WOOLCOCK INSTITUTE OF MEDICAL RESEARCH
UNIVERSITY OF SYDNEY

PROTOCOL

Test and Treat to End TB

Trial code: ACT5

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Version and date of protocol	Version 2.0, date 14 September 2021

STATEMENT OF COMPLIANCE

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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List of abbreviations:

ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CRF	Case Report Form
CSDP	Centers for Social Disease Prevention
ECP	Expert Clinical Panel
eCRF	Electronic Case Report Form
Eos	Eosinophils
FBC	Full Blood count
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
Hb	Haemoglobin
HIV	Human Immuno-deficiency Virus
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
LTBI	Latent Tuberculosis Infection
MCV	Mean corpuscular volume
MTB	Mycobacterium Tuberculosis
Neut	Neutrophils
NTP	National Tuberculosis Program
PCF	Participant consent form
PIS	Participant Information Statement
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
TB	Tuberculosis
TST	Tuberculin skin test
ULN	Upper limit of normal
WCC	White cell count
WHO	World Health Organization

Project overview

Title: Test and Treat to End TB

Duration: Four years (2021 to 2025)

Participating provinces: Ca Mau province

Investigators:

Name	Title	Office
Chief investigators – International		
Guy Marks (PI)	Professor	Woolcock & University of NSW (UNSW) Sydney
Greg Fox	Professor	Woolcock & University of Sydney
Stephen Graham	Professor	University of Melbourne & Burnet Institute
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James Wood	Associate Professor	UNSW Sydney
Warwick Britton	Professor	Centenary & University of Sydney
Nguyen Nhat Linh	Dr	World Health Organization
Chief investigators – Vietnam		
Nguyen Viet Nhung	Associate Professor	National Tuberculosis Program (NTP), Vietnam Ministry of Health; Hanoi Medical University; University of Sydney
Nguyen Binh Hoa	Dr	NTP
Nguyen Thu Anh	Dr	Woolcock & University of Sydney

1) Synopsis

This study is 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 disease.

The **primary objective** of the study is to estimate, among people aged 15 years and over living in Ca Mau Province, southern Vietnam, the effect of universal testing for and treatment of latent TB infection, together with active case finding for TB, on the population prevalence of bacteriologically-confirmed TB two years after the intervention.

The **secondary objectives** are

1. To estimate the incidence of severe adverse events attributable to the intervention;
2. To estimate the effect of the intervention on all-cause mortality;
3. To estimate the costs and cost effectives of the intervention.
4. To estimate the prevalence of latent TB infection four years after the intervention among children born between 2008 and 2016,

This **design** is an open-label, parallel-group, cluster-randomised controlled trial. The **study population** is people living in Ca Mau Province, Vietnam. The **intervention** is 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 to healthcare facilities. The **primary outcome** is the population prevalence of TB two years after the intervention.

2) Background

Global burden of tuberculosis and global goals and targets

Every year, more people die due to tuberculosis (TB) than any other infectious disease. TB is one of the top 10 causes of death worldwide (1). This is in spite of the fact that we have had tests to diagnose both active disease and the presence of TB infection for more than a century, as well as effective anti-TB drugs for more than half a century. Hence, it is extraordinary that in 2019, 10 million people developed the disease, nearly 2 million people will die from TB and 2 billion people remain infected with *M. tuberculosis* (1).

The United Nations' Sustainable Development Goal 3 ("Ensure healthy lives …") includes a target of ending the TB epidemic by 2030. WHO have set ambitious targets to END TB by the 2035, including reducing deaths by 95% and incident cases by 90% compared with 2015 levels (2). However, currently, it is estimated that the current global annual rate of decline in TB incidence is 2.3% per annum (1), which is far lower than the 10% decline required to achieve the 2035 target (3). We are not on track to achieve these targets on present trends.

Limitations of existing approaches and of some alternatives

The long-standing dominant global strategy for TB control has enhanced passive case finding and treatment at its core. This strategy focuses on improving access to TB diagnosis, treatment and care to ensure that patients who have TB disease are diagnosed and treated appropriately when they present with symptoms of TB. Although there have been substantial gains in TB control in some rapidly developing, middle income countries (particularly in China) (4), the decline in incidence of TB has been exceedingly slow in many high TB burden countries and the prevalence remains very high (5*), ensuring ongoing transmission of TB infection. Barriers to the implementation of the current strategy include health system weakness, particularly in primary care (6), and the fact that many patients with pulmonary TB do not report typical or diagnostic symptoms (5*) or delay seeking treatment due to the indolent nature of the disease and due to social stigma (7). As a consequence, a significant proportion of new TB patients (2.9 million in 2019 (1)) are not diagnosed and treated. Although economic development and health system strengthening will lead to a decline in TB burden in many countries (6), at the present rate of progress this will take many decades (3). Consequently, the high burden of TB will continue, with little progress towards targets, despite substantial ongoing investment in TB control programs (8).

Considerable resources and hopes have been invested in the development of new drugs, to shorten the duration of treatment, and new vaccines to prevent infection, progression or reactivation (3). Sadly, while new drugs have been developed for management of TB that is resistant to the existing first- and second-line drugs, the much anticipated blockbuster drugs for drug-susceptible TB and vaccines (9) have not eventuated and will not arrive in time to achieve these targets.

Rationale for community-wide active case finding

Reducing the pool of prevalent infectious cases of pulmonary TB by finding and treating as many cases as possible, as early as possible, and reducing ongoing transmission of TB is key to controlling the epidemic (3). Active case finding, in which people not seeking health care for symptoms of TB are invited to be screened for TB

disease, has played an important role in TB control in higher income settings since before the anti-tuberculous chemotherapy era. There was a dramatic decline in mortality due to TB in North America and in Britain coinciding with the introduction of community-wide mass radiography and anti-tuberculous antibiotics during the 1950s (10-12). In Alaska, community-wide screening, accompanied by treatment of latent TB infection, was associated with a steep reduction in TB incidence, which was maintained over decades (13). Mass radiography screening was also widely implemented in Australia around this time (14), coinciding with a period of rapid decline in TB incidence and mortality in this country.

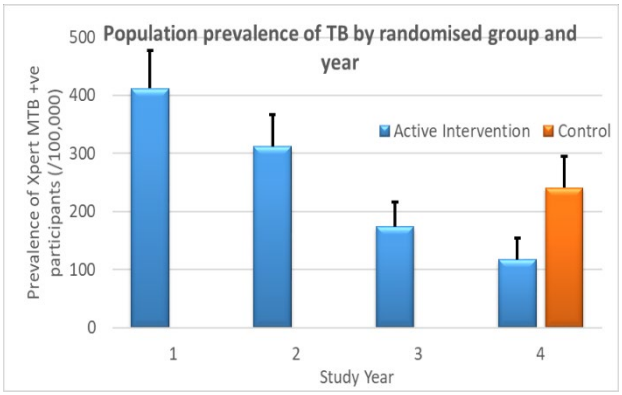
There have been some attempts to implement active case finding in high-burden countries (15, 16). These have mainly focused on screening high-risk subsets of the population, primarily known contacts of people with active TB. Indeed, we have recently shown, for the first time in a highly endemic setting, that active case finding in household contacts of patients with TB increases detection of smear positive (infectious) cases 6.4 fold compared to standard care (17*). However, despite this high yield of contact tracing (18*), most newly identified cases of TB in highly endemic settings are not recognised as contacts of patients who have been diagnosed with TB (19), implying that most transmission occurs outside this context. Similarly, most people with TB do not belong to other identified high-risk groups (such as, prisoners, illicit drug users or people with diabetes). Apart from sub-Saharan Africa, most people with TB do not have HIV infection. In fact, most cases and deaths due to TB occur in south and south-east Asia, where the prevalence of HIV is low. Hence, the impact of targeted active case finding in high-risk groups on the pool of prevalent cases of TB, and consequently on ongoing transmission within the whole population, will be relatively small (20). Therefore, in high burden settings, it will be necessary to screen the entire population and treat all, or nearly all, prevalent cases to reduce transmission (21). By interrupting transmission from cases with infectious TB, only cases resulting from reactivation of latent infection will occur.

A new approach to active case finding

Historically, mass chest radiography has been used as a community-wide screening tool in high-income settings (10). It has also been used in low-middle income settings to conduct TB prevalence surveys (e.g., 5*). However, problems with infrastructure and logistics, human resources, cost, and radiation exposure all limit the utility of radiography as a tool for repeated community-wide screening in low-income and remote settings.

The availability of a fully automated rapid nucleic acid amplification test for diagnosis of TB (Xpert® MTB/RIF, Cepheid, Sunnyvale, CA) has several advantages as a potential screening tool. It is suitable for operation at district-level facilities with a minimal level of training and technician handling of specimens and has a turn-around-time of less than 2 hours. There is no requirement for a biosafety cabinet. This test has been rapidly adopted as a diagnostic tool in low and middle-income countries (22). We have shown that it has very high specificity (23*). A recent enhanced version (Xpert® MTB/RIF Ultra, Cepheid) has improved sensitivity and similar specificity (24).

We have recently completed a cluster-randomised controlled trial of active case finding for TB in Ca Mau, a province of Vietnam ("ACT3", 23*). Residents of 60 active intervention clusters (n = ~ 50,000 adults) were subjected to annual screening for pulmonary TB for three years. Screening involved collecting spontaneously expectorated sputum from all adults, regardless of symptoms. These sputum specimens were tested using Xpert MTB/RIF. Participants who screened positive were secondarily evaluated by chest xray and sputum mycobacterial culture. Those in whom TB was confirmed received treatment through the National TB Program. There was no intervention in the control clusters, where passive case detection continued. The primary study endpoint was the prevalence of pulmonary TB disease in persons aged 15 years and over in the fourth year of the study.



The study demonstrated a 44% lower prevalence of TB disease among adults (figure) and a 50% lower prevalence of TB infection (positive interferon gamma release assay) among children aged 6 to 14 years in the actively screened clusters, compared with the control clusters at the conclusion of the study(25). This study provides strong preliminary evidence for an effective intervention for TB control.

Rationale for "universal test and treat" approach to latent TB infection

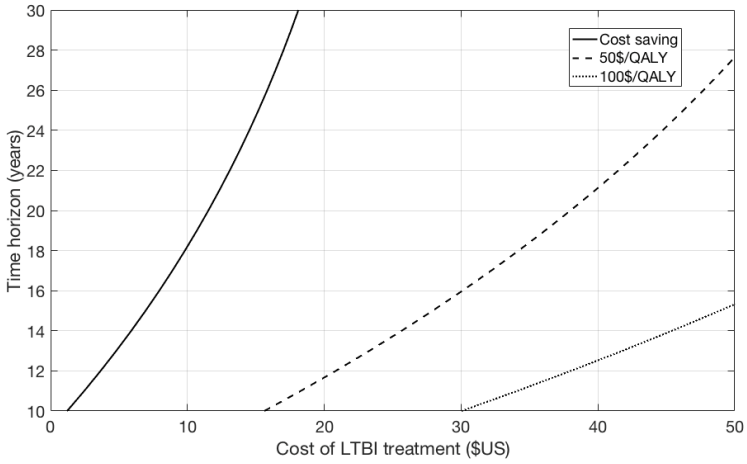
Although we have shown that active case finding is effective in substantially reducing the prevalence of TB, we recognise that it will not be sufficient to eliminate TB. This is because of the large pool of people who are latently infected with TB. Indeed, we have shown, in Ca Mau, Vietnam, that 38% of adults have latent TB infection (26*). This large cohort of individuals represents a reservoir from which new cases of active TB, with consequent ongoing transmission, will continue to arise for decades to come (27*, 28). Hence, as the late eminent U.S. TB researcher, George Comstock, recognised many years ago (13, 29), ending TB in high burden countries will require widespread treatment of latent TB infection in the general population. This proposal investigates how to achieve this, at scale and in a sustainable manner, in a setting endemic for TB.

New tools that make this new approach more feasible

Until recently, the standard treatment for latent TB infection was isoniazid administered daily for six to nine months. The demonstration that a 12-dose, once weekly regimen (3HP) comprising isoniazid and rifapentine is as effective in preventing TB, has better adherence and is better tolerated than nine months of isoniazid in adults and children with latent TB infection (30) has made the prospect of supervised, large-scale, community-based treatment campaigns more feasible. Such a treatment campaign could be considered analogous to multi-dose vaccination campaigns.

Modelling the cost-effectiveness of "universal test and treat"

We have implemented a TB transmission model with seven population categories representing TB states (31) calibrated to Vietnam-specific demographic and epidemiological data. We assumed that 80% of people would consent to be screened for latent TB infection and that the efficacy of treatment in reducing reactivation of latent TB infection was 60%. The cost of a course of treatment (3HP) was assumed to be US$50. Our preliminary findings, summarised in the adjacent figure, are that the proposed universal test and treat intervention is highly cost-effective with an incremental cost-effectiveness ratio (ICER) of US$170 per QALY gained over a 10-year time horizon. Over a 30-year time horizon the intervention is predicted to cost <$US 50 per QALY gained and if the price of rifapentine can be reduced below $US 18 per course, the program is predicted to be cost-saving to the government of Vietnam over a time horizon of 10 years. In this study we will acquire data on effectiveness and costs that will enable better quality estimates of cost-effectiveness.



3) Aim and hypothesis

The **overall goal** of this project is 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.

Hypothesis: That universal testing and treatment for latent TB infection, added to active case finding for TB disease, will reduce the prevalence of TB by at least 75% after 2 years.

We also hypothesise that this intervention will be highly cost effective within a 10-year time horizon and will be cost saving within a 20-year time horizon.

4) Objectives

The **primary specific objective** is to estimate, among people aged 15 years and over living in Ca Mau, southern Vietnam, the effect of universal testing and treatment of latent TB infection, together with active case finding for TB, on the population prevalence of bacteriologically-confirmed TB two years after the intervention.

The **secondary objectives** are

1. To estimate the incidence of severe adverse events attributable to the intervention;
2. To estimate the effect of the intervention on all-cause mortality;
3. To estimate the costs and cost effectiveness of the intervention.
4. To estimate the prevalence of latent TB infection four years after the intervention among children born between 2008 and 2016,

5) Outcome – primary endpoint

The primary endpoint is the prevalence of bacteriologically confirmed pulmonary TB, as assessed two years after the intervention. **A prevalent case of bacteriologically confirmed pulmonary TB** will be defined as a study participant whose sputum tests positive for MTB on Xpert Ultra.

Sensitivity analyses will be conducted using alternative definitions based on clinical, radiological and additional microbiological (culture) data.

6) Study Design

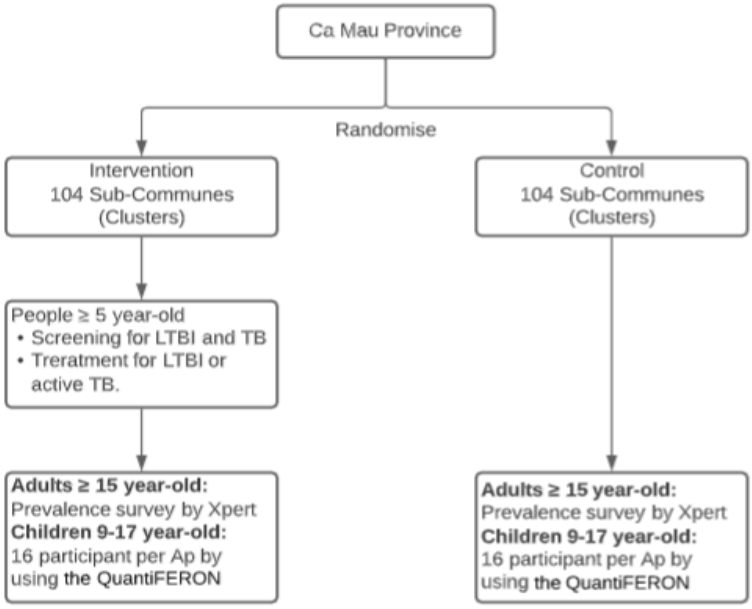
Study setting and population

Vietnam has a nationally administered, centralised TB control program administered by the National TB Program. Most TB cases are diagnosed and managed at district level, where the diagnosis of pulmonary TB is based on sputum smear microscopy for people presenting with symptoms of TB. The standard treatment regimen for TB is oral isoniazid, rifampicin, pyrazinamide, and ethambutol for two months followed by isoniazid, rifampicin and ethambutol for four months.

The study will be conducted in Ca Mau, the southern-most province of Vietnam, which has a population of 1,216,400 people living in 101 communes within nine districts. In 2017, there were 1,045 reported cases of pulmonary TB in Ca Mau. Multi-drug resistant (MDR) TB (n=21, 2.0% in 2017) and HIV co-infection (n=19, 1.8% in 2017) are both relatively uncommon in Ca Mau. After our recent RCT in Vietnam (17*), active case finding in household contacts is being scaled up and is being established in Ca Mau under the direction of AI Nhung and CI Hoa.

Trial design

The study participants will be the residents of randomly selected clusters in the province of Ca Mau. Clusters, which are defined sub-communes, will be randomly assigned to active and control status at baseline. There will be no measurements at baseline. People aged five years and older living in active intervention clusters will be screened, and where appropriate treated, for active and latent TB at baseline. All people in the control clusters will have routine care for detection and treatment of TB, with no active study intervention. The primary study endpoint, the prevalence of bacteriologically-confirmed pulmonary TB, will be assessed in people aged 15 years and over, two years after the intervention, using community-wide active case finding in both intervention and control clusters. The primary comparison will be between the primary endpoints in the active intervention and control arms.



7) Selection of study population

Cluster selection

Clusters are sub-communes (known as 'Ấp', roughly equivalent to a village, suburb or hamlet) with an average population of ~ 1,000 persons aged 15 years and over. Sub-communes are grouped in communes, which are grouped in districts. There are 946 sub-communes among the 101 communes in Ca Mau. In ACT3 (see page 9) we screened 120 sub-communes (~90,000 people) for TB on one or four occasions. These sub-communes will be excluded from participation in the present study. From the remaining 826 sub-communes we will randomly select the required number of clusters stratified by district and with a probability proportional to population size.

Cluster allocation to treatment groups

The selected clusters will be randomly assigned to active intervention and control status, again stratified by district and by population size (32). This will ensure both representative selection and balanced allocation of clusters from within the province.

Eligibility for the intervention

All enumerated residents of the sub-communes selected and randomized to the intervention arm will be assessed for eligibility in two phases: initially, they will be assessed for eligibility for the testing phase and, subsequently, those who have consented to this phase will be assessed for eligibility for the treatment of LTBI phase.

In each phase, individuals will only be included if they have given written informed consent to participate in that phase of the study.

All enumerated residents of the sub-communes selected and randomized to both the intervention and control arms will be assessed for eligibility for the prevalence survey (endpoint evaluation) two years after the intervention.

Eligiblity criteria for testing phase

1. Aged 5 years or older on the date of enumeration; AND

2. Capable of giving informed consent or, if aged < 15 years, having a parent or guardian who can give consent. Assent will also be routinely sought from children aged 10 to <15 years; AND
3. Not currently taking treatment for tuberculosis.

Eligibility criteria for treatment of LTBI phase

1. Meet eligibility criteria for testing and consented to screening; AND
2. Tuberculin skin test (TST) reaction size ≥ 10mm (or > 0mm if known to be HIV +ve) AND
3. Either no abnormality consistent with TB on chest radiograph OR abnormal radiograph but two sputum specimens are culture negative for *M. tuberculosis*
4. Not pregnant or planning to be pregnant in next 6 months
5. No important potential drug interactions with the intervention regimen, defined by attending medical officer in accordance with a schedule.
6. No known allergy or hypersensitivity to the active substance or any of the ingredients of the study drugs
7. Has not completed a course of treatment for TB within the preceding two years.
8. Serum transaminases (AST and ALT) are both < 3 x upper limit of normal
9. No severe or life-threatening illness that is considered by the attending medical officer to make treatment for LTBI inappropriate.

Eligibility for the prevalence survey (outcome evaluation)

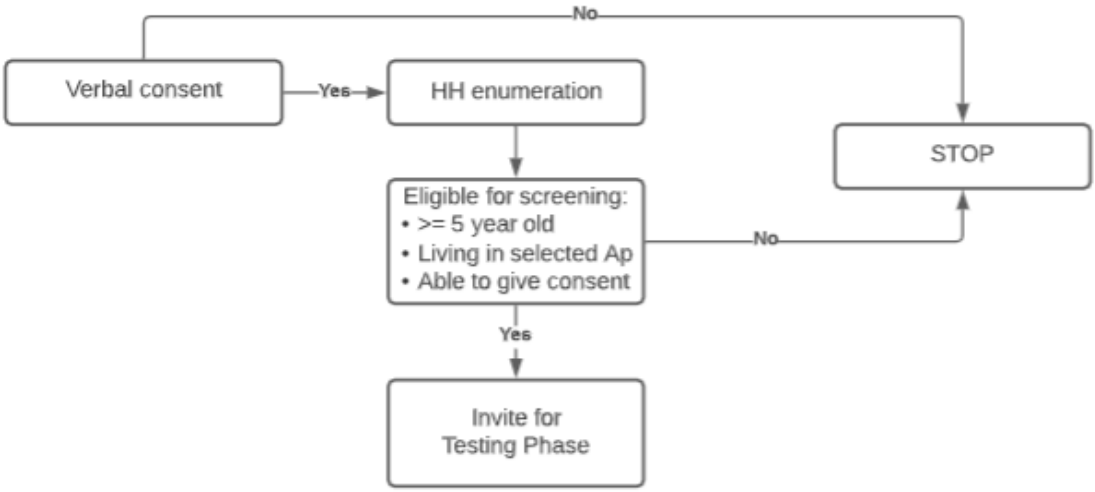
1. Aged 15 years or older on the date of enumeration for the prevalence survey
2. Capable of giving informed consent.

8) Study Procedures

Preparation

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

Enumeration



Testing phase

Initial Household visit

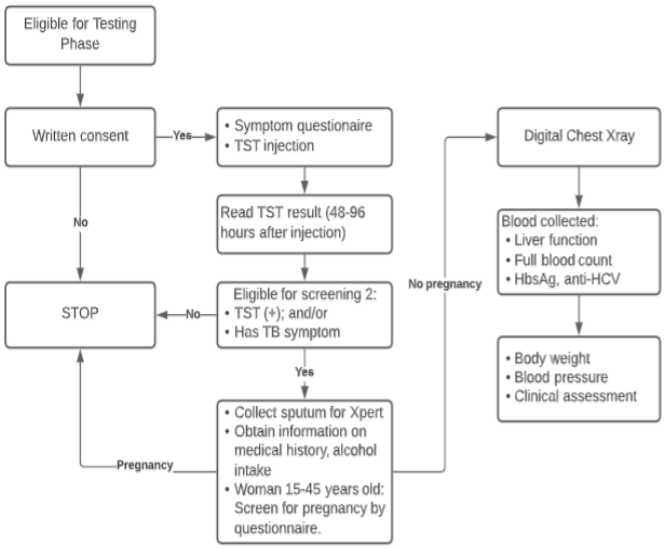
Screening for latent tuberculosis infection and for TB will be undertaken by a pair of study team members in participants' households.

Participants aged 5 years or older at the date of enumeration (or their parents or guardians) will be asked to provide written informed consent for testing (see "PCF1 – Test") (see page 33 for details of consent procedure).

The following procedures will be performed for all individuals who have provided consent to participate in screening:

1. Take a digital photograph of the face of the participant (for the purpose of subsequent re-identification). This will be stored in a secure online database.
2. Participants will be asked if they have any current symptoms of TB (cough, sputum or haemoptysis, swelling in neck or weight loss) (see "Symptom screening questionnaire").
3. A tuberculin skin test (TST) will be placed using the standard Mantoux technique.

Household visit 48-96 hours after TST injection



Field workers will return to the household 48-96 hours after placement of the TST to read the size of the induration. The induration will be digitally photographed and measured (perpendicular to the long axis of the forearm) using the 'ballpoint pen' technique. Callipers will be used to measure the size of the reaction. Reactions ≥ 10mm (or > 0mm for participants known to be HIV +ve) will be classified as positive. ("Tuberculin test forms – placement and reading").

Screened participants who have a positive TST or who report symptoms of TB will be asked to:

1. Provide a single, spontaneously expectorated sputum specimen, if possible. 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, or equivalent test, within 48 hours of collection. If the initial Xpert test is reported as "invalid", the test will be repeated.
2. Provide information on concomitant medications taken in the past seven days or planned to take in the next seven days, and on presence of known liver disease or HIV infection, drug allergy and consumption of alcohol will be acquired using a questionnaire (see "Pre-treatment Assessment Form - fieldworker"). The fieldworker will consult with the study medical officer if the participant reports he / she is taking any medication. The participants will not be required to cease any of their current medications to participate in this study.
3. In addition, women aged 15-45 years will be asked if they are pregnant or are attempting to fall pregnant or are breastfeeding (see "Pregnancy and lactation screening form").

Patients who report that they are HIV +ve and have TST reaction > 0mm will be referred to the HIV program for further management.

Assessment for LTBI treatment phase

Evaluation at central location

Participants who have a positive TST or who report symptoms of TB will be asked to have:

1. A chest Xray in a mobile x-ray van located at central location, in or near their village. Images will be exported to our online data repository. Images will either be read by an onsite radiologist or initially assessed using a validated artificial intelligence program for detection of TB. In the latter case, those images flagged as abnormal will be re-read by an onsite radiologist (see "Chest radiograph report form"). Chest xrays will be classified by each reader as: "consistent with TB", "abnormality, other

than TB" and "normal or no significant abnormality". Women who state they are pregnant or attempting to fall pregnant will be excluded from chest radiography.

2. Baseline measurement of body weight, blood pressure and blood tests for liver function tests (LFT), full blood count (FBC). The physical examination findings will be recorded on the "Body weight, Blood Pressure forms".

Further assessment of pregnant women, those attempting to fall pregnant and those who are breastfeeding

Women who say they are pregnant or who say they are attempting to fall pregnant 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 single sputum specimen for Xpert testing, as described above.

Women who are breastfeeding, but who are not currently pregnant or trying to become pregnant, will be referred for chest radiograph and counselled about their risk of TB. However, they will not be considered for treatment of LTBI.

Further assessment of participants with abnormal chest xray or with positive sputum Xpert tests

Those with chest Xray reported as "consistent with TB" or with any Xpert MTB positive sputums will be asked to produce two further sputum specimens for sputum microscopy, mycobacterial culture, and drug susceptibility testing (see "Sputum culture form"). Those participants whose sputum sample tests positive for Xpert MTB and/or have sputum mycobacterial cultures reported as positive for *M. tuberculosis* (on antigen testing) will be notified and referred to a central location for further evaluation. If TB diagnosis is confirmed, standardized TB treatment will be provided to the patients by the National TB Programme in accordance with policy. The outcome of the evaluation and the decision on TB treatment will be recorded.

No person who has a chest Xray reported as "consistent with TB" will be considered eligible for treatment of LTBI unless and until they have two sputum mycobacterial cultures reported as negative for *M. tuberculosis*.

Those with chest xray reported as "abnormality, other than TB" will be referred for clinical evaluation at the Provincial TB Program, or elsewhere, at the discretion of the study medical officer.

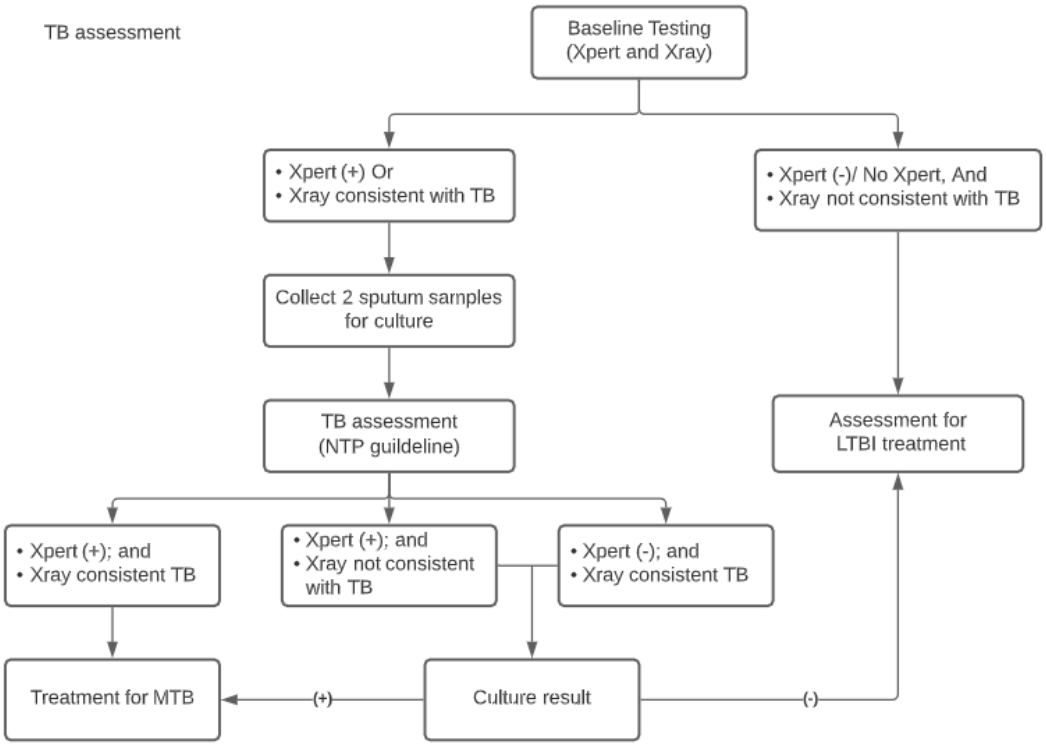


Figure 2: Flow chart of assessment for active TB

<u>TB preventive treatment in those with LTBI but without active TB</u>

Participants who meet **all** of the following criteria will be eligible for treatment for LTBI:

- Are aged ≥ 5 years and have consented to the screening phase; AND
- Have a TST ≥ 10 mm (and are not known to be HIV +ve); AND
- Are not excluded from 3HP regimen by the pregnancy or lactation screening questionnaire; AND
- Have not completed a course of treatment for TB within the preceding two years; AND
- Do not have a history of allergy or known hypersensitivity to any of the study drugs; AND
- Do not have active TB according to the following criteria:
    1. Expectorated sputum tested negative for MTB on GeneXpert or did not produce a sputum specimen for Xpert testing **AND** have a chest x-ray that was not reported as "consistent with TB" **OR**.

    2. Did not have a chest radiograph **BUT** have two sputum specimens that both tested negative for MTB on GenXpert **OR**

    3. Have a chest x-ray that was reported as "consistent with TB" **BUT** have two sputum cultures that have been reported as negative for TB and any GeneXpert tests (if collected) are negative for TB.

will be recommended for further assessment for treatment of LTBI by field worker.

Informed consent for treatment for LTBI

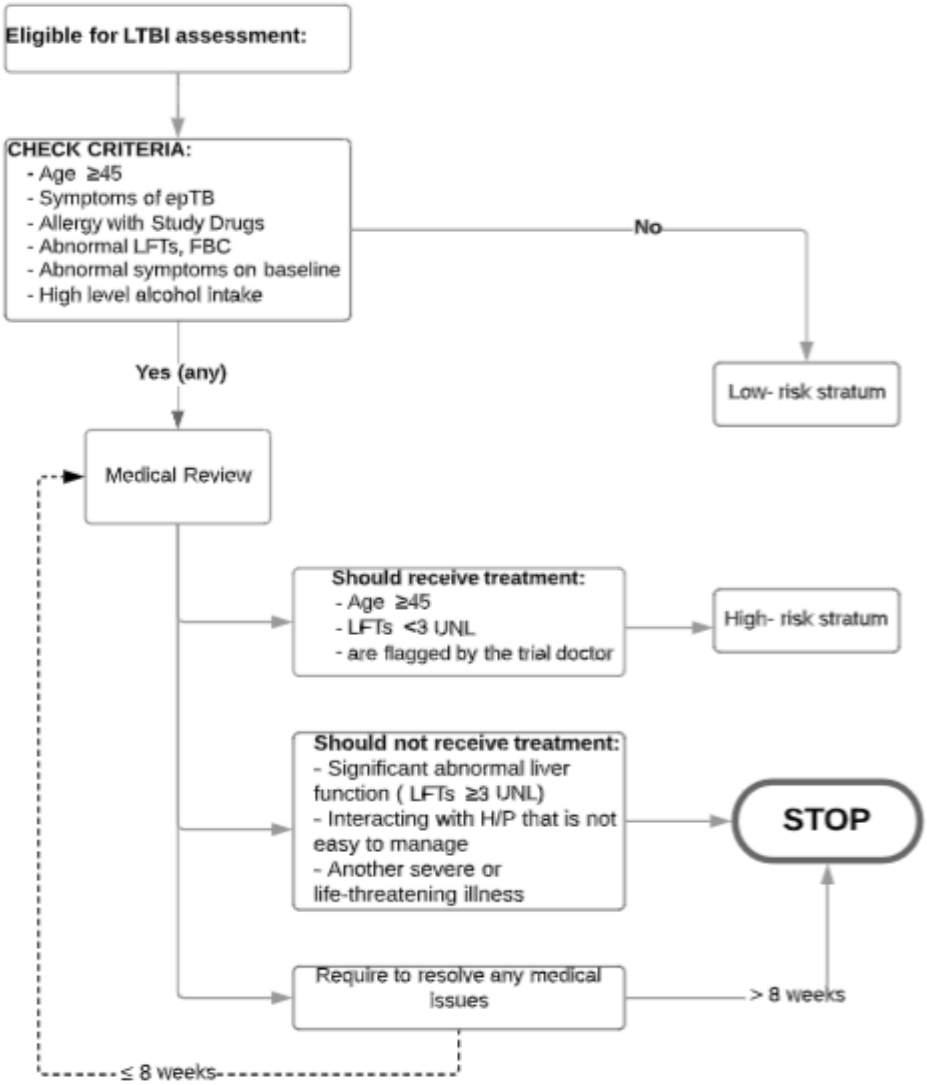
If eligible for treatment, according to the above criteria, participants will be provided with a written and oral explanation of the rationale for treatment (see "PIS2 – Treat" / "PCF2 – Treat") (see page 33). Written informed consent for participation in the LTBI treatment phase of the study will be sought.

Check criteria

If one or more the following criteria are met, participants will be reviewed by a doctor prior to treatment:

- Have symptoms of extrapulmonary TB (neck swelling or weight loss)
- Are noted to be taking any regular medications.
- Report allergy to rifampicin, rifapentine or isoniazid
- Report known liver disease or hepatitis
- Have baseline transaminases that are abnormal
- Have baseline Hb, WCC or plts that are outside the laboratory normal range
- Respond positively to any of the symptoms on the checklist for screening prior to each treatment administration
- Currently (in the last month) drink more than 14 standard drinks of alcohol per week for men and 7 standard of alcohol per week for women

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



Medical Review

The study doctor will conduct a medical review prior to commencing TB preventive treatment (see "Medical assessment – baseline") for eligible participants who meet one or more criteria, defined as above

The objectives of the 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. If the participant has an acute illness (unrelated to TB) at the time of medical review, LTBI treatment may be delayed for up to 8 weeks from that date. If the patient's symptoms persist after 8 weeks, the participant will not be eligible for treatment of LTBI in the current phase.
2. Decide, in consultation with the participant, whether the participant should receive treatment for LTBI. Among the relevant considerations are the following:
    a. 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.

b. Participants who are regularly taking medications that interact with rifamycins, where the interactions cannot easily be managed, will not be offered treatment (see Appendix to Manual of Procedures).

c. 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. This will be at the discretion of the trial medical officer.

3. If it is decided that the participant should receive treatment for LTBI, define whether he or she is in the low- or high-risk monitoring for adverse events below).

Monitoring for adverse events

Participants who meet **one or more** of the following criteria

- aged ≥ 45 years,
- 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 the high-risk monitoring for adverse event

will have liver function tests repeated **at two weeks, at four weeks** after commencement of treatment and **then at four weekly intervals throughout treatment.**

Follow-up during the TB preventive treatment period

At the first visit a Treatment Officer, together with a member of the commune health staff assigned by the commune health post/ap coordinator, will visit study participants in individual to:

- Confirm name of participant ID (matching PID, names, age and photograph)
- Provide participant screening results
- Obtain written informed consent for treatment of LTBI.

At each follow-up visit during treatment, the treatment team will evaluate the participant for the presence of adverse events and dispense medications, as described below.

Participant identification

The visit may be conducted at the household or at the Ap central office, depending upon the requirements of the participant.

A Treatment Officer, together with a member of the commune health staff assigned by the commune health post/ap coordinator, will visit study participants to confirm the identity of the participant (matching PID, names, age and photograph).

Symptom screening

The participant will be interviewed using the "Symptom Screening prior to Administering Medications questionnaire. This may be completed by phone or face-to-face interview. If the participant responds positively to any of the symptoms on the checklist, the **Adverse event management** procedure will be implemented and a the **eCRF "Adverse events"** form will be submitted within 24 hours (even if unsure about whether it is an adverse event). If the Treatment Officer is unsure about whether a

participant has had an Adverse Event, or whether Active TB should be investigated, he/she should discuss with the Medical Advisor by telephone.

If the participant has experienced any of the symptoms on the Symptom Screening checklist, do NOT dispense medication unless and until instructed to do so by Medical Advisor.

Dispense medication
If

- The identity of the participant has been confirmed using matching of their PID, names, age and photograph, AND
- "Symptom screening prior to administering treatment" is negative or the Medical Advisor has authorised dispensing medication

then give the study participant one package of one week of medication (1 dose of 3HP) and record the following information in the eCRF

- Directly Observed Therapy (DOT) or Self-administered therapy (SAT) method
- date of delivery,
- package number,
- PID,
- signature of person receiving the medication,
- signature of the Treatment Officer (see MOP- Supply Chain and Pharmacy Management)

If DOT method is implemented, observe participant swallowing the medication and record that this has been observed in the "Drug Dispensing- Field worker".

If the patient is untraceable at the time of the scheduled follow-up visit
Re-schedule the visit, where possible either by phone call or home visit. If patient wishes to withdraw from treatment, complete treatment withdrawal form.

For participants in high-risk risk stratum group in Weeks 2, 4, 8, 12, 16 only

- Collect one biochemistry blood tube for liver function test.
- Record collection date and time in eCRF
- Despatch to laboratory
- Record results in eCRF. The sample should arrive to lab within 24 hours at a suitable temperature.

Unexpected events during treatment

- Management of adverse events is described below.
- Lost or misplaced doses of the medication should be replaced after checking that they cannot be found and checking with the study Doctor.
- If the participant states that he/she vomited after taking the study drug, this should be discussed with the study doctor. This may be an adverse event.

Indications for cessation of TB preventive treatment
If a participant experiences one or more of the conditions/situations listed below, the Investigator will permanently discontinue study drugs

1) Participants deprived of freedom by an administrative or court order
2) SAE-related to the study drug.
3) Diagnosed with (and treated for) active TB
4) Pregnancy reported by the participant

5) Onset of a condition that would have made the participant ineligible for commencing TB preventive treatment.

Survey to measure prevalence of pulmonary TB (primary endpoint)

Two years after the intervention (2023), we will undertake a prevalence survey in both active intervention and control groups. This survey will be analogous to the survey conducted in the final year of the ACT3 study (25).

The survey will begin with household enumeration census (as described above, page 14). The screening team 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.

A census of all households in all participating sub-communes (Aps), in both intervention and control arms, will be conducted. The nature of the census will be explained and verbal consent to proceed will be sought and documented in the eCRF. With consent, we will collect information on names, year of birth or age, sex and phone number of each household member. At this time household members will be provided with written information about the survey. No identifying information will be collected from participants who are incapable of providing and from those who decline.

All consenting, eligible individuals aged ≥ 15 yrs, will be asked about the following symptoms (on the day of testing and on any day in the previous two weeks):

- Cough
- Sputum production
- Coughing up blood.

Each individual who has given consent will be asked to produce a single, spontaneously expectorated sputum specimen.

All specimens will be transported to the central laboratory, stored in at $4^{O}C$ and tested within 48 hours using the Xpert Ultra system (Cepheid).

Those who test positive on Xpert Ultra will be invited to attend the provincial TB centre for further clinical evaluation. They will also be requested to produce two further sputums for mycobacterial culture and to have a chest radiograph performed.

Endpoints will be defined based on these results, as descripted above (see page 11). Those who are unable to produce sputum for Xpert Ultra testing will be assumed not to have pulmonary TB for the purposes of this endpoint evaluation.

Survey to measure prevalence of latent TB in children

The purpose of this survey is to estimate the effect of the intervention on TB transmission, as indicated by the difference in prevalence of latent TB infection among children in the intervention and control arms four years after the commencement of the intervention in the intervention arm.

The study population will be children who were born between 2008 and 2016, who would be aged 5 to 13 in 2021 (when the trial begins). The proposal is to measure the prevalence of latent TB infection in this population in 2025 (four years after commencing the intervention), when the participants will be aged 9 to 17 years.

Eligible participants will be children who

1. were born between 1st January 2008 and 31st December 2016;
2. are resident in the active intervention or control clusters during the population enumeration in 2021-2022;
3. whose parents or legal guardians are capable of giving informed consent
4. who themselves are capable of giving assent.

The presence of latent TB infection will be assessed using the QuantiFERON®-TB Gold Plus test kit, which will be used in accordance with the manufacturer's instructions.

We will randomly select 16 eligible participants per sub-commune. After gaining written informed consent (from parent or guardian) and assent (from the child), 1 mL of blood will be collected into each of the four test tubes, which will be transferred to the laboratory.

Timeline

Study Year	Semester	Activity*	Study Population
One	Oct21-Mar22	Test & Treat intervention	All persons aged 5 and over in active intervention sub-communes
	Apr22-Sep22		
Two	Oct22-Mar23		
	Apr23-Sep23		
Three	Oct23-Mar24	TB prevalence survey	Persons aged 15 and over in the active intervention and control sub-communes
	Apr24-Sep24		
Four	Oct24-Mar25		
	Apr25-Sep25		
Five	Oct25-Mar26	LTBI prevalence survey	Children born 2008-2016** in active intervention and control sub-communes

* "Test & Treat" is the screening intervention; "TB prevalence survey" is to measure the prevalence of active TB disease; "LTBI prevalence survey" is to measure the prevalence of latent TB infection.

** Aged 5-13 years at start of trial, now aged 9-17 years

9) Study treatment

Those eligible and consenting for treatment of LTBI in the active intervention arm will receive the 3HP regimen. This regimen includes oral treatment with

- Once weekly oral combination rifapentine / isoniazid
- This table of weight range dosage applies to children aged 5 years to < 15 years of age

Weight range	Weekly rifapentine dose	Weekly isoniazid dose	Number of combination tablets (300mg/300mg)
10–14 kg	300 mg	300 mg	1
14.1–25 kg	450 mg	450 mg	1.5
25.1–32 kg	600 mg	600 mg	2
32.1–49.9 kg	750 mg	750 mg	2.5
≥50 kg	900 mg	900 mg	3

- All participants aged 15 years of age and older receive a once weekly dose of 900mg rifapentine and 900mg isoniazid.

Treatment will be dispensed 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 (30) and is approved for treatment of LTBI in children and adults by the US Food and Drug Administration (FDA). It is recommended in US Centre for Disease Control (CDC) (33) and World Health Organization (WHO) (34) guidelines and is approved for use in Vietnam for treatment of LTBI in contacts of patients with active TB, and other high risk populations.

Treatment administration
The procedure for treatment administration is described on page 20.

Monitoring adherence to therapy
The importance of adherence will be emphasized during each week visit. If participants are non-adherent, the study staff should endeavour to identify any problems contributing to non-adherence (e.g. side effects) and seek support from the clinical staff to manage the issue. Adherence will also be assessed by direct phone call or face to face interview.

If contacts do not attend a scheduled appointment during the period of their treatment or respond to a phone call and arrange an alternative time, then a household visit will be arranged within the next 7 days. If contacts miss one appointment (by 7 days or more after the due date) the Trial Coordinator will be notified and a plan made to ensure follow-up is completed. The outcome of visit attempts will be documented and included in a report to the Trial Steering Committee. An attempt will then be made to continue follow-up at the next scheduled weekly follow-up time.

Follow-up the post-treatment period
The end of treatment date will be either

- The date on which the 12th dose of treatment is taken or
- 16 weeks after treatment initiation

whichever comes first.

The final visit should be scheduled two weeks after the "end of treatment" date.

At this visit

- Interview the participant using the "Symptom Screening prior to Administering Medications" questionnaire. If the participant responds positively to any of the

symptoms on the checklist, follow instructions in **Adverse event management** and submit the **eCRF "Adverse events"** form within 24 hours (even if unsure about whether it is an adverse event). If the Treatment Officer is unsure about whether a participant has had an Adverse Event, or whether Active TB should be investigated, discuss with the Medical Advisor by telephone.

- Complete the "Close-out" form, recording the total medication the participant had during the treatment, any adverse event occurred and the outcomes of adverse event.

Packing and labelling

Packaging and labelling of the medicinal products will be performed by the Woolcock Institute in Vietnam in accordance national regulatory requirements. Isoniazid and rifapentine are commercially available.

Dispensing and product accountability

The trial medication delegate will maintain dispensing logs detailing the dates, quantities and batch numbers of dispensed and returned study drugs for each participant. The trial medication delegate will also manage the overall drug accountability.

Missed doses

If a missed dose occurs ≤ 3 days past the scheduled dosing time, then the participant will be administered the missed dose and the next dose should be taken as scheduled. If the missed dose is discovered > 3 days past the scheduled dosing time, re-dose and re-schedule next dose to 1 week after the current dose.

10) Laboratory assessments

All below listed blood tests will be performed by the central and local laboratory

Test	Reference value
Full blood count	
WBC	3.70-10.1 (10^3/µL)
NEU	39.3 - 73.7%
LYM	18.0 - 48.3%
MONO	4.40 - 12.7%
EOS	0.6 - 7.30%
BASO	0.0 - 1.70%
RBC	4.06-4.69 (10^3/µL)
RET	0.3 - 2.0%
HGB	12.9- 14.2 g/dL
HCT	37.7 - 53.7%
MCV	81.1 - 96.0 fL
MCH	27.0 - 31.2 pg
MCHC	31.8 - 35.4 g/L
RDW	11.5 - 14.5%
PLT	155-366 (10^3/µL)
Liver Function Tests	
Albumin	38 – 54 g/l
GOT (AST)	10 - 37 U/L
GPT (ALT)	10 - 40 U/L
Gamma GT	12 - 45 U/L
Bilirubin (total)	< 1 mg/dl

11) Adverse event reporting

Definition of terms

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product. It does not necessarily have a causal

relationship with this treatment. An adverse event can be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An adverse event is any adverse occurrence that occurs after study participant signs the consent form, even if it may not be directly related to the treatment.

Adverse Event of Special Interest (AESI)
An adverse event (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterise and understand them. AESIs may be added or removed during a Study by protocol amendment.

Adverse Drug Reaction (ADR)
Adverse event that is assessed as possibly, probably or certainly attributable to the study medication.

Adverse events that occur more than 14 days after the date of taking the last dose of the study drug will be deemed to be unrelated to the study drug.

Serious adverse event (SAE)
Any adverse event that

a) results in death,
b) is life-threatening,
c) requires inpatient hospitalization or prolongation of existing hospitalization,
d) results in persistent or significant disability/incapacity,
e) is a congenital anomaly/birth defect,
f) where the investigator or trial medical officer considers that medical intervention is required to prevent one of the preceding circumstances from arising,
g) where the investigator or trial medical officer considers the circumstances are serious for other medical reasons.

Unexpected Adverse Event (UAE) / Unexpected Adverse Drug Reaction (UADR)
An adverse event or adverse reaction, the nature or severity of which is not consistent with the applicable product information (Product Information/Data Sheet). An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labelling specifically states that the ADR might be associated with a fatal outcome.

Serious Unexpected Suspected Adverse Drug Reactions (SUSARs)
An adverse event that meets the criteria for a serious adverse event (SAE) and also for unexpected adverse drug reaction; that is:

A. It is serious
    a. Results in death,
    b. Is life threatening,
    c. Requires inpatient hospitalisation or results in prolongation of existing hospitalisation;
    d. Results in persistent or significant disability/incapacity,
    e. Is a congenital anomaly/birth defect, or
    f. Is a medically important event or reaction.

AND

B. It is attributable to the study medications / intervention (possibly, probably or certainly)

AND

C. It is unexpected, that is, it is not consistent with the applicable product information (the Investigator's Brochure for an unapproved investigational medicinal product or Product Information/Data Sheet for an approved product)

Framework

The following committees, that are relevant to the patient safety and pharmacovigilance will oversee the trial:

a) a trial management committee (TMC), comprising the senior investigators and trial management staff, who will conduct the day-to-day operations of the trial;
b) a trial steering committee (TSC), including independent expert members and chair, who will review and approve protocols and key study documents as well as reports from the IDMC;
c) an independent data monitoring committee (IDMC), who will review safety and efficacy data, independent of the TMC, and provide advice to the TMC and the TSC; and
d) an expert clinical panel (ECP), who will review individual adverse event data, adjudicate event severity and attribution to study drug and report to the IDMC.

Adverse events of special interest in this study

The AESI for rifapentine are:

- hepatotoxicity and
- systemic drug reaction/hypersensitivity reaction.

Systemic reactions have been reported in 3.5% of patients taking rifapentine(35). In a recent study, symptoms occurred after a median of 3 doses, 4 hours after the dose; median time to resolution was 24 hours.

The definition of a systemic drug reaction will that used in the PREVENT study (35):

- hypotension (systolic blood pressure <90 mm Hg), urticaria (hives), angioedema, acute bronchospasm, or conjunctivitis (red eyes); OR
- > four of the following symptoms occurring concurrently (more than one of which had to be grade 2 or higher): weakness, fatigue, nausea, vomiting, headache, fever, aches, sweats, dizziness, shortness of breath, flushing, or chills.

AEs that meet either of the above criteria were termed systemic drug reactions.

There are no adverse events of special interest for isoniazid.

Expected adverse drug reactions

This will be based on registered product information for isoniazid and on the Investigators Brochure for rifapentine. Currently, these identify the following adverse effects as expected with the study drugs.

Rifapentine*	**Isoniazid**
Hypersensitivity reactions Hepatotoxicity	Hepatitis

Headache Skin reaction (To be updated when IB is received)	Gastrointestinal symptoms Peripheral neuropathy Immunologic reactions

* The following additional adverse events have also been observed when rifapentine has been taken in combination with other anti-TB drugs: neutropenia, lymphocytopenia and anaemia.

Pregnancy during treatment

All pregnancies should be reported if they occur between the time the participant signs the consent form and 2 weeks after last dose. The "Pregnancy form" in the RedCAP eCRF should be used to report as follows:

- Initial report: to be completed within 24 hours of study staff becoming aware of the pregnancy.
- Follow up report: to be completed within one month after the end date of pregnancy

Any complication during pregnancy period that meets the criteria for SAE will be reported as SAE, SAE form will be completed.

Reports

Vietnamese IRB and Ministry of Health

In accordance with Circular 29/2018/TT-BYT dated 29 October 2018, issued by MOH, details of all SAEs will be reported to Principal Investigator in Viet Nam, the responsible Institutional Review Board (IRB) in Viet Nam, the Ministry of Health (MOH) and the National Centre of Drug Information and Adverse Drug Reactions Centre according the following timetable:

- For all SAEs that are life-threatening or result in death, initial report must be reported to the MOH within 7 working days of event notice;
- For other SAEs, initial report must be sent to MOH within 15 working days of event notice;
- All SAE need to be informed to National Lung hospital EC within 24 hours (according to Vietnam national guideline for pharmacovigilance, 2015).
- Progress of SAEs must be updated via follow up reports until study participants are recovered.
- All non-serious AEs occurring in Viet Nam must be recorded, summarized and reported in a periodic report or study outcome report to be sent to the MOH's IRB and the Scientific and Education Department in the MOH.

University of Sydney HREC

The Trial Safety Officer is responsible for notifying the University of Sydney HREC of the following:

- All SAEs, within 72 hours of study staff becoming aware
- SUSARs, a line listing of all SUSARs at six monthly intervals
- Serious breaches should be reported to the reviewing HREC, usually by the Sponsor, within 7 calendar days of confirming a serious breach has occurred.

Reports to Data Safety Monitoring Committee

The Trial Safety Officer, working with the DSMB statistician, is responsible for preparing, at six-monthly intervals, an aggregate report of all AEs including their SOC, grade, outcome and attribution to study drug.

The DSMB will review these, and other, data and make recommendations to the Trial Management Committee about the conduct of the trial. The report of the DSMB will be provided to the University of Sydney HREC.

12) Data analysis

Primary study objective is to estimate, among people living in Ca Mau Province, the effect of universal testing for and treatment of LTBI, together with active case finding **and treatment** for TB, on the population prevalence of **pulmonary** TB after **two** years.

The analysis will be by intention-to-treat. We will use a two-level (sub-commune and household) hierarchical generalised linear model with a Poisson error distribution to test the effect of treatment group allocation on number of prevalent cases of pulmonary TB in persons aged ≥ 15 years. Treatment group allocation will be the main (fixed) effect. Clusters will be treated as a random intercept term. The enumerated cluster population aged ≥ 15 years will be the offset. A p value < 0.05 will be treated as significant. No covariates will be included in the primary analysis. Prevalence rate ratios will be estimated with 95% confidence intervals, adjusted for clustering.

A secondary objective is to estimate the incidence of adverse events attributable to 3HP preventive therapy (safety analysis). The incidence of all adverse events grade 3 or higher, together with specific, expected adverse events in the intervention group will be enumerated and reported as rates per person-year of participation in the study.

Sample size and study power

Primary outcome

The intra-class (cluster) correlation coefficient for prevalent TB cases in the first year of screening of the ACT3 study was 0.0091. The prevalence of TB in the control clusters screened for the first time in 2017-18 was 0.233%. The average number of eligible participants in each cluster was 720. Active case finding alone was able to achieve a 50% reduction in prevalence over the four years study period. We expect that the composite intervention proposed here, which additionally includes treatment of the reservoir of latent TB infection, will achieve at least a 75% reduction.

We estimate that 104 clusters in each group, that is 74,800 eligible participants in each group, will be required in the final prevalence survey to have 90% power to detect a 75% lower prevalence of TB in the active intervention group, compared to the control group, as significant at the 5% level (two-sided test, PASS 2015 software, “Two proportions in a cluster-randomized design”).

Secondary outcome (LTBI in children)

In ACT3, the prevalence of positive QFT (indicating latent TB infection) in the control arm was 8.3%. Assuming 104 clusters in each arm and ICC as above (0.009), we would need 8 participants per cluster to have 90% power to detect a prevalence ratio of 0.5 (i.e. a 50% lower prevalence of LTBI in the intervention arm) as significant at $P < 0.05$. To allow for non-response, we will randomly select 16 eligible participants per cluster.

13) Data management

Data Collection and storage

We will use a customised database system to acquire data, manage workflow and communication and generate management reports. Data are acquired through two interfaces: tablet computers or smart phones running Android software and operated by field team members and web-based software in laboratories and in managers' offices. Input is by text entry and by scanning QR codes containing identifying details for participants and for laboratory specimens. Management reports are generated to review progress and support trial supervision. We will use this facility to build in both automated and manual quality assurance procedures to eliminate missing data and minimise the risk of data errors. Finally, the database system archives all the acquired data and enables output of datasets for analysis. A list of all authorized data originators will be created and maintain and filed in investigator site file.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

Data Confidentiality

All aspects of the study, including results, will be strictly confidential and only the researchers will have access to information on participants. A report of the study may be submitted for publication, but individual participants will not be identifiable in such a report.

The IECs/IRBs, and regulatory agencies, require direct access to all study records, and will treat these documents in a confidential manner.

Study Record Retention

Study records of this study will be stored a minimum of 15 years post-study completion or last publication.

14) Governance and ethical issues

The Woolcock Institute of Medical Research, an independent Sydney-based medical research institute, will be the trial sponsor. We will establish the following committees to oversee the trial:

e) a trial management committee (TMC), comprising the senior investigators and trial management staff, who will conduct the day-to-day operations of the trial;
f) a trial steering committee (TSC), including independent expert members and chair, who will review and approve protocols and key study documents as well as reports from the IDMC;
g) an independent data monitoring committee (IDMC), who will review summary safety and efficacy data, independent of the TMC, and provide advice to the TMC and the TSC;
h) an expert clinical panel (ECP), who will review individual adverse event data, adjudicate event severity and attribution to study drug and report to the IDMC; and
i) a community stakeholder committee, include representatives of the local community, to advise on matters relating to their interaction with the trial.

Equipoise
The effectiveness of the intervention is plausible but has not previously been evaluated in the context of general population screening and treatment. Hence, it meets the criterion of equipoise. Participants are informed about the trial including the risks and benefits of participation and their right not to participate. Those not capable of giving informed consent are excluded. No coercion or excessive financial incentives are used to gain participation. The local community will be consulted in meetings before the intervention is implemented in each sub-commune. The protocol will be reviewed by institutional review boards in Australia and in Vietnam.

Registration and data availability
The trial will be prospectively registered with the Australian and New Zealand Clinical Trials Register. Data management and publication plans will developed and agreed prior to commencement of recruitment. We intend to make de-identified data available to other *bona fide* researchers after the results are reported. Findings will be published in a peer-reviewed journal.

Protocol deviations
The University of Sydney HREC will be notified of any protocol deviations.

15) Trial administration and supervision

Training
All staff participating in recruitment, registration and follow-up of study participants will participate in a training course prior to the commencement of the study in their Province. The training will address eligibility criteria, consent, registration, randomization, data management and confidentiality, serious adverse events (the investigation, management and reporting of adverse events), the standard operating procedures, drug management, counseling of potential participants, protection of research subjects, treatment of TB and the principles of good practice in clinical research (GCP).

Staff will also be trained in enrolling and evaluating children. Staff will be trained to collect samples from children and refer as appropriate.

Staff and students from Australia will be required to have “working with children” clearance from Australian authorities before participating in the research. There is no equivalent system for clearance of Vietnamese resident staff and students.

Supervision
The Trial Coordinator will visit to observe the screening and treatment activities frequently. During visits, the Trial Coordinator will perform monitoring, evaluation of compliance with the study protocol, study documentation, adequacy of consent procedures, data quality checks and training of staff.

5% of all interviews will be randomly selected and audited by the Data management team to confirm that study participants gave correct information. These interviews will be conducted per Ap (village). If discrepancies are identified between the Monitoring Phone calls and the original data, then further investigation will be performed.

Good Clinical Practice

The broad principles of Good Clinical Practice (GCP) will be adhered to, in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines and local Vietnamese regulations.

The study team will have training in the principles of Good Clinical Practice. The Trial Coordinator and WIMR staff with a leadership role at the Provincial level will obtain a certificate of Good Clinical Practice prior to the start of the trial. Some ethical considerations relating to GCP are outlined below, under 'Ethical considerations'.

Independent audit

An independent audit will be conducted within 12 months of commencing the study, and at least every 2 years during the remainder of the study. This will include an audit of the ACT5 project including study documentation, data storage, adherence to study protocols, and severe adverse event reporting. A report from each internal audit will be distributed to the Trial Steering Committee and all Project Managers. The Trial Manager will be responsible for ensuring that difficulties that are identified are addressed, and report back to the Trial Steering Committee with evidence of resolution of the problems.

Ethical considerations

Informed consent

There are five stages of consent in this study:

1. Enumeration and collection of identifying information in the household census (verbal consent)
2. Screening for latent TB infection (written consent)
3. Evaluation for active TB and for TB preventive treatment (written consent)
4. Participation in the primary endpoint evaluation survey (prevalence of TB) (verbal consent)
5. Participation in the secondary endpoint evaluation survey (testing LTBI in children) (written consent)

Verbal consent will be sought for the first stage and written consent for the second and third stages, for those who are eligible.

Written informed consent will be obtained from all adults aged 15 and above. For those below 15 years written informed consent will be obtained from parents or the guardian and verbal assent documented for the participants.

Confidentiality

All records will be kept confidential and will not be made publically available.

All printed study documents, including CRFs, will contain the participant's study identifier (SID) and participant's initials. If the names of participants appear on documents (such as blood test results, pathologist reports), they will be erased before they are stored, following the completion of the study. Study documents will be stored in a locked room or cupboard within each Province.

Study data will be stored on password protected electronic devices. Passwords will only be given to study staff and will be changed regularly.

The Institutional Review Boards, or external auditors, may review the medical records to verify the integrity of data collected for the study.

When the results of the study are published, the identity of individuals will remain confidential.

Participant reimbursement

Expenses that are directly related to the subject's participation in the trial (for example cost of transportation for attending visits, if any) will be compensated. Subjects/parents/legal representatives will not receive any remuneration for participation in the trial.

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