

Immune Reconstitution Syndrome: When Patient Deteriorates After Starting Highly Active Antiretroviral Therapy

Jintanat Ananworanich, M.D.*

Praphan Phanuphak, M.D.*,**

Kiat Ruxrungtham, M.D.*,**

ABSTRACT

Immune reconstitution syndrome (IRS) is an overwhelming immunological response to latent antigens (infection or autoantigen) after the introduction of highly active antiretroviral therapy (HAART). This immunological response usually occurs in some patients with advanced HIV disease and low baseline CD4, and results in tissue destruction. Diagnosis is by exclusion of other illnesses, especially active opportunistic infections (OI) and antiretroviral drug-related toxicity. Diagnosis and control of active OI prior to HAART initiation may prevent IRS. The mainstay of treatment is immunosuppressive therapy especially corticosteroids. (*J Infect Dis Antimicrob Agents* 2003;20:109-18.)

INTRODUCTION

Since the introduction of highly active antiretroviral therapy (HAART), human immunodeficiency virus (HIV) disease is now a chronic disease. Patients are expected to live a normal life expectancy and be in good health. The tides have turned from treating patients for opportunistic infections (OI) and acquired immunodeficiency syndrome (AIDS) to treating problems related to short- and long-term effects of HAART. Lipodystrophy and metabolic imbalances are examples of long-term side effects. Common short-term effects of treatment are gastrointestinal and dermatological side effects.

Immune reconstitution syndrome (IRS) represents an important HAART-related adverse event that usually occurs early after HAART initiation and can cause death and long-term consequences if undetected. Understanding this condition will aid appropriate diagnosis and treatment and help patients follow the road to good health.¹

Definition

IRS is an exaggerated immune response to a latent antigen, an OI antigen or autoantigen, during the immune recovery period after HAART.

*The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT) and The Thai Red Cross AIDS Research Center, 104 Rajdumri Road, Pathumwan, Bangkok 10330, Thailand.

**Allergy and Clinical Immunology Section, Department of Internal Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

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Reprint requests: Jintanat Ananworanich, M.D., HIV-NAT, 104 Rajdumri Road, Pathumwan, Bangkok 10330, Thailand.

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Etiology

After HAART, two phases of CD4 T cell increase occur. A first-phase cellular increase occurs within the first 8-12 weeks when viral replication is markedly reduced. There is an increase mainly in memory CD4 cells (CD4+45RO+) as a result of redistribution from the lymph nodes, which experience a decrease in cellular adhesion molecules and undergo apoptosis. Memory CD4 cells recognize pre-exposed antigens such as latent pathogens. A second, slower phase of CD4 increase is from newly produced CD4 cells from the thymus. These are naïve CD4 T cells (CD4+CD45RA+), which have the capability to respond to new antigens. There is significant improvement of CD4 and CD8 T cell function as well. Immune response against previously encountered antigens are more brisk following HAART.²⁻⁴ An increased number of antigen-specific peripheral blood mononuclear cells and increased production of interferon- γ , interleukin-2 and interleukin-12 in response to a host of organisms after initiation of HAART occurs.^{5,6} HAART results in reversal of anergy to pre-exposed antigens on delayed hypersensitivity skin testing.⁶ HIV RNA (viral load) reduction following HAART lowers the destruction of CD4 and inappropriate immune activation and boosts T cell functions.

In patients with low baseline CD4 and advanced HIV disease, the increases in CD4 count and function can be very extensive and very fast especially with the memory CD4 T cell population.⁷ If such an overwhelming immune response encounters opportunistic organisms or autoantigens previously ignored in the immunosuppressed state, the result is an exaggerated attack on the tissues where these antigens reside causing tissue inflammation and destruction (Figure 1).

Who is at risk?

The typical patient has advanced HIV disease with a low pre-HAART CD4 and exhibits a dramatic increase in CD4 and/or reduction of viral load after HAART.^{8,9} The patient may be on OI treatment or

may have had completed the treatment.¹⁰

Clinical manifestation

IRS typically manifests as symptoms of OI (if the trigger is an organism) or autoimmune disease (if the trigger is an autoantigen). OI is more common, and when investigated, reveals culture-negative OI. IRS should be suspected in a patient who is on treatment for OI and manifests worsening of symptoms after a previous successful control. Other patients may have a recurrence of symptoms in a previously diagnosed and treated OI. Although, recurred symptoms usually follow the same pattern as previous episodes, they can occur at different sites as well. Examples are patients with previous cryptococcal meningitis developing IRS-cryptococcal lymphadenitis.¹¹ IRS tends to develop early after HAART initiation (within 2 months) but can develop later in some cases. The latter includes Graves disease and leukoencephalopathy.^{12,13}

Most of IRS reports are small case series. Examples of IRS manifestations are described below.

IRS-related tuberculosis

The most reported IRS manifestation termed a "paradoxical reaction", is IRS-associated *Mycobacterium tuberculosis*.¹⁴ Paradoxical tuberculosis reaction can occur regardless of HIV status and antiretroviral (ARV) treatment. In the pre-HAART era, most HIV-infected patients with the paradoxical reaction were those with extrapulmonary tuberculosis where the cause was attributed to partial immune recovery following anti-tuberculosis therapy.¹⁵ Since the introduction of HAART, the incidence of paradoxical reaction has risen significantly to around 30-40 percent in cohorts of advanced HIV patients compared to 7 percent in historical control when only anti-tuberculosis agents were used.^{16,17}

Wendel KA et al described some distinctive features between the paradoxical reaction in HAART-treated and untreated patients: 1) patients on HAART had a more rapid onset of paradoxical

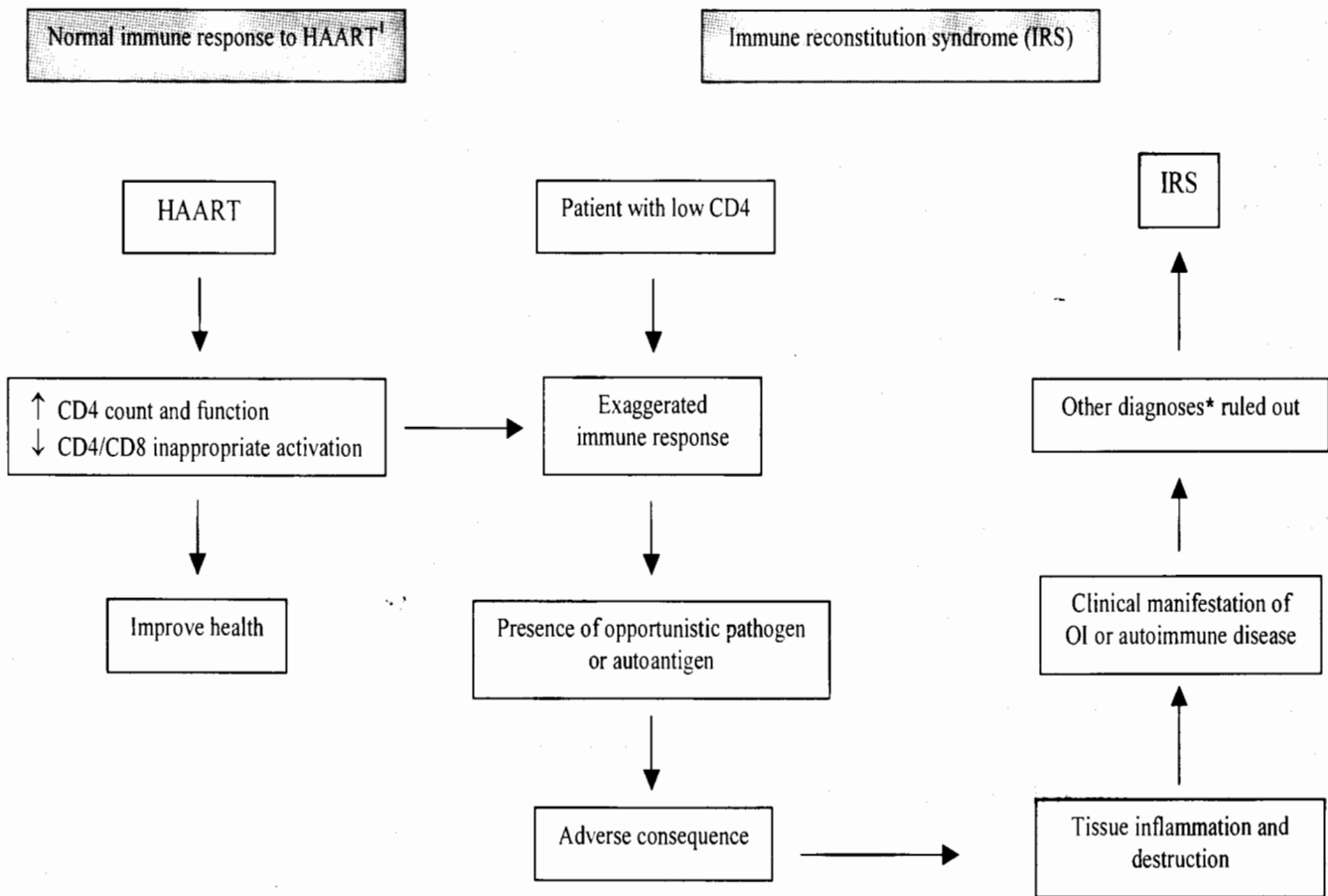


Figure 1. Pathogenesis of immune reconstitution syndrome.

Note: HAART=highly active antiretroviral therapy, OI=opportunistic infection, *Examples are active OI, OI or HAART treatment failure, antiretrovirals side effects

worsening (within 4 weeks of starting HAART and tuberculosis treatment compared to 4 to 10 weeks after tuberculosis treatment), 2) patients on HAART had more severe symptoms, usually large abscesses requiring surgical intervention.¹⁸

Furrer H et al described a male patient with liver and intestinal tuberculosis who started HAART 4 weeks after anti-tuberculosis agents. Two weeks after HAART, high fever, abdominal pain and hepatosplenomegaly developed. CT scan showed hepatosplenomegaly and enlarged abdominal lymph nodes. Repeat cultures of initial infected sites were negative. Signs and symptoms resolved within 10 days when corticosteroids were added to the therapy. After 3 months on HAART, the CD4 count increased from 25 to 70 cells/mm³ and viral load decreased from more

than 750,000 to 236 copies/ml.¹⁹ Biopsy of enlarged lymph nodes in these cases is culture-negative with granulomatous inflammation, and acid fast bacilli organisms are usually seen.^{15,17,19}

In patients treated with HAART, the time between the initiation of tuberculosis treatment and HAART may affect the likelihood of paradoxical reaction. Navas E et al found that patients who had paradoxical reaction had a median time 22.5 days between tuberculosis treatment and HAART, compared to 110 days in patients who did not have paradoxical reaction.¹⁷ Lower pre-HAART CD4, and higher median CD4 count increase and/or viral load reduction in response to HAART are seen more in patients with paradoxical reaction compared to those without.^{14,18} In a prospective study of 33 HIV-infected patients treated

with both antituberculosis agents and HAART, Narita M et al found that a reduction of viral load without a corresponding increase of CD4 after HAART predicted the risk for paradoxical reaction. In this cohort, patients with paradoxical reaction were more likely to have a reversal of their purified protein derivatives anergy.¹⁶

Paradoxical tuberculosis occurs within the first 2 months of HAART following an apparent initial control of infection.¹⁸ It can involve extrapulmonary sites, and multiple episodes can occur.²⁰ The addition of corticosteroids to antituberculosis agents and HAART result in rapid improvement. Temporary discontinuation of HAART may be required to control the exaggerated immune reaction to the *M. tuberculosis*.

IRS-related *Pneumocystis carinii* pneumonia (PCP)

Transient clinical deterioration in HIV patients with PCP after starting HAART is well known and occurs in about 20 percent of patients.²¹ IRS-related PCP usually develops within the first 2 to 3 weeks after HAART.²¹⁻²³

Wislez M et al reported 3 out of 65 patients treated for PCP who developed acute respiratory failure after HAART.²² These 3 patients shared the same pre-HAART characteristics i.e. low CD4 count, high viral load and advanced PCP with hypoxemia. After cotrimoxazole and corticosteroids was added to the treatment regimen, their PCP symptoms resolved within 2 weeks. HAART was then started with excellent response. In one patient, the CD4 rose by 31 cells/mm³ and the viral load reduced from 140,000 copies/ml to an undetectable level within a period of 2 weeks. Within 3 weeks, IRS-related acute respiratory failure occurred.²² Investigation showed bronchoalveolar lavage fluid with 1 million cells, predominantly lymphocytes, and a few *P. carinii* cysts. Lung biopsy showed an intense cellular infiltration of both CD4 and CD8 T cells. Alternative anti-PCP agents and other anti-infective agents were used without improvement. The patient responded to stopping HAART for 2 weeks

and corticosteroid treatment.²²

Dean GL et al retrospectively reviewed PCP cases treated with HAART and found that 3 out of 10 cases had IRS-related PCP. All three had advanced HIV disease with a baseline median CD4 count of 26 cells/mm³ and a viral load of 5.5 log. They started HAART after 2 weeks on anti-PCP agents with apparently good control and had a dramatic response to HAART, with a median viral load drop of 2.6 log and a median CD4 rise of 36 cells/mm³ within 2 weeks. At a median time of 5 days after starting HAART, acute respiratory failure developed. Bronchoalveolar lavage revealed only *P. carinii* cysts. All patients responded to corticosteroids and alternative anti-PCP agents.²¹ Patients can develop IRS-related acute respiratory failure even if they had minimal PCP symptoms initially.²³

Treatment of PCP results in a rapid clearance of *P. carinii* larva. However, *P. carinii* cysts can be present longer, leaving small amounts of antigens to trigger IRS.²³

IRS-related cryptococcosis

IRS-related cryptococcosis occurs as sterile meningitis, increased intracranial pressure, cerebral infarction, lymphadenitis and pulmonary abscesses.^{10, 11, 24} Blanche P et al reported two patients previously treated for cryptococcal meningitis who developed culture-negative cryptococcal lymphadenitis while taking HAART and appropriate secondary prophylaxis for cryptococcus. Both patients responded dramatically to treatment with corticosteroids after not responding to amphotericin treatment.¹¹

Jenny-Avital ER et al did a retrospective review of patients at risk of IRS-related cryptococcosis. These patients had a history of culture-positive cryptococcal infection prior to HAART and a good virological response to HAART (viral load < 50 copies/ml or viral reduction of more than 3 log). Of these 10 patients, five had IRS-related cryptococcosis approximately 1-2 months after HAART and while on fluconazole

maintenance. All five had significant reduction in viral load, but only 3 had marked increases of CD4. The IRS manifestations varied; two had relapse of meningitis with typical symptoms (mild pleocytosis, high cerebrospinal fluid pressure, low cryptococcal serum titers, and negative india ink and culture) and the other three had granulomatous inflammation of the lungs and lymph nodes. Biopsy specimens showed pathogens consistent with *Cryptococcal neoformans*; however, cultures were negative.¹⁰ In this report, there was no difference in the characteristics of patients who did and did not develop IRS. Unlike to most IRS reports, all five patients recovered without the need for immunosuppressive therapy with corticosteroids; two recovered spontaneously and three recovering after amphotericin retreatment. It has been shown that serial lumbar punctures significantly relieve symptoms of increased intracranial pressure associated with cryptococcal meningitis.

IRS-related hepatitis B and C

The prevalence of HIV and hepatitis B virus coinfection differ in various parts of the world, e.g. in Thailand, the adult prevalence is usually close to 10 percent.²⁵ When such patients start HAART, there is a risk for hepatitis B reactivation.²⁶ Proia LA et al reported two patients with HIV-hepatitis B coinfection who had deterioration in the liver enzymes and a rise in serum hepatitis B DNA levels which coincided with the increase in CD4 count and decrease in viral load after starting HAART. Both patients had low mean CD4 counts of 10 cells/mm³, negative hepatitis E antigen and normal transaminases before starting HAART. The onset of IRS-related acute hepatitis were 4 and 19 months after HAART in the first and second patients respectively. Similar to other IRS reports, both patients had responded well to HAART with significant rise in CD4 count and drop in viral load. Liver biopsy showed portal and lobular hepatitis of mixed cellularity which most probably due to a cytotoxic T cell response against hepatitis

B antigen. In one patient, the transaminases returned to baseline and the hepatitis B DNA returned to undetectable level three months after stopping HAART, and the symptoms did not recur after re-starting HAART. The other patient unfortunately died shortly after developing acute liver failure.²⁷ Similarly, patients with HIV and hepatitis C virus coinfection can experience reactivation of hepatitis C.^{8,28} Other manifestations such as enteropathy have also been reported.^{29,30}

IRS-related cytomegalovirus (CMV) eye diseases

CMV eye disease, usually termed immune recovery uveitis (IRU), is a leading cause of blindness in patients with CMV retinitis treated with HAART.³¹⁻³³ IRU a severe inflammatory reaction to CMV antigen as a result of immune recovery and includes vitreous haze, cataract, vitreous hemorrhage, epiretinal membrane, and edema of the optic disc and the macular. IRU occurs within the first few weeks to months after HAART and only in eyes with CMV retinitis.³⁴ Symptoms include floaters and decreased vision. The differential diagnosis includes complications from ganciclovir intraocular injection and implantation. Interestingly, when IRU occurs, CMV retinitis is often inactive. Patients who developed IRU usually show favorable HAART response including high CD4 count and low viral load. Strong specific CMV lymphocyte proliferative responses are the likely cause of IRU. Patients with significant involvement of CMV retinitis have a higher chance of developing IRU likely due to the higher CMV antigenic load.³⁵ Biopsy of epiretinal membrane revealed predominant T lymphocytes infiltration and presence of CMV DNA.³⁶ IRU can be self-limiting. Treatment with corticosteroids has been successful in small case series. Oral and topical corticosteroids appear to work well without triggering CMV retinitis relapse, however, corticosteroid complications such as cataracts need to be monitored. Anti-CMV agents may be used concomitantly in order to decrease the CMV load.^{37,38} It is important to

continue long-term HAART as this has been shown to keep CMV retinitis from relapsing.³⁹

IRS-related Guillain-Barre syndrome (GBS)

Following HAART, demyelination can occur and is probably caused by clonal expansion of T cells with self destruction or from pathogens resulting in the breakdown of blood-nerve barrier. Makela P et al reported one man with GBS associated with HIV seroconversion who then develop recurrent GBS one month after starting HAART. He had a significant response to HAART with the CD4 count increasing by 424 cells/mm³ and the viral load reduced from 217,075 to less than 50 copies/ml. He had a poor response to intravenous immunoglobulin, corticosteroids was commenced resulting in CD4 decline and gradual improvement of GBS.⁹

IRS-related Graves' disease

Graves' disease is an example of autoimmunity occurring in the setting of immune restoration after highly active antiretroviral therapy.¹² Graves' disease can occur late after HAART. Patients with IRS-related Graves' disease have similar clinical and laboratory manifestations and are treated in the same way as non-IRS-related Graves. Other autoimmune diseases can be associated with Graves' disease. Sereti I et al reported a man with a pre-HAART CD4 count of 64 cells/mm³ and a viral load of two million copies/ml. Two months after starting HAART, he developed alopecia universalis, an autoimmune disease with T lymphocytes targeting follicular autoantigen. He had a dramatic response to HAART with an increase of the CD4 count to 694 cells/mm³ and a marked suppression of viral load after only one month on HAART. Two years later, he developed Graves' disease which was successfully treated with ¹³¹Iodide.¹²

Diagnosis

IRS is a diagnosis of exclusion. Conditions that can result in worsening of symptoms after HAART

must be excluded. Important examples are

1. Active OI

Untreated OI can manifest during the first 3 months of HAART initiation. Similar to IRS, these patients often have advanced HIV disease with an immune system that fails to recognize latent antigens. Although previously subclinical, they harbor highly infectious load; therefore, soon after HAART, the recovered immunity attacks the infection site revealing the OI. This has been shown in tuberculosis, *Mycobacterium avium* complex (MAC), CMV retinitis and cryptococcal meningitis.^{7,17,24} The important distinction between active OI and IRS is the documentation of a positive culture or a substantial amount of infectious organisms on biopsy samples in active OI. Appropriate treatment for the OI should control the infection.

2. OI treatment failure

When OI treatment fails to control symptoms especially if active OI was documented, the causes of OI treatment failure other than IRS need to be considered as drug resistance, one of the most common causes especially for tuberculosis. Non-compliance, prevalence of drug resistance organisms in the community, and cultures and drug susceptibility testing should help document OI treatment resistance.

3. Side effects from ARV

ARV-related side effects usually occur in the first 1 to 2 months after HAART. Headache shortly after starting HAART in a patient with previous cryptococcal meningitis may suggest IRS. The relationship between the time of drug ingestion and time of onset of symptoms, the characteristic symptoms and response to supportive treatment are evidence for ARV-related side effects. Side effects from ARV may subside spontaneously, by lowering the dose or by switching the culprit drug to a different one. Some other ARV side effects; may occur late as with GBS due to nucleoside analog-related mitochondrial toxicity.⁴⁰ This can mimic IRS-related GBS although in IRS, it usually develop soon after HAART initiation.⁹

4. HAART treatment failure from resistance development

Any HIV-infected person has a risk of developing HAART treatment failure if he or she was infected with a resistant viral strain or, more commonly, had poor adherence. Treatment failure usually occurs after 6 months on HAART. Symptoms from HIV-related illnesses are seen. A declining in CD4 count and an increasing in viral load should prompt the physician to think of HAART failure rather than IRS.

IRS should be considered in the following patients:

1. Favorable response after HAART defined as significant increases of CD4 cell counts and/or decreases of viral load
2. Symptoms consistent with an OI, or with autoimmune disease
3. Work up for OI shows culture-negative. Biopsy shows inflammatory cells infiltration and tissue destruction with no or only small amounts of organisms.
4. Poor response to appropriate OI treatment

5. Good response to corticosteroids

IRS Treatment

IRS treatment is provided to dampen down the immune response (Table 1). This can be done by using immunosuppressive agents such as corticosteroids. A dose of 1 to 2 mg/kg/day is suggested, sometimes up to 12 weeks.^{11,14,19} Since most patients develop IRS while on HAART and OI therapy, corticosteroids are added to the current therapy. Patients should continue OI treatment according to the standard period or longer. In patients who have already stopped OI treatment, reintroduction of such therapy may help lower the antigen load such as in herpes zoster infection or cryptococcosis.

Prevention of IRS may be achieved by delaying the initiation of HAART until the OI is in controlled.²¹ The amount of time needed prior to initiation of HAART is unclear.²² At least 2 weeks of tuberculosis treatment before starting HAART has been proposed.²⁰ A period of 2 months between treatment is

Table 1. Preventative and treatment strategies for immune reconstitution syndrome.

Strategies	Rationale
Prevention	
Delay HAART initiation after OI control	No or little infection to induce inflammatory response
Co-administration of corticosteroids with OI treatment	Suppress inflammatory response
Continuing anti-infective agents for longer than the standard treatment periods	Reduce infectious load until sustained immune recover is seen
Treatment	
Corticosteroids	Suppress inflammatory response
Temporary discontinuation of HAART	Lower number and function of CD4 capable of causing inflammatory response
Specific treatment for IRS disease	Treat consequence of IRS such as anti-thyroid agents in Graves' disease
Supportive care	Providing care to alleviate symptoms

Note: HAART = highly active antiretroviral therapy, OI = opportunistic infections

sufficient to lower the risk of most IRS-related OI. In patients who present with severe OI, however, early initiation of HAART may be crucial for patients' recovery. The physician must balance HAART treatment between the risks and benefits.

Prior to starting HAART in patients with a low CD4 count, a detailed history and physical examination is required to detect latent OI and initiate treatment. A routine ophthalmologic examination in patients with a CD4 less than 50 cells/mm³ to detect CMV retinitis is recommended. Patients should have appropriate primary and secondary prophylaxis for OI prior to HAART initiation.

Generally, HAART should only be stopped if the addition of corticosteroids fail to control IRS.⁸ In patients who have stopped HAART temporarily, HAART should be reintroduced after resolution of IRS when a recurrence is unlikely.²⁷ Supportive treatment for symptoms related to IRS cannot be overlooked. For examples, pain management and serial lumbar puncture can provide great relief for patients with increased intracranial pressure associated with IRS-related cryptococcal meningitis.

CONCLUSION

IRS is a syndrome of tissue destruction resulting from an overwhelming immune response to a latent antigen that usually occurs in an HIV-infected individual with advanced disease after commencing HAART. Other diagnoses should be excluded, especially active OI and drug-related toxicity. Diagnosis and control of active OI prior to starting HAART may prevent IRS. Corticosteroids is the mainstay therapy.

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