Recurrence of *Mycobacterium avium* Infection in Patients Receiving Highly Active Antiretroviral Therapy and Antimycobacterial Agents

Sandro K. Cinti,1 Daniel R. Kaul,1 Paul E. Sax,2 Laurence R. Crane,3 and Powel H. Kazanjian1

From the 1Department of Internal Medicine, University of Michigan Health System, Ann Arbor, Michigan; 2Brigham and Women’s Hospital, Boston, Massachusetts; and 3Wayne State Medical Center, Detroit, Michigan

The known effects of highly active antiretroviral therapy (HAART) on opportunistic infections (OIs) range from immune restoration disease to remission of specific OIs. In the present study, *Mycobacterium avium* complex infection recurred in 3 persons receiving antimycobacterial therapy and HAART. At the time of the initial *M. avium* infection, the mean CD4 cell count was 22.3 cells/mm³, and the HIV viral load was 181,133 copies/mL. Relapse occurred a mean of 14.3 months after the first episode; the mean follow-up CD4 cell count was 89/mm³ (mean elevation of 66 cells/mm³), and the HIV viral load was <400 copies/mL in each patient. *M. avium* was isolated from blood (1 patient), blood and lymph node (1), and small-bowel tissue (1). *M. avium* infection may recur as a generalized or focal disease in those who are receiving antimycobacterial agents but whose HAART-associated CD4 cell recovery, although significant, is not optimal.

In addition to reducing the rates of opportunistic infections (OIs) [1, 2], highly active antiretroviral therapy (HAART) may affect the clinical course of OIs. Immune restoration disease, for example, may occur within 6 months after beginning HAART in patients who have established or clinically latent OIs, such as infections due to *Mycobacterium avium* complex [3, 4], *Cryptococcus neoformans* [5, 6], *Mycobacterium tuberculosis* [7], or cytomegalovirus [8, 9], or who have herpes zoster [10]. In those with a microbiologically established OI, the responsible pathogen has not been recovered when immune reconstitution disease is recognized [6, 7], which suggests a pathogen-specific immune response rather than a reactivation of infection.

HAART has also impacted the management of several AIDS-associated OIs. Remission of OIs [11–15] may occur in persons receiving HAART, despite discontinuation of specific antimicrobial treatment. To our knowledge, however, recurrence of an OI in a patient receiving HAART and appropriate antimicrobial therapy for that particular OI has not been reported. We describe the clinical features of 3 persons receiving antimycobacterial treatment in whom *M. avium* infection recurred after a virological response to HAART had been demonstrated.

**Patients and Methods**

Patients identified in this report were admitted to the University of Michigan Health System (Ann Arbor, MI) or the Detroit Medical Center (Detroit) from March 1996 through January 1999. Clinical data were abstracted from medical records.

**Results**

The clinical features of each patient are described in the individual case reports below and are outlined in table 1. The mean (±SD) age of the 3 patients with recurrent *M. avium* infection was 40 ± 5.7 years (range, 32–50 years). All were male; 2 were white and 1 was black. No patient had an HIV-associated illness other than *M. avium* infection. At the time of the initial episode of *M. avium* infection, the mean CD4 cell count was 22.3 ± 6.8 cells/mm³, and the HIV viral load was 181,133 ± 23.1 copies/mL. HAART was begun within 2 weeks of initiation of antimycobacterial therapy for each patient.

After HAART, the mean CD4 cell count was 89 ± 9.5 cells/mm³ (mean elevation of 66 cells/mm³), and the HIV viral load was below the limit of detection in each patient (mean decline in HIV RNA, 180,000 copies/mL). Each patient’s *M. avium*-associated symptoms completely resolved; *M. avium* infection recurred 14.3 ± 3.9 months (range, 7–23 months) after the first episode. *M. avium* was isolated from the following sites during the second episode of *M. avium* infection: blood (1), blood and lymph node (1), and small bowel tissue (1).

**Case 1.** Patient 1 was a 37-year-old white man whose HIV infection was diagnosed when he developed fever, weight loss, and skin lesions on his right leg that enlarged over 3 months. Administration of clarithromycin and ethambutol was begun when *M. avium* complex was isolated in cultures of blood and skin lesions. The CD4 cell count was 5 cells/mm³, and the HIV...
viral load was 205,000 copies/mL. Administration of zidovudine, lamivudine, and indinavir was initiated 10 days after the start of antymycobacterial treatment. The patient fully regained the lost weight, and his fever and skin lesions resolved within 21 days of the beginning of antymycobacterial treatment.

Eleven months after the beginning of HAART, the follow-up CD4 cell count was 66 cells/mm³, and the HIV viral load was <400 copies/mL. The CD4 cell count had been measured 3 times after HAART; it had been stable and had not exceeded 66 cells/mm³. Within 1 month of the most recent CD4 cell measurement, he developed lower back pain and recurrent fever, of 2 weeks’ duration; no night sweats or weight loss occurred. Splenomegaly was noted for the first time on examination.

Abdominal CT scanning confirmed this finding and revealed multiple retroperitoneal lymph nodes (3- to 4-cm diameter). A percutaneous CT-guided biopsy of 1 retroperitoneal node revealed granulomas containing numerous acid-fast organisms. M. avium complex was isolated on day 18 in 2 cultures: 1 of blood drawn 10 days before the CT-guided procedure and 1 of the retroperitoneal lymph node. Ciprofloxacin, rifabutin, and prednisone (30 mg/d) were added to the treatment regimen, and the fever and back pain resolved within 2 weeks.

Case 2. Patient 2 was a 50-year-old white man whose HIV infection was diagnosed when he presented with fever and sweats that persisted for 2 months. Administration of clarithromycin and ethambutol was begun when M. avium complex was isolated in a culture of bone marrow. The CD4 cell count was 34 cells/mm³, and the HIV viral load was 188,400 copies/mL. Administration of zidovudine, lamivudine, and nelfinavir was initiated within 14 days of the start of treatment. His fever resolved within 28 days of the beginning of antymycobacterial treatment.

Twenty-five months after the beginning of HAART, the follow-up CD4 cell count was 69 cells/mm³, and the HIV viral load was <400 copies/mL. The CD4 count had been measured 7 times after HAART; it had been stable and had not exceeded 69/mm³. Within 2 weeks of the most recent CD4 cell measurement, he developed recurrent fever and abdominal pain that persisted for 2 weeks.

Thickening of the wall of the small intestine was identified on an abdominal CT scan. Endoscopy revealed numerous raised pink nodules (1- to 2-cm diameter) in the lumen of the small bowel at the distal duodenum and proximal jejunum. Granulomas containing acid-fast organisms were seen on histopathology of the small bowel mucosa and muscularis layers. M. avium complex was isolated in cultures of small-bowel specimens after 19 days of growth; isolate cultures of blood drawn 2 weeks before the bowel biopsy revealed no growth. Ciprofloxacin, rifabutin, and prednisone (40 mg/d) were added to the treatment regimen, and the fever and abdominal pain resolved within 1 week.

Case 3. Patient 3 was a 33-year-old black man who presented because of fever, diarrhea, and hepatomegaly. Administration of clarithromycin and ethambutol was begun when M. avium complex was isolated in cultures of blood. The CD4 cell count was 28 cells/mm³, and the HIV viral load was 150,000 copies/mL. Administration of zidovudine, lamivudine, saquinavir, and ritonavir was begun within 1 week. The fever, diarrhea, and hepatomegaly resolved within 1 month.

Four months after the beginning of HAART, the follow-up CD4 cell count was 132 cells/mm³, and the HIV viral load was <400 copies/mL. The CD4 cell count had been measured once, 1 month after HAART; it was 141/mm³. Seven months after beginning HAART, he developed abdominal pain and recurrent fever of 3 weeks’ duration. M. avium complex was isolated in cultures of blood, and ofloxacin and rifabutin were added to the treatment regimen. No clinical follow-up data are available.

Discussion

We describe 3 persons receiving antymycobacterial agents in whom M. avium infection recurred as a focal or generalized infection, long after the beginning of HAART (mean interval, 14.3 months). In case 2, the clinical features (abdominal pain), radiological findings (thickened small bowel), endoscopic appearance (nodules in the bowel lumen), histopathologic features (granulomas with acid-fast organisms), culture results, and clinical response to additional antymycobacterial agents favor a diagnosis of focal gastrointestinal M. avium infection rather than colonization [16]. To our knowledge, recurrence of M. avium infection or other AIDS-associated OIs in those responding virologically to HAART and appropriate antimicrobial treatment has not been described. The virological response suggests that the patients were adhering to their HAART regimen, which is probably an indicator of adherence to specific anti-

Table 1. Clinical features of 3 patients receiving highly active antiretroviral therapy (HAART) and antymycobacterial therapy (AMT) in whom Mycobacterium avium infection recurred.

<table>
<thead>
<tr>
<th>Characteristic of M. avium infection</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Mean value for all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of culture isolate</td>
<td>Blood, skin</td>
<td>Blood, lymph node (abdomen)</td>
<td>Bone marrow</td>
<td>Blood</td>
</tr>
<tr>
<td>Initial episode, before HAART</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence, after HAART</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of recurrence after AMT, mo</td>
<td>11</td>
<td>19</td>
<td>25</td>
<td>14.3</td>
</tr>
<tr>
<td>CD4 cells/mm³ (change in value)</td>
<td>66 (+61)</td>
<td>69 (+35)</td>
<td>132 (+104)</td>
<td>89 (+66)</td>
</tr>
<tr>
<td>HIV plasma viral load, copies/mL (change in value)</td>
<td>&lt;400 (~204,600)</td>
<td>&lt;400 (~188,000)</td>
<td>&lt;400 (~149,600)</td>
<td>&lt;400 (~180,000)</td>
</tr>
</tbody>
</table>
mycobacterial therapy. In light of the absence of diarrhea or known malabsorption, poor adherence to therapy with antimycobacterial agents or poor absorption is an unlikely explanation for the recurrence of \textit{M. avium} infection.

The manifestations in the cases described in this report are distinct from the currently recognized manifestations of immune reconstitution disease [6, 7, 13]. The late onset after initiation of HAART and the recovery of the responsible pathogen at the time of relapse of symptoms in those with a microbiologically established OI are features that distinguish the cases in our series from previously described cases of immune restoration syndrome [6, 7]. It is possible, however, that our cases represent a previously unrecognized variation of immune restoration disease.

Immune restoration disease has been described as occurring in 25% of persons within 6 months of receipt of HAART [6]. OIs such as herpes zoster [10], \textit{M. avium} infection [3, 4], cryptococcal meningitis [4], and cytomegalovirus retinitis [8] may first appear only after the beginning of HAART. It is possible that clinically silent infections first become evident when functionally competent immune cell expansion takes place after initiation of HAART in this setting [6, 7].

Immune restoration disease may also occur in those who are receiving appropriate treatment for a previously recognized OI as well as HAART, when a focal organ such as a lymph node enlarges [6, 7]. In this setting, inflammation, possibly resulting from a pathogen-specific immune response rather than reactivation of infection, is demonstrated in the resected tissue in the absence of the organism causing the infection.

The CD4 cell recovery in persons with recurrence of \textit{M. avium} infection in this series was of lower magnitude than that reported in HAART intervention trials [17–19]. In the clinical setting, as many as 20% of patients receiving HAART do not have an increase in CD4 cell count above the baseline value [13]. In addition, the mean restored CD4 cell count of patients in this report, 89/mm$^3$, is within the range at which OIs continue to occur despite HAART. For example, among persons receiving HAART whose CD4 cell counts fail to increase above this range, the rate of primary OI is greater than among those whose CD4 cell counts increase to $>200$/mm$^3$ [13, 20, 21]. Furthermore, persons receiving HAART who have primary OIs and persons not receiving HAART have similar CD4 cell counts (44 cells/mm$^3$ and 25 cells/mm$^3$, respectively) [22]. The present report extends these observations by documenting that an OI may recur in persons who do not have a significant HAART-associated CD4 cell count recovery.

The breakthrough of specific OIs in persons receiving HAART described in this series contrasts with reports of HAART-associated remission of OIs, such as \textit{M. avium} infection [11], cytomegalovirus retinitis [13], and cryptosporidiosis [15], after withdrawal of specific therapy. The marked quantitative elevation of CD4 cell counts in those cases of HAART-associated OI remission (means of 212 cells/mm$^3$ [11], 242 cells/mm$^3$ [13], and 226 cells/mm$^3$ [15]) distinguishes those from the cases in our series. In our series, for example, the restored mean CD4 cell count of 89/mm$^3$, although above the 50/mm$^3$ threshold below which \textit{M. avium} infection most often occurs, is well below the mean value reported in these series [11, 13, 15].

It is possible that changes in qualitative CD4 cell responses may also contribute to HAART-associated remission of specific OIs. Improved immunologic function, such as lymphoproliferative responses to \textit{M. avium} [23, 24] and cytomegalovirus [25–27], for example, may also contribute to remission of these specific OIs in persons receiving HAART. Given that each episode recurred with a CD4 cell count above the threshold for risk of \textit{M. avium} infection, it is possible that the patients in this series lacked these \textit{M. avium}–specific immune responses. Measurements of lymphoproliferative responses in each case to verify this hypothesis, however, were not performed.

Recurrence of \textit{M. avium} infection may occur in HAART recipients with advanced HIV infection who have significant but suboptimal CD4 cell count recovery. This series supports the conclusion of the US Public Health Service guidelines that state that discontinuation of chronic maintenance antimycobacterial therapy for patients with \textit{M. avium} infection who have a HAART-associated CD4 cell increase of $>100$ cells cannot be sanctioned [28]. The HAART-associated CD4 cell count elevations in this series were of lower magnitude than the average elevations reported in HAART trials [17–19].

Recurrence of an OI with features distinct from the currently described manifestations of immune reconstitution disease may represent a new variation of this disease. Although remission of OIs in patients receiving HAART has been described, this series supports the strategy of continuing specific therapy for a microbiologically established OI in persons whose CD4 cell number does not increase significantly above the level at which there is risk for that OI.

References


