

# Mycobacterial infection in patients infected with the human immunodeficiency virus

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## Abstract

Of 207 homosexual or bisexual patients with the acquired immune deficiency syndrome (AIDS), 24 with the AIDS related complex, and 39 with asymptomatic HIV infection, 32 patients were found to have mycobacterial infection. *Mycobacterium tuberculosis* was found in 13 patients with AIDS and in two with the AIDS related complex. *M avium-intracellulare* was found in 15 patients with AIDS and was disseminated in 12. One patient was infected with *M kansasii* and one with *M ulcerans*. Invasive procedures were frequently required to obtain positive bacteriological results. Subclinical carriage of *M avium-intracellulare* and other mycobacteria thought to be non-pathogenic was common in patients seronegative for the human immunodeficiency virus and at all stages of human immunodeficiency virus infection. All but one isolate of *M tuberculosis* were fully sensitive to standard anti-mycobacterial antibiotics. Response to treatment was usually rapid. *M avium-intracellulare* isolates were all resistant to first line agents in vitro, and antibiotics such as ansamycin and amikacin were required to obtain a clinical response.

Mycobacterial infection causes considerable morbidity and mortality in patients with human immunodeficiency virus (HIV) infection.<sup>1</sup> Tuberculosis may occur at any stage of the disease, often at extrapulmonary sites.<sup>2</sup> The prevalence of tuberculosis in patients with AIDS in the United States is from 2% to 20% and is higher in intravenous drug abusers.<sup>3,4</sup> HIV infection is common in Zambian patients with tuberculosis.<sup>5</sup> Infection with *M avium-intracellulare* occurs in patients with AIDS and profound immunosuppression, the incidence being reported as 17-56% in American patients (the higher figures are from necropsy data<sup>6,7</sup>). The prevalence of *M avium-intracellulare* infection in British patients with AIDS has been reported as 5% and of *M tuberculosis* infection as 11%.<sup>8,9</sup>

We have studied mycobacterial infections in patients with AIDS retrospectively and in HIV seropositive homosexual and bisexual men.

## Methods

Clinical, bacteriological, and treatment data were collected from case notes from the start of

the UK AIDS epidemic (1983) until March 1988. Chest radiographs were reviewed blind and independently by two radiologists in conjunction with chest radiographs from patients with other HIV related conditions. Data on BCG vaccination were insufficient for analysis.

Data were obtained from two sources: (1) the records of 207 patients with AIDS attending St Mary's Hospital; (2) a study of the prevalence of carriage of stool mycobacteria in 63 homosexual and bisexual men (39 with asymptomatic HIV infection and 24 with the AIDS related complex).

Smears from all specimens were stained for acid fast bacilli with auramine. Kirschner medium was inoculated (solid samples were not crushed) and incubated for up to 14 weeks. Growth of mycobacteria was confirmed in cultures that became turbid with auramine staining. If positive, these were subcultured on Lowenstein-Jensen medium. Blood samples for culture of mycobacteria were taken into Dupont isolators. Lysed blood samples, stool specimens, and bronchoalveolar lavage fluid were treated as above as well as being cultured by the Bactec radiometric method.<sup>10</sup> Necropsy material was not available.

Indications for treatment in individual cases are outlined below. The likely benefits were discussed before treatment was initiated. Despite the frequency of side effects and of other medication, compliance appeared to be good. Patients attended for follow up at least monthly.

After review of the case notes non-tuberculous mycobacterial isolates that did not appear to be related to clinical disease were considered to be contaminants.

## Results

### *Mycobacterium tuberculosis*

Tuberculosis was established bacteriologically in 15 homosexual and bisexual patients without a history of intravenous drug abuse. All had symptoms; fever (11 patients) and respiratory symptoms (10 patients) were common. Six patients had diarrhoea, four lymphadenopathy, and two hepatomegaly. Extrapulmonary tuberculosis in an HIV seropositive individual is now a diagnostic criterion for AIDS<sup>11</sup> and was the first reason to diagnose AIDS in four patients (table 1). Two patients with the AIDS related complex presented with pulmonary tuberculosis limited to the lungs; one progressed to AIDS within five months, when he developed cryptosporidiosis; and the other is

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Table 1 Site of *Mycobacterium tuberculosis* infection in 207 patients with AIDS and 24 with AIDS related complex

	Gastro-intestinal	Lung	Disseminated
AIDS related complex		2	
First AIDS infection	2		2
Previous AIDS diagnosis	2	4	3

clinically stable. For the nine patients who had previously had a major opportunist infection, such as *Pneumocystis carinii* pneumonia, or Kaposi's sarcoma, the mean time between the diagnosis of AIDS and the development of tuberculosis was 5.4 (range 2–12) months.

Seven chest radiographs from patients with pulmonary or disseminated disease without copathogens were available for review; two were normal and three showed cavities, two reticulonodular shadowing, and five air space shadowing. Reticulonodular shadowing or cavitation in the upper zone was considered suggestive of *M. tuberculosis* infection. On the basis of these criteria, four of the seven chest radiographs suggested tuberculosis.

Positive cultures were obtained from bronchoalveolar lavage fluid (5), transbronchial biopsy material (3), lavage fluid and transbronchial biopsy material (2), stool (6), lymph node biopsy material (2), pleural fluid, lavage fluid, stool, and marrow aspirate (1). Acid fast bacilli were never seen on direct examination of bronchoalveolar lavage fluid. Coinfections with *P. carinii*, *Staphylococcus*, and *Haemophilus influenzae* each occurred in one patient; all were diagnosed from bronchoalveolar lavage fluid.

All *M. tuberculosis* isolates tested were sensitive to streptomycin and isoniazid and all except one to rifampicin and ethambutol. Eleven patients were treated with rifampicin, ethambutol, isoniazid, and pyrazinamide and nine responded clinically. The two non-responders had AIDS. Death was a direct result of tuberculosis in only one patient, who declined treatment. The median survival of the eight patients with AIDS from the time of diagnosis of tuberculosis was five months.

#### *Mycobacterium avium-intracellulare*

**Isolation** *M. avium-intracellulare* was isolated from 20 patients. Isolation in one patient occurred only during a bacterial chest infection, which resolved with amoxicillin alone. This isolate was considered to be a contaminant or asymptotically carried organism.

**Enteritis** Seven patients had *M. avium-intracellulare* isolated from stool alone. Two had no symptoms and, of the remainder with diarrhoea or abdominal pain, two had other enteric pathogens (cytomegalovirus in one and cytomegalovirus with cryptosporidiosis in the other). Hence symptomatic enteritis apparently due to *M. avium-intracellulare* alone occurred in three patients only, all of whom had AIDS (mean duration nine months). It did not contribute directly to death in the two who died. Two patients were treated, one with rifampicin, isoniazid, ethambutol, and pyrazinamide and the other with ansamycin instead of rifampicin; neither responded clinically or microbiologically.

Table 2 Antibiotic sensitivities of *Mycobacterium avium-intracellulare* isolates

Antibiotic	No of isolates	
	sensitive	tested
Amikacin	2	5
Ansamycin	7	9
Capreomycin	2	15
Ciprofloxacin	0	20
Clofazamine	0	20
Cycloserine	11	13
Ethambutol	0	20
Isoniazid	0	20
Rifampicin	1	12
Streptomycin	0	20

**Disseminated infection** Isolation from two or more sites or from blood was interpreted as disseminated infection. This occurred in 12 patients with AIDS (mean time after first opportunist infection 10.4 months). All were febrile, six had diarrhoea, five cough or dyspnoea, three lymphadenopathy, and three hepatomegaly. No other pathogens were isolated to account for these features. Culture positive samples came from sputum (4) cases, liver biopsy specimens (4), lymph node biopsy specimens or aspirates (4), blood culture (3), bronchoalveolar lavage and fluid and urine (1). Acid fast bacilli were present on a direct smear of one sputum sample only (and in bronchoalveolar lavage fluid from the same patient). Four patients had pure isolates from sputum and lavage fluid. The chest radiographs showed a perihilar haze in three of these cases, which was interpreted as *P. carinii* pneumonia. One chest radiograph showed reticulonodular shadowing and cavities, attributed to mycobacterial infection. Median survival from diagnosis of disseminated *M. avium-intracellulare* infection was five months in the patients not treated.

**Treatment** The in vitro antibiotic sensitivities of *M. avium-intracellulare* isolates are given in table 2. Treatment was attempted in eight patients; four patients received conventional quadruple chemotherapy (rifampicin, isoniazid, ethambutol, and pyrazinamide) with no response. Two were treated with ansamycin, isoniazid, and pyrazinamide and improved clinically. The addition of amikacin produced clinical improvement in two further patients.

#### *Mycobacterium ulcerans*

*M. ulcerans* was isolated from an indolent leg ulcer in a patient with the AIDS related complex; antibiotic sensitivities were not determined. The patient was treated initially with conventional antimycobacterial drugs, but improved only when amikacin and ansamycin were given.

Table 3 *Mycobacterial stool contaminants*

	No of patients tested	Mycobacteria isolated
Asymptomatic HIV infection	39	1 not typed
AIDS related complex	24	1 <i>M. avium-intracellulare</i> 1 not typed
AIDS	87	1 <i>M. fortuitum</i> 3 <i>M. avium-intracellulare</i> 3 not typed

Table 4 Isolates of mycobacteria from patients with AIDS considered to be contaminants

Source (n)	Other isolates and disease
	<i>M xenopi</i>
BAL (2)	<i>Staphylococcus aureus</i>
BAL (1)	<i>Pneumocystis carinii</i>
Sputum (1)	<i>S aureus</i> and <i>P carinii</i>
EMU (1)	Lymphoma
	<i>M chelonae</i> or <i>M fortuitum</i>
BAL (2)	<i>P carinii</i> , other bacteria
TBB (2)	<i>P carinii</i> , other bacteria
Stool (1)	Asymptomatic
	<i>M flavescens</i>
EMU (2)	

BAL—bronchoalveolar lavage fluid; EMU—early morning urine; TBB—transbronchial biopsy specimen.

#### *Mycobacterium kansasii*

*M kansasii* was isolated from retroperitoneal lymph node material and from pleural fluid from a patient with AIDS and fever, dyspnoea, and weight loss. He recovered partially with rifampicin, ethambutol, isoniazid, and pyrazinamide, but died of progressive HIV encephalopathy.

Ten stool isolates were considered contaminants (table 3). This included the four *M avium-intracellulare* isolates discussed above. Three further isolates were cultured from stools of patients without gastrointestinal symptoms (one with asymptomatic HIV infection and two with AIDS). In three patients with gastrointestinal symptoms other pathogens were isolated. One patient with the AIDS related complex had salmonellosis and two patients with AIDS had cytomegalovirus colitis. Symptoms improved in all cases without treatment directed at the mycobacterium isolated. These mycobacterial isolates were considered to be contaminants.

Twelve other isolates were cultured from various other sites, usually as part of a screen investigating pyrexia of unknown origin. They were also regarded as contaminants because other pathogens were found to account for the symptoms (table 4). None was smear positive at the initial examination.

#### Discussion

Tuberculosis occurred in 6% of the patients with AIDS. The prevalence of HIV infection in British patients with tuberculosis is unknown but in the United States up to 12% of patients with tuberculosis have HIV infection.<sup>12</sup> Intravenous drug abuse was a risk factor for tuberculosis before the human immunodeficiency virus epidemic.<sup>13</sup> Patients with a history of drug abuse account for a small but increasing number of cases of AIDS at St Mary's Hospital, so the prevalence of tuberculosis in our patients may increase. Atypical pulmonary or disseminated tuberculosis suggests the possibility of underlying HIV infection. Owing to lack of data on prior BCG inoculation it is not clear whether tuberculosis in these patients was due to reactivation or reinfection.

Tuberculin testing of patients with HIV disease is unhelpful as many are anergic.<sup>14</sup> Radiological features of pulmonary tuberculosis in our patients were frequently atypical or

absent. This small survey suggests that bronchoalveolar lavage may be useful for confirming the diagnosis of tuberculosis and excluding copathogens.

The patients with tuberculosis who were treated conventionally with four agents usually showed a good clinical response; the two patients who did not respond well both had AIDS, suggesting that a satisfactory response was limited by profound immunosuppression. Sunderam<sup>15</sup> reported a patient with tuberculosis treated with rifampicin, isoniazid, and pyrazinamide who, after a good clinical response, had an extrapulmonary relapse after pyrazinamide had been stopped. The patient was subsequently found to have HIV infection. Treatment with three or even four agents would seem to be most appropriate in this setting, and lifelong treatment with isoniazid has been recommended.<sup>16</sup> Similarly, it may be judicious to offer chemoprophylaxis to HIV positive individuals with a history of tuberculosis or recent exposure.

Treatment difficulties are compounded by side effects, which are more common in HIV infected patients, and by concurrent multiple opportunist infections or neoplasms requiring complex treatment regimens.<sup>17</sup> For example, deterioration in visual acuity may be due to ethambutol retinopathy or cytomegalovirus retinitis.

*M tuberculosis* infection might hasten disease progression in HIV infected individuals by activating CD4 positive ("helper") lymphocytes and increasing virus replication. Patients with tuberculosis who are HIV antibody positive should perhaps be considered early for treatment with zidovudine.

We identified homosexual men infected with HIV who were symptomless stool carriers of mycobacteria. The suggestion that sexual practices might explain the tendency for *M avium-intracellulare* to cause primarily gastrointestinal disease in homosexual patients with AIDS seems unlikely as stool carriage of this organism occurs in healthy heterosexuals,<sup>19</sup> though the prevalence in this group is unknown. An alternative explanation is that *M avium-intracellulare* infection in patients not infected with HIV frequently affects old tuberculous cavities, so that this group by contrast has a propensity for pulmonary disease. A positive stool culture in an HIV positive patient may imply little more than the need to search for *M avium-intracellulare* from sources other than the lung in symptomatic patients.

Changes on the chest radiographs of patients with *M avium-intracellulare* infection were not specific and tended to suggest *P carinii* pneumonia. Confirmation of *M avium-intracellulare* infection was obtained more frequently from sputum than by bronchoscopy. Obtaining a blood culture positive for *M avium-intracellulare* was a convenient non-invasive method of proving disseminated infection. A system that lyses white blood cells is required as most organisms are intracellular. Radio-metric systems such as Bactec provides positive results within 14 days.

In an American series patients with AIDS

who were infected with *M avium-intracellulare* did not have a worse prognosis than those with no such infection; the mean survival was 8.2 months for patients with pneumocystis pneumonia and 10.2 months for those infected with *M avium-intracellulare* in addition to *P carinii* (P Demopoulos *et al*, paper presented to the 25th Interscience Conference on Antimicrobial Agents and Chemotherapy, Minneapolis, 1985). This was not so in our study, though numbers of patients were small; the mean survival after diagnosis of *M avium-intracellulare* infection was five months compared with 12 months after diagnosis of pneumocystis pneumonia. This may reflect greater immunosuppression in patients with *M avium-intracellulare*. Infection was associated with symptoms and contributed to death. Attempts at treatment are therefore justified.

*M avium-intracellulare* isolates from patients with AIDS show increased antimicrobial resistance.<sup>20</sup> Ansamycin was useful in four cases and amikacin in two cases. These agents may also be effective in treating the intercurrent Gram negative bacteraemia that may be present in these patients<sup>21,22</sup> and may have clinical effects due to actions other than their antimycobacterial effects. Treatment with ansamycin reduces the yield of *M avium-intracellulare* in blood culture,<sup>23</sup> and the drug is also active in vitro against HIV,<sup>24</sup> which might explain the clinical findings. Ethambutol in vitro acts synergistically with both rifampicin and ansamycin on some strains of *M avium-intracellulare*.<sup>25</sup>

In our series *M tuberculosis* and *M avium-intracellulare* accounted for most mycobacterial infection in patients with AIDS and other HIV related diseases. Other mycobacterial isolates were usually considered to be contaminants as other pathogens were found to account for symptoms.

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