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The effectiveness, safety, and benefit risk balance of one month of daily rifapentine with isoniazid added to diabetes standard of care, compared to diabetes standard of care alone, to prevent TB in people with diabetes

Submission date
12/12/2024

Recruitment status
Recruiting

Registration date
27/01/2025

Overall study status
Ongoing

Last Edited
30/01/2026

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims

Diabetes mellitus (diabetes) increases the risk of tuberculosis (TB) 3-fold. However, WHO does not recommend TB preventive treatment (TPT) for people with diabetes except if they are people living with HIV (PLHIV) or contacts of persons with TB, for whom the benefit of treatment outweighs the harm. There is insufficient evidence to inform the benefit-risk balance for TB prevention using isoniazid for 6 or 9 months; the regimen used in many countries. We and others, however, have shown in mathematical models that TB prevention for people with HIV will only have a modest impact on community-level transmission. Additionally targeting at-risk groups who are HIV-uninfected (HIV-ve), such as people living with diabetes, is important to accelerate reductions in TB incidence. There is a need to evaluate the evidence base for TB prevention in people living with diabetes, starting with assessing the benefits versus the harms of providing novel ultra-short treatments for prevention.

One month of daily rifapentine with isoniazid (1HP) was shown to be non-inferior to 9 months of isoniazid (9H) to prevent TB in PLHIV. 1HP had a better safety profile as well as superior completion rates when compared to 9H (BRIEF-TB Trial). It is hypothesised that, compared to the WHO standard of care (SoC) for diabetes, 1HP may beneficially alter the risk trade-off due to the potent sterilising mycobactericidal effect of rifamycins, significantly shorter treatment duration, a safer toxicity profile and less burden on the health system, whilst also saving costs. A sufficiently powered trial to evaluate these trade-offs would influence policy.

There is further equipoise in examining this question for Mycobacterium tuberculosis (Mtb)-infected HIV-uninfected persons with diabetes who are on optimal diabetic care and concomitant therapy such as metformin. Metformin, a widely used first-line type 2 diabetes drug, may have potential as a host-directed therapy against Mtb. Its anti-TB effect appears independent of its glucose-lowering ability. A counterhypothesis would be that optimal diabetes care alone may effectively modify TB risk, thus avoiding unnecessary use of anti-TB drugs. Other studies suggest that, regardless of the diabetes drug used, TB risk could be reduced with better

glycaemic control (6% increase in risk for TB per 10-mg/dl increase in fasting plasma glucose). 1HP may thus not have a better benefit-risk trade-off than SoC provided the goals of SoC are met. The BALANCE study will test the hypothesis that; compared to standard diabetes care alone, 1HP with standard diabetes care has superior effects and a favourable benefit-risk balance for prevention of TB among HIV-negative people with diabetes who have latent TB infection.
The study will define the best pragmatic strategy for TB prevention in HIV-uninfected individuals with diabetes who are at high risk of developing active TB disease, and establish whether TB preventive treatment should be prescribed to people with diabetes by determining its added value over and above standard diabetes care.

Who can participate?
HIV-negative adults (aged ≥15 years old) with diabetes and reactive tests for TB infection (i. e. positive LTBI test) will be recruited from chronic care outpatient clinics at both private and public healthcare facilities in high-TB burden regions in South Africa and the Philippines.
The study will be conducted in South Africa from the EkhayaVac Clinical Research Site, Khayelitsha, Cape Town and from CareCT, Manilla, Philippines.

What does the study involve?
Participants will be randomised 1:1 across one intervention (1HP + SoC, n ~1,955) and one standard of care (SoC only, n ~1,955) arms. The intervention arm will receive daily 300 milligrams of isoniazid and 600 milligrams of rifapentine for one month (1HP) with the standard of care for diabetes care. The control arm in this study will comprise individuals prescribed standard of care for diabetes alone. There are 12 scheduled study visits over 4 years, which will occur at study sites or affiliated step-down facilities. Visits will involve interviews, clinical examination, phlebotomy, urine test, chest x-ray, and sputum collection at designated time points. Trial participation will be for four years post-randomisation: the primary endpoint will be evaluated at the end of year 2.

What are the possible benefits and risks of participating?
Participants benefit from a thorough medical examination at each study visit. Participants will be screened for TB, HIV and any disease or condition that is identified will be treated early. If any co-morbidities are detected, individuals will be referred to the appropriate clinic in the public health system, helping to fast-track their entry into the system.
There are minor risks related to phlebotomy, including discomfort, hematoma, and rarely an infection. In general, phlebotomy is considered to be a safe procedure.
The safety profiles of 1HP are well known. Clinical staff at sites will be trained on how to recognise the expected side effects of 1HP and how to explain these to participants. Important side effects include (although rare) liver injury. The potential risks of hepatotoxicity induced by 1HP will be monitored through blood ALT testing. Adverse events will be reported to all the necessary authorities as appropriate.
There are no anticipated psychological, social or economic harms following participation in this trial.

Where is the study run from?
Clinical Infectious Diseases Research Institute, University of Cape Town, South Africa

When is the study starting and how long is it expected to run for?
July 2025 to July 2029

Who is funding the study?
1. Wellcome Trust
2. UK Research and Innovation (UKRI)

Who is the main contact?
1. Prof. Molebogeng X. Rangaka (Principal Investigator), l.rangaka@ucl.ac.uk
2. Dr Lauren Barron (CIDRI Africa / UCT Research Medical Officer), lauren.barron@uct.ac.za

Contact information

Type(s)
Public, Scientific, Principal investigator

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Study information

Scientific Title
An open-label randomised controlled trial to evaluate the effectiveness, safety, and benefit-risk balance of one month of daily rifapentine with isoniazid added to diabetes standard of care, compared to diabetes standard of care alone, to prevent TB in people with diabetes.

Acronym
BALANCE

Study objectives
Compared to standard diabetes care alone, 1HP with standard diabetes care has superior efficacy and favourable benefit-risk balance for prevention of TB among HIV-negative people with diabetes who have TB infection.

Ethics approval required
Ethics approval required

Ethics approval(s)

approved 21/11/2024, University of Cape Town Human Research ethics Committee (E53-Room 46, Old Main Building, Groote Schuur Hospital, Observatory, 7925, Cape Town, 7925, South Africa; -; hrec-enquiries@uct.ac.za), ref: HREC number: 561/2024

Study design
Open-label randomized clinical trial

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Prevention of tuberculosis in people with diabetes

Interventions
Current interventions as of 18/03/2025:
There are two arms:
1. Intervention arm - a 1-month regimen (total treatment duration) of daily Rifapentine (600 mg) and Isoniazid (300 mg) in addition to the standard of care for people with diabetes as per their local healthcare provider.
2. Standard of care arm - This group will only receive the standard care for people with diabetes as per their local healthcare provider. This group will not receive placebo.

Both arms will be followed up for a minimum duration of 2 years for the primary outcome, and up to 4 years to evaluate the durability of the protective effect.

Previous interventions:
There are two arms:
1. Intervention arm - a 1-month regimen (total treatment duration) of daily Rifapentine (600 mg) and Isoniazid (300 mg) in addition to the standard of care for people with diabetes as per their local healthcare provider.

2. Standard of care arm - This group will receive no intervention and no placebo. This group will only receive the standard care for people with diabetes as per their local healthcare provider.

Both groups will be followed up for a minimum duration of 2 years for the primary outcome, and up to 4 years for secondary outcomes.

Regarding the process of randomisation,
We will use the randomisation tool in the REDCap database software. The REDCap randomisation module is a core function provided by the REDCap electronic data system used in the trial. The module allows the implementation of a defined randomisation model in the REDCap project. A randomisation allocation schedule will be generated by the study statistician and uploaded to REDCap and will be used to randomise participants to the study treatment arm. Permuted block randomisation will be used, with varying block size. Randomisation will be stratified by a number of clinically important factors including, for example, country, age group and gender.

Intervention Type

Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Rifapentine, isoniazid

Primary outcome(s)
1. Microbiologically confirmed active TB disease measured using TB-NAAT (e.g Xpert® MTB/RIF Ultra) or standard culture at over 2 years

Updated 30/10/2026: Previous Primary outcome:
Microbiologically confirmed active TB disease measured using Xpert® MTB/RIF Ultra or standard culture over 2 years

Key secondary outcome(s))
Current secondary outcome measures as of 30/01/2026:
1. The following alternate effectiveness outcome variables will be measured using provincial healthcare data and clinical notes/ laboratory results over 1 year, 2 years, and up to 4 years:
1.1. Probable and definite diagnosis of TB disease
1.2. Probable, possible or definite diagnosis of TB disease or death from any cause except violent or accidental deaths
1.3. Disease-specific deaths (including TB, caused by or related to diabetes, including cardiovascular deaths)
1.4. Microbiologically confirmed active TB regardless of symptoms and chest X-ray abnormality
1.5. Sub-clinical TB (microbiologically confirmed active TB without signs and symptoms)
2. Safety outcome variables will be measured using provincial healthcare data and clinical notes/ laboratory results:
2.1. Pre-specified clinically relevant grade ≥3 AE: clinical hepatitis, elevated liver enzymes (transaminases), peripheral neuropathy, rashes, hospitalisation within 12 weeks
2.2. Any Grade ≥3 AE (except related to violent or accidental deaths) within 12 weeks
2.3. Serious adverse events within 12 weeks
2.4. Treatment discontinuation due to any AE
2.5. Rifampicin-resistant TB at measured throughout the clinical trial until end of study visit
2.6. Progression or exacerbations of clinical condition(s) and biomarkers measured using provincial healthcare data, clinical and laboratory records within 1 year, including:
2.6.1. HbA1c
2.6.2. Diabetes-related complications (retinopathy and neuropathy)
2.6.3. Blood pressure
2.6.4. Total cholesterol and LDL cholesterol
2.6.5. Estimated glomerular filtration rate (eGFR)
2.6.6. Change in the management of diabetes
2.6.7. Emergency room admission for at least 24 hours
2.6.8. Unplanned care visits
2.7 Incident of cardiovascular events (a composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke)

3. Process outcomes measured using provincial healthcare data, clinical and laboratory records:
3.1. TPT treatment completion (taking at least 26 doses within 8 weeks)
3.2. Adherence to anti-diabetes medications within 8 weeks assessed using the Medication

Adherence Report Scale (MARS-5 tool)
4. Benefit-risk measures
5. Cost-effectiveness: costs, QALYs and DALYs measured using the EQ-5D-5L questionnaire at baseline, at weeks 4, 12, 24, 48, and every 24 weeks from week 96 until week 112

Updated 30/10/2026: Previous key secondary outcomes:
1. The following alternate effectiveness outcome variables will be measured using provincial healthcare data and clinical notes/ laboratory results over 1 year, 2 years, and up to 4 years:
1.1. Probable and definite diagnosis of TB disease
1.2. Probable, possible or definite diagnosis of TB disease or death from any cause except violent or accidental deaths
1.3. Disease-specific deaths (including TB, caused by or related to diabetes, including cardiovascular deaths)
1.4. Microbiologically confirmed active TB regardless of symptoms and chest X-ray abnormality)
1.5. Sub-clinical TB (microbiologically confirmed active TB without signs and symptoms)
2. Safety outcome variables will be measured using electronic case report forms:
2.1. Pre-specified clinically relevant grade ≥3 AE: clinical hepatitis, elevated liver enzymes (transaminases), peripheral neuropathy, rashes, hospitalisation within 12 weeks
2.2. Any Grade ≥3 AE (except related to violent or accidental deaths) within 12 weeks
2.3. Serious adverse events measured throughout the clinical trial until end of study visit
2.4. Treatment discontinuation due to any AE at 2 months
2.5. Rifampicin-resistant TB at measured throughout the clinical trial until end of study visit
2.6. Progression or exacerbations of clinical condition(s) and biomarkers measured using provincial healthcare data, clinical and laboratory records within 1 year, including:
2.6.1. HbA1c
2.6.2. Diabetes-related complications (retinopathy and neuropathy)
2.6.3. Blood pressure
2.6.4. Total cholesterol and LDL cholesterol
2.6.5. Estimated glomerular filtration rate (eGFR)
2.6.6. Incident of cardiovascular events (a composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke)
2.6.7. Change in the management of diabetes
2.6.8. Emergency room admission for at least 24 hours
3. Process outcomes measured using provincial healthcare data, clinical and laboratory records:
3.1. TPT treatment completion (taking at least 26 doses within 8 weeks)
3.2. Adherence to anti-diabetes medications within 8 weeks (% prescribed doses taken) measured using electronic case report forms to record pill count/ drug returns
4. Benefit-risk measures
5. Cost-effectiveness: costs, QALYs and DALYs measured using the EQ-5D-5L questionnaire at baseline, at weeks 12, 24, 48, and every 24 weeks from week 96 until week 112

Completion date
01/07/2029

Eligibility

Key inclusion criteria
1. Male and female, age ≥15 years old, living in the study area at the time of signing the informed consent form
2. Diabetes Mellitus (all types) receiving care, with or without the presence of other non-communicable diseases

3. HIV-negative
4. Positive Interferon-gamma release assays (IGRA)
5. Able to understand and give informed consent form (witnessed consent if the person is illiterate)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
15 years

Upper age limit
110 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. TPT already recommended in standard of care as per WHO guidelines for TB care (people living with HIV or contacts);
2. Current treatment with fluoroquinolones or other antibiotics with anti-tuberculous activity;
3. Contraindications to study drugs (Rifapentine or Isoniazid), including those who must continue medications that are not permitted with the study drugs (see section 4. Participants who are breastfeeding, pregnant, or of childbearing potential* who do not agree to use an effective method of contraception** from the time consent is signed until 4 weeks after discontinuation or completion of the IMP;
5. Previous active TB within 1 year;
6. Previous course of TPT within 1 year;
7. ALT over three times upper limit of normal (ULN) at baselineOther clinical conditions deemed ineligible for LTBI treatment by the clinician (e.g. clinical diagnosis of cirrhosis), as per national and local guidelines on provision of TB preventive treatment.
8. Social context (e.g excessive active alcohol use) likely to impact ability to understand, provide consent or adhere to the study schedule, as assessed by the study investigator.
9. Presence of active TB disease;
*A woman of child bearing potential (WOCBP): 12 years of age or older having had their first menstruation and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
**Effective contraception: only barrier (including spermicidal gel) or intrauterine contraceptive

measures within the trial period. Hormonal contraceptives, including oral contraceptives, intramuscular, and implant contraception are not considered effective methods due to drug interactions with rifampicin/rifapentine, which results in loss of efficacy.

Date of first enrolment
14/07/2025

Date of final enrolment
01/07/2029

Locations

Countries of recruitment
Philippines

South Africa

Study participating centre
EkhayaVac (CIDRI) Clinical Research Site
C/O Sulani and Bonga Drive Site B Khayelitsha, Cape Town, South Africa
Cape Town
South Africa
7784

Study participating centre
CareCT
CARE Clinical Trial Group Inc., Commercial Spaces A-D, 2nd Floor, Elijah Hotel and Residences, Salawag Crossing, Barangay Salawag, Molino-Paliparan Road, City of Dasmariñas, Province of Cavite, Philippines, 4114
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Philippines
4114

Sponsor information

Organisation
University of Cape Town

ROR
https://ror.org/03p74gp79

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
UK Research and Innovation

Alternative Name(s)
UKRI

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Current IPD sharing plan as of 18/03/2025:
The researchers intend to contribute to IPD repositories. Further details will be made available at a later date.

Previous IPD sharing plan:
The data-sharing plans for the current study are unknown and will be made available at a later date.

Unpublished information given to the investigator by the Sponsor shall not be published or disclosed to a third party other than to the responsible research ethics committee (REC), within the understanding of the confidentiality of their nature, without the prior written consent of the Sponsor. Data generated from this trial will be made available to individual participant data repositories.

IPD sharing plan summary

Stored in non-publicly available repository, Stored in publicly available repository