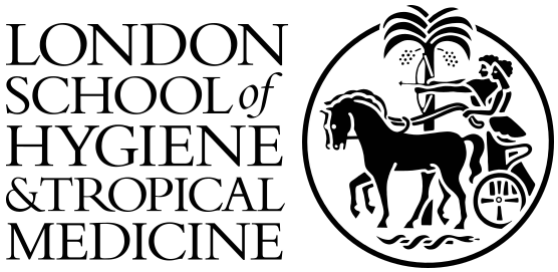

TB Fast Track: a study to evaluate the effect of a point-of-care TB test-and-treat algorithm on early mortality in people with HIV accessing ART, a trial with randomisation at clinic level

Short title: TB Fast Track

Protocol version 6.2, 8 July 2015

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Study summary

Background: Despite remarkable progress in improving coverage of antiretroviral therapy (ART) in resource-constrained settings, early mortality among people with HIV starting ART remains high. Tuberculosis (TB) is the most important cause of death in people with HIV globally, including those starting ART. TB is common among individuals presenting to start ART in southern Africa, but existing diagnostic strategies perform poorly: the diagnostic pathway is slow, and many cases are missed. New TB diagnostics have potential to transform this situation. Urine lipoarabinomannan (LAM) antigen testing has high specificity and moderate sensitivity among HIV-positive individuals with advanced immunosuppression. This test is now available formulated for point-of-care use, at low cost, and could be used in primary care settings to identify TB among those at highest risk of both TB and of death. Haemoglobin and body mass index are also associated with risk of prevalent TB among people with HIV.

Aim: To determine 6-month mortality among adults with HIV and CD4≤150, presenting for ART, managed using a point-of-care technology-based algorithm to rapidly identify individuals at high risk of TB and ensure they start TB treatment, then ART; and to compare this to 6-month mortality among adults managed according to standard practice based on South African guidelines.

Methods: Open-label, pragmatic cluster-randomised trial, with primary health clinics as the unit of randomisation. Adults (at least 18 years) with CD4≤150 cells/µl who have not had TB treatment in the last 3 months will be eligible. In intervention clinics, consenting adults will be assessed based on symptoms, urine LAM, haemoglobin concentration and body mass index. The study algorithm will use the results of these assessments to classify individuals as high, medium or low probability of TB. Those with high probability will start TB treatment immediately, followed by ART after 2 weeks. Those with medium probability of TB will follow the South African guidelines (sputum smear, chest radiography and trial of antibiotics) and will be reviewed after one week, to be re-categorised as low or high risk of TB. Those categorised as low probability of TB will start ART as soon as possible. All participants in both arms will be followed up to 6 months. The primary outcome is all-cause mortality at 6 months. We will also explore the cost-effectiveness of this management strategy.

Significance: If the study management strategy proves effective in reducing mortality, this algorithm could be implemented in resource-constrained settings and could substantially reduce early on-ART mortality.

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1. Background

The challenge of tuberculosis and HIV

With an estimated 33.3 million people living with HIV in 2009, the management of HIV disease represents one of the most pressing challenges to global public health. Tuberculosis (TB) is the most important cause of death among people with HIV in resource-constrained settings,[1] and the HIV epidemic is the main cause of the resurgence of TB over the last 30 years. Increasing access to antiretroviral therapy (ART) has dramatically improved survival, but individuals with advanced HIV disease continue to experience high mortality both while waiting to start[2] and soon after starting ART,[3] with TB a leading cause of death.[2,4,5]

The problem of tuberculosis diagnosis in people with HIV

Traditional diagnostic algorithms for TB, based on sputum smear microscopy, serve people with advanced HIV disease poorly, because smear microscopy has very low sensitivity, and for the majority of individuals whose sputum smears are negative, the diagnostic process is often protracted. Mycobacterial culture on automated liquid systems has better sensitivity than sputum smear but is expensive, prone to contamination, takes several weeks to give results, and laboratory capacity remains very limited in most settings of high HIV prevalence. Even where available, it is not clear that access to mycobacterial culture has a major impact on patient-relevant outcomes.[6]

Tuberculosis among individuals presenting for ART in southern Africa

In South Africa, 19-25% of individuals eligible to start ART have undiagnosed culture-positive tuberculosis.[7,8] South African guidelines recommend a TB symptom screen at every HIV clinic visit, and 2 sputum specimens sent for smear and culture for TB suspects, but this is poorly implemented. In a retrospective review of a South African HIV programme, we found that 1524/4502 (33.9%) patients had two or more or cough, fever, night sweats or weight loss recorded, yet only 27/1524 (1.8%) were documented to have had sputum samples sent.[9]

In a separate prospective study in a South African clinic, we systematically screened individuals presenting to start ART for TB using symptoms, chest radiography and sputum culture (on liquid media). Only 9/350 (2.6%) were sputum smear positive, but 64/350 (18%) were culture positive for *M. tuberculosis*, and a total of 114/350 (32%) started TB treatment based on laboratory, clinical and radiological findings combined (Hanifa Y, personal communication, manuscript submitted). For individuals diagnosed by sputum culture, the median time from assessment to the start of TB treatment was 37 days. The median time from assessment to the start of ART, in this study where a full set of TB investigations were performed at enrolment, was 93 vs. 64 days for individuals with and without TB, respectively; in routine practice with investigations conducted sequentially, delays may be even longer. Most ART algorithms suggest that if TB is suspected, it should be ruled out, or diagnosed and treated, before ART is started. This is clearly desirable, to reduce TB case fatality and the risk of TB-immune reconstitution syndrome. However, in practice, this study shows that even when WHO-recommended diagnostic pathways are initiated promptly and correctly, patients experience long delays before starting treatment for either TB or ART or both, which may prove fatal.[2]

In summary, limitations in existing TB diagnostic pathways result in two life-threatening problems for people presenting for ART; first, those who have active TB may be diagnosed and treated late, or not diagnosed or treated at all; second, the complex diagnostic pathway for smear negative TB results in considerable delay in ART initiation, both for those eventually diagnosed with TB, and also for those whose symptoms necessitate investigation, but are not diagnosed with TB.

New diagnostic tests for tuberculosis

Genotypic detection systems allow more rapid identification of *M. tuberculosis*. Xpert MTB/RIF (GeneXpert, Cepheid) has potential to provide same-day results with greatly improved sensitivity over smear microscopy. It has excellent performance characteristics for smear-positive patients, but sensitivity was only 72% among smear-negative, culture-positive patients.[10] HIV-positive individuals with low CD4 counts are often smear negative, and Xpert MTB/RIF will miss a substantial number of individuals in this group, who are at highest risk of death from TB. In addition, Xpert MTB/RIF is expensive, and unlikely to be widely available in primary health centres in resource-constrained settings in the near future.[6]

There is thus an urgent need for management algorithms, using tools available at point-of-care in primary health care clinics, to identify individuals with advanced HIV disease who have a high probability of active TB, and of death from TB, in order that TB treatment can be initiated rapidly, followed by ART.

Another newly-evaluated TB diagnostic test is an ELISA assay for lipoarabinomannan (LAM), a cell wall lipopolysaccharide specific to mycobacteria[11] which is released from metabolically-active or degrading bacterial cells and is detectable in urine.[12] A urine test is attractive because samples are easily collected and pose low infection risk to staff and other patients. Following evaluations of an early urinary LAM immunoassay[13] and an analogous prototype test LAM-ELISA (Chemogen, South Portland, ME, USA) in sub-Saharan Africa and India,[8,14-17] a commercial version marketed as Clearview TB ELISA (Inverness Medical Innovations Inc, Scarborough, ME, USA) has also been evaluated.[18-20] Among HIV-negative patients, LAM assays are insufficiently sensitive, with a pooled sensitivity estimate of 14% in recent meta-analyses.[21,22] Sensitivity is better, ranging from 21-81%, among HIV-positive TB patients.[14,17-19,23] The wide variation in sensitivity between studies most likely reflects differences in methodology, study population and the gold standard for tuberculosis diagnosis. Sensitivity is consistently higher in patients with low CD4 counts[19,22] (61% at CD4<50 cells per µl, 48% for all <100, 44% for all <150, 36% for all <200[23]), probably because of higher mycobacterial load. Specificity of this assay is high irrespective of HIV status, and among HIV-positive patients ranges from 83-100%.[8,17,19,20,23] Clearview TB ELISA detects both pulmonary and extrapulmonary TB,[18] advantageous for HIV-positive patients.

The Clearview TB ELISA assay provides results in less than 3 hours but is a laboratory-based test requiring urine processing within 24 hours (unless samples are frozen) which limits its utility in resource-constrained settings. A new point-of-care lateral-flow formulation of this test (Determine TB-LAM Ag [Alere, Waltham, MA, USA]) has recently been evaluated among ambulant patients screened for TB prior to starting ART in South Africa.[23] Sensitivity was 27% overall vs. a gold standard of culture positivity, similar to sputum microscopy and to Clearview TB ELISA. Among hospitalised HIV-infected TB suspects, Determine® sensitivity was 74% in all TB cases, 85% among patients with CD4 count <100 cells per µL, and 75% in smear-negative culture-proven TB cases with CD4 count <200 cells per µL.[24] Determine® TB provides results within 30 minutes, i.e. within a single clinic visit, and does not require refrigerated storage or sample processing. Inter-observer variability for reading the strips is good. [23,24] It is currently marketed in South Africa at $3.50 per strip and these preliminary evaluations suggest it has potential to be a useful low-cost point-of-care diagnostic test, particularly amongst patients with low CD4 cell counts.

The performance characteristics of the urine LAM test are summarized in Table 1.

Table 1: Performance characteristics of urine LAM test

Author, Country	Type of test	Patient characteristics (n)	Sensitivity		Specificity	
			HIV-	HIV+	HIV-	HIV+
Lawn[23] South Africa	Determine® TB (POC)	ART clinic enrollees with C+ TB (85)	N/A	Determine: 28.2% Clearview: 27.1%	N/A	
	Clearview® TB-ELISA	ART clinic enrollees without TB (431)	N/A	N/A	N/A	Determine: 98.6% Clearview: 98.1%
Peter [24] South Africa	Determine® TB (POC)	Hospitalised TB suspects with TB[a]	N/A	Determine: 74% Clearview: 58%	N/A	N/A
	Clearview® TB-ELISA	Hospitalised TB suspects without TB	N/A	N/A	N/A	Determine: 95% Clearview: 95%
Gounder[20] South Africa	Clearview® ELISA	HIV-care attendees with microbiologically-proven TB (30)	N/A	32% (SSM+ 40%, SSM- 20%)	N/A	N/A
		Attendees without TB (392)	N/A	N/A	N/A	98%
Dheda[19] South Africa	Clearview® ELISA	Ambulant TB suspects with C+ TB (141)	13%		N/A	N/A
			6%	21% (SSM- Cx+ 25%)	N/A	N/A
		Ambulant TB suspects with probable TB (127)	2%		N/A	N/A
		Ambulant TB Suspects without TB (172)	N/A	N/A	99%	
					99%	100%
Shah[18] South Africa	Clearview® ELISA	Hospitalized TB suspects with microbiologically confirmed TB (193)	59%		N/A	N/A
			14%	67%		
		Hospitalized TB suspects with possible TB (89)	0%	18%	N/A	N/A
		Hospitalized TB suspects without TB (122)	N/A	N/A	96%	
					100%	94%
Daley[15] India	Chemogen LAM-ELISA	TB suspects with Cx+ TB (47)	17.8% (SSM+ 23%, SSM- 25%)		N/A	
				20%	N/A	N/A
		TB suspects without TB (153)	N/A	N/A	87.7%	
						83.3%
Lawn[8] South Africa	Chemogen LAM-ELISA	ART clinic enrollees with C+ TB (58)	N/A	38%	N/A	N/A
		ART clinic enrollees without TB (177)	N/A	N/A	N/A	100%
Mutetwa[17] Zimbabwe	Chemogen LAM-ELISA	Adult and adolescent C+ TB cases (161)	44% (SSM+ Cx+ 50%, SSM- CX+ 28%)		N/A	N/A
			52%	21%	N/A	N/A
		Probable TB cases (34)	27%		N/A	N/A
		Patients without TB (114)	N/A	N/A	89%	
					93%	86%
Reither[16] Tanzania	Chemogen LAM-ELISA	Ambulant TB suspects with C+ TB (69)	50.7% (SSM+ 56.3%, SSM- 38.1%)		N/A	N/A
			21%	62.0% (SSM+ 74.2%, SSM- 42%)		
		Ambulant TB suspects without TB (82)	N/A		87.8%	
					91%	84%
Boehme[14] Tanzania	Chemogen LAM-ELISA	TB suspects with C+ TB (132)	80.3% (SSM+ 82.9%, SSM- 76%)		N/A	N/A
			73.5%	81.2%	N/A	N/A
		TB suspects with probable TB (17)	76.5%		N/A	N/A
		Healthy volunteers (103)	N/A	N/A	99.0%	
Tessema[13] Ethiopia	In-house urine LAM	Ambulant TB suspects with TB[b] (200)	74% (SSM+ 81.3%, SSM- 57.4%)		N/A	N/A
		Ambulant TB suspects without TB[b] (800)	N/A	N/A	86.9%	
		Healthy controls (50)	N/A	N/A	90%	

[a] Not all TB cases were culture-confirmed; [b]The diagnostic work up for TB did not include mycobacterial culture. POC, point of care; SSM-, sputum smear negative; SSM+, sputum smear positive; C+, Culture positive

A point-of-care algorithm for tuberculosis

Other data which could identify individuals with a high probability of TB, and which could be available at the point of care, are haemoglobin (Hb) concentration and body mass index (BMI). Low haemoglobin and low BMI predict both prevalent TB among ART-eligible patients (Hanifa Y, personal communication, as above and table 2), and also early (<6 months) incident TB among patients starting ART (table 2).[25] In addition, both low haemoglobin and low BMI are consistently associated with early mortality among people with HIV, including those starting ART.[26-28] Additional analysis of South African data evaluating LAM among hospitalised patients[18] suggests that among individuals with CD4<150, a tool comprising any of positive LAM, BMI<18.5 and Hb<10 has a sensitivity of 92% and positive predictive value of 54% vs. a gold standard of culture-positive TB (Shah M, personal communication). We propose to combine haemoglobin, BMI and urine LAM with symptom screening for TB[29] to classify study patients as having high, medium or low probability of active TB (see Figure, Appendix 1), and accordingly start presumptive TB treatment, ART, or both, with minimal delay. An important strength of this algorithm is that we will identify individuals at highest risk of death (low Hb, low BMI and TB symptoms) and at highest risk of TB; by promptly starting appropriate therapy for these individuals, we will maximise the reduction in mortality.

Table 2: Baseline haemoglobin and BMI as predictors of prevalent and early (<6 months) incident TB among patients starting ART or attending for HIV care

Author Country Study type Study population	Study procedures Median CD4 count (N)	Association with prevalent TB + / or Association with early incident TB (< 6months) after ART initiation	
		Baseline haemoglobin (g/dl)	Baseline BMI (kg/m^2)
Van Rie[25] South Africa Observational cohort Adults initiating ART [a]	ACF: at enrolment + follow-up (N=7536)	**<13 (m) / <12 (f) / <11 (pregnancy) vs. not anaemic** aHR (95% CI) incident TB [b] 2.54 (1.92-3.37)	**< 18.5, 18.5-24.9, vs. ≥ 25** aHR (95% CI) incident TB [b] 2.03 (1.34-3.07), and 1.69 (1.18-2.42)
Lawn[30] South Africa Prospective study Adults enrolling for ART	Systematic screening using sputum culture at enrolment 171 cells/µl (N=468)		**< 18, >25, vs. 18-25** aRR undiagnosed prevalent TB [b] 2.94 (*P*=0.009) and 0.70 (*P*=0.24)
Komati[31] South Africa Prospective trial Adults initiating ART [a]	ACF: at enrolment + follow-up 106 cells/µl (N=1771)	Baseline BMI and haemoglobin significant risk factors for incident TB [c] (data not shown).	
Moore[4] Uganda Prospective cohort Adults initiating ART [a]	ACF: at enrolment + follow-up 127 cells/µl (N=1044)		**≤ 18 vs. > 18** aOR undiagnosed prevalent TB [d] 4.95 (*P*<0.001)
Kufa T [e] South Africa Cross-sectional Patients attending for HIV care [a]	Systematic screening using sputum culture at enrolment 215 cells/µl (N=422)	**< 10 vs. ≥ 10** aOR undiagnosed prevalent TB [c] 3.12 (P=0.02)	**< 18.5 vs. ≥18.5** aOR undiagnosed prevalent TB [d] 2.70 (P=0.004)
Hanifa Y [e] South Africa Prospective cohort Adults initiating ART [a]	Systematic screening using sputum culture at enrolment 120 cells/µl (N=293)	**≥ 10 vs. < 10** aOR undiagnosed prevalent TB [b] 0.32 (P=0.02)	**≥18.5 vs. < 18.5** aOR undiagnosed prevalent TB [b] 0.59 (P=0.12) aOR undiagnosed prevalent TB [d] 0.53 (P=0.02)

[a] Participants had not received isoniazid preventive therapy; [b] culture-proven TB; [c] microbiologically confirmed TB (smear or culture positive, any site); [d] TB cases included patients without microbiological confirmation; [e] Personal communication, manuscript submitted

ACF: active case finding for TB (clinical assessment followed by further investigation of TB suspects); aHR: adjusted hazard ratio; aOR: adjusted odds ratio; aRR: adjusted risk ratio; BMI: body mass index; CI: confidence interval; m: male; f: female

Rationale for targeting individuals with CD4≤150 cells/µl

We have selected the CD4 threshold of 150 cells/µl for the following reasons:

(1) high risk for early mortality on ART
(2) high risk for prevalent and incident TB disease
(3) marked increase in mortality with delay in ART initiation with CD4 ≤ 150
(4) relevant to many patients initiating ART in South Africa and other resource limited settings.

Recently-published data from three randomized clinical trials are relevant to rapid ART initiation in this group, specifically in patients receiving treatment for TB. The SAPIT,[32] CAMELIA,[33] and STRIDE[34] studies all reported decreased mortality among individuals who started ART within about 2 weeks of initiating TB treatment, compared with between 8 and 13 weeks of starting ART. However, in the SAPIT and STRIDE studies this decrease in mortality was only observed among participants with baseline CD4 <50, and not those with CD4 50-500 or 50-200. Sample size limited narrower CD4 strata, thus the 25-35% of the patients in the higher CD4 category had CD4 >150. Thus there are fewer data to guide the optimal timing of ART start among patients with CD4 > 50.

A further important point is the difference between those studies and the context of this proposed study. In all three studies (SAPIT, CAMELIA and STRIDE), participants experienced mortality rates considerably lower than those we have observed in ART clinics in South Africa. For example, the median CD4 count at entry into the CAMELIA study was 25, however, mortality was only 8 per 100 person-years in the earlier ART arm vs. 13 per 100 person-years in the later ART arm.[33] By contrast, in workplace and community setting ART care in South Africa, mortality during the first 12 months of ART for individuals with CD4<50 ranges from 18-30 per 100 person-years. It is unclear why the mortality in CAMELIA was so much lower than the overall South African experience, as the inclusion criteria did not specifically exclude particularly sick individuals. However, one point about the inclusion criteria is worth noting: participants had to be sputum smear positive for acid-fast bacilli. As smear negative TB has a worse prognosis than smear positive,[35-37] the individuals included in this trial may have been at lower risk of mortality. The overall lower risk in mortality may have translated into a lower risk in overall mortality and a lower increase in mortality with ART delay. The SAPIT study included patients with a wider CD4 range but all were required to be smear positive, thus also potentially selecting individuals with lower risk of dying.[32] The STRIDE study included smear negative, TB culture positive patients, but excluded individuals with a haemoglobin ≤7 g/dl, absolute neutrophil count of ≤500, and platelets ≤ 50,000 thus (probably) eliminating individuals in most need of urgent cART initiation.

Thus for the following reasons we believe that a CD4 threshold of ≤150 is appropriate for this study:

(1) Lack of clear data from randomized clinical trials as to the optimal threshold for early ART among individuals starting TB therapy, particularly those who are sputum smear negative.
(2) High mortality while waiting for ART and early on ART in the South African populations with which we have worked.

Study hypothesis

We hypothesise that a care pathway for adults with HIV presenting for ART with CD4≤150, using point-of-care technology to rapidly identify individuals at high risk of TB and ensure they start TB treatment, then ART, will markedly reduce early mortality. This will be via two mechanisms. Firstly, most people with active TB will initiate TB treatment rapidly and prior to ART, thus reducing TB-specific mortality. Secondly, our strategy will reduce time to ART initiation among most individuals in the intervention arm, both with and without TB, which will reduce all-cause mortality. We hypothesise that the increase in survival due to this strategy will greatly outweigh the risks of treatment toxicities overall among individuals at high risk of early mortality presenting for ART.

Systematic review for published studies addressing this issue

We searched Medline and Embase using the terms
1. (presumptive or empiric*) adj3 (treatment or therap*)
2. AIDS or HIV or acquired immunodeficiency syndrome
3. TB or tuberculosis
4. 1 and 2 and 3

We also searched "Africa wide information" using equivalent terms; and clinical trials databases. These searches yielded no studies of the type we propose.

Other clinical trials addressing this issue

ACTG A5274 (REMEMBER) is a multi-centre individually-randomised trial among individuals with CD4<50 and no evidence of definite or possible TB. The intervention comprises presumptive 4-drug TB treatment, started as soon as possible after (within 7 days of) the start of ART, compared to TB treatment given according to local practice (http://clinicaltrials.gov/ct2/show/NCT01380080). The trial is estimated to complete in August 2015.

PROMPT (http://clinicaltrials.gov/ct2/show/study/NCT01417988) is an individually-randomised trial in four African countries among individuals with CD4<50 and BMI<18, who are sputum smear negative and do not fulfil WHO criteria for smear negative TB. The intervention comprises 4-drug TB treatment, followed by ART within 2 weeks, compared with standard treatment with ART alone. This EDCTP-funded trial is estimated to complete in June 2014.

Both these studies address the same problem as our trial, but using different approaches, and individually-randomised designs. At the time of writing (November 2011), neither has started recruitment. Our trial, with its innovative focus on accessible technology for point-of-care triage, will provide novel and complementary results, and will be particularly relevant to under-resourced primary care settings where chest radiography is not readily available. By evaluating this novel approach at clinic rather than individual level, we will be able to compare our strategy to the current TB diagnostic pathway as it is implemented in routine practice.

Proposed study sites

The Aurum Institute is funded by the President's Emergency Plan for AIDS Relief (PEPFAR) to provide health systems strengthening support to primary health clinics in the Greater Tubatse and Ephraim Mogale subdistricts of Limpopo province. This support consists of training, mentoring of nurses to initiate antiretroviral therapy, data management support and monitoring and evaluation. In addition, the Aurum Institute provides HIV counselling and testing services in these districts and refers HIV-infected patients to the primary health centres. Similar health systems strengthening is also provided by the Foundation for Professional Development in primary health clinics in the Tshwane district of Gauteng province and the Bojanala district of North West province. Primary health clinics and health centres supported by Aurum and FPD are proposed as sites for this study, and a provisional list of clinics which may participate is shown below. We are currently in discussion with the relevant local health authorities concerning the participation of these clinics, and updating data concerning numbers of individuals initiating ART at each clinic in order to inform the final selection of clinics for this study.

Table 3: potential study clinics

DISTRICT	**SITE NAME**	**ART ENROLLMENTS PER MONTH (mean over 3 months)**
GREATER TUBATSE	PRAKTISEER	12
GREATER TUBATSE	BURGERSFORT CHC	33
GREATER TUBATSE	DILOKONG	44
GREATER TUBATSE	MECKLENBERG CCMT	22
GREATER TUBATSE	NGWAABE	8
GREATER TUBATSE	MAHUBEHUBE	8
EPHRAIM MOGALE	LEEWFONTEIN	13
EPHRAIM MOGALE	ELANDSKRAAL	10
TSHWANE	MARIA RONTO	30
TSHWANE	SOSH 2	33
TSHWANE	SOSH BLOCK TT	39
TSHWANE	SOSH CHC	70
TSHWANE	BLOCK X	34
TSHWANE	KGABO	79
TSHWANE	WINTERVELDT	20
TSHWANE	PHEDISONG 1	32
TSHWANE	PHEDISONG 4	35
TSHWANE	TLAMELONG	54

TSHWANE	SHOSH BLOCK JJ	33
TSHWANE	KJ MOTUBATSE	70
TSHWANE	BOIKUTSONG	33
TSHWANE	GARANKUWA	16
TSHWANE	DR G MUKHARI	57
TSHWANE	ODI HOSP	54
BOJANALA	MATHIBESTAD	41
BOJANALA	MAUBANE	25
BOJANALA	SEAPARANKWE	16

Potential risks to the trial: Xpert MTB/RIF roll-out
A potential "risk" to the trial is the roll-out of new diagnostic tests for TB. In particular, Xpert MTB/RIF is being rolled out to laboratories in South Africa, and is under evaluation as a point-of-care test in primary health clinics in South Africa and elsewhere. Discussion with the South African Department of Health indicates that their top priority is to implement Xpert MTB/RIF within existing laboratories, before implementation in primary care centres. Preliminary costing data suggest that Xpert MTB/RIF costs will be highly sensitive to throughput, making it much more expensive to implement small Xpert instruments in clinics compared with larger instruments in laboratories. It is unlikely that Xpert MTB/RIF will be widely available in primary health centres, particularly in rural areas, during the timeframe of this study. In our final selection of study sites, we aim to avoid clinics likely to acquire this technology. Where Xpert MTB/RIF machines are placed in laboratories which are distant from the clinics they serve, the turn-around time is likely be similar to that for smear microscopy, which in our experience may be up to a week, and thus the availability of Xpert MTB/RIF is unlikely to reduce this turn-around time or the primary default rate (i.e. the proportion of individuals with a positive sputum result who never start TB treatment). In addition, Xpert MTB/RIF has relatively low sensitivity among individuals with advanced HIV-related immunosuppression (58% among individuals presenting to start ART in Cape Town[30]) and therefore, even if it can feasibly be used in rural primary health centres, it is not an ideal screening test in our target population.

Our study will provide data which will complement studies evaluating Xpert MTB/RIF. Even if some participating clinics start to use Xpert MTB/RIF technology (on- or off-site), our study remains valid, and we will be able to document how implementation affects the diagnostic process and patient outcomes.

2. Aims and objectives

Primary objective
To compare 6-month mortality among patients with HIV disease and CD4≤150 cells/µl referred to start ART between *intervention clinics* implementing a point-of-care algorithm to identify individuals with a high probability of active TB, and facilitate rapid initiation of TB treatment, followed by ART; vs. *control clinics* delivering standard of care management according to South African TB/HIV care guidelines.

Secondary objectives:
1. To compare severe morbidity in intervention vs. control arms, as measured by the duration of hospital admission in the first 6 months
2. To compare time from enrolment to ART start in intervention vs. control arms

3. To compare overall retention in ART care, and retention among those known alive, at 6 months in intervention vs. control arms
4. To document serious adverse events, and severe adverse events in specified categories, in the intervention and control arms
5. To estimate the cost per disability-adjusted life year (DALY) gained

Exploratory objectives
1. To estimate the frequency of immune reconstitution syndrome in intervention vs. control arms
2. To estimate mortality to 12 months in intervention and control arms

3. Methods

3.1 Study design

Open (unblinded) pragmatic cluster-randomised trial, with primary health clinics as the unit of randomisation.

3.2 Study sites

The study will be conducted at primary health centres and community health centres in a mixture of urban and rural settings in Gauteng, North West and Limpopo provinces, South Africa, with which our teams already have working relationships.

Inclusion criteria for participating clinics:
- capacity to initiate and deliver both TB treatment and ART
- rates of ART initiation which will allow us to recruit the required numbers (12 patients per month with CD4≤150 at each clinic) within the proposed timeline.

Exclusion criteria for participating clinics:
- on-site mycobacterial laboratory facilities
- on-site Xpert MTB/RIF testing.

Note added to protocol version 5.0, 31 August 2013: during the course of the study to date, Xpert MTB/RIF has been rolled out nationwide in South Africa, such that many of our study clinics are now using Xpert MTB/RIF as their first diagnostic test for people with HIV with symptoms suggesting TB. In this amendment we propose to expand the number of study clinics. Where possible, we will continue to avoid recruiting at any clinic where Xpert MTB/RIF is used with results delivered to patients on the same day, but we may include new clinics which use Xpert MTB/RIF routinely for HIV positive people.

3.2.1 Randomisation of study clinics

Clinics will be randomly allocated to intervention or control arms. Since site assessment data showed little variability in the proportion of patients potentially eligible for the study with CD4<50, the random allocation will not be stratified. Randomisation will be restricted based on urban/rural (which also provides restriction by province since all urban clinics are in Gauteng province), mean CD4 at ART initiation, and total number of patients initiating ART per month, in order to help achieve overall balance between the study arms. The senior statistician will be responsible for the randomisation.

Note added to protocol version 5.0, 31 August 2013: we propose to extend enrolment to four additional clinics in order to ensure that the study remains adequately powered to detect an important difference in mortality between arms, assuming that four additional clinics can be found

where recruitment is predicted to be rapid, in order to minimise the impact on study timelines.These four clinics will be randomised in a ratio of 1:1 to the intervention and control arms.

3.3 Study population

The study population comprises adults with HIV infection, with CD4≤150 cells/µl, and willing to start ART. In order to maximise generalisability, we plan to make the trial as inclusive as possible.

3.3.1 Patient selection criteria

Inclusion criteria:

- documented HIV seropositive status;
- eligible and willing to start ART;
- CD4≤150 cells/µl.

Exclusion criteria:

- age <18 years;
- currently on TB treatment, or completed TB treatment in last 3 months;
- any ART taken in the last 6 months;

- contraindication to efavirenz (based on current South African ART guidelines);
- too sick to be managed in ambulatory care;
- other symptoms necessitating immediate referral to secondary care;
- known chronic hepatitis or high alcohol intake (per week, >28 units (men) or >21 units (women)
- intending to move away from the study clinic area in the next 6 months.

3.4 Patient selection procedures

Consecutive patients referred (either internally within the clinic or from another facility) for ART initiation who have CD4≤150 cells/µl will be referred by health service staff, with the patient's agreement, to study staff for explanation of the study, and enrolment if they are eligible and give consent. A log will be kept of patients who refuse referral to the study team or are not enrolled, for whatever reason.

3.5 Intervention

The intervention comprises a management strategy which aims to identify, among HIV-positive patients with CD4≤150 cells/µl, presenting to start ART, those at highest risk of TB, so that they can start TB treatment immediately, followed by ART.

After a consenting patient has been determined to be eligible to join the study, the study nurse will complete a questionnaire to determine TB symptoms (cough, fever, weight loss, night sweats), TB history and WHO stage. The nurse will then determine the BMI, perform a point-of-care urine LAM assay, and, if no haemoglobin result is available, determine haemoglobin concentration using a point-of-care assay.

The study algorithm is illustrated in the Figure (appendix 1). Patients with any of: positive LAM, Hb<10 g/dl, BMI<18.5 (along with any patient known to be sputum smear positive, or Xpert MTB/RIF positive) will be categorised as high probability TB, and will start TB treatment immediately. The algorithm is applicable regardless of whether the suspected TB is pulmonary or extrapulmonary. In line with WHO and South African guidelines, they will start ART as soon as possible (usually two weeks) afterwards. Patients who have no symptoms suggesting TB, negative LAM, Hb≥10 g/dl and BMI≥18.5 (and not known sputum smear positive) will be categorised as low probability TB, and will

start ART (without TB treatment) as soon as possible. All others (symptomatic but negative LAM, Hb≥10 g/dl, BMI≥18.5) will be categorised as medium probability TB, and will be managed in accordance with national guidelines for smear-negative TB, i.e. given broad spectrum (non-quinolone) antibiotics if indicated; an additional routine sputum sample will be taken for smear and mycobacterial culture in line with routine practice, and chest radiography will be arranged if not recently performed, with review within one week wherever possible. At review, they will be classified as high or low probability of TB, based on symptom review, response to antibiotic treatment, sputum smears, chest radiograph report, and repeat urine LAM. Those with high TB probability will start TB treatment, then ART as soon as possible; those with low TB probability will start ART as soon as possible. Patients with specific symptoms suggesting diagnoses other than TB will be managed in accordance with national guidelines.

Patients in intervention clinics who start TB treatment based on the study algorithm will, when they start ART, need to take efavirenz-based ART in order for their ART to be compatible with TB treatment, and any unable or unwilling to do so will be excluded from the trial. Outside this situation, patients can take any ART regimen appropriate for them, as specified in South African ART guidelines.

3.6 Outcome measures

Primary outcome:
All-cause mortality at 6 months after enrolment

Secondary outcomes:
1. Duration of hospital admission in first 6 months after enrolment
2. Time from enrolment to ART start
3. Proportion of patients retained in care, i.e. documented to have attended clinic for HIV care at 6 months (window: 150-240 days) after enrolment
4. Study-defined serious adverse events, and severe adverse events in specified categories (particularly hepatotoxicity, hypersensitivity, peripheral neuropathy, and nephrotoxicity)
5. Economic outcomes, detailed below

We explain above our rationale for defining mortality as the primary outcome; we will assess this at 6 months because the risk of death reduces substantially with increasing time after ART start. It is possible that there may be increased morbidity in the intervention arm as a result of drug toxicity or immune reconstitution syndrome. A secondary outcome is therefore severe morbidity, defined by duration of hospitalisation (determined by patient report supplemented by notes review). We will compare time to ART start and retention in care to 6 months between study arms. To assure patient safety, we will report study-defined serious adverse events, and severe adverse events in specified categories.

3.7 Study procedures

3.7.1 Enrolment procedures: intervention and control clinics

Participants will be enrolled at the time they are determined eligible to start ART.
At enrolment, following informed consent, participants will complete a questionnaire covering
- locator information, including national ID number
- demographic information
- past history of TB, HIV (including date of HIV tests and previous ART exposure) and other illnesses

- TB symptoms (using WHO screening tool, also including symptom duration)
- height and weight (for BMI)
- most recent CD4, from clinic notes
- haemoglobin, from clinic notes
- any TB test results, from clinic notes

Participants in both intervention and control clinics will also be asked to give:
i) a urine specimen for storage for study purposes: this will be tested at a later date for tuberculosis, and for LAM using the lateral flow or laboratory ELISA assay. We may also perform laboratory tests for evidence of other relevant conditions such as cryptococcal disease and pneumococcal disease.
ii) a finger-prick blood sample to be stored as around 3 dried blood spots, which will be tested later for evidence of relevant conditions such as cryptococcal disease or hepatitis B infection.
These specimens will be transported to BARC laboratories, Johannesburg, and stored for later testing in batches; results will not be returned to clinics and will not be available for patient management. Any specimens remaining after these tests have been performed at BARC will be transferred to the Aurum Institute laboratories, Johannesburg, and stored for up to five years after the end of the study, in case tests become available which can be performed on urine or dried blood spots which help us understand causes of disease in our study participants. If we propose to do any tests which are not listed above, we will seek additional approval from Research Ethics Committees.

3.7.2 Clinical pathway in intervention clinics

In *intervention* clinics, a research nurse will assess patients at enrolment, determine their BMI, haemoglobin, perform a point-of-care urine LAM test, and facilitate their treatment pathway based on the study algorithm (appendix 1). Patients assigned by the algorithm to start TB treatment will be managed in accordance with national guidelines. Research staff will promote treatment literacy and adherence to both TB treatment and ART, to offset the anticipated increased burden on routine TB services because of higher numbers of patients on TB treatment as the study rolls out (ART treatment support is standard of care in South Africa). It is possible that retention in care could be lower in the intervention arm because patients will start treatment sooner, with less delay to allow pre-ART counselling. Retention in care is thus is a secondary outcome of the study.

A sputum sample will be taken from all intervention arm participants at enrolment for study purposes, to allow determination of a "gold standard" TB diagnosis (defined as culture positive for *M. tuberculosis*). If the study sputum sample taken at enrolment yields positive results on culture or drug susceptibility testing (DST) (based on the MTB DR Plus or other assay), these results will be communicated to the clinic so that patients' treatment can be modified accordingly.

Symptomatic enrolees will have a sputum sent for smear (or Xpert MTB/RIF) via the routine system operating in their clinic, in accordance with national guidelines.

Study staff will endeavour to ensure that study participants are managed in accordance with the study management algorithm. However, since participants remain under the care of clinic staff throughout the study, if a clinic doctor considers that a participant's management should differ from the pathway proposed by the study algorithm, their opinion will be respected. Such decisions will be documented by study staff in order that adherence to the study algorithm can be determined.

3.7.3 Procedures in control clinics

In *control clinics*, we will similarly recruit HIV-positive patients with CD4≤150 at the point they receive their CD4 result. Consenting patients will similarly be interviewed by a study nurse concerning locator information, complete the baseline questionnaire, and have BMI determined. No

further study procedures are required, and further assessment for TB and preparation for ART will be undertaken by clinic staff according to routine practice following national guidelines: symptomatic patients submit sputum for microscopy; TB treatment is started if the sputum smear (or Xpert MTB/RIF) is positive; and further investigations with sputum culture and chest radiography will be undertaken if the sputum smear is negative.

At all clinics taking part in the study, whether assigned to intervention or control arm, if management guidelines for TB suspects change during the study period (for example if Xpert MTB/RIF becomes standard of care in any study clinic) then TB suspects will be managed according to the updated guidelines. Senior clinically-qualified investigators on the study team will be available to discuss clinical management of study participants if clinic staff have uncertainties or concerns.

Study procedures are summarised in Table 4.

Table 4: summary of study procedures

		INTERVENTION CLINICS				CONTROL CLINICS			
	Enrolment	1 week (or less)	2 weeks	2 months	6 months	Enrolment	1 week (or less)	2 months	6 months
Informed consent	√					√			
Locator information	√					√			
Baseline questionnaire	√					√			
TB symptom screen	√	√*				√			
BMI	√					√			
Lab tests									
Haemoglobin	√								
Urine LAM	√	√*							
Sputum TB microscopy & culture	√								
Urine / dried blood spot for storage	√					√			
TB patient follow up visit			√**						
Patient record review		√		√	√		√	√	√
6 month questionnaire					√				√
12 month questionnaire (subset of participants)					√				√

* For those with medium probability of TB according to the study algorithm

** For those started on TB treatment, to check if stable on TB treatment and ready to start ART

3.7.4 Follow up procedures

Patients in the intervention arm who are classified by the algorithm as medium probability TB will be reviewed by study staff within one week wherever possible. At this visit, if there is evidence of tuberculosis based on continuing symptoms, non-response to antibiotics, positive sputum smear, positive Xpert MTB/RIF result, mycobacterial culture, radiographic evidence or urine LAM, they will start TB treatment. If they are asymptomatic and have no other evidence to suggest active TB, they will start ART. If there is uncertainty, clinical judgement will be used, in discussion with clinic staff and if necessary study clinicians.

Patients in the intervention arm who start TB treatment will be reviewed by study staff around two weeks later, to facilitate the start of ART if there is no clinical reason to defer the start of ART.

Subsequent management of patients in both arms will be primarily by clinic staff, following South African guidelines. If there are uncertainties or concerns, particularly concerning patients in the intervention arm who start TB treatment on the basis of the study algorithm alone without other supporting evidence, clinic staff will be encouraged to discuss management with study clinicians, one of whom will be available at all times. It may be appropriate for some patients to discontinue TB treatment if there is no supporting evidence and no evidence of improvement. Such decisions will be made by clinic staff, supported by study staff as required, and referral to higher level care for additional investigation and treatment may be needed.

Clinic records of all patients in both arms will be reviewed after about one week, to capture routinely sent pre-ART baseline blood tests (haemoglobin, liver function tests, creatinine etc), and again at about 2 months, to determine TB treatment start date; progress on TB treatment; any adverse events on TB treatment; ART start date; any adverse events on ART; laboratory results since enrolment (particularly any sputum smear or culture results, CD4 counts etc) and reports of any other investigations, such as radiology; treatment given, health service use including number and nature of clinic visits, and referrals to other services. If this record review uncovers any positive results, particularly positive TB microbiological results, which have not been appropriately acted upon, study clinicians will be consulted and the clinical team informed if it appears that the patient's management should be reviewed.

All patients in both arms will be reviewed 6 months after enrolment, wherever possible by face-to-face interview, to determine health status, treatments received and health service use (e.g. number and type of clinic visits; duration and nature of any hospitalisation) since enrolment. This information will be supplemented by review of clinic records, similarly to determine use of health services, (particularly any hospitalisation), any additional diagnoses made and adverse events documented, and treatment given. For patients who have been hospitalised, hospital records will be reviewed to determine duration of hospitalisation, level of care given and proposed diagnoses. The interview will include questions relevant to the economic outcomes described in section 4.

A subset of participants recruited in the early phase of the study will be asked for permission for extended follow-up to 12 months, to determine vital status and major morbidity, particularly any new TB episodes. A short interview will be undertaken at 12 months either in person, preferably to coincide with a clinic visit, or by telephone if this is more convenient.

3.8 Pilot study work

All case report forms will be piloted in an anonymised fashion i.e. collecting data without any personal identifiers, in order to ensure that the forms are acceptable to, and easily comprehensible by, participants, that they fulfil their purpose well, and to test study systems. These data will not contribute to the final analysis.

To help the study team understand current practice and patient pathways in the study clinics, we will collect anonymised data from routine records to document usual practice for management of patients with HIV presenting to start ART before the start of the intervention. This will involve only record review: no patient contact will be required. If feasible, we will collect data on 50-100 patients per clinic. This will include time from first HIV positive test to CD4 result being given; among those eligible to start ART, TB screening practice and time from CD4 result to start of ART; 6-month outcomes on ART; TB treatment outcomes among patients with HIV. We will also review TB and ART treatment records to collect anonymised information from a sample of patients at each clinic concerning health service use (number and nature of clinic visits; any hospital referrals and / or hospitalisations) and records of adverse events or symptoms suggesting immune reconstitution syndrome, in order to refine and pilot test our case note extraction procedures.

The validity of the study will depend on successful follow-up of a high proportion of participants, with accurate ascertainment of outcomes. We will therefore specifically test these procedures on around 10-20 patients per clinic (both intervention and control); however, no study tests (LAM or haemoglobin) will be performed as part of this pilot study, and patient management will be as per usual practice. We will collect data at enrolment as for control clinics, with follow up to around 2 months (timed to coincide with a routine clinic visit). At follow-up, we will seek information on vital status, diagnoses since enrolment, treatments and health care use, based on interview of the patient, or if they are not contactable, their designated contacts, and review of medical records. In addition we will seek feedback from participants concerning their experience, in order to refine our procedures for the main study. A specific participant information sheet will be used for this pilot phase.

3.9 Ascertainment of outcomes

All study patients will be reviewed 6 months after enrolment to determine primary (vital status) and secondary outcomes as above (plus retention in care at 6 months), based both on patient interview and on medical records. Study patients will be actively traced, if necessary, using locator information obtained at enrolment. Study patients who cannot be traced will be matched against South African mortality registration using their national ID number. In addition, to minimise ascertainment bias, a record review will be conducted for all study patients (intervention and control arm) after 2 months to document vital status, and any secondary outcomes (ART start date, TB treatment start date, documented symptoms suggesting immune reconstitution syndrome, documented health service use including hospitalisations etc).

As part of routine care, clinic staff should ensure that patients' contact details are up to date at every attendance. As part of routine support to the participating clinics, during the study period, Aurum and FPD programme staff will work with clinic staff to strengthen these existing systems for TB and HIV patients. This will assist study staff with tracing of any participants who are lost to follow up, but will be of benefit to staff and TB/HIV patients at all participating sites, regardless of study arm.

3.9.1 Definition of adverse events

All drugs used in this study are licensed drugs, used for their licensed indications. The purpose of adverse event reporting in this study is not to identify potential new adverse events associated with drugs used in the study, but rather to ensure that the study management strategy does not cause harm to participants. We therefore do not propose to report all adverse events, but to report serious and severe adverse events in study-defined criteria.

A serious adverse event will be defined, conventionally, as one which:

- results in death
- is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does include an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or prolongation of existing hospitalization (hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE) or
- results in persistent or significant disability/incapacity

AND is in one or more of the study-defined categories of hepatitis, hypersensitivity, peripheral neuropathy, optic neuritis or nephrotoxicity.

We will also report severe adverse events, defined as those graded 3 or 4 using the Division of AIDS classification (appendix 2), in the study-defined categories. We will report all deaths in either study arm, regardless of cause.

3.9.2 Ascertainment of adverse events

Data sources for ascertainment of adverse events include:

- participant interview at the 6 month visit
- if the participant cannot be contacted at 6 months, reports from friends and / or relatives
- participant medical records and patient registers, reviewed systematically at 2 and 6 months after enrolment.

Given the additional study visits early after enrolment for intervention arm participants categorised to high or medium probability, we anticipate that ascertainment of adverse events is likely to be much higher in the intervention arm. We will document the method of ascertainment for possible adverse events so that we can compare those ascertained in a similar way (i.e. based on case note review and 6 month interview) in the two arms. However, we expect that in the intervention arm, events are more likely to be recorded in routine case notes, as a consequence of study activities. The frequency of adverse events compared between study arms will need to be interpreted with these issues in mind.

3.9.3 Management of adverse events

Since all the drugs used in this study are licensed drugs being used for licensed indications, management of suspected drug-related adverse events will be according to national and local clinic guidelines.

3.10 Barriers to implementation: a sub-study among health care workers

If the intervention has a positive effect, we will motivate for its implementation. In anticipation of this, we would like to learn from the experience of staff involved with delivering the intervention, to identify potential barriers to implementation.

We propose to interview clinic and study staff primarily in intervention clinics. The clinics will be purposively sampled to include urban and rural sites, and high and low case-load clinics. The main focus will be on intervention clinics but we might include control clinics if necessary for comparison.

Staff to be interviewed will be selected on a clinic by clinic basis (since clinics are staffed differently, and key personnel will vary by clinic) and may include clinic doctors and nurses; study nurses and co-ordinators; and more senior personnel such as clinic facility managers, HAST managers and TB co-ordinators.

The interviews will be conducted by a Masters' level student, supervised by the investigators. The MSc student will not have had previous involvement in the study and thus may be seen by interviewees as distinct from the study team (although we recognise that social desirability bias is still likely to influence responses). Interviews will include both closed and open questions (see interview guide, provided as a separate document) and may be tape recorded if the participant gives consent. All paper and soft copies of field notes, audio files, consent forms and any other notes will be kept securely and if in digital format will be on a password protected computer, backed up regularly. The content of discussions and interviews will not be revealed to anyone other than authorized study staff, investigators, and monitors. All information collected during the course of this study will be kept securely and confidentially in a locked cupboard for at least five years after the study is finished.

A coding template will be developed from a few of the early transcripts, and will be used to code later transcripts. Each line, or few lines, will be coded and labelled according to the idea(s) in the transcript, using a short title, and used to create a new tree node. As coding develops and themes emerge, nodes will be arranged in groups under a parent node labelled with the theme. Descriptive statistical analysis will be performed on demographic and other quantitative data in Excel, Epi-Info or Stata.

Written informed consent will be sought from potential participants using standardised information sheets and consent forms, provided as a separate document.

3.11 Time to ART start post trial: a sub-study

Addition to protocol v 6.2, 8 July 2015

The presence of research teams in study clinics has the potential to influence routine clinic practices with respect to important processes such as time to ART start. In addition, South African national guidelines concerning the management of TB and HIV have changed since the trial was conceptualised. In particular, Xpert MTB/RIF has become the universal first line investigation for TB (as anticipated), and individuals with CD4 counts below 200 cells/µl should now be “fast tracked” to start ART. In order to better understand how these policy changes have affected relevant aspects of

patient management in the trial clinics over the calendar period of the trial, we propose to repeat the retrospective pilot study outlined in section 3.8.

In all clinics which took part in the trial, we will collect anonymised data from routine records to document usual practice for management of patients with HIV presenting to start ART. This will involve only record review: no patient contact will be required. We aim to collect data for a consecutive sample of around 50 patients per clinic, starting after trial recruitment was complete. Key data include time from first HIV positive test to CD4 result being given; among those eligible to start ART, TB screening practice and time from CD4 result to start of ART; 6-month outcomes on ART; TB treatment outcomes among patients with HIV.

Research staff will collect these data on standardised case report forms that will later be entered into a customised database.

These data will help us understand whether and how TB investigation practice and time to ART start has changed over the period of the study. The results will be important in enabling us to understand and interpret our trial results.

4 Economic analyses

Demonstration of affordability and cost-effectiveness will be essential in making a case for implementation of our management strategy, should it prove effective. We will estimate the following economic outcomes:

- diagnostic cost per TB suspect
- total diagnostic cost of the study cohort in intervention and control arms
- cost per month of TB treatment (intensive and continuation phase)
- cost per month of ART
- episode costs of treating relevant opportunistic infections
- total TB and HIV care and treatment cost of the study cohort, per patient, in intervention and control arms
- incremental diagnostic cost of intervention compared to control
- incremental treatment cost of intervention compared to control
- incremental cost per DALY, taking into account:
    - costs of i) diagnosis and ii) treatment
    - cost savings from reduced hospitalisations during the study period
    - DALYs averted from morbidity associated with opportunistic infection episodes and deaths averted during the study period

The economic evaluation will be conducted using a health service perspective, conservatively assuming no broader societal costs. All costs of TB suspect identification, TB diagnosis and treatment, and HIV care and treatment given during the period of follow-up will be estimated. Given the complexity of diagnosis and treatment pathways in each arm, we will estimate health service costs by combining the unit cost of each procedure along the diagnostic and treatment pathway across all study sites, with the probabilities of following each pathway for each study arm cohort. These probabilities will be derived from health service record review and the follow-up interview at six months. The aim will be to identify treatment-related health service use, and any major events such as hospitalisation.

The unit cost of each procedure will be measured using an ingredients approach, based on financial records and directly observed resource use. This will include the collection of data on staff time use,

based on a mixture of observation and time sheet reporting. Staff will be asked questions about the time they spend on each different procedure related to TB/HIV diagnosis, treatment and care. They will also be observed carrying out patient consultations to measure the time that each consultation takes. Time use will then be combined with salary costs to estimate the personnel cost associated with each procedure. Time use data will also be used to assign overhead costs.

We will cost diagnostic procedures at all study sites to ensure a full range of costs is captured. Treatment costs will be estimated from a stratified sample of sites (based on location, size and patient load). We may also refer to other costing studies where treatment is provided outside the study sites (such as hospitalisation). Diagnostic costs will be collected 2 months and 5 months after the start of the study to estimate both start up and routine costs. Treatment costs will be collected from month 3 after the start of the study and will be considered routine.

We will estimate DALYs averted from trial outcomes on mortality and morbidity. We do not propose to include quality of life measures, and will used standard DALY disease weightings for morbidity during the study period. We will conservatively assume no beneficial health effects from the intervention after the study period, since most deaths occur in the first few months on ART.
As we have no prior knowledge of the costs (particularly of averted hospitalisation) in the intervention arm, we have not powered the trial to establish differences in cost-effectiveness. Instead, we will address any uncertainty due to low power using probabilistic and a range of one- and two-way sensitivity analyses, presenting acceptability curves where relevant.

4.1 Patient costs: an exploratory sub-study

The intervention might be anticipated to reduce patient costs overall. The costs to patients of being treated for TB are reported to be very high, but few data are available concerning costs incurred by patients as a result of investigation for TB before starting ART. In a sub-study, we propose to identify and explore the affordability, indirect costs and catastrophic spending, by individuals and families, among participants in the TB Fast Track study.

Participants in the TB Fast Track study who are attending the clinic for a 6-month visit will be invited to take part in this sub-study. A purposive sampling strategy will be used to gather data e.g. from people with fewer socioeconomic resources, and contrasting those in urban vs. rural settings. We will aim to interview around 50 participants in urban/ peri-urban clinics and around 50 in rural clinics. We will explore differences between people in the intervention and control arms, but, due to limited staff resources, this sub-study is likely to have limited power for a formal comparison between study arms. If resource permit the study may be extended to a larger number of participants.

Direct and indirect costs to be assessed will include costs incurred attending out-patient visits; costs of any hospitalisation; costs of complementary care; costs incurred by carers; costs due to loss of employment; reduced household activities; decreased productivity; coping strategies.
A draft questionnaire is supplied.

In order to reduce the length of the interview and to reduce any repetition, participants will be asked also for permission to use for this sub-study data previously provided as part of the main TB Fast Track study.

Quantitative data will be analysed, using Stata, based on established statistical and economic methods, including the Human Capital Method. Open-ended questions will be analysed thematically.

Consent to participate will be sought from TB Fast Track participants who are being seen for their 6-month study visit, using the participant information sheet and informed consent form provided.

This sub-study will be led by a Masters' student studying health economics, supervised by the investigators.

5. Data management

5.1 Data management responsibilities

- Oversee and coordinate the management of data;
- Provide training and guidance to staff with respect to data management issues;
- Oversee data quality control, including running data queries;
- Ensure the availability of databases to capture data from participant interview and case note abstraction from medical records;
- Ensure the safekeeping of data and access control;
- Ensure proper data management documentation is maintained;
- Manage data reporting processes;
- Manage integration of data from different sources;
- Ensure processes are in place for backup and data recovery.

5.2 Application and database

A client/server architecture will be used. The database and the capturing application will be developed using appropriate software. Scheduled backups will be done on a daily, weekly and monthly basis. A password will be required to gain access to the Aurum Institute for Health Research network to access data. Study staff will be trained to generate reports from the application. When data sets are generated for data analysis, personal identifiers will be removed.

5.3 Quality control

Data will be validated on entry, using range and consistency checks. Quality control procedures will include review of case report forms (CRFs) for completion and correctness. Logical data checks will also be performed on the data. Incomplete and incorrect data queries will be sent back to sites electronically for error resolution. Errors will be reviewed and corrected on a weekly basis. The study will be monitored by internal monitors.

Study records (consent forms, CRFs, screening logs) will be kept in a secure location accessible only to authorised study staff, investigators, and monitors. All records will be archived in a secure storage facility for at least ten years after the completion of the study.

6. Statistical considerations

6.1 Sample size estimation

In our ART programme, mortality in the first 6 months after ART start among those with a baseline CD4<150 was 24/100 person years (pyrs);[28] however, ascertainment of deaths did not include a search of national death registrations, and thus this is a minimum estimate of on-ART mortality. Our study cohort will be recruited at the point of assessment for ART, some weeks before ART would be routinely started; pre-ART mortality exceeds on-ART mortality,[2] and 6-month mortality in the study cohorts, recruited at ART assessment, will therefore exceed observed on-ART mortality. We assume

that TB accounts for 60% of early deaths among patients initiating ART in South Africa; we hypothesise that, by earlier initiation of TB treatment, 66% of these could be averted. In addition, we estimate (based on our TB screening study, outlined above, section 2) that our strategy will result in ART being initiated in the intervention arm, on average, 2 months earlier than in the standard of care arm. Analyses of our ART programme data suggest that, among individuals with baseline CD4 100-150 cells/µl, a 2 month delay in ART initiation results in a 150% increase in mortality by 6 months (from 7% if ART is initiated immediately to 18% if there is a 2-month delay).[39] Clearly, there must be overlap of preventable deaths between these two estimates, which we cannot determine precisely. It is also possible that some individuals who start TB treatment as part of the study may elect to discontinue it, which could reduce the magnitude of the intervention effect. Overall, we assume, conservatively, that the intervention will result in a 40% reduction in mortality by 6 months after study enrolment.

Assuming 10 clusters per arm, 175 patients per cluster, 5% individuals whose vital status cannot be ascertained at 6 months, mortality estimated conservatively at 25/100 pyrs in the standard of care arm and taking account of the clustered design,[40] using between-cluster coefficients of variation of 0.2 and 0.25, there will be 91% and 85% power to assess 40% reduction in mortality, respectively. If the coefficient of variation is 0.2 there will be 81% power to assess 35% reduction in mortality.

Note added to protocol version 5.0, 31 August 2013: we propose to extend enrolment to four additional clinics, in order to assure adequate study power despite slower than anticipated enrolment at some clinics. Assuming 12 clusters per arm, an harmonic mean of 109 participants per cluster, with other assumptions unchanged, using between-cluster coefficients of variation of 0.2 and 0.25, there will be 90% and 84% power to assess 40% reduction in mortality, respectively. If the coefficient of variation is 0.2, there will be 80% power to assess 35% reduction in mortality.

Note added to protocol version 6.1, 30 January 2015: enrolment was extended to a target harmonic mean of 117 participants per cluster, to be conservative with respect to the proportion of individuals whose vital status cannot be ascertained at 6 months.

6.2 Statistical analysis

Analyses will use methods appropriate for the clustered randomised trial design, giving each cluster equal weight. Quantitative outcomes will be summarised as the mean for each cluster and the difference of means for intervention vs. standard of care arm. For binary outcomes or rate outcomes the overall risk (rate) for each cluster will be calculated, and the ratio for intervention vs. standard of care arm. The standard error for each effect measure will take into account stratified randomisation. An adjusted analysis will be conducted to help reduce variability across clinics with respect to primary and secondary outcomes and, after visual inspection, if imbalance across study arm of patient or clinic level factors is observed.[40] In a supplementary analysis restricted to intervention clusters, we will assess for trends in the primary outcome across levels of success of implementing the intervention. A detailed analysis plan will be finalised prior to the end of data collection.

Subgroup analyses will be conducted for the primary outcome for baseline CD4 count (<50, ≥50) and previous TB history (from self-report; no previous TB, previous TB).

Given the relatively short recruitment period, and primary outcome measured at 6 months, we do not anticipate being able to perform a valid interim analysis. However, the Data Monitoring Committee will review the protocol and analysis plan and we will take further advice from them on this issue.

7. Protection of human participants

This study will be conducted according to Good Clinical Practice (GCP) guidelines, in accordance with requirements of the funders and approving ethics committees.

7.1 Regulatory approvals

Approval will be sought from the Research Ethics Committees of the University of Witwatersrand and the London School of Hygiene and Tropical Medicine, UK. The study has been discussed with and has the support of senior staff responsible for tuberculosis control in the National Department of Health. Approval from relevant Provincial Research Committees will be obtained, and the protocol will be submitted to the South African Medicines Control Council for approval as a phase 4 clinical trial.

The London School of Hygiene & Tropical Medicine will act as the main sponsor for this study. Delegated responsibilities will be assigned locally. London School of Hygiene & Tropical Medicine holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, protocol and all applicable local regulations.

The study may be subject to audit by the London School of Hygiene & Tropical Medicine under their remit as sponsor, and inspection by regulatory authorities, to ensure compliance to the protocol, Good Clinical Practice and all applicable regulatory requirements.

7.2 Risks and benefits for participants

7.2.1 Risks and benefits

Due to anticipated imperfect specificity of the algorithm, some individuals who do not have active TB, as defined by standard diagnostic methods, will receive TB treatment that they would not otherwise have received, with attendant risks, particularly of drug toxicities and drug interactions. However, BMI<18.5 and low haemoglobin identify individuals at high risk of active TB within the first six months on ART[25] and these individuals are very likely to benefit from immediate TB treatment, in terms of a lower risk of incident TB and death. Individuals with latent TB will also benefit, by receiving treatment which will adequately treat their latent infection and thus reduce the future risk of active TB resulting from reactivation of latent infection. By circumventing the delays to ART initiation associated with traditional investigation pathways for smear-negative TB, we anticipate that time to ART in the intervention arm will be much shorter overall. We anticipate that the risk of serious manifestations of immune reconstitution syndrome will be lower in those with active TB who start TB treatment prior to ART, as compared with no TB treatment. We will monitor safety by reviewing available data concerning likely cause of death among all study participants, and by monitoring study-defined adverse events in the intervention arm (as a secondary outcome).

Participants, both in intervention and control arms, will receive ZAR150 if they attend for a study review visit 6 months after enrolment, as compensation for their time and travel expenses. They will not be given any payment at the enrolment visit since this will be at the time of a clinic visit, although we may offer refreshments, particularly if participation results in increased time in clinic. Participants in the intervention arm who start TB treatment may be reviewed after 2 months to check that their treatment is appropriate; this will coincide with a routine clinic visit and will not be compensated. We may contact participants, by cell phone if possible, periodically during the study to confirm contact details, and may offer cell phone airtime of small value (around R12) when

contact details are confirmed. If confirmation of contact details requires the participant to travel specifically for study purposes then travel expenses will be reimbursed at a level reflecting anticipated travel costs (around R20).

7.3 Consent

Clinic participation

Participation of clinics will be by the consent of senior staff and managers.

Individual participation

Informed consent will be sought from potential participants using information sheets available in relevant languages (such as Sepedi, isiZulu, Xitsonga, English - appendix 3). Written informed consent will be sought, with the assistance of a translator where necessary, using standard consent forms. Participants unable to read or write will be asked to make a mark or thumbprint in the presence of a witness.

7.4 Confidentiality

All study records will be managed in a secure and confidential fashion. All records will be stored at the participating clinics and offices at provincial level in locked filing cabinets and access to the records will be restricted to specified study team members. Case report forms will be identified using the participant's study number only, with locator information stored separately.

7.5 Study discontinuation

The study may be discontinued at any time by the funder, the trial steering committee, or by any of the relevant regulatory bodies.

8. Trial governance and management

8.1 Trial steering committee

The trial steering committee will oversee the trial, monitoring its progress and receiving reports from the Data Monitoring Committee. The Trial Steering Committee will advise the Chief Investigator (CI) and investigator team, and will report to the trial funder and sponsor.

Membership of the trial steering committee (as of September 2012) includes Prof Bertel Squire, Liverpool School of Tropical Medicine and President, International Union Against Tuberculosis (chair); Dr Lindiwe Mvusi, Director, DOTS Strategy Coordination, South African Department of Health; Bonginkosi Mthembu, Treatment Action Campaign; Dr Harry Hausler, Director, TB/HIV Care Association, South Africa; Prof Francois Venter, Wits Reproductive Health and HIV Institute, along with Prof. Grant (CI) and Dr Charalambous (PI for South Africa) and other investigators as needed.

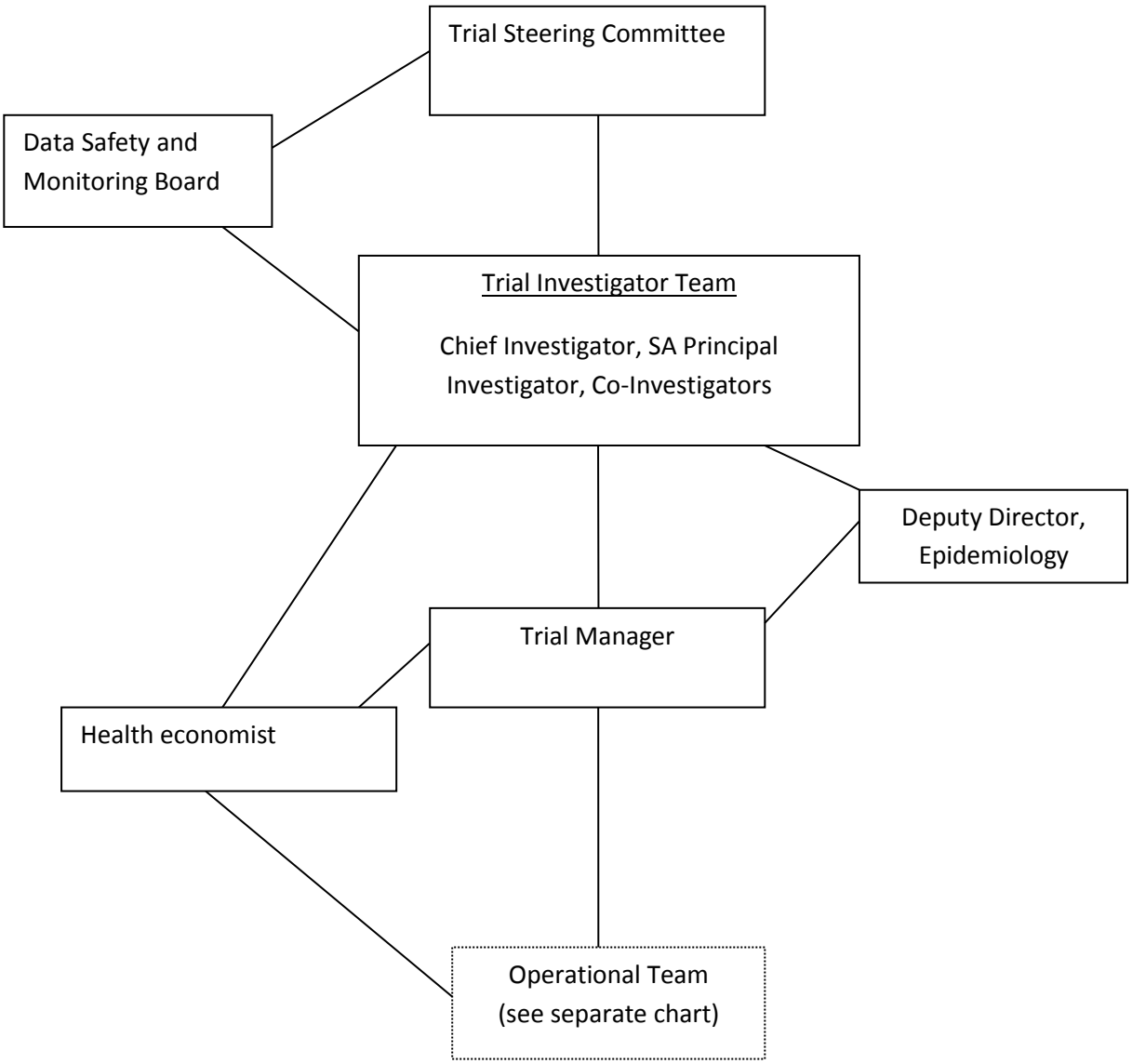
8.2 Trial investigator team

The trial will be led by Prof. Alison Grant (CI; epidemiologist and HIV/infectious diseases specialist physician, LSHTM), in close collaboration with Dr Salome Charalambous (co-PI; Director of Research, Aurum Institute) and Dr Mpho Tlali (Trial Manager). Dr Katherine Fielding (LSHTM) is the trial senior statistician, also overseeing data management. Dr Anna Vassall (health economist, LSHTM) will be responsible for the economic components of the study, supervising an SA-based junior economist. At Aurum Institute Dr Christopher Hoffmann (infectious diseases physician / epidemiologist, Director of ART programme) will provide clinical and epidemiological support, and Prof. Gavin Churchyard (Chief Executive Officer) senior managerial support.

Lead investigator for Foundation for Professional Development will be Suzanne Johnson (Head of Strategic Information); she will provide senior support at their collaborating sites. Dr Susan Dorman (Johns Hopkins University) will advise on diagnostics issues.

LSHTM and Aurum Institute have had a highly productive collaboration since 1998: major projects include a cluster-randomised trial of community-wide tuberculosis preventive therapy in gold mines (80,000 participants in 15 clusters over 3 South African provinces; PI: Churchyard, co-PIs: Fielding and Grant) with nested projects on new TB diagnostics (Dorman) including cost-effectiveness; and development and evaluation of a multisite HIV care programme with over 18,000 patients, including studies of screening for tuberculosis among people with HIV (Charalambous, Churchyard, Hoffman, Fielding, Grant). Vassall brings to the team particular expertise in economic evaluation of new TB diagnostics which will be invaluable in assessing the cost and cost-effectiveness of this strategy, important to guide policy based on the results of the study.

Figure 1: Organisational chart: trial governance and senior management



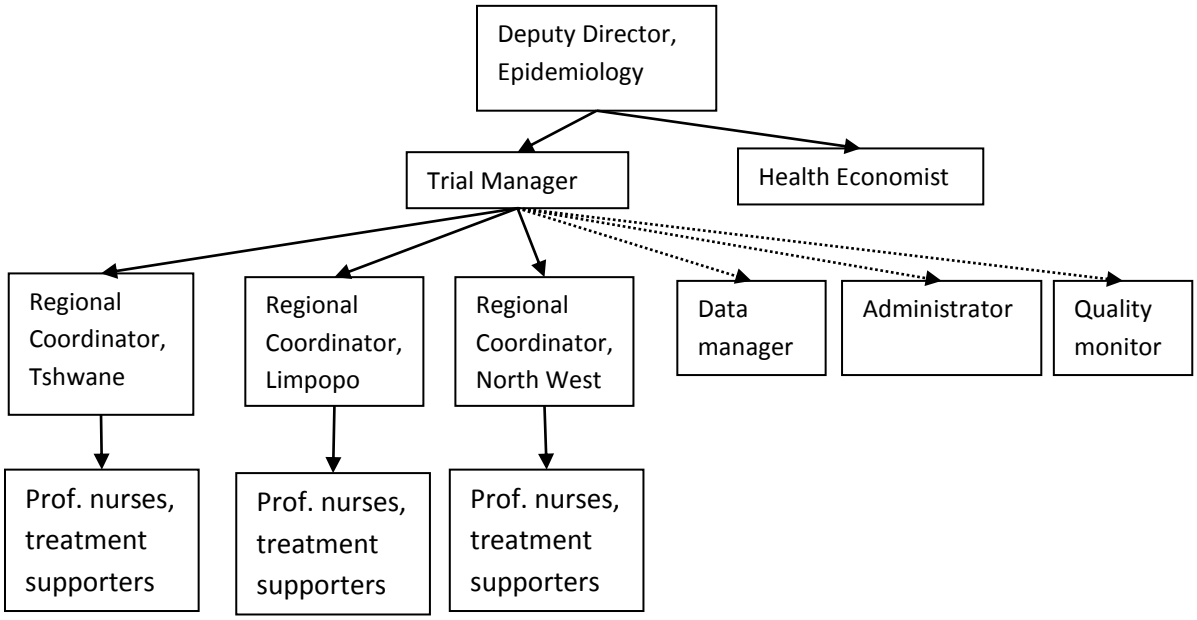
8.3 Trial operations team

A full-time trial manager will lead the operational team, directed by the investigator team. Three regional co-ordinators will oversee field activities. The senior statistician and data manager will oversee all aspects of study data management. The operational team will meet by phone or in person weekly, and senior operational staff will meet the core investigator team at least monthly (more frequently during trial preparation and initiation). Clinical decision making will remain with the primary care team wherever possible, but clinically-qualified senior team members will be available to discuss any clinical problems. Data management is described in section 5, above.

8.4 Data Monitoring Committee

The Data Monitoring Committee will monitor study data and make recommendations to the Trial Steering Committee concerning whether there are any safety reasons why the study should not continue.

Figure 2: Organisational chart, trial operations team



8.5 Trial registration

The trial has been registered as a clinical trial (ISRCTN35344604; DOH-27-0812-3902 [South Africa]) and will be registered on the South African National Health Research Database.

9. Logistics

9.1 Timeline

	Y1 (2012)				Y2 (2013)				Y3 (2014)			
	q1	q2	q3	q4	q1	q2	q3	q4	q1	q2	q3	q4
Preparation												
Recruitment												
Follow up												
Analysis/write-up												

10. Publication policy

Local stakeholders will be kept updated with trial progress. The research findings will be presented first to national stakeholders, and disseminated to stakeholders and participants in each province by means of local meetings. The results will be written up as one or more articles for submission to a suitable scientific journal.

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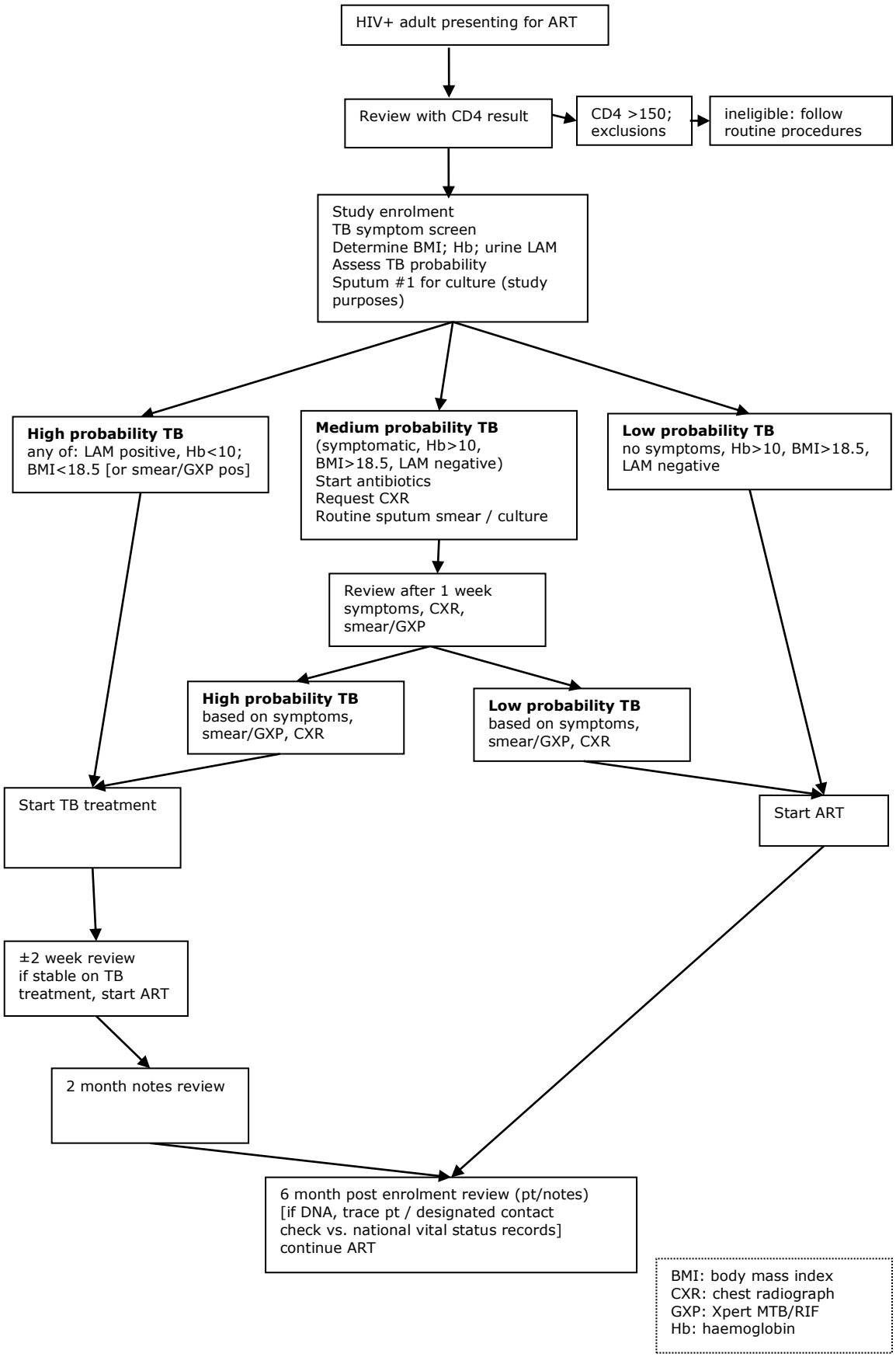
Appendix 1: Study algorithm



Appendix 2: Classification of adverse events

We will use the Division of AIDS classification of adverse events, as revised in 2004 with clarifications in 2009 (available at: http://rcc.tech-res-intl.com). Relevant sections are reproduced below:

PARAMETER	***GRADE 1*** MILD	***GRADE 2*** MODERATE	***GRADE 3*** SEVERE	***GRADE 4*** POTENTIALLY LIFE-THREATENING
Liver enzymes (LFT)				
AST (SGOT)	1.25–2.5 x ULN	2.6–5.0 x ULN	5.1–10.0 x ULN	>10.0 x ULN
ALT (SGPT)	1.25–2.5 x ULN	2.6–5.0 x ULN	5.1–10.0 x ULN	>10.0 x ULN
Bilirubin (total)	1.1–1.5 x ULN	1.6–2.5 x ULN	2.6–5.0 x ULN	>5.0 x ULN
Cutaneous				
Cutaneous reaction - rash	Localized macular rash	Diffuse macular, maculopapular, or morbiliform rash OR target lesions	Diffuse macular, maculopapular, or morbiliform rash with vesicles or limited number of bullae OR superficial ulcerations of mucous membranes limited to one site	Extensive or generalised bullous lesions OR Stevens Johnson syndrome OR ulceration of mucous membrane involving two or more distinct mucosal sites OR toxic epidermal necrolysis (TEN)
Neurological				
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam, or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Gastrointestinal				
Nausea	Transient (<24hrs) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24-48 hours	Persistent nausea resulting in decreased oral intake for >48 hours OR aggressive rehydration indicated (e.g. IV fluids)	Life-threatening consequences (e.g. hypotensive shock)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with mild or no dehydration	Persistent vomiting resulting in orthostatic hypotension OR aggressive rehydration indicated (e.g. IV fluids)	Life-threatening consequences (e.g. hypotensive shock)
Nephrotoxicity				
Creatinine	1.1-1.3xULN	1.4-1.8xULN	1.9-3.4xULN	≥3.5xULN
Visual				
Visual changes (from baseline)	Visual changes causing no or minimal interference with usual social and functional activities	Visual changes causing greater than minimal interference with usual social and functional activities	Visual changes causing inability to perform usual social and functional activities	Disabling visual loss in affected eye(s)
Other clinical event not specified above	Symptoms causing no or minimal interference with usual social and functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care functions; OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability or death

Definition of descriptions of relationship of adverse event to study agent

Classification	Description
Not associated	The adverse event is clearly explained by another cause not related to the study agent.
Probably not associated	The adverse event is more likely explained by another cause than by the study agent
Associated: possible	The adverse event and administration of study agent are reasonably related in time, and the adverse event can be explained equally well by causes other than study agent.
Associated: probable	The adverse event and administration of study agent are reasonably related in time, and the adverse event is more likely explained by study agent than other causes.
Associated: definite	The adverse event and administration of study agent are related in time, and a direct association can be demonstrated.

Appendix 3: Participant information sheets and consent forms

[these have been updated and are now presented in a separate document]

Appendix 4: Case report forms

[these have been updated and are now a separate document]