

# Isolation of mycobacteria from patients seropositive for the human immunodeficiency virus (HIV) in south east England: 1984-92

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## Abstract

**Background**—Tuberculosis and other mycobacterial infections are well recognised complications of HIV infection and surveillance is thus required.

**Methods**—All mycobacteria isolated from HIV positive subjects and referred to the Public Health Laboratory Service South East Regional Tuberculosis Centre (SERTC) from the first such case in 1984 until the end of 1992 were reviewed.

**Results**—A total of 803 mycobacteria isolated from 727 HIV positive subjects were referred to the SERTC during the study period. A single species was isolated from 660 patients: 150 members of the tuberculosis complex (146 *M tuberculosis*, two *M bovis*, and two *M africanum*), 356 *M avium-intracellulare* (MAI), and 154 other environmental mycobacteria. More than one mycobacterium was isolated from 67 patients. In 12 cases *M tuberculosis* and MAI were isolated from the same patient, almost always in that sequence, with an interval of 8-41 months between isolations. Most of the 407 isolates of MAI (74%) were considered to be clinically significant and often caused disseminated disease. In other cases single isolates of MAI were obtained from sputum or faeces and occasionally such isolates preceded disseminated disease by several months. Only 33 (14%) of the 229 isolates of environmental mycobacteria other than MAI were considered clinically significant.

**Conclusions**—HIV related mycobacterial disease is increasing in incidence in south east England. Further studies are required to determine the significance of single isolates of MAI and other environmental mycobacteria as a guide to the need for preventive chemotherapy or immunotherapy.

(Thorax 1993;48:990-995)

It is well established that the human immunodeficiency virus (HIV) predisposes the infected subject to mycobacterial disease.<sup>1</sup> Tuberculosis is usually the result of reactivation of dormant disease and tends to develop in the HIV positive subject before the AIDS

defining diseases.<sup>2</sup> Disease due to the environmental ("atypical") mycobacteria, by contrast, tends to occur much later in the course of the HIV infection and usually after an AIDS defining diagnosis has already been made.

For reasons that are not understood, *Mycobacterium avium* is the most frequent environmental species to cause such AIDS related disease. This species is usually grouped together with the very closely related species *M intracellulare* to form the *M avium-intracellulare* (MAI) complex, although most strains isolated from patients with AIDS conform to the species *M avium*.<sup>3</sup> The impact of opportunist disease due to *M avium* on AIDS varies from region to region. In the USA about 50% of patients with AIDS ultimately develop this disease,<sup>4</sup> while in Sweden the incidence is about 10%.<sup>5</sup>

Although able to cause overt disease in HIV positive subjects, environmental mycobacteria may occur as transient saprophytes in the respiratory tract and the intestines and often contaminate the lower urethra and external genitalia. Thus, as in HIV negative subjects, the isolation of environmental mycobacteria from sputum, faeces or urine must be interpreted with caution. On the other hand, it is important to establish whether apparently casual isolates may proceed to disseminated disease and therefore point to the need for preventive antibacterial therapy.

The aim of this study is to document the types of mycobacteria isolated from patients known to be HIV positive and referred to the PHLS South East Regional Tuberculosis Centre, Dulwich, from the time that such patients were first seen (1984) until the end of 1992. This regional centre receives mycobacteria isolated by about 90 client laboratories in London and south east England, amounting to about 95% of all isolates in the region.<sup>6</sup> It serves as a reference laboratory to several HIV units in south east England, including all but one of the major units in London.

## Methods

Information on the age, sex, and HIV status of the patients and the site of isolation of the organisms was supplied by the client labora-

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Received 11 March 1993  
Returned to authors  
27 April 1993  
Revised version received  
21 June 1993  
Accepted 6 July 1993

tories. In the case of disease due to mycobacteria other than tubercle bacilli, a further check was made by asking the referring laboratory if the HIV status was known. This was, however, not practical in the case of tuberculosis in view of the large number of strains received. The ethnic origins of the patients were determined by their names, with the assistance of laboratory staff from various ethnic groups. This is not an ideal method<sup>7</sup> because patients of Afro-Caribbean origin are included in the European group.

Mycobacteria were identified by routine cultural and biochemical tests<sup>8</sup> with, in some cases, use of DNA probes to confirm the identity of strains in the *Mycobacterium avium-intracellulare* complex. Strains identified as members of the tuberculosis complex were divided into the constituent species *M tuberculosis*, *M bovis*, and *M africanum*.<sup>9</sup> Strains in this group were tested for susceptibility to isoniazid, streptomycin, rifampicin, pyrazinamide, and ethambutol. The incidence of drug resistance was compared with overall figures for south east England for 1984-91.<sup>10</sup>

The putative clinical significance of mycobacteria other than those of the tuberculosis complex was assessed from the site and frequency of isolation. Strains considered to be of doubtful clinical significance included single isolates, or more than one isolate within a period of one month from the same or different non-sterile sites (sputum, bronchial washings, stool, or urine). Strains considered to be of probable clinical significance included those isolated from blood, bone marrow, bone, lymph nodes, other tissue lesions, and multiple isolations including at least one from a site that is usually sterile. Pulmonary isolates were considered significant if two or more isolates were obtained over a period exceeding one month or if there was evidence of extrapulmonary spread of disease.

Data were analysed statistically by the

Student's *t* test and Fisher's exact test as indicated in the text.

## Results

A total of 803 mycobacteria from 727 subjects infected with HIV were received during the study period 1984-92. The annual isolation rate of mycobacteria is shown in table 1. In 660 cases a single species was isolated: 150 members of the tuberculosis complex (146 *M tuberculosis*, two *M bovis*, and two *M africanum*), 356 *M avium-intracellulare* (MAI), and 154 other species of environmental mycobacteria. More than one mycobacterium was isolated from 67 patients: 12 *M tuberculosis* with MAI, five *M tuberculosis* with other environmental mycobacteria, 39 MAI with other environmental mycobacteria, and 11 cases of two or more other environmental mycobacteria. Members of the tuberculosis complex were thus isolated from 167 patients (23%) and MAI from 407 patients (56%). A total of 229 environmental mycobacteria other than MAI were isolated from 209 patients (29%).

Table 2 shows the sex and ethnic origins of the patients. Most were men of European ethnic origin. The proportion of women in the African group was significantly higher than in the European group (34% *v* 4.2%,  $p < 0.00001$ , Fisher's exact test).

The mean (SD) age of the European patients was 37.3 (8.8) years (range 9-86), for patients from the Indian subcontinent it was 35.2 (7.9) years (range 27-55), and for the African patients it was 32.0 (7.1) years (range 19-48). The age difference between the European and African patients was significant ( $t = 3.84$ ,  $p < 0.001$ ).

Figure 1 shows the annual isolation rate of members of the tuberculosis complex from 167 patients and table 3 shows the sites of isolation: 81 isolations (49%) were from single or multiple non-pulmonary sites. Members of the tuberculosis complex were

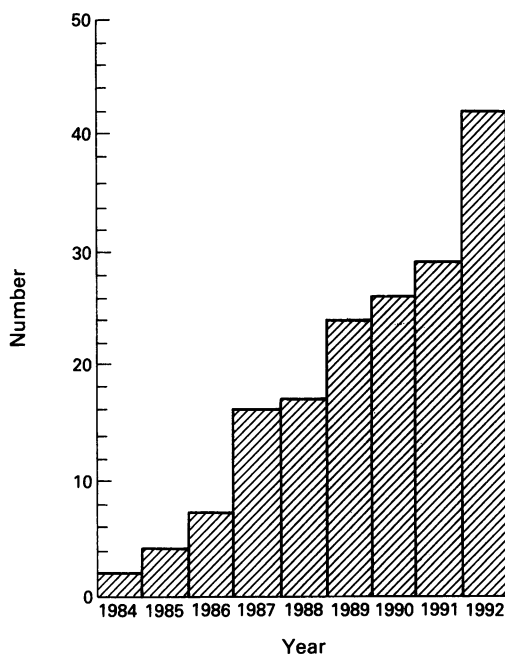
Table 1 Annual numbers of members of the tuberculosis complex, *M avium-intracellulare* (MAI) and other environmental mycobacteria isolated from HIV positive patients and the total number of strains received

Species	1984	1985	1986	1987	1988	1989	1990	1991	1992	Total
<i>Strains from known HIV positive patients:</i>										
Tuberculosis complex	2	4	7	16	17	24	26	29	42	167
MAI	1	1	18	13	27	48	61	77	161	407
<i>M kansasii</i>	—	—	5	4	2	4	7	9	11	42
<i>M xenopi</i>	2	—	1	2	9	4	15	20	16	69
<i>M chelonae</i>	—	—	—	2	4	—	3	10	3	22
<i>M fortuitum</i>	—	—	—	—	1	1	5	8	7	22
<i>M gordonae</i>	—	—	—	—	1	1	7	12	24	45
<i>M malmoense</i>	—	—	1	—	—	—	—	6	1	8
<i>M flavescens</i>	—	—	—	1	2	—	4	4	3	14
<i>M scrofulaceum</i>	—	—	—	—	2	—	1	—	—	3
<i>M szulgai</i>	—	—	—	—	—	—	1	—	—	1
<i>M haemophilum</i>	—	—	—	—	—	—	1	—	—	1
<i>M simiae</i>	—	—	—	—	—	—	—	—	1	1
Unidentified	—	—	—	—	—	—	—	1	—	1
Total other environmental mycobacteria	2	—	7	9	21	10	44	70	66	229
<i>Total number of strains received:</i>										
Tuberculosis complex	1183	1236	1206	1148	1028	1088	1178	1252	1263	10582
MAI	36	46	61	43	65	89	123	142	250	855
Other environmental mycobacteria	357	333	255	272	291	283	297	350	371	2809

Table 2 Sex and ethnic origin of HIV positive patients from whom mycobacteria were isolated

Sex	Ethnic origin						Total
	European	African	Indian Subcontinent	Far East	Other	Unknown	
Male	608	35	13	7	3	9	675
Female	27	18	—	2	1	1	49
Unknown	2	—	—	—	—	1	3
Total	637	53	13	9	4	11	727

Figure 1 Annual numbers of members of the tuberculosis complex (*M. tuberculosis*, *M. bovis*, and *M. africanum*) isolated from HIV positive subjects.



isolated from 38 (72%) of the 53 patients of African ethnic origin, and from 124 (20%) of the 637 patients of European ethnic origin. The respective numbers from whom MAI were isolated were 14 (26%) and 374 (59%). The difference in frequency of isolation of members of the tuberculosis complex and MAI in both of these ethnic groups was highly significant ( $p < 0.001$ , Fisher's exact test).

Nine (5%) of the 167 isolates of *M. tuberculosis* were resistant to one or more of the tested drugs. These strains were isolated from

six (16%) of the 38 patients of African ethnic origin (three strains resistant to isoniazid, one to streptomycin, and one to both isoniazid and streptomycin) and from three (2%) of the 124 patients of European ethnic origin (two strains resistant to isoniazid and one to rifampicin). These percentages did not differ significantly from the overall percentages of drug resistance in the two ethnic groups (11% and 2.9% respectively, Fisher's exact test).

In 12 cases (nine European and three African) MAI was isolated from patients from whom *M. tuberculosis* was also isolated. In 11 cases MAI was isolated after *M. tuberculosis* with a mean interval of 21 months (range 7–41). In one case there was a single isolate of MAI from stool one month before isolation of *M. tuberculosis* from sputum. Eight of these 12 MAI infections were disseminated and four were of doubtful clinical significance (isolates from sputum, stool and bile). In five cases (three European and two African) other environmental mycobacteria were isolated from patients from whom *M. tuberculosis* was isolated. The environmental mycobacteria were isolated before, after, or simultaneously to *M. tuberculosis*. All were single isolates from the lung, stool or urine and were of doubtful clinical significance.

Table 4 shows the site(s) from which MAI was isolated. In most cases (74%) the site indicated that the patient had disseminated or other forms of clinically significant disease. In 15 (5%) of the 300 cases that were probably clinically significant MAI had been isolated from sputum or bronchoalveolar lavage fluid (four cases), stool (eight cases), or both lung and stool (three cases) more than three months previously (mean 8.5 months, range 3–23). The annual numbers of MAI of probable and doubtful significance are shown in fig 2.

Table 5 shows patients from whom environmental mycobacteria of probable and of doubtful clinical significance were isolated. In four cases of probable disease (due to *M. fortuitum*, *M. xenopi*, and two *M. malmoense*) the patient also had disease due to MAI: simul-

Table 3 Type of disease, according to site of isolation, caused by the tuberculosis complex in HIV positive patients

	1984	1985	1986	1987	1988	1989	1990	1991	1992	Total
<i>M. tuberculosis</i>										
Pulmonary	—	2	4	9	9	11	16	14	20	85
Disseminated*	—	—	—	3	1	6	3	6	6	25
Lymphadenitis	1	2	2	4	5	2	2	6	10	34
Central nervous system	1	—	—	—	—	1	2	—	1	5
Genitourinary	—	—	—	—	—	2	—	2	3	7
Pericardium	—	—	—	—	—	1	—	—	—	1
Stool	—	—	1	—	—	1	1	—	—	3
Abdomen	—	—	—	—	1	—	—	—	1	2
Skin	—	—	—	—	—	—	—	—	1	1
<i>M. bovis</i>										
Pulmonary	—	—	—	—	—	—	1	—	—	1
Lymphadenitis	—	—	—	—	—	—	—	1	—	1
<i>M. africanum</i>										
Disseminated	—	—	—	—	1	—	1	—	—	2
Total	2	4	7	16	17	24	26	29	42	167

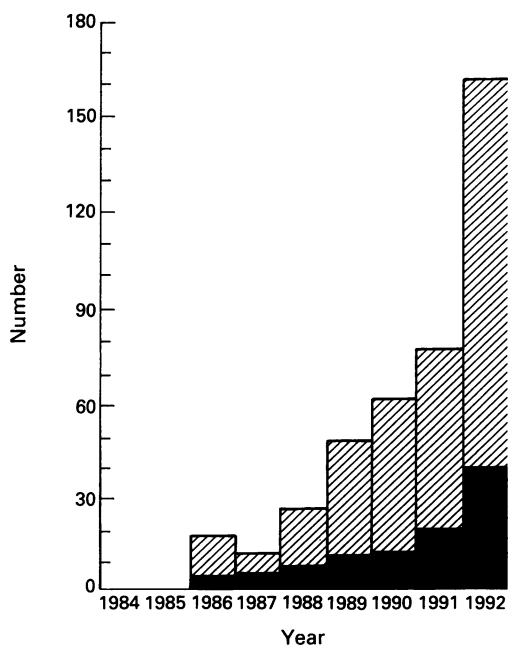
\*Isolations from blood, bone marrow, or multiple sites.

Table 4 Source of isolation of *M avium-intracellulare* (MAI) and putative clinical significance of the isolations

Site	Number of isolates			
	MAI only	MAI+TBC	MAI+EM	Total
<b>Doubtful clinical significance:</b>				
Sputum only	59	1	8	68
Stool only	24	1	2	27
Sputum + stool	10	—	1	11
Urine + stool	1	—	—	1
Total	94	2	11	107 (26%)
<b>Probable clinical significance:</b>				
Pulmonary	6	1	1	8
Lymph node only	8	—	—	8
Blood only	134	5	16	155
Blood + stool	39	2	3	44
Bone marrow only	14	—	2	16
Bone marrow + blood	10	—	1	11
Bone marrow + stool	5	—	—	5
Multiple sites	41	1	5	47
Other*	5	1	—	6
Total	262	10	28	300 (74%)

TBC—tuberculosis complex; EM—environmental mycobacteria. \*Caecal mass, thumb, bronchial biopsy, liver only (two cases), bile.

Figure 2 Annual numbers of *M avium-intracellulare* (MAI) of doubtful (■) and probable (▨) clinical significance isolated from HIV positive subjects.



taneously in two cases and three and four months later respectively in the other two cases. The tendency to cause disease varied from species to species. The scotochromogens, *M gordonae* and *M flavescens*, did not cause disease; *M kansasii* was the commonest cause of disease, mostly disseminated, while *M xenopi*, the next commonest, tended to be associated with pulmonary disease.

The 196 environmental mycobacteria of doubtful clinical significance were isolated from sputum or bronchial washings (101 isolations), stool (32 isolations), sputum and stool (four isolations), and urine (six isolations).

A smaller proportion (33 of 229, 14%) of environmental mycobacteria other than MAI were probable causes of disease in comparison with MAI (300 of 407, 74%,  $p < 0.001$ , Fisher's exact test). Of the total of 333 mycobacteria other than tubercle bacilli that were probable causes of disease, 300 (90%) were MAI.

## Discussion

It is possible that the HIV status of patients with mycobacterial disease was not always determined or declared by the client laboratory. By 30 June 1991, 4360 patients with AIDS in all of England and Wales had been reported to the Communicable Disease Surveillance Centre (CDSC) and 200 (4.6%) of these were also reported to have tuberculosis.<sup>11</sup> By 31 December 1991 we had received tubercle bacilli from 125 known HIV positive patients (table 1) which is comparable with the notification figures as about 75% of all cases of AIDS in England and Wales notified to the CDSC occur in south east England.<sup>12</sup> In 1988 nine of 2163 (0.4%) notified patients with tuberculosis in England and Wales were known to be infected with HIV.<sup>11</sup> In the same year 17 of our 1028 patients with tuberculosis (1.6%, table 1) were likewise known to be infected: a significantly higher proportion. The information conveyed to us therefore

Table 5 Source of isolations of environmental mycobacteria other than *M avium-intracellulare* and putative clinical significance of the isolations

Species	Probable clinical significance					Total	Doubtful clinical significance
	Multi-site	Blood and/or bone marrow	Lung	Lymph node	Other		
<i>M kansasii</i>	2	6	—	—	4*	12	30
<i>M xenopi</i>	—	2	6	1	—	9	60
<i>M chelonae</i>	—	—	—	—	—	—	22
<i>M fortuitum</i>	—	3	1	1	—	5	17
<i>M gordonae</i>	—	—	—	—	—	—	45
<i>M malmoense</i>	1	1	2	—	—	4	4
<i>M flavescens</i>	—	—	—	—	—	—	14
<i>M scrofulaceum</i>	—	1	—	—	—	1	2
<i>M szulgai</i>	—	—	1	—	—	1	—
<i>M haemophilum</i>	—	—	—	—	1**	1	—
<i>M simiae</i>	—	—	—	—	—	—	1
Unidentified	—	—	—	—	—	—	1
Total	3	13	10	2	5	33	196
No. of patients	3	13	10	2	5	33	176

\*Elbow, tibia, finger, "abscess"; \*\*foot.

appears to be as inclusive and representative as that obtained by the notification system.

Most patients of European ethnic origin were men, reflecting pattern I spread of HIV in Europe. There were relatively more women in the African ethnic group, reflecting migratory patterns from pattern II endemic areas of HIV infection. Members of the tuberculosis complex were isolated relatively more frequently from the ethnic African patients, almost certainly because a greater proportion of this group had previously been infected by tubercle bacilli. By contrast, MAI was isolated less frequently from ethnic African patients and it has been found that HIV related opportunist MAI disease, for unknown reasons, is relatively uncommon in Africa.<sup>13</sup>

During this study period a total of 10 582 cases of bacteriologically proven tuberculosis due to *M tuberculosis* were registered at the South East Regional Tuberculosis Centre (SERTC) (table 1). The 167 HIV related cases of tuberculosis due to this species therefore make up only a small proportion of the total (1.6%). The real incidence could, however, be higher as testing for antibody to HIV is not undertaken in all cases of tuberculosis. Nevertheless, the impact of HIV on the overall tuberculosis situation in Great Britain appears, at present, to be limited.<sup>14</sup>

The two cases of HIV related pulmonary tuberculosis due to *M bovis* give cause for concern. This species is usually regarded as being less virulent for man than *M tuberculosis* and less likely to lead to open or infectious post primary disease. Thus evidence for person-to-person transmission of *M bovis* is limited and anecdotal. Infection by HIV could, however, abrogate any immunological factors that limit the development of open tuberculosis and could thus facilitate transmission of this bacillus within the human population, and thence to animals.<sup>15</sup> Two of 123 cases of HIV related tuberculosis in France were caused by *M bovis*.<sup>16</sup>

Extrapulmonary manifestations of tuberculosis, including disseminated disease, are more likely to occur in HIV infected persons than in HIV negative subjects.<sup>12</sup> In this study 47% of patients of European ethnic origin had such manifestations, with or without pulmonary disease, compared with 19% of all patients registered at the SERTC during the same study period.<sup>10</sup>

Drug resistance was detected in some strains of *M tuberculosis* but the incidence was not significantly different from that in the overall population. In another study conducted in London, 14 strains of *M tuberculosis* isolated from HIV positive patients were susceptible to drugs and one was resistant to rifampicin and ethambutol.<sup>17</sup> The serious problem of multidrug resistance that has occurred, for example, in New York and Florida<sup>18 19</sup> has therefore not yet been encountered in London and south east England. This, however, does not exclude the need for careful continuing surveillance.

In patients from whom both tubercle

bacilli and MAI were isolated, the latter was almost always isolated after the former. This agrees with the finding in the USA that tuberculosis is an early manifestation of HIV infection whereas MAI disease occurs as a late event.<sup>1</sup> By contrast, there was no temporal relationship between isolation of tubercle bacilli and environmental species other than MAI. The latter isolations were of doubtful clinical significance and were probably coincidental contaminants.

In 5% of cases of disseminated MAI disease a member of this group had been isolated from sputum or stool several months before the detection of disseminated infection. As MAI is common in the environment, the significance of its isolation from sputum and stool is uncertain. While some workers consider that HIV related MAI disease follows recent infection via the lung or intestine, others suggest that it arises from longstanding dormant infection of lymphatic tissue.<sup>20</sup> It is important to determine the significance of early isolates as this has implications for the deployment of preventive chemotherapy or immunotherapy.

The clinical significance of environmental mycobacteria other than MAI is also difficult to determine unless they are clearly implicated in non-pulmonary and disseminated disease. These mycobacteria are common in the environment and may easily gain access to the respiratory and alimentary tracts and may contaminate the external genitalia and urine of healthy persons. In HIV negative subjects a diagnosis of pulmonary or genitourinary disease resulting from environmental mycobacteria must be made with caution.<sup>21 22</sup> The large number of isolations in this study may well reflect the intensity of bacteriological examinations. Although stringent diagnostic criteria are required in the case of HIV positive subjects, 33 patients had definite or very probable overt disease to other environmental mycobacteria. Likewise, in the USA several species have caused disseminated disease<sup>1</sup> and some cases of pulmonary disease due to *M kansasii* in patients with advanced HIV infection have been successfully treated.<sup>23</sup>

As the total population of HIV positive subjects in south east England is unknown, the incidence of mycobacterial disease in this population cannot be assessed. A London based study of 270 HIV positive subjects (207 AIDS, 24 AIDS related complex, and 39 asymptomatic) revealed that 32 (12%) had mycobacterial disease: 15 *M tuberculosis*, 15 MAI, one *M kansasii* and one *M ulcerans*.<sup>17</sup> Subclinical intestinal carriage of MAI and other environmental mycobacteria was commonly encountered. In a study in France 123 (2%) of 5730 HIV positive subjects had tuberculosis (121 *M tuberculosis* and two *M bovis*) and other mycobacteria were isolated from 105 (2%) persons (63 MAI, 16 *M xenopi*, and 26 other environmental mycobacteria) but the sites of isolation and clinical significance of the latter were not recorded.<sup>16</sup> The lower proportion of patients

with mycobacterial disease in the French study is probably explained by a lesser overall degree of immunosuppression than in the London study. In contrast to our findings, no patient in the French study was infected by more than one mycobacterium.

In conclusion, mycobacteria are an important cause of HIV related disease but isolation of species other than MAI and members of the tuberculosis complex may not be clinically significant. Continued close bacteriological surveillance is required to determine the impact of HIV on tuberculosis in the community and to clarify the management of patients from whom other species are isolated.

We are most grateful to Dr Anne Uttley for her support and advice and Dr PA Jenkins and his staff of the Mycobacterium Reference Unit, Cardiff for confirmation of the identity of some of the species and for confirmation of drug resistance.

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