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Rapid urine-based screening tests increase the yield of same-day tuberculosis diagnoses among patients living with advanced HIV disease

Running head: TB Screening in Advanced HIV Disease

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Abstract

Objective

Investigation of the diagnostic yield of urine-based tuberculosis (TB) screening in patients with advanced HIV disease.

Design

Cross-sectional screening study

Setting

HIV outpatient clinics and wards at two hospitals in Johannesburg, South Africa between June 2015 and October 2017

Subjects, participants

Two hundred and one patients living with advanced HIV disease (CD4 T-lymphocytes <100 cells/uL) attending healthcare facilities following cryptococcal antigen (CrAg) screening.

Intervention

Screening for TB using sputum for microscopy, culture and Xpert MTB/Rif and urine for lipoarabinomannan (LAM) and Xpert Ultra.

Main outcome measures

Proportion of positive results using each testing modality, sensitivity and specificity of urine-based testing compared to culture, and survival outcomes during six months follow up.

Results

Urine was obtained from 177 of 181 (98%) participants and sputum from 91 (50%). Urine-based screening increased same-day diagnostic yield from 7 (4%) to 31 (17%). A positive urine test with either LAM or Xpert Ultra had 100% sensitivity (95% CI 59%-100%) for detecting culture-positive TB at any site. Patients with newly diagnosed TB on urine-based screening were initiated on treatment and did not have excess mortality compared to the remainder of the cohort.

Conclusions

Urine is an easily obtainable sample with utility for detecting TB in patients with advanced HIV disease. Combining urine and sputum-based screening in this population facilitates additional same-day TB diagnoses and early treatment initiation, potentially reducing the risk of TB-related mortality. Urine-based as well as sputum-based screening for TB should be integrated with CrAg screening in patients living with advanced HIV disease.

Keywords: tuberculosis; lipoarabinomannan; point-of-care systems; diagnostic techniques and procedures; acquired immunodeficiency syndrome

Introduction

Rapid detection of opportunistic infections, such as cryptococcal disease and tuberculosis (TB), is essential among patients with advanced HIV disease(1). Screening (irrespective of symptoms) for TB and cryptococcosis is recommended for this population due to the risk of early or sub-clinical infection and immune reconstitution inflammatory syndrome (IRIS) following ART(1). Cryptococcal antigen (CrAg) screening and pre-emptive antifungal treatment reduces mortality in patients with low CD4 T-lymphocyte counts (CD4 counts)(2,3), and has been widely implemented using lateral flow assays (LFAs)(4–6). Point of care methods for diagnosing TB are also available, however only urine lipoarabinomannan (LAM) is currently recommended for screening those with low CD4 counts irrespective of symptoms(7).

GeneXpert molecular testing platforms (Cepheid, Sunnyvale, CA) can be used for near-patient TB testing, providing results within two hours. However, reliance on sputum samples limits their value in patients with low CD4 counts, who are more likely to have disseminated disease and difficulty producing sputum. Sputum induction increases the risk of nosocomial transmission of TB, is poorly tolerated, costly, and not always successful(8).

Several studies demonstrate the utility of testing urine for mycobacterial DNA using GeneXpert assays (9,10), and for lipoarabinomannan (LAM), using LFAs such as the Determine TB LAM (Alere, Waltham, MA)(11,12). However, evidence from high burden countries indicates that neither is widely used for TB screening among patients with advanced HIV disease(13,14).

To determine the incremental same-day diagnostic yield of screening urine for TB among HIV-positive adults with CD4 counts <100 cells/μL, we performed LAM and Xpert MTB/Rif Ultra on urine, in addition to sputum-based tests. We estimated diagnostic accuracy of urine-based tests compared to TB culture, and report mortality rates following TB diagnoses.

Methods

TB screening was carried out among participants of a a prospective CrAg screening study described elsewhere(15). HIV-positive adults with CD4 counts <100 cells/μL were invited to participate during inpatient or outpatient attendance at two hospitals in Johannesburg, South Africa between June 2015 and October 2017. Patients with asymptomatic cryptococcal antigenaemia, and CrAg-negative patients with similar CD4 counts (1:2 ratio) were consecutively enrolled if they provided consent. Ethical approvals were obtained from the University of the Witwatersrand and the London School of Hygiene and Tropical Medicine.

A detailed TB history was obtained from interview and clinical records. All participants were tested for TB using pre- and/or post-induction sputum Xpert MTB/Rif, smear microscopy (auramine stain) and liquid culture (BACTEC MGIT, Becton Dickinson, Franklin Lakes, NJ). Urine was tested using LAM (Determine) and Xpert Ultra (FDA unapproved use). Results were available immediately for urine LAM (performed at point-of-care by research staff), and within 24 hours for sputum Xpert MTB/Rif and microscopy (performed at a reference laboratory). Culture results were reported when positive within 42 days. Urine Xpert Ultra tests were performed retrospectively on stored frozen and thawed samples (median volume 11.5 mL; inter-quartile range (IQR), 11-13 mL), following centrifugation at 3000*g* for 15 minutes, and suspension of the pellet in 1 mL of phosphate-buffered saline. Urine samples that were positive using Xpert Ultra were also tested using the Xpert MTB/Rif platform. Patients who tested positive for TB on sputum or urine testing were referred to TB clinics for further management. New TB diagnoses (using routine investigations instigated by particpants' usual clinicians), and survival during 6 months were recorded.

The number of new TB diagnoses made on the same day as testing (by urine LAM or urine/sputum Xpert), was determined. Sensitivity and specificity of urine-based tests were estimated compared to a reference standard of TB culture, in those who had culture performed on any sample. The effect of newly diagnosed TB on mortality was estimated using Cox regression, adjusting for baseline CD4 count.

Results and discussion

Two hundred and one participants were enrolled in the study (Supplentary Figure 1, http://links.lww.com/QAD/C449, Tables 1, http://links.lww.com/QAD/C450 and 2, http://links.lww.com/QAD/C451). Twenty (10%) were taking TB treatment and excluded from further analysis. Of the remaining 181 participants, median age was 39 years (IQR, 33-48), 48% were female, median CD4 count was 36 cells/μL (IQR, 13-62), 26 (14%) were already taking ART, and 29 (16%) were inpatients. Fifty-nine patients were CrAg-positive and 122 CrAg-negative.

Urine and sputum samples were requested from all participants; sputum induction was attempted when equipment was available in 114 (63%). Urine samples were obtained from 177/181 (98%) and sputum from 91/181 (50%). Of 114 participants undergoing attempted

induction, 39 (34%) were unable to produce sputum. Tissue samples for histology and culture were available from 8 (4%) patients within 2 weeks of enrolment.

Thirty-one (17%) participants were newly diagnosed with TB at enrolment (figure 1); 17% (10/59) CrAg-positive individuals and 17% (21/122) CrAg-negative individuals. Sputum Xpert MTB/Rif was positive in 7 individuals (3 sputa also AFB positive). Urine testing yielded an additional 24 TB diagnoses (positive using LAM only (19), Xpert Ultra only (2) or both urine tests (3)). All individuals with TB diagnosed by sputum testing were also positive using urine. There was no difference in the rates of positive urine-based tests between CrAg-positive and CrAg-negative participants. Twelve (50%) individuals with TB diagnosed using urine tests alone were unable to produce sputum. One individual who was unable to produce sputum had a positive urine Xpert Ultra result, with a *rpo*B mutation. On repeat testing of Xpert Ultra positive urine samples, 5/10 (50%) were positive using the Xpert MTB/Rif platform. Anti-tuberculous medication was started in 28/31 (90%) participants following diagnosis; no treatment was documented for three participants who were lost to follow up.

One hundred (55%) participants had mycobacterial cultures performed on any sample obtained concurrently (table 1). Restricting analysis to these participants, urine LAM had a sensitivity of 71% (95% CI, 19%-96%) and specificity of 87% (95% CI, 77%-94%). Testing urine using Xpert Ultra had a sensitivity of 71% (95% CI, 29%-96%) and a specificity of 99% (95% CI, 92%-100%). A positive urine test with either LAM or Xpert Ultra had a sensitivity of 100% (95% CI, 59%-100%) and specificity of 86% (95% CI, 75%-92%) (Table 1). Specificity was likely underestimated due to the poor sensitivity of TB culture in this population. Sensitivity of urine-based tests remained at 100% (95% CI 66% - 100%) and specificity increased to 90% (95% CI, 83% - 95%) using a composite of culture, histology and PCR of sputum or any tissue as the reference standard. Two patients with positive urine LAM but negative urine Xpert Ultra, had non-tuberculous mycobacteria identified in sputum samples, without evidence of TB co-infection.

During six months follow up, 22/181 (12.1%) participants died; 5/31 (16%) with newly diagnosed TB at enrolment, and 17/150 (11%) who were negative following TB screening. Same-day diagnosis of TB (including by urine-based screening) was not significantly associated with mortality on unadjusted analysis or following adjustment for CD4 cell count (adjusted hazard ratio 1.52, 95% CI 0.55–4.17). While there were no cases of cryptococcal meningitis in 122 patients who were CrAg-negative at enrolment, there were an additional 7 (5%) TB diagnoses during follow up, occurring at a median of 61 (IQR 43–111) days.

Conclusions

Screening individuals with advanced HIV disease using urine LAM and Xpert Ultra in addition to sputum testing increased same-day detection of active TB by over four-fold, from 4% to 17%. Using both tests had 100% sensitivity compared to TB culture. A new diagnosis of TB following screening was not found to be associated with an increased risk of death in our analysis. This is in contrast to the high risk of death associated with a diagnosis of TB

previously reported among patients with advanced HIV disease [7,17,18], and consistent with findings of the STAMP trial, which found a reduced risk of death among hospitalised patients with CD4 counts <100 cells/uL who were tested for TB with LAM and urine Xpert MTB/Rif, in addition to sputum Xpert MTB/Rif (aOR 0.72 (95% CI 0.53-0.98))[19].

Uptake of the Determine LAM for TB screening has been limited due to reports of relative low sensitivity compared to culture (56% (41%-70%) in patients with CD4 counts ≤100 cells/μL[11]). However, in keeping with prior studies[10,12,13,19,20], we found that urine LAM was positive in a distinct group of patients with negative sputum cultures, or who were sputum-scarce. The reported poor performance of urine LAM compared to largely sputum-based diagnostics may therefore underestimate its potential benefit. Furthermore, a novel assay using two high affinity monoclonal antibodies to LAM epitopes (Fujifilm SILVAMP TB LAM, Tokyo, Japan) has been developed with higher sensitivity than the Determine LAM[21–23], offering greater potential for implementation as a screening tool.

Urine LAM can be detected in patients with non-tuberculous mycobacteria (NTM), leading to false-positive results (25). In our study, NTM disease likely accounted for 2/28 (7%) patients initially diagnosed with TB on the basis of a positive urine LAM result. This highlights the importance of thorough investigation of urine LAM positive patients using TB culture and molecular diagnostics of obtainable samples including urine.

As with LAM, Xpert sensitivity in urine is greater in severely immunocompromised patients[13], and identifies a distinct patient group as compared to sputum-based testing[10 - 12, 19]. The Xpert Ultra platform has greater sensitivity than Xpert MTB/Rif on sputum(26,27) and CSF(28) samples. We found urine Xpert Ultra was positive in twice as many patients compared to Xpert MTB/Rif, two of whom were negative using other point-of-care tests, and one with undetected drug resistance.

Our study selected patients on the basis of CrAg status, and may therefore represent a biased sample. However we found that active TB was equally common in both CrAg-positive and CrAg-negative patients (Supplementary Table 1, http://links.lww.com/QAD/C450). Additionally, our results are consistent with previous studies showing increased yield of same-day TB diagnoses using urine in addition to sputum samples. In Malawi and Mozambique, the use of LAM increased diagnostic yield in ambulatory patients by 34.6% compared to sputum Xpert MTB/Rif (29). In South Africa, using Xpert MTB/Rif for urine as well as sputum yielded an additional 69/139 (50%) TB diagnoses within 24 hours of admission to hospital(8). Screening hospitalised HIV-positive patients with LAM and urine Xpert MTB/Rif diagnosed an additional 125 (60%) patients with TB in addition to those diagnosed using sputum Xpert MTB/Rif(21) in South Africa and Malawi.

Patients with advanced HIV disease are at risk of TB and cryptococcal-related mortality, but diagnosis is challenging. Urine provides a readily available sample for TB screening that can be used in addition to blood CrAg screening in patients with advanced HIV disease. This approach identified all patients at risk of cryptococcal disease and many cases of TB on the

same day as testing, allowing early treatment initiation. Rapid urine-based diagnostics are particularly useful in this group; many are sputum-scarce, disseminated TB is more likely and early ART initiation key. A combined screening approach, utilising newer more sensitive diagnostics for TB on urine, as well as sputum samples should be integrated with CrAg screening for patients living with advanced HIV disease.

Competing interests: none

Author's contributions: RW designed and led study and drafted manuscript; SO, FI, CT, NG, TH, JJ involved in protocol development and reviewing and editing the manuscript.

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Figure 1Venn diagram to show yield of same-day TB diagnoses using each test. There were a total of 31 new diagnoses using urine LAM, urine Xpert Ultra (5 positive, 5 trace positive), sputum microscopy for acid fast bacilli (AFB] and sputum Xpert MTB/Rif, in all patients who were not taking anti-tuberculosis therapy at the time of enrolment, n=181. LAM, lipoarabinomannan scarlett

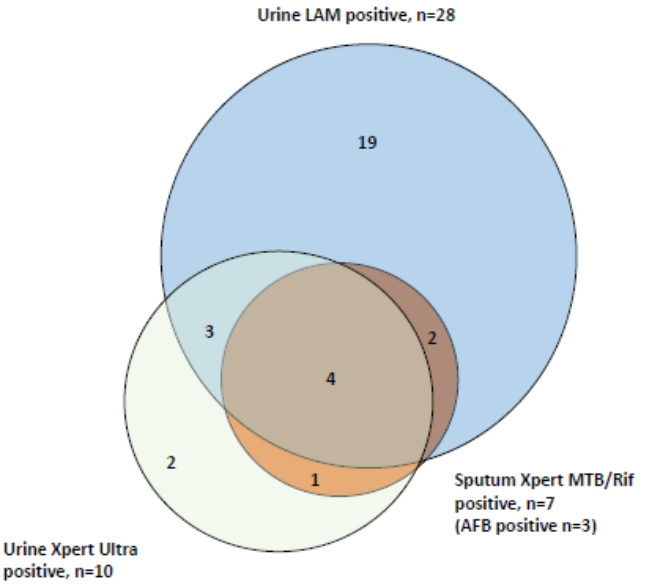

Table 1 Sensitivity and specificity of the urine Xpert ultra, urine LAM, or of either urine Xpert ultra or LAM test positive, compared to culture† for TB of any sample within 2 weeks of the urine test

	Sensitivity (n/d, %, 95% CI)	**Specificity (n/d, %, 95% CI)**
Urine Xpert Ultra	‡5/7, 71% (29 - 96%)	68/69, 99% (92 – 100%)
Urine LAM	§5/7, 71% (29 – 94%)	67/77, 87% (77 – 94%)
Urine -based test (either urine Xpert Ultra or urine LAM)	7/7, 100% (59-100%)	60/70, 86% (75 – 93%)

†100 participants had samples obtained for culture: 90 sputa (7 had additional lymph node, blood, cerebrospinal fluid (CSF) and bone marrow (BM) samples); 6 blood; 1 skin biopsy; 2 BM; 1 CSF

‡Urine Xpert Utra was positive in 5 patients with positive TB cultures (3 sputum, 2 blood cultures), and negative in 2 patients with positive sputum cultures.

§Urine LAM was positive in 5 patients with positive TB cultures (4 sputum (1 also lymph node), 1 blood culture), and negative in 2 patients with positive TB cultures (1 sputum, 1 blood).

Abbreviations: n, numerator; d, denominator; CI, confidence interval; Xpert Ultra, Xpert MTB/Rif Ultra assay; LAM, lipoarabinomannan