Cost-effectiveness of urine-based tuberculosis screening among hospitalized people with HIV in Africa

Krishna P. Reddy[1,2], Ankur Gupta-Wright[3,5], Katherine L. Fielding[3], Sydney Costantini[1], Amy Zheng[1], Elizabeth L. Corbett[3,5], Liyang Yu[1], Joep J. van Oosterhout[4,5], Stephen C. Resch[6], Douglas P. Wilson[7], C. Robert Horsburgh[8], Robin Wood[9], Kenneth A. Freedberg[1,2,6,8], Stephen D. Lawn[3,9], Rochelle P. Walensky[1,2]

[1]Massachusetts General Hospital, [2]Harvard Medical School, [3]London School of Hygiene & Tropical Medicine, [4]Dignitas International, [5]University of Malawi College of Medicine, [6]Harvard T.H. Chan School of Public Health, [7]Edendale Hospital, University of KwaZulu-Natal, [8]Boston University School of Public Health, [9]Desmond Tutu HIV Foundation, University of Cape Town

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Background

- Tuberculosis (TB) accounts for approximately 40% of hospital deaths among people with HIV (PWH) in resource-limited settings, and nearly half of these are undiagnosed at the time of death (Cohen et al., *PLoS Med* 2010; Gupta et al., *AIDS* 2015).
- The Rapid Urine-based Screening for Tuberculosis to Reduce AIDS-related Mortality (STAMP) trial showed that urine-based TB screening in PWH hospitalized in Malawi and South Africa reduced all-cause mortality at 2 months by 2.8% and increased TB diagnoses by 7.3% (Gupta-Wright et al., CROI 2018, Abstract #3510).

Objective

- To project longer-term clinical and economic outcomes and cost-effectiveness of urine-based TB screening among unselected hospitalized people with HIV in Malawi and South Africa, in conjunction with the STAMP trial

Methods

- We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-International microsimulation model (http://www.massgeneral.org/mpec/cepac) to project clinical and economic outcomes of 2 TB screening strategies among hospitalized PWH, regardless of suspicion or symptoms, in Malawi and South Africa:
  (1) Standard of Care (SOC): sputum Xpert MTB/RIF (Xpert)
  (2) Intervention: sputum Xpert, urine Determine TB-LAM (LAM), and concentrated urine Xpert
- The modeled cohort reflected STAMP trial participants (Table 1), and individuals were tracked monthly from TB screening to death.
- We applied resource utilization data from STAMP and derived costs from published sources.
- We calibrated model mortality results to STAMP results at 2 months, and then projected outcomes over longer time horizons.
- In sensitivity analysis, we varied key parameters including TB prevalence, sputum provision rate, and empiric TB treatment rate.
- We evaluated 2 alternative scenarios: a) limiting testing to those with CD4<100/µL (a prespecified subgroup analysis in STAMP); b) a modified intervention consisting of sputum Xpert and urine LAM only (no urine Xpert).
- We considered the Intervention cost-effective if its incremental cost-effectiveness ratio (ICER), measured in USD/year of life saved (YLS) was less than that of 2nd-line antiretroviral therapy (ART): $750/YLS in Malawi and $940/YLS in South Africa.

Table 1. Model input parameters: cohort characteristics, resource utilization, and diagnostic test performance.

	Malawi	South Africa	Source
Cohort			STAMP trial
Age, years, mean (SD)	40 (12)	39 (12)	
Men/women, %	37/63	50/50	
CD4 count at admission, cells/µL, median (IQR)	219 (86-431)	236 (70-445)	
Patients on ART at time of hospital admission, %	78	64	
Prevalence of active TB, % [range][1]	23.5 [5-50]	28.5 [5-50]	
Patients able to provide sputum, % [range]	39 [20-100]	75 [20-100]	
Probability of empiric treatment, % [range][2]	4 [0-45]	10 [0-45]	
Resource Utilization			
Median length of hospitalization, days	6	6	STAMP trial
Hospital bed cost per day, USD	$1	$56	World Health Organization WHO-CHOICE 2008
Mean additional hospital resource utilization cost per admission, USD	$23	$98	STAMP trial, NHLS pricelist, Maheswaran personal communication, Int. Medical Products Guide 2015
Treatment			
DS-TB treatment costs, monthly (6-month duration), USD	$7	$7	Pooran et al., *PLoS Med* 2013
1st-line ART costs (TDF/3TC/EFV), monthly, USD	$11	$11	Clinton Health Access Initiative Pricelist 2016
TB Diagnostics			
Cost per test, USD			
Sputum Xpert	$25	$15	NHLS pricelist, Maheswaran personal communication
Urine LAM [range]	$3 [$1-$10]	$3 [$1-$10]	Sun et al., *Int J Tuberc Lung Dis* 2013
Urine Xpert (concentrated)	$26	$15	NHLS pricelist, Maheswaran personal communication
	Sensitivity	**Specificity**	
Sputum Xpert, CD4<100/µL / ≥100/µl [range]	40%/43% [±20%/±20%]	95%/93%	Theron et al., *Am J Respir Crit Care Med* 2011
Urine LAM, CD4<100/µL / ≥100/µL [range]	53%/42% [±20%/±20%]	95%/93%	Lawn et al., *BMC Med* 2017
Urine Xpert, CD4<100/µL / ≥100/µL [range]	31%/13% [±20%/±20%]	98%/93%	Peter et al., *PLoS One* 2011

SD: Standard deviation. IQR: interquartile range. ART: antiretroviral therapy. TB: tuberculosis. DS: drug-susceptible. TDF: tenofovir. 3TC: lamivudine. EFV: efavirenz. LAM: lipoarabinomannan. NHLS: National Health Laboratory Service (South Africa). Range: values assessed in sensitivity analysis.
All costs were converted to 2017 USD. Costs of diagnostic tests includes personnel time.
[1]TB prevalence was estimated as 1.25 times the number of microbiologically confirmed cases in each site plus the number of clinically diagnosed cases (i.e., diagnoses without microbiologic confirmation), divided by the study population size.
[2]Those who were diagnosed clinically without microbiologic confirmation were empirically treated starting in the first month of the simulation.

Results

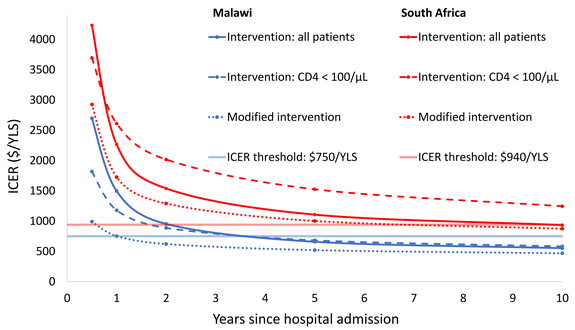
Table 2. Clinical and economic outcomes and cost-effectiveness of strategies to screen for tuberculosis among hospitalized people with HIV in Malawi and South Africa. Cost-effectiveness threshold was $750/YLS in Malawi and $940/YLS in South Africa.

Strategy	Mortality 2m	Mortality 2y	Mortality 5y	Lifetime outcomes: Life-years (undisc.)	Life-years*	Cost (USD)*	ICER ($/YLS)*
(A) All patients							
Malawi							
SOC	24%	39%	49%	12.9	8.6	$3,580	-
Intervention	21%	35%	46%	13.7	9.1	$3,830	470
South Africa							
SOC	18%	35%	45%	13.4	9.1	$8,350	-
Intervention	16%	31%	42%	14.2	9.6	$8,750	780
(B) Patients with CD4<100/µL							
Malawi							
SOC	41%	64%	74%	6.6	4.5	$2,200	-
Intervention	34%	58%	70%	7.6	5.2	$2,530	490
South Africa							
SOC	32%	58%	70%	7.7	5.3	$6,830	-
Intervention	24%	51%	65%	8.9	6.1	$7,610	950
(C) Modified intervention: sputum Xpert + urine LAM (all patients)							
Malawi							
SOC	24%	39%	49%	12.9	8.6	$3,580	-
Mod. Interv.	22%	36%	46%	13.5	9.0	$3,750	420
South Africa							
SOC	18%	35%	45%	13.4	9.1	$8,350	-
Mod. Interv.	16%	32%	42%	14.0	9.5	$8,650	760

ICER: incremental cost-effectiveness ratio. YLS: years of life saved. SOC: standard of care.
Mod. Interv.: modified intervention. *Outcomes discounted 3% per year.

- **The Intervention increased life expectancy by ~0.8y and <u>was cost-effective in Malawi and South Africa</u>.**
- **ICER changed by <10% in one-way parameter sensitivity analyses (data not shown).**
- **In those with CD4<100/µL, the Intervention increased life expectancy by ~1.0-1.2y. It remained cost-effective in Malawi but was marginally above the cost-effectiveness threshold in South Africa, due to greater incidence and costs of other diseases in those with very low CD4 count.**
- **The modified intervention (only urine LAM + sputum Xpert) increased life expectancy by ~0.6y. <u>It was even more cost-effective than the trial Intervention</u> in both Malawi and South Africa.**

Figure 1. Incremental cost-effectiveness ratios of urine-based tuberculosis screening strategies among hospitalized people with HIV in Malawi and South Africa, varying the time horizon.



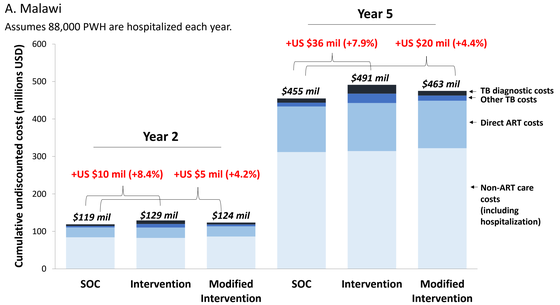
ICER: incremental cost-effectiveness ratio. YLS: years of life saved.

- **The Intervention became more cost-effective compared to Standard of Care over time.**
- **The trial Intervention became cost-effective in Malawi by 5 years and in South Africa by 10 years**
- **The modified intervention was even more cost-effective than the trial Intervention at all time horizons.**

Figure 2. Two-year and five-year budget impact of implementing urine-based tuberculosis screening countrywide among hospitalized people with HIV in Malawi and South Africa.

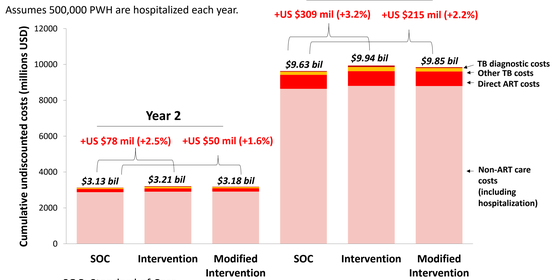
A. Malawi

Assumes 88,000 PWH are hospitalized each year.



B. South Africa

Assumes 500,000 PWH are hospitalized each year.



SOC: Standard of Care.

- **Countrywide implementation of the Intervention over 5 years: <u>Malawi</u>: healthcare expenditures for screened individuals would increase by $36 million (7.9%). <u>South Africa</u>: healthcare expenditures would increase by $309 million (3.2%).**
- **Much of the increase in healthcare expenditures would be due to people living longer (with greater long-term care costs).**
- **The modified intervention would require less of an increase in healthcare expenditures.**

Limitations

- Our study is subject to limitations inherent in any model-based analysis, including uncertainties in model structure and input parameters, though the structure and most key parameters reflected the STAMP trial.
- The STAMP trial found an overall small reduction (larger for those with CD4<100/µL) in 2-month mortality from the Intervention. Even so, there may still be longer-term benefits resulting from increased diagnoses of TB.
- The true prevalence of active TB may differ from that which we estimated, but sensitivity analysis demonstrated that the Intervention remained cost-effective across a wide range of possible TB prevalences (5-50%).

Conclusions

- Urine-based TB screening in hospitalized PWH can reduce mortality while demonstrating excellent value in resource-limited settings, including both low-income and middle-income countries.
- Adding urine LAM alone to current TB screening strategies is particularly attractive, given its relatively high diagnostic yield in hospitalized PWH, low cost, and relative ease of implementation.
- Our findings suggest that recommendations for urine-based TB screening, especially with LAM, should be expanded to all hospitalized PWH in high HIV-burden TB-endemic regions (World Health Organization 2015, http://www.who.int/tb/publications/use-of-lf-lam-tb-hiv/en).