$2R^2$: Higher dose Rifampin for 2 months vs Standard dose Rifampin for Latent TB: a 3-arm randomized trial – Summary

Rationale: Shorter regimens of high dose daily rifampin may be safe, and as effective as the standard rifampin regimen when taken for 4 months to treat latent TB (LTBI). However, there is insufficient evidence on the optimal dose of rifampin that has similar efficacy and safety as the standard 4-month rifampin regimen.

Objectives: The general purpose of this study is to determine if rifampin at double or triple the standard dose for 2 months is as safe and effective as the standard dose of rifampin when taken for 4 months to treat latent tuberculosis (TB).

Design: Randomized, phase 2b, partially blind, three-arms (1:1:1) controlled trial. Treatment will be: standard dose (10mg/kg/day) for 4 months in control arm; double dose (20mg/kg/day) for 2 months in intervention arm 1; triple dose (30mg/kg/day) for 2 months in intervention arm 2. Participants and providers will be aware of the duration of the regimen, but they will both remain blinded to the specific dose (i.e. 20 or 30 mg/kg/day) for those randomized to 2-months regimens. All members of the same household will be randomized together (i.e. cluster randomized).

Population and setting: Eligible participants are adults and children aged 10 years and above (with weight of at least 25kg) who have latent TB infection and are recommended to take treatment for latent TB.

The study is conducted in Canada (Calgary, Edmonton, Montreal and Vancouver), Indonesia (Bandung) and Vietnam (Ho Chi Min City and Ha Noi). Recruitment is planned to be of 1359 participants (about 1/3 per each Country) to be reach by Fall of 2022.

Study procedures: Treatment will start at randomization. Follow up during treatment consists of three clinic visits (at 2, 4 and 8 weeks in high dose arms and at 4, 8 and 16 weeks in standard arm). At each visit, a pill count and monitoring of possible side effects will be performed. At 2 weeks (for participants in the experimental arms) and at 4 weeks visit (for participants in all arms) there is also a blood draw for monitoring of toxicity and for pharmacokinetic sub-study. Follow-up after treatment consists of contacting participants by phone every 3 months to check for symptoms of active TB, until 26 months from randomization.

Primary outcomes: 1) Treatment completion (defined as taking at least 80% of the doses in 120% of the allowed time); 2) Grade 3-5 adverse events that result in permanent discontinuation of study drug and are considered probably or possibly related to the study drug by an independent 3-member adjudication panel blinded to study treatment.

Secondary outcomes: 1) Grade 1-2 adverse events that result in permanent discontinuation of study drug and are considered probably or possibly related to the study drug by the same panel. 2) Efficacy, comparing rates of active TB in the 26 months post-randomization