


RESEARCH ARTICLE

Open Access



Treatment decisions and mortality in HIV-positive presumptive smear-negative TB in the Xpert[®] MTB/RIF era: a cohort study

Sabine M. Hermans^{1,2,3*} , Juliet A. Babirye¹, Olive Mbabazi¹, Francis Kakooza¹, Robert Colebunders^{4,5}, Barbara Castelnovo¹, Christine Sekaggya-Wiltshire¹, Rosalind Parkes-Ratanshi^{1,6} and Yukari C. Manabe^{1,2,7}

Abstract

Background: The Xpert[®] MTB/RIF (XP) has a higher sensitivity than sputum smear microscopy (70% versus 35%) for TB diagnosis and has been endorsed by the WHO for TB high burden countries to increase case finding among HIV co-infected presumptive TB patients. Its impact on the diagnosis of smear-negative TB in a routine care setting is unclear. We determined the change in diagnosis, treatment and mortality of smear-negative presumptive TB with routine use of Xpert MTB/RIF (XP).

Methods: Prospective cohort study of HIV-positive smear-negative presumptive TB patients during a 12-month period after XP implementation in a well-staffed and trained integrated TB/HIV clinic in Kampala, Uganda. Prior to testing clinicians were asked to decide whether they would treat empirically prior to Xpert result; actual treatment was decided upon receipt of the XP result. We compared empirical and XP-informed treatment decisions and all-cause mortality in the first year.

Results: Of 411 smear-negative presumptive TB patients, 175 (43%) received an XP; their baseline characteristics did not differ. XP positivity was similar in patients with a pre-XP empirical diagnosis and those without (9/29 [17%] versus 14/142 [10%], $P = 0.23$). Despite XP testing high levels of empirical treatment prevailed (18%), although XP results did change who ultimately was treated for TB. When adjusted for CD4 count, empirical treatment was not associated with higher mortality compared to no or microbiologically confirmed treatment.

Conclusions: XP usage was lower than expected. The lower sensitivity of XP in smear-negative HIV-positive patients led experienced clinicians to use XP as a “rule-in” rather than “rule-out” test, with the majority of patients still treated empirically.

Keywords: Empirical treatment, Molecular diagnostic techniques/methods, Tuberculosis, pulmonary/diagnosis, Tuberculosis, pulmonary/epidemiology, HIV Infections/complications

Background

Tuberculosis (TB) remains the main cause of death among HIV-infected patients in sub-Saharan Africa. Sputum smear microscopy has a low sensitivity for detecting TB particularly among people living with HIV. Because of its low cost, it is the mainstay of diagnosis in many high burden countries. In December 2010 the

World Health Organization (WHO) endorsed Xpert[®] MTB/RIF (Cepheid, Sunnyvale, California, USA) (XP) [1], the first fully automated, real-time nucleic acid amplification technology for the rapid detection of TB [1, 2] which can be performed with only 1 day of training by most health care workers. A WHO policy statement came out in 2011 recommending its use as the initial diagnostic test among people suspected of multi-drug resistant (MDR) or HIV-associated TB [2]. WHO policy updates in October 2013 recommending broad use of Xpert for TB diagnosis [3] and concessionary

* Correspondence: s.hermans@aighd.org

¹Infectious Diseases Institute, Makerere University College of Health Sciences, P.O. Box 22418, Kampala, Uganda

²Department of Internal Medicine, School of Medicine, Makerere University College of Health Sciences, Kampala, Uganda

Full list of author information is available at the end of the article



pricing for high-burden countries have resulted in wide-spread roll-out in routine care settings [4].

Because of a higher sensitivity than sputum smear microscopy and a running time of two hours, routine use of XP was predicted to increase case finding and improve TB treatment outcomes [5–7]. However, this impact has not been realized in trials to date [8–11]. Some have argued that the impact may be blunted by high rates of empirical treatment in sub-Saharan Africa: up to 40% of TB cases are treated empirically due to diagnostic uncertainties and the risk of severe morbidity and mortality if TB treatment is delayed [12]. It is therefore still unclear what impact XP will have on case finding and TB treatment outcomes in routine care settings [13]. To date no studies have investigated the impact of XP on health care workers' pre- and post-test management [13].

In an integrated TB-HIV clinic with adequate staffing and training in Kampala, Uganda, we implemented XP for use as an add-on test in sputum smear negative presumptive TB patients. We investigated if and how clinicians changed their diagnostic decision-making on the basis of the additional test available to them. Considering the high level of experience of the clinicians, we hypothesized that this would be limited. We analyzed XP usage and yield compared to empirical diagnosis without access to XP, and examined treatment decisions subsequent to an XP result. We also compared mortality in the first year after being investigated for TB between patients who were treated empirically, treated on the basis of microbiological confirmation, or not treated at all.

Methods

Study setting

This study was performed at the integrated adult TB/HIV clinic of the Infectious Diseases Institute, part of the Makerere University College of Health Sciences located at Mulago Hospital in Kampala, Uganda. This clinic has been described in detail previously [14, 15]. In brief, this clinic provided a one-stop-shop outpatient TB and HIV service for all patients suspected of having TB among the over 30,000 registered HIV-positive patients of the Adult Infectious Diseases Clinic. It is staffed by medical officers, nurses and counsellors who provide care for both TB and HIV during the same clinic visit.

All patients were screened for TB symptoms in the overall HIV clinic waiting area, in accordance with guidelines of the WHO and the Ugandan Ministry of Health [15]. Those who screened positive were referred to the TB/HIV clinic, where the clinicians followed local guidelines to diagnose TB. At the time of the study, 2 sputum samples were tested with smear microscopy, one collected immediately and one on the following

morning. Additional available investigations included chest X-ray, lymph node aspirate and abdominal ultrasound where applicable (fee-for-service). Sputum cultures were not routinely available. Treatment of smear-negative patients was based on the clinician's interpretation of any ongoing symptoms and the chest X-ray. Prior to XP implementation, 22% of patients treated for TB were smear-negative [14, 15]. At the time of the study, although the green light committee of the WHO had approved Uganda for multi-drug resistance (MDR) TB treatment, drugs were not yet available. All patients in whom MDR was detected were referred to the national TB clinic in Mulago Hospital, to await the arrival of the drugs.

Study design and population

This was a prospective cohort study in which we included all presumptive TB patients of the TB/HIV clinic who were sputum smear microscopy negative from 1 May 2012–1 May 2013. Clinicians could order an XP using a request form which included the following question: "with the current clinical and diagnostic information available to you, would you start this patient on TB treatment?", which was to be answered by ticking a box either "yes" or "no". Clinicians were trained how to use the form and there were ongoing checks of their understanding. The XP was performed immediately while the patient waited for the results. The result was returned to the clinician; the request forms were retained in the laboratory. Treatment was initiated on the same day according to the clinician's interpretation of the XP result. Patients were followed up for 1 year to determine their outcome.

Ethical review statement

The Adult Infectious Diseases Clinic has ongoing approval by the Makerere University Research Ethics Committee and the Uganda National Council of Science and Technology to utilize routinely collected data for operational research purposes. A written consent waiver to do retrospective analysis of routinely collected data was granted; data were analysed after removal of unique personal identifiers.

Data management and definitions

The results on the XP laboratory request forms were entered into a study database by a laboratory technician and then merged with routinely collected clinical, diagnosis and treatment electronically collected data of the TB/HIV clinic. A *pre-XP empirical diagnosis* was defined as the intention to treat for TB before access to the XP result (at the time of XP request). *Post-XP empirical TB treatment* was defined as the decision by a clinician to treat for TB without a positive XP result. We further

categorized patients according to their final diagnostic and treatment profile: TB treatment on the basis of microbiological confirmation (positive XP), post-XP empirical treatment (negative or no XP) or no treatment (negative or no XP).

During the period of our study the CD4+ T cell (CD4) counts were only determined once a year. We therefore used the closest measurement within 6 months before or after the date of presentation as a presumptive TB patient. HIV viral load monitoring was not routinely available.

Statistical methods

We used descriptive statistics for the baseline characteristics of the study population at first presentation to the TB clinic, and to determine XP usage (the proportion of patients who were evaluated with XP) and to compare diagnostic and treatment decisions. Differences were tested using Chi-2, Fisher's Exact, Student's t-test, Kruskal-Wallis or Wilcoxon rank sum tests, as appropriate. Logistic regression was used to calculate the odds ratio of TB treatment by pre-XP empirical diagnosis, overall and stratified by XP result. To prevent overfitting of the model due to the small number of outcomes in this group only multivariable analyses with two independent variables was done. Survival analysis, the log-rank test for equality of survivor functions and Cox regression were used to compare mortality in the first year after the presentation at the TB/HIV clinic by the different diagnostic and treatment profiles. The proportional hazards assumption was checked using log(-log(survival)) curves and Schoenfeld residuals. Adjusted hazard ratios (aHR) of the risk of death in the first year were calculated using Cox regression and adjusting for a priori risk factors (sex, CD4 count and ART at date of presumptive TB). Age was omitted due to risk of overfitting; initial univariable analysis showed no association however. Data were analysed using STATA 12.0 SE (StataCorp, College Station, Texas, USA).

Results

A total of 495 patients were evaluated for tuberculosis with a sputum smear between 1 May 2012 and 1 May 2013. Of these, 84 (17%) were sputum smear-positive. The 411 (83%) patients who were sputum smear-negative were included in this analysis. The median age of the study participants was 38 years (interquartile range 31, 44), 56% were female, 15% had been previously treated for TB, 50% were on ART at the time of investigation, and the median CD4 count at presentation was 275/mm³ (interquartile range, 141–440) (Table 1).

A flow diagram outlining the diagnostic process and treatment decisions in the included patients is shown in

Fig. 1. Among the 411 smear-negative presumptive TB patients, 175 (43%) were sent for an XP. There were no technical problems with the machine during the study period. There were no differences in baseline characteristics between patients who did or did not receive an XP test, including symptomatology at presentation (Table 1). However, patients who underwent an XP received a chest X-ray more often (94% versus 78%, $P < 0.001$) which was more likely to be abnormal (69% versus 54%, $P 0.008$). Patients who received an XP were equally likely to be diagnosed with TB (23% versus 21%, $P 0.59$) as those who did not, but were less likely to be diagnosed with extrapulmonary TB (17% versus 50%, $P 0.001$).

The minority of the patients for whom an XP was requested received a pre-XP empirical diagnosis (29 [17%]). Nonetheless, there were no differences in baseline characteristics among patients with and without a pre-XP empirical diagnosis (Table 2). There was also no difference in XP positivity (17% versus 10%, $P = 0.23$). We identified rifampicin resistance in one of the patients without a pre-XP empirical diagnosis.

There was a slight decrease in the total number of patients who would have been treated empirically (from 79 [20%] pre-XP to 72 [18%] post-XP). However, these were not the same individuals: 11 [38%] patients with a pre-XP empirical diagnosis were treated compared to 28 [20%] patients without a pre-XP diagnosis (Fig. 1). Patients with a pre-XP empirical diagnosis were more likely to be treated for TB despite a negative XP (post-XP empirical treatment, 7 [30%] versus 14 [11%], $P = 0.014$), however this effect disappeared on adjusting to the CD4 count (adjusted odds ratio [aOR] 2.5 [95% confidence interval, 0.8–8.0]; aOR per 50 cells/ul higher CD4 count 0.9 [95% CI 0.8–1.1]). There were no differences in baseline characteristics between those who were and were not treated empirically after a negative XP (Table 3), and no risk factors of empirical treatment could be identified in multivariable logistic regression (data not shown).

Whilst simple analysis of mortality in the first year after presentation at the TB clinic was higher among those treated empirically (with no or negative XP result) compared to those treated with a positive XP or those not treated at all (22% versus 5% and 9% respectively, Fig. 2) there are multiple possible confounders of this relationship. In multivariable Cox regression analysis, adjusting for possible confounders that we had data for, including CD4 count, sex and ART usage at presentation, no association between post-XP empirical treatment or microbiologically confirmed treatment and the hazard of death was found (aHR 1.8 [95% CI, 0.8–3.9], and aHR 0.8 [95% CI, 0.1–6.3] respectively). For every 50 cells' increase in CD4 count, it decreased by 18% (aHR 0.8 [95% CI, 0.7–0.9], $P < 0.001$). Male sex was associated with higher mortality (aHR 2.7 [95% CI, 1.3–

Table 1 Baseline characteristics of smear-negative presumptive TB patients, overall and by whether they had received an Xpert® MTB/RIF

Characteristic	No XP	XP	Total	P-value	
Total (n [%])	236 (57.4)	175 (42.6)	411 (100)		
Age (mean [SD])	38 (9)	40 (11)	39 (10)	0.10	
Female sex (n [%])	133 (56.4)	99 (56.6)	232 (56.4)	0.97	
CD4 count (median [IQR])*	274 (147, 422)	275 (179, 478)	275 (162, 426)	0.73	
ART at TB treatment initiation (n [%])	116 (49.2)	89 (50.9)	205 (49.9)	0.73	
Prior TB treatment (n [%])	34 (14.4)	29 (16.6)	63 (15.3)	0.55	
Symptomatology at presentation (n [%])	Cough	228 (96.6)	173 (98.9)	401 (97.6)	0.14
	Fever	169 (71.6)	124 (70.9)	293 (71.3)	0.87
	Night sweats	112 (47.5)	88 (50.3)	200 (48.7)	0.57
	Weight loss	80 (33.9)	63 (36)	143 (34.8)	0.66
	Anorexia	113 (47.9)	84 (48)	197 (47.9)	0.98
	Chest pain	64 (27.1)	57 (32.6)	121 (29.4)	0.23

IQR interquartile range, n number, SD standard deviation, TB tuberculosis, XP Xpert® MTB/RIF

*On 200, 152 and 352 patients, respectively

5.9)), but no association was found for ART usage at presentation (aHR 0.5 [95% CI, 0.3–1.1]).

Discussion

This study investigated the impact of XP usage on the diagnosis, treatment and mortality of HIV- positive smear-negative presumptive TB patients. Despite current WHO guidelines recommending the use of XP as the first diagnostic test rather than as an add-on to a negative sputum smear [3], this study offers insights into clinicians’ diagnostic and treatment decisions with the availability of XP and the associated treatment outcomes.

We found that XP was only used in 43% of eligible patients despite free access to the test. The higher likelihood of an X-ray being ordered in this same group of patients suggests clinicians had a higher level of clinical suspicion compared to those not sent for XP. High levels of empirical treatment prevailed although XP testing did change who was ultimately treated for TB. A pre-XP empirical diagnosis by an experienced clinician did not predict XP positivity.

Although XP availability led to little change in the total proportion of presumptive TB patients actually treated for TB, the use of XP led to treatment of those who would not have been treated pre-XP and vice versa.

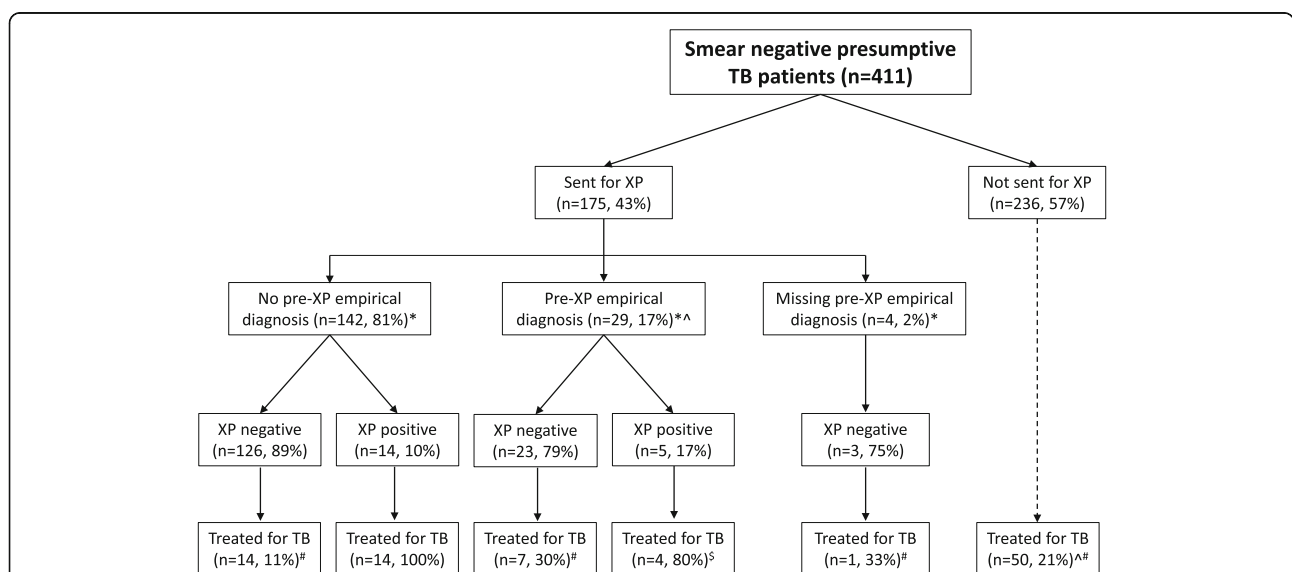


Fig. 1 Flow diagram of study patients. A pre-XP empirical diagnosis was defined as the recorded intention to start treatment for TB without access to XP (as determined by the clinician at the time of the XP request). TB, tuberculosis; XP, Xpert® MTB/RIF. *Invalid XP results in 2, 1 and 1 patients respectively. ^Patients treated empirically pre-XP. #Patients treated empirically post-XP. ⁵1 patient died before being started on TB treatment

Table 2 Baseline characteristics of smear-negative presumptive TB patients who received an Xpert® MTB/RIF by whether the clinician would have treated them without access to the Xpert result or not

Characteristic	No pre-XP empirical diagnosis	Pre-XP empirical diagnosis	Missing response	Total	P-value	
Total (n [%])	142	29	4	175		
Age (mean[SD])	40 (11)	39 (9)	47 (11)	40 (11)	0.52	
Female sex (n [%])	80 (56.3)	16 (55.2)	3 (75)	99 (56.6)	0.75	
CD4 count (median [IQR])*	280 (189, 483)	238 (132, 343)	403 (390, 983)	275 (179, 478)	0.66	
ART at TB treatment initiation (n [%])	72 (50.7)	16 (55.2)	1 (25)	89 (50.9)	0.53	
Prior TB treatment (n [%])	23 (16.2)	6 (20.7)	0 (0)	29 (16.6)	0.55	
Symptomatology at presentation (n [%])	Cough	140 (98.6)	29 (100)	4 (100)	173 (98.9)	0.79
	Fever	101 (71.1)	19 (65.5)	4 (100)	124 (70.9)	0.36
	Night sweats	72 (50.7)	13 (44.8)	3 (75)	88 (50.3)	0.51
	Weight loss	48 (33.8)	14 (48.3)	1 (25)	63 (36)	0.3
	Anorexia	67 (47.2)	14 (48.3)	3 (75)	84 (48)	0.55
	Chest pain	46 (32.4)	10 (34.5)	1 (25)	57 (32.6)	0.93

IQR interquartile range, n number, Rx treatment, SD standard deviation, TB tuberculosis, XP Xpert MTB/RIF

*On 124, 26, 2 and 152 patients, respectively

Despite the clinicians' experience, XP positivity was not more likely among patients with than without a pre-XP empirical diagnosis. This corroborates previous work on the poor accuracy of empirical diagnoses (using sputum culture as gold standard) in this clinic and in Tanzania [16, 17]. Despite having access to all clinical data, we were not able to determine which clinical factors most influenced clinicians in their decision-making process pre-XP. Among hospitalized patients, a recent study in Kampala identified productive cough, fever and tachycardia as predictors of empirical treatment [18].

The lack of sputum culture in our clinic precludes the determination whether empirical treatment was true- or false-positive (both pre- and post-XP).

Our data suggests that clinicians used the XP test as a "rule-in" test and only partly as a "rule-out" test. This is justifiable as the test is known to have low sensitivity as an add-on test to a negative sputum smear (61% in a HIV-positive population) [19, 20]. Nevertheless, the clinicians decided against treatment in just over half of the patients whom they would have treated without access to an XP, which may indicate an overestimated

Table 3 Baseline characteristics of included smear-negative presumptive TB patients who had a negative Xpert® MTB/RIF result by actual empirical TB treatment initiation

Characteristic	Post-XP empirical Rx	No post-XP empirical Rx	Total	P-value	
Total (n [%])	22	130	152		
Age (mean [SD])	36 (12)	41 (11)	40 (10)	0.04	
Female sex (n [%])	13 (59.1)	71 (54.6)	84 (55.3)	0.70	
CD4 count (median [IQR])*	239 (139, 329)	289 (133, 456)	283 (133, 441)	0.25	
ART at presentation	12 (54.5)	69 (53.1)	81 (53.3)	0.90	
Prior TB treatment (n [%])	1 (4.5)	25 (19.2)	26 (17.1)	0.09	
Symptomatology at presentation (n [%])	Cough	21 (95.5)	129 (99.2)	150 (98.7)	0.15
	Fever	16 (72.7)	91 (70)	107 (70.4)	0.80
	Night sweats	11 (50)	61 (46.9)	72 (47.4)	0.79
	Weight loss	10 (45.5)	38 (29.2)	48 (31.6)	0.13
	Anorexia	13 (59.1)	55 (42.3)	68 (44.7)	0.14
	Chest pain	8 (36.4)	42 (32.3)	50 (32.9)	0.70

IQR interquartile range, n number, Rx treatment, SD standard deviation, TB tuberculosis, XP Xpert® MTB/RIF

*On 17, 118 and 135 patients, respectively

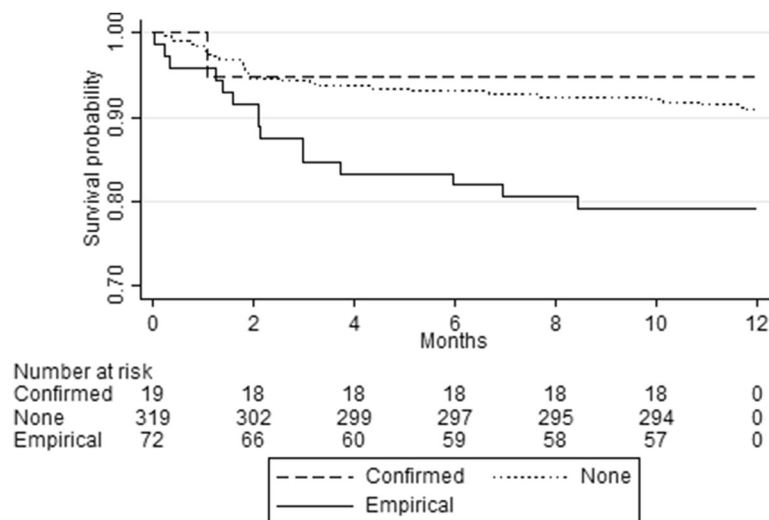


Fig. 2 All-cause mortality in the first 12 months after presentation to the TB clinic among presumptive smear-negative TB patients, stratified by TB treatment on the basis of microbiological confirmation (positive XP), post-XP empirical treatment (negative or no XP) or no treatment (negative or no XP). Log-rank test for equality of survivor functions: P 0.01. Confirmed, microbiologically confirmed treatment; Empirical, post-Xpert® MTB/RIF empirical treatment; None, no treatment

confidence in a negative XP. This potential false sense of security has also been described during roll-out of routine XP as the first-line diagnostic in South Africa [21]. This is likely to be exaggerated in rural areas where more mid-level health care workers are present with more limited TB diagnostic training [22]. In future, this risk might be mitigated by use of the next generation Xpert cartridge, the Xpert MTB/RIF Ultra, which has been shown to have a higher sensitivity [23].

Low XP utilisation has also been described in a study evaluating its use in 18 health facilities throughout Uganda (21%) [24], as well as in studies from the Democratic Republic of Congo (37%) and Swaziland (51%) [25, 26]. It has been suggested that the varying degrees of utilisation may be associated with the level of training and support provided to health care workers [24]. It may also take time for clinicians to get used to the new test. This has been shown in Swaziland where the utilisation increased to 73% in the second and third years after implementation, and in Cape Town, where the impact on empirical treatment reached its maximum in the third year after implementation [26, 27].

The lack of association between post-XP empirical treatment or microbiologically confirmed treatment and the risk of death was also found by three recent studies among both ambulant and hospitalized ART naïve patients [18, 28–30]. However, a recent systematic review on the impact of tuberculosis nucleic amplification tests, such as Xpert® MTB/RIF, concluded that the evidence has been of limited scientific rigour and from a relatively small number of settings, limiting its validity and

generalisability [13]. We found that CD4 count confounded the negative association between empirical treatment and mortality. It is well known that a low CD4 count is a strong risk factor for mortality, and is likely to be associated with being treated empirically for TB [12]. Our study design was also not optimal to investigate this association, however, and we may not have captured potential confounding factors of the relationship between empirical treatment and mortality, including anemia, comorbidities such as malignancies, and others.

The main limitation of this study was the risk of misclassification bias if clinicians failed to answer the clinical decision question truthfully due to misunderstanding of its purpose (whether it might affect the procedure in the laboratory or be used to review their performance). This was minimized with continued training and regular checks of their understanding. More than half of eligible patients were not sent for an XP; their higher probability of an EPTB diagnosis suggests a higher clinical suspicion of extrapulmonary involvement on the basis of additional information not captured in our data.

Conclusions

XP usage to aid the diagnosis of smear-negative TB by experienced clinicians was lower than expected. In those tested, experienced clinicians mainly used the XP as a “rule-in” test and only partly as a “rule-out” test. The lower sensitivity of XP in smear-negative HIV-positive patients led to the majority of patients still being treated empirically.

Abbreviations

aHR: adjusted hazard ratio; aOR: adjusted odds ratio; CD4: CD4+ T cell; HIV: Human Immunodeficiency Virus; IQR: Interquartile range; MDR: Multi-drug resistant; N: Number; Rx: Treatment; SD: Standard deviation; TB: Tuberculosis; WHO: World Health Organization; XP: Xpert MTB/RIF

Acknowledgements

The authors would like to thank the TB/HIV clinic team at the Infectious Diseases Institute for their input and assistance in this project, and Joseph Musazzi for his help with data management.

Funding

Xpert® MTB/RIF test cartridges were supplied by a project of the University of Antwerp funded by the Flemish Interuniversity Council. This study was supported by the Infectious Diseases Network for Treatment and Research in Africa (INTERACT) programme, funded by the Netherlands Organization for Scientific Research – WOTRO Science for Global Development: NACCAP [grant number W07.05.20100] and the European Union [grant number SANTE/2006/105–316]. Salary support to SH was provided by the INTERACT programme followed by a European Union Marie Curie International Outgoing Fellowship for Career Development [PIOF-GA-2012-332,311]. Support was also provided under the National Institutes of Health (DMID under the Tuberculosis Clinical Diagnostics Research Consortium [NIH/NIAID], HHSN272200900050C for YM) and the Office of the Global AIDS Coordinator-funded Medical Education Partnership Initiative-Medical Education for Services to all Ugandans (RFA-TW-10-008) for YM and CSW, and the NIH Fogarty International Center (D43TW009771) for YM. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SH, JB and YM conceived and designed the study. SH analysed the data. SH, JB, OM, FK, BC, CW and RPR were involved in collecting the data. All authors interpreted the data and critically reviewed the manuscript. SH wrote the first draft. All authors read and approved the final manuscript.

Competing interests

BC is a member of the editorial board of this journal. The other authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The Adult Infectious Diseases Clinic has ongoing approval by the Makerere University Research Ethics Committee and the Uganda National Council of Science and Technology to utilize routinely collected data for operational research purposes. A written consent waiver to do retrospective analysis of routinely collected data was granted; data were analysed after removal of unique personal identifiers.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details

¹Infectious Diseases Institute, Makerere University College of Health Sciences, P.O. Box 22418, Kampala, Uganda. ²Department of Internal Medicine, School of Medicine, Makerere University College of Health Sciences, Kampala, Uganda. ³Department of Global Health, Academic Medical Center, University of Amsterdam, Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands. ⁴Institute for Tropical Medicine, University of Antwerp, Antwerp, Belgium. ⁵Global Health Institute, University of Antwerp, Antwerp, Belgium. ⁶Institute of Public Health, University of Cambridge, Cambridge, UK. ⁷Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, USA.

Received: 10 March 2017 Accepted: 7 June 2017

Published online: 16 June 2017

References

- World Health Organization. WHO endorses new rapid tuberculosis test. 2010. Available from: http://www.who.int/mediacentre/news/releases/2010/tb_test_20101208/en/. Accessed on 15/12/2014.
- World Health Organization. Policy statement: automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system; 2011. Available from: http://whqlibdoc.who.int/publications/2011/9789241501545_eng.pdf. Accessed on 31–01-2012.
- World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy update. Geneva: World Health Organization; 2013. Available from: http://apps.who.int/iris/bitstream/10665/112472/1/9789241506335_eng.pdf. Accessed on 15/12/2014.
- Albert H, Nathavitharana RR, Isaacs C, Pai M, Denkinger CM, Boehme CC. Development, roll-out and impact of Xpert MTB/RIF for tuberculosis: what lessons have we learnt and how can we do better? *Eur Respir J*. 2016;48(2):516–25.
- Menzies NA, Cohen T, Lin HH, Murray M, Salomon JA. Population health impact and cost-effectiveness of tuberculosis diagnosis with Xpert MTB/RIF: a dynamic simulation and economic evaluation. *PLoS Med*. 2012;9(11):e1001347.
- Meyer-Rath G, Schnippel K, Long L, MacLeod W, Sanne I, Stevens W, et al. The impact and cost of scaling up GeneXpert MTB/RIF in South Africa. *PLoS One*. 2012;7(5):e36966.
- Dowdy DW, Davis JL, den Boon S, Walter ND, Katamba A, Cattamanchi A. Population-level impact of same-day microscopy and Xpert MTB/RIF for tuberculosis diagnosis in Africa. *PLoS One*. 2013;8(8):e70485.
- Theron G, Zijenah L, Chanda D, Clowes P, Rachow A, Lesosky M, et al. Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. *Lancet*. 2014;383(9915):424–35.
- Cox HS, Mbhele S, Mohess N, Whitelaw A, Muller O, Zemanay W, et al. Impact of Xpert MTB/RIF for TB diagnosis in a primary care clinic with high TB and HIV prevalence in South Africa: a pragmatic randomised trial. *PLoS Med*. 2014;11(11):e1001760.
- Durovni B, Saraceni V, van den Hof S, Trajman A, Cordeiro-Santos M, Cavalcante S, et al. Impact of replacing smear microscopy with Xpert MTB/RIF for diagnosing tuberculosis in Brazil: a stepped-wedge cluster-randomized trial. *PLoS Med*. 2014;11(12):e1001766.
- Churchyard GJ, Stevens WS, Mametja LD, McCarthy KM, Chihota V, Nicol MP, et al. Xpert MTB/RIF versus sputum microscopy as the initial diagnostic test for tuberculosis: a cluster-randomised trial embedded in South African roll-out of Xpert MTB/RIF. *Lancet Glob Health*. 2015;3(8):e450–7. doi:10.1016/S2214-109X(15)00100-X.
- Theron G, Peter J, Dowdy D, Langley I, Squire SB, Dheda K. Do high rates of empirical treatment undermine the potential effect of new diagnostic tests for tuberculosis in high-burden settings? *Lancet Infect Dis*. 2014;14(6):527–32.
- Schumacher SG, Sohn H, Qin ZZ, Gore G, Davis JL, Denkinger CM, et al. Impact of molecular diagnostics for tuberculosis on patient-important outcomes: a systematic review of study methodologies. *PLoS One*. 2016;11(3):e0151073.
- Hermans SM, Castelnovo B, Katabira C, Mbidde P, Lange JM, Hoepelman A, et al. Integration of HIV and TB services results in improved TB treatment outcomes and earlier, prioritized ART initiation in a large urban HIV clinic in Uganda. *J Acquir Immune Defic Syndr*. 2012;60(2):e29–35.
- Hermans SM, Nasuuna E, Van Leth F, Byhoff E, Schwarz M, Hoepelman A, et al. Implementation and effect of intensified case finding on diagnosis of tuberculosis in a large urban HIV clinic in Uganda: a retrospective cohort study. *BMC Public Health*. 2012;12:674.
- Nakiyingi L, Bwanika JM, Kirenga B, Nakanjako D, Katabira C, Lubega G, et al. Clinical predictors and accuracy of empiric tuberculosis treatment among sputum smear-negative HIV-infected adult TB suspects in Uganda. *PLoS One*. 2013;8(9):e74023.
- Bakari M, Arbeit RD, Mtei L, Lyimo J, Waddell R, Matee M, et al. Basis for treatment of tuberculosis among HIV-infected patients in Tanzania: the role of chest x-ray and sputum culture. *BMC Infect Dis*. 2008;8:32.

18. Katagira W, Walter ND, Den Boon S, Kalema N, Ayakaka I, Vittinghoff E, et al. Empiric TB treatment of severely ill patients with HIV and presumed pulmonary TB improves survival. *J Acquir Immune Defic Syndr*. 2016;72(3):297–303.
19. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert(R) MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev*. 2014;1:CD009593. doi:10.1002/14651858.CD009593.pub3.
20. Boehme CC, Nicol MP, Nabeta P, Michael JS, Gotuzzo E, Tahirli R, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet*. 2011;377(9776):1495–505.
21. McCarthy KM, Grant AD, Chihota V, Ginindza S, Mvusi L, Churchyard GJ, et al. Implementation and operational research: what happens after a negative test for tuberculosis? Evaluating adherence to TB diagnostic algorithms in South African primary health clinics. *J Acquir Immune Defic Syndr*. 2016; 71(5):e119–26.
22. Manabe YC, Zawedde-Muyanja S, Burnett SM, Mugabe F, Naikoba S, Coutinho A. Rapid improvement in passive tuberculosis case detection and tuberculosis treatment outcomes after implementation of a bundled laboratory diagnostic and on-site training intervention targeting mid-level providers. *Open Forum Infect Dis*. 2015;2(1):ofv030. doi:10.1093/ofid/ofv030.
23. Schumacher SG, Nabeta P, Boehme C, Ellner J, Alland D, Dorman SE, et al. A multicenter diagnostic accuracy study of the Xpert Ultra for tuberculosis diagnosis. Conference for Retrovirology and Opportunistic Infections; 13–16 February 2017; Seattle, USA, 2017. Abstract 76LB.
24. Hanrahan CF, Haguma P, Ochom E, Kinera I, Cobelens F, Cattamanchi A, et al. Implementation of Xpert MTB/RIF in Uganda: Missed Opportunities to Improve Diagnosis of Tuberculosis. *Open Forum Infect Dis*. 2016;3(2):ofw068. doi:10.1093/ofid/ofw068.
25. Mbonze NB, Tabala M, Wenzi LK, Bakoko B, Brouwer M, Creswell J, et al. Xpert((R)) MTB/RIF for smear-negative presumptive TB: impact on case notification in DR Congo. *Int J Tuberc Lung Dis*. 2016;20(2):240–6.
26. Sikhondze W, Dlamini T, Khumalo D, Maphalala G, Dlamini S, Zikalala T, et al. Countrywide roll-out of Xpert((R)) MTB/RIF in Swaziland: the first three years of implementation. *Public Health Action*. 2015;5(2):140–6.
27. Hermans S, Caldwell J, Kaplan R, Cobelens F, Wood R. The impact of the roll-out of rapid molecular diagnostic testing for tuberculosis on empirical treatment in Cape Town, South Africa. *Bull World Health Organ*. 2017; E-pub date 28–04-2017. Available from: http://www.who.int/bulletin/online_first/BLT.16.185314.pdf?ua=1
28. Hosseinipour MC, Bisson GP, Miyahara S, Sun X, Moses A, Riviere C, et al. Empirical tuberculosis therapy versus isoniazid in adult outpatients with advanced HIV initiating antiretroviral therapy (REMEMBER): a multicountry open-label randomised controlled trial. *Lancet*. 2016;387(10024):1198–209.
29. Manabe YC, Worodria W, van Leth F, Mayanja-Kizza H, Traore AN, Ferro J, et al. Prevention of early mortality by presumptive tuberculosis therapy study: an open label. *American Journal of Tropical Medicine and Hygiene: Randomized Controlled Trial*; 2016.
30. Grant A, Charalambous S, Tlali M, Johnson S, Dorman SE, Hoffman C, et al. Empirical TB Treatment in Advanced HIV Disease: Results of the TB Fast Track Trial. Conference on Retroviruses and Opportunistic Infections; 22–25 February 2016; Boston, Massachusetts, USA, 2016.

Submit your next manuscript to BioMed Central and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at
www.biomedcentral.com/submit

