POSTER NUMBER

833

Culture-negative TB is associated with increased mortality in HIV-infected persons

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Background

- In settings where cultures are routinely obtained, ~20% of TB is culture-negative
- Rates of culture-negative TB are higher in resource-limited settings, due in part to less frequent use of acid-fast bacilli (AFB) cultures
- AFB smear-negative TB is associated with increased mortality in HIV+ persons; there are few data on mortality risk in culture-negative TB

Methods

Study design: observational cohort study
Study population: HIV+ persons treated for TB at or after their first clinic visit at sites in Argentina, Brazil, Chile, Honduras, Mexico, and Peru from 2000-2013. Excluded if date of TB treatment relative to HAART initiation was unknown.
TB treatment: 2 months of INH, rifampin, pyrazinamide +/- ethambutol followed by continuation phase treatment: INH + rifampin
TB diagnosis date = date of TB treatment initiation
TB recurrence = new TB diagnosis > 180 days after initial TB episode
TB endpoints validated by medical record review
Statistical analysis: Kaplan-Meier curves and Cox proportional hazards models of time to death from TB diagnosis. Cox models were stratified by study site.
Multiple imputation performed for missing data in the multivariable Cox model.

Results

Table 1. Characteristics of the study population.

Characteristic	N	Median or count	(IQR) or percent
Median age	772	36	(30-43)
Male sex	772	583	76%
Study site	772		
Argentina		85	11%
Brazil		255	33%
Chile		62	8%
Honduras		28	4%
Mexico		26	3%
Peru		316	41%
Site of TB disease	772		
Any pulmonary		536	69%
Any extrapulmonary		399	52%
Median CD4 at TB Diagnosis	625	100	(45-228)
AFB smear	654		
Positive		312	48%
Negative		342	52%
AFB culture	536		
Positive		332	62%
Negative		204	38%
TB diagnosis relative to HAART	772		
Never on HAART		50	6%
HAART stopped before TB		14	2%
HAART concurrent with TB Rx		627	81%
HAART started after TB Rx		81	10%

Total TB patients	**1,586**
+ treated with standard therapy	**1,308**
+ TB diagnosed at/after 1st visit	**884**
+ TB treatment relative to HAART start known	**772**
Isoniazid resistance:	**26/276 (9%)**
Rifampin resistance:	**19/276 (7%)**

Table 2. Mortality rates according to culture and smear status.

Characteristic	Negative	Positive	P
Culture	44/204 (22%)	45/332 (14%)	0.02
Smear	56/342 (16%)	56/312 (18%)	0.67

Figure 1. Kaplan-Meier curve of time to death according to AFB culture status.

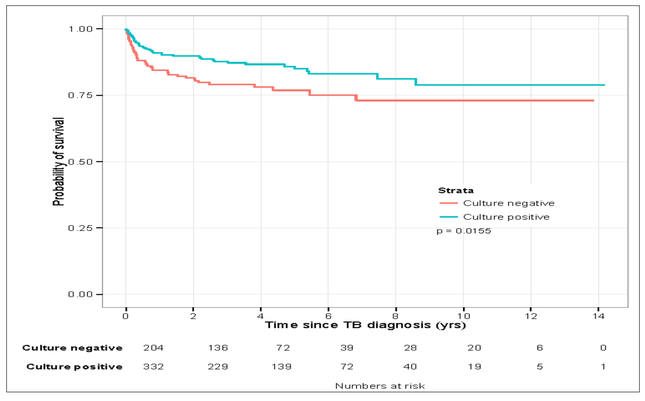
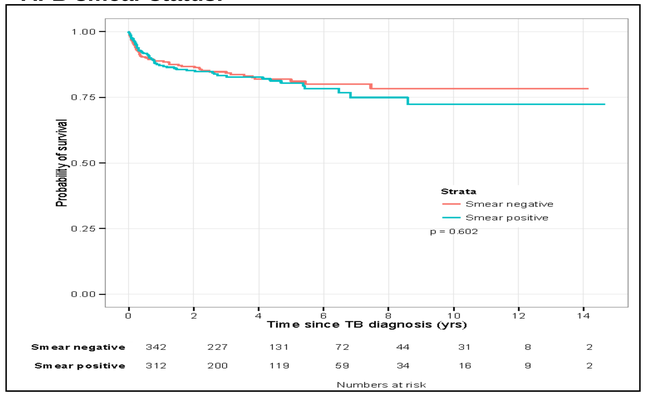


Figure 2. Kaplan-Meier curve of time to death according to AFB smear status.



There were 17 episodes of recurrent TB occurring > 180 days after initiation of TB treatment; recurrence tended to occur more frequently in culture-negative compared to culture-positive persons (log-rank P = 0.10)

Table 3. Risk Factors for Death Among TB Patients. Cox proportional hazards models.

Characteristic	Univariate			Multivariable		
Study population	HR	95% CI	P value	aHR	95% CI	P value
TB culture positive	1.0			1.0		
TB culture negative	1.67	1.10, 2.5	0.017	1.79	1.23, 2.63	0.002
CD4 at TB diagnosis			<0.001			<0.001
50	3.69	2.01, 6.76		4.05	2.14, 7.68	
100	2.78	1.51, 5.12		3.16	1.71, 5.85	
200	1.74	1.03, 2.92		1.97	1.20, 3.24	
350 (ref)	1.00			1.00		
500	0.60	0.32, 1.14		0.51	0.28, 0.94	
TB Dx relative to HAART			<0.001			<0.001
Never on HAART (ref)	1.00			1.00		
HAART stopped before TB	0.38	0.14, 1.00		0.23	0.08, 0.63	
HAART concurrent with TB	0.18	0.11, 0.30		0.13	0.08, 0.23	
HAART started after TB Rx	0.20	0.11, 0.39		0.19	0.09, 0.40	
Age at TB diagnosis			0.71			0.18
25	0.90	0.60, 1.35		0.84	0.55, 1.29	
30	0.95	0.80, 1.13		0.92	0.76, 1.10	
35 (ref)	1.00			1.00		
40	1.04	0.95, 1.14		1.09	0.99, 1.20	
50	1.09	0.78, 1.54		1.30	0.92, 1.84	
Site of TB			0.59			0.79
Pulmonary only	1.00			1.00		
Any extrapulmonary TB	0.84	0.59, 1.18		0.93	0.65, 1.33	
Unknown	0.88	0.22, 3.60		1.46	0.34, 6.32	

Limitations

Information on cause of death was not available.

There were no data on drug resistance in culture-negative TB cases.

Conclusions

In this large, multi-center cohort study, culture-negative TB was associated with a 79% increased hazard of death compared to persons with culture-confirmed TB.

These findings raise the possibility that persons diagnosed with culture-negative TB may not have had TB, and died of other causes.

This underscores the importance of accurate TB diagnosis in HIV + persons.

References

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CCASAnet Sites, Investigators, and Funding

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Funded by US NIH/NIAID grant U01 AI069923.