

Baseline Screening for Tuberculosis Among Patients Enrolling in an Antiretroviral Treatment Service in South Africa



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ABSTRACT

Background: The burden of tuberculosis (TB) in patients in antiretroviral treatment (ART) services in Africa is very high. Diagnosis is difficult and time-consuming, leading to morbidity, mortality, delays in ART initiation and the potential for nosocomial TB transmission. We determined the prevalence of TB in patients enrolling in a local ART service and explored optimal means of screening for TB.

Methods: ART-naïve adult patients not receiving TB treatment were recruited as they enrolled within a community-based ART service in a South African township. A detailed symptom screen was completed. Paired spot and induced sputum samples underwent fluorescence microscopy, automated liquid culture, drug susceptibility testing and spoligotyping. Chest x-rays were done and urine was tested for liparabinomannan (LAM) by ELISA.

Results: Of 236 patients 73% were female, 10% were pregnant, the mean age was 34 years, the mean CD4+ count was 129 cells/μL, 46% had WHO Stage III disease, the mean BMI was 24.1 kg/m², and 34% had a history of TB. 62 patients (26.3% [95% CI 21.0-32.2]) were found to have culture-positive TB. In those with CD4 counts of <100 or >100 cells/μL the prevalence of TB was 38% and 19%, respectively. The sensitivity of sputum microscopy was very low (13%) and the mean time to positive culture was 23 days (range=6-50). 5 patients had drug resistant TB, including 2 with MDR-TB. Spoligotyping of isolates revealed no evidence of cross-contamination. The sensitivity and specificity of individual symptoms for TB diagnosis were low. An optimum screen using a combination of symptoms of cough, weight loss, fever and night sweats had a sensitivity of 78%, but specificity was very low (35%). 22% of TB cases were sub-clinical. Sputum induction immediately following spot sputum showed no incremental diagnostic yield. Chest radiographs were normal in approximately one third of cases. LAM ELISA had a specificity of 99% and sensitivity of 31% overall. However, the sensitivity was 51% in those with a CD4 count <100 cells/μL.

Conclusions: Over one quarter of patients had culture-positive TB. Symptom screening, sputum smears and chest radiology were poorly predictive for TB. Sputum culture was slow. New more rapid diagnostic tests are urgently needed. A point of care urinary LAM assay has potential utility among those with CD4 cell counts <100 cells/μL.

METHODS

Study Period: May 2007 - April 2008

Eligibility criteria:

- Referred for ART
- Adult
- ART-naïve
- Not already receiving TB treatment

At ART programme enrollment visit:

- Standard TB symptom screen
- History and physical examination
- Obtained one spot sputum followed by one induced sputum
- Chest x-ray (pregnant patients excluded)
- Urine sample collected

Laboratory:

- Sputum samples - fluorescence microscopy, automated liquid culture (Becton Dickinson MGIT 960)
- Positive cultures: drug susceptibility, spoligotyping
- Urine - liparabinomannan (LAM) ELISA (Chemogen)

TB case definition: ≥1 positive sputum culture

Ethics:

- Approved by Research Ethics Committee, University of Cape Town
- All enrolled patients provided written informed consent

MYCOBACTERIAL CULTURE

- Positive culture: 62 / 236
- **TB Prevalence: 26.3%** [21.1%-32.2%]
CD4 count < 100 = 38.0% [28.8%-48.3%]
CD4 count > 100 = 18.8% [13.2%-25.9%]
- Mean time to positive MGIT culture: 23 days [range: 6-50]
- 2 patients (<1%) with Mycobacterium other than tuberculosis

MICROSCOPY

- 54 of 62 patients (87%) were sputum smear negative
- **Sensitivity of fluorescence microscopy: 13%**

DRUG RESISTANCE

- Mean time to drug sensitivity testing results: 37 days (no PCR)
- 5 patients (8%) had phenotypic drug resistance
2 patients resistant to Isoniazid
1 patient resistant to Rifampicin
2 patients with multi-drug resistance (sensitive to Ethambutol, Ethionamide, Ofloxacin, Amikacin)

SPOLIGOTYPING

- Paired isolates from the same patient were identical.
- When ordered by date, isolates are different between patients.
- Therefore **NO evidence of cross-contamination**
- 28% Beijing family, 21% LAM3, 10% S family, 10% LAM9

URINARY LAM ELISA

Introduction:

Liparabinomannan (LAM) is a 17.5 kDa cell wall lipopolysaccharide specific to *Mycobacterium*. It is released from metabolically active or degrading bacterial cell walls, circulates in the bloodstream, and is filtered by the kidneys. It may be detectable in the urine of patients with active TB with potential utility as a diagnostic tool (Boehme *et al*, *Trans R Soc Trop Med Hyg* 2005;99:893-900)

Hypothesis:

In view of the high frequency of disseminated disease in patients with advanced HIV, we hypothesized that urinary LAM-ELISA would have high sensitivity for TB in these patients.

Methods:

- Used commercially available kit from Chemogen (Portland, Maine USA)
- Urine processed per manufacturer's instructions

Results:

- In all TB culture positive patients: sensitivity 31%, specificity 99%
- **CD4 count <100: sensitivity 51%, specificity 98%**
- CD4 count >100: sensitivity 4%, specificity 99%

Conclusion:

Although sensitivity in patients with CD4<100 is only moderate, specificity is very high. Urinary LAM ELISA may therefore be useful as a dipstick point-of-care diagnostic test.

BACKGROUND

The burden of TB in ART programmes in sub-Saharan Africa is high, and time to diagnosis is often prolonged. TB in ART programmes is a major cause of morbidity, mortality, nosocomial disease transmission, and is associated with delays in ART initiation. The optimal means to rapidly detect TB in these patients must be determined in order to decrease these risks.

STUDY AIMS

- To determine the total prevalence of TB (symptomatic + asymptomatic) in patients enrolling in an ART programme
- To evaluate standard TB screening tools in this population (symptom screen, chest radiology, sputum smear microscopy) compared to routine culture (gold standard)
- To evaluate urinary liparabinomannan (LAM) ELISA as a TB screening tool

SETTING

Guguletu- Nyanga District, Cape Town, South Africa

TB notification rate: >1,500 / 100,000 / yr

Antenatal HIV prevalence : ~30%

RESULTS

PATIENT CHARACTERISTICS

	Total n=236	TB n=64	No TB n=172	p *	
Age [years] (median,IQR)	33 (26.5-39)	34 (28-39)	33 (29-37)	0.33	
Female (n,%)	172 (73)	48 (79)	124 (71)	0.24	
Pregnant (n,%)	24 (10)	7 (11)	17 (10)	0.70	
BMI (median,IQR) **	22.9 (20.1-27.4)	21.8 (19.6-24.2)	22.6 (19.8-27.0)	0.18	
Baseline WHO Stage (n,%)	Stages 1 & 2	110 (47)	21 (34)	89 (51)	0.055
	Stage 3	109 (46)	33 (53)	76 (43)	
	Stage 4	17 (7)	7 (11)	10 (6)	
Baseline CD4 cell count [cells/μL] (median,IQR)	127 (67-185)	78 (33-169)	144 (84-189)	0.001	
Previous TB (n,%)	79 (34)	15 (25)	64 (37)	0.07	

* Chi-square test for proportions, Wilcoxon rank-sum (Mann-Whitney) for continuous variables
** Pregnant patients excluded

TB SYMPTOM SCREENING

- Using a positive response to any combination of cough, fever, night sweats, or weight loss>5kg:
Sensitivity: 78%
Specificity: 35%
- **22% of patients were defined as asymptomatic using this screen**
- Multivariate analysis using models that included baseline patient characteristics showed that only CD4 count<100 is significantly predictive of TB
- TB symptoms were **NOT** independently associated with TB status in this population and setting

CHEST RADIOLOGY

- 209 patients (89%) had a chest x-ray obtained during screening visit
- Each chest x-ray was read and reported separately by two study clinicians for any evidence of TB disease
Sensitivity: 67%
Specificity: 47%.
- **1/3 of TB cases had a normal chest radiograph.**

CONCLUSIONS / DISCUSSION

1. The prevalence of sputum culture positive TB in patients accessing ART is very high (26.3%).
2. Sputum fluorescence microscopy has low sensitivity (12.9%) in this population with advanced HIV.
3. Culture based diagnosis is very slow (mean 23 days). Delays may contribute to morbidity, mortality, and TB transmission.
4. Subclinical TB presents a diagnostic challenge: 1/5 of TB cases were subclinical.
5. Symptoms are poorly predictive of TB, and symptoms are not independently associated with TB in this population.
6. 1/3 of TB patients had a normal chest radiograph.
7. CD4 count is the main predictor of TB status.
8. Routine microbiological screening of patients irrespective of symptoms may be warranted in this population.
9. Urinary LAM ELISA has some potential utility as a very specific point of care test in those with very low CD4 count.