

# HOSPITAL PHYSICIAN®

## INFECTIOUS DISEASES BOARD REVIEW MANUAL

### STATEMENT OF EDITORIAL PURPOSE

The *Hospital Physician Infectious Diseases Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in infectious diseases. Each manual reviews a topic essential to current practice in the subspecialty of infectious diseases.

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## Immune Reconstitution Inflammatory Syndrome

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# Immune Reconstitution Inflammatory Syndrome

Rajasekhar Jagarlamudi, MD, and Varsha Moudgal, MD

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## INTRODUCTION

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The introduction of highly active antiretroviral therapy (HAART) in the mid 1990s has led to improved survival in patients with HIV infection.<sup>1</sup> HAART improves patients' CD4 cell counts and immune function and also suppresses HIV viral replication. As a direct result of this immune reconstitution, opportunistic infections occur less frequently, resulting in decreased mortality and morbidity in patients with HIV infection.<sup>2,3</sup>

As an interesting consequence of the immune reconstitution phenomenon, a subgroup of patients experience a paradoxical clinical deterioration during the period of early rapid immunological recovery. This clinical deterioration can be marked by an excessive inflammatory response against both infectious and non-infectious antigens. Usually occurring during the first 3 months after initiation of HAART, this dysregulated antigen-specific immune response is termed the *immune reconstitution inflammatory syndrome*, or IRIS.<sup>4</sup>

IRIS consists of a group of inflammatory disorders with atypical presentations of opportunistic infections and also includes flares of preexisting autoimmune disorders. Recognition of this clinical entity is critical as these paradoxical inflammatory reactions can worsen the clinical course and may be misinterpreted as failure of antiretroviral therapy (ART) or antimicrobial therapy. IRIS significantly impacts treatment decisions, especially in resource-limited settings where there is a high prevalence of co-infections like tuberculosis.<sup>5</sup> Though mainly described in the context of HIV-related settings, IRIS has been described in non-HIV-related conditions such as solid organ transplants, neutropenic patients, women during the postpartum period, and recipients of tumor necrosis factor antagonists.<sup>6,7</sup>

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## EPIDEMIOLOGY

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The proportion of patients developing IRIS after starting ART has been described in different studies

as ranging from 10% to 50%. A retrospective study by Shelburne et al<sup>8</sup> evaluated the development of IRIS in 180 HIV patients coinfecting with *Mycobacterium tuberculosis*, *Mycobacterium avium complex* (MAC), and *Cryptococcus neoformans* in whom ART was initiated. In this study, 32% of patients demonstrated evidence of IRIS.<sup>8</sup> In a retrospective study of 199 ethnically diverse HIV patients in the United Kingdom who initiated ART, 44 patients (23%) developed IRIS at a median of 12 weeks after ART initiation.<sup>9</sup> A prospective study from South Africa by Murdoch et al<sup>10</sup> included 423 ART-naïve HIV-infected patients initiating ART. The incidence of IRIS in this patient population was 10% during the first 6 months.<sup>10</sup> A systematic review and meta-analysis of 54 cohort studies demonstrated that IRIS developed in approximately 1700 (13%) of 13,000 patients starting ART.<sup>11</sup> In patients with AIDS-defining illness, the incidence of IRIS was high for cytomegalovirus (CMV) retinitis (38%) followed by cryptococcal meningitis (20%), progressive multifocal leukoencephalopathy (PML, 17%), and tuberculosis (16%). Mortality attributed to IRIS in this meta-analysis was 4%.

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## RISK FACTORS

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Risk factors for IRIS include lower CD4 cell count before therapy (nadir CD4 cell count < 100 cells/ $\mu$ L), disseminated opportunistic infection at the time of initiation of ART, timing of initiation of ART after onset of opportunistic infection, and rapid decline in HIV viral load with high baseline viral load.<sup>8-11</sup> A case-control study conducted at the Johns Hopkins HIV clinic assessed clinical risk factors associated with development of IRIS in 49 patients with IRIS who presented at a median of 29 days from the initiation of ART. Low CD4 cell counts and the magnitude of viral load decline were associated with increased risk of developing IRIS. However, absolute CD4 T-cell increase did not correlate with that risk.<sup>12</sup> In this study, use of the most potent antiretroviral regimens—in particular, boosted protease inhibitor—was an independent risk factor for the development of IRIS.