Standardized urine-based tuberculosis screening with TB-LAM and Xpert MTB /Rif Ultra in Ugandan adults with advanced HIV disease and suspected meningitis

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BACKGROUND

- Tuberculosis (TB) is a common cause of HIV-related death with 250,000 deaths due to TB/HIV in 2019 [1]
- It is estimated that half of all TB diagnoses remain undiagnosed at the time of death [2]
- In STAMP trial, use of urine TB-lipoarabinomannan lateral flow assay (LAM) reduced missed TB diagnoses and mortality in HIV+ inpatients with CD4 <100, severe anemia and suspected TB [3]
- The utility of the novel Xpert MTB/Rif Ultra (Ultra) assay on urine has not been evaluated
- We sought to determine the prevalence of disseminated TB by testing urine with TB-LAM and Ultra in hospitalized adults with suspected meningitis in Uganda

METHODS

- We prospectively enrolled HIV+ adults with suspected meningitis in Kampala or Mbarara, Uganda.
- Participants were screened for meningitis etiologies using a stepwise algorithm for cryptococcal, tuberculous meningitis (TBM), bacterial and viral meningitis.
- Inclusion criteria for diagnostic testing were HIV-positive adults (≥18 years) presenting with suspected meningitis (e.g. headache or altered mental status, clinical signs of meningism).
- In parallel, participants underwent systematic urine-based screening for TB using the TB-LAM (Alere) and Ultra (Cepheid).
- 60 µL of unconcentrated urine was tested with the TB-LAM . All remaining urine was centrifuged and the cell pellet re-suspended in 2mL of urine for Ultra testing.
- Results were reported to clinicians in real-time.
- Univariate logistic regression was performed to see explore whether urine TB test positivity is associated with death

Urine TB tests detected 25% prevalence of disseminated TB in hospitalized Ugandan adults with advanced HIV disease and suspected meningitis and were associated with higher mortality in definite TB meningitis

RESULTS

From Jan 2018 to Sept 2019, we enrolled 251 HIV-positive inpatients. Median CD4 = 37 cells/mcL (IQR 12-85). The majority had cryptococcal meningitis 59% (148/251), and 15% (38/251) had definite/probable TB meningitis **(Table 1)**

Table 1. Baseline Characteristics

Characteristics	Cryptococcal Meningitis N=148	TB meningitis, confirmed N=28	TB meningitis, probable N=10	Unknown Other Meningitis[1] N=65	P-value [2] 251
Age, years	35 [28, 42]	32 [28, 37]	38 [35, 40]	36 [29, 42]	0.26
Women	59 (40%)	12 (44%)	6 (60%)	27 (43%)	0.64
HIV FACTORS					
CD4+ T cells/µL[3]	19 [6, 66]	74 [46, 122]	133 [47, 336]	125 [30, 325]	<0.01
Currently on ART	73 (49%)	15 (54%)	3 (33%)	42 (65%)	0.13
Months on ART[4]	2.3 [0.6, 29.4]	1.3 [0.5, 55.7][5]	14.3 [8.3, 126.2]	12.2 [2.0, 79.6][5]	0.01
CLINICAL					
Fever	56 (38%)	22 (79%)	9 (90%)	30 (46%)	<0.001
Headache	142 (96%)	23 (82%)	8 (80%)	46 (71%)	<0.001
Duration of headache	14 [12, 21]	14 [7, 14]	14 [7, 17.5]	14 [7, 30]	0.27
Focal neurologic deficit	6 (4.1%)	12 (43%)	3 (30%)	12 (18%)	<0.001
Wasting	61 (42%)	11 (39%)	3 (30%)	23 (35%)	0.77
Glasgow coma score<15	49 (33%)	24 (89%)	10 (100%)	30 (47%)	<0.001
Seizure	33 (22%)	9 (32%)	2 (20%)	15 (21%)	0.63
Weight, kg	52 [45.5, 58]	55 [50, 60]	56 [55, 60]	51 [50, 59]	0.11
Cough	45 (49%)	17 (77%)	4 (57%)	21 (51%)	0.12
Night sweats[6]	22 (31%)	10 (71%)	4 (67%)	11 (34%)	0.02
BASELINE CSF RESULTS					
Opening pressure, cm H_2O	25 [17, 36]	22 [13.5, 32.5]	14.5 [9, 23]	18 [12.5, 23]	<0.01
Opening pressure <20 cm H_2O	40 (32%)	8 (38%)	4 (67%)	27 (61%)	<0.01
CSF white cells/µL	<5 [<5, 80]	170 [<5, 282]	200 [35, 275]	<5 [<5, 10]	<0.001
CSF white cells < 5 /µL	58 (61%)	6 (30%)	1 (20%)	34 (74%)	<0.01
CSF protein, mg/dL	40 [26, 78]	119 [49, 217]	158 [147, 194]	31 [22, 71]	<0.001
CSF WBC <5/mL & prot < 45 mg/dL	45 (48%)	4 (21%)	1 (20%)	25 (64%)	0.01

Data are n (%) or median [IQR]. 1 Includes possible and non-tuberculous meningitis diagnoses. 2 Kruskal-Wallis test for medians; chi-square test for proportions. 3 Among those on ART at diagnosis

- Overall, 25% (63/251) had a positive urine TB test.
- Amongst the 178 participants who had both TB-LAM and Ultra results available 18% (32/178) were positive by TB-LAM only, 11% (20/178) were positive by Ultra only and 4% (8/178) were positive by both tests **(Figure 1)**

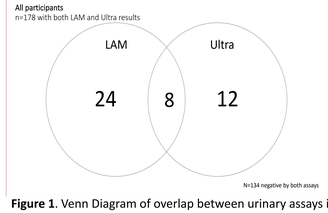

Figure 1. Venn Diagram of overlap between urinary assays in the n=178 participants with both TB-LAM and Ultra results

- In cryptococcal patients, 20% (29/145) had evidence of disseminated TB by TB-LAM and 5% (5/96) by Ultra.
- In definite TBM 44% (12/27) had a positive Ultra, 33% (9/27) had a positive TB-LAM and 26% (7/27) were positive by both tests **(figure 2)**
- In definite/probable TBM, 32% (12/37) had a positive urine LAM and 33% (12/36) had a positive Ultra.

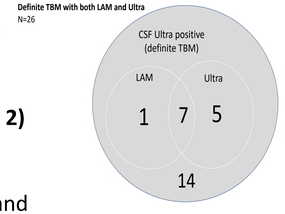

Figure 2. Venn diagram illustrating overlap of TB-LAM and urine Ultra amongst those with definite TBM

Figure 1: Proportion with Positive Urine Test by Aetiology

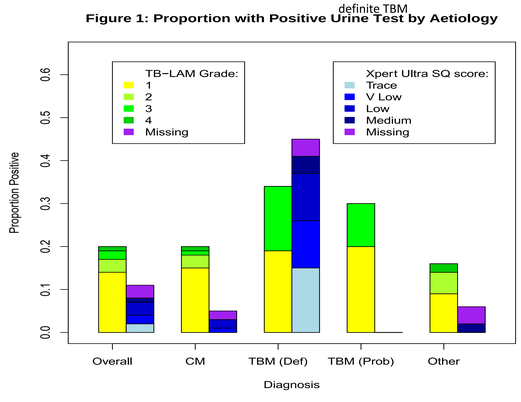

Figure 3 visualises the distribution of the 51 positive urine TB-LAM (and grade) and 20 positive urine Ultra (and semi-quantitative category) results by disease aetiology. Both TB-LAM grade and Ultra semi-quantitative category crudely quantify the burden of Mycobacterium tuberculosis antigen in the sample.

- Mortality was higher in patients with evidence of disseminated TB by either urine assay, although these results were not statistically significant (Odds Ratio = 1.65; 95%CI, 0.87 to 3.12, P=0.12)
- Mortality was 7-fold higher in those with definite TB meningitis who were urine Ultra-positive (Odds Ratio = 7.20; 95%CI, 1.07 to 48.6, P=0.04) **(Table 2)**

RESULTS CONTD…

Meningitis Group	TB-LAM				Xpert Ultra				Either TB Assay Positive[1]	
	Positive	Negative	Odds Ratio (95%CI)	P-value	Positive	Negative	Odds Ratio (95%CI)	P-value	Odds Ratio (95%CI)	P-value
Overall	36% (17/47)	27% (47/175)	1.54 (0.78, 3.05)	0.21	42% (8/19)	24% (36/149)	2.28 (0.85, 6.11)	0.10	1.65 (0.87, 3.12)	0.12
Cryptococcal	36% (10/28)	32% (34/106)	1.18 (0.49, 2.82)	0.72	40% (2/5)	27% (23/86)	1.83 (0.29, 11.6)	0.52	1.37 (0.60, 3.13)	
TBM, definite	56% (5/9)	25% (4/16)	3.75 (0.66, 21.3)	0.14	55% (6/11)	14% (2/14)	7.20 (1.07, 48.6)	0.04	6.42 (1.00, 41.2)	0.05
TBM, probable	50% (1/2)	29% (2/7)	2.50 (0.10, 62.6)	0.58	37.5% (3/8)	--				
Other / unknown	12.5% (1/8)	15% (7/46)	0.80 (0.08, 7.51)	0.84	0% (0/3)	20% (8/41)			0.51 (0.06, 4.68)	

Table 2. In-hospital mortality by urine diagnostic result and meningitis aetiology by univariate logistic regression

LIMITATIONS

- Our study was not powered to detect an association between TB-LAM and/or Xpert Ultra positivity and death, a larger prospective study is therefore required.
- Either due to low urine volume (<30mL), or due to Ultra test unavailability, not all patients had both TB-LAM and Ultra performed. Cconcordance and diagnostic yield was only compared in patients who had both test results available (n=178).
- Due to the study setting and population we were unable to perform an extensive array of other TB diagnostics (e.g. imaging or sputum collection to corroborate the urine results.

CONCLUSIONS

- We detected high prevalence of disseminated TB (25%) by urine testing.
- Cryptococcosis and TB co-infection was common (20%). Given the overlap in symptoms, TB may be missed in this setting without systematic testing.
- In those with TB meningitis, urine tests were positive in one-third; these tests may represent rapid, non-invasive adjunctive tests for TBM diagnoses.
- There was little concordance of Ultra and LAM, the reason for which warrants further investigation.

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