

# Inflammatory Reactions in HIV-1–Infected Persons after Initiation of Highly Active Antiretroviral Therapy

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**Purpose:** To review reported inflammatory reactions occurring after initiation of highly active antiretroviral therapy (HAART) in persons infected with HIV-1 and to explore the mechanisms leading to these reactions.

**Data Sources:** MEDLINE search of biomedical literature reporting inflammatory reactions after HAART. Bibliographies of retrieved reports were also reviewed.

**Study Selection:** Articles describing patients infected with HIV-1 who had immunologic and virologic responses to HAART and subsequently developed inflammatory reactions.

**Data Extraction:** Data on the immune status, clinical characteristics, and therapeutic management of patients who were seropositive for HIV-1 and had inflammatory reactions after HAART.

**Data Synthesis:** Inflammatory reactions involving opportunistic infections, AIDS-associated malignant conditions, and other non-

infectious diseases have recently been described in patients infected with HIV-1. These conditions often appeared shortly after the introduction of HAART and were associated with pronounced reductions in plasma HIV-1 viral load and increases in CD4<sup>+</sup> T-lymphocyte counts. Clinical presentation was often atypical of that in patients with untreated HIV-1 infection, probably because of restored immunity. Most cases improved despite continuation of HAART, although some patients required anti-inflammatory drugs or specific antimicrobial agents.

**Conclusions:** Clinicians caring for patients who are infected with HIV-1 and receiving HAART must be aware of this new and diverse clinical syndrome. As more HAART recipients are studied, new presentations will probably be observed.

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Highly active antiretroviral therapy (HAART)—combination antiretroviral therapy that has potent in vivo effects on HIV-1 replication—has led to significant decreases in AIDS-associated morbidity and mortality (1). Although patients receiving HAART have reduced plasma HIV-1 viral load and increased CD4<sup>+</sup> T-lymphocyte counts, they still develop AIDS-defining events, particularly in the first 2 months of treatment (2, 3). A delay in restoration of immune function may account for the development of opportunistic infections. It is possible, however, that HAART may actually promote the clinical expression and development of such infections, as well as AIDS-related malignant conditions and other noninfectious diseases. Several authors have recently reported cases that may represent progression of previously quiescent disorders to symptomatic diseases after initiation of HAART. We searched MEDLINE for studies of such cases, which some authors have referred to as immune restoration disorders (4–8). Bibliographies of relevant studies were also reviewed. In this paper, we summarize clinical presentations (Table 1) and potential mechanisms of these conditions and describe therapeutic methods (Table 2).

For the cases reported in this review, HAART refers to the initiation of a regimen that involves nucleoside reverse

transcriptase inhibitors with one or more protease inhibitors or the addition of a protease inhibitor to a regimen of nucleoside reverse transcriptase inhibitors. Similarly, the usual response to HAART in the following cases involves marked reductions in plasma HIV-1 RNA levels and increases in CD4<sup>+</sup> T-lymphocyte counts. It should be noted, however, that degrees of response to HAART varied.

## ***Mycobacterium avium* Complex**

Several case reports have discussed the development of *Mycobacterium avium* complex and other nontuberculous mycobacterial infections in patients receiving HAART (6, 9–16). Many affected patients presented with focal or diffuse lymphadenitis within 2 months of initiating HAART. Mycobacteremia was rarely demonstrated, but the lymph nodes (some of which were suppurative) were usually culture positive for *M. avium* complex. In a retrospective chart review, Phillips and colleagues (17) found that patients who developed *M. avium* complex lymphadenitis within 12 weeks of starting HAART had higher CD4<sup>+</sup> T-lymphocyte counts, were more likely to develop a localized draining sinus, and were less likely to have weight loss and disseminated *M. avium* complex disease than patients

**Table 1. Clinical Presentation of Specific Opportunistic Infections in HIV-1–Infected Patients with and without Highly Active Antiretroviral Therapy**

Opportunistic Infection	Common Clinical Presentation	Presentation after Highly Active Antiretroviral Therapy
<i>Mycobacterium avium</i> complex	Disseminated disease, weight loss, diarrhea, mycobacteremia	Focal lymphadenitis, granulomatous masses; mycobacteremia rare
Cytomegalovirus	Retinitis, vitritis uncommon	Vitritis, retinitis, extraocular disease
<i>Cryptococcus neoformans</i>	Meningitis occasionally indolent, cerebrospinal fluid leukocytosis uncommon	Overt meningitis, marked cerebrospinal fluid leukocytosis
Progressive multifocal leukoencephalopathy	Neurologic deficits, magnetic resonance imaging hypodensities without contrast enhancement	Neurologic deficits; magnetic resonance imaging hypodensities, frequently with peripheral enhancement
Herpes zoster	May be severe, accompanied by complications	Mild presentation, uncomplicated

who had been receiving HAART for more than 12 weeks. Of interest, a case of recurrent leprosy, in the tuberculoid form secondary to increased anti-*M. leprae* immunity, has been reported in an HIV-1–infected person after initiation of HAART (18).

Uncommon presentations of *M. avium* complex, such as granulomatous masses, osteomyelitis, bursitis, Addison disease, and skin nodules, were also seen after HAART (6, 11). Of note, similar focal *M. avium* complex disease was noted as early as 1988 in patients receiving zidovudine monotherapy (19, 20). In the above cases, antimycobacterial therapy, corticosteroids, or local surgical drainage alone was successful, usually in conjunction with HAART.

***Mycobacterium tuberculosis***

Inflammatory reactions in HIV-1–infected patients receiving antituberculous therapy and HAART have been

**Table 2. Successful Treatments Used for Opportunistic Infections in HIV-1–Infected Patients after Highly Active Antiretroviral Therapy\***

Opportunistic Infection	Treatment
<i>Mycobacterium avium</i> complex	Corticosteroids, antimycobacterial chemotherapy, local surgical drainage
<i>Mycobacterium tuberculosis</i>	Anti-inflammatory agents in conjunction with antituberculous chemotherapy
Cytomegalovirus	Topical medications, periocular steroids, anticytomegalovirus chemotherapy
Hepatitis C virus	Interferon- $\alpha$ , discontinuation of HAART
Hepatitis B virus	Continuation of HAART, discontinuation of HAART
<i>Histoplasma capsulatum</i>	Antifungal chemotherapy
<i>Cryptococcus neoformans</i>	Antifungal chemotherapy
Progressive multifocal leukoencephalopathy	Continuation of HAART
Herpes zoster	Anti-herpesvirus chemotherapy

\* HAART = highly active antiretroviral therapy.

well documented (21–27). Affected patients had pansensitive pulmonary or extrapulmonary tuberculosis and developed inflammatory reactions several weeks after initiation of HAART despite initial response to antituberculous therapy. Examples of such reactions included fever, worsening pulmonary infiltrates, lymphadenopathy, and in some cases intracranial tuberculomas. Cultures of sputum and lymph nodes usually did not reveal acid-fast bacilli. All patients improved when anti-inflammatory agents were added to HAART. A case of regional lymphadenitis secondary to Calmette–Guérin bacillus has also been reported in an HIV-1–infected child after initiation of antiretroviral therapy (16).

Narita and coworkers (24) noted that HIV-1–infected patients treated with antituberculous therapy and HAART had a higher incidence of paradoxical reactions (new fever; worsening or emergence of lymphadenopathy, pulmonary infiltrates, or pleural effusion; or worsening of other tuberculous lesions) than HIV-1–infected patients not treated with HAART. Patients in the former group developed paradoxical reactions a mean of 11 to 15 days after initiation of HAART and had a larger decrease in plasma HIV-1 viral load than those in the latter group.

**Cytomegalovirus**

Both ocular and extraocular cytomegalovirus infections have been reported after HAART. One of the earliest reports described five HIV-1–infected patients with no history of ocular disease who received a first diagnosis of cytomegalovirus retinitis after CD4<sup>+</sup> T-lymphocyte counts increased from less than  $0.085 \times 10^9$  cells/L to more than  $0.195 \times 10^9$  cells/L with HAART (28). Similarly, cytomegalovirus viremia, colitis, pancreatitis, and submandib-

ular inflammation have also been reported after HAART in patients with no history of cytomegalovirus infection (29).

Other authors have described the development of vitritis in patients treated with HAART who previously had active or inactive cytomegalovirus retinitis (30–35). Patients with a history of unilateral cytomegalovirus retinitis developed vitritis in the same eye after HAART. In one patient with vitritis, anterior chamber paracentesis showed no evidence of cytomegalovirus by polymerase chain reaction or antibody titer and no evidence of other infectious agents. Most cases improved without evidence of relapse, regardless of therapy (topical medications, periocular injection of steroids, or anticytomegalovirus agents).

Karavellas and colleagues (36) conducted a cohort study of 30 patients with cytomegalovirus retinitis who responded to HAART. Nineteen patients (63%) developed “immune recovery vitritis” after a median of 43 weeks. All affected patients reported “floaters,” and 17 of 19 had decreased visual acuity. All patients had inactive cytomegalovirus retinitis in the affected eye when vitritis was diagnosed. In a retrospective review by Jabs and coworkers (37), this disorder was observed in only 6 of 33 patients, perhaps because of previous therapy with ganciclovir implants for cytomegalovirus retinitis.

### Hepatitis C Virus

Several patients with previously quiescent hepatitis C virus (HCV) infection developed acute hepatitis, cirrhosis, or an HCV-associated disorder, such as cryoglobulinemia, within 1 to 9 months after initiation of HAART (5, 38–41). Hepatitis C virus was implicated because HCV IgG antibody developed or plasma HCV RNA level increased after introduction of HAART, although this was not observed in all cases. Some patients improved with interferon- $\alpha$  therapy; however, in other patients, protease inhibitor therapy had to be discontinued.

The response of plasma HCV RNA to HAART in patients co-infected with HIV-1 has been evaluated (40, 42–46). One study found that mean plasma HCV RNA level initially increased 6 weeks after addition of HAART and later decreased to below baseline, with minimal changes in serum aminotransferase levels (42). Other studies, however, noted a moderate increase in plasma HCV RNA level after HAART, and liver biopsy showed associated lobular necrosis and inflammation in some patients (40, 43, 46).

### Hepatitis B Virus

Some studies have attributed acute hepatitis in the setting of HAART to hepatitis B virus (HBV) (47–51). Affected patients had previous HBV infection and developed clinical hepatitis 5 to 12 weeks after beginning HAART. Most of these patients demonstrated newly detectable plasma HBV RNA or increased levels of HBV RNA during acute hepatitis. In some cases, serologic tests for HBV also showed active HBV infection. Researchers discontinued HAART in one patient (51), but most other patients improved without changes in therapy.

### *Cryptococcus* and *Histoplasma* Species

A case report of *Histoplasma capsulatum* infection and a retrospective review of cryptococcal infection occurring after HAART have been described. Bottaro and coworkers (52) described a 35-year-old South American HIV-1-infected man with a CD4<sup>+</sup> T-lymphocyte count of  $0.005 \times 10^9$  cells/L who received a diagnosis of disseminated histoplasmosis on the basis of blood culture results. Successful treatment with amphotericin B was followed by itraconazole therapy. Three weeks after initiation of HAART, the patient’s inguinal lymph node became enlarged; excisional biopsy revealed a granulomatous reaction and *H. capsulatum* by culture. The CD4<sup>+</sup> T-lymphocyte count had increased to  $0.066 \times 10^9$  cells/L. Itraconazole therapy and HAART were continued, and the patient’s symptoms improved.

A retrospective review of all HIV-1-infected patients with culture-proven cryptococcal meningitis between 1996 and 1999 identified three patients who developed cryptococcal meningitis in temporal association with initiation of HAART (53). Two patients developed clinical meningitis within 1 to 6 weeks after introduction of HAART. Studies of cerebrospinal fluid were remarkable for leukocytosis (leukocyte count  $\geq 14 \times 10^9$  cells/L) and the presence of *Cryptococcus neoformans* by culture. A third patient developed recrudescence of previously suppressed *C. neoformans* meningitis, also marked by cerebrospinal fluid leukocytosis (leukocyte count,  $100 \times 10^9$  cells/L) and an elevated cerebrospinal fluid *C. neoformans* antigen titer within 10 days of beginning HAART. Therapy was not changed in this patient, and meningeal signs and symptoms resolved over 2 weeks.

## Herpes Zoster

Several studies have reported development of herpes zoster after HAART (8, 54, 55). One study noted that incidence of herpes zoster increased markedly in conjunction with HAART (non-nucleoside reverse transcriptase inhibitors were used in 2 patients) (55). The mean time to development of zoster was 16.6 weeks after initiation of or switching to HAART. Martinez and colleagues (54) prospectively collected data on 193 HIV-1-infected patients after addition of a protease inhibitor to nucleoside reverse transcriptase inhibitors. Fourteen patients developed first or recurring herpes zoster after a median follow-up of 64 weeks; most cases occurred from week 4 to week 16. Manifestations of zoster were mild and uncomplicated. Acyclovir or famciclovir was administered to most patients, with universally good clinical response. The only risks associated with the development of zoster were the baseline CD8<sup>+</sup> T lymphocyte percentage (>66%) and an increase in percentage of CD8<sup>+</sup> T lymphocytes (>5%) 1 month after HAART.

## Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy is a demyelinating disease of cerebral white matter caused by the JC papovavirus. In several studies, patients presented with neurologic deficits shortly after HAART and findings on magnetic resonance imaging were consistent with progressive multifocal leukoencephalopathy (56–58). Many lesions demonstrated peripheral enhancement with gadolinium contrast. One patient had stereotactic brain biopsy, which revealed extensive demyelination, perivascular mononuclear infiltration, and oligodendrocytes immunoreactive for papovavirus antigen (58). During follow-up, radiologic and clinical improvements were seen when HAART was continued.

## Other Potential Infectious Disorders, Malignant Conditions, and Noninfectious Disorders

Noninfectious autoimmune diseases may be exacerbated by immune reconstitution in patients receiving HAART. Exacerbations of Graves disease, autoimmune thyroiditis, and systemic lupus erythematosus have been temporally correlated with HAART (59–62). Similarly, AIDS-related malignant conditions, such as lymphoma and Kaposi sarcoma, have developed or recurred shortly after initiation of HAART (63–65). Immune recovery af-

ter HAART has been implicated as the cause of other disorders, such as folliculitis and Castleman disease (66, 67). In persons infected with HIV-1, Castleman disease is associated with human herpesvirus type VIII infection (66). Finally, two studies described the development of pulmonary sarcoidosis and sarcoidlike disorders in HIV-1-infected patients receiving HAART (7, 68).

## Discussion

We reviewed cases of inflammatory reactions occurring shortly after the addition of HAART in HIV-1-infected patients. The pathogenesis of these reactions has not yet been clearly defined, but restoration of CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes after HAART may explain their development. Studies have shown that the cellular response to *M. avium* complex infection can be restored as soon as 2 weeks after HAART in HIV-1-infected patients (15, 69, 70). Similarly, cytomegalovirus-specific restoration of CD4<sup>+</sup> T lymphocytes after HAART has been documented (71). Other mycobacterial diseases, such as tuberculosis and leprosy, have long been known to present with paradoxical reactions shortly after initiation of antimycobacterial chemotherapy, presumably because delayed-type hypersensitivity is restored (72–77). Also, patients not infected with HIV-1 have developed similar inflammatory reactions after withdrawal of medical immunosuppression, probably because cellular immunity has returned (78–81). The presumed opportunistic infection could not be identified by culture or by other diagnostic methods in some cases; however, this may be explained by pathogen-specific inflammation rather than actual reactivation of the opportunistic infection.

The increase in CD8<sup>+</sup> T-lymphocyte count after HAART, independent of the CD4<sup>+</sup> T-lymphocyte count, may itself account for some of these reactions. An increase in CD8<sup>+</sup> T-lymphocyte count in response to potent antiretroviral agents has been described elsewhere (82, 83). Martinez and colleagues (54) showed that CD8<sup>+</sup> T-lymphocyte count was the only risk factor associated with development of herpes zoster after HAART. Other authors believe that the increase in CD8<sup>+</sup> T-lymphocyte count after HAART may result in clinical hepatitis caused by HBV as well as HCV (5, 42, 49).

Pathogenesis of some of these reactions may also be cytokine-mediated. For example, it has been postulated that decreasing levels of interferon- $\alpha$ , resulting from a

lower HIV-1 plasma viral load, may lead to an increase in HCV viremia (42, 84). Similarly, levels of interleukin-12, a mediator of anticryptococcal activity, may be altered when HIV-1 viral load decreases and may result in clinical meningitis (53, 85, 86).

A common feature of these cases is that the clinical presentation of the opportunistic infection was often atypical compared with that usually observed in HIV-1-infected patients. For example, local *M. avium* complex infection without bacteremia, cryptococcal meningitis with a marked cerebrospinal fluid pleocytosis, vitreal disease due to cytomegalovirus, mild herpes zoster, and progressive multifocal leukoencephalopathy with contrast-enhancing magnetic resonance imaging lesions are all unusual in untreated HIV-1-infected patients (87–90). These atypical patterns are probably caused by restored immunity after HAART.

The clinician caring for HIV-1-infected patients must be aware of these somewhat uncommon but important manifestations of opportunistic disease. In many cases, the diagnostic challenge will lie in determining the difference between immune restoration disease, opportunistic infection treatment failure, and adverse reactions to medications. For example, acute hepatitis after HAART has frequently been attributed to direct toxicity from protease inhibitor therapy (91–93). Complicating this matter is the fact that, in some cases, the presumed opportunistic infection could not be identified by culture or other diagnostic methods.

In most of the reviewed studies, opportunistic infection improved despite continuation of HAART, although some patients required anti-inflammatory agents and specific antimicrobial therapy. Given the atypical and sporadic presentation of these reactions, it will be difficult to conduct formal controlled trials and make recommendations regarding therapy for these inflammatory disorders. It will be even more difficult to predict the ways in which these reactions will affect recommendations for prophylaxis against opportunistic infection. Some authors have reported favorable outcomes after discontinuation of therapy for the localized mycobacterial immune reconstitution syndrome (94), and others have described development of the syndrome in patients receiving mycobacterial therapy (95). It is important to note that few inflammatory reactions have been reported in patients receiving non-nucleoside reverse transcriptase inhibitors, perhaps because these agents have only recently been recommended as a compo-

nent of HAART. As we study more patients receiving HAART and as newer and perhaps more potent antiretroviral regimens are devised, additional inflammatory disorders will probably be observed and further therapeutic recommendations may be developed.

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