

The Immune Reconstitution Inflammatory Syndrome

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Abstract

The use of highly active antiretroviral therapy (HAART) has led to a substantial decrease in the frequency of opportunistic infections among HIV-infected individuals, along with a significant reduction in their mortality rate. However, a subgroup of HAART-treated patients will exhibit paradoxical deterioration in their clinical status, despite satisfactory control of viral replication and improvements in CD4 lymphocyte counts. This clinical deterioration, known as the immune restoration syndrome or immune reconstitution inflammatory syndrome (IRIS), is a result of an exuberant inflammatory response towards previously diagnosed or incubating opportunistic pathogens, as well as responses towards other as yet undefined antigens. A variety of manifestations of IRIS have been described, most prominently including *Mycobacterium avium* complex lymphadenitis, paradoxical exacerbations of pulmonary and CNS *Mycobacterium tuberculosis* infection, paradoxical exacerbations of *Cryptococcus neoformans* meningitis and cytomegalovirus uveitis. Treatment for this disorder includes continuation of primary therapy against the offending pathogen in order to decrease the antigenic load, continuation of effective HAART, and judicious use of anti-inflammatory agents. Although the clinical manifestations of IRIS are sometimes dramatic, and result in substantial morbidity, the fact that these patients are capable of generating an inflammatory response allows many of them to ultimately discontinue secondary prophylaxis for the offending pathogen.

Key words

Immune reconstitution inflammatory syndrome. Immune reconstitution. Opportunistic infections. HAART.

Introduction

Since the introduction, in the mid-1990's, of protease inhibitors for the treatment of HIV infec-

tion, the outcome of patients with AIDS has significantly improved. The use of combination drug regimens, known as highly active antiretroviral therapy (HAART), has allowed for a significant proportion of patients to effectively control HIV viral replication. This, in turn, has permitted patients with AIDS to, at least partially, reconstitute their compromised immune systems, while other HIV-infected patients on HAART have not progressed to AIDS at all. The effects of HAART have led to a decrease in opportunistic infections among HIV-infected patients, along with a significant reduction in their mortality rate¹.

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The clear benefits of HAART have been tempered by problems with demanding dosing regimens, drug toxicities, and the emergence of viral resistance. Another difficulty with the use of HAART emerged soon after its introduction. Practitioners observed that, shortly after initiating HAART, some patients had clinical deterioration, even while the markers of HIV viral replication and CD4+ T-lymphocyte counts were improving. These patients appeared to have gained a striking capacity to mount an inflammatory response against microbes that had either established a subclinical infection or had been previously treated prior to starting HAART. This entity, which carries such labels as immune reconstitution disease (IRD) or immune reconstitution inflammatory syndrome (IRIS), has now been described for a wide variety of both infectious and non-infectious diseases^{2,3}. The presentations of the syndrome are diverse and depend on the underlying etiologic agents⁴. Autoimmune disorders that occur following the initiation of HAART may also be considered part of this same process.

Although a precise definition of IRIS is difficult to establish, most researchers in this area would agree that the underlying process is one of an augmented inflammatory response following HAART, which leads to clinical worsening despite improvements in HIV viral loads and CD4+ cell counts. In order for the diagnosis of IRIS to be invoked, the patient's presentation cannot follow the expected clinical course of an either previously recognized or unrecognized opportunistic infection or be secondary to drug toxicity. Recognition of this entity is critical because treatment is based on protecting the patient against the effects of the inflammatory response, without compromising antimicrobial or antiviral therapy.

Basic science of immune reconstitution after HAART

The effect that HAART has on HIV replication, and therefore the immune system, can be used to attempt to understand the nature of the inflammatory response that underlies IRIS. Treatment with combination antiretrovirals usually leads to a 90% decrease in circulating HIV RNA levels within 1-2 weeks of initiating therapy⁵. Coincident with this fall in HIV concentrations is an early rise in CD4+ T-lymphocyte counts, the majority of which are of the memory class as defined by CD45RO⁶. Whether this represents lymphocyte proliferation, cellular redistribution from lymphoid tissue, or the effect of decreased apoptosis, is debated^{7,8}. With the continuation of HAART for 4-6 weeks, naive CD4+ cells, defined as CD45RA+, CD62L+, begin to increase⁹. The proliferation of these cells, which have not been previously activated by antigen exposure, accounts for the majority of the numerical improvement in total CD4+ T-lymphocyte counts seen with prolonged HAART¹⁰. The source of this

sustained increase is likely the thymus¹¹. Whereas HIV infection impairs thymic function, HAART leads to enlargement of the thymus and augmented thymic production of naive T-lymphocytes^{12,13}.

These numerical increases are accompanied by functional evidence of immune reconstitution following HAART. As early as four weeks into HAART, patients have evidence of amplified delayed hypersensitivity testing (DHT) and *in vitro* lymphocyte proliferation assays to common antigens such as *Candida* species¹⁴. With continued therapy, responses improve towards both common antigens as well as towards antigens from microbes that cause opportunistic infections¹⁵. Such common opportunistic pathogens as cytomegalovirus (CMV) and *Mycobacterium avium* complex (MAC) appear to elicit an enhanced response¹⁶. The improvement in immune system reactivity is not limited to patients who are treated early in their disease course; even patients with advanced AIDS can show marked increases in functional tests of immune response^{17,18}. Thus, there are multiple phases of immune restoration that occur following HAART, with both numerical and functional increases in immune system parameters occurring both acutely and during prolonged therapy.

Historical background

The concept that treatment of an infectious agent can lead to an augmented immune response is certainly not unique to the era of HAART. Physicians treating patients for infection with *Mycobacterium leprae* (leprosy) have long recognized that, up to several years after initiating mycobacterial therapy, patients may present with inflammation-induced skin and nerve damage. HIV-negative patients treated for *Mycobacterium tuberculosis* infection may develop hectic fevers, increasing lymphadenopathy, pleural effusions, or even intracranial tuberculomas while on appropriate anti-MTB drugs^{19,20}. In one series of HIV-negative patients with tuberculosis, 25% had a negative PPD at time of presentation; 75% of these converted to a positive PPD during antimycobacterial therapy²¹.

Following the introduction of zidovudine (AZT) for the treatment of HIV, there were reports from Australia of patients with atypical presentations of opportunistic infections occurring during AZT therapy^{22,23}. However, it was following the initiation of protease inhibitor therapy in 1995 that disorders of immune reconstitution in HIV began to be more widely appreciated. Phillips, et al. presented cases of localized *Mycobacterium avium* complex lymphadenitis following HAART at an AIDS conference in early 1997²⁴. Later that year, an article appeared describing a patient who had severe hepatitis after starting HAART; serologic analysis revealed that, during the hepatic flare, the patient had cleared their chronic hepatitis B virus infection²⁵. Over the next two years similar cases were published, describing worsening of pulmonary and extrapulmo-

nary MTB infection, localized MAC lymphadenitis, and inflammatory CMV diseases of the eye, all associated with the institution of HAART²⁶⁻²⁸. Review papers on the subject were initially published out of Australia and then in major medical journals in the United States, moving the concept of disorders related to immune reconstitution in HIV into everyday clinical practice^{2,29}.

Pathogen-specific immune reconstitution inflammatory syndrome

***Mycobacterium avium* complex (MAC).**

As noted above, the first case reports describing an exuberant immune response to a subclinical infectious agent, after the initiation of HAART, dealt with MAC^{24,27}. Whereas MAC infection in advanced HIV disease is characterized by a disseminated process with positive blood and bone marrow cultures, MAC-associated IRIS is usually localized, often presenting with caseous necrosis of single lymph node regions^{30,31}. The presence of granulomas, which are rarely seen in advanced AIDS, suggests that the clinical presentation is due to a heightened inflammatory response^{32,33}. The granulomatous inflammation can result in the autologous production of 1,25(OH)₂ vitamin D leading to hypercalcemia³.

The vigorous HAART-induced immune response can uncover MAC-related lesions in unusual locations (Table 1)^{34,35}. Endobronchial "tumors", soft tissue abscesses, small bowel disease, osteomyelitis, and focal brain lesions have been reported in this setting^{36,37}. On pathologic examination, the organisms in these lesions are surrounded by an intense inflammatory response consisting of both granulocytes as well as mononuclear cells³⁸⁻⁴¹. While the short-term effects of this inflammation may be detrimental to the patient, the presence of such a vigorous response to the organisms portends for excellent long-term outcome, even in the absence of specific anti-mycobacterial therapy⁴².

Based on a review of the 35 cases of MAC-related IRIS described in the literature, there appears to be a biphasic presentation. The majority of cases present in the first several weeks of therapy usually as a localized lymphadenitis (Fig. 1)⁴³. In individual cases, there have been reports of MAC-related IRIS starting as long as 25 months later, which presents as focal involvement of deep organ or soft tissue structures^{35,36}. It is speculated that these later cases may represent an absence of reconstitution of the anti-MAC portion of the immune system, rather than an exuberant response against persistent MAC antigens.

***Mycobacterium tuberculosis* (MTB).** As noted above, there is evidence that infection with MTB alone is immunosuppressive²¹. Thus, a brisk inflammatory response might be expected in HIV-infected patients with pulmonary MTB disease

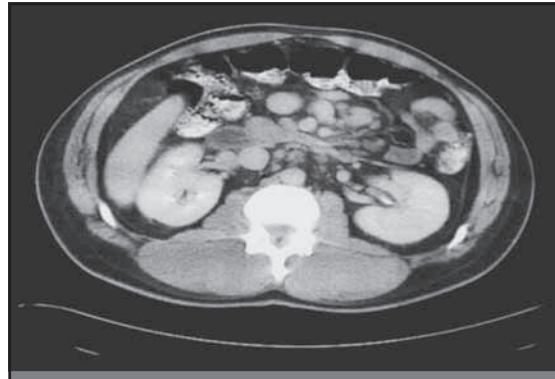


Figure 1. Abdominal CT scan that demonstrates prominent, symptomatic intra-abdominal lymphadenopathy in a patient who developed the immune reconstitution inflammatory syndrome in association with disseminated *Mycobacterium avium* complex infection.

who are treated for both infections. Indeed, there have been reports of increasing respiratory symptoms following the initiation of anti-MTB therapy in combination with HAART⁴⁴⁻⁴⁶. In the two largest series of MTB-associated IRIS, paradoxical clinical worsening occurred in about 35% of patients with combined HIV-MTB infections after initiation of HAART during anti-MTB therapy^{47,48}. The presentations included prolonged fever of > 101.5 °F, increased cough or shortness of breath, worsened lymphadenopathy, as well as the development of cutaneous lesions and ascites. A review of radiographic manifestations from one of these cohorts revealed progressive findings in 45% of patients, such as increased lymphadenopathy, lobar consolidations and pleural effusions⁴⁹. In the second study, only the patients treated with HAART developed paradoxical worsening; all of these patients started HAART within two months of initiating their MTB regimen⁴⁸. In contrast, another review of a cohort of co-infected patients showed no difference in the incidence of paradoxical reactions during therapy for MTB between patients who did, or did not, receive HAART⁵⁰. However, the reactions which did develop were of a greater severity in the HAART treated group.

MTB often disseminates in patients with HIV infection; therefore the inflammatory process seen in MTB-associated IRIS may involve organs other than the lung^{51,52}. When the immune response leads to inflammation in the central nervous system, the patient can be severely affected⁵³. One review of co-infected patients treated with both HAART and anti-MTB therapy found an incidence of paradoxically enlarging CNS tuberculomas in 8.7% of patients⁵⁴. These patients had vasogenic edema found on neuroimaging and received glucocorticoids with good symptomatic and radiologic response. The inflammatory response in MTB-related IRIS may also affect the bowels; in two cases it has led to the need for surgical procedures to repair perforations^{3,55}.

In a fashion similar to MAC, MTB-associated IRIS seems to occur in two distinct phases. The majority

Table 1. Reported clinical manifestations of the immune reconstitution inflammatory syndrome

Organism	Clinical presentation	References	
<i>Mycobacterium avium</i> complex	Cervical lymphadenitis	27, 30, 31, 32, 33	
	Mediastinal lymphadenitis	27	
	Retroperitoneal lymphadenitis	27	
	Vertebral osteomyelitis	35, 41	
	Cutaneous lesions	38, 40	
	Endobronchial masses	34, 37	
	Focal brain lesion	36	
	Ileitis	3, 39	
	Hypercalcemia	3	
<i>Mycobacterium tuberculosis</i>	Increased cervical or mediastinal lymphadenopathy	3, 44, 46, 48	
	Increased pulmonary infiltrates/consolidations	52	
	Increased pleural effusions	45, 47, 48, 49, 52	
	Prolonged fever	47, 49, 51	
	CNS tuberculomas	53, 54	
	Inflammatory bowel perforations	3, 55	
	Serositis	51	
	Psoas abscess	50	
<i>Cryptococcus neoformans</i>	Initial presentation of meningitis	56	
	Exacerbation of previously diagnosed meningitis	3, 57, 58	
	Necrotizing mediastinal lymphadenitis	57, 59, 61	
	Necrotizing cervical lymphadenitis	60	
	Recurrent cutaneous abscesses	62	
	Intracranial cryptococcoma	63	
	Intramedullary abscess	64	
	Necrotizing pneumonitis	3, 56, 57	
	Hypercalcemia	57	
Cytomegalovirus	Intraocular disease (retinitis, retinal detachment, macular edema, epiretinal membrane formation, uveitis, neovascularization of the optic disc)	3, 65, 70, 71, 72, 74, 75, 76, 77	
	Pneumonitis	3, 80	
	Disseminated lesions	79	
	Cutaneous ulcerations	81	
<i>Pneumocystis carinii</i>	Pneumonitis (patchy alveolar or reticulonodular infiltrates)	3, 88, 89, 90, 91	
Herpes viruses	Varicella zoster	Dermatomal zoster	3, 93, 94, 95
	Herpes simplex	Erosive herpes simplex	3, 96
	Human herpes virus-8	Kaposi's sarcoma	3, 97
Hepatitis B virus	Hepatitis flare accompanied by seroconversion	110, 111, 112, 113, 114	
Hepatitis C virus	Hepatitis flare accompanied by seroconversion	37, 109	
	Rapidly progressive cirrhosis	108	
	Cryoglobulinemia	109	
JC virus	Inflammatory PML (worsening clinical status or radiographic contrast enhancement)	119, 120, 121, 122	
Graves' disease	Hyperthyroidism (with thyroid autoantibodies)	3, 123, 124, 125	
Sarcoidosis	Pulmonary infiltrates	128, 129, 131, 132, 134	
	Erythema nodosum	126, 127, 130, 133	
	Lymphadenopathy	3, 127	
	Interstitial nephritis	129	
Guillain-Barré syndrome	Relapsing disease	135	
<i>Toxoplasma gondii</i>	Primary encephalitis	136	
<i>Leishmania major</i>	Vitreitis	137	
Tuberculoid leprosy	Cutaneous lesions	138	
Human immunodeficiency virus	Cerebral aneurysms	139	

of cases with pulmonary involvement, such as lymphadenopathy or pleural effusions, have occurred within a few weeks of starting HAART (Table 1). In contrast, involvement of extrathoracic lymph nodes (Figs. 2a and 2b), the small or large bowel, or the central nervous system, seems to occur after several months of therapy, although the case numbers here are much smaller. When the inflammation threatens vital structures, such as the central nervous system, corticosteroids have been used with good efficacy.

***Cryptococcus neoformans*.** The most common manifestation of *C. neoformans* infection in patients with AIDS is a meningitis, where the burden of organisms is high but the inflammatory response, as judged by white blood cell (WBC) counts in the cerebrospinal fluid (CSF), is low. When the disease presents in the midst of HAART-induced immune reconstitution, however, the inflammatory reaction may be quite brisk⁵⁶. When *C. neoformans* meningitis is the initial presentation of HIV-infection, patients often respond well to anti-fungal therapy. Soon after HAART is initiated, however, these patients may return with increasing meningeal symptoms, along with an increased WBC count in the CSF, despite having negative CSF cultures and declining *C. neoformans* CSF antigen titers^{3,57}. Intracranial pressure may be markedly elevated in this situation (in excess of 30-50 cm H₂O), necessitating either repeated large-volume lumbar punctures or shunting procedures⁵⁸. Neurologic imaging procedures that usually fail to demonstrate contrast enhancement during the acute meningitis episode, frequently reveal striking contrast enhancement as the inflammatory response progresses (Figs. 3a and 3b).

In addition to an augmented inflammatory response to CSF infection, there have been reports of novel *C. neoformans* presentations during HAART. Multiple cases of suppurative mediastinal as well as cervical lymphadenitis have developed in patients with previous *C. neoformans* meningitis who had been on HAART for several months^{56,57,59,60}. The histology of these lymph nodes has been one of granulomatous inflammation surrounding material which looks like *C. neoformans* but does not grow on culture^{56,61}. A similar clinical picture has been described for patients who present with inflammation surrounding what appears to be dead *C. neoformans* organisms in the subcutaneous tissue, spinal cord, and central nervous system⁶²⁻⁶⁴. Hypercalcemia, as a result of extrarenal hydroxylation of 25(OH) vitamin D, has occurred in a patient with intrathoracic lymphadenopathy. Finally, there have been three reports of patients with known cryptococcal disease who developed cavitary pneumonia shortly after starting HAART^{3,56,57}.

The experience with *C. neoformans* - associated IRIS is limited versus that with mycobacterial diseases. Nevertheless, like IRIS associated with MAC or MTB, there appears to be a bimodal presentation of illness. Within weeks of starting HAART, patients may present with either their initial onset or a clinical relapse of an inflammatory form of *C.*

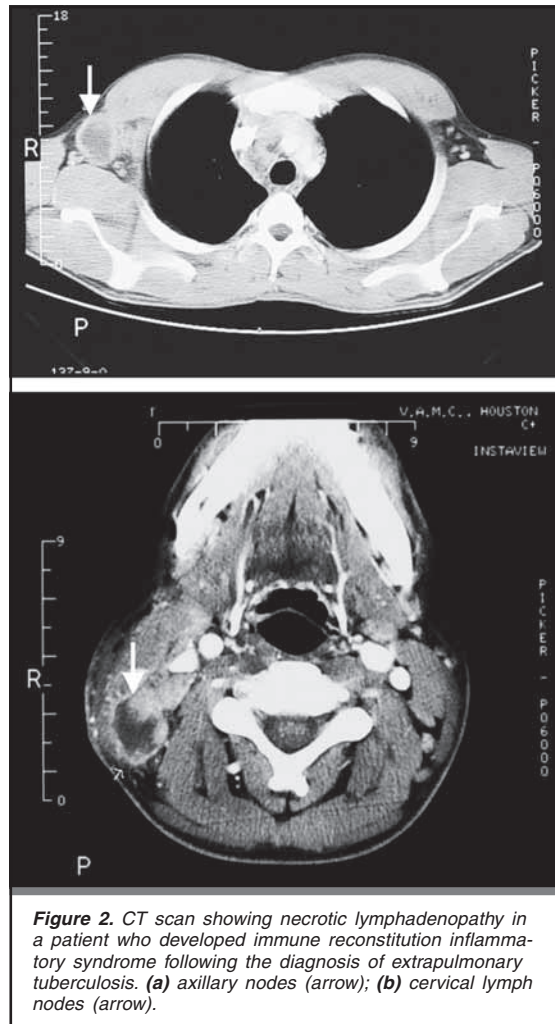


Figure 2. CT scan showing necrotic lymphadenopathy in a patient who developed immune reconstitution inflammatory syndrome following the diagnosis of extrapulmonary tuberculosis. (a) axillary nodes (arrow); (b) cervical lymph nodes (arrow).

neoformans meningitis. After several months or even years of HAART, patients with previous *C. neoformans* meningitis may develop localized inflammatory foci, often in lymph nodes, although CNS presentations have also been described.

Cytomegalovirus (CMV). Prior to the widespread use of HAART, retinitis due to CMV was a common feature of late stage AIDS. Classic CMV ocular disease is characterized by a necrotizing retinitis with a minimal inflammatory component. In contrast, a new type of inflammatory eye disorder associated with CMV was recognized shortly after the introduction of HAART (Table 1)^{65,66}. Given that the disease occurs in patients who are undergoing immune reconstitution, and that the inflammatory component may involve the entire eye, this entity has been termed "immune recovery uveitis"⁶⁷⁻⁷⁰. Consequences of this inflammatory response include a proliferative retinopathy and posterior subcapsular cataracts which may lead to visual compromise^{71,72}. There have been widely-variable time courses from starting of HAART to development of this disorder and the time for resolution has also been reported from days to months^{37,73-75}. An accurate differentiation between an inflammatory vitreitis and a necrotizing retinitis

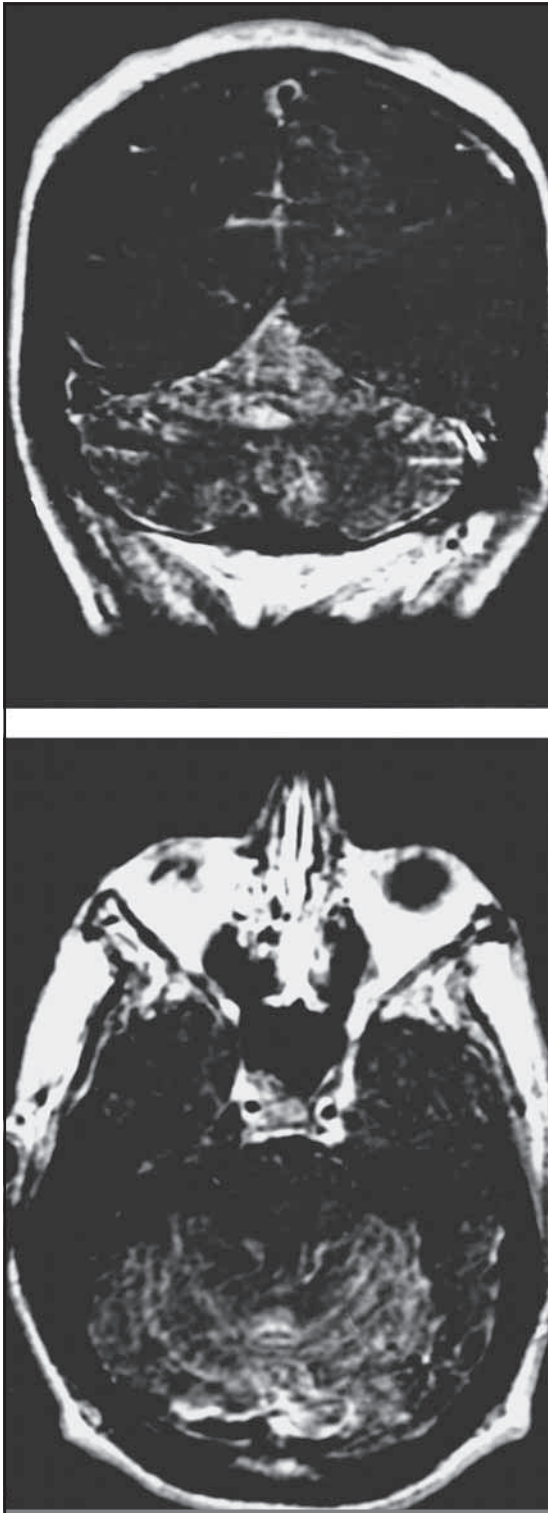


Figure 3. MRI scan that demonstrated diffuse meningeal enhancement, most prominent in the posterior fossa in a patient with immune reconstitution syndrome in the setting of treated cryptococcal meningitis. The patient presented with fevers, headache and loss of vision due to a marked increase in intracranial pressure. (a) axial post-contrast T1-weighted image; (b) coronal post-contrast T1-weighted image. Reprinted with permission from reference 3.

is essential because not all patients who have increasing CD4+ cell counts after HAART reconstitute a CMV-specific immune response^{76,77}. This subset of patients remains at risk for classic CMV

retinitis, rather than the development of CMV-associated "immune recovery uveitis"⁷⁸.

While the eye is the area where CMV disease occurs most often in patients with AIDS, it also can present with central nervous system, intestinal, or pulmonary involvement. Similar extra-ocular presentations have occurred in CMV-associated IRIS in which inflammatory lesions have involved such diverse organs as the colon, pancreas, lung and skin⁷⁹⁻⁸¹. The positive side of the increased capacity of the immune system to respond to CMV is that specific anti-CMV therapy can be safely stopped in the vast majority of patients whose CD4+ cell counts recover^{82,83}.

***Pneumocystis carinii* pneumonia (PCP).**

Perhaps the most common situation where physicians attempt to ameliorate the immune response to an opportunistic pathogen in AIDS is with *Pneumocystis carinii* infection. It is standard practice to administer corticosteroids to patients with moderate-to-severe PCP, to decrease the inflammatory response to dying organisms^{84,85}. HAART has dramatically lowered the incidence of PCP and allowed the discontinuation of preventive therapy in patients whose CD4+ cell count rises above 200/ μ ^l^{86,87}. Recently, however, there have been a series of case reports of patients with PCP who were treated for their acute illness and then had respiratory compromise shortly after starting HAART^{3,88-91}. All of the patients had thorough pulmonary evaluations including bronchoscopy, which revealed an intense inflammatory response, often composed of CD4+ cells, along with residual *Pneumocystis carinii* cysts. Radiographic manifestations typically include patchy alveolar opacities (Fig. 4) or reticulonodular infiltrates with cystic changes^{88,91}. The majority of affected patients were treated with steroids and continued anti-*Pneumocystis* therapy, with complete recovery within a few weeks.

Herpes viruses. As opposed to other opportunistic infections associated with HIV, herpes zoster occurs at a relatively consistent rate, regardless of the CD4+ cell count⁹². Studies have shown a several-fold increase in dermatomal herpes zoster in HIV-infected patients who are treated with HAART^{93,94}. The greatest increased risk appears to occur in the first four months of therapy and is related to the absolute increase in CD8+ T-lymphocytes⁹⁵.

There have been two case reports of unusually severe and persistent herpes simplex infection in association with HAART^{3,96}. Both reports described ulcerative disease in the genital tract that occurred after several months of HAART. Similarly, there have two case reports of a rapidly-progressive form of Kaposi's sarcoma, a disease associated with human herpes virus-8 (HHV-8) infection^{3,97}. In the vast majority of cases, HAART is helpful in controlling the lesions of KS⁹⁸. Occasionally, however, HAART has led to dramatic clinical presentations, perhaps incited by an augmented inflammatory response to HHV-8.

Hepatitis B and C viruses. Given that hepatitis B (HBV) and C (HCV) viruses and HIV share similar routes of acquisition, it is not surprising that a significant proportion of HIV-infected patients are infected with either or both HBV and HCV^{99,100}. In the HAART era, end-stage liver disease due to hepatotropic viruses has become one of the leading causes of death in HIV-infected patients¹⁰¹. The effect that HAART has on HBV and HCV levels, and the immune response to these viruses, is still debated¹⁰². Because antiretrovirals are metabolized by the liver, distinguishing direct drug toxicity from immune-induced exacerbations of hepatitis is difficult. In the majority of patients infected with HIV and HCV, initiation of HAART is followed by a transient rise in HCV levels and alanine aminotransferase (ALT)¹⁰³. This is postulated to occur because of increasing numbers of cytotoxic CD8+ T-lymphocytes targeting HCV-infected hepatocytes, leading to release of the virus into the circulation where it can be measured. While some studies have shown a rise in HCV RNA levels in the initial period following the start of HAART, the true nature of the effect of HAART on HCV RNA levels remains to be elucidated¹⁰⁴. What effect HAART has on HBV DNA levels also remains unclear, although patients co-infected with HBV and HIV have a significant incidence of liver function test elevation after starting HAART^{105,106}. The contribution that drug toxicity contributes versus immune mediated lysis of HBV-infected hepatocytes is unknown.

Dramatic presentations of the interaction between a recovering immune system and hepatitis B and C viruses have been reported, however. Two patients who had no detectable antibodies to HCV prior to HAART developed hepatitis and anti-HCV antibodies after starting antiretroviral therapy¹⁰⁷. Retrospective analysis of their serum taken prior to HAART revealed the presence of HCV RNA by PCR. Another patient infected with HCV had rapidly-progressive liver failure after starting HAART; liver biopsy revealed marked hepatic necrosis and inflammatory activity consistent with viral hepatitis¹⁰⁸. There was an increase in hepatic CD8+ T lymphocytes that mirrored the patient's overall immune reconstitution. Symptomatic cryoglobulinemia in association with HCV infection has also been reported in close proximity to initiation of HAART¹⁰⁹. Analysis of HBV antigen/antibody profiles have shown that some patients co-infected with HBV and HIV, who develop hepatitis after starting HAART, probably have immune-mediated disease^{110,111}. In one illustrative case, a patient who developed elevated liver enzymes after HAART had clearance of HBeAg with appearance of anti-HBc and anti-HBe in conjunction with their clinical presentation¹¹². In other cases there have been documented rises in HBV DNA in conjunction with the appearance of various antibodies, suggesting that immune-mediated destruction of hepatocytes caused the acute hepatitis^{113,114}.

The diagnosis of IRIS in patients with HIV, and co-infection with HBV and/or HCV, is quite chal-

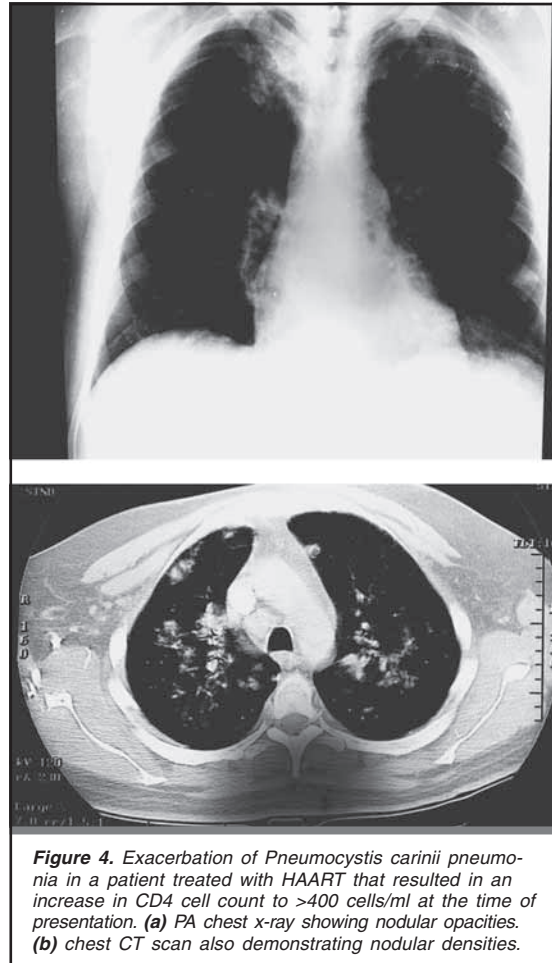


Figure 4. Exacerbation of *Pneumocystis carinii* pneumonia in a patient treated with HAART that resulted in an increase in CD4 cell count to >400 cells/ml at the time of presentation. (a) PA chest x-ray showing nodular opacities. (b) chest CT scan also demonstrating nodular densities.

lenging. Many patients will have increases in liver enzymes after starting HAART. Whether this is due to direct drug toxicity, or an interplay between a recovering immune system and the hepatotropic viruses, is not easily distinguished. Physicians prescribing HAART in this context need to be aware of this interaction so that patients can be monitored closely for progressive toxicity while not stopping HAART prematurely. Repeating hepatitis serologies may be revealing. On occasion, a liver biopsy may be required to clarify the pathogenesis.

Progressive multifocal leukoencephalopathy (PML). The use of HAART has dramatically decreased the incidence of PML in HIV patients, and prolonged survival in patients already diagnosed with the disease, presumably because of an increased immune response to the JC virus, the causative organism^{115,116}. HAART has been shown to both decrease the amount of JC virus in the CSF as well as increase JC-specific antibody levels^{117,118}. Nevertheless, an atypical, inflammatory version of PML has developed in several patients treated with HAART¹¹⁹⁻¹²¹. In addition, three patients with previously diagnosed PML had clinical deterioration and increasing radiologic PML lesions shortly after starting HAART¹²². As opposed to the usual neuroimaging in PML, these patients had contrast enhancement on MRI, sug-

gesting a strong inflammatory component. Biopsy of these lesions revealed extensive demyelination with perivascular infiltrates consisting of lymphoplasmoid cells. The rarity of PML-associated IRIS precludes generalizations about its clinical outcomes versus standard AIDS-related PML.

Autoimmune disorders. In the same manner in which HAART may incite an inflammatory reaction against foreign antigens, there is increasing evidence that immune reconstitution can lead to autoimmune diseases. There have been numerous reports of patients developing Graves' disease following the institution of HAART^{3,123,124}. At the time of clinical presentation, the patients had antibodies to the thyrotropin receptor; retrospective analysis of their stored serum demonstrated the absence of these antibodies prior to starting HAART¹²⁵. All of the patients who have developed Graves' during HAART have done so after several months of therapy, suggesting that a late stage in immune recovery is involved.

A similar time sequence has been observed in patients receiving HAART who contracted sarcoidosis during therapy^{126,127}. CD4+ T-lymphocytes are thought to play a critical role in sarcoidosis, and their increase following HAART may have been responsible for development of the disorder^{128,129}. The addition of IL-2 to HAART preceded the onset of sarcoid in one patient¹³⁰, while two other patients who had asymptomatic sarcoidosis diagnosed many years previously developed symptomatic pulmonary sarcoidosis while on HAART^{131,132}. Extrapulmonary manifestations of sarcoidosis such as erythema nodosum, hepatomegaly, retroperitoneal lymphadenopathy, and interstitial nephritis, have all been described in the setting of immune reconstitution^{3,127,133}. Most of the cases have been relatively mild and have responded well to corticosteroids^{3,134}. It has been speculated that in both Graves' and sarcoidosis, thymic dysfunction allows the propagation of autoreactive T-lymphocytes, leading to the clinical manifestations of the diseases.

A similar autoimmune dysregulation may be responsible for the development of the Guillain-Barré syndrome (GBS), which is well described as a manifestation of acute HIV infection. One patient who had excellent response to HAART developed multiple relapsing episodes of GBS, despite therapy with intravenous immunoglobulin¹³⁵. The addition of corticosteroids led to clinical improvement.

Miscellaneous syndromes. There have been several single-case reports of unusual manifestations of opportunistic infections developing after the initiation of HAART. A 45-year-old woman presented with signs and symptoms of toxoplasma encephalitis three weeks after starting HAART, despite having a CD4+ count of over 200 cells/ μ l¹³⁶. A 34-year-old African man, with previously diagnosed cutaneous and ganglionic leishmaniasis, developed granulomatous anterior uveitis six months after starting HAART¹³⁷. The inflammatory response in the eye led to enucleation; pathologic

examination showed the amastigote form of *Leishmania*, but cultures were negative. There has been one report to date of the cutaneous lesions of borderline tuberculoid leprosy, with reversal reaction developing after the initiation of HAART¹³⁸. Finally, a 12-year-old boy with perinatally acquired HIV-infection developed multiple cerebral aneurysms and ischemic strokes during immune reconstitution¹³⁹. This may have been due to an immune response to chronic endothelial cell infection by HIV.

Pathogenesis

The development of IRIS appears to be mediated by an increased capacity of the immune system to respond to microbial agents or antigens that were present in the patient prior to beginning HAART. *In vitro* and *in vivo* pathogen-specific responses have been shown to increase with HAART^{14,43}. Antiretroviral therapy also shifts the balance between Th-1 and Th-2 responses, which leads to increases in IL-2 and IFN- γ , both of which have powerful pro-inflammatory properties^{140,141}. Thus, IRIS occurs in an environment in which the immune system has both regained microbe-specific activity as well as shifted towards an increasing inflammatory state.

Why, however, IRIS occurs in some HIV-infected patients treated with HAART, while other patients have uneventful immune reconstitution, is not understood at present. Significant compromise of the immune system is usually necessary to allow the majority of pathogens associated with IRIS to establish either latent or clinically-apparent infection. Therefore, it seems reasonable that the patients at the highest risk for developing IRIS would be those who started with the lowest CD4+ cell counts¹⁴². One study showed that patients who had a better virological response to HAART had an increased risk of developing MTB-related IRIS; there was no significant difference when CD4+ responses were compared⁴⁸. There has been some suggestion of a genetic predisposition, as patients with certain MHC haplotypes may be at increased risk¹⁴³. The possibility that different cytokine profiles make patients more likely to develop IRIS is also being explored. So far, it seems that patients with higher levels of IL-6 and soluble IL-6 receptor are more likely to develop IRIS¹⁴⁴. The further discriminating characteristics, which separate IRIS patients from those who do not develop the disorder, remain to be elucidated.

Treatment

The heterogeneity of patient presentations, and limited numbers of cases, makes treatment recommendations for IRIS premature at the present time. Probably the most important aspect of patient care is the ability of the physician to recognize the entity, thereby limiting unnecessary procedures, and

continuing with the administration of vital medications. Given that the inflammatory response is a marker for immune restoration, HAART should be continued in all cases where the inflammatory reaction does not immediately threaten mortality or result in significant morbidity. In addition, most physicians have continued therapy for the underlying infectious agent in an attempt to minimize the antigens driving the immune response. The finding that all patients who developed MTB-related IRIS received HAART within two months of starting MTB therapy suggests that it may be prudent to wait to begin specific anti-HIV therapy in these patients, if their clinical situation allows⁴⁸.

The most extensive experience with modifying the inflammatory response comes in IRIS associated with *M. tuberculosis*, *C. neoformans*, and CMV infections. The predilection that these organisms have for the central nervous system makes an augmented inflammatory response to these agents quite dangerous. There have been case reports of both local and systemic corticosteroid use in ocular CMV-associated IRIS with encouraging results^{68,69}. Whether this is more effective than prolonged anti-CMV therapy is not known¹⁴⁵. The use of systemic corticosteroids has been more widely employed in MTB-associated IRIS, perhaps because of the previously accepted role for immune modulation in some forms of MTB infection^{3,44,47}. The method of delivery, dosing, or duration of therapy is not currently well established. Short-term prednisone administration, in doses of 0.5 mg/kg daily, appears to be well tolerated and safe when given to individuals maintained on stable HAART regimens¹⁴⁶.

The development of *C. neoformans* meningitis-associated IRIS is often accompanied by significant elevations in intracranial pressure^{3,58}. Detection and management of this complication is crucial for successful treatment of all patients with cryptococcal meningitis^{147,148}. Repeated, large-volume lumbar punctures form the cornerstone of therapy; refractory cases may require lumbar or lumbar-peritoneal drains¹⁴⁹. There have been anecdotal reports of the addition of corticosteroids being useful in IRIS-associated cryptococcal meningitis, although this has not been confirmed in a systematic fashion³. In our experience, doses of prednisone of 60 mg daily tapered over one month have been dramatically effective in alleviating most of the symptoms and signs associated with the IRIS-elevated intracranial pressure in patients with cryptococcal meningitis. However, it has not been unusual for selected patients to require multiple courses of corticosteroids over several months in order to effectively control the inflammatory response.

Conclusion

The use of HAART has dramatically improved the outlook for patients infected with HIV. Clinicians caring for these patients must be cognizant of the potential for this therapy to lead to a

paradoxical decline in the patient's clinical status. In order to be confident that IRIS is indeed the cause, one must search carefully for confounding infectious agents, as well as be alert for drug toxicities. At the same time, it is important to recognize that improved immune function, in and of itself, may be the causative process. Management of patients with this disorder should focus on attempting to maintain the patient on appropriate anti-HIV and specific anti-microbial therapy, while closely monitoring for complications secondary to the inflammatory process. If the inflammation threatens significant morbidity or mortality then anti-inflammatory measures may be considered, although there is no conclusive evidence of their efficacy at present. Perhaps, as this disorder becomes better understood, more definitive guidelines may be developed in the near future.

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