

What's New in ...

DANIEL L. O'DONOGHUE, PA-C, PhD; TARA GLEAVES, PA-C, MHS; MICHELLE R. SALVAGGIO, MD, FACP

... HIV/AIDS TREATMENT

IRIS complicates recovery of immune status

Patients being treated for immune system diseases are expected to improve as the treatment progresses. However, recent guidelines and the medical literature show that an inflammatory process that poses a significant threat to these patients can occur even though their immune status is improving.^{1,3} Guidelines from a few years ago recognized the importance of reconstituting immune function to prevent opportunistic infections.⁴ In the past several years, a growing number of papers have described this inflammatory reaction to antiretroviral treatment in patients infected with HIV. The phenomenon is referred to as *immune reconstitution inflammatory syndrome (IRIS)*^{5,6} or *immune restoration disease*.⁷

The onset of IRIS symptoms can occur as early as 1 week after the initiation of antiretroviral treatment. Yet, symptoms may also manifest as late as 1 year or more after initiation of treatment. More than 75% of patients symptomatic for IRIS, however, will have manifestations within 90 days of starting antiretroviral therapy.^{2,3}

Pathogenesis The constellation of issues that arise as a result of immune reconstitution are driven by pathogen and host-specific factors.^{2,5,8} Whereas reduced CD4⁺ T cells lie at the heart of HIV pathology, IRIS may be a manifestation of immune regulators in addition to pathogen-specific reactions. IRIS has two characteristic presentations or classifications: *unmasking* and *paradoxical*.^{3,5} Both represent symptoms that manifest as immune function begins to improve and cells in the immune system are restored.

In the **unmasking presentation**, the patient has an unrecognized infection or neoplasm that, consequently, is not being treated. The symptoms of the infection or skin lesions increase as antiretroviral therapy reestablishes immune func-

tion. The goal is to identify the underlying infectious agent and administer appropriate treatment. Commonly unmasked conditions are tuberculosis, *Mycobacterium avium* infection, and leprosy.^{3,5,7,9}

In the **paradoxical reaction**, the patient is receiving appropriate therapy for a recognized infection. However, as the immune deficiency is corrected, the symptoms of the infection worsen. This causes concern as other causes for the worsening symptoms must be ruled out. The antimicrobial therapy may not have been optimal, and the worsening symptoms indicate the breakthrough of a resistant agent.

All clinicians should be aware that IRIS is a fairly common result of treatments that increase immune function in patients with HIV/AIDS. However, certain underlying conditions may further increase a patient's risk of developing IRIS.^{3,5,6} The inflammatory reaction is more likely to occur in patients with higher disease burden at the start of treatment. If the CD4⁺ T cell count is low—certainly less than 200 cells/ μ L, but most likely less than 50 cells/ μ L—and the viral load is high—100,000 HIV viral copies/ μ L or more—the patient is more likely to have the reaction. Ironically, the faster the immune system clears the viral load in HIV-infected patients, the greater the risk of developing IRIS.³ A patient who is antiretroviral naive is more likely to develop symptoms.

This **case report** illustrates the phenomenon. Infectious disease specialists treated a 30-year-old woman with HIV/AIDS and pulmonary *M avium* infection with ethambutol, clarithromycin, efavirenz, zidovudine, and lamivudine while she was in the hospital. In clinic approximately 3 months later, her HIV viral load was reduced but still detectable. Resistance typing indicated the HIV was resistant to lamivudine. Her antiretrovirals were changed to abacavir, tenofovir, darunavir, and ritonavir. Following this change, her HIV viral load decreased from 10 million HIV RNA

TAKE-HOME POINTS

- Improving immune function can be associated with an inflammatory process that poses a significant threat to patients even though their immune status is improving.
- The onset of immune reconstitution inflammatory syndrome (IRIS) symptoms can occur as early as 1 week after the initiation of antiretroviral treatment. Yet, symptoms may also manifest as late as 1 year or more after treatment initiation.
- IRIS is estimated to affect approximately one-quarter of patients who start antiretroviral therapy.
- A paradoxical worsening of symptoms has been noted with other disease processes that are similar to HIV infection. Thus, although most of the information we have focuses on HIV, the implications for IRIS may be broader.

The authors work at the College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City. **Daniel O'Donoghue** is a professor in the Department of Family and Preventive Medicine. **Tara Gleaves** works in the Department of Internal Medicine, Section of Infectious Diseases. **Michelle Salvaggio** is Assistant Professor, Department of Internal Medicine, Section of Infectious Diseases. All have indicated no relationships to disclose relating to the content of this article.

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copies/ μL of blood plasma to 4,000 copies in 1 month; and her CD4^+ count increased from 134 to 176 cells/ μL . Within a few more weeks, she presented to her primary care provider with worsening shortness of breath and pleuritic chest pain. She was readmitted to the hospital, and bronchoscopy reconfirmed infection with *M avium*. The patient experienced a paradoxical worsening of symptoms brought on by the recurring *M avium* infection. This type of phenomenon is becoming more common in this era of highly active antiretroviral therapy.^{2,4}

IRIS is not an obscure reaction or an occasional occurrence. It is estimated to affect approximately one-quarter of patients who start antiretroviral therapy, especially those patients placed on effective antiretroviral therapy who experience at least a log rhythmic reduction in HIV viral burden.

As an inflammatory response, IRIS is self-limiting. An increase in mortality associated with onset is not apparent, but morbidity and symptoms may require hospitalization to institute supportive measures.³ Obviously, this would pose a bigger threat in the setting of limited resources or in areas with tremendous disease burden.

MANIFESTATIONS OF IRIS

The list of conditions that can be affected by the reconstitution of immune function is extensive.^{2,4} Tuberculosis and infection with cytomegalovirus, *M avium*, or *Cryptococcus neoformans* are some of the most common conditions that are complicated by the initiation of antiretroviral medications. Cryptococcal meningitis is also a fairly common exacerbation and can be devastating. A number of disease processes have cutaneous components (such as herpes simplex or zoster, molluscum contagiosum, and genital warts [human papillomavirus]). Autoimmune diseases (thyroiditis, systemic lupus, and autoimmune alopecia) manifest with worsening symptoms. A number of inflammatory diseases (sarcoidosis and folliculitis) may become symptomatic. Lastly, neoplasias have been associated with IRIS and include exacerbations of lung cancer, lymphoma, and Kaposi sarcoma.

Management options for patients with IRIS are not well-established.⁵ Even though IRIS is self-limiting, treatment is utilized in the hope of assuaging the morbidity. Treatment strategies include corticosteroids, discontinuation of antiretrovirals, and other modalities. The approach should be tailored to the patient and the opportunistic infection or situation encountered.³

The appearance of IRIS may play an even greater role as efforts continue to make antiretrovirals available to underserved populations and in areas of the world where the burden of HIV is greatest and treatment is currently limited.³ The association of antiretrovirals and the onset of latent leprosy⁹ may add a complicating factor in areas where leprosy is endemic, such as India.¹⁰

A paradoxical worsening of symptoms has also been noted with other disease processes that are similar to HIV

infection. Thus, although most of the information we have focuses on HIV, the implications for IRIS may be broader.¹¹

WHAT PAs NEED TO KNOW

- IRIS is a host response to the presence of pathogens that occurs as the immune system recovers.
- Patients with immune-compromising disease are at risk for the emergence of acute symptoms that may be explained by IRIS.
- IRIS is a diagnosis of exclusion that requires a thorough work-up to characterize needed therapeutic interventions.
- If IRIS is suspected, communication with and referral to specialty care may be needed on an emergent basis. A history of new medications is especially important.
- This phenomenon may not be strictly limited to HIV-infected patients. IRIS may be a pathogenesis that also occurs with other diseases. [JAAPA](#)

Sarah Zarbock, PA-C, department editor

DRUGS MENTIONED

Abacavir (Ziagen)
Clarithromycin (Biaxin, generics)
Darunavir (Prezista)
Efavirenz (Sustiva)
Ethambutol (Myambutol, generics)
Lamivudine (EpiVir, EpiVir-HBV)
Ritonavir (Norvir)
Tenofovir (Viread)
Zidovudine (Retrovir, generics)

REFERENCES

1. Kaplan JE, Benson C, Holmes KH, et al; Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2009;58(RR-4):1-207.
2. Ratnam I, Chiu C, Kandala NB, Easterbrook PJ. Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1-infected cohort. *Clin Infect Dis*. 2006;42(3):418-427.
3. French MA. HIV/AIDS: Immune reconstitution inflammatory syndrome: a reappraisal. *Clin Infect Dis*. 2009;48(1):101-107.
4. Aberg JA, Gallant JE, Anderson J, et al; HIV Medicine Association of the Infectious Diseases Society of America. Primary care guidelines for the management of persons infected with human immunodeficiency virus: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2004;39(5):609-629.
5. Dhasmana DJ, Dheda K, Ravn P, et al. Immune reconstitution inflammatory syndrome in HIV-infected patients receiving antiretroviral therapy: pathogenesis, clinical manifestations and management. *Drugs*. 2008;68(2):191-208.
6. Shelburne 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.
7. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS*. 2004;18(12):1615-1627.
8. Kestens L, Seddiki N, Bohjanen PR. Immunopathogenesis of immune reconstitution disease in HIV patients responding to antiretroviral therapy. *Curr Opin HIV AIDS*. 2008;3(4):419-424.
9. Martiniuk F, Rao SD, Rea TH, et al. Leprosy as immune reconstitution inflammatory syndrome in HIV-positive persons. *Emerg Infect Dis*. 2007;13(9):1438-1439.
10. Lawn SD, Lockwood DN. Leprosy after starting antiretroviral treatment. *BMJ*. 2007;334(7587):217-218.
11. Langer-Gould A, Atlas SW, Green AJ, et al. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N Engl J Med*. 2005;353(4):375-381.