Screening for Tuberculosis With Xpert MTB/RIF Assay Versus Fluorescent Microscopy Among Adults Newly Diagnosed With Human Immunodeficiency Virus in Rural Malawi: A Cluster Randomized Trial (Chepetsa)

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Background. Tuberculosis (TB) remains the leading cause of death among human immunodeficiency virus (HIV)-infected individuals globally. Screening for TB at the point of HIV diagnosis with a high-sensitivity assay presents an opportunity to reduce mortality.

Methods. We performed a cluster randomized trial of TB screening among adults newly diagnosed with HIV in 12 primary health clinics in rural Thyolo, Malawi. Clinics were allocated in a 1:1 ratio to perform either point-of-care Xpert MTB/RIF assay (Xpert) or point-of-care light-emitting diode fluorescence microscopy (LED-FM) for individuals screening positive for TB symptoms. Asymptomatic participants were offered isoniazid preventive therapy in both arms. Investigators, but not clinic staff or participants, were masked to allocation. Our primary outcome was the incidence rate ratio (RR) of all-cause mortality within 12 months of HIV diagnosis.

Results. Prevalent TB was diagnosed in 24 of 1001 (2.4%) individuals enrolled in clinics randomized to Xpert, compared with 10 of 841 (1.2%) in clinics randomized to LED-FM. All-cause mortality was 22% lower in the Xpert arm than in the LED-FM arm (6.7 vs 8.6 per 100 person-years; RR, 0.78 [95% confidence interval {CI}, .58–1.06]). A planned subgroup analysis suggested that participants with more advanced HIV (World Health Organization clinical stage 3 or 4) disease had lower mortality in clinics randomized to Xpert than to LED-FM (RR, 0.43 [95% CI, .22–.87]).

Conclusions. In rural Malawi, using point-of-care Xpert MTB/RIF to test symptomatic patients for TB at the time of HIV diagnosis reduced all-cause 12-month mortality among individuals with advanced HIV.

Clinical Trials Registration. NCT01450085.

Keywords. tuberculosis; HIV; diagnosis; randomized controlled trial; Malawi.

Tuberculosis (TB) is the leading single-agent infectious cause of mortality and the leading cause of human immunodeficiency virus (HIV)-associated mortality worldwide [1]. Xpert MTB/RIF (hereafter “Xpert”; Cepheid, Inc, Sunnyvale, California) is a molecular assay [2, 3] first recommended for TB diagnosis among HIV-infected individuals in 2010 [4]. Subsequent trials have compared Xpert, performed in central laboratories, against sputum smear microscopy among symptomatic patients [5–9].

Although Xpert significantly improved same-day diagnosis in South Africa [5] and shortened time to treatment in Brazil [7], a benefit on all-cause mortality has not been conclusively demonstrated.

In most previous trials, the potential role of Xpert for active screening among HIV-infected individuals was not investigated. One-year mortality remains $\geq 8\%$ for individuals starting antiretroviral therapy (ART) in sub-Saharan Africa [10–12], and TB is the leading cause of death [13, 14]. A small randomized trial in Zimbabwe showed a nonsignificant reduction in 3-month mortality (6% vs 10%) with Xpert vs sputum smear using light-emitting diode fluorescence microscopy (LED-FM) [15]. We performed a cluster randomized trial of point-of-care (POC) screening for active TB among adults newly diagnosed with HIV in rural Malawi. Our primary hypothesis was that 1-year all-cause mortality would be lower in clinics (clusters) provided with POC Xpert vs POC LED-FM.

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METHODS

Study Population

The Chepetza trial was a cluster randomized trial of POC TB screening in 12 primary health centers in rural Thyolo District, Malawi. Cluster randomization was used to minimize risks of contamination with this clinic-level intervention. Inclusion criteria for clinics included primary health center status, provision of HIV testing and ART, and sufficient patient volume. After receiving consent from clinic representatives and the Ministry of Health, eligible clinics were randomized (6 clinics per arm) to TB screening using Xpert MTB/RIF on a single expectorated sputum specimen vs LED-FM on 2 spot expectorated sputum specimens. All adults (≥ 18 years old) receiving a new diagnosis of HIV were screened for eligibility; allocation was based on clinic attended. Exclusion criteria were (1) existing diagnosis of TB; (2) currently taking isoniazid preventive therapy (IPT); (3) currently taking treatment for active TB or HIV (ie, ART); (4) unable to speak English or Chichewa; (5) not living in an area where follow-up would be feasible; and (6) refusal of written informed consent. Eligible participants were asked about 4 TB symptoms: cough of any duration, fever, night sweats, and severe weight loss; those reporting any symptom were tested for TB using Xpert or LED-FM, according to cluster. The trial is registered on ClinicalTrials.gov (NCT01450085).

Procedures

Symptom screening and sputum evaluation were performed on-site by trained study personnel, and results were provided to participants on the same day. Participants testing positive for active TB were referred for treatment; those without TB symptoms were provided IPT (isoniazid 300 mg daily plus pyridoxine 25 mg daily). Participants with TB symptoms but negative Xpert or LED-FM results were asked to return in 1 month and provided IPT at that time if asymptomatic. IPT was given for 6 months in accordance with World Health Organization (WHO) guidelines and was dispensed by study staff at initiation and after 1 and 3 months of treatment.

In accordance with contemporary Malawian guidelines, all participants were seen by a (nonstudy) nurse or clinical officer for clinical staging; those with WHO stage 3 or 4 disease (including any participants diagnosed with TB) were started immediately on ART. Participants with WHO stage 1 or 2 disease had CD4⁺ T-cell testing; those meeting CD4 count criteria (≤ 350 cells/ μ L until July 2014, then ≤ 500 cells/ μ L thereafter) were started on ART, at a subsequent visit. Participants not given ART had repeat CD4⁺ testing every 6 months. All CD4⁺ testing and HIV care were provided by nonstudy clinicians under routine conditions.

Outcomes and Ascertainment

Our primary outcome was all-cause mortality within 12 months following HIV diagnosis. Secondary outcomes included TB

treatment outcomes, TB incidence, and mortality in subgroups of age (≤ 35 vs > 35 years old), sex, clinical stage (stage 1/2 vs 3/4), and ART eligibility/CD4 count. The ART threshold change to ≤ 500 cells/ μ L required us to alter a prespecified subgroup analysis according to ART eligibility to one according to CD4⁺ T-cell count above or below 350 cells/ μ L.

All outcomes were assessed at the cluster level. All participants were asked to return to study clinics for assessment every 3 months (with 1 extra visit when on IPT); those who did not attend scheduled appointments were traced at their homes and through routine HIV clinic records. At each study visit, participants were screened for any TB symptom and tested using Xpert or LED-FM if symptomatic. Point-of-care Xpert and LED-FM were not available for routine TB diagnosis. Study staff underwent quarterly quality assessments of smear and Xpert procedures, with retraining as necessary.

All patients with positive Xpert or LED-FM results had sputum taken for confirmatory microscopy and culture (Mycobacteria Growth Indicator Tube, MGIT, BD Diagnostics, Sparks, Maryland), performed at a central laboratory, and were referred for treatment through the routine healthcare system. Diagnoses of TB made outside of the study were reviewed by a study clinician (E. L. C.). TB was defined as any diagnosis of microbiologically confirmed active TB or initiation of active TB treatment, occurring at the time of the enrollment visit (prevalent) or afterward (incident).

Study Sites, Randomization, and Power

Twelve study sites were initially selected based on volume of HIV diagnoses, presence of an ART delivery program, and geographic location. Most clinics did not have stable electricity; in the Xpert arm, solar panels and uninterrupted power supply were therefore installed to support Xpert testing before recruitment began.

Randomization was constrained to provide balance on 5 variables: annual volume of HIV diagnoses, proportion of newly HIV-infected individuals who were pregnant, presence of ART initiation (vs delivery only), prerandomization mortality among ART initiators, and study wave/geography (2 clinics in each arm per wave, with waves selected prior to randomization based on geography). Randomization was performed by the study statistician (L. H. M.), who identified all possible randomizations that would achieve the prespecified balance criteria [16]. In a public ceremony, a Ministry of Health official randomly selected 1 of the 50 possible (concealed) schemes, with allocation of Xpert vs LED-FM determined by coin flip. Allocation was based on clinic/cluster; neither clinics nor participants were blinded to allocation, but investigators and central laboratory staff remained blinded to allocation until final unmasking.

Recruitment was conducted in 3 waves of 4 clinics each. Enrollment began on 30 August 2012, and ended on 8 December 2015; follow-up concluded on 20 December 2016.

Each wave consisted of 1 year of recruitment followed by 1 year of follow-up; follow-up for each wave overlapped with recruitment for the subsequent wave. The trial ended when the final wave of clinics completed the follow-up year. After randomization but before the start of recruitment, 1 study clinic stopped providing HIV care services and was replaced with the clinic that had the next-highest number of HIV diagnoses made in the previous year.

The study was powered based on anticipated enrollment of 1800 participants per arm, with an estimated 80% power (type I error of 5%) to detect a halving of mortality (4% vs 8%) in the Xpert vs LED-FM arms, accounting for variability in clinic sizes (anticipated 200–700 participants) and a coefficient of variation of 0.25 (a common default value) [17].

Actual enrollment was about half of anticipated enrollment, due primarily to lower numbers of individuals being diagnosed with HIV during the study period than in the preceding years. This was a national phenomenon, reflecting the successful scale-up of ART and a corresponding reduction in HIV incidence.

Statistical Analysis

In each clinic, we calculated the mortality rate (number of deaths divided by total person-time). Contributed person-time was considered to end at the earliest of death, last documented contact, refusal to participate, or at 12 months (for those with documented contact at or after 12 months). In the primary analysis, we calculated the log mortality rate for each clinic, then took the difference of the means for each study arm and exponentiated to obtain the rate ratio, comparing Xpert to LED-FM clinics. Secondary analyses included Poisson regression with multivariable adjustment [18] and planned subgroup analyses according to age, sex, and WHO clinical stage (all factors associated with increased risk of prevalent TB and/or lower probability of subsequent follow-up). All subgroup analyses were adjusted for these other covariates. Statistical significance was assessed by Student *t* test of the log rates at the clinic level and defined as a 2-tailed *P* value <.05. Analyses were performed by the blinded study statistician (L. H. M.).

Ethical Considerations

This trial was approved by the institutional review boards of Johns Hopkins Medicine, the London School of Hygiene and Tropical Medicine, and the Malawi College of Medicine.

RESULTS

Of 3040 individuals assessed for eligibility, 1842 were enrolled: 1001 in 6 clinics randomized to Xpert, and 841 in 6 clinics randomized to LED-FM (Figure 1). Primary reasons for exclusion were residence outside a traceable area (*n* = 583) and age <18 years (*n* = 254). Participants in clinics randomized to Xpert vs LED-FM were similar on most baseline characteristics,

except that more participants in the LED-FM arm reported either “poor” or “excellent” general health (Table 1). In the Xpert arm, 24 participants (2.4%) were diagnosed with prevalent TB at enrollment (21 Xpert-positive, 18 culture confirmed, 15 Xpert-positive and diagnosed within 1 week of enrollment; Figure 2), compared with 10 (1.2%) in the LED-FM arm (10 smear-positive, 9 culture confirmed, 10 smear-positive and diagnosed within 1 week) (*P* = .06).

Participants in the Xpert arm contributed 823 person-years of follow-up vs 697 in the LED-FM arm (mean 0.82 vs 0.83 years per participant). Losses to follow-up before 350 days post-enrollment totaled 220 of 1001 (22%) in Xpert clinics and 187 of 841 (22%) in LED-FM clinics. Losses were similar (within 3%) across arms among patients with WHO stage 3 or 4 disease, men, and patients ≤35 years old. During follow-up, 744 (74%) patients initiated ART in the Xpert arm compared with 609 (72%) in the LED-FM arm.

As shown in Table 2, the cluster-adjusted rate of all-cause mortality was 22% lower in the Xpert arm (55 deaths, 6.7 per 100 person-years) than in the LED-FM arm (58 deaths, 8.6 per 100 person-years; rate ratio [RR], 0.78 [95% confidence interval {CI}, .58–1.06]); this difference was not statistically significant (*P* = .10). Twelve of the 113 (11%) deaths occurred after a diagnosis of TB (5 in Xpert clinics, 7 in LED-FM clinics). Adjustment for age, sex, pregnancy status, and clinical stage had little effect on this primary result (adjusted RR, 0.67 [95% CI, .44–1.01], *P* = .06), as did exclusion of the clinic not originally part of the randomization (RR, 0.77 [95% CI, .55–1.10], *P* = .13). Very little heterogeneity was observed across clinics: The coefficient of variation for the primary analysis was <0.01.

Subgroup analysis suggested that all-cause mortality was lower in clinics randomized to Xpert than in those randomized to LED-FM among participants with more severe (WHO clinical stage 3 or 4) disease (RR, 0.43 [95% CI, .22–.87]). There was little mortality difference among participants with less severe (stage 1 or 2) HIV (RR, 1.08 [95% CI, .53–2.23], *P* value for interaction = .24; Figure 3). Most deaths occurred in participants with stage 3/4 disease, between 1 and 6 months after enrollment (Figure 4). Mortality was lower in clinics randomized to Xpert than in LED-FM clinics among patients ≤35 years old (RR, 0.40 [95% CI, .23–.69]) but not those >35 years old (RR, 0.93 [95% CI, .43–2.02], *P* value for interaction = .08). Mortality was also lower in the Xpert arm than in the LED-FM arm among men (RR, 0.58 [95% CI, .40–.85]); this difference was not statistically significant among women (RR, 0.72 [95% CI, .32–1.63], *P* value for interaction = .79).

Excluding prevalent TB diagnosed at enrollment, the cluster-adjusted incidence of TB in the Xpert arm (8 cases, 1.1 per 100 person-years) was lower than in the LED-FM arm (12 cases, 2.5 per 100 person-years) (RR, 0.45 [95% CI, .17–1.20]), though this difference was not statistically significant (*P* = .09). Of 54 total TB diagnoses, 15 (11 in the Xpert arm and 4 in the

Figure 1. Study population. *One clinic stopped offering human immunodeficiency virus services prior to enrolling any participants and was replaced by the next-largest clinic. Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IPT, isoniazid preventive therapy; LED, light-emitting diode; TB, tuberculosis.

LED-FM arm) were made through routine care outside of the study; 9 of these routine diagnoses (8 in the Xpert arm and 1 in the LED-FM arm) lacked microbiological confirmation. There were no confirmed cases of rifampin-resistant or multidrug-resistant TB. All patients diagnosed with TB by Xpert or LED-FM were referred for treatment within 1 week, and all patients diagnosed with TB, except 1 in the LED-FM arm, successfully initiated treatment.

DISCUSSION

In this cluster randomized trial across 12 primary healthcare clinics in rural Malawi, screening for TB symptoms at the time of HIV diagnosis followed by POC Xpert (vs POC LED-FM) did not significantly reduce all-cause mortality over 12 months. However, screening with Xpert doubled the proportion of people diagnosed with prevalent TB and reduced all-cause mortality by 57% among individuals presenting with stage 3/4 disease, 42% among men, and 60% among those aged ≤ 35 years.

To our knowledge, this is the first randomized trial of Xpert to show a meaningful reduction in all-cause mortality in readily identifiable subgroups. We also observed an increase in TB diagnoses at baseline of approximately similar magnitude,

consistent with the hypothesis that Xpert is detecting individuals with active TB who are otherwise at high risk of death in the early ART period [19–22]. In the LED-FM arm, some individuals with prevalent TB at baseline were likely diagnosed later in the study period, when death was already imminent. Along with a trial of urine lipoarabinomannan screening among hospitalized adults with TB symptoms [23], this is one of the first studies to demonstrate a mortality benefit to systematic screening for TB [24]. By contrast, most other studies of systematic screening have focused on relatively healthy populations, such as household contacts [25] or residents of congregate settings such as mines [26] or prisons [27], and have not been powered to detect differences in mortality at the population level. Both of these trials suggest that TB screening may have greatest benefit for high-risk populations, including hospitalized patients and individuals with advanced HIV and poor access to healthcare.

Our observed mortality benefit differs from the findings of previous diagnostic trials, which include randomized trials of Xpert vs sputum smear microscopy [5–9] and of risk stratification and empirical TB treatment in patients with advanced HIV [28]. This apparent discrepancy may reflect important differences in study design. First, we recruited patients with newly

Table 1. Participant Characteristics at Enrollment

Characteristic	Xpert Arm (n = 1001)	LED-FM Arm (n = 841)
Age, y, median (IQR)	33 (27–40)	32 (26–40)
Sex		
Male	410 (41)	309 (37)
Female (nonpregnant)	434 (43)	369 (44)
Female (pregnant)	157 (16)	163 (19)
WHO clinical stage ^a		
1/2	707 (71)	656 (79)
3/4	290 (29)	173 (21)
Self-reported general health		
Excellent	81 (8)	108 (13)
Good	495 (49)	369 (44)
Fair	378 (38)	261 (31)
Poor	47 (5)	103 (12)
Smoking status		
Current	125 (12)	104 (12)
Former	70 (7)	50 (6)
Never	806 (81)	687 (82)
Previous treatment for TB		
Yes	24 (2)	15 (2)
No	977 (98)	826 (98)
Self-reported symptoms of TB		
Cough	217 (22)	193 (23)
Fever	137 (14)	122 (15)
Weight loss	157 (16)	110 (13)
Night sweats	249 (25)	163 (19)
Any symptom	307 (31)	258 (31)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: IQR, interquartile range; LED-FM, light-emitting diode fluorescence microscopy; TB, tuberculosis; WHO, World Health Organization; Xpert, Xpert MTB/RIF assay.

^aClinical stage was not recorded in 4 participants in the Xpert arm and 12 in the LED-FM arm; 2 of the 12 in the LED-FM arm subsequently died.

diagnosed HIV rather than patients with TB symptoms attending general diagnostic services. Second, we deliberately investigated rural clinics, anticipating higher barriers to accessing services such as radiology and empirical TB treatment. These services may mitigate the impact of Xpert by facilitating timely treatment of individuals testing false-negative for TB [29]. Indeed, in contrast to prior studies, we observed more clinical diagnoses in the Xpert arm than in the LED-FM arm, suggesting that the increased sensitivity of Xpert was not offset by fewer clinical diagnoses in this setting. Third, most prior studies performed Xpert at central laboratories, whereas we performed Xpert and LED-FM directly in the clinic, aiming to provide results and initiate TB therapy (when indicated) on the same day.

An important consideration is the substantial investment required to establish and maintain POC TB screening services. In rural Malawi, introducing Xpert required developing infrastructure for solar electrical supply, positioning and continuous training of on-site personnel, and provision and maintenance of equipment and diagnostic supplies. Decisions about scale-up of Xpert-based screening must therefore balance the potential mortality benefit against these substantial implementation challenges. Importantly, Xpert can be performed to high standards

by nurses in primary care clinics [5, 8], and a more portable, robust, battery-operated Xpert platform (GeneXpert Omni) may soon be available [30], as may similar products from alternative manufacturers. In the interim, decentralized HIV care clinics could aim to develop and strengthen specimen referral systems [31] to provide rapid screening for TB (eg, concomitant with CD4 testing) among people newly diagnosed with HIV in settings where on-site Xpert is not available.

The results of this study should be interpreted in light of certain limitations. First, we were unable to reliably ascertain causes of death, and so cannot be certain that observed mortality differences between arms reflect differences in TB mortality. Second, due to a lower number of new HIV diagnoses than anticipated, we were only able to enroll approximately half of our target sample size, affecting study power. Third, participants were recruited after randomization of clusters, leading to potential identification bias, though our inclusion of all adults receiving new HIV diagnoses using few exclusion criteria may mitigate this concern. Fourth, while designed to be a pragmatic trial with minimal disturbance of routine clinical management (other than the intervention itself), implementation of POC screening for TB required substantial support and changes to the existing infrastructure, as described above. Our results may

Figure 2. Patient flow. Shown are the numbers of patients in each arm who were successfully tested, tested positive, and started on treatment (either treatment for active tuberculosis or isoniazid preventive therapy). Of the 180 patients receiving valid light-emitting diode fluorescence microscopy results within a week, 174 (97%) had 2 smears performed, whereas 6 (3%) had only 1 smear performed. Numbers in the boxes at the bottom represent the total number of patients tested (and testing positive), including the initial baseline assessment and the 1-year follow-up period. Abbreviations: LED-FM, light-emitting diode fluorescence microscopy; TB, tuberculosis.

therefore not fully generalize to settings in which such investments are not possible. Finally, our level of follow-up (mean 8.2 months of follow-up out of a desired 12) was lower than anticipated. While we did not see any evidence of differential

losses to follow-up between our study arms, these results should nonetheless be interpreted in light of this incomplete follow-up.

In summary, this cluster randomized trial of POC screening for tuberculosis among rural Malawian adults recently

Table 2. All-cause Mortality by Clinic

Study Wave ^a	Clinic ID	Deaths Observed	PYFU	Mortality Rate (per 100 PY)	Summary Mortality Rate ^b (95% CI)
Xpert arm					
1	1A	17	270	6.23	
1	1B	12	154	7.78	
2	2A	8	130	6.17	
2	2D	9	132	6.84	
3	3B	2	30	6.60	
3	3D	7	102	6.86	
Total		55	818		6.74 (6.18–7.35)
LED-FM arm					
1	1C	11	143	7.69	
1	1D	20	192	10.42	
2	2B	8	161	4.97	
2	2C	6	68	8.79	
3	3A	6	67	8.91	
4	3C	7	54	13.08	
Total		58	685		8.61 (6.13–12.11)

Abbreviations: CI, confidence interval; ID, identifier; LED-FM, light-emitting diode fluorescence microscopy; PY, person-years; PYFU, person-years of follow-up; Xpert, Xpert MTB/RIF assay.

^aThe study was conducted in 3 consecutive waves, each consisting of 1 year of enrollment followed by 1 year of follow-up. See Methods for further details.

^bSummary mortality rate in each arm, per 100 PY, accounting for within-clinic correlation.

Figure 3. All-cause mortality in clinics randomized to Xpert vs light-emitting diode fluorescence microscopy (LED-FM). Shown on the x-axis is the rate ratio for all-cause mortality in clinics randomized to Xpert vs LED-FM for tuberculosis screening among adults recently diagnosed with human immunodeficiency virus in rural Malawi. Diamonds denote point estimates, horizontal lines denote 95% confidence intervals, and the vertical line represents no effect (rate ratio, 1.0). The outcome in the entire population after adjustment for covariates ("Overall") is shown at the bottom, with subgroup analyses and corresponding *P* values for interaction shown above. Note that the primary study outcome, adjusted only for clinic (cluster), is not shown in this graph; rather, the covariate-adjusted overall outcome is shown for comparability to the prespecified subgroup analyses, which were adjusted for both clinic and other covariates. Abbreviations: CI, confidence interval; LED-FM, light-emitting diode fluorescence microscopy; PY, person-years; WHO, World Health Organization.

diagnosed with HIV showed no significant difference in 12-month all-cause mortality, comparing screening with Xpert to LED-FM. However, all-cause mortality was 22% lower in the Xpert arm, with particularly large reductions in mortality among younger individuals, men, and those with more

advanced disease. These findings suggest that, in settings with poor existing health infrastructure, screening for TB with a high-sensitivity test at the point of HIV diagnosis may save lives among those with highest risk of mortality and/or loss to clinical follow-up. Decisions about scale-up of this intervention

Figure 4. Kaplan-Meier survival estimates, by study arm and clinical stage. The y-axis shows survival according to study arm (Xpert vs light-emitting diode fluorescence microscopy [LED-FM]) and clinical stage (stage 1/2 [less severe] vs stage 3/4 [more severe]). The upper 2 (dashed) lines correspond to participants with stage 1/2 disease in the Xpert (black) and LED-FM (grey) arms. The lower lines correspond to participants with stage 3/4 disease in the Xpert and LED-FM arms. Time is given in days. The majority of deaths occurred in those participants with stage 3/4 disease, for whom diagnosis at a clinic randomized to Xpert was associated with lower all-cause mortality. Abbreviation: LED-FM, light-emitting diode fluorescence microscopy.

should balance challenges in implementation and the lack of an observed benefit in the population as a whole against the need to prevent deaths among the highest-risk patients.

Notes

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