CSF TB Bacillary Load Predicts Two-Week Mortality in HIV-Associated TB Meningitis

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Emily Martyn[1], Ananta Bangdiwala[2], Enock Kagimu[1], Morris K. Rutakingirwa[1], John Kasibante[1], Michael Okirwoth[1], Gavin Stead[1], Vincent Wadda[3], Matt Pullen[2], Tyler Bold[2], Alison M. Elliott[4,5], David B. Meya[1], David R. Boulware[2], Nathan C. Bahr[6], Fiona V. Cresswell[1,4,5]

[1]Infectious Diseases Institute, Kampala, Uganda, [2]University of Minnesota, Minneapolis, MN, USA, [3]Mulago National Referral Hospital, Kampala, Uganda, [4]London School of Hygiene & Tropical Medicine, London, UK
[5]MRC-UVRI LSHTM Uganda Research Unit, Entebbe, Uganda, [6]University of Kansas, Kansas City, KS, USA,

High CSF TB bacillary load, measured by Xpert MTB/RIF Ultra cycle threshold, is associated with 60% two-week mortality in HIV-associated TB Meningitis

over two-fold greater than intermediate (18%) and low (26%) bacillary loads

BACKGROUND

- TB meningitis (TBM) results in death or disability in >50% affected, with worse outcomes in HIV co-infection.[1]
- GeneXpert MTB/RIF Ultra (Xpert Ultra), a fully automated PCR assay, is the World Health Organization recommended initial diagnostic test.[2]
- Configuration of positivity of 4 *rpoB* probes and 2 multicopy DNA amplification targets (*IS6110* and *IS1081*) gives a semi-quantitative result: trace, very low, low, medium and high.
- The PCR cycle threshold (Ct) represents the number of PCR cycles required for a probe signal to reach a detection threshold and can act as a proxy for TB bacillary load (**low Ct value = high bacillary load**).

METHODS

- Between April 2015 to August 2019, as part of a meningitis diagnostic study, Xpert Ultra was used to test the cerebrospinal fluid (CSF) of 107 Ugandan Adults with probable or definite TBM.[3]
- Ct values for the *IS6110/IS1081* multicopy amplification targets were used as a proxy for TB bacillary load. *RpoB* probes were excluded as they are negative in trace category calls.
- We analyzed 2-week survival and baseline characteristics according to Ct tertiles: low (16.2 – 20.0), intermediate (20.0 – 24.5) and high (24.6 – 32.7).

References
[1]Donovan J, Figaji A, Imran D, Phu NH, Rohlwink U, Thwaites GE. The neurocritical care of tuberculous meningitis. Lancet Neurol 2019; 18(8): 771-83.
[2]World Health Organization. WHO Meeting Report of a Technical Expert Consultation: Non-inferiority analysis of Xpert MTB/RIF Ultra compared to Xpert MTB/RIF. Available at: http://www.who.int/tb/publications/2017/XpertUltra/en/. Accessed 2 Feb 2020
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BASELINE CHARACTERISTICS

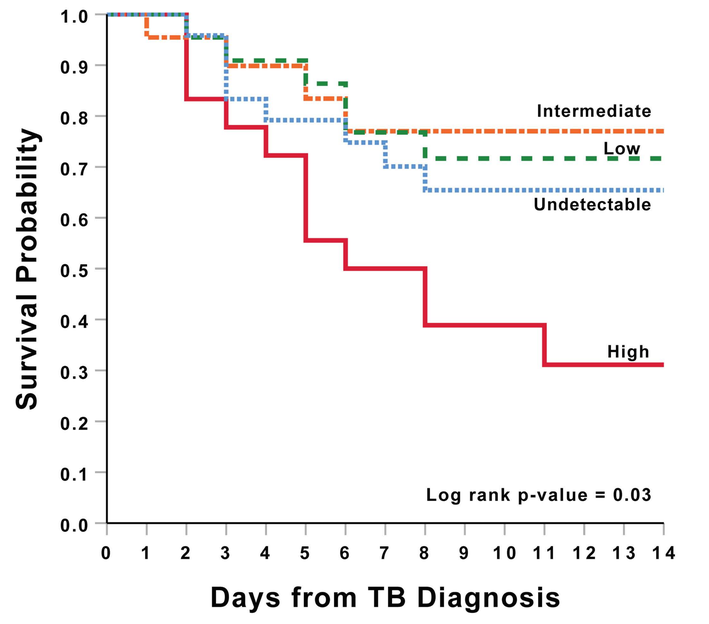
Table 1: Comparison of baseline demographics, clinical characteristic and cerebrospinal fluid (CSF) parameters according to Xpert Ultra cycle threshold (Ct) tertile categories.

	High Bacillary Load Ct [16.2, 20.0] n=23	Intermediate Bacillary Load Ct [20.0, 24.5] n=23	Low Bacillary Load Ct [24.5, 32.7] n=25	Ultra Negative n=29	p-value[1]
Demographics					
Age (years)	32 [28, 36]	34 [32, 38]	31 [27, 37]	35 [30, 40]	0.10
Female	11 (47.8)	10 (43.5)	6 (25.0)	12 (41.4)	0.40
Clinical characteristics					
HIV positive	21 (91.3)	22 (95.7)	25 (100)	27 (93.1)	0.56
Currently on ART	10 (45.5)	12(54.5)	13 (52.0)	13 (50.0)	0.94
Months on ART[2]	9.7 [3.1, 22.2]	2.3 [0.3, 7.0]	1.1 [0.7, 3.4]	11.3 [3.8, 38.1]	0.09
CD4 count	58 [48, 73]	85 [45, 170]	74 [19, 122]	95 [70, 144]	0.51
Focal neurologic deficit	26 (26.0%)	4 (17.4%)	10 (40.0%)	6 (20.7%)	0.28
BMRC severity grade					0.18
Grade I	2 (9.1)	5 (21.7)	2 (8.3)	0 (0.0)	
Grade II	13 (59.1)	15 (65.2)	15 (62.5)	21 (75.0)	
Grade III	7 (31.8)	3 (13.0)	7 (29.2)	7 (25.0)	
CSF results					
Opening pressure (mmH_20)	180 [70, 270]	185 [100, 240]	220 [135, 300]	230 [115, 270]	0.73
Total WBC count (cells/μL)	115 [4, 243]	48 [4, 250]	35 [4, 165]	93 [14, 225]	0.49
Protein (mg/dL)	116 [50, 199]	177 [90, 316]	133 [101, 195]	158 [58, 200]	0.71
Lactate (mmol/L)	**10.6 [9.5, 12.0]**	**7.9 [5.7, 10.4]**	**7.4 [4.6, 9.6]**	**9.4 [4.6, 10.4]**	**0.04**
Glucose (mg/dL)	26 [18, 33]	31 [18, 61]	30 [22, 67]	54 [27, 84]	0.06

Data presented as Median [IQR] or N(%). [1]Kruskal-Wallis Test for medians, Chi-squared test for proportions. [2]Among those on ART at diagnosis. Antiretroviral therapy (ART), British Medical Research Council (BMRC), White Blood Cell (WBC).

TWO-WEEK MORTALITY

Figure 1. Two-week mortality by Ultra PCR cycle threshold (Ct) among participants with probable (negative Xpert Ultra) or definite TB meningitis. High bacillary load = lowest Ct tertile.



High bacillary load [Ct 16.2-20.0]: 20 persons, 12 (60%) events
Intermediate bacillary load [Ct 20.0-24.5]: 22 persons, 4 (18%) events
Low bacillary load [Ct 24.5, 32.7]: 23 persons, 6 (26%) events
Undetectable bacillary load [Ct negative]: 26 persons, 8 (31%) events

RESULTS

- 107 participants had definite or probable TBM, 7 were excluded due a missing *IS6110/IS1081* Ct result.
- Participants with the highest bacillary load (lowest Ct tertile) had a 60% 2-week mortality, significantly worse than intermediate (18%) and low (26%) bacillary loads and negative Xpert Ultra (31%) probable TBM cases. (**Figure 1**)
- 2-week mortality analysis using Xpert Ultra semi-quantitative results also trended towards a higher mortality in medium-low compared to trace and negative, but did not reach statistical significance (p=0.39).
- TB bacillary load was significantly associated with high CSF lactate levels (p=0.04). Association with CSF glucose trended toward significance (p=0.06) (**Table 1**)

CONCLUSIONS

- High CSF TB bacillary load, as measured by Xpert Ultra, is associated with approximately 2-fold higher mortality in HIV-associated TBM when compared to intermediate, low and undetectable bacillary loads.
- These data suggest Ct tertiles are a better predictor of outcome in HIV-associated TBM than semi-quantitative category alone.
- Xpert Ultra Ct tertiles may identify a subgroup of patients at higher risk of early mortality who may benefit from enhanced supportive care or intensified treatment.
- One limitation of this study is the relatively small cohort size. Further independent confirmation in HIV and non-HIV cohorts in other geographical settings and investigation of the biological mechanism of our observations are required.

emily.martyn@doctors.org.uk
@EmilyMartyn2