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Algorithm-guided empirical tuberculosis treatment for people with advanced HIV (TB Fast Track): an open-label, cluster-randomised trial



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Summary

Background Tuberculosis, which is often undiagnosed, is the major cause of death among HIV-positive people. We aimed to test whether the use of a clinical algorithm enabling the initiation of empirical tuberculosis treatment by nurses in primary health-care clinics would reduce mortality compared with standard of care for adults with advanced HIV disease.

Methods In this open-label cluster-randomised controlled trial, we recruited individuals from 24 primary health-care clinics in South Africa. The clinics were randomly assigned (1:1) to either deliver an intervention or routine care (control) using computer-generated random numbers. Eligible participants were HIV-positive adults (aged ≥ 18 years) with CD4 counts of 150 cells per μL or less, who had not had antiretroviral therapy (ART) in the past 6 months or tuberculosis treatment in the past 3 months, and did not require urgent hospital referral. In intervention clinics, study nurses assessed participants on the basis of tuberculosis symptoms, body-mass index, point-of-care haemoglobin concentrations, and urine lipoarabinomannan assay results. Participants classified by a study algorithm as having high probability of tuberculosis (positive urine lipoarabinomannan assay, body-mass index $< 18.5 \text{ kg/m}^2$, or haemoglobin concentration $< 100 \text{ g/L}$) were recommended to start tuberculosis treatment immediately followed by ART 2 weeks later; participants classified as medium probability (tuberculosis symptoms, no high probability criteria) were recommended to have symptom-guided investigation; and participants classified as low probability (no tuberculosis symptoms or high probability criteria) were recommended to start ART immediately. In standard-of-care clinics, participants received treatment in accordance with South African guidelines. Investigators and participants were aware of treatment allocation. The primary outcome was all-cause mortality at 6 months, assessed in the intention-to-treat population. Safety was also analysed in the intention-to-treat population. This trial is registered with the ISRCTN registry, ISRCTN35344604, and the South African National Clinical Trials Register, DOH-27-0812-3902.

Findings Between Dec 19, 2012, and Dec 18, 2014, 3091 individuals were screened for eligibility, of whom 3053 were recruited, and 3022 (1507 participants in the intervention group and 1515 participants in the control group) were analysed for the primary outcome. 930 (61.7%) of 1507 participants in the intervention group versus 172 (11.4%) of 1515 participants in the control group had started tuberculosis treatment by 2 months. At 6 months, the mortality rate was 19.0 deaths per 100 person-years for the intervention group versus 21.6 deaths per 100 person-years in the control group (unadjusted hazard ratio [HR] 0.92, 95% CI 0.67–1.26, $p=0.58$; adjusted HR 0.87, 0.61–1.24, $p=0.41$). 28 (1.9%) of 1507 participants in the intervention group and ten (0.7%) of 1515 participants in the control group reported serious or severe adverse events. Grade 3 or 4 nausea and vomiting was the most common adverse event (ten participants in the intervention group and four participants in the control group). Among participants with adverse events, eight participants (six participants in the intervention group and two participants in the control group) died; none of the six deaths in the intervention group were attributed to the study intervention.

Interpretation Our intervention substantially increased coverage of tuberculosis treatment in this high-risk population, but did not reduce mortality.

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Introduction

Despite antiretroviral therapy (ART), early mortality among HIV-positive people with advanced disease remains high in low-income and middle-income countries.¹ Tuberculosis is consistently identified as the

leading cause of death among people with HIV, and is often undiagnosed before death.² Diagnostic tests for tuberculosis remain unsatisfactory; no available test that is logistically feasible for point-of-care use in primary-level health-care clinics has adequate sensitivity for use

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Research in context**Evidence before this study**

We searched MEDLINE, Embase, Africa-Wide Information, and the ClinicalTrials.gov database from inception to Dec 31, 2010, using the search terms “(presumptive or empiric*) adj3 (treatment or therap*)” AND “AIDS or HIV or acquired immunodeficiency syndrome” AND “TB or tuberculosis”, or equivalent terms. Our search yielded no relevant studies.

Since our search, the REMEMBER trial found that empirical tuberculosis treatment conferred no mortality benefit compared with isoniazid preventive therapy among individuals with CD4 counts of less than 50 cells per μL who had negative investigations for tuberculosis. The STATIS trial found that antiretroviral therapy (ART) plus empirical tuberculosis treatment compared with ART plus extensive investigation for tuberculosis resulted in no reduction in death or severe infections among individuals with CD4 counts of less than 100 cells per μL .

Added value of this study

This is the first study to test an algorithm enabling nurses to initiate empirical tuberculosis treatment in primary health-care centres using point-of-care diagnostic tests. The intervention resulted in high coverage of tuberculosis treatment but did not accelerate ART initiation. No differences in mortality at 6 months were identified between participants in the intervention group and the control group. The intervention was designed to make use of simple, currently available point-of-care measures to guide empirical tuberculosis treatment, and thus to be feasible to implement in low-income settings.

Implications of all the available evidence

Accumulating evidence suggests that HIV-positive adults with advanced disease are unlikely to gain a large mortality benefit from untargeted empirical tuberculosis treatment. More sensitive tuberculosis diagnostic tests suitable for use by nurses in primary health-care clinics in low-income settings remain a key priority.

among people with HIV, particularly those with advanced disease. Consequently, empirical tuberculosis treatment (ie, initiation of treatment without bacteriological confirmation) is common.^{3–5} Empirical tuberculosis treatment generally requires a physician’s decision,⁶ but in many primary care settings physicians are not easily accessible. The process of investigating for tuberculosis might therefore be slow and might delay ART initiation.⁷

Wider use of empirical tuberculosis treatment has been discussed.⁸ Advantages of empirical treatment include rapid initiation of tuberculosis treatment, with potential mortality benefits for individuals with active tuberculosis, and protection against reactivation of latent tuberculosis for individuals without active tuberculosis. For individuals without active tuberculosis, disadvantages of empirical treatment include drug toxicity, drug interactions, increased pill burden, and, potentially, failure to identify and treat other comorbidities.⁸

2010 South African Antiretroviral Treatment Guidelines⁹ recommended ART initiation for people with WHO stage 4 HIV disease, or a CD4 count of 200 cells per μL or less, or for people with tuberculosis and pregnant women, 350 cells per μL or less, with so-called fast-track initiation (ie, within 2 weeks) for people with CD4 counts of less than 100 cells per μL . The guidelines emphasised the need for symptom screening and among individuals who are symptomatic, investigation for tuberculosis before ART initiation. Before 2011, the first-line test for tuberculosis was sputum smear microscopy, which was progressively replaced by the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) that was introduced nationally between 2011 and 2013.

ART initiation was recommended within 2–4 weeks of tuberculosis treatment initiation. From March, 2013, fast-track ART initiation (ie, within 7 days) was

recommended for all HIV-positive people with CD4 counts of less than 200 cells per μL , and individuals with tuberculosis with CD4 counts of less than 50 cells per μL .

We hypothesised that a management algorithm that allowed nurses to triage HIV-positive patients with advanced immunosuppression, identify those with the highest probability of tuberculosis, and start tuberculosis treatment immediately, followed by ART, would reduce early mortality. We reasoned that this reduction in mortality would be achieved by two mechanisms: by reducing the number of people with active tuberculosis who remained untreated and by removing delays associated with investigation for tuberculosis, we assumed that time to ART initiation would be reduced in all patients (including those treated for tuberculosis), with an additional mortality benefit.¹⁰

We designed a tuberculosis triage tool to enable nurses to assess tuberculosis risk, using measures that provide an in-session result in a primary care setting. A candidate component of our tuberculosis triage tool was an assay for mycobacterial lipoarabinomannan, which is commercially available as a urine-based point-of-care lateral flow assay (Determine TB LAM; Abbott, Chicago, IL, USA). However, the sensitivity of the assay is too low to be used alone as a screening test,^{11,12} and other measures were needed to increase triage tool sensitivity.

Haemoglobin concentrations and body-mass index are consistently associated with risk of mortality among HIV-positive people, and risk of active tuberculosis.^{13–15} We constructed a clinical algorithm on the basis of this tuberculosis triage tool to enable nurses to assess HIV-positive patients with advanced disease, and guide their treatment on the basis of patient’s probability of having tuberculosis. In the TB Fast Track trial, we aimed to investigate whether the use of this clinical algorithm

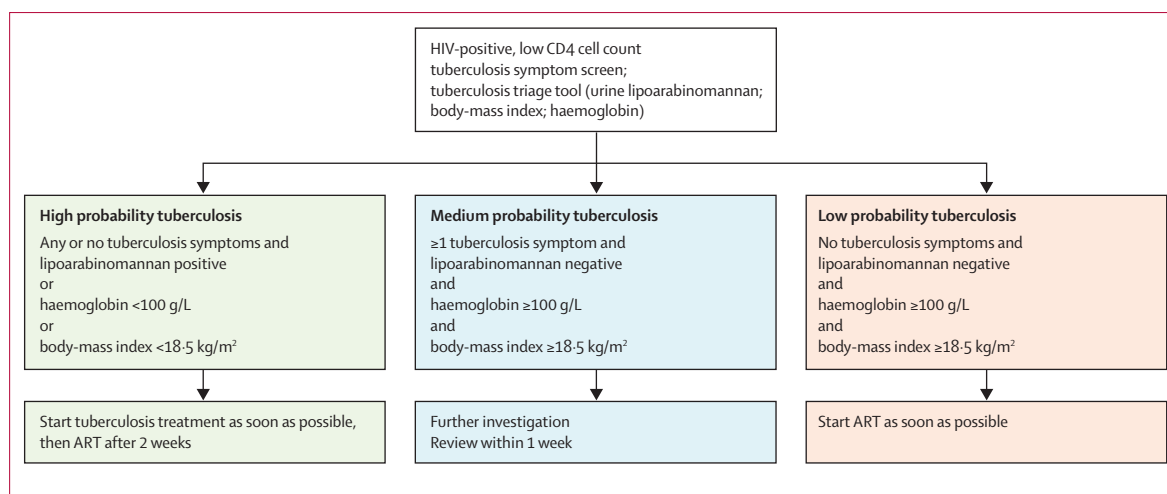


Figure 1: TB Fast Track intervention management algorithm
ART=antiretroviral therapy.

would reduce mortality at 6 months compared with standard of care for patients with advanced HIV disease.

Methods

Study design and participants

This pragmatic, open-label, parallel, cluster-randomised controlled trial was done at 24 primary health-care clinics in South Africa. The methods of the TB Fast Track study have been described previously,¹⁶ and the study protocol is available online. Since the intervention was a management strategy involving assessment of risk of active tuberculosis, we hypothesised that individual randomisation would alter the clinical management of patients in the control group (ie, those receiving standard of care) substantially compared with routine care.

After obtaining approval from district health staff and clinic managers, we randomly assigned clusters rather than individuals, whereby clusters comprised primary health-care clinics in Gauteng, Limpopo, and North West provinces. Eligible primary health-care clinics delivered both ART and tuberculosis treatment, had ART initiation rates that were estimated to be high enough to produce enough study participants, and did not have on-site tuberculosis testing facilities; Xpert MTB/RIF became the first-line test for tuberculosis at all clinics during the course of the trial, and was done at off-site laboratories. In most primary health-care clinics a doctor was available for morning sessions 3–5 days per week.

Adults (aged ≥ 18 years) with a recorded HIV-positive test result were eligible if they had a CD4 count of 150 cells per μL or less, and had not taken ART in the previous 6 months, or had tuberculosis treatment in the previous 3 months. We excluded adults at higher risk of adverse events from tuberculosis treatment, specifically individuals reporting chronic liver disease, or alcohol intake exceeding 28 units for men or 21 units for women per week; individuals with clinical signs necessitating

urgent referral to secondary care, based on WHO guidelines;⁶ and people planning to leave their clinic catchment area within 6 months.

South African Antiretroviral Treatment Guidelines⁹ effective at the time of study initiation recommended that women in the first trimester of pregnancy should not take efavirenz-based ART. Therefore, women of child-bearing potential were initially required to have a negative pregnancy test to be included. However, from July, 2013, when this caution had been removed from guidelines, enrolment was open to all women regardless of childbearing potential.

Study staff offered enrolment to all eligible participants until the required sample size for each clinic was reached. The study was approved by the research ethics committees of the University of the Witwatersrand and the London School of Hygiene & Tropical Medicine, and the South African Medicines Control Council. All participants provided written or witnessed verbal informed consent.

Randomisation and masking

A statistician randomised primary health-care clinics (1:1), using computer-generated random numbers, to the intervention or standard of care (control), based on restriction to achieve reasonable balance, separately, for mean CD4 count, peri-urban versus rural clinic location, and total monthly ART initiations. The random allocation was selected at a public ceremony involving clinic representatives.¹⁶ Early participant recruitment was slower than anticipated, and therefore in October 2013, we randomly assigned four additional primary health-care clinics, yielding a total of 24 clusters; we considered these additional four clinics as a separate stratum in the analysis. Due to the nature of the intervention being examined, participants, research staff, and clinic staff were aware of group allocation.

For the study protocol see https://researchonline.lshtm.ac.uk/4653158/1/TBfasttrack_protocol_v6.2_8jul15_clean.pdf

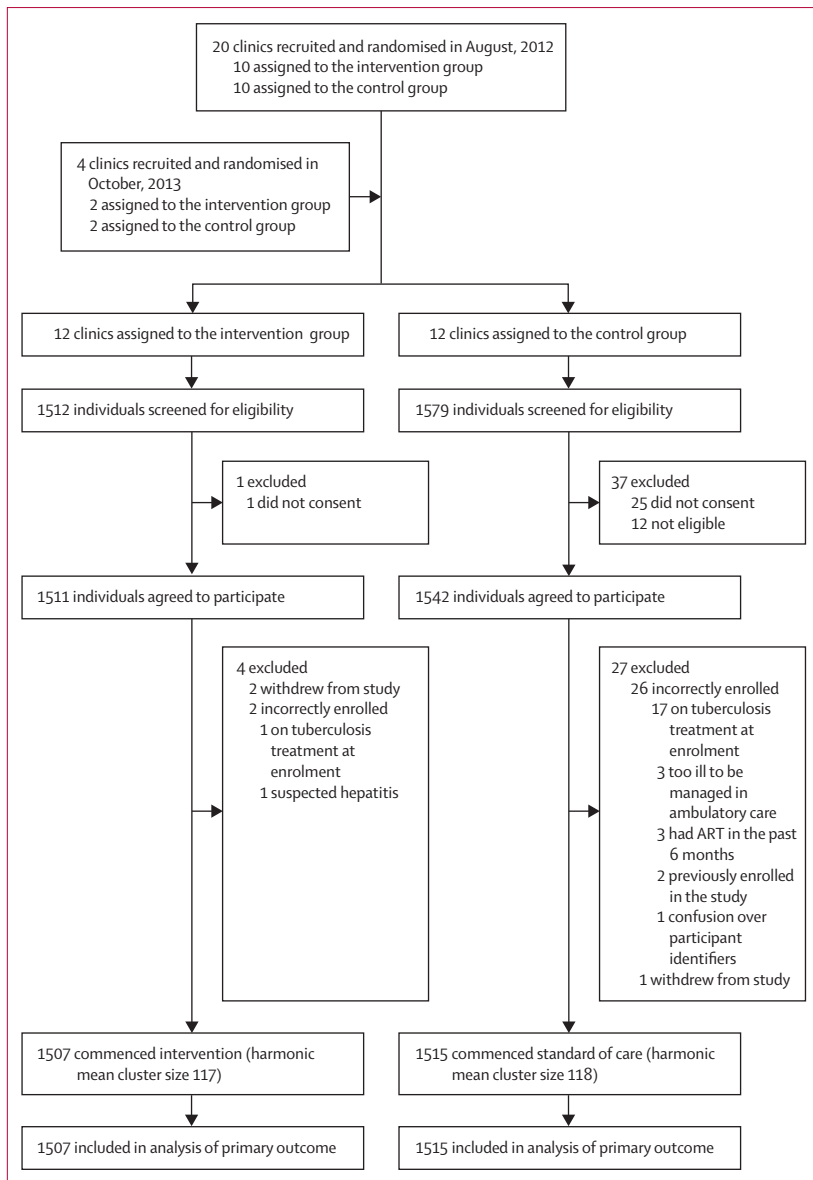


Figure 2: Trial profile
ART=antiretroviral therapy.

Procedures

In intervention clinics, study nurses assessed participants for tuberculosis symptoms, with screening based on the WHO screening tool (any of cough, weight loss, night sweats, or fever);¹⁷ measured height and weight to determine body-mass index; haemoglobin concentration on the basis of a finger prick blood sample (Hemocue 201+; Hemocue, Angelholm, Sweden); and urine lipoarabinomannan antigen detection using the lateral flow assay (Determine TB LAM), according to manufacturer's instructions. Study nurses then used the study algorithm (figure 1; appendix p 1) to classify participants on the basis of probability of tuberculosis. Individuals were classified as having a high probability of

tuberculosis if the urine lipoarabinomannan assay was positive (band of intensity grade 1 or higher, as recommended by the company until January, 2014), their body-mass index was less than 18.5 kg/m², or haemoglobin concentration was less than 100 g/L.

Individuals were classified as having a medium probability of tuberculosis if they did not fulfil any of the high probability criteria but had one or more tuberculosis symptoms, or a low probability of tuberculosis if they did not fulfil any high probability criteria and reported no tuberculosis symptoms. For participants classified as high probability, study nurses facilitated the start of tuberculosis treatment as soon as possible, with ART initiation 2 weeks later, in accordance with national guidelines,⁹ unless a contraindication was identified. Individuals classified as low probability started ART as soon as possible.

Individuals classified as medium probability were further assessed in accordance with national guidelines for management of sputum smear-negative tuberculosis with chest radiography, sputum for smear and mycobacterial culture (or Xpert MTB/RIF, as it became available), or a course of antibiotics, or any combination of the three, as clinically appropriate. Study staff reviewed medium probability participants within 1 week wherever possible, aiming to start tuberculosis treatment or ART at that timepoint.

At enrolment in intervention clinics, research staff collected a single spot sputum sample for smear, mycobacterial culture, organism identification, and sensitivity testing for isoniazid and rifampicin; the results of which were sent to clinic staff. We intended this sample to provide a minimum reference standard to indicate which participants had active tuberculosis, acknowledging that this approach would have suboptimal sensitivity. Research staff did not collect sputum specimens from participants in the control group because this was not standard of care.

After lipoarabinomannan testing, residual urine was frozen at -80°C for mycobacterial culture at the end of the study. Study staff reviewed participants in the intervention group to facilitate early management according to the study algorithm; clinic staff delivered subsequent HIV care (and tuberculosis treatment, if initiated) according to their usual practice.

In standard of care clinics, study staff enrolled participants and collected a urine sample, which was frozen and cultured for mycobacteria at the end of the study; all subsequent care was by clinic staff. For all participants, laboratory monitoring was done according to South African guidelines;⁹ liver function tests were not standard of care, and no laboratory evaluations were done for study purposes after the enrolment visit. Research staff reviewed patients' case notes at 2 and 6 months, and did a study visit at 6 months to determine vital status, tuberculosis treatment and ART start dates, and hospital admission and other important events.

See Online for appendix

Outcomes

The primary outcome was all-cause mortality at 6 months, defined as a known death before 6 months, or known to be alive after 150 days, on the basis of reports from participant-nominated contacts and clinic staff, and South African vital status registration data. We defined outcomes at 6 months because the risk of death was expected to be highest in the first 3 months and because, by 6 months, participants who started tuberculosis treatment as part of the intervention would be nearing tuberculosis treatment completion.

Secondary outcomes, ascertained by self-report or record review, were hospital admission in the 6 months after enrolment; time from enrolment to ART initiation; a binary outcome of whether ART was started within 30 days of enrolment; proportion of patients retained in HIV care at 6 months (defined as any HIV-related visit between 4 and 8 months after enrolment); economic outcomes; and adverse events. Economic outcomes will be reported elsewhere. All-cause mortality at 12 months was prespecified as an exploratory outcome. We did two post-hoc analyses of the primary outcome. In the first post-hoc analysis, we assumed individuals with unknown vital status at 6 months had died, with date of death defined as the midpoint between date last known alive and 6 months after enrolment; in the second post-hoc analysis, we excluded two control clusters in which more than 25% of participants self-reported taking isoniazid preventive therapy at enrolment. We also did a post-hoc analysis of the risk of starting ART by 6 months. All outcomes were measured at the individual level.

To ascertain possible serious and severe (grade 3 or 4) adverse events in specified categories relevant to the intervention (specifically hepatotoxicity, hypersensitivity, peripheral neuropathy, optic neuritis, and nephrotoxicity), research nurses and research assistants enquired about symptoms and history suggesting possible adverse events at every study visit, including early study review visits for participants in the intervention group, and sought relevant data in case note reviews. Due to the pragmatic trial design, no equivalent early study visits were done for participants in the control group; thus we anticipated that adverse events would be more completely ascertained in the intervention group.

Study clinicians classified adverse events according to the National Institute of Allergy and Infectious Diseases Division of AIDS criteria¹⁸ after detailed review of all available research and routine data, including hospital admission records, and assigned relationship to the intervention on the basis of the likelihood of association with empirical tuberculosis treatment. As part of a substudy, when possible, we did minimally invasive autopsies on study participants who died, the results of which have already been published.¹⁹ An independent panel assigned causes of death, based on clinical information from this study and available health facility and autopsy data.²⁰

	Intervention group (n=1507)	Control group (n=1515)
Sex		
Female	820 (54.4%)	849 (56.0%)
Male	687 (45.6%)	666 (44.0%)
Age (years)	37 (32–44)	36 (31–43)
CD4 count* (cells per μ L)	73 (35–111)	70 (35–113)
CD4 count* <50 cells per μ L	508 (33.7%)	521 (34.4%)
Body-mass index† (kg/m ²)	21.2 (18.8–24.7)	21.6 (19.2–24.8)
Body-mass index† <18.5 kg/m ²	320 (21.2%)	271 (17.9%)
Haemoglobin concentration‡ <100 g/L	428 (28.4%)	322 (29.8%)
Positive urine lipoarabinomannan assay§	181 (12.0%)	222 (15.2%)
≥1 tuberculosis symptom(s)¶	1095 (72.7%)	993 (65.7%)
Previous tuberculosis treatment**	151 (10.0%)	136 (9.0%)
Taking isoniazid preventive therapy††	51 (3.4%)	158 (10.4%)
Taking co-trimoxazole‡‡	691 (45.9%)	718 (47.4%)
Tuberculosis tests done in past 6 months (self-reported)§§	737 (48.9%)	645 (42.7%)
Sputum sent for tuberculosis testing in 28 days before enrolment (record review)	471 (31.3%)	412 (27.2%)
Xpert MTB/RIF result recorded	357/471 (75.8%)	321/412 (77.9%)
Chest radiograph done in 28 days before enrolment (record review)	79 (5.2%)	38 (2.5%)

Data are n (%), median (IQR), or n/N (%). *Data missing for one participant in the intervention group. †Data missing for three participants in the control group. ‡Data missing for one participant in the intervention group and 435 participants in the control group. §Data missing for two participants in the intervention group and 52 participants in the control group. ¶Tuberculosis symptoms defined as any of cough, fever, unintentional weight loss, or night sweats. ||Data missing for one participant in the intervention group and four participants in the control group. **Data missing for one participant in the intervention group. ††Data missing for one participant in the intervention group and one participant in the control group. ‡‡Data missing for one participant in the intervention group and one participant in the control group. §§Data missing for one participant in the intervention group and six participants in the control group.

Table 1: Baseline characteristics of study participants

Statistical analysis

Sample size calculations are detailed elsewhere.¹⁶ Briefly, assuming ten clinics per study group, with a harmonic mean of 175 participants per clinic, 5% of participants with unknown vital status at 6 months, a mortality rate of 25 deaths per 100 person-years in the standard of care group, and coefficients of variation of 0.20 and 0.25, the study would have 91% and 85% power to assess a 40% reduction in mortality, respectively. If the coefficient of variation was 0.20, the study would have 81% power to assess a 35% reduction in mortality. 6 months after initiation of the study, we reassessed sample size calculations because recruitment was slower than anticipated. We needed to randomise an additional four clinics to achieve a harmonic mean of 109 participants

	Intervention group (n=1507)	Control group (n=1515)	Unadjusted measure (95% CI)	p value	Adjusted measure (95% CI)*	p value
Primary outcome						
6-month mortality rate (deaths per 100 person-years)†	19·0‡	21·6§	HR 0·92 (0·67 to 1·26)	0·58	HR 0·87¶ (0·61 to 1·24)	0·41
Secondary outcomes						
Hospital admission in the 6 months after enrolment (n/N [%])	201/1507 (13·3%)	158/1515 (10·4%)	RR 1·19 (0·94 to 1·50)	0·14	RR 1·11 (0·89 to 1·38)	0·34
Retention in care at 6 months (n/N [%])	934/1507 (62·0%)	945/1515 (62·4%)	RR 1·01 (0·82 to 1·23)	0·94	RR 1·02 (0·83 to 1·24)	0·87
ART initiated within 30 days of enrolment (n/N [%])	1001/1507 (66·4%)	1104/1515 (72·9%)	RR 0·89 (0·76 to 1·04)	0·13	RR 0·91** (0·79 to 1·05)	0·17
6-month ART initiation rate (ART initiations per 100 person-years)	834·5	1034	HR 0·68 (0·41 to 1·15)	0·14	HR 0·69†† (0·46 to 1·04)	0·07
Post-hoc analysis						
Risk of starting ART by 6 months (n/N [%])	1338/1507 (88·8%)	1347/1515 (88·9%)	RR 0·99 (0·94 to 1·04)	0·75	RR 1·0†† (0·95 to 1·04)	0·84

HR=hazard ratio. RR=risk ratio. ART=antiretroviral therapy. *Analyses adjusted for sex, age, body-mass index, CD4 cell count, taking isoniazid preventive therapy at baseline, tuberculosis symptoms, tuberculosis tests in the previous 6 months, previous treatment for tuberculosis, and randomisation strata; analysis of time to initiation of ART was also adjusted for follow-up time; because of missing data for some adjustment factors, all adjusted analyses included 3009 participants (1504 participants in the intervention group and 1505 participants in the control group). †Unadjusted rate difference -2·14 (95% CI -7·76 to 3·49; p=0·44); adjusted rate difference -2·19 (-5·43 to 1·05; p=0·17); adjusted rate difference includes 284 participants who died (134 participants in the intervention group and 150 participants in the control group). ‡131 deaths in 704 person-years. §151 deaths in 699 person-years. ¶Includes 284 participants who died (134 participants in the intervention group and 150 participants in the control group). ||Includes 1872 outcomes (932 in the intervention group and 940 in the control group). **Includes 2098 outcomes (999 in the intervention group and 1099 in the control group). ††Includes 2677 outcomes (1336 in the intervention group and 1341 in the control group).

Table 2: Effect of the intervention on primary and secondary outcomes

per clinic to ensure the study maintained similar power and effect sizes as with the original calculation.

All analyses were done in the intention-to-treat population. Analysis was done on the basis of a cluster-level approach, appropriate for the small number of clusters included.¹⁶ For rate or binary outcomes, we calculated the overall rate or risk for each cluster. We calculated the rate ratio as the geometric mean of cluster-level rates in the intervention group divided by the control group, accounting for the stratified randomisation. We calculated the SE for each log (effect measure) by regressing the log(rate) on the study group, strata and their interaction.

We based the 95% CI and p value on 20 degrees of freedom. We adjusted the analyses if, after visual inspection, we observed imbalances between study groups in individual-level factors, using a two-stage approach²¹ suitable for a small number of clusters. Briefly, in stage 1, an individual-level regression model was fitted, including terms for the adjustment factors and strata, but not study group, and the expected number of outcomes accumulated at the cluster level was calculated. In stage 2, at the cluster level, linear regression of the log (observed divided by expected outcomes) on stratum and group was used to estimate the risk or rate ratio. We calculated an approximate SE for the log (risk or rate ratio) using a similar approach.

We did prespecified subgroup analyses for the primary outcome for baseline CD4 count (<50 or ≥50 cells per μL), self-reported tuberculosis history (no previous or previous tuberculosis), baseline body-mass index (<18·5 or ≥18·5 kg/m²), and baseline haemoglobin concentration (<80 or ≥80 g/L). The study was not powered to detect differences in these subgroups. An independent trial steering committee and independent data monitoring committee oversaw the study. This trial is registered with the ISRCTN registry, ISRCTN35344604,

and the South African National Clinical Trials Register, DOH-27-0812-3902.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 19, 2012, and Dec 18, 2014, we recruited 3053 participants from 12 intervention clinics (n=1512) and 12 control clinics (n=1567). 1507 participants in the intervention group and 1515 participants in the control group were included in the analysis of the primary outcome (figure 2). The median age of participants was 37 years (IQR 31–43), 1669 (55·2%) were women, and median CD4 count was 72 cells per μL (IQR 35–112; table 1).

Baseline variables were similar between the study groups, with the exception of symptoms compatible with tuberculosis, recent tuberculosis tests, and isoniazid therapy: participants in the intervention group were more likely to report one or more symptoms compatible with tuberculosis than those in the control group; to have had tuberculosis tests done in the 6 months before enrolment; and were less likely to be taking isoniazid preventive therapy (table 1). The difference in isoniazid preventive therapy use between the groups was attributable to two control clusters, in which more than 20% of participants reported taking isoniazid preventive therapy at enrolment.

In the intervention group, study nurses used the algorithm to assign 689 (45·7%) of 1507 participants to the high probability of tuberculosis category, 475 (31·5%)

of 1507 participants to the medium probability of tuberculosis category, and 342 (22.7%) of 1507 participants to the low probability of tuberculosis category (data missing for one participant; appendix pp 2, 9–11).

In the 14 days after enrolment, based on record review, 264 (17.4%) of 1515 participants in the control group gave a sputum sample, of whom 195 (73.9%) had an Xpert MTB/RIF result recorded, and 130 (8.6%) had a chest radiograph request documented; investigation was slightly more frequent among individuals who reported one or more symptoms at enrolment (195 [19.7%] of 992 gave a sputum sample, 104 [10.5%] of 992 had a chest radiograph request documented, and 271 [27.3%] of 992 gave either a sputum sample or had a chest radiograph requested) than those who reported no symptoms (69 [13.3%] of 519 gave a sputum sample, 26 [5.0%] of 519 had a chest radiograph request documented, and 91 [17.5%] of 519 gave either a sputum sample or had a chest radiograph request documented). Overall, 60 days after enrolment, 930 (61.7%) of 1507 participants in the intervention group had started tuberculosis treatment compared with 172 (11.4%) of 1515 participants in the control group (appendix p 12).

The total follow-up time was 1404 person-years. Vital status at 6 months was determined for 1487 (98.7%) of 1507 participants in the intervention group and 1485 (98.0%) of 1515 participants in the control group. At 6 months, the mortality rate was 19.0 deaths per 100 person-years (134 deaths in 704 person-years) in the intervention group versus 21.6 deaths per 100 person-years (151 deaths in 699 person-years) in the control group (unadjusted hazard ratio [HR] 0.92, 95% CI 0.67–1.26, $p=0.58$; adjusted HR 0.87, 0.61–1.24, $p=0.41$; table 2, figure 3, appendix p 3).

The results of prespecified subgroup analyses for CD4 and body-mass index strata were similar for the intervention effect on mortality (appendix p 4). Estimation of the intervention effect for individuals reporting previous tuberculosis treatment and by haemoglobin concentration was not possible because when data were restricted to these subgroups, no deaths were recorded at six and five clinics, respectively. The coefficient of variation for the primary outcome in all clusters was 0.09.

In a post-hoc sensitivity analysis of the primary outcome, assuming the 50 individuals with unknown vital status at 6 months (19 patients in the intervention group and 31 patients in the control group) had died, the adjusted HR was 0.86 (95% CI 0.61–1.21, $p=0.37$). In a second post-hoc sensitivity analysis, excluding the two control clusters in which more than 25% of participants self-reported taking isoniazid preventive therapy at enrolment, the effect estimates for the primary outcome were similar (unadjusted HR 0.95, 95% CI 0.68–1.32, $p=0.75$; adjusted HR 0.88, 0.61–1.28, $p=0.50$). The 12-month mortality rate was 13.1 deaths per 100 person-years in the intervention group versus 14.7 deaths per 100 person-years in the control group (unadjusted HR 0.97, 95% CI

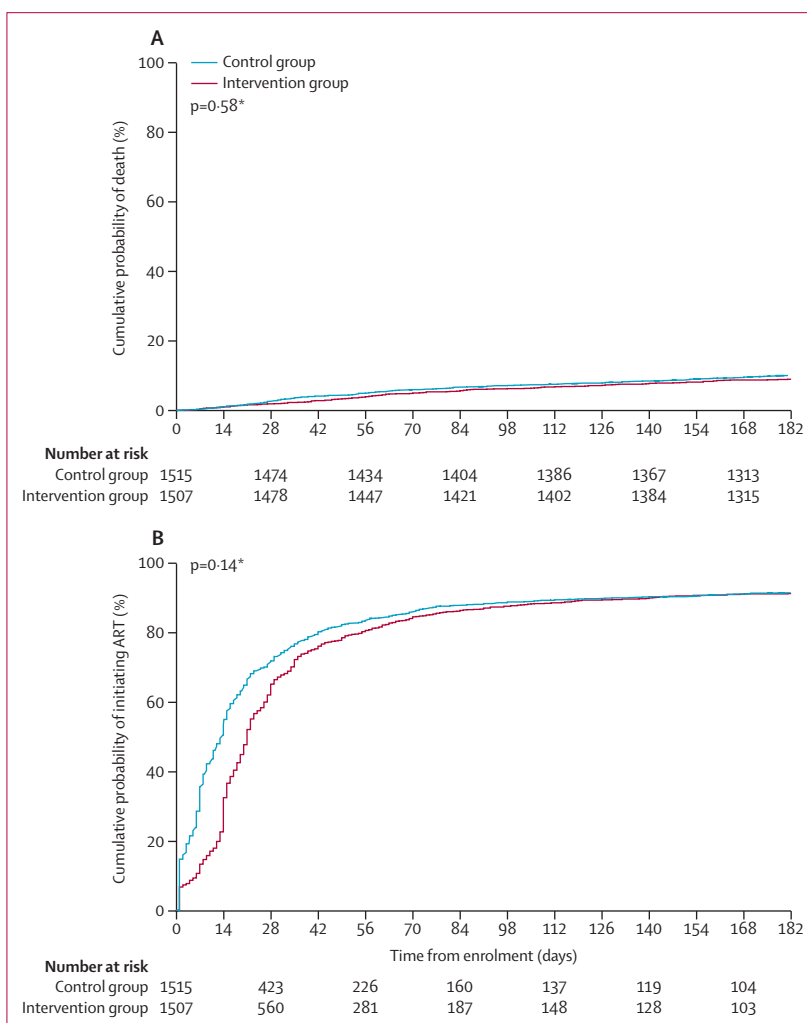


Figure 3: Kaplan-Meier curves of time from enrolment to death (A) and initiation of ART (B). ART=antiretroviral therapy. *Adjusted for clustering.

0.75–1.25, $p=0.78$; adjusted HR 0.92, 0.69–1.24, $p=0.57$; appendix p 5).

The proportion of patients admitted to hospital during the 6-month follow-up period was similar between study groups: 201 (13.3%) of 1507 participants in the intervention group versus 158 (10.4%) of 1515 participants in the control group (adjusted risk ratio [RR] 1.11, 95% CI 0.89–1.38, $p=0.34$; table 2).

A smaller proportion of participants in the intervention group started ART within 30 days of enrolment than the control group (1001 [66.4%] of 1507 participants vs 1104 [72.9%] of 1515 participants), however, the evidence for a difference between study groups was weak (adjusted RR 0.91, 95% CI 0.79–1.05, $p=0.17$; table 2; figure 3B). The median time to initiation of ART was 21 days (IQR 14–39) in the intervention group versus 13 days (6–31) days in the control group. In the control group, no differences in the median time to initiation of ART were identified between participants who reported one or

	Intervention group (n=1507)	Control group (n=1515)
Participants with adverse events (n [%])	28 (1.9%)	10 (0.7%)
Events (n)	29	11
Median age (years [range])	35 (22–52)	39 (30–55)
Sex (n [%])		
Female	14 (50%)	4 (40%)
Male	14 (50%)	6 (60%)
Median CD4 count at enrolment (cells per μ L [range])	68 (4–143)	50.5 (21–142)
Adverse events (n [%])		
Nausea or vomiting*	10 (33%)	4 (36%)
Suspected peripheral neuropathy	8 (27%)	2 (18%)
Skin rash or hypersensitivity	6 (20%)	2 (18%)
Abnormal liver function tests or hepatitis	4 (13%)	3 (27%)
Generalised body weakness	1 (7%)	0
Median time from enrolment to onset of adverse event (days [IQR; range])	26 (13–79; 0–169)	29 (8–109; 7–166)
Adverse event occurred after ART initiation† (n [%])		
At least one day after	14 (48%)	5 (45%)
Before or on the same day as ART initiation	12 (41%)	3 (27%)
Did not start ART	3 (10%)	3 (27%)
Median time from starting ART to adverse event, restricted to adverse events after ART initiation (days [range; n])	53.5 (3–162; 14)	103 (18–144; 5)
Adverse event occurred after initiation of tuberculosis treatment‡ (n [%])		
At least 1 day after	19 (66%)	5 (45%)
Before or same day as initiation of tuberculosis treatment	4 (14%)	1 (9%)
Did not start tuberculosis treatment	6 (21%)	5 (45%)
Median time from initiation of tuberculosis treatment to adverse event, restricted to adverse events after initiation of tuberculosis treatment (days [range; n])	21 (1–165; 19)	14 (5–125; 5)
Outcome of adverse event (n [%])		
Resolved	15 (52%)	8 (73%)
Resolved with sequelae	1 (3%)	0
Ongoing	7 (24%)	1 (9%)
Fatal*	6 (21%)	2 (18%)
Association with intervention (n [%])		
Not associated	9 (31%)	11 (100%)
Probably not associated	1 (3%)	0
Possibly associated	7 (24%)	0
Probably associated	8 (28%)	0
Definitely associated*	4 (14%)	0

Two participants reported two adverse events each: one participant in the control group reported hepatitis and nausea or vomiting 5 days after starting tuberculosis treatment (patient did not start ART); one participant in the intervention group reported nausea or vomiting on the same day as ART was initiated and had suspected peripheral neuropathy after starting ART (patient did not start tuberculosis treatment). ART=antiretroviral therapy. *One adverse event of nausea or vomiting was deemed to be definitely associated with a fatal outcome because no resolution was documented; the patient was lost to follow-up from tuberculosis treatment, subsequently admitted to hospital with vomiting and diarrhoea, and died 48 days after enrolment; hospital-assigned cause of death was meningitis and renal failure. At minimally invasive autopsy, *Mycobacterium tuberculosis* (sensitive to isoniazid and rifampicin) was isolated from the liver and spleen but not from the cerebrospinal fluid. Panel-assigned cause of death was disseminated tuberculosis; therefore, the adverse event was considered associated, but death was considered not associated with the intervention. †33 of 38 participants initiated ART (eight of ten participants in the control group and 25 of 28 participants in the intervention group). ‡28 of 38 participants started tuberculosis treatment (five of ten participants in the control group and 23 of 28 participants in the intervention group).

Table 3: Serious and severe adverse events

more symptoms at enrolment than those who reported no symptoms (13 days [IQR 6–29] vs 13 days [6–31]). The incidence rate of starting ART within 6 months of enrolment was 30% lower in the intervention than the control group (adjusted HR 0.69, 95% CI 0.46–1.04, $p=0.07$), although the 95% CI crossed 1; however, by 6 months, no differences in the proportion of participants who had started ART were identified between study groups (88.8% vs 88.9% for the intervention group versus the control group).

Among participants who started tuberculosis treatment followed by ART, the median time between initiation of tuberculosis treatment and initiation of ART started was 19 days (IQR 14–32; $n=820$) in the intervention group compared with 25 days (15–49; $n=131$) in the control group. Retention in HIV care at 6 months was similar between the study groups: 934 (62.0%) of 1507 participants in the intervention group versus 945 (62.4%) of 1515 participants in the control group (adjusted RR 1.02, 95% CI 0.83–1.24).

Among 774 participants in the intervention group who started tuberculosis treatment within 60 days of enrolment (thus likely attributable to the intervention), 666 (85.0%) remained on tuberculosis treatment 168 days after initiation of tuberculosis treatment.

28 (1.9%) of 1507 participants in the intervention group and ten (0.7%) of 1515 participants in the control group reported 40 serious or severe adverse events (29 events in the intervention group vs 11 events in the control group; table 3). Grade 3 or 4 nausea and vomiting was the most common adverse event (ten participants in the intervention group vs four participants in the control group), followed by symptoms that could indicate peripheral neuropathy at grade 3 or worse (eight participants in the intervention group vs two participants in the control group), and grade 3 or worse skin rash (six participants in the intervention group vs two participants in the control group). Abnormal liver function tests were recorded in clinic records for four participants in the intervention group and three participants in the control group.

In the intervention group, 19 (66%) of 29 adverse events occurred at least 1 day after the start of tuberculosis treatment (median 21, range 1–165). Six (21%) of 29 adverse events in the intervention group versus two (18%) of 11 adverse events in the control group had a fatal outcome. Following review, none of the six deaths in the intervention group were attributed to the study intervention (appendix pp 6–8). Among 17 decedents in the intervention group who had minimally invasive autopsy, none had fulminant hepatitis.¹⁹

970 (64.4%) of 1507 participants in the intervention group produced a sputum specimen for mycobacterial culture, of whom 36 (2.4%) had a positive smear and 102 (6.8%) were culture positive for *Mycobacterium tuberculosis* (classifying participants who could not produce sputum as smear negative and culture negative). Eight participants had stored urine that was *M tuberculosis*

culture positive at the end of the study (seven participants in the intervention group and one participant in the control group); of the seven participants in the intervention group, four had a bacteriologically positive sputum result at enrolment (three culture positive, one smear positive but culture negative; the remaining three participants were unable to provide sputum). The proportion of patients in the intervention group with a positive sputum culture by study algorithm-assigned probability of tuberculosis was 11.2% (77 of 689 participants) for the high tuberculosis probability category, 4.0% (19 of 475 participants) for the medium probability category, and 1.8% (six of 342 participants) for the low probability category. The overlap between sputum smear and culture positivity and urine lipoarabinomannan positivity is shown in the appendix (p 13). Among 102 participants with *M tuberculosis* cultured from sputum, four (3.9%) isolates were isoniazid mono-resistant, and one (1.0%) was resistant to both isoniazid and rifampicin.

The 6-month mortality rate among participants in the intervention group assigned to the high probability of tuberculosis was 14.2%, 5.5% among those assigned to the medium probability category, and 2.9% among those assigned to the low probability category (appendix p 14); this compared to 14.6%, 7.4%, and 3.7% for participants in the control group when probabilities were applied retrospectively on the basis of lipoarabinomannan testing of stored urine and haemoglobin estimation from routine records, where available (n=1039; appendix p 15).

Discussion

Our study triage tool successfully identified individuals who were at high risk of tuberculosis and of mortality, and our algorithm resulted in higher coverage of tuberculosis treatment in the intervention group than the control group. However, the intervention did not reduce mortality or improve other clinical outcomes. The large anticipated effect size was dependent on the assumption that the intervention would reduce tuberculosis-specific mortality by increasing coverage of tuberculosis treatment to individuals with active tuberculosis who would not be detected in routine practice, reducing all-cause mortality by accelerating ART initiation. In practice, the intervention did not accelerate ART initiation compared with the control group, and we found that a substantial increase in coverage of tuberculosis treatment did not result in the large reduction in mortality that the trial was powered to detect.

The absence of a mortality benefit could be explained by tuberculosis not being a major cause of mortality among our participants. This hypothesis is contradicted by evidence from autopsy studies;² furthermore, in a small subset of deaths (n=34) among study participants who had minimally invasive autopsy, almost half had prevalent tuberculosis.¹⁹ Among 212 decedents included in a sub-study validating verbal autopsy, 61 (28.8%) were assigned

tuberculosis as cause of death by an independent panel.²⁰ We believe that the intervention is unlikely to have increased mortality due to unnecessary tuberculosis treatment, considering the low number of serious and severe adverse events. Additionally, it is unlikely that the intervention effect was undermined by undetected drug-resistant tuberculosis, considering the low prevalence of drug-resistant tuberculosis among participants in the intervention group.

However, more than 40% of participants in both study groups reported having tuberculosis tests as part of their routine care in the 6 months before enrolment. Furthermore, around 30% of participants in both study groups were documented to have had a sputum test in the 28 days before enrolment, which is substantially higher than our pilot work (unpublished) suggested, possibly reflecting increased awareness of tuberculosis as a result of the roll-out of Xpert MTB/RIF, study activities, or a combination of both. Increased awareness of tuberculosis, and subsequent increases in testing and treatment, could have reduced the prevalence of active tuberculosis among the enrolled population, especially later in the study as the roll-out of Xpert MTB/RIF progressed; the intervention might have a larger effect in populations in which less tuberculosis investigation was done before ART initiation.

The absence of mortality benefit could be partly explained by the fact that the intervention did not result in the acceleration of ART initiation. The main reason for slower ART initiation in the intervention group than the control group was the high proportion (62%) of intervention participants who started tuberculosis treatment, combined with faster than expected ART initiation in the control group. Participants in the intervention group given empirical tuberculosis treatment were intended to start ART 2 weeks later, but in practice the median time to start ART after tuberculosis treatment among the intervention group was 19 days, which is slightly shorter than that observed among the control group (25 days).

We do not have detailed data to explain why ART initiation was slower than planned. In some cases there were understandable explanations for delay, such as abnormal renal function, but often the reason was unclear. We observed that some clinic staff were reluctant to start ART in people who were perceived to be unwell; further work to understand and correct misconceptions might be needed, and this is particularly relevant in the context of efforts to accelerate ART initiation.

The presence of the study team in control clinics might have had an unplanned effect to increase the speed of ART initiation: the median time from enrolment to ART initiation in the TB Fast Track control group was 13 days, compared with 25 days in a pilot study⁷ done at 21 study clinics in 2011; secular change might also have contributed. We believe that it is unlikely that the overall 1-week difference in time to ART initiation between study groups

would account for a large difference in mortality at 6 months; however, our assumption that empirical tuberculosis treatment would accelerate ART initiation overall was incorrect. Thus, our intervention, in practice, comprised much higher coverage of tuberculosis treatment, without any additional benefit from earlier ART, and the observed intervention effect is likely to reflect this.

In the control group, no differences in time to ART initiation were identified between participants who reported symptoms consistent with tuberculosis (67%) and those participants without symptoms (33%). Thus, in the control group, any investigation or treatment for active tuberculosis did not delay ART initiation. This absence of a delay might be partly explained by the unexpectedly high frequency of investigation for tuberculosis before enrolment. Nonetheless, symptomatic individuals should have had sputum sent for mycobacterial culture (or, as it was rolled out, Xpert MTB/RIF if not previously sent); in the 14 days after enrolment only 20% of symptomatic participants in the control group were recorded to have had a sputum sample sent. These data suggest that any adverse outcomes attributable to early ART initiation without comprehensive tuberculosis investigation among symptomatic participants in the control group were not outweighed by empirical tuberculosis treatment in the intervention group, suggesting that guidelines might overemphasise the requirement to delay ART start until active tuberculosis has been excluded. Strategies for rapid ART initiation among symptomatic people with advanced HIV disease merit further evaluation.

The REMEMBER trial²² similarly addressed the mortality benefit of empirical tuberculosis treatment. The trial showed no benefit of empirical tuberculosis treatment compared with isoniazid preventive therapy, in a selected population with CD4 counts of less than 50 cells per μL , and no evidence of tuberculosis based on clinical presentation and initial investigation, which included chest radiography in 65% of participants and Xpert MTB/RIF testing in around 91% of participants.²²

The PROMPT²³ trial individually randomised individuals in four countries in Africa with CD4 counts less than 50 cells per μL and no evidence of tuberculosis on sputum smear or chest radiography to presumptive tuberculosis treatment or control; it was stopped early because of slow recruitment.

The STATIS trial²⁴ found no difference in death or invasive bacterial disease by 24 weeks among adults with CD4 counts of less than 100 cells per μL who were individually randomised to ART plus extensive tuberculosis investigation versus ART and empirical tuberculosis treatment. The lipoarabinomannan assay is feasible for use in primary health-care clinics but, as reported elsewhere, the sensitivity in our study was too low to be used in isolation.²⁵ New, high-sensitivity lipoarabinomannan assays hold promise if they can be formulated for point-of-care use in primary health-care clinics.

Strengths of the trial include the pragmatic design, with broad inclusion criteria, which maximised generalisability. The intervention algorithm was based on existing, low-cost measures and was delivered by nurses, who were integrated into routine primary health care. Completeness of follow-up was high.

Some limitations of the trial were due to its pragmatic design. We did few non-routine investigations, and thus have little information from which to determine which participants genuinely had tuberculosis at enrolment, and causes of death. We minimised study-specific follow-up visits to approximate how the intervention would be delivered in routine conditions.

The small number of follow-up visits meant that adverse events were under-ascertained in both study groups; additional visits to implement the study algorithm for most participants in the intervention group are likely to have resulted in more complete recording of possible adverse events in the intervention group than the control group. However, ascertainment of deaths was high in both groups, and thus we can be confident that fatal adverse events did not outweigh any benefit of the intervention.

Hospital admissions might have been under-ascertained in control clinics because fewer study visits were done and participants would have had less interaction with study staff. Participants in the intervention group might also have had a higher probability of referral to hospital because of increased contact with research and clinic staff.

The TB Fast Track intervention enabled nurses in primary health-care clinics to identify HIV-positive adults at high risk of tuberculosis and of death, and achieved high coverage of empirical tuberculosis treatment. However, the intervention did not result in the large mortality benefit that the trial was powered to detect.

People with advanced HIV disease presenting for care need a package of care in which tuberculosis diagnosis and treatment are a key component. More sensitive, rapid tuberculosis diagnostic tests suitable for use by nurses in primary health-care clinics are urgently needed so that people with tuberculosis can be correctly identified and promptly treated. Strategies for rapid ART initiation among symptomatic people with advanced HIV disease merit further evaluation.

Contributors

ADG, SC, SED, CJH, SJ, AV, GJC, and KLF conceived, designed, and secured funding for the study. ADG, SC, MT, ASK, SJ, and KLF were responsible for data collection. ADG, SC, MT, and KLF analysed the data. ASK and KLF produced the figures. ADG, SC, and KLF drafted the manuscript. All authors contributed to data interpretation and critically reviewed the manuscript.

Declaration of interests

ADG, SC, MT, ASK, CJH, SJ, AV, GJC, and KLF report grants from Joint Global Health Trials (UK Medical Research Council, Department of International Development, and Wellcome Trust) during the conduct of the study. GJC reports grants from the Aurum Institute during the conduct of the study. GJC is supported by ACT4TB/HIV, funded by the South African Medical Research Council. SED declares no competing interests.

Data sharing

Deidentified individual participant data and a data dictionary will be available by Dec 31, 2019, from <https://datacompass.lshtm.ac.uk/> and the study protocol is already available from the same site.

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