A fatal case of Kaposi sarcoma due to immune reconstitution inflammatory syndrome. *Am J Med Sci* 2012;343(5):421–25. [PMID: 22227511] <https://pubmed.ncbi.nlm.nih.gov/22227511>
- Summers NA, Kelley CF, Armstrong W, et al. Not a disease of the past: a case series of progressive multifocal leukoencephalopathy in the established antiretroviral era. *AIDS Res Hum Retroviruses* 2019;35(6):544–52. [PMID: 30834775] <https://pubmed.ncbi.nlm.nih.gov/30834775>
- Tan K, Roda R, Ostrow L, et al. PML-IRIS in patients with HIV infection: clinical manifestations and treatment with steroids. *Neurology* 2009;72(17):1458–64. [PMID: 19129505] <https://pubmed.ncbi.nlm.nih.gov/19129505>
- Török ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. *Clin Infect Dis* 2011;52(11):1374–83. [PMID: 21596680] <https://pubmed.ncbi.nlm.nih.gov/21596680>
- Uthman OA, Okwundu C, Gbenga K, et al. Optimal timing of antiretroviral therapy initiation for HIV-infected adults with newly diagnosed pulmonary tuberculosis: a systematic review and meta-analysis. *Ann Intern Med* 2015;163(1):32–39. [PMID: 26148280] <https://pubmed.ncbi.nlm.nih.gov/26148280>
- Valin N, Pacanowski J, Denoed L, et al. Risk factors for 'unmasking immune reconstitution inflammatory syndrome' presentation of tuberculosis following combination antiretroviral therapy initiation in HIV-infected patients. *AIDS* 2010;24(10):1519–25. [PMID: 20549841] <https://pubmed.ncbi.nlm.nih.gov/20549841>
- Volkow P, Cesarman-Maus G, Garciadiego-Fossas P, et al. Clinical characteristics, predictors of immune reconstitution inflammatory syndrome and long-term prognosis in patients with Kaposi sarcoma. *AIDS Res Ther* 2017;14(1):30. [PMID: 28558783] <https://pubmed.ncbi.nlm.nih.gov/28558783>
- Volkow P, Cornejo P, Zinser JW, et al. Life-threatening exacerbation of Kaposi's sarcoma after prednisone treatment for immune reconstitution inflammatory syndrome. *AIDS* 2008;22(5):663–65. [PMID: 18317012] <https://pubmed.ncbi.nlm.nih.gov/18317012>
- von Both U, Laffer R, Grube C, et al. Acute cytomegalovirus colitis presenting during primary HIV infection: an unusual case of an immune reconstitution inflammatory syndrome. *Clin Infect Dis* 2008;46(4):e38–40. [PMID: 18199043] <https://pubmed.ncbi.nlm.nih.gov/18199043>
- Walker NF, Scriven J, Meintjes G, et al. Immune reconstitution inflammatory syndrome in HIV-infected patients. *HIV AIDS (Auckl)* 2015;7:49–64. [PMID: 25709503] <https://pubmed.ncbi.nlm.nih.gov/25709503>
- Warner NC, Shishido A, Fulco PP, et al. Immune reconstitution inflammatory syndrome due to monkeypox in two patients with AIDS. *AIDS* 2023;37(7):1187–88. [PMID: 37139659] <https://pubmed.ncbi.nlm.nih.gov/37139659>
- Wijting IEA, Wit FW, Rokx C, et al. Immune reconstitution inflammatory syndrome in HIV infected late presenters starting integrase inhibitor containing antiretroviral therapy. *EClinicalMedicine* 2019;17:100210. [PMID: 31891143] <https://pubmed.ncbi.nlm.nih.gov/31891143>
- Zhao Y, Hohlfeld A, Namale P, et al. Risk of immune reconstitution inflammatory syndrome with integrase inhibitors versus other classes of antiretrovirals: a systematic review and meta-analysis of randomized trials. *J Acquir Immune Defic Syndr* 2022;90(2):232–39. [PMID: 35175970] <https://pubmed.ncbi.nlm.nih.gov/35175970>
- Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One* 2009;4(5):e5575. [PMID: 19440326] <https://pubmed.ncbi.nlm.nih.gov/19440326>

Supplement: Guideline Development and Recommendation Ratings

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program

Developer	New York State Department of Health AIDS Institute (NYSDOH AI) Clinical Guidelines Program
Funding source	NYSDOH AI
Program manager	Clinical Guidelines Program, Johns Hopkins University School of Medicine, Division of Infectious Diseases. See Program Leadership and Staff .
Mission	To produce and disseminate evidence-based, state-of-the-art clinical practice guidelines that establish uniform standards of care for practitioners who provide prevention or treatment of HIV, viral hepatitis, other sexually transmitted infections, and substance use disorders for adults throughout New York State in the wide array of settings in which those services are delivered.
Expert committees	The NYSDOH AI Medical Director invites and appoints committees of clinical and public health experts from throughout New York State to ensure that the guidelines are practical, immediately applicable, and meet the needs of care providers and stakeholders in all major regions of New York State, all relevant clinical practice settings, key New York State agencies, and community service organizations.
Committee structure	<ul style="list-style-type: none"> • Leadership: AI-appointed chair, vice chair(s), chair emeritus, clinical specialist(s), JHU Guidelines Program Director, AI Medical Director, AI Clinical Consultant, AVAC community advisor • Contributing members • Guideline writing groups: Lead author, coauthors if applicable, and all committee leaders
Disclosure and management of conflicts of interest	<ul style="list-style-type: none"> • Annual disclosure of financial relationships with commercial entities for the 12 months prior and upcoming is required of all individuals who work with the guidelines program, and includes disclosure for partners or spouses and primary professional affiliation. • The NYSDOH AI assesses all reported financial relationships to determine the potential for undue influence on guideline recommendations and, when indicated, denies participation in the program or formulates a plan to manage potential conflicts. Disclosures are listed for each committee member.
Evidence collection and review	<ul style="list-style-type: none"> • Literature search and review strategy is defined by the guideline lead author based on the defined scope of a new guideline or update. • A comprehensive literature search and review is conducted for a new guideline or an extensive update using PubMed, other pertinent databases of peer-reviewed literature, and relevant conference abstracts to establish the evidence base for guideline recommendations. • A targeted search and review to identify recently published evidence is conducted for guidelines published within the previous 3 years. • Title, abstract, and article reviews are performed by the lead author. The JHU editorial team collates evidence and creates and maintains an evidence table for each guideline.
Recommendation development	<ul style="list-style-type: none"> • The lead author drafts recommendations to address the defined scope of the guideline based on available published data. • Writing group members review the draft recommendations and evidence and deliberate to revise, refine, and reach consensus on all recommendations. • When published data are not available, support for a recommendation may be based on the committee’s expert opinion. • The writing group assigns a 2-part rating to each recommendation to indicate the strength of the recommendation and quality of the supporting evidence. The group reviews the evidence, deliberates, and may revise recommendations when required to reach consensus.

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program

Review and approval process	<ul style="list-style-type: none"> Following writing group approval, draft guidelines are reviewed by all contributors, program liaisons, and a volunteer reviewer from the AI Community Advisory Committee. Recommendations must be approved by two-thirds of the full committee. If necessary to achieve consensus, the full committee is invited to deliberate, review the evidence, and revise recommendations. Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication.
External reviews	<ul style="list-style-type: none"> External review of each guideline is invited at the developer’s discretion. External reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback.
Update process	<ul style="list-style-type: none"> JHU editorial staff ensure that each guideline is reviewed and determined to be current upon the 3-year anniversary of publication; guidelines that provide clinical recommendations in rapidly changing areas of practice may be reviewed annually. Published literature is surveilled to identify new evidence that may prompt changes to existing recommendations or development of new recommendations. If changes in the standard of care, newly published studies, new drug approval, new drug-related warning, or a public health emergency indicate the need for immediate change to published guidelines, committee leadership will make recommendations and immediate updates and will invite full committee review as indicated.

Table S2: Recommendation Ratings and Definitions

Strength	Quality of Evidence	
A: Strong B: Moderate C: Optional	1	Based on published results of at least 1 randomized clinical trial with clinical outcomes or validated laboratory endpoints.
	*	Based on either a self-evident conclusion; conclusive, published, in vitro data; or well-established practice that cannot be tested because ethics would preclude a clinical trial.
	2	Based on published results of at least 1 well-designed, nonrandomized clinical trial or observational cohort study with long-term clinical outcomes.
	2†	Extrapolated from published results of well-designed studies (including nonrandomized clinical trials) conducted in populations other than those specifically addressed by a recommendation. The source(s) of the extrapolated evidence and the rationale for the extrapolation are provided in the guideline text. One example would be results of studies conducted predominantly in a subpopulation (e.g., one gender) that the committee determines to be generalizable to the population under consideration in the guideline.
	3	Based on committee expert opinion, with rationale provided in the guideline text.