with protean disease manifestations, including diabetes mellitus, inflammatory skin conditions, or polycythemia vera. They also had features of chronic lymphocytic leukemia, including thrombocytopenia, splenomegaly, and splenic vein thrombosis. The syndrome was associated with immune dysfunction and was characterized by the development of autoantibodies. The cause of this syndrome is not well understood, but it is thought to be related to the immune system's inability to properly control the immune response to antigens.

**CONCLUSIONS.** PD-1 is an important regulator of immune function and is upregulated in patients with HIV infection. The study results suggest that PD-1 expression on CD8+ T cells is associated with disease progression and that PD-1 blockade may offer therapeutic benefit in patients with HIV infection.

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**HUMAN IMMUNODEFICIENCY VIRUS**

**Immune Reconstitution Syndrome After Highly Active Antiretroviral Therapy in Human Immunodeficiency Virus-Infected Thai Children**


**PURPOSE OF THE STUDY.** Immune reconstitution inflammatory syndrome (IRIS) is a clinical phenomenon characterized by paradoxical worsening of the clinical status of patients with HIV who receive highly active antiretroviral therapy (HAART). It is presumed that this is a result of improvement in cellular immune functions and secondary immunopathology in response to organisms that had not been recognized previously. This syndrome has been well described in adult patients. The purpose of this study was to describe IRIS after initiation of highly active antiretroviral therapy in HIV-infected children.

**STUDY POPULATION AND METHODS.** There were 153 HIV-infected children enrolled at initiation of antiretroviral therapy and then followed prospectively.

**RESULTS.** Of the 153 children, 29 (19%) experienced 32 episodes of IRIS. The median time of onset was 4 weeks after initiation of antiretroviral therapy. Fourteen episodes were caused by mycobacterial organisms, 7 by varicella-zoster virus, 7 by herpes simplex virus, 3 by Cryptococcus neoformans, and 1 by Guillain-Barré syndrome. In general, treatment was not interrupted, and only 2 patients were treated with short courses of corticosteroids. However, 3 patients died as a result of IRIS or its complications. It is important to note that patients who reactivated mycobacterial disease had substantially lower CD4+ T-cell counts at the time that their antiretroviral therapy was started, compared with patients who reactivated herpes viruses.

**CONCLUSIONS.** IRIS is common among HIV-infected children who initiated antiretroviral therapy in an advanced stage of HIV disease.

**REVIEWER COMMENTS.** Ideally, this type of experience will become less common as patients have access to antiretroviral therapy before profound immunosuppression. However, we had a recent experience with a nonadherent teenager who, after developing disseminated Mycobacterium avium complex, decided to take his medication; a serious IRIS picture developed with persistent high-grade fever, severe abdominal pain, and dramatic intraabdominal adenopathy. Symptoms resolved rapidly with initiation of corticosteroid therapy. The challenge in such patients is to balance the management of their underlying HIV disease, their complicating opportunistic infection, and their immunosuppression to allow for resolution of the infection, reconstitution of immune function, and reduction in the complexity of their treatment regimen.

**PD-1 Expression on HIV-Specific T Cells Is Associated With T-Cell Exhaustion and Disease Progression**


**Upregulation of PD-1 Expression on HIV-Specific CD8+ T Cells Leads to Reversible Immune Dysfunction**


**PURPOSE OF THE STUDIES.** Recent evidence from a mouse model of chronic viral infection suggests a crucial role for the programmed death 1 (PD-1)/programmed death 1 ligand (PD-L1) signaling pathway in downregulating the functions of virus-specific CD8+ T cells. PD-1 is an inhibitory receptor that negatively regulates activated T cells, and it is markedly upregulated on the surface of “exhausted” virus-specific CD8+ T cells in mice. HIV similarly induces a virus-specific impairment of T-cell functions. The purpose of these 2 studies was to investigate the expression of PD-1 on HIV-specific T cell in patients infected with the virus.

**STUDY POPULATION AND METHODS.** Both studies evaluated subjects with HIV and healthy controls and compared PD-1...
Upregulation of PD-1 Expression on HIV-Specific CD8+ T Cells Leads to Reversible Immune Dysfunction

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