

# Screening for tuberculosis with Xpert MTB/RIF versus fluorescent microscopy among adults newly diagnosed with HIV in rural Malawi: a cluster randomized trial (CHEPETSa)

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Summary: In this randomized trial of screening for tuberculosis among adults in rural Malawi with newly-diagnosed HIV, all-cause mortality was 22% lower overall, and 57% lower among participants with clinically advanced HIV, when using point-of-care Xpert MTB/RIF versus point-of-care fluorescence microscopy.

## **ABSTRACT**

**Background:** Tuberculosis (TB) remains the leading cause of death among HIV-positive 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 (clinicaltrials.gov NCT01450085). Clinics were allocated in a 1:1 ratio to perform either point-of-care Xpert MTB/RIF (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 (2.4%) of 1001 individuals enrolled in clinics randomized to Xpert, versus 10 (1.2%) of 841 in clinics randomized to LED FM. All-cause mortality was 22% lower in the Xpert arm than in the LED FM arm (6.7 versus 8.6 per 100 person-years, RR 0.78; 95% confidence interval [CI]: 0.58-1.06). A planned subgroup analysis suggested that participants with more advanced HIV (World Health Organization clinical stage III or IV) disease had lower mortality in clinics randomized to Xpert than to LED FM (RR 0.43, 95%CI: 0.22-0.87).

Conclusion: 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.

## INTRODUCTION

Tuberculosis (TB) is the leading single-agent infectious cause of mortality and the leading cause of HIV-associated mortality worldwide.<sup>1</sup> Xpert MTB/RIF (Xpert, Cepheid, Inc., Sunnyvale, CA, USA) is a molecular assay<sup>2,3</sup> first recommended for TB diagnosis among HIV-positive individuals in 2010.<sup>4</sup> Subsequent trials have compared Xpert, performed in central laboratories, against sputum smear microscopy among symptomatic patients.<sup>5-9</sup> Although Xpert significantly improved same-day diagnosis in South Africa<sup>5</sup> and shortened time to treatment in Brazil,<sup>7</sup> 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-positive individuals was not investigated. One-year mortality remains  $\geq 8\%$  for individuals starting antiretroviral therapy (ART) in sub-Saharan Africa,<sup>10-12</sup> and TB is the leading cause of death.<sup>13,14</sup> A small randomized trial in Zimbabwe showed a non-significant reduction in three-month mortality (6% versus 10%) using Xpert versus sputum smear using light-emitting diode fluorescence microscopy (LED FM).<sup>15</sup> 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 one-year all-cause mortality would be lower in clinics (clusters) provided with POC Xpert versus POC LED FM.

## **METHODS**

### *Study Population*

The CHEPETSAs 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 (six clinics per arm) to TB screening using Xpert MTB/RIF on a single expectorated sputum specimen versus LED FM on two spot expectorated sputum specimens. All adults ( $\geq 18$  years old) receiving a new diagnosis of HIV were screened for eligibility; allocation was based on clinic attended. Exclusion criteria were: (a) existing diagnosis of TB; (b) currently taking isoniazid preventive therapy (IPT); (c) currently taking treatment for active TB or HIV (i.e., ART); (d) unable to speak English or Chichewa; (e) not living in an area where follow-up would be feasible; and (f) refusal of written informed consent. Eligible participants were asked about four 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](https://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 300mg daily plus pyridoxine 25mg daily). Participants with TB symptoms but negative Xpert or LED FM results were asked to return in one month and provided IPT at that time if asymptomatic. IPT was given for six months in accordance with World Health Organization (WHO) guidelines and was dispensed by study staff at initiation and after one and three months of treatment.

In accordance with contemporary Malawian guidelines, all participants were seen by a (non-study) nurse or clinical officer for clinical staging; those with WHO stage III or IV disease (including any participants diagnosed with TB) were started immediately on ART. Participants with WHO stage I or II disease had CD4<sup>+</sup>T-cell testing; those meeting CD4 count criteria ( $\leq 350$  cells/mm<sup>3</sup> until July 2014, then  $\leq 500$  cells/mm<sup>3</sup> thereafter) were started on ART, at a subsequent visit. Participants not given ART had repeat CD4<sup>+</sup> testing every six months. All CD4<sup>+</sup> testing and HIV care was provided by non-study 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 ( $\leq 35$  versus  $> 35$  years old), sex, clinical stage (stage I/II versus III/IV), and ART eligibility/CD4 count. The ART threshold change to  $\leq 500$  cells/mm<sup>3</sup> required us to alter a pre-specified subgroup analysis according to ART eligibility to one according to CD4<sup>+</sup> T-cell count above or below 350 cells/mm<sup>3</sup>.

All outcomes were assessed at the cluster level. All participants were asked to return to study clinics for assessment every three months (with one 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 re-training 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, MD, USA), 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 (ELC). 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 five variables: annual volume of HIV diagnoses, proportion of newly HIV-positive individuals who were pregnant, presence of ART initiation (versus delivery only), pre-randomization mortality among ART initiators, and study wave/geography (two clinics in each arm per wave, with waves selected prior to randomization based on geography). Randomization was performed by the study statistician (LHM) who identified all possible randomizations that would achieve the pre-specified balance criteria.<sup>16</sup> In a public ceremony, a Ministry of Health official randomly selected one of the 50 possible (concealed) schemes, with allocation of Xpert versus 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 three waves of four clinics each. Enrollment began on August 30, 2012, and ended on December 8, 2015; follow-up concluded on December 20, 2016. Each wave consisted of one year of recruitment followed by one 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, one 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% versus 8%) in the Xpert versus LED FM arms, accounting for variability in clinic sizes (anticipated 200 to 700 participants) and a coefficient of variation of 0.25 (a common default value).<sup>17</sup>

Actual enrollment was about half of anticipated enrolment, 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 antiretroviral therapy 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<sup>18</sup> 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's t-test of the log rates at the clinic level and defined as a two-tailed p-value <0.05. Analyses were performed by the blinded study statistician (LHM).

### *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 six clinics randomized to Xpert, and 841 in six clinics randomized to LED FM (Figure 1). Primary reasons for exclusion were residence outside a traceable area (n=583) and age <18 years old (n=254). Participants in clinics randomized to Xpert versus 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 one week of enrollment, Figure 2), compared to 10 (1.2%) in the LED FM arm (10 smear-positive, nine culture confirmed, 10 smear-positive and diagnosed within one week) (p=0.06).

Participants in the Xpert arm contributed 823 person-years of follow-up versus 697 in the LED FM arm (mean 0.82 versus 0.83 years per participant). Losses to follow-up before 350 days post-enrollment totaled 220 (22%) of 1001 in Xpert clinics and 187 (22%) of 841 in LED FM clinics. Losses were similar (within 3%) across arms among patients with WHO stage III or IV disease, men, and patients ≤35 years old. During follow-up, 744 (74%) patients initiated ART in the Xpert arm, versus 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]: 0.58–1.06); this difference was not statistically significant ( $p=0.10$ ). Twelve (11%) of the 113 deaths occurred after a diagnosis of TB (five in Xpert clinics, seven 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: 0.44–1.01,  $p=0.06$ ), as did exclusion of the clinic not originally part of the randomization (RR 0.77, 95%CI: 0.55–1.10,  $p=0.13$ ). 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 III or IV) disease (RR 0.43, 95%CI: 0.22–0.87). There was little mortality difference among participants with less severe (stage I or II) HIV (RR 1.08, 95%CI: 0.53–2.23,  $p$ -value for interaction = 0.24) (Figure 3). Most deaths occurred in participants with stage III/IV disease, between one and six months after enrollment (Figure 4). Mortality was lower in Xpert clinics randomized than in LED FM clinics among patients  $\leq 35$  years old (RR 0.40, 95%CI: 0.23–0.69) but not those  $>35$  years old (RR 0.93, 95%CI: 0.43–2.02,  $p$ -value for interaction = 0.08). Mortality was also lower in the Xpert arm than in the LED FM arm among men (RR 0.58, 95%CI: 0.40–0.85); this

difference was not statistically significant among women (RR 0.72, 95%CI: 0.32–1.63, p-value for interaction = 0.79).

Excluding prevalent TB diagnosed at enrolment, 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: 0.17–1.20), though this difference was not statistically significant ( $p=0.09$ ). Of 54 total TB diagnoses, 15 (11 in the Xpert arm and four in the LED FM arm) were made through routine care outside of the study; nine of these routine diagnoses (eight in the Xpert arm and one 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 one week, and all patients diagnosed with TB, except one in the LED FM arm, successfully initiated treatment.

## **DISCUSSION**

In this cluster randomized trial across 12 primary health care clinics in rural Malawi, screening for TB symptoms at the time of HIV diagnosis followed by point-of-care Xpert (versus point-of-care LED fluorescence microscopy) 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 III/IV disease, 42% among men, and 60% among those 35 years old or younger.

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.<sup>19-22</sup> 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 (LAM) screening among hospitalized adults with TB symptoms,<sup>23</sup> this is one of the first studies to demonstrate a mortality benefit to systematic screening for TB.<sup>24</sup> By contrast, most other studies of systematic screening have focused on relatively healthy populations such as household contacts<sup>27</sup> or residents of congregate settings such as mines<sup>28</sup> or prisons<sup>29</sup> 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 versus sputum smear microscopy<sup>5-9</sup> and of risk

stratification and empirical TB treatment in patients with advanced HIV.<sup>25</sup> This apparent discrepancy may reflect important differences in study design. First, we recruited patients with newly 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.<sup>26</sup> 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 point-of-care 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,<sup>5,8</sup> and a more portable, robust, battery-operated Xpert platform (GeneXpert Omni) will be available,<sup>30</sup> as may similar products from alternative manufacturers. In the



interim, decentralized HIV care clinics could aim to develop and strengthen specimen referral systems<sup>31</sup> to provide rapid screening for TB (for example, 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 point-of-care screening for TB required substantial support and changes to the existing infrastructure, as described above. Our results may 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 point-of-care screening for tuberculosis among rural Malawian adults recently diagnosed with HIV showed no significant difference in 12-month all-cause mortality, comparing screening with Xpert MTB/RIF to LED fluorescence microscopy. However, all-cause mortality was 22% lower in the Xpert arm and was reduced even further 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 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.

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## **Conflict of Interest**

None of the authors has any conflict of interest to declare.

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**Table 1. Participant Characteristics at Enrolment**

<b>Characteristic</b>	<b>Xpert Arm (n=1001)</b>	<b>LED Arm (n=841)</b>
Age (in years, median/interquartile range)	33 (27-40)	32 (26-40)
Gender		
Male	410 (41%)	309 (37%)
Female (non-pregnant)	434 (43%)	369 (44%)
Female (pregnant)	157 (16%)	163 (19%)
World Health Organization Clinical Stage <sup>a</sup>		
1 or 2	707 (71%)	656 (79%)
3 or 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 Tuberculosis

Yes	24 (2%)	15 (2%)
No	977 (98%)	826 (98%)

#### Self-Reported Symptoms of Tuberculosis

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%)

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<sup>a</sup> Clinical stage was not recorded in four participants in the Xpert arm and 12 in the LED FM arm; two of the 12 in the LED FM arm subsequently died.

**Table 2. All-Cause Mortality by Clinic**

Study Wave <sup>a</sup>	Clinic ID	Deaths Observed	Person-Years of Follow-Up	Mortality Rate (per 100 person-years)	Summary Mortality Rate <sup>b</sup> (95% confidence interval)
<i>Xpert MTB/RIF Arm</i>					
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	
<b>Total</b>		<b>55</b>	<b>818</b>		<b>6.74 (6.18-7.35)</b>
<i>LED FM Arm</i>					
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	
<b>Total</b>		<b>58</b>	<b>685</b>		<b>8.61 (6.13-12.11)</b>

LED FM, Light-emitting diode fluorescence microscopy

<sup>a</sup> The study was conducted in three consecutive waves, each consisting of one year of enrolment followed by one year of follow-up. See Methods for further details.

<sup>b</sup> Summary mortality rate in each arm, per 100 person-years, accounting for within-clinic correlation.

## FIGURE LEGENDS

### Figure 1. Study Population

\* One clinic stopped offering HIV services prior to enrolling any participants and was replaced by the next-largest clinic.

### 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 TB or isoniazid preventive therapy). Of the 180 patients receiving valid LED FM results within a week, 174 (97%) had two smears performed, whereas six (3%) had only one. Numbers in the boxes at the bottom represent the total number of patients tested (and testing positive), including the initial baseline assessment and the one-year follow-up period.

### Figure 3. All-cause mortality in clinics randomized to Xpert versus LED FM

Shown on the x-axis is the rate ratio for all-cause mortality in clinics randomized to Xpert versus light emitting diode fluorescence microscopy (LED FM) for TB screening among adults recently diagnosed with HIV 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 pre-specified subgroup analyses, which were adjusted for both clinic and other covariates.

#### **Figure 4. Kaplan-Meier survival estimates, by study arm and clinical stage**

The y-axis shows survival according to study arm (Xpert versus LED FM) and clinical stage (stage I/II [less severe] versus stage III/IV [more severe]). The upper two (dashed) lines correspond to participants with stage I/II disease in the Xpert (blue) and LED FM (red) arms. The lower lines correspond to participants with stage III/IV disease in the Xpert and LED FM arms. Time is given in days. The majority of deaths occurred in those participants with stage III/IV disease, for whom diagnosis at a clinic randomized to Xpert was associated with lower all-cause mortality.

Figure 1.

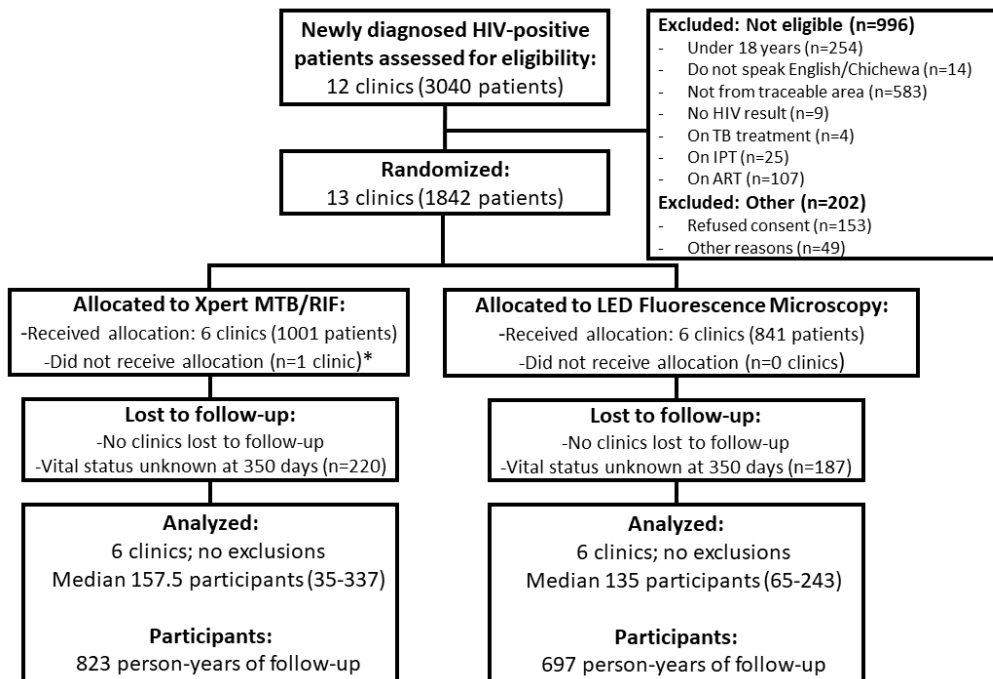


Figure 2.

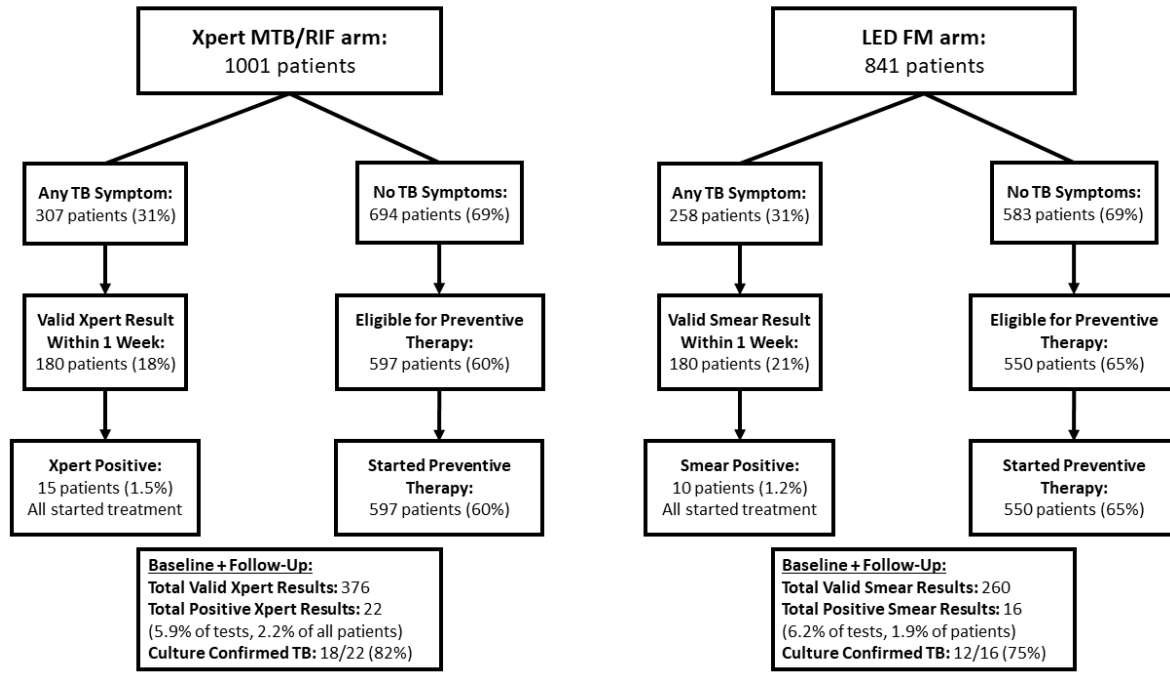


Figure 3.

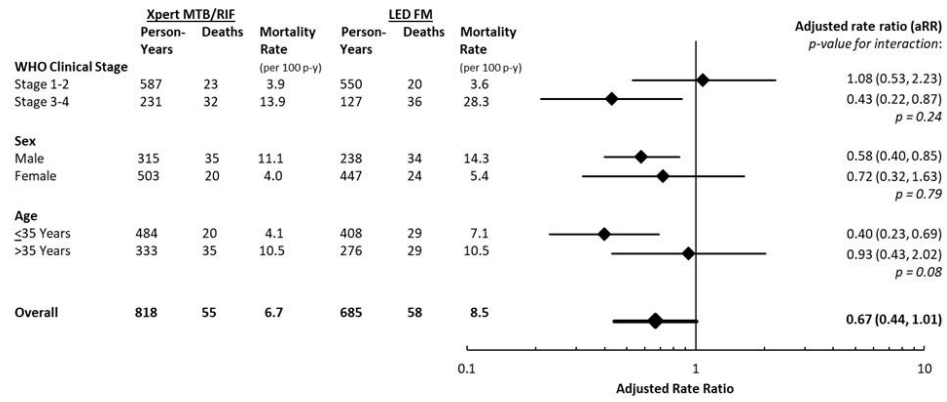
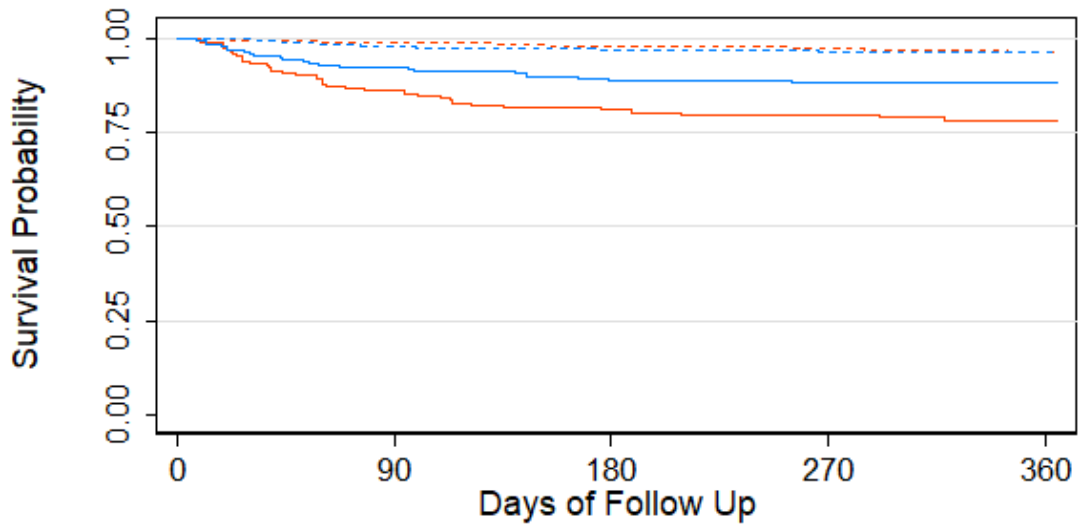




Figure 4.



Number at risk					
	0	90	180	270	360
LED FM, Stage 1-2	617	580	549	523	474
LED FM, Stage 3-4	167	139	121	115	111
Xpert, Stage 1-2	665	618	587	554	515
Xpert, Stage 3-4	275	246	226	217	202

