Human Immunodeficiency Virus Type 1–Related Pulmonary *Mycobacterium xenopi* Infection: A Need to Treat?

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We report treatment decisions and outcomes for 20 patients who were infected with human immunodeficiency virus type 1 (HIV-1) and were receiving highly active antiretroviral therapy (HAART) who had respiratory symptoms and from whom *Mycobacterium xenopi* was isolated. All patients also had coexisting pulmonary pathologic conditions. The median blood T cell CD4 count was 37 cells/μL (range, 2–480 cells/μL). Fifteen of 20 patients received no antimycobacterial therapy and remain healthy after a median of ∼4 years of follow-up, and 2 patients required treatment specifically for *M. xenopi* infection, both showing clinical improvement. We conclude that pulmonary *M. xenopi* isolation in HIV-1 patients receiving HAART does not usually require specific treatment.

*Mycobacterium xenopi* is an opportunistic pathogen that most commonly infects the lungs, bones, and joints [1]. Infection may occur through aerosol inhalation, water ingestion, or contact with contaminated surgical instruments. Nosocomial colonization and infection have been associated with colonization of hospital water systems [2]. Although fairly rare, isolation of nontuberculous mycobacteria (NTM) has been increasing among both HIV-1–negative and HIV-1–positive individuals, at least in part because of improved culture-detection systems and identification techniques [3, 4]. This has recently prompted a British Thoracic Society (BTS) and Joint Tuberculosis Committee review of diagnosis and management of NTM infection [5]. However, there is still very little evidence from controlled clinical trials on the basis of which to make treatment decisions, particularly in the context of immunosuppressive disorders such as HIV-1, and this is reflected in these guidelines. Most of the evidence predates the widespread use of HAART; but it has been suggested that lifelong treatment with rifampicin or rifabutin, ethambutol, and clarithromycin be employed. Given the success of HAART at reconstituting the immune system, this may no longer be necessary. For example, before the advent of HAART, lifelong primary and secondary prophylaxis for *Mycobacterium avium* complex (MAC) infection was recommended for patients with blood CD4 cell counts of <50 cells/μL. It has been demonstrated that, once CD4 cell counts are consistently >100 cells/μL while receiving HAART, MAC prophylaxis can be stopped safely [6]. Many opportunistic infections among patients with advanced HIV-1 are now treated effectively with antiretroviral therapy. Clinical practice is changing in advance of high-quality published evidence. We therefore sought to retrospectively review treatment decisions and outcomes after *M. xenopi* isolation among patients treated with HAART at 2 large Academic Medical Centers in London.

**Methods.** The medical and laboratory records of all HIV-1–positive patients who were found to have significant isolation of *M. xenopi* from respiratory cultures in 1996 or later, when widespread use of HAART was implemented, were examined. Data were collected for the period through the patient’s last clinic visit in 2001 or until the patient’s death. An isolation of *M. xenopi* was considered to be significant if the isolate was obtained from bronchoalveolar lavage fluid (BAL) samples or from multiple sputum samples obtained from a patient with respiratory symptoms. Blood culture results were also recorded. All radiological findings from the time at which the sample was obtained were reviewed, as were the findings of any subsequent imaging.

**Results.** In the 5-year period under review, 20 patients were identified as meeting the study criteria (table 1). Eighteen of the 20 patients were male, and the median age was 38 years (range, 24–49 years). Most patients (14 [70%] of 20) were identified on the basis of positive BAL culture results, although, for 3 of these patients, an *M. xenopi* isolate was also obtained from multiple sputum samples. Six patients were identified on the basis of isolates obtained from multiple sputum samples alone. For 9 patients, *M. xenopi* was isolated at initial presentation with advanced HIV-1 infection. None of the subjects had *M. xenopi* isolates obtained from mycobacterial blood cultures.

All 20 patients had ≥1 coexisting pulmonary disease at the time when the samples that subsequently revealed *M. xenopi* were obtained. Bacterial pneumonia was the most common
<table>
<thead>
<tr>
<th>Patient</th>
<th>Symptoms (duration in weeks)</th>
<th>CD4 cell count, cells/µL</th>
<th>Source of isolate</th>
<th>Copathogens and/or alternative diagnosis</th>
<th>Therapy for <em>M. xenopi</em> infection</th>
<th>Duration, months</th>
<th>Pulmonary response</th>
<th>Final diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Productive cough, breathlessness, fever (2)</td>
<td>2</td>
<td>S, B</td>
<td>Bacterial pneumonia, pulmonary KS</td>
<td>Inh (300), Rbt (300), Eth (1200), Pza (2000)</td>
<td>1</td>
<td>Good</td>
<td>Bacterial pneumonia</td>
</tr>
<tr>
<td>2</td>
<td>Dry cough, breathlessness (4)</td>
<td>5</td>
<td>B</td>
<td>Pulmonary KS, PCP</td>
<td>NA</td>
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<td>Good</td>
<td>Pulmonary KS, PCP</td>
</tr>
<tr>
<td>3</td>
<td>Productive cough (4)</td>
<td>10</td>
<td>S, B</td>
<td>Bacterial pneumonia</td>
<td>NA</td>
<td>NA</td>
<td>Good</td>
<td>Bacterial pneumonia</td>
</tr>
<tr>
<td>4</td>
<td>Productive cough, breathlessness, fever (8)</td>
<td>10</td>
<td>S</td>
<td>Bacterial pneumonia, bronchiectasis</td>
<td>NA</td>
<td>NA</td>
<td>Good</td>
<td>Bacterial pneumonia</td>
</tr>
<tr>
<td>5</td>
<td>Chest pain, cough (1)</td>
<td>20</td>
<td>B</td>
<td>PCP</td>
<td>NA</td>
<td>NA</td>
<td>Good</td>
<td>PCP</td>
</tr>
<tr>
<td>6</td>
<td>Dry cough, breathlessness, fever (3)</td>
<td>20</td>
<td>B</td>
<td>Pulmonary KS, PCP</td>
<td>NA</td>
<td>NA</td>
<td>Good</td>
<td>Pulmonary KS, PCP</td>
</tr>
<tr>
<td>7</td>
<td>Productive cough, chest pain, breathlessness, fever (8)</td>
<td>20</td>
<td>S</td>
<td>Bacterial pneumonia</td>
<td>Inh (300), Rbt (300), Eth (900), Clm (1000)</td>
<td>16</td>
<td>Good</td>
<td><em>M. xenopi</em> infection</td>
</tr>
<tr>
<td>8</td>
<td>Dry cough, breathlessness, night sweats (2)</td>
<td>20</td>
<td>B</td>
<td>Pulmonary cryptococcus</td>
<td>NA</td>
<td>NA</td>
<td>Good</td>
<td>Pulmonary cryptococcus</td>
</tr>
<tr>
<td>9</td>
<td>Productive cough, fever, weight loss (4)</td>
<td>20</td>
<td>B</td>
<td>Previous cavitatory PCP, pulmonary KS</td>
<td>Rbt (300), Eth (900), Clm (1000)</td>
<td>36</td>
<td>Good</td>
<td><em>M. xenopi</em> infection</td>
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<tr>
<td>10</td>
<td>Productive cough, breathlessness, fever, weight loss (8)</td>
<td>32</td>
<td>S, B</td>
<td>PCP</td>
<td>NA</td>
<td>NA</td>
<td>Good</td>
<td>PCP</td>
</tr>
<tr>
<td>11</td>
<td>Dry cough, breathlessness, night sweats (1)</td>
<td>41</td>
<td>B</td>
<td>Bacterial pneumonia</td>
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<td>NA</td>
<td>Good</td>
<td>Bacterial pneumonia</td>
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<td>12</td>
<td>Productive cough, fever, weight loss (8)</td>
<td>48</td>
<td>S</td>
<td>Tuberculosis</td>
<td>Inh (300), Rbt (300), Eth (900), Pza (2000)</td>
<td>6</td>
<td>Death(^a)</td>
<td>Tuberculosis</td>
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<td>13</td>
<td>Productive cough, breathlessness, fever (1)</td>
<td>50</td>
<td>S</td>
<td>Bacterial pneumonia</td>
<td>NA</td>
<td>NA</td>
<td>Good</td>
<td>Bacterial pneumonia</td>
</tr>
<tr>
<td>14</td>
<td>Breathlessness, fever (2)</td>
<td>50</td>
<td>B</td>
<td>PCP</td>
<td>NA</td>
<td>NA</td>
<td>Good</td>
<td>PCP</td>
</tr>
<tr>
<td>15</td>
<td>Intermittent cough (3), fever (1)</td>
<td>70</td>
<td>S</td>
<td>Pulmonary KS, extrapulmonary pneumocystosis</td>
<td>NA</td>
<td>NA</td>
<td>Good</td>
<td><em>M. xenopi</em> infection</td>
</tr>
<tr>
<td>16</td>
<td>Breathlessness, fever, sweats (1)</td>
<td>90</td>
<td>B</td>
<td>PCP, recent cavitating bacterial pneumonia</td>
<td>NA</td>
<td>NA</td>
<td>Good</td>
<td>PCP</td>
</tr>
<tr>
<td>17</td>
<td>Dry cough, breathlessness, fever (2)</td>
<td>116</td>
<td>B</td>
<td>Pulmonary KS, bacterial pneumonia</td>
<td>NA</td>
<td>NA</td>
<td>Good</td>
<td>Pulmonary KS, bacterial pneumonia</td>
</tr>
<tr>
<td>18</td>
<td>Sweats, myalgia, weight loss (3)</td>
<td>160</td>
<td>B</td>
<td>CMV pneumonitis</td>
<td>NA</td>
<td>NA</td>
<td>Good</td>
<td>CMV pneumonitis</td>
</tr>
<tr>
<td>19</td>
<td>Night sweats (2), breathlessness (4)</td>
<td>380</td>
<td>B</td>
<td>Bacterial pneumonia</td>
<td>NA</td>
<td>NA</td>
<td>Good</td>
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</tr>
<tr>
<td>20</td>
<td>Productive cough, sweats, weight loss, diarrhoea (6)</td>
<td>480</td>
<td>S</td>
<td>MAC cervical adenitis, cryptococcal meningitis</td>
<td>Inh (300), Rbt (300), Eth (900), Clm (1000)</td>
<td>9</td>
<td>Good</td>
<td>MAC cervical adenitis</td>
</tr>
</tbody>
</table>

**NOTE.** B, positive bronchoalveolar lavage fluid culture; CMV, cytomegalovirus; Clm, clarithromycin; Eth, ethambutol; Inh, isoniazid; KS, Kaposi sarcoma; MAC, *Mycobacterium avium* complex; NA, not applicable; PCP, *Pneumocystis carinii* (jiroveci) pneumonia; Rbt, rifabutin; S, multiple positive sputum cultures; Pza, pyrazinamide.

\(^a\) Death due to hepatitis C cirrhosis.
coexisting pulmonary disease (found in 45% of patients), followed by Pneumocystis carinii (jiroveci) pneumonia (PCP) (35%), Kaposi sarcoma (25%), MAC infection (5%), cytomegalovirus infection (5%), Mycobacterium tuberculosis (TB) infection (5%), and pulmonary cryptococcoma associated with disseminated cryptococcal disease (5%).

The median CD4 cell count at diagnosis was 37 cells/μL (range, 2–480 cells/μL), with only 2 patients having counts of >200 cells/μL. HAART was initiated for all patients, and regimens consisted of a combination of 3 or 4 agents, including zidovudine, lamivudine, stavudine, efavirenz, nevirapine, ritonavir, indinavir, and saquinavir. After a median follow-up of 44 months (range, 15–66 months), the median CD4 cell count had risen to 324 cells/μL (range, 113–970 cells/μL).

Five patients received antimycobacterial antibiotics, but for only 2 patients was the initiation of therapy the consequence of suspected M. xenopi infection. The other patients required treatment for coexisting TB or MAC, and 1 patient received treatment with empirical antituberculosis therapy until M. xenopi was identified after 1 month (table 1).

The 2 patients treated for M. xenopi infection both had baseline blood CD4 cell counts of 20 cells/μL. Their cases were managed with a combination of rifabutin, ethambutol, isoniazid, and clarithromycin, one for 16 and the other for 36 months. In both cases, a satisfactory clinical response was achieved. M. xenopi isolates were grown from respiratory secretions obtained from the latter subject until month 12 of therapy.

Radiological changes were attributed to the coexisting pathologic conditions in all untreated cases and were resolved with specific medication. The subject who required prolonged treatment for coexisting TB or MAC, and 1 patient received treatment with empirical antituberculosis therapy until M. xenopi was identified after 1 month (table 1).

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During follow-up, 1 of 20 patients died. The death occurred >1 year after isolation of M. xenopi and arose from hepatic failure secondary to chronic hepatitis C. The patient had been successfully treated for pulmonary tuberculosis (table 1).

**Discussion.** Improved culture techniques and a better understanding of opportunistic mycobacteria are leading to an increasing number of isolations of M. xenopi [7]. It is difficult to get accurate figures concerning the incidence of M. xenopi infection, as it is not a notifiable disease. A study conducted in Germany demonstrated an incidence of 16.6 cases per 100 person-years among hospitalized patients with AIDS prior to 1994, but this rate is 2.5 times higher among patients with a CD4 cell counts of <40 cells/μL [8]. There are >500 cases reported in the literature, but, of these, only 70 cases seem to document true instances of disease [9], suggesting that colonization of the respiratory tract may be the most common explanation for isolation of M. xenopi.

The patients who were identified each fulfilled the accepted criteria for M. xenopi infection, but only 2 patients were felt to require therapy [5]. Fifteen patients received no antimycobacterial treatment, despite having advanced HIV-1 infection and median CD4 cell counts of <50 cells/μL. Immune reconstitution occurred in all patients who received antiretroviral therapy, with a median increase in CD4 cell count to 324 cells/μL. The success of HAART in improving immune function may mean that opportunistic organisms like M. xenopi do not increase rates of morbidity or mortality, as has previously been suggested [8]. The research committee of the BTS described a 5-year mortality rate of 57% between 1987 and 1992 among HIV-1–negative individuals who were infected with M. xenopi. The rate of mortality from M. xenopi infection found in this BTS study was higher than that from MAC or Mycobacterium malmoense infection [10]. In an HIV-1–positive population, El-Sohil et al. [11] reported a pre-HAART survival rate of only 27% among untreated patients with NTM infection between 1989 and 1995. This compares with a survival rate of 95% in our patient population 4 years after isolation of M. xenopi from patients with respiratory symptoms.

All of the patients in this series had additional pulmonary pathologic findings at the time of M. xenopi isolation, as has been previously demonstrated [12]. The response of the coexisting pathologic condition to treatment implies that M. xenopi infection is usually not responsible for symptomatic disease at the time of presentation, in contrast to the findings of some previous studies [13–16]. It has previously been suggested that patients become colonized with this mycobacterium as their immunity declines and that immune reconstitution after HAART may be associated with clinical symptoms [17]. Our study did not demonstrate this, though it is certainly a possibility, given the reported frequency of this phenomenon among patients with mycobacterial infection.

Two patients had clinical and radiological features suggestive of disease progression and were specifically treated for M. xenopi infection. Both patients had low CD4 cell counts, though these were much the same as the median value for the whole population. There appeared to be no features that could distinguish these 2 subjects from the other patients. It is interesting to note that 1 individual remained culture positive after 1 year. He had preexisting pulmonary cysts, and it may be that he was unable to rapidly clear his M. xenopi infection because it was relatively inaccessible to both antibiotics and his new (possibly more focused) immune response.

Although our study subjects all had other pulmonary pathologic conditions, the question arises: what should be done if
a patient has respiratory symptoms and only *M. xenopi* is isolated? We would suggest that a reasonable strategy is to initiate HAART if possible and withhold specific therapy for *M. xenopi*. Clearly, this could be regarded as a high risk approach, and there are patients for whom this policy may not currently be advisable. If a decision is taken to treat with HAART alone, then it would seem important to monitor respiratory secretion cultures for the development of *M. xenopi* negativity. This may be difficult, as sputum will often disappear on treatment and serial BAL may be impractical. We found no evidence for dissemination of *M. xenopi*, as measured by mycobacterial blood culture. Thus, the infections seem localized to the lung; blood culture is not a useful way to assess response.

Treatment regimens for *M. xenopi* infection vary substantially in most published series [18–23], and no clearly superior combination therapy has been demonstrated. The number of participants in our study is too small for us to add to this debate. However, it should be remembered that drug interactions, as well as side effects, a large pill-burden, and potentially poor adherence to therapy, are commonly associated with the drugs used in treating HIV-mycobacterial coinfection.

Laboratory contamination has been reported as a cause of *M. xenopi* isolation. This explanation is unlikely in our series, as the case records were collected from different hospitals with independent laboratories. In addition, the inclusion criteria required either an isolate obtained from BAL samples or multiple isolates obtained from sputum samples. Thus, if laboratory contamination were responsible for any of these cases being identified, it would likely be a small proportion. Given this, it is surprising that *M. xenopi* infection was associated with such a benign outcome. This further adds to the evidence supporting the use of HAART.

Radiologic findings are frequently unhelpful in diagnosing *M. xenopi* infection at the time of isolation because of the high incidence of additional pulmonary pathologic conditions [12], as was the case in our study. However, once these additional pulmonary pathologic conditions have been treated, radiological findings may have a role in monitoring the disease or its progression. There are no characteristic radiological signs, the most-commonly seen abnormalities being a unilateral, basal area of consolidation or a reticular interstitial infiltration [24]. Lymphadenopathy is rarely noted, and there are no features that enable the different mycobacteria to be distinguished [11]

This study provides evidence to support the proposal that *M. xenopi* infection has a benign outcome among HIV-1 patients receiving effective HAART. It suggests that the advantages of withholding mycobacterial treatments—advantages which include avoidance of both drug-interactions and increased pill-burden—outweigh the small risk of clinical deterioration. Adding multiple-drug antimycobacterial therapy to HAART may lead to poor adherence and to inadequate treatment of both conditions.

**Summary.** Our study confirms that the isolation of pulmonary *M. xenopi* in an HIV-1 infected population is usually associated with severe immune suppression and the presence of other pathogens. Provided that there is a sustained improvement in systemic immunity with antiretroviral therapy, the isolation of *M. xenopi* from respiratory secretions may not indicate that specific treatment is required. Our study suggests that, in most cases, effective immune reconstitution is sufficient, without the need for antimycobacterial drugs. Mortality rates among these patients now appear to be considerably lower than previously reported.

**References**


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