

# HIV-associated tuberculosis in Auckland

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## ABSTRACT

**AIM:** New Zealand has low rates of disease caused by *Mycobacterium tuberculosis* (TB) and Human Immunodeficiency Virus (HIV). This study is the first to describe a New Zealand cohort of patients with HIV-associated TB.

**METHOD:** We retrospectively reviewed the clinical records, laboratory data and chest radiographs of all patients who were diagnosed with HIV-associated TB and who commenced treatment for TB disease at Auckland City Hospital between January 1997 and July 2009.

**RESULTS:** During the 12-and-a-half year study period, 40 patients were diagnosed with HIV-associated TB. The median age was 37 years and the median CD4 count was 130 cells/mm<sup>3</sup>. Only 2 patients were New Zealand born. Twenty-four (60%) patients had known HIV infection prior to their diagnosis of TB disease. Two patients with known HIV infection and positive tuberculin skin tests had not received treatment for latent tuberculosis infection (LTBI). Twenty-three (58%) patients received antiretroviral treatment during their TB treatment. There were 21 episodes of treatment interruption or immune reconstitution inflammatory syndrome. Three (8%) patients died.

**CONCLUSIONS:** New Zealand continues to have a low incidence of HIV-associated TB. Early HIV diagnosis with universal screening and the treatment of LTBI in persons living with HIV infection is key to minimising the disease burden.

## Introduction

Tuberculosis (TB) is the most common opportunistic infection and cause of death in persons living with Human Immunodeficiency Virus infection (PLWHIV) in the world, with the greatest burden of disease in those living in sub-Saharan Africa.<sup>1</sup> HIV infection is the strongest risk factor for progression from latent tuberculosis infection (LTBI) to TB disease.<sup>2</sup>

New Zealand has a low incidence of TB (7.8/100,000) and a low prevalence of HIV infection (<1/1,000).<sup>3,4</sup> This study describes the demographics, clinical features and outcomes of patients diagnosed with HIV-associated TB in Auckland, New Zealand, between 1997 and 2009 as to define the cohort and identify potential preventative strategies.

## Methods

### Study Population

The infectious diseases department at Auckland City Hospital (ACH) is the tertiary referral centre for all PLWHIV in the Auckland and Northland regions, serving an adult population of approximately 1.1 million people.<sup>5</sup> All adults (≥15 years old), with diagnosed HIV infection, who were notified to the Auckland or Northland Regional Public Health Services as having TB disease between 1 January 1997 and 30 June 2009 were included if treatment for TB disease was initiated at ACH. PLWHIV diagnosed with or treated for LTBI were not included.

### Data collection

We reviewed the clinical records of all patients with HIV-associated TB to obtain

**Table 1:** Demographics and co-morbidities of patients with HIV-associated tuberculosis

Characteristic	Number (%)
Male gender	26 (65%)
Ethnicity	
African	20 (50%)
Asian	17 (42%)
New Zealand European	2 (5%)
South American	1 (3%)
Viral hepatitis co-infection	10 (25%)
Hepatitis B	4 (10%)
Hepatitis C	5 (12%)
Hepatitis B and Hepatitis C	1 (3%)
Diabetes mellitus	2 (5%)
Steroid treatment at diagnosis of tuberculosis	2 (5%)
History of intravenous drug use	4 (10%)
History of alcohol abuse	3 (8%)
Psychiatric diagnosis	3 (8%)
HIV related co-morbidity <sup>†</sup>	3 (8%)

<sup>†</sup>Pancytopenia (n = 1), peripheral neuropathy (n = 1), cardiomyopathy and dementia (n = 1).

information on patient demographics, presenting features, radiographic findings, treatment and clinical outcomes. Patients were classified as having definite TB disease if *M. tuberculosis* was cultured from a clinical specimen. Patients were classified as having probable TB disease if there was no positive culture of *M. tuberculosis* but strong clinical suspicion of TB disease, with or without visualisation of acid-fast bacilli on microscopy, leading to treatment for TB disease. TB resistance testing during the study period was phenotypic only and did not include identification of gene mutations (eg, rpoB gene).

All available chest radiographs were reviewed and reported by a single respiratory radiologist. Previously defined criteria were used to classify chest radiograph findings into those most consistent with primary disease, post-primary disease (reactivation), atypical patterns, miliary TB, minimal change or normal.<sup>6</sup>

The study received approval from the Northern X Regional Ethics Committee.

### Statistical methods

Results are presented as medians (range) or frequencies (percentages).

## Results

### Initial assessment

We identified 40 patients who had HIV-associated TB diagnosed between 1 January 1997 and 30 June 2009. There were 1 to

6 patients identified each year without a trend in incidence over time. These 40 patients represent 1.6% of the 2,429 persons notified with TB disease and 3.5% of the 1,133 PLWHIV cared for at ACH during the audit period. Thirty-seven (92%) patients had definite TB disease and 3 (8%) patients had probable TB disease.

Patient demographics and co-morbidities at initial assessment are outlined in Table 1. The median age was 37 (range 21–63) years.

All but 2 (5%) patients were migrants from Africa (n = 20), Asia (n = 17) or South America (n = 1). The remaining 2 patients were New Zealand-born Europeans, both with a recent history of incarceration in Thailand (for 5 and 10 years). The self-reported ethnicity of the 1,133 PLWHIV under the care of ACH during the audit period was European (n = 595), African (n = 226), Asian (n = 116), Māori (n = 85), Pacific Person (n = 46), South American/Caribbean (n = 16), Middle Eastern (n = 4) and not reported (n = 45).

### Previous tuberculosis history

Five (13%) patients had previously received treatment for TB disease. One patient received 20 days of treatment in Africa 5 months before diagnosis of HIV-associated TB in Auckland. Two patients had completed a 6 month course of treatment in South America and Africa; 1 year and 5 years respectively before diagnosis of HIV-associated TB. Two patients had completed 14 month treatment courses

in New Zealand centres. Of the patients treated in New Zealand, there were concerns regarding compliance in one and the other was treated with a rifampicin sparing regimen following an episode of rifampicin associated hepatitis.

Twenty-four (60%) patients were known to be living with HIV prior to their diagnosis of TB disease. The median duration of known HIV infection prior to the diagnosis of TB disease was 50 (range 4–144) months in the 22 patients for whom this information was available. Of the 24 patients known to have HIV infection, 7 (29%) had documented results of either a tuberculin skin test (TST) or a QuantiFERON-TB Gold assay prior to their presentation with TB disease. Two had positive TST results but had not received LTBI treatment. The remaining 5 patients had negative LTBI screening test results. Two of these 5 patients had a positive TST or QuantiFERON-TB Gold during investigations for TB disease. Previous treatment for LTBI was not documented to have been given to any patient.

### Clinical findings

The most common symptoms at presentation were fever (n = 29, 73%), cough (n = 26, 65%), weight loss (n = 22, 55%) and sweats (n = 19, 48%). One or more of these symptoms were present in 35 (88%) patients. Haemoptysis was reported in

2 (5%) patients. Lymphadenopathy (n = 19) was the most common physical examination finding and was present in 2 patients who had none of the symptoms mentioned above. One patient presented with a chest wall mass and 2 patients were asymptomatic. One asymptomatic patient had a history of prior partial treatment for TB disease in Africa and was found to have an abnormal chest radiograph on immigration screening. The other asymptomatic patient, a contact of a patient with pulmonary TB disease, was diagnosed on the basis of a TST conversion and a chest radiograph showing mediastinal lymphadenopathy.

### Distribution of tuberculosis

Thirty-two (80%) patients presented with pulmonary TB disease (PTB) including 20 who also had extra-pulmonary involvement. Extra-pulmonary TB disease (EPTB) with no identifiable PTB was seen in 8 (20%) patients (Table 2). Overall, 28 (70%) patients had extra-pulmonary involvement. Lymph nodes were the most common site of EPTB (19/28).

### Radiography

Chest radiographs were available for review in 24 of 32 (75%) patients with PTB (Table 3). Five (21%) were normal or had minimal change and one (4%) had an atypical pattern. Of the 5 patients with

**Table 2:** Distribution of tuberculosis disease

Distribution of disease	Number (%)
Pulmonary	32 (80%)
pulmonary only	12
pulmonary & extra-pulmonary	20
Lymph node	16
Blood culture	5
Urine	5
Pleural effusion	2
Central nervous system	2
Extra-pulmonary only	8 (20%)
Lymph node	3
Gastrointestinal tract	2
Urine	1
Prostate	1
Chest wall	1
Pleural effusion	1
Pericardial effusion	1

**Table 3:** Chest x-ray appearances in cases with pulmonary tuberculosis (n = 24)

Chest radiograph pattern	Number (%)
Normal	4 (17%)
Minimal change	1 (4%)
Atypical	1 (4%)
Miliary	2 (8%)
Primary tuberculosis pattern	7 (29%)
Consolidation	4
Enlarged thoracic lymph nodes	4
Pleural effusion	2
Post-primary tuberculosis pattern	9 (38%)
Consolidation	7
Cavitation	3
Tuberculoma	2
Endobronchial spread	3

normal or minimal changes on chest radiographs, 3 were smear and culture positive from sputa and 2 were considered to have probable TB disease. Cavitation was seen in 3 (12%) patients.

### Microbiology

Thirty-seven (92%) patients had *M. tuberculosis* cultured from at least 1 clinical specimen. One case of probable HIV associated TB was culture negative despite being sputum smear positive on 2 occasions. Of those with PTB, 28 of 32 (88%) had positive sputum cultures and 19 of 32 (59%) were smear positive. Extrapulmonary specimens yielding  $\geq 1$  positive cultures for *M. tuberculosis* were lymph node biopsy (n = 9), urine (n = 6), blood (n = 5), pleural aspirate (n = 4), gastrointestinal tract biopsy (n = 2), pleural biopsy (n = 2), liver biopsy (n = 1), chest wall biopsy (n = 1) and prostate biopsy (n = 1).

Seven of 37 (19%) *M. tuberculosis* isolates were resistant to one or more first line anti-tuberculous agents: rifampicin and isoniazid (n=1), rifampicin alone (n=2), streptomycin alone (n=1), isoniazid and streptomycin (n=1), and rifampicin, ethambutol and streptomycin (n=1).

### HIV status and management

Twenty-four (60%) patients were known to have HIV infection prior to their diagnosis of TB disease. Of these, 8 were already established on antiretroviral treatment (ART) with a median CD4 count of 315 (range 64-466). The median CD4 count for the 16 patients with known HIV not on ART was 142 (range 21-420).

Sixteen (40%) patients were diagnosed with HIV infection at the time of their presentation with TB disease. The median CD4 count was 54 (range 4-423). The median duration of residence in New Zealand prior to their diagnosis of TB disease was 14 (range 0-83) months.

Thirty-two (80%) patients were ART naïve at the time they were diagnosed with TB disease. Fifteen (47%) started ART during treatment for TB disease (median CD4 count 54 (range 2-418) cells/mm<sup>3</sup>), 10 in the first 8 weeks of treatment and 5 after more than 8 weeks of treatment. Two patients stopped ART during treatment for TB disease. One could not tolerate ART due to nausea and vomiting and declined to start ART again. The other patient developed lactic acidosis,

hepatitis and multi-organ failure 12 days after initiation of ART, reintroduction of ART failed to achieve complete viral suppression and ART was subsequently deferred until after completion of treatment for TB disease. Of the remaining 17 (53%) patients who did not start ART during TB treatment; 7 (22%) patients started ART after completion of treatment for TB disease (median CD4 count 240 (range 233-361) cells/mm<sup>3</sup>), 4 (12%) patients either transferred to another centre for ongoing care or were lost to further follow-up and 6 (19%) patients remained ART naïve at the time this study.

Six of 23 (26%) patients receiving ART during treatment for TB disease developed immune reconstitution inflammatory syndrome (IRIS) that consisted of fever with new pulmonary infiltrates (n = 1) or increased pain/swelling at a site of known TB disease (n = 5). The median presenting CD4 count at the start of TB treatment for these patients was 54 (range 31-131) cells/mm<sup>3</sup>. Two of these patients required treatment with prednisone including one in whom ART was also temporarily withheld.

Nineteen (48%) patients, all with CD4 counts < 200 cells/mm<sup>3</sup>, received trimethoprim-sulphamethoxazole (TMP-SMX) prophylaxis during their treatment for TB disease, usually at a dose of 480mg daily. Five (26%) patients were intolerant of TMP-SMX due to one or more of the following: rash (n = 4), pancytopenia (n = 2) or vomiting (n = 1).

### Tuberculosis treatment

Treatment for TB disease was interrupted in 8 (20%) patients due to one or more of the following adverse events: hepatitis (n = 6), severe rash (n = 2), optic neuropathy (n = 1), angioedema (n = 1) and severe abdominal pain (n = 1). Three patients had more than one treatment related adverse event. Two patients who developed treatment-related hepatitis had pre-existing viral hepatitis; 1 was co-infected with hepatitis B and another with hepatitis B and hepatitis C. First line treatment for TB disease was successfully re-established in 3 patients (including the patient with hepatitis B co-infection). Five (13%) patients with treatment related adverse events received one or more second line anti-tuberculous agents; 3 because of treatment related adverse events with first line anti-tuberculous agents and 2 because

of treatment related adverse events and susceptibility test results that demonstrated resistance to one or more first line anti-tuberculous agents.

### Outcomes

The median follow-up was 2.7 (range 0–12.2) years. Twenty-eight (70%) patients were followed by the ACH infectious diseases department until completion of TB treatment and 1 patient (3%) continued to receive treatment at the time of this study. Three (7%) patients died during TB treatment: 1 with fulminant PTB after 7 days of TB treatment; 1 from B-cell lymphoma after 7 months of TB treatment and 1 after he declined all further treatment. The remaining 8 (20%) patients were transferred to another centre during TB treatment.

There were no cases of TB disease relapse. Four (10%) patients developed opportunistic infections (OIs) after initiation of TB treatment; *Pneumocystis jiroveci* pneumonia (n = 2), cerebral toxoplasmosis (n = 1) and cryptococcal meningitis (n = 1). Both *P. jiroveci* infections occurred in patients soon after initiating ART. Both of these patients commenced ART 2 months after being diagnosed with TB. The other 2 OIs occurred in patients who did not receive ART, 15 months and 10 months after the start of TB treatment.

## Discussion

Our study demonstrates ongoing cases of HIV-associated TB over a 12-and-a-half-year period. New Zealand has a low incidence of TB disease (7.8/100,000) and a low prevalence of HIV infection (<1/1000).<sup>3,4</sup> All patients identified in our cohort either originated from countries with high rates of TB and HIV infection or had been incarcerated in countries with high rates of TB and HIV infection. The bulk of disease in our cohort is more likely due to reactivation of LTBI rather than endemic cross-transmission. With the ongoing trend of globalisation and an annual intake of 750 United Nations mandated refugees to New Zealand from countries known to have high rates of TB and HIV infection (including refugees diagnosed with HIV infection), we expect to continue to see patients with HIV-associated TB disease in the future.

In view of the likely predominance of reactivation disease, the low rate (29%) of retrospectively available LTBI screening results in known PLWHIV was concerning. This may in part be explained by the lack of a centralised recording system for LTBI screening results for the majority of the study period, raising the possibility that tests may have been performed but that the results of these tests were unable to be obtained retrospectively. TST results for example, the most commonly utilised LTBI screening test during the study period, were found only when documented in handwritten clinic notes. All hospital and community TST and QuantiFERON-TB Gold test results are now recorded in a unified electronic laboratory reporting system which is easily interrogated.

Also of concern was the finding that 2 PLWHIV with positive LTBI screens who did not receive LTBI treatment and subsequently progressed to TB disease, represented missed opportunities to prevent TB disease. It was not evident retrospectively whether LTBI treatment had been offered. HIV infection is the greatest risk factor for reactivation of LTBI to TB disease.<sup>2</sup> There is convincing evidence that LTBI treatment for PLWHIV significantly decreases their chances of developing TB disease. For PLWHIV, with a positive TST, treatment of LTBI was associated with a 0.38 relative risk of TB disease.<sup>7</sup> International and New Zealand guidelines now advocate universal LTBI screening for all PLWHIV, and in the absence of strong contraindications or a suspicion of active TB disease, all PLWHIV identified with LTBI should be offered LTBI treatment.<sup>4,8,9</sup> In our cohort, 5 of 7 patients known to have HIV infection had negative Mantoux or QuantiFERON-TB Gold tests. Although this highlights the real possibility of false negatives in PLWHIV, because the majority of the benefit from preventive therapy remains in Mantoux positive cases, we would not advocate universal preventive therapy for PLWHIV from endemic countries with negative LTBI screening in the absence of literature supporting benefit in this cohort.<sup>10</sup>

Early diagnosis of HIV infection represents another important intervention for the prevention of TB disease. The risk of

LTBI reactivation increases with increasing immune deficiency.<sup>11</sup> The majority of patients in our cohort presented with advanced HIV infection (median presenting CD4 count 130 cells/mm<sup>3</sup>) including a significant proportion diagnosed with HIV infection only during their presentation with TB disease. For some, this presentation was their first encounter with New Zealand health services, however this was not universally the case. Earlier detection of HIV infection could potentially have led to a decrease in the risk of LTBI reactivation by virtue of earlier treatment of HIV infection, thereby avoiding more advanced immunosuppression, and also by detection and treatment of LTBI via the routine screening of all PLWHIV for LTBI.

Diagnosis and management of HIV-associated TB remains challenging. The presentation of HIV-associated TB in our cohort was similar to other previously reported cohorts with 35 of 40 presenting with WHO screening symptoms of fever, current cough, night sweats or weight loss.<sup>12-14</sup> However, a significant proportion of patients did not present with classical symptoms. Although chest radiography is an important screening tool for PTB, it is an insensitive one. Our study identified 5 cases of PTB where the presentation chest radiograph was normal or showed only minimal change. This is consistent with a previous study that found that 19% of HIV-associated pulmonary TB cases had normal or minimal change chest radiographs.<sup>6</sup> These findings emphasise the importance of clinical vigilance and a high index of suspicion for the detection of HIV-associated pulmonary TB.

HIV-associated TB and its treatment is associated with a high rate of morbidity and

mortality.<sup>13, 15, 16</sup> In our cohort there were 21 episodes of adverse treatment reactions (IRIS or an adverse reaction necessitating interruption of TB treatment, ART or TMP-SMX prophylaxis) and an 8% mortality rate. These rates are similar to the 54% adverse reaction rate and an 8.5% mortality rate in a London cohort managed in the late 1990s in whom 54% received ART during their TB treatment course.<sup>16</sup> Since the 1990s, the treatment of HIV-associated TB has undergone significant change. The evidence for earlier introduction of ART is compelling with large randomised control trials demonstrating clear mortality benefits when ART is introduced within the first 2 months of TB treatment.<sup>17, 18</sup> This mortality benefit is most marked in the subgroup of patients with CD4 counts <50cells/mm<sup>3</sup>.<sup>18, 19</sup> The benefits of an earlier introduction of ART has come with a cost; all three randomised control trials found high rates of adverse events with significant increases in the incidence of IRIS with earlier ART.<sup>17-19</sup>

## Conclusions

HIV-associated TB continues to be an important problem in PLWHIV in New Zealand. Reactivation disease was a significant contributor to the burden of disease in our cohort. Earlier HIV diagnosis and treatment and the universal screening and treatment of LTBI in PLWHIV remains crucial to the control of both infections. Despite rapid advances in treatment guidelines for HIV-associated TB the morbidity and mortality associated with HIV-associated TB remains high, further emphasising the importance of disease prevention.

**Competing interests:** Nil**Acknowledgements:**

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