SUPPLEMENTARY MATERIAL INDEX

I. Figure 1. XPHACTOR main study flow and procedures ................................................................. 2
II. XPHACTOR main study procedures .................................................................................................. 4
I. **Figure 1. XPHACTOR main study flow and procedures**

**XPHACTOR enrolment**

- **XPHACTOR HIGH PRIORITY** OR newly diagnosed HIV-positive OR pre-ART with CD4<200: 
  - *Sputum for immediate Xpert*
  - Xpert negative: Further evaluation in accordance with national guidelines
  - Xpert positive: start TB treatment

- **XPHACTOR MEDIUM / LOW PRIORITY**
  - *Sputum stored* †
  - Xpert negative: Further evaluation in accordance with national guidelines
  - Xpert positive: start TB treatment

**XPHACTOR assessment at 1 and 2 months**

- **XPHACTOR HIGH PRIORITY**: 
  - *Sputum for immediate Xpert*
  - Xpert negative: Further evaluation in accordance with national guidelines
  - Xpert positive: start TB treatment

**XPHACTOR assessment at 3 months**

- **ALL**: *Sputum and blood for mycobacterial culture*
  - Consecutive sample: screened for eligibility for substudy §
  - Xpert negative: Further evaluation in accordance with national guidelines
  - Xpert positive: start TB treatment

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* XPHACTOR algorithm at enrolment: high priority (any of: current cough, fever ≥ 3 weeks, body mass index (BMI) <18.5 kg/m², CD4 <100x10⁶/l, measured weight loss ≥10% in preceding 6 months, or other feature raising high clinical suspicion of TB); medium priority (any of: fever < 3 weeks, night sweats, measured weight loss <10% in preceding 6 months); low priority = no TB symptoms.
† Samples tested with Xpert at the end of the study to enable comparison of sensitivity and specificity of the XPHACTOR study algorithm to detect TB cases against sensitivity and specificity if Xpert had been performed immediately for all with any WHO tool symptom.

‡ XPHACTOR algorithm at monthly follow up: high priority (any of: current cough, fever ≥ 3 weeks, night sweats ≥ 4 weeks, BMI <18.5 kg/m², CD4 <100x10⁶/l, measured weight loss ≥10% in preceding 6 months, or other feature raising high clinical suspicion of TB); medium priority (any of: fever < 3 weeks, night sweats <4 weeks, measured weight loss <10% in preceding 6 months); low priority = no TB symptoms.

§ Screened by research nurse between October 2013 and April 2014. Eligible if not on TB treatment & persistent TB symptoms, defined as: (i) any of cough, fever, or night sweats reported at enrolment and at 3-month visit; OR (ii) ≥5% measured weight loss at 3-month visit and reported unintentional weight loss.
II. XPHACTOR main study procedures

Enrolment

At enrolment, research staff administered a standardised questionnaire which incorporated the WHO tool, collected details of TB and HIV treatment, and basic demographic and socioeconomic information. Further investigation was prioritised according to the XPHACTOR algorithm with an immediate spot sputum sample sent for Xpert for individuals at a priori highest risk of active TB: (i) all assigned “high priority” (any of: current cough, fever ≥ 3 weeks, BMI <18.5 kg/m², CD4 <100x10⁶/l, measured weight loss ≥10% in preceding 6 months, or other feature raising high clinical suspicion of TB); (ii) those in pre-ART group with CD4<200x10⁶/l at enrolment (iii) all in HTC group (whose CD4 count was unknown) at enrolment. For all other participants, a spot sputum sample was collected at enrolment and frozen at -80 ºC within 24 hours, for testing with Xpert at the end of the study (figure 1). This enabled comparison of sensitivity and specificity of the XPHACTOR study algorithm to detect TB cases against sensitivity and specificity if Xpert had been performed immediately for all with any WHO tool symptom.

All participants with CD4<200x10⁶/l were asked to provide a spot urine sample in a sterile container at enrolment, which was stored at 2-8 ºC prior to freezing at -80 ºC within 24 hours of collection. At the end of the study samples were thawed to ambient temperature and tested with lateral-flow LAM assay (LF-LAM) (Determine TB-LAM; Alere, USA) by two trained laboratory technologists in accordance with training provided by Alere representatives. The technologists did not have access to other bacteriological results when performing LF-LAM tests. Each test was graded once, using the pre-January 2014 manufacturer’s reference card comprising five grades of colour intensity with the least intense band assigned grade 1, absence of a band graded negative, and absence of control band deemed a failed test.

Follow-up

Participants were reviewed monthly to three months, with repeat WHO symptom screen and a spot sputum requested for Xpert if “high priority” by the study algorithm at that visit, with the exception of those in the “on ART” group who were asymptomatic at enrolment who were telephoned at 1 and 2 months to update locator information but were not asked about TB symptoms. At the 3-month visit sputum (induced if necessary) and blood were collected for mycobacterial culture on liquid media (Bectec MGIT 960 and 9240 systems) from all study participants, regardless of symptoms (figure 1). We allowed a broad window period around the scheduled 3-month visit, until around six months, in order to maximise study follow-up.

Participants who submitted an Xpert sample were reviewed within one week. If Xpert-positive, TB treatment was initiated; if negative, research staff repeated the WHO symptom screen and facilitated
the Xpert-negative algorithm which comprised chest radiograph, spot sputum for TB culture, and/or antibiotic trial as clinically appropriate (Figure 1).

Investigation results were returned to clinic staff, who were responsible for management decisions. Clinic records were reviewed at the end of the study to ascertain any additional relevant investigations and/or TB diagnoses. Deaths were identified through reports from participant-nominated contacts, clinic staff, and by accessing the Department of Home Affairs vital statistics database using participants’ South African identification numbers.