Performance of Urine Xpert Ultra vs Alere LAM for Diagnosing TB in HIV Inpatients

Poster 761

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BACKGROUND

- Rapid urine-based TB diagnostics, including lateral flow urinary lipoarabinomannan (LF-LAM), reduce mortality in HIV-positive inpatients.
- *Xpert MTB/RIF Ultra* (Ultra) has improved sensitivity on sputum, but this assay's performance on urine samples has not been well studied.
- We compared the performance of urine Ultra versus LF-LAM in HIV-positive medical inpatients with suspected TB.

METHODS

- A cross-sectional study at two hospitals in East London, South Africa, was conducted over 7 months in 2018/9.
- Sequential HIV-positive adults (≥18yrs) admitted with ≥1 WHO TB symptom or clinical suspicion of TB were eligible.
- TB cultures of blood, sputum and urine were taken.
- Bedside urine LF-LAM was performed, with a 1+ intensity result regarded as positive per manufacturer instructions.
- Urine Ultra was tested on the pellet of 15ml centrifuged sample.
- Diagnostic classifications were: 'definite TB' (positive TB culture or molecular test), 'probable TB' (clinico-radiological features of TB and response to TB therapy), 'not TB' (remained well without TB therapy), and 'unclassifiable' (unable to assign due to death of unknown cause, on-going symptoms or loss-to-follow-up).
- Urine Ultra results were not used for the classification of 'definite TB'.
- Diagnostic yield was calculated as the proportion positive by the index test, amongst all with definite TB (or definite and probable TB), regardless of whether index sample obtained.

Table 1. Baseline demographics

	Participants (n=238) (n, % unless specified)
Age (years) median (IQR)	39 (32-48)
Female sex	124 (52%)
Currently on ART	105 (44%)
Previously treated TB	99 (42%)
CD4 count (cells/mm^3) (Median, IQR)	76 (22-203)
<50	97 (42%)
50-100	36 (15%)
101-200	40 (17%)
>200	60 (26%)
Haemoglobin (g/dl) (Median, IQR)	9.9 (7.7-12.1)
Unable to walk unaided	159 (67%)

In inpatients with advanced HIV and TB symptoms, urine Ultra had a yield of 68% vs urine LAM 45% for definite TB. Combined, this rose to 73%.

RESULTS

- 238 participants were enrolled, 89 (37%) produced a spontaneous sputum sample and urine was collected on all patients as per the inclusion criteria.
- Definite TB was diagnosed in 62 (26%) and either definite or probable TB in 92 (39%).
- Diagnostic yields for definite TB were 34% for sputum Ultra, 45% for urine LAM, 68% for urine Ultra, and 73% for urine LAM and urine Ultra combined.
- Diagnostic yields for definite plus probable TB were 23% for sputum Ultra, 39% for urine LAM, 57% for urine Ultra , and 64% for urine LAM and urine Ultra combined.
- The sensitivity and specificity using definite TB as a reference were 45% and 93% for LF-LAM, and 70% and 100% for urine Ultra, respectively.
- Positive urine Ultra results were 69% (n=37) rifampicin susceptible, 9% (n=5) resistant, and 22% (n=12) indeterminant, with no discordancy with rifampicin susceptible or resistant results detected on TB cultures or sputum Ultra.
- When *post-hoc* revised criteria by clinician consensus for probable TB were applied in view of the 43% unclassifiable per protocol, the unclassifiable category was reduced to 14%. This resulted in minor differences in respective diagnostic yields (data not shown).

Table 2. TB diagnostic categories

TB diagnosis	Per protocol definitions (n=238)(n,%)
Definite TB	62 (26%)
Probable TB	30 (13%)
Unclassifiable	102 (43%)
Not TB	44 (18%)

Table 3. Diagnostic yield

TB diagnostic test(s)	Participants with definite TB (n=62) (n,%)	Participants with definite or probable TB (n=92) (n, %)
Urine LAM	28 (45%)	36 (39%)
Urine Ultra	42 (68%)	52 (57%)
Sputum Ultra	21 (34%)	21 (23%)
LAM + urine Ultra	45 (73%)	59 (64%)
LAM + sputum Ultra	40 (65%)	48 (52%)
LAM + sputum Ultra + urine Ultra	55 (89%)	69 (75%)

Table 4. Performance characteristics

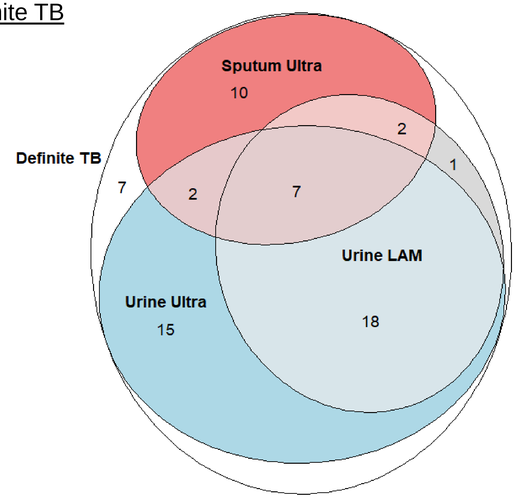
Definite TB*	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	LR+	LR-
Urine LAM (n=106)	45	93	55	90	6.43	0.59
Urine Ultra (n=103)	70	100	70	100	NA^	0.3
Definite or probable TB**						
Urine LAM (n=136)	39	93	42	92	5.57	0.66
Urine Ultra (n=133)	58	100	53	100	NA^	0.42

* Performance characteristics calculated on urine LAM results for all definite TB vs not TB participants. The same for urine Ultra less 3 inconclusive results.
** Calculated on all definite or probable TB vs not TB participants with urine LAM results. The same for urine Ultra less 3 inconclusive results.
^ Positive Likelihood Ratios incalculable due to 100% specificities
NPV: negative predictive value; PPV: positive predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio

CONCLUSIONS

- Combined urine testing (Ultra + LF-LAM) identified three-quarters of HIV-positive medical inpatients with definite TB.
- Urine Ultra had improved sensitivity and specificity compared to LF-LAM and has the added benefit of providing rapid rifampicin susceptibility results.
- There were no false positive rifampicin resistance results detected with urine Ultra.

Figure 1. Venn diagram of comparative diagnostic yields for definite TB



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