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TITLE

Latent tuberculosis screening using interferon-gamma release assays in an Australian HIV-infected cohort: is routine testing worthwhile?

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ABSTRACT

Background

There is limited data from high-income countries on the performance of interferon-gamma releasing assays in screening for latent tuberculosis infection (LTBI). We analysed the routine application of the Quantiferon-TB Gold (QFT-G) assay, to detect and predict latent and active tuberculosis among HIV-infected patients in Australia.

Methods

A retrospective cohort study included all HIV-infected patients attending the Melbourne Sexual Health Service between March 2003 and February 2011 who were screened for LTBI using QFT-G. Clinical data was analysed in multivariable models to determine predictors for QFT-G positivity using logistic regression, and active tuberculosis development using Cox proportional hazards.

Results

917 HIV-infected patients had ≥1 QFT-G performed, of whom 884 (96.4%) were negative, 29 (3.2%) positive, and four (0.4%) indeterminate. The mean age was 40.9 years, 88% were male, with median follow-up of 26.4 (IQR 15.4-30.7) months. 550 (63%) were Australian-born, while 198 (23%) were born in Asia or Africa. QFT-G was positive in 2.0% of Australian-born and 5.3% overseas-born patients (odds ratio[OR] 2.6, 95% CI 1.2-5.6, p=0.017); and 12.7% African-born patients (OR 7.1, 95% CI 2.9-17.3, p<0.001). Two cases of culture-positive tuberculosis occurred after QFT-G screening in 3.4% of QFT-G-positive and 0.1% of QFT-G-negative patients (adjusted hazard ratio 42.4, 95% CI 2.2-827, p=0.013); a rate of 111 (95% CI 27.8-445) per 100,000 person-years:.

Conclusions

In this context, QFT-G has a high negative predictive (99.9%) value with few indeterminate results. A risk-stratification approach to LTBI screening, where HIV-infected patients with

epidemiological risk-factors for tuberculosis infection undergo QFT-G testing, might be clinically appropriate and potentially cost-effective in similar settings.

Keywords

Human immunodeficiency virus (HIV), latent tuberculosis, interferon-gamma release assay, Quantiferon-TB Gold, screening

MAIN TEXT

BACKGROUND

Latent tuberculosis infection (LTBI) is an asymptomatic condition, following inhalation of aerosolised *Mycobacterium tuberculosis* (TB) organisms[1]. While a proportion of individuals progress immediately to active disease, a partially effective host immune response results in containment of the bacilli within pulmonary granulomata[2]. In this state, viable bacilli can remain dormant for decades prior to reactivation. It is commonly quoted that acquisition of latent tuberculosis is associated with a 10% lifetime risk of active disease, with half of subsequent infections occurring in the first 2 years after exposure[3]. However, immunosuppressive conditions, particularly Human Immunodeficiency Virus (HIV)-infection, markedly increase the risk of progression, while effective anti-tuberculosis therapy reduce its likelihood substantially.[4]

Due to the increased risk of active infection, routine testing and treatment for LTBI is recommended in HIV-infected individuals; a practice which has been shown to reduce subsequent active tuberculosis and mortality in high tuberculosis prevalence settings[5-7]. Testing for LTBI may include the use of tuberculin skin tests (TST) or whole-blood interferon-gamma releasing assays (IGRAs). While both tests are in active clinical usage internationally, the predictive power of each is limited by the absence of a gold-standard diagnostic test and limited comparative assessment in the setting of HIV infection[8, 9]. Limitations of the tuberculin skin test, which measures response to tuberculin purified protein derivative, include cross reactivity with non-tuberculous mycobacteria and bacille Calmette-Guerin [10], poor sensitivity among HIV-infected patients [11, 12], and requirements for skilled reading of skin induration on subsequent patient visits by health care workers [13]. In some high-income

countries, convenience, control for impaired T-cell response, and potentially improved detection of latent tuberculosis has led to IGRA being used for LTBI testing [14-16]. International guidelines recommend anti-tuberculosis therapy for any HIV-infected patient with a positive screening IGRA or TST[17]. However, existing LTBI testing recommendations and evidence for LTBI treatment are based predominantly on TST results and meta-analyses establishing clinical benefits (including reduced incident TB) when treating HIV-infected individuals with a reactive TST [18]. Further, there is limited evidence from high-income, low tuberculosis prevalence countries on the clinical utility of IGRA use in HIV-infection [6, 17]. In Victoria, Australia, the incidence of active tuberculosis was 7 cases per 100,000 person-years (PY) in 2008 with >80% of cases occurring among overseas-born individuals [19, 20].

This study aimed to describe the frequency and predictors of latent tuberculosis assessed by the Quantiferon-TB Gold (QFT-G) (Cellestis, Melbourne), and how its use influenced clinical management among HIV-infected individuals in a high income, low tuberculosis prevalence country. It further aimed to describe the risk and predictors of active tuberculosis development in a well-controlled Australian HIV-infected cohort.

METHODS

Study design and participants

A retrospective cohort study was conducted among HIV-infected patients undergoing latent tuberculosis screening at a large urban sexual health service in Melbourne, Australia. All HIV-infected patients who attended the Melbourne Sexual Health Centre between March 2003 and March 2011, and had at least one QFT-G performed, were included in the cohort. There were followed up to their most recent HIV clinic visit where HIV monitoring blood tests were performed. The QFT-G is one of two commercially available IGRAs, and was introduced into

this health service in 2003. Since 2008, HIV-infected patients routinely had one QFT-G test performed free-of-charge close to their first visit at the HIV service.

All patients had demographic and risk factor information including age, gender, country of birth and indigenous status extracted from their electronic registration records. For patients with positive QFT-G results, medical records were reviewed for clinical information regarding potential tuberculosis exposures and past tuberculosis treatment, current symptoms, chest radiograph results and subsequent anti-tuberculosis therapy. Active tuberculosis cases were defined by microbiological evidence (culture and/or polymerase chain reaction) of *Mycobacterium tuberculosis* and/or health department case notification. Diagnosis and management information of active tuberculosis cases was obtained from clinic records and from reference laboratory surveillance.

Laboratory results for the cohort were collected from Victorian Infectious Diseases Reference Laboratory (VIDRL) records, including QFT-G test-specific data (ESAT-10 or CFP-10 antigens, mitogen and negative control value), HIV confirmation testing and monitoring including HIV viral load and CD4-lymphocyte cell count. The same laboratory was used for all HIV monitoring and tuberculosis testing during the investigation period. VIDRL also act as the state-wide reference laboratory for tuberculosis diagnosis, receiving all new tuberculosis isolates for drug susceptibility testing and mycobacterial interspersed repetitive unit/variable number of tandem repeats (MIRU/VNTR) genetic typing, which should ensure complete detection of microbiologically confirmed active tuberculosis cases within this cohort.

A positive QFT-G assay was defined according to the manufacturer's instructions with either ESAT-10 or CFP-10 antigens ≥0.35 IU/mL in the presence of a mitogen response ≥0.50 IU/mL

(corrected for negative control). Indeterminate QFT-G results were classified as either: low mitogen responses (<0.50 IU/mL); or high negative controls (≥2.0 IU/mL). Results with high normal ESAT-10 or CFP-10 antigens (0.30-0.35 IU/mL) were re-tested[17]. Where the first QFT-G result was indeterminate or patients had multiple testing, the first subsequent definitive QFT-G test result was used in the analysis instead. Approval was obtained from our institutions' human research ethics committee.

Statistical methods

Baseline demographic variables (age, gender, country of birth) and clinical variables (CD4 count, HIV viral load) were tested for potential associations with positive QFT-G result using logistic regression. A second analysis added QFT-G to these predictors to examine active tuberculosis development over time using Cox proportional hazard models. The active TB analysis removed individuals who had previously received had a TB diagnosis or received any tuberculosis (active or latent) treatment. Univariable and multivariable models for active TB estimated crude and adjusted hazard ratios (HR) with 95% confidence intervals using these pre-specified predictors in the final multivariable model. Proportionality assumptions were checked graphically and statistically using Schoenfeld residual estimation. . All statistical tests were undertaken using STATA (Version 11.2, StataCorp, College Station, Texas).

RESULTS

There were 917 HIV-infected patients seen at least once with a QFT-G test performed at our centre over eight years. The cohort had a mean age 41 years (range 18-84), with largely well controlled HIV with median CD4 T-cell count 490 cell/uL (interquartile range[IQR] 348-676) and 64% had HIV RNA completed suppressed at the time of their QFT-G test. The majority of the cohort was Australian or New Zealand born (63%) and known of non-Indigenous

background (97.8%) (Table 1). The median length of time between the first QFT-G test last and last follow up was 26.4 months (IQR 15.3-30.7 months), generating a total of 1796 person-years (PY) of follow-up for active tuberculosis cases. There were no differences in CD4 count or viral load between those who received a QFT-G test, and those who did not (Table 1). However, the proportion born overseas was high among those undertaking QFT-G compared with no QFT-G (37% v 28%, difference 9.0% 95% CI 3.8-14.2, p<0.001).

29 (3.2%) of patients had a positive QFT-G result, while 12 (1.3%) had an initially indeterminate QFT-G test due to high negative controls (n=8) or low mitogen controls (n=4). Eight (0.9%) patients were re-tested given high normal TB-antigens of which 7 were definitively QFT-G negative and one QFT-G positive. The mean CD4 count in those with initially indeterminate QFT-G was 496 cells/uL (IQR 363-793) with no difference from those with definitively positive or negative results (Wilcoxon rank-sum, p=0.6). Ultimately, only four (0.4%) QFT-G results remained indeterminate – 3 due to high negative controls and 1 due to low mitogen control – and were excluded from later logistic regression analyses. There was no difference in the proportion of patients testing QFT-G positive between CD4 cell counts greater than or less than 200 cells/ul: 3.2% v 2.8% respectively (risk difference -0.3%, 95% CI -4.4 to 3.7%, p=0.8).

Participants born overseas were more likely to have a positive QFT-G result compared to those born in Australia or New Zealand (5.3 v 2.0%; OR 2.6, 95% CI 1.2-5.6, p=0.017) (Table 2). Being born in Africa was the strongest predictor of being QFT-G positive (12.7% v 2.0%; OR 7.1, 95% CI 2.90-17.3, p<0.001). There was no significant difference in QFT-G result by age, gender, CD4 cell count, HIV viraemia, or indigenous status, so no adjustment was made for these pre-specified factors.

After medical record review of the management of all 29 positive QFT-G tests, it was found that six patients had known of prior tuberculosis exposure (4/6 born overseas) and five had previously been treated for LTBI (3/5 born overseas) (Table 3). In retrospect, one patient born overseas had respiratory symptoms of active tuberculosis at the time of QFT-G testing. Of the 24 patients without previous tuberculosis or LTBI treatment, 21 underwent chest radiograph and 19 later commenced anti-tuberculosis treatment (13/19 born overseas) with median age 38 years (range 24-52). Four patients, aged 40-62 years of whom one was born overseas and the other two had no epidemiology of tuberculosis exposure, did not receive isoniazid therapy and toxicity concerns were recorded as the main reason. One patient had been lost to follow up after QFT-G testing.

There were two cases of active tuberculosis diagnosed after QFT-G testing was performed, at an incidence rate of 111.4 (95% CI 27.8-445) per 100,000PY in this context. Both patients occurred with two years of QFT-G screening, were born in Sub-Saharan Africa and had immigrated to Australia 3 months and 2 years previously, and neither had received isoniazid therapy. Extended MIRU/VNTR genotyping to 21 loci showed neither strain of tuberculosis had been previously diagnosed in Victoria. This suggests that both tuberculosis exposures occurred overseas in keeping with their known epidemiological links, and did represent tuberculosis re-activation rather than a new locally-acquired infection.[21] QFT-G positivity was the strongest predictor of active tuberculosis in both univariable and multivariable analyses adjusted for CD4 cell count (adjusted hazard ratio[HR] 42.4, 95% CI 2.2-827, p=0.013). There was a trend toward lower CD4 cell count increasing risk of active tuberculosis, most notable when CD4 cell count <200 cell/uL (adjusted HR 25.4, 95% CI 0.70-918, p=0.08). HIV-infected patients born in Africa were more likely to develop active tuberculosis than those born

in Australia or New Zealand (incidence rate 1202 v 0 per 100,000PY; incidence rate ratio indeterminate, 95% CI 1.87 – infinite; Exact test p=0.009). Age and ethnicity were not shown to be predictive of active tuberculosis development based on these limited number of cases (Table 4). As a screening test in our low tuberculosis prevalence population, the positive predictive value for active tuberculosis during the two year median follow up period was 3.4% (95% CI 0.1-17.8%). The negative predictive value over the same period was 99.9% (95% CI 99.4-99.9%). The number needed to screen to detect one case of active tuberculosis was 913[22].

Sensitivity analysis

In a sensitivity analysis, variables used in the multivariable analyses were removed sequentially to examine for co-linear effects on the data and no other new predictor variables achieved significance at the $p<0.05$ level. There was no difference on the model whether independent variables (age, CD4 count, HIV viral load) were used as binary or continuous variables; however, the binary predictors are presented for ease of interpretation.

DISCUSSION

Our study is one of the largest cohort studies performed on QFT-G testing in HIV-infected patients in high-income countries, and the only published report on QFT-G performance in this context from Australia. The results demonstrate that country of birth is a strong predictor of QFT-G positivity, and that QFT-G positivity is a very strong relative predictor of active tuberculosis development. Further, the QFT-G assay can be performed with very low indeterminate results even in the setting of HIV and immunodeficiency. Despite overall good immunological and virological control of HIV across our cohort, we also confirmed an increased rate of tuberculosis among people with HIV-infection in this setting: 111 per

100,000PY (95% CI 13.2-395 per 100,000PY) in our cohort compared to the population rate of 7 per 100,000PY[19]. However, the positive predictive value of the QFT-G assay for development of active tuberculosis is limited by the low prevalence – by global standards – of tuberculosis in Australia.

While other studies from high-income countries have examined the role of the QFT-G in testing HIV-infected patients for symptomatic tuberculosis[23, 24], or used an alternative IGRA[25], only one paper has similarly used QFT-G to screen asymptomatic patients for latent or active tuberculosis. Aichelburg and others' study from Austria calculated the predictive value of QFT-G in HIV-infection and included 830 patients followed for a median of 19 months[13]. They found an increased odds of positive QFT-G results among patients born in Africa compared with Austria (OR 6.6, 95% CI 2.9-14.25, p <0.001) or born in countries of high versus low tuberculosis burden (>99 cases versus <25 cases per 100,000 population, OR 5.9, 95% CI 2.4-13.4%)[13]. Only three cases of active tuberculosis developed during follow up, all among those who tested QFT-G positive compared to QFT-G negative (8% versus 0%, risk difference 8%, 95% CI -0.7% to 17%, p<0.001). In our study and Aichelburg's, country of birth is probably a proxy for true exposure to tuberculosis, supported by the observation in both cohorts that LTBI risk increases across countries of increasing tuberculosis prevalence.

While the QFT-G was widely used and accepted in this clinical setting as a screening test due to its convenience and reproducibility, we observed that the QFT-G result did not always change clinical decision-making. That is, in a minority of cases, a clinical decision was made that positive QFT-G results would not be followed by anti-tuberculosis chemotherapy. Despite the relative odds of active tuberculosis among QFT-G positive, routine use of QFT-G in every HIV-infected patient in our context leads to tests being performed on some patients with low

likelihood of true tuberculosis exposure. A targeted testing process, first involving a clinical assessment of likely tuberculosis exposure based epidemiological risk factors, followed by a QFT-G test for those patients born abroad or with other potential tuberculosis exposures could improve the clinical usefulness of the QFT-G test. Improving the pre-test probability would increase the positive predictive value and may assist clinicians in diagnosing LTBI, and then better weight the benefits and toxicities of chemoprophylaxis. A targeted testing strategy would also reduce the number needed to screen to predict one future active tuberculosis case.

One recent cost effectiveness study of tuberculosis control in the United States showed that IGRA screening cost more than not screening, but was cost saving over the tuberculin skin test among HIV-infected patients, with an incremental cost effectiveness ratio of IGRA compared to TST of <US$100,000 per quality adjusted life year gained [26]. Given the public health importance of tuberculosis in the setting of HIV-infection, we suggest that a detailed cost-effectiveness evaluation comparing universal and targeted LTBI screening strategies is now warranted.

These results also demonstrated a very low proportion (0.4%) of unresolved indeterminate QFT-G test results among HIV-infected patients, compared with previously published reports. One meta-analysis synthesised indeterminate rates from 7 studies from high-income settings using QFT-G to detect LTBI and calculated a pooled proportion of indeterminate QFT-G results at 4% (95% CI 3-6%) among HIV-infected patients[12]. Another recent meta-analysis included 3 studies from high-income countries using QFT-G to diagnose, rather than predict, active TB and found a pooled proportion of indeterminate results of 8.4% (95% CI 6.8-10.2%)[27]. We also did not observe a decline in the proportion of patients testing QFT-G positive at lower CD4 T-cell counts which had been previously observed in the HIV

context[28]. Two explanations might account for our findings. First, that our HIV-infected cohort was generally well controlled on effective treatment. Only 8% of patients had CD4<200 cells/ul and 24% had CD4 <350 cell/ul, and only one of the four tests that remained indeterminate after repeating was due to a low mitogen response. However, the small sample with low CD4 T-cell counts limits ability to make observations about test performance in advanced immunodeficiency. Secondly, the QFT-G assays were all performed at the same reference laboratory soon after collection in a well-controlled setting, reducing processing delays, handing errors and enhancing reproducibility. Given the short-comings of the conventional tuberculin skin testing among HIV-infected patients, these findings provide support for the use of QFT-G among HIV-infected patients in well-resourced settings.

Limitations

This study had several limitations. While a large cohort was screened for LTBI using the QFT-G, active tuberculosis cases were rare, limiting our study power. We are not able to make robust estimates of test parameters like sensitivity, or the number of tests required to detect one active tuberculosis case. We used a retrospective cohort study design to deliberately capture all patients who had been routinely QFT-G tested, and provide for a practical lengthy follow up period. But the low tuberculosis incidence would require either a substantially larger cohort, or a longer period of observation to find more tuberculosis cases in Australia.

While selection biases possible in any retrospective study, any censoring by physicians in this cohort appears to favour selecting patients of perceived higher TB risk, based on the slightly higher proportion of non-Australian born individuals receiving QFT-G testing. Importantly, CD4 count and viral load suppression were comparable between QFT-G participants and non-participants, and there were no cases of active TB development subsequently among the non-

QFT-G testing group. Any clinician censoring therefore is more likely to *lower* further our estimates of QFT-G positivity and active TB risk.

There was potential for active tuberculosis cases to have been under-estimated if patients were diagnosed at a different health service following their initial QFT-G test. For this reason, we captured active tuberculosis case report information from the statewide Mycobacterium Reference Laboratory. While any interstate or overseas tuberculosis diagnosis could still occur and under-estimate the rate of active tuberculosis, in our experience it would be uncommon. Our tuberculosis incidence is thus reported cautiously. However, due to privacy considerations limiting data linkage by statutory health protection agencies in our jurisdiction, this is the first local estimate of incident tuberculosis among HIV-infected patients.

The retrospective nature of the study also limits our ability to collect epidemiological information on LTBI risk factors or clinical management decisions given our reliance on contemporaneous medical records. Our health clinic database helps overcome this by consistently collected demographic data with complete country of birth data in 96% of the cohort. However, a prospective design would be needed to obtain more detailed survey information on travel, occupational or other exposure risks.

Conclusions

This study demonstrated that the QFT-G assay is a strong predictor of active tuberculosis development in HIV-infected patients, and in these practical conditions produced few indeterminate results. However, active tuberculosis is rare in the setting of well controlled HIV and low population tuberculosis prevalence making its negative predictive value most helpful.

This raises questions about the clinical utility of routine QFT-G testing all HIV-infected patients born in low TB-prevalence countries. A targeted, rather than routine testing approach based on epidemiological risk factors for tuberculosis exposure may better assist clinicians to predict active tuberculosis development.

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Table 1: Baseline characteristics of the HIV-infected individuals (n=1378) and those undergoing Quantiferon-TB Gold testing for latent tuberculosis

Characteristic		QFT-G assay result			Overall QFT-G tested (n=917)	QFT-G not tested (n=461)
		Positive (n=29)	Negative (n=884)	Indeterminate (n=4)[1]		
Median age (IQR)		38.3 (34-43)	41.0 (33-48)	43.4 (39-56)	40.9 (33-48)	42.4 (36-49)
Male gender		23 (79%)	780 (88%)	3 (75%)	806 (88%)	413 (90%)
Median CD4+ T-cell count, cells/uL (IQR)		536 (389-835)	491 (347-672)	503 (408-940)	491 (348-677)	470 (344-704)
Median HIV viral load, copies/ml (IQR)		<50 (<50-4550)	<50 (<50-18700)	<50 (<50-1360)	<50 (<50-17900)	<50(<50-15000)
Median follow up post QFT-G, years (IQR)		2.3 (1.6-2.6)	2.2 (1.3-2.6)	2.4 (1.2-2.6)	2.2 (1.3-2.6)	n/a
Country of birth[2]	Australia or New Zealand	11 (41%)	536 (64%)	3 (100%)	550 (63%)	333 (72%)
	Overseas:	17 (59%)	302 (36%)	0 (0%)	319 (37%)	128 (28%)
	Europe	1 (3.8%)	86 (10%)	0 (0%)	87 (10%)	55 (12%)
	Americas	0 (0%)	32 (3.9%)	0 (0%)	32 (3.7%)	15 (3.3%)
	Africa	10 (37%)	69 (8.2%)	0 (0%)	79 (9.1%)	17 (3.7%)
	Asia	6 (21%)	113 (13%)	0 (0%)	119 (14%)	37 (8.0%)
	Pacific Islands	0 (0%)	2 (0.2%)	0 (0%)	2 (0.2%)	4 (0.2%)
Aboriginal or Torres Strait Islander		0 (0%)	12 (1.4%)	0 (0%)	12 (1.3%)	4 (0.9%)
English as primary language[3]		19 (86%)	661 (88%)	3 (100%)	683 (88%)	414 (90%)

[1]Quantiferon result indeterminate included patients with high negative control valve (n=3) or low mitogen response (n=1) despite repeat testing.
[2]Country of birth not completely documented, n=1330
[3]English use as primary language not completely documented, n=1233
QFT-G=Quantiferon-TB Gold. IQR=interquartile range. n/a=not applicable.

Table 2: Predictors of a positive Quantiferon-TB Gold assay, using univariable logistic regression

Characteristics (n=29)		QFT-G positive % (n)	Odds Ratio (95% CI)	p value
Age	≥35 years	20 (3.1%)	1	-
	<35	9 (3.4%)	1.09 (0.49-2.42)	0.83
Gender	Male	23 (2.9%)	1	-
	Female	6 (5.5%)	1.98 (0.79-4.98)	0.14
CD4 count	≥200 cells/ul	27 (3.2%)	1	
	<200 cells/ul	2 (2.9%)	0.90 (0.21-3.82)	0.87
HIV viral load[1]	Undetectable (<50 copies/ml)	8 (2.5%)	1	
	Detectable	20 (3.4%)	1.39 (0.61-3.20)	0.43
Country of birth[1]	Australia/New Zealand	11 (2.0%)	1	-
	Overseas:	17 (5.3%)	2.58 (1.18-5.62)	**0.017**
	Europe	1 (1.1%)	0.57 (0.07-4.45)	0.59
	America	0 (0%)	-	-
	Africa	10 (12.7%)	7.08 (2.90-17.3)	**<0.001**
	Asia	6 (4.2%)	2.14 (0.73-6.28)	0.17
	Pacific Islands	0 (0%)	-	-
Australian Indigenous	non-indigenous	9 (1.8%)	1	-
	Indigenous	0 (0%)	-	-
	not stated	2 (5.4%)	2.38 (0.80-7.09)	0.12
Primary language	English	19 (2.8%)	1	-
	other than English	3 (3.3%)	1.19 (0.34-4.10)	0.79
	not stated	7 (4.9%)	1.79 (0.74-4.35)	0.20

[1]Viral load and country of birth data missing in one patient lost to follow up, n=28
QFT-G=Quantiferon-TB Gold.

Table 3: Previous exposure and management of patients with positive Quantiferon-TB Gold assay, by country of birth

Characteristics (n=28)[1]		Australia/New Zealand born, n=11	Overseas born, n=17	p value (Exact-test)
Past tuberculosis exposure?	Yes 6 (21%)	2 (18%)	4 (24%)	
	No	9 (82%)	12 (70%)	1.0
	Unknown	-	1 (6%)	
Past anti-tuberculosis treatment?	Yes 5 (18%)	2 (18%)	3 (18%)	
	No	9 (82%)	14 (82%)	0.69
Current tuberculosis symptoms?	Yes 1 (4%)	0 (0%)	1 (6%)	
	No	11 (100%)	16 (94%)	1.0
Chest X-Ray following positive QFT-G?	Yes 21 (75%)	9 (82%)	13 (76%)	
	No	2 (18%)	4 (24%)	0.61
Anti-tuberculosis treatment prescribed?	Yes 19 (68%)	6 (55%)	13 (76%)	
	No	5 (45%)	4 (24%)	0.40

[1]Excludes one patient lost to follow up after Quantiferon-TB Gold test performed.
QFT-G=Quantiferon-TB Gold

Table 4: Predictors of development of active tuberculosis, using Cox proportional hazards model

Characteristics		Active TB incidence rate, per 100,000PY (n)	univariable		multivariable	
			Hazard Ratio (95% CI)	p value	Adjusted Hazard Ratio (95% CI)	p value
Age	≤35 years	76.3 (1)	1		1	
	>35 years	206 (1)	2.6 (0.17-43.1)	0.49	2.7 (0.15-47.4)	0.68
Gender	Male	64.5 (1)	1		1	
	Female	409 (1)	7.3 (0.45-116.2)	0.16	2.2 (0.11-46.4)	0.61
CD4 count	≥200 cells/ul	60.5 (1)	1		1	
	<200 cells/ul	702 (1)	12.7 (0.80-202.5)	0.07	25.4 (0.70-918)	0.08
HIV viral load	Undetectable	149.5 (1)	1		1	
	Detectable	89.0 (1)	0.58 (0.04-9.4)	0.70	0.14 (0.01-4.70)	0.27
Country of birth	Australia/New Zealand	0 (0)				
	Overseas:	328 (2)	n/a†	-	-	-
	Africa	1209 (2)	n/a†	-	-	-
Quantiferon	negative	57.7 (1)	**1**		1	
	positive	1753 (1)	**34.6 (2.2-554.5)**	**0.016**	**42.4 (2.2-827)**	**0.013**

† Hazard ratio indeterminate
PY= person years. n/a=not applicable