4-month DS-TB regimen: Evidence gaps and next steps

TB Think Tank meeting

30 May 2023

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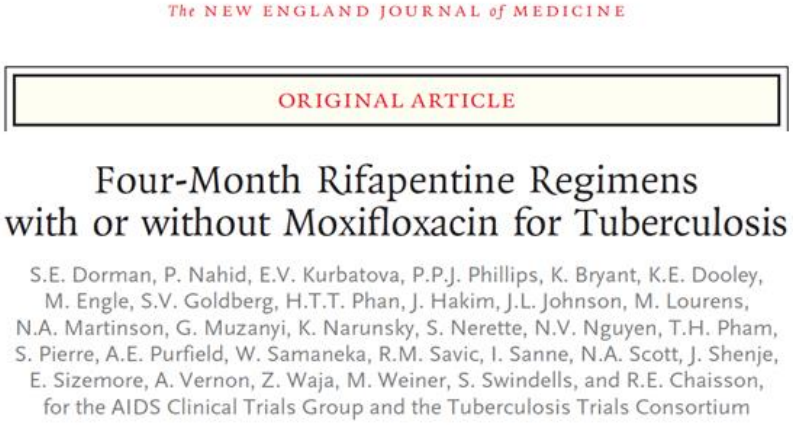
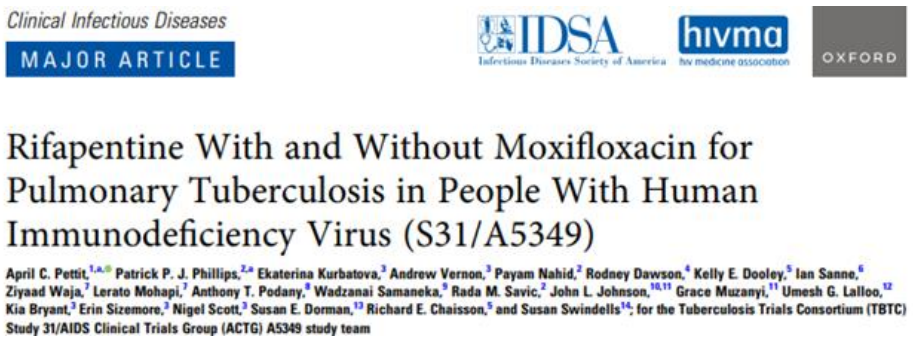
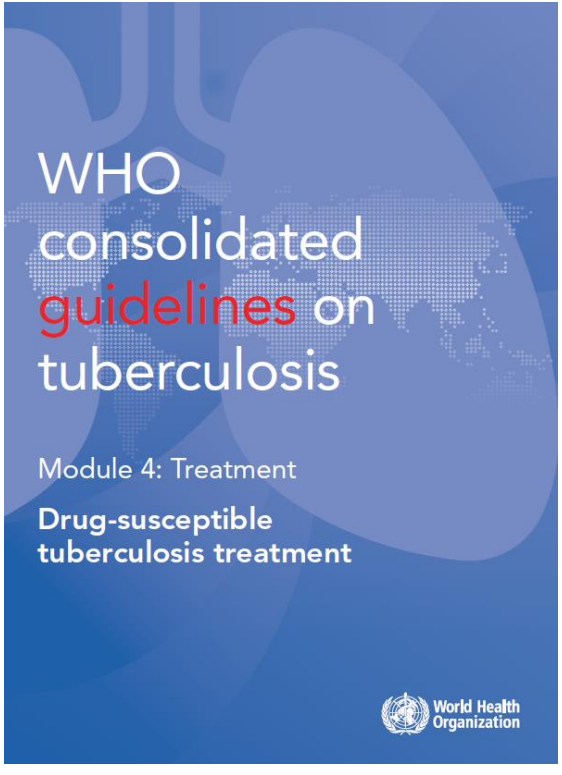
4-month regimen for DS-TB

- Multicountry, open-label, phase 3 randomised control trial
- 2343 participants in 13 countries
- Non-inferiority study design comparing:
  - Standard 6-month regimen: rifampin, isoniazid, pyrazinamide, and ethambutol (control)
  - 4-month regimen: rifapentine, isoniazid, pyrazinamide, and ethambutol
  - 4-month regimen: rifapentine, isoniazid, pyrazinamide, and moxifloxacin
- Outcome: Survival free of TB at 12 months
- Rifapentine without moxifloxacin not noninferior to the control (17.7% vs. 14.6% with an unfavorable outcome).
- **Rifapentine with moxifloxacin was noninferior to the control (15.5% vs. 14.6% had an unfavorable outcome).**





WHO recommendation in 2022



Treatment of drug-susceptible TB using 4-month regimens

Recommendation 6.

People aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide (conditional recommendation, moderate certainty of evidence) – new recommendation.

Considerations for implementation and uptake of the 4-month regimen for adults (2HPMZ/2HPM)

Phase 3 clinical trial:

Participants excluded:

- People weighing < 40kgs
- Extrapulmonary TB (TB meningitis, disseminated TB, osteoarticular TB, abdominal TB)
- People with extensive disease (using a cut-off of >50% lung area affected on CXR)
- Only participants ≥ 12 years included: Children (Karen to cover), but what should the age limit be?
- Pregnant, breastfeeding and postpartum women
- Rifapentine dosed with food to increase uptake
- People with comorbidities (eg diabetes mellitus), substance users

Is this regimen safe and effective in PLHIV?

- In study arm only 194 (8%) HIV+ participants
- PLHIV only included if CD4>100. Median CD4: 344 cells/µL (interquartile range: 223–455)
- All PLHIV on efavirenz-based ART. What about dolutegravir? (PK studies needed before combination can be used)

Practical considerations for implementation and uptake of the 4-month regimen for adults (2HPMZ/2HPM)

- Although subgroup analysis suggested regimen less efficacious in those with extensive disease, WHO guidelines suggest 4-month regimen can be used in patients with extensive disease.

  How are facilities with no CXR facilities to determine extent of disease?

- WHO recommend fluoroquinolone resistance testing before initiating 4-month regimen.

  GeneXpert XDR assay has been rolled out, but has limited capacity.

- WHO suggest 4-month regimen can be used in diabetics and less severe forms of EPTB (pleural /isolated lymph node TB).

  WHO suggest careful monitoring for AEs and treatment outcomes in those excluded in clinical trials.

- Pregnant women should not receive the 4-month regimen.

  What if a woman on this regimen falls pregnant?

- In clinical trials adherence is always much better than in operational settings.

  Will treatment outcomes with the 4-month regimen be as good if adherence is sub-optimal?

More practical considerations for implementation and uptake of the 4-month regimen for adults (2HPMZ/2HPM)

- **Drug-resistance:**
  - Will the new regimen increase resistance to the rifamycins and the fluoroquinolones?
  - Fluorquinolones are a key drug in the treatment of RR/MDR-TB. (Including in the new 6-month BPaLL regimen. Using fluoroquinolones widely may increase resistance. Is this wise given increasing BDQ resistance?
- **Higher TB recurrence rates with a shorter regimen:**
  - Patients should be followed up for a year post-treatment to document recurrence. (This is not something we do at all well, even for patients with RR/MDR-TB.)
- **Operational complexity:**
  - One facility with two streams of patients being treated for DS-TB - different regimens, different durations, different eligibility criteria and different management of treatment failure.
- **Lack of a FDC:**
  - This will result in individual drug stock-outs and adherence issues (pill burden).
- **Rifapentine:** Cost and availability in the short to medium term

Possible Way Forwards

Implement and evaluate the 4-month DS-TB regimen in pilot sites to inform wider roll-out:

- Identify a limited number of pilot sites in each province;
- Develop their operational research capacity;
- Develop rigorous M&E systems;
- Develop a training programme & helpline for front-line HCWs;
- Identify and define study questions, patient eligibility and study outcomes;
- Monitor outcomes for up to 12 months post-treatment completion
- Evaluate HCW perceptions/experiences of implementation to inform future roll out;
- Monitor patient experiences of the new regimens.

Questions to answer

- Is PLHIV is the regimen safe and effective? (In study arm only 194 HIV+ CD4 >200)
    - In PLHIV on ART what are the interactions with ART?
    - What are treatment outcomes in those whose CD4<200?
- Is the recurrence rate higher in people on the 4-month regimen?
- Is this regimen suitable for all patients with TB, or just those with minimal disease/1st time TB? (CXR facilities will be needed at pilot sites.)
- Will fluoroquinolone resistance testing be necessary prior to initiation patients on the new regimen?
- In people with comorbidities (DM, substance users) is regimen effective, side effects?
- What are the treatment outcomes if adherence is poor?
- Health systems factors: Detail obstacles to implementation to inform wider roll-out.
    - Selection of patients for regimen;
    - Pharmaceutical issues – no FDC combination, stock outs;
    - What complications arise in administering two different TB regimens at the same facility?
    - Patient and HCW perceptions of new regimen;
- Not addressed: Children/adolescents
- Costing study planned

References

- Dorman SE, Nahid P, Kurbatova EV, et al. Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis. New England Journal of Medicine 2021;384:1705-18.
- Pettit AC, Phillips PPJ, Kurbatova E, et al. Rifapentine With and Without Moxifloxacin for Pulmonary Tuberculosis in People With Human Immunodeficiency Virus (S31/A5349). Clin Infect Dis 2023;76:e580-e9.
- WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-susceptible tuberculosis treatment. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

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Thank you