International Journal of Infectious Diseases xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Xpert MTB/RIF on urine samples to increase diagnosis of TB in people living with HIV in Guinea-Bissau

Alexander Dutschke[1,2,6,*], Ditte Steiniche[1,2,6], Sanne Jespersen[1,2], Joao Paulo Nanque[1,4], Candida Medina[4], Bo Langhoff Hønge[1,2,3], Christian Wejse[1,2,5]

[1] Bandim Health Project, Indepth Network, Bissau, Guinea-Bissau
[2] Department of Infectious Diseases, Aarhus University Hospital, Denmark
[3] Department of Clinical Immunology, Aarhus University Hospital, Denmark
[4] National HIV Programme, Ministry of Health, Bissau, Guinea-Bissau
[5] GloHAU, Center for Global Health, School of Public Health, Aarhus University, Denmark

ARTICLE INFO

Article history:
Received 4 February 2022
Revised 17 March 2022
Accepted 19 March 2022
Available online xxx

Key words:
TB
HIV
diagnostic yield
Xpert
urine
Guinea-Bissau

ABSTRACT

Objectives: We investigated if Xpert MTB/RIF (Xpert) testing on urine samples among newly diagnosed HIV-patients as an adjunctive test to Xpert testing on sputum increases diagnosis. We sought to define subgroups of patients, for whom testing with either test is especially advantageous.
Methods: We included patients >15 years, newly diagnosed with HIV, that delivered a urine sample on the day of HIV-diagnosis at the biggest HIV-clinic in Guinea-Bissau between September 5, 2016 and October 13, 2017 into a cross-sectional study. Patients were asked for a sputum sample, which was Xpert tested if returned within 30 days. A questionnaire and physical examination were completed on day of inclusion.
Results: We included 390 patients. TB prevalence was 12.6%. Adding Xpert urine test to all newly diagnosed HIV-patients increased diagnostic yield of TB by 58% compared with testing on sputum alone. Patients who tested positive by Xpert on urine samples were clinically similar to those tested with sputum, except that the sputum positives reported more cough (p=0.03).
Conclusions: Indiscriminate Xpert urine testing in newly diagnosed HIV-patients with advanced disease increased diagnostic yield. Xpert testing for TB on urine and sputum should be offered as screening in Guinea-Bissau and possibly in similar settings.
© 2022 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Background

Globally an estimated 38 million people were living with HIV in 2019 and sub-Saharan Africa is home to 66.7% of all people living with HIV (PLWH) (UNAIDS 2020).

TB is the leading contributor of death in this group accounting for approximately 1/3 of AIDS-related deaths (UNAIDS 2019a), suggesting difficulties in screening and diagnosis in this group.

According to WHO in 2019 an estimated 10 million people contracted TB, 1.4 million died of TB and out of those 208,000 had HIV (WHO 2020).

The country Guinea-Bissau has both a high HIV and TB burden in PLWH. UN AIDS describes a HIV prevalence among adults of 3% in the country (UNAIDS 2019b), but a recent study reported that the HIV prevalence in the capital is 6.7% (Olesen et al., 2018). TB prevalence in Guinea-Bissau in newly diagnosed PLWH was recently measured to 13.4% but may be higher with intensified focus of diagnosis (Aunsborg et al., 2020).

Screening is recommended by WHO to be done via a clinical algorithm (WHO 2013a). If any HIV-patient presents with one of the following: current cough, fever, weight loss or night sweats, they should be evaluated for active TB. This algorithm has a sensitivity of 79% and a specificity of 50% (WHO 2010).

Culture is the gold standard diagnostic test for TB (Achkar et al., 2011), but is not recommended as an initial diagnostic tool due to

* Corresponding author: Alexander Dutschke, Department of Infectious Diseases, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus, Denmark, Telephone: +45 52178273
E-mail address: alexander.ajasd2@gmail.com (A. Dutschke).
[6] These authors contributed equally

https://doi.org/10.1016/j.ijid.2022.03.035
1201-9712/© 2022 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Please cite this article as: A. Dutschke, D. Steiniche, S. Jespersen et al., Xpert MTB/RIF on urine samples to increase diagnosis of TB in people living with HIV in Guinea-Bissau, International Journal of Infectious Diseases, https://doi.org/10.1016/j.ijid.2022.03.035

resource and waiting requirements (2-3 weeks before answer on a positive test (SSI 2018)) and is often difficult in low-income countries (Lawn & Wood, 2011), compared with Xpert MTB/RIF (Xpert) and sputum-smear microscopy, which can provide results within a day (WHO 2013a).

Xpert test is used in initial TB diagnosis and is accurate when testing sputum diagnosing 90% of TB in culture-positive patients with a specificity of 99% (Boehme et al., 2011), however op to one-third of HIV-TB co-infected patients fail to produce sputum samples within 24 hours (Lawn et al., 2017; Lawn et al., 2015). In PLWH with a TB positive blood culture, strongly indicating disseminated disease, Xpert sputum and/or sputum smear mircroscopy detect TB in 19.5% of positive cases (Kerkhoff et al., 2017). HIV-TB co-infected patients are more likely to have atypical findings of TB including: sputum smear negative TB, radiographically non-specific TB, (Dawson et al., 2010; Getahun et al., 2007) and uncharacteristic/lack of symptoms (Sterling et al., 2010). They more often present with disseminated TB, with up to 57% having TB in the kidneys, which often remains undiagnosed resulting in rapid and fatal disease (Crump et al., 2012; Gupta et al., 2015; Lanjewar, 2011).

Xpert testing on urine show promising results to increase diagnostic yield (Lawn et al., 2015) as an adjunctive test, since most patients can produce the sample and it is quicker to obtain (Lawn et al., 2013) compared to Xpert sputum. Xpert urine is especially promising when testing samples from HIV-infected patients with advanced immunodeficiency (Lawn et al., 2012; Peter et al., 2012).

Objectives

This study conducted in the capital Bissau of Guinea-Bissau seeks to contribute to the evidence of Xpert testing on urine samples for TB to increase diagnostic yield of TB in PLHIV and its relevance as an adjunctive test with Xpert testing on sputum. Also, it investigates which screening options that can be used to identify subsets of patients for whom urine or sputum tests should be offered exclusively.

Methods

Setting, design and study population

The outpatient HIV clinic at Hospital National Simão Mendes (HNSM) is the largest anti retro-viral therapy (ART) center in Guinea-Bissau. The clinic is home to a part of the Bissau HIV Cohort, a clinical cohort of HIV-infected patients started in 2007 (Jespersen al., 2015a). A high rate of loss-to-follow-up is seen in the cohort (Hønge et al., 2013), as well as treatment failure (Jespersen et al., 2015b) and subsequently high mortality (Engell-Sørensen et al., 2021).

This cross-sectional study was conducted at the HIV clinic at HNSM between September 5, 2016 and October 13, 2017. Newly diagnosed HIV-positive patients >15 years were asked to deliver a urine sample on the day of HIV-diagnosis at HNSM. All patients that did were included in the study and enrolled into the Bissau HIV Cohort. The included patients were the same day instructed how to perform a sputum sample, given a specimen container and asked to return to HNSM with the sample the following day. Patients were told that time between collecting the sputum and delivering it to the clinic should preferably be done within 24 hours. Sputum samples were included if returned to the clinic within 30 days of HIV-diagnosis. A questionnaire regarding demography, lifestyle and symptoms and a physical examination was completed. Blood samples were taken the day after HIV-diagnosis. All patients were included regardless of symptoms.

HIV-screening

Screening for HIV was performed using Determine HIV-1/2 assay (Abbott laboratories, Illinois, USA). The confirmatory HIV test also used for HIV type discrimination varied between SD Bioline HIV 1/2 3.0 (Standard Diagnostics Inc, Kyonggi-do, South Korea), First Response HIV Card 1-2.0 (PMC Medical, Mumbai, India) and Genie III HIV-1/HIV-2 (Bio-Rad, Steenvorde, France (Hønge et al., 2014). CD4 cell count analyses were performed at the National Public Health Laboratory by Partec CyFlow® SL_3 (Cyflow SL, Partec, Munster, Germany).

Urine and sputum

All tests were delivered to the National Laboratory of Public Health (LNSP) for analysis on the same day of testing.

Sputum samples were analyzed continually as part of the laboratory's routine analysis. Tests were taken early in the morning up to 8 o' clock at HNSM and arrived at the laboratory at 9. They were analyzed using the Xpert MTB/RIF assay shortly after with answers delivered the same day.

Urine samples were collected and stored at -20C. They were analyzed using the Xpert MTB/RIF assay, when access to Xpert test equipment was possible and when the running of the laboratory allowed it, usually occurring after a month.

Any TB positives detected were called on telephone and offered treatment. If unavailable treatment was offered on the next follow-up.

Symptom screening

We used two scoring systems to evaluate their potential as screening tools based on symptoms for TB in PLWH.

Bandim TBscoreII (Rudolf et al., 2013) consists of 3 patient reported symptoms: cough, dyspnea, chest pain and 3 signs evaluated by a clinician: anemia (pale inferior conjuctivae), low body mass index (BMI) or low mid upper arm circumference (MUAC). Each positive finding gives 1 point, with the exception of BMI and MUAC where values of <16 mg^m2 and <200 mm give 2 points.

Severity classes for TBscoreII: I, score < 2, II, score 2–3; III, score 4–7; and IV, score > 7 (Rudolf et al., 2013).

WHO symptom screening evaluates patients on the presence of one or more of the following symptoms: cough, self-reported fever, weight-loss or night sweats. Presence of ≥1 symptoms result in further testing for TB.

Statistical analysis

Data was analyzed using Stata/IC 13.0 (StataCorp LP, College Station, TX, USA). Chi-square test was used to assess categorical valuables and in cases with <5 observations in a group Fiscers Exact test. Continuous variables were compared using ttest and in cases where assumptions failed the non-parametric Wilcoxon rank-sum test. Wilcoxon-Mann-Whitney test was used to compare Xpert testing of urine samples and sputum samples. Missing data was excluded from analysis.

Ethical considerations

Written information was given in the official language Portuguese and oral information in the widely spoken Portuguese Creole. Informed written consent, or a fingerprint if illiterate, was provided by all included patients.

Table 1
Number of patients with TB positive and TB negative urine and sputum results.

	Sputum not available	Sputum negative	Sputum positive	
Urine negative	174	167	26	367
Urine positive	13	5	5	23
	187	172	31	390

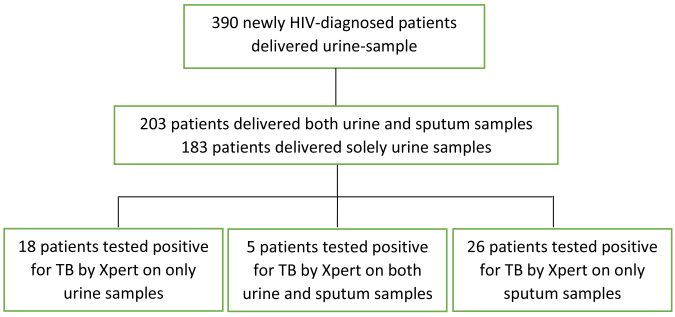

Fig 1. Diagram of TB positives by test.

Results

In total 390 newly HIV-diagnosed patients were included between September 5, 2016 and October 13, 2017. Within 30 days from inclusion, 203 (52.1 %) patients returned with a sputum sample. Median age was 37 years (IQR, 30 to 45) and 33,6% were male. Among the 390 patients included, 260 (66.7%) were HIV-1 positive, 28 (7.2%) HIV-2 positive, 24 (6.2%) HIV 1/2 dually-infeted and 78 (20%) had unknown HIV-types. Median CD4 cell count was 211 cells/uL (IQR=97:423). Median hemoglobin was 9.3 g/dL (IQR=7.9:10.7). The median Bandim TBscoreII was 1 (IQR, 0 to 3) and 345 (96.4%, n=353) showed ≥1 WHO symptom. Twenty-six patients were previous to the study tested positive for TB. Of these six still registered positive, five only on Xpert sputum and one on sputum and urine. Date of previous infection was unknown.

Fig. 1.

49 (12.6%) of the included patients tested positive for TB either by sputum or urine sample (Table 1). The positive rate was 10.3% (CI 4.7%-16%) higher for the sputum test versus the urine test, when comparing the two. Five patients who tested negative on the sputum test had a positive urine test and 13 patients who did not return with a sputum sample tested positive for TB in the urine sample. In total 18 patients which equals 36.7% of the total number of TB positive patients had not been found if they had not been asked to deliver a urine sample. This is an increase in diagnostic yield of 49/31 = 58%. Clinically the urine positives reported 100% fever, 94% weight loss, 70.6% night sweat and 35.3% cough (n=17).

Comparison of TB positives vs TB negatives (Table 2).

The TB positive patients were significantly younger (mean=35.3 years) than TB negative patients (mean=38.9, p=0.04). TB positive patients suffered more from cough (p<0.01), fever (p<0.01) and night sweats (p=0.02) compared with TB negatives. TB positive patients had a significantly higher Bandim TBscoreII (median=3, p=0.01) than TB negative patients (median=1). CD4 cell count and hemoglobin were significantly lower for TB positive patients compared with TB negative (p<0.01 for both)

Comparison of patients that solely delivered a urine sample vs patients that also delivered sputum samples (Table 3).

These patients were comparable on most variables. Patients that also delivered a sputum sample had lower hemoglobin (p<0.05), CD4 level (p=0.01), more had lower BMI<18 kg/m^2 (p=0.02), more coughed (p=0.03) and they tended to suffer more from fever (p=0.07) and weight loss (p=0.07) compared with patients who only delivered a urine sample. There were no differences between the groups regarding Bandim TBscoreII (median 1, p=0.49).

Comparison of patients with a positive urine sample vs sputum samples.

Twenty-six tested positive only with Xpert on sputum and 18 only with Xpert on urine. The 5 positive patients found by both tests were excluded from this analysis. To further assess if urine Xpert should be offered only to specific groups of HIV-infected we tested if patients diagnosed only with a urine-sample were different with regards to any variables compared to those diagnosed via sputum only. The sputum positives experienced more cough (n=43, p=0.03) and more had a BMI<18 mg/m^2 (n=39, p=0.04), otherwise no differences were found. Both groups suffered from severe immunodeficiency with median CD4=138 (IQR=28:248) in sputum positives and 108 (IQR=45:187) in urine positives, with >75% having AIDS defining CD4 levels among urine positives.

Discordant pairs

In 26 cases the sputum results were TB positive and urine negative. In 5 cases the urine results were positive and sputum negative. Analysis showed a tendency of higher TBscoreII (n=27, p=0.09), cough (n=31, p=0.06) and BMI<18kg/m^2 (n=30, p=0.052) in the 26 sputum test positive, urine test negative patients.

Discussion

We found adding an Xpert test on urine samples on all newly diagnosed HIV-infected patients increased diagnosis of TB by 36.7%. Overall TB prevalence in the study was found to be 12.6% with Xpert testing on urine and 7.9% without, an increase of 59%. Inability to produce sputum and difficulty of follow-up on patients for sputum collection resulted in a large group of 48% of patients that remained sputum untested within <30 days of HIV diagnosis. Of the increase in TB diagnosis by Xpert urine testing 26.5% came from this group. Urine samples are compared with sputum samples easier and quicker to obtain, handle and quality of samples is less of an issue (Lawn et al., 2013), which is advantageous in a setting where follow-up on patients for sputum collection is limited.

TB positive and negative patients differed on many variables, but not in ways that allowed us to identify specific subsets to test with Xpert on urine samples. Self-reported cough had the highest difference of 26.8% between TB positives and negatives, but only 56.3% of positives reported cough, so using this as the defining screening tool would lead to underdiagnosis of TB. Using Bandim TBscoreII to screen and identify candidates for Xpert testing on urin is suboptimal in this study since 17.9% of TB positive patients scored 0 and 35.9% scored <2. These TB positive patients would not be found if the screening algorithm discarded patients for further diagnostic tests with low scores. 96.4% of all patients reported ≥1 WHO symptom, so using this as a screening algorithm hardly limits the scope of testing.

Another way of identifying a subset of patients for whom testing with Xpert urine test is particularly advantageous is to identify those who lack the ability to produce sputum and offer them the urine test instead. Patients that only delivered urine samples were

Table 2
Characteristics of TB negative and TB positive patients.

	TB negative	TB positive	
	n = 341, n (%)	n = 49, n (%)	p-value
Age (years) n=390	Mean=38.9	Mean=35.3	0.04
Sex n=390			0.41
Women	229 (67.2)	30 (61.2)	
Men	112 (32.8)	19 (38.8)	
HIV type n=312			0.29
HIV-1	226 (82.2)	34 (91.9)	
HIV-2	27 (9.8)	1 (2.7)	
HIV-1/2	22 (8)	2 (5.4)	
WHO TB symptoms reported			
Cough n=370	95 (29.5)	27 (56.3)	<0.01
Fever n=373	250 (76.9)	46 (95.8)	<0.01
Night sweats n=368	162 (50.5)	32 (68.1)	0.02
Weight loss n=369	284 (88.5)	45 (93.8)	0.27
Bandim TBscoreII			
Cough n=370	95 (29.5)	27 (56.3)	<0.01
Dyspnea n=373	77 (23.6)	17 (36.2)	0.06
Chest pain n=374	143 (43.9)	26 (54.2)	0.18
Anemia n=341	30 (10.1)	6 (13.3)	0.52
BMI < 18 kg/m^2 n=354	49 (15.8)	16 (37.2)	<0.01
BMI <16 kg/m^2 n=354	38 (12.2)	5 (11.6)	0.91
MUAC < 220 mm N=369	44 (13.7)	10 (21.3)	0.17
MUAC < 200 mm n=369	24 (7.5)	4 (8.5)	0.79
Median total Bandim TBscoreII n=315	1 (IQR=0:3)	3 (IQR=1:4)	<0.01
Bandim TBscoreII >1 n=315	126 (45.7)	25 (64.1)	0.03
Haemoglobin n=222			<0.01
Mean	9.67 (95% CI: 9.28:10.06)	7.72 (95% CI: 6.85:8.59)	
Mean difference		1.95 (95% CI: 0.91:2.99)	
CD4 n=353			<0.01
Median	232 (IQR=109.5:459)	108 (IQR=30:208)	

Table 3
Characteristics of patients who solely delivered a urine sample vs. patients who delivered both a urine and sputum sample.

	Solely urine sample	Urine and sputum sample	
	n (%), n = 187	n (%), n = 203	p-value
Age (years) n=390	Mean=38.9	Mean=38	0.43
Sex n=390			
Women	118 (63.1)	141 (69.5)	0.18
Men	69 (36.9)	62 (30.5)	
HIV type n=312			
HIV-1	120 (83.9)	140 (82.8)	0.65
HIV-2	14 (9.8)	14 (8.3)	
HIV-1/2	9 (6.3)	15 (8.9)	
WHO TB symptoms reported			
Cough n=370	47 (27.3)	75 (37.9)	0.03
Fever n=373	131 (75.3)	165 (82.9)	0.07
Night sweats n=368	90 (52.3)	104 (53.1)	0.89
Weight loss n=369	148 (86.1)	181 (91.9)	0.07
Bandim TB-II score			
Cough n=370	47 (27.3)	75 (37.9)	0.03
Dyspnea n=373	49 (24.6)	45 (25.9)	0.78
Chest pain n=374	70 (40.2)	99 (49.5)	0.07
Anemia n=341	19 (11.8)	17 (9.4)	0.48
BMI < 18 kg/m^2 n=354	22 (13.3)	43 (22.9)	0.02
BMI <16 kg/m^2 n=354	25 (15.1)	18 (9.6)	0.12
MUAC < 220 mm n=369	30 (17.5)	24 (12.1)	0.14
MUAC < 200 mm n=369	13 (7.6)	15 (7.6)	0.99
Median total Bandim TB-II score n=315	1 (IQR=0:3)	1 (IQR=0:3)	0.49
Haemoglobin n=222			<0.05
Mean	9.87 (95% CI: 9.17:10.58)	9.11 (95% CI: 8.71:9.51)	
Mean difference		-0.77 (95%CI: -1.51:0.02)	
CD4 cell count n=353			0.01
Median	253 (IQR=109:493)	194 (IQR=83:368)	

compared with patients that were also able to produce a sputum sample. Overall the groups were very identical. Identification of patients unable to produce sputum cannot help limit scope of Xpert testing on urine in this study.

We tested if positive patients found only by Xpert urine were different from positive patients found only by Xpert sputum on variables such as CD4, hemoglobin and symptoms of TB. We found no major differences in clinical presentation or biomarkers between the two groups, hence offering different tests based on level of immunodeficiency is not warranted. Both groups were severely immunocompromised, and it is possible that the conclusion could be different in patients with higher CD4 counts, since urine-based

tests are more sensitive at low CD4 counts (Bjerrum et al., 2019; Lawn et al., 2012).

Discordant pair analysis showed us that Xpert test on sputum samples tended to be better at diagnosing those with more cough (indicative of pulmonal TB).

Strengths of this study is the recruitment of well-characterized patients in a well-documented cohort (Jespersen et al., 2015a). The patients included in the present study are similar on parameters like sex, age at inclusion and median CD4 count compared with the Bissau HIV Cohort and results are likely applicable to the background population. Weaknesses of the study include a lack of a gold-standard of testing, therefore the actual prevalence of TB in the study-population is unknown and consequently sensitivity and specificity analysis are impossible.

The study population was not an unselected sample of individuals with HIV. Only those who delivered a urine test were included. However, urine tests are easy to obtain from patients (Lawn et al., 2017) and it is unlikely that a significant number of patients were discarded. The study was conducted at a single site in Guinea-Bissau and the extent of generalizability to other similar settings outside of Guinea-Bissau is uncertain, however this study builds upon previous studies that have also demonstrated increased diagnostic yield of Xpert urine testing in PLWH for TB (Lawn et al., 2015; Schutz et al., 2019), especially in the severely immunocompromised (Lawn et al., 2012; Peter et al., 2012). Concentration of urine was seen to significantly increase diagnosis of TB compared with unconcentrated urine (Lawn et al., 2015; Peter et al., 2012), but this was not possible in our setting due to centrifuge requirements.

Conclusion

We found that Xpert testing on urine increased diagnostic yield if given as an adjunctive test to Xpert testing on sputum and we recommend screening all newly diagnosed HIV positive patients in Guinea-Bissau for TB with both Xpert on sputum and urine. Our study found no relevant screening parameters to limit Xpert sputum and/or urine testing for patient subsets. These results may be applicable in similar low-resource settings, where testing capabilities and follow-up on patients are similarly challenged and we recommend further research into this to better diagnosis and outcome.

Transparency declaration

This article is part of a supplement entitled Commemorating World Tuberculosis Day March 24th, 2022: “Invest to End TB. Save Lives” published with support from an unrestricted educational grant from QIAGEN Sciences Inc.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors contributions

AD, DS, SJ, BLH, JP, CM and CW conceived the study; DS, JP and CM carried out data collection; AD, DS and BLH carried out analysis and interpretation of data. AD and DS drafted the manuscript; all authors critically revised the manuscript for intellectual content. All authors read and approved the final manuscript of the paper. BLH, SJ and CW are guarantors of the paper.

Acknowledgements

The authors are grateful to the staff working in the HIV clinic at HNSM and the National Public Health Laboratory for their work effort and their professionalism. We are furthermore grateful for the staff at the Bandim Health Project, for making this study possible.

The Bissau HIV cohort study group consists of Amabelia Rodrigues, David da Silva, Zacarias da Silva, Candida Medina, Ines Oliviera-Souto, Lars Østergaard, Alex Laursen, Peter Aaby, Anders Fomsgaard, Christian Erikstrup, Christian Wejse, Bo Langhoff Hønge, and Sanne Jespersen (chair).

Funding

This study was funded by Aarhus Universities research fund for research at the Institute for Clinical Medicine, Aarhus University Hospital. 120.000 dkk for principal researchers’ salary.

References

Achkar JM, Lawn SD, Moosa M-YS, Wright CA, Kasprowicz VO. Adjunctive Tests for Diagnosis of Tuberculosis: Serology, ELISPOT for Site-Specific Lymphocytes, Urinary Lipoarabinomannan, String Test, and Fine Needle Aspiration. The Journal of Infectious Diseases 2011;204(suppl_4):S1130–41. doi:10.1093/infdis/jir450.

Aunsborg JW, Hønge BL, Jespersen S, Rudolf F, Medina C, Correira FG, Johansen IS, Wejse C. A clinical score has utility in tuberculosis case-finding among patients with HIV: A feasibility study from Bissau. Int J Infect Dis 2020;92s:S78–84. doi:10.1016/j.ijid.2020.03.012.

Bjerrum S, Schiller I, Dendukuri N, Kohli M, Nathavitharana RR, Zwerling AA, Denkinger CM, Steingart KR, Shah M. Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in people living with HIV. Cochrane Database Syst Rev 2019;10(10). doi:10.1002/14651858.CD011420.pub3.

Boehme CC, Nicol MP, Nabeta P, Michael JS, Gotuzzo E, Tahirli R, Gler MT, Blakemore R, Worodria W, Gray C, Huang L, Caceres T, Mehdiyev R, Raymond L, Whitelaw A, Sagadevan K, Alexander H, Albert H, Cobelens F, Cox H, Alland D, Perkins MD. 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. doi:10.1016/s0140-6736(11)60438-8.

Crump JA, Ramadhani HO, Morrissey AB, Saganda W, Mwako MS, Yang LY, Chow SC, Njau BN, Mushi GS, Maro VP, Reller LB, Bartlett JA. Bacteremic disseminated tuberculosis in sub-saharan Africa: a prospective cohort study. Clin Infect Dis 2012;55(2):242–50. doi:10.1093/cid/cis409.

Dawson R, Masuka P, Edwards DJ, Bateman ED, Bekker LG, Wood R, Lawn SD. Chest radiograph reading and recording system: evaluation for tuberculosis screening in patients with advanced HIV. Int J Tuberc Lung Dis 2010;14(1):52–8.

Engell-Sørensen T, Rieckmann A, Medina C, da Silva Té D, Rodrigues A, Fisker AB, Aaby P, Erikstrup C, Jespersen S, Wejse C, Hønge BL. Life expectancy of HIV-infected patients followed at the largest hospital in Guinea-Bissau is one-fourth of life expectancy of the background population. Infection 2021;49(4):631–43. doi:10.1007/s15010-020-01574-6.

Getahun H, Harrington M, O'Brien R, Nunn P. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. Lancet 2007;369(9578):2042–9. doi:10.1016/s0140-6736(07)60284-0.

Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. Aids 2015;29(15):1987–2002. doi:10.1097/qad.0000000000000802.

Hønge BL, Bjarnason Obinah MP, Jespersen S, Medina C, S TD, da Silva ZJ, Østergaard L, Laursen AL, Wejse C, Erikstrup C. Performance of 3 rapid tests for discrimination between HIV-1 and HIV-2 in Guinea-Bissau, West Africa. J Acquir Immune Defic Syndr 2014;65(1):87–90. doi:10.1097/QAI.0b013e3182a97b81.

Hønge BL, Jespersen S, Nordentoft PB, Medina C, da Silva D, da Silva ZJ, Ostergaard L, Laursen AL, Wejse C. Loss to follow-up occurs at all stages in the diagnostic and follow-up period among HIV-infected patients in Guinea-Bissau: a 7-year retrospective cohort study. BMJ Open 2013;3(10). doi:10.1136/bmjopen-2013-003499.

Jespersen S, Hønge BL, Medina C, da Silva Té D, Correira FG, Laursen AL, Erikstrup C, Østergaard L, Wejse C. Lack of awareness of treatment failure among HIV-1-infected patients in Guinea-Bissau - a retrospective cohort study. J Int AIDS Soc 2015b;18(1):20243. doi:10.7448/ias.18.1.20243.

Jespersen S, Hønge BL, Oliveira I, Medina C, da Silva Té D, Correira FG, Erikstrup C, Laursen AL, Østergaard L, Wejse C. Cohort Profile: The Bissau HIV Cohort-a cohort of HIV-1, HIV-2 and co-infected patients. Int J Epidemiol 2015a;44(3):756–63. doi:10.1093/ije/dyu201.

Kerkhoff AD, Barr DA, Schutz C, Burton R, Nicol MP, Lawn SD, Meintjes G. Disseminated tuberculosis among hospitalised HIV patients in South Africa: a common condition that can be rapidly diagnosed using urine-based assays. Sci Rep 2017;7(1):10931. doi:10.1038/s41598-017-09895-7.

Lanjewar DN. The spectrum of clinical and pathological manifestations of AIDS in a consecutive series of 236 autopsied cases in mumbai, India. Patholog Res Int 2011;2011. doi:10.4061/2011/547618.

Lawn SD, Kerkhoff AD, Burton R, Schutz C, Boulle A, Vogt M, Gupta-Wright A, Nicol MP, Meintjes G. Diagnostic accuracy, incremental yield and prognostic value of Determine TB-LAM for routine diagnostic testing for tuberculosis in HIV-infected patients requiring acute hospital admission in South Africa: a prospective cohort. BMC Med 2017;15(1):67. doi:10.1186/s12916-017-0822-8.

Lawn SD, Kerkhoff AD, Burton R, Schutz C, van Wyk G, Vogt M, Pahlana P, Nicol MP, Meintjes G.). Rapid microbiological screening for tuberculosis in HIV-positive patients on the first day of acute hospital admission by systematic testing of urine samples using Xpert MTB/RIF: a prospective cohort in South Africa. BMC Medicine 2015;13(1):192. doi:10.1186/s12916-015-0432-2.

Lawn SD, Kerkhoff AD, Vogt M, Wood R. High diagnostic yield of tuberculosis from screening urine samples from HIV-infected patients with advanced immunodeficiency using the Xpert MTB/RIF assay. J Acquir Immune Defic Syndr 2012;60(3):289–94. doi:10.1097/QAI.0b013e318258c6af.

Lawn SD, Kerkhoff AD, Vogt M, Wood R. HIV-associated tuberculosis: relationship between disease severity and the sensitivity of new sputum-based and urine-based diagnostic assays. BMC Medicine 2013;11(1):231. doi:10.1186/1741-7015-11-231.

Lawn SD, Wood R. Tuberculosis in antiretroviral treatment services in resource-limited settings: addressing the challenges of screening and diagnosis. J Infect Dis 2011;204(Suppl 4):S1159–67 *Suppl 4*. doi:10.1093/infdis/jir411.

Olesen JS, Jespersen S, da Silva ZJ, Rodrigues A, Erikstrup C, Aaby P, Wejse C, Hønge BL. HIV-2 continues to decrease, whereas HIV-1 is stabilizing in Guinea-Bissau. Aids 2018;32(9):1193–8. doi:10.1097/qad.0000000000001827.

Peter JG, Theron G, Muchinga TE, Govender U, Dheda K. The diagnostic accuracy of urine-based Xpert MTB/RIF in HIV-infected hospitalized patients who are smear-negative or sputum scarce. PLoS One 2012;7(7):e39966. doi:10.1371/journal.pone.0039966.

Rudolf F, Lemvik G, Abate E, Verkuilen J, Schön T, Gomes VF, Eugen-Olsen J, Østergaard L, Wejse C. TBscore II: refining and validating a simple clinical score for treatment monitoring of patients with pulmonary tuberculosis. Scand J Infect Dis 2013;45(11):825–36. doi:10.3109/00365548.2013.826876.

Schutz C, Ward A, Burton R, Nicol MP, Blumenthal L, Meintjes G, Kerkhoff AD. False rifampicin resistant results using Xpert MTB/RIF on urine samples in hospitalised HIV-infected patients. South Afr J HIV Med 2019;20(1):978. doi:10.4102/sajhivmed.v20i1.978.

Sterling TR, Pham PA, Chaisson RE. HIV infection-related tuberculosis: clinical manifestations and treatment. Clin Infect Dis 2010;50(Suppl 3):S223–30. doi:10.1086/651495.

SSI2018. SSI, Tuberkulosebekæmpelse i Danmark et nationalt tuberkuloseprogram 2018, TB guideline, 2018, https://www.ssi.dk/-/media/arkiv/indhold/dk-dansk/sygdomsleksikon/tb-guideline_dk_2018.pdf?la=da (accessed 06.08.2021).

UNAIDS 2019a. Tuberculosis and HIV- Progress towards the 2020 target, https://www.unaids.org/en/resources/documents/2019/tuberculosis-and-hiv-progress-towards-the-2020-target (accessed 20.07.21).

UNAIDS 2019b. Guinea-Bissau, https://www.unaids.org/en/regionscountries/countries/guinea-bissau (accessed 15.07.2021)

UNAIDS 2020. *Global HIV and AIDS statistics - 2020 fact sheet* https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf. (accessed 01.07.2021).

WHO 2010. Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings, http://apps.who.int/iris/bitstream/handle/10665/44472/9789241500708_eng.pdf;jsessionid=9A04B22D2BF378C9987F90B1FE7823AB?sequence=1, WHO Global TB Programme, 2010 (accessed 05.07.21).

WHO 2013a. Systematic screening for active tuberculosis, Principles and recommendation, https://www.who.int/tb/publications/Final_TB_Screening_guidelines.pdf, WHO, 2013 (accessed 15.07.21).

WHO 2020. Global Tuberculosis Report 2020, World Health Organization. https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf (accessed 15.07.21).