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| **WOOLCOCK INSTITUTE OF MEDICAL RESEARCH** |
| **UNIVERSITY OF SYDNEY** |

**Test and Treat to End TB
A Pilot Study**

PROTOCOL

Version 1.0

**Summary changes table**

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# Project overview

1. **Title:** Test and Treat to End TB: A Pilot Study
2. **Duration: Four months**
3. **Participating provinces / cities in Vietnam:** 3 Aps in Ca Mau province

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# Synopsis

This study is a pilot study for a proposed community-based cluster-randomised controlled trial of universal testing and treatment for latent TB infection, together with active case finding for TB disease, to reduce the prevalence of TB.

The aim of this pilot study is to develop the detailed procedures for implementing the universal testing for, and treatment of, LTBI infection and to demonstrate the feasibility, safety and acceptability in preparation for the RCT.

The study will be conducted in three Aps (sub-communes) that participated in the active screening among of ACT3. The procedures to be implemented in the pilot study include the following elements:

1. Preparation and engagement with the communities through meetings and in-depth interviews with key individuals;
2. Enumeration of the eligible study population by household census;
3. Screening the eligible study population for TB infection, using the tuberculin skin test (TST), and for symptoms of TB;
4. Screening for active TB in those who have TB infection or symptoms of TB;
5. Treating active TB in those in whom it is detected;
6. Treating latent TB infection in those in whom TB infection is detected and active TB is not detected using either a four-month daily regimen of rifampicin (4R), observed once weekly, or (when available) a directly observed 12-dose once weekly regimen of isoniazid and rifapentine (3HP);
7. Monitoring for, and managing, adverse events during treatment (pharmacovigilance)
8. Assessing acceptability of the intervention

The primary outcome will be the proportion of eligible participants with LTBI who completed at least 80% of the scheduled doses daily rifampicin or at least 10 of the 12 scheduled weekly doses of 3HP. Secondary outcomes will be indices of participation and acceptability of the intervention.

# Background

This study is a pilot study for a community-wide interevention to reduce the prevalence of tuberculosis. It will develop the evidence required to implement a large scale trial – Test and Treat to End TB.

The **overall goal** of the Test and Treat to End TB main study will be to acquire and present the evidence that will underpin a transformation in the global approach to TB elimination in low and middle-income countries with a high burden of TB. Our hypothesis is that universal testing and treatment for latent TB infection, added to active case finding for TB disease, will reduce the prevalence of TB among adults in the general community by at least 75% within 4 years.

The Test and Treat to End TB study, which addresses this overall goal, will be an **open-label, parallel-group, cluster-randomised controlled trial** to estimate the effect of universal testing for, and treatment of, latent TB infection together with active case finding for TB on the population prevalence of TB after four years. For this study, the study **population** will be people living in Ca Mau, Vietnam. The **intervention** will be universal testing for, and treatment of, latent TB infection combined with active case finding for TB. The **comparison** is usual care, that is, routine detection of TB cases based on self-presentation of symptomatic people. The primary **outcome** is the population prevalence of TB at the end of the intervention period.

Before we implement this cluster RCT, it is important to determine the optimal method for implementing the universal test and treat intervention. This will provide evidence to ensure the feasibility, acceptability and safety of a large-scale intervention.

# Aim

The aim of the Test and Treat to End TB pilot study is to develop the detailed procedures for implementing the universal testing for, and treatment of, LTBI infection and to demonstrate the feasibility, safety and acceptability in preparation for the implementation of the Test and Treat to End TB cluster randomised controlled trial.

# Objectives

1. To estimate, in three selected Aps in Ca Mau Province, in which the universal test and treat intervention is implemented, the following parameters:
	1. Proportion of the census population that meet the eligibility criteria (for the screening phase)
	2. The proportion of the eligible population in whom
		1. Informed consent is obtained to participate in the study
		2. Data on TB symptoms are acquired
		3. A TB skin test is placed
		4. A TB skin test is read
	3. The proportion of persons with a positive test for LTBI in whom screening for active TB disease is completed.
	4. The proportion of persons, who are eligible for treatment for LBTI, who:
		1. Provide consent to commence treatment
		2. Ingest at least one dose of treatment under observation
		3. Complete treatment
		4. Complete at least 80% of doses
		5. Have treatment permanently discontinued prematurely, by the investigators
		6. Permanently discontinue treatment prior to completion, without being asked to do so by the investigators
		7. Report Grade 3 or 4 adverse reactions
2. To establish the major themes related to acceptability of the intervention and associated procedures amongst
	1. Participants
	2. Commune and Ap level health and political personnel
	3. Fieldworkers engaged in the project

# Outcome measures

The primary outcome of this study will be the proportion of eligible patients who complete at least 80% of the required treatment (i.e. at least 100 days treatment with daily rifampicin or at least 10 of the 12 doses of 3HP). Secondary outcomes will include process indicators listed above.

# Study design

## Study setting

The study will be conducted in three Aps (sub-communes) that participated in the active screening among of ACT3. The adult population of the selected Aps ranges from 600 to 1500 people, with a total sample size of 3,020. For the purpose of this pilot study, we will select three Aps where the Commune and Ap leadership were supportive of the ACT3 project and willing to have this pilot study conducted (see Implementation Plan on page 19).

Our plan is to complete the pilot study in one Ap initially and to review the findings before proceeding to the second Ap and third Ap, respectively. This will allow us to modify the intervention between Aps, if the findings support this.

## Research methods

The procedures include the following elements:

1. Preparation and engagement with the communities
2. Enumeration of the eligible study population
3. Screening the eligible study population for TB infection and for symptoms of TB;
4. Screening for active TB in those who have TB infection or symptoms of TB;
5. Treating active TB in those in whom it is detected;
6. Treating latent TB infection in those in whom TB infection is detected and active TB is not detected
7. Monitoring for, and managing, adverse events during treatment (pharmacovigilance)
8. Assessing acceptability of the intervention

### Preparation phase

In the preparation phase, the screening team (four fieldworkers) will conduct a series of meetings with local health and government officials to brief them on the procedures and to generate political and community support. The residents of the Ap will be informed about the survey by announcements broadcast over loudspeakers and banners deployed throughout the sub-commune.

We will also conduct a series of indepth qualitative interviews with members of the community to guide the implementation of the intervention.

Finally, we will hold a public meeting to explain the study and to answer any questions from members of the local community.

### Enumeration phase

A household census of the entire Ap will be conducted. We will collect information on names, year of birth or age, and sex of each household member. At this time household members will be provided with written information about the study and verbal consent to proceed is sought (see “PIS1 –Test”). No information will be collected from participants who are incapable of providing consent or who withhold consent.

### Screening for LTBI and symptoms of TB

The screening will be undertaken by a pair of study team members in the participant’s household or at a central location within the Ap.

Participants will be asked to provide written informed consent at this stage (see “PCF1 – Test”).

The following procedures will be performed:

* Participants will be asked about current symptoms of TB (cough, sputum or haemoptysis) (see “Symptom screening questionnaire”).
* A TB skin test will be placed using the standard Mantoux technique. Field workers will return 72 hours later to measure read the TB skin test. Induration will be digitally photographed and measured (perpendicular to the long axis) using the ballpoint pen technique. Reactions ≥ 10mm will be classified as positive. (see Procedure in Appendix 1 and “Mantoux test form”).

### Screening for active TB in those with TB infection or symptoms of TB

All screened participants who have a positive TST or who report symptoms of TB will be visited in their household and asked to provide a single, spontaneous sputum specimen and to have a chest x-ray in our mobile x-ray van.

The study team member will explain how to expectorate sputum using a pictorial guide. All sputum specimens will be transferred in a foam-insulated cool box to our laboratory in Ca Mau City (see “Sputum Xpert form”).

At the laboratory, specimens will be tested using Xpert MTB/RIF Ultra within 36 hours of collection. Participants with Xpert MTB positive sputum will be immediately notified and referred to the CSDP for further evaluation, including collection of two further sputum specimens for sputum microscopy, mycobacterial culture and drug susceptibility testing (see “Sputum culture form”).

Women aged 15-45 years will be asked if they are pregnant or are attempting fall pregnant (see “Pregnancy screening form”). Those who state they are not pregnant and not attempting to fall pregnant will be asked to provide a urine specimen for a urine pregnancy test (beta HCG). Women who say they are pregnant, who say they are attempting to fall pregnant or who have positive urine beta HCG will not be referred for chest radiograph or for consideration for treatment of LTBI. However, if they meet the symptom or TST criteria for screening for active TB, they will be asked to provide a sputum specimen for Xpert testing, as describe above.

Those who are not excluded as a result of the pregnancy screening form will be referred to the mobile digital xray facility where digital chest xray will performed. Images will be exported to our online data repository. They will be reported by the onsite radiologist (in the xray unit) and re-read by an independent second reader (see “Chest radiograph report form”). Chest xrays will be classified as: “consistent with TB”, “significant abnormality, other than TB” and “normal or no significant abnormality”. Those with chest xrays reported as “consistent with TB” will have two further sputum specimens collected for mycobacterial culture (in addition to Xpert testing performed as above). Those with chest xray reported as “significant abnormality, other than TB” will be referred to for clinical evaluation at the CSDP.

### Treatment with 3HP or 4RIF in those with TB infection but without active TB

Participants who

* Are aged ≥ 15 years and have consented to the screening phase;
* Have a TST ≥ 10 mm;
* Are not excluded by the pregnancy screening questionnaire; AND
* Do not have active TB, that is,
	+ Are Xpert negative or did not produce a sputum specimen for Xpert testing; AND
	+ Either have a chest x-ray that was not reported as “consistent with TB” OR had an abnormal chest xray but have had two sputum cultures that have been reported as negative for Mtb

will be further evaluated for treatment for LTBI.

They will be provided with a written and oral explanation of the rationale for this treatment and of the benefits and risks of taking treatment or not taking treatment (see “PIS2 – Treat” / “PCF2 – Treat”. Consenting participants will have baseline measurement of body weight and blood tests for Liver function test and Full blood count. These will be recorded on the relevant forms. Information on concomitant medications taken in the past seven days or planned to take in the next seven days and presence of known liver disease or HIV infection will be acquired using a standardised questionnaire (see “Pre-treatment Assessment Form - fieldworker”). The fieldworker will check the list of medications against a list of drugs known to interact with rifamycins and isoniazid. Participants will then be asked to complete the questionnaire for “Symptom screening prior to each treatment administration”.

**Check criteria**

Participants who:

* Are noted to be taking medications that interact with rifamycins or isoniazid
* Report allergy to rifamycins or isoniazid
* Report known liver disease or hepatitis
* Are known to be HIV positive
* Are HBV or HCV positive on testing
* Have baseline LFTs that are abnormal
* Have baseline FBC that is abnormal
* Respond positively to any of the symptoms on the checklist for screening prior to each treatment administration

will be flagged for review by the trial doctor prior to treatment. If they do not meet any of the preceeding check criteria they proceed directly to treatment without medical review.

**Medical Review**

Participants who meet any of the check criteria will be referred for medical review prior to commencing treatment (see “Medical assessment – baseline”). The objectives of this medical review are as follows.

1. To resolve any medical issues that require resolution as a result of the checks (symptom screen and blood tests) performed at baseline. If this cannot be done based on the information available at the time of the initial assessment, it is expected that the trial doctor will refer the patient to an appropriate clinic or other medical facility.
2. Decide, in consultation with the participant, whether the participant should receive treatment for LTBI. Among the relevant considerations are the following:
	1. Participants who have significant liver function abnormalities defined as an AST or ALT level greater than or equal to three times higher than the Upper Limit of Normal (ULN) will not be offered treatment. They will be offered referral to a liver clinic.
	2. Participants who are regularly taking medications that interact with rifamycins, where the interactions cannot easily be managed, will not be offered treatment.
	3. If, as a result of this assessment, it is apparent that the participant has another severe or life-threatening illness, he or she will not be offered treatment for LTBI.
3. If it is decided that the participant should receive treatment for LTBI, decide whether he or she is in the low- or high-risk stratum for pharmacovigilance (see “Pharmacovigilance” below).

**Treatment Regimens**

The 3HP regimen includes oral treatment with isoniazid (15 mg/kg if aged ≥ 12 years or 25 mg/kg if aged < 12 years, with 900 mg maximum) and rifapentine (900 mg if ≥50 kg, otherwise 15 mg / kg if aged ≥ 12 years or 25 mg / kg if aged < 12 years) which will be administered once weekly for 12 weeks by a study team member based in the Ap. This treatment regimen has been shown to be safe and effective in a phase 3 clinical trial (1) and is approved for treatment of latent TB infection in children and adults by the US Food and Drug Administration (FDA). It is recommended in US Centers for Disease Control (CDC) (2) and World Health Organization (WHO) (3) guidelines and is approved for use in Vietnam for treatment of latent TB infection in contacts of patients with active tuberculosis, and other high risk populations.

The 3HP regimen is not currently approved within Vietnam and so while we are awaiting approval of 3HP we will treat LTBI with a rifampicin regimen (RIF). Oral treatment will commence with rifampicin (600mg/day for > 50 kg or 400mg/day < 50 kg body weight) as a single daily dose dispensed weekly at the participants home by a study team member. This treatment will continue for 18 weeks.

### Pharmacovigilance

All participants will complete a symptom screening checklist / questionnaire prior to each dose and two weeks after the last dose (see “Symptom screening prior to administering medications”). In addition, participants who are:

* aged ≥ 45 years,
* are HBV or HCV positive (at baseline),
* have baseline AST or ALT higher than normal (but less than three times the upper limit of normal), OR
* are flagged by the trial doctor for high-risk stratum pharmacovigilance

will have liver function tests repeated at two weeks and at four weeks after commencement of treatment.

Those who screen positive for any symptoms on the checklist or whose scheduled surveillance liver function tests is abnormal will be reviewed by the trial doctor prior to receiving the next dose (see “Medical assessment – during treatment”). The trial doctor will order further investigations as required to investigate reported symptoms. Details of adverse events will be reported using case report forms, which will be submitted to an Expert Clinical Panel. Adverse events (AE) will be adjudicated by an expert clinical panel (ECP) and classified in accordance with the Division of AIDS Table for grading severity (4). The trial will manage adverse events in accordance with ICH/GCP Standards. Adverse events graded 3 and above will be submitted to the Principal Investigator, and the Australian ethics committee, within 48 hours of their discovery by trial staff. The occurrence of and details about Adverse Drug Reactions (ADR) and Severe Adverse Events (SAE) will be reported in a timely manner according to requirements using the appropriate form.

### Assessing acceptability

At the conclusion of the treatment period we will conduct a series of focus group discussions with representatives of the following three groups associated with the Aps:

1. Participants
2. Commune and Ap level health and political personnel
3. Fieldworkers engaged in the project

Information from these focus groups will be analysed to ascertain the major barriers and facilitators to effective implementation of all aspects of the intervention.

# Data analysis

Proportions will be estimated for binary variables and distributions examined for continuous variables.

# Ethical considerations

The study is a pilot study for a future RCT. The procedures are generally safe and the treatment regimen has been tested in previous RCTs and is recommended in guidelines for treatment of LTBI.

All participation will be with informed consent.

# Implementation plan

### Selected population from ACT3

* Khom 5- Phuong Tan Xuyen in Ca Mau city, population: 592, 10 Sub-Ap
* Bá Huê - Tân Duyệt in Đầm Dơi district, population: 963, 10 Sub-Ap
* Cái Rắn A - Phú Hưng in Cai Nước district, population: 1465, 12 Sub-Ap

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| **Activities** | **Estimated date** | **Notes** |
| Enumeration of the eligible study population | Week 1- Week 2 | For 3 Ap |
| Screening the eligible study population for TB infection and for symptoms of TB;Measurement of respiratory symptoms, FeNO, spirometry and peripheral blood eosinophils in the elible study population;  | Week 2-Week 16  | Round 1: 2 days for 1 sub-Ap to perform TST & QFT/FBC, respiratory symptoms, FeNO, spirometryRound 2: 1 days for 1 sub-Ap Read TST results, screen for TB & mop-UpRound 3: 3 last days in the Ap to get all of the TST results & screen for TB |
| Screening for active TB in those who have TB infection or symptoms of TB;  |
| Treating latent TB infection in those in whom TB infection is detected and active TB is not detected (12 doses/15 weeks) | Week 6 – Week 30 |  |
| Treating active TB in those in whom it is detected; | 6 months | NTP |
| Data Analysis & Report |  |  |
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