

# Alternatives to Isoniazid Monotherapy for Preventing Active Tuberculosis in HIV-Negative Persons at Risk of Developing Active Tuberculosis

Soumyadeep Bhaumik<sup>1</sup>

<sup>1</sup>Senior Research Scientist, South Asian Cochrane Centre, Prof BV Moses & ICMR Centre for Research and Training in Evidence-Informed Healthcare and Health Policy, Christian Medical College, Tamil Nadu, India

**THE STUDY:** CD007545. DOI: 10.1002/14651858.CD007545.pub2.

**Sharma SK, Sharma A, Kadhiraivan T, Tharyan P. Rifamycins (Rifampicin, rifabutin and Rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. Cochrane Database of Systematic Reviews 2013, Issue 7.**

## BACKGROUND

Tuberculosis (TB) is estimated to affect about a third of the world's population. However, only a small proportion of those affected manifest active TB. Rest of the affected population remain in a state of sub-clinical disease with no manifestation (latent TB infection) but have the potential for reactivation of the lesion to develop active TB in future. While the risk of developing active TB in people with latent TB is only about 10%, certain groups are at higher risk. Apart from HIV-positive and other immune-compromised population, other high risk populations include close contacts of pulmonary TB patients- including healthcare workers, children less than 5 years, prisoners and those with diabetes mellitus, silicosis and severe malnutrition. The risk of developing active TB in HIV-negative individuals with latent TB infection and at high risk of developing active TB can be reduced by up to 60% (95% CI 42% to 69%) [1].

Current international guidelines as outlined by the World Health Organization, Centers for Disease Control and Prevention, USA and National Institute for Clinical Excellence, UK recommend isoniazid (INH) monotherapy for six to nine months in people with latent TB infection and at high risk of developing active TB. However the need to administer INH monotherapy for such a long period in asymptomatic individuals has been particularly disadvantageous with regards to adherence leading to concerns about the potential emergence of drug-resistance. Concerns have also been raised about adverse drug events and

particularly hepatotoxicity with use of INH. The high costs involved as well as the need to treat a large number of people with latent TB infection in developing nations with high disease burden are other concerns for health policy makers. All this makes it imperative to evaluate various alternatives to isoniazid monotherapy for preventing active tuberculosis in HIV-negative persons at risk of developing active TB

## HOW WAS THE STUDY DONE?

Authors of this study used the standard methodologies as per the Cochrane handbook and identified 10 RCT's reported in 17 reports. These 10 RCT's had randomized 10,717 participants.

## WHAT DID THIS STUDY FIND?

The trials identified in the review had compared the following four regimens:

- ✓ Rifampicin versus INH
- ✓ Rifampicin plus INH versus INH
- ✓ Rifampicin plus pyrazinamide versus INH
- ✓ Rifapentine (another drug belonging to the same class of rifamycin to which Rifampicin belongs) plus INH weekly for three months (DOT) versus daily INH for three months (self-administered)

The evidence from this review found no difference between shorter regimens of rifampicin or weekly, directly observed rifapentine plus INH compare to INH monotherapy in preventing active TB in at-risk HIV-negative people. However, the review found that the shorter rifampicin regimen of four months and weekly directly-observed rifapentine plus INH for three months "may have additional advantages of higher treatment completion and improved safety."

*Conflict of Interest: SB is a Senior Research Scientist at the South Asian Cochrane Network and Centre, India which is a partner to the Effective Healthcare Research Consortium which receives a grant in aid for developing countries from UKAid (the Department for International Development, UK-DFID). SB has also previously received grants from ICMR, under its STS program. The Cochrane systematic review was funded by DFID and ICMR.*

*This article has been peer-reviewed*

*Article Submitted on: 29<sup>th</sup> October 2013*

*Article Accepted on: 22<sup>nd</sup> December 2013*

*Funding Sources: None declared*

*Correspondence to: Dr. Soumyadeep Bhaumik*

*Address: 2, A. Sen Road, Kolkata-48, India*

*Email: [drsoumyadeepbhaumik@gmail.com](mailto:drsoumyadeepbhaumik@gmail.com)*

*Cite this article: Bhaumik S. Alternatives to isoniazid monotherapy for preventing active tuberculosis in HIV-negative persons at risk of developing active tuberculosis. J Pioneer Med Sci 2014; 2 (4): 71-72*

All the trials in this review were conducted in nations with low to moderate TB transmission. The results from this review might not be generalizable to low and middle income nations in Asia and Africa, regions with a high burden of TB and where re-infection rates and co-morbidities such as malnutrition are higher and health systems not so well developed. In addition, the trials in this study did not include any participants in especially vulnerable groups such as pregnant, lactating women, malnourished children and children less than 2 years of age. The data for children is based on only one trial with a sample size of 100.

The overall quality of evidence for most outcomes were very low (indicating uncertainty of the estimate on further research) to moderate (indicating uncertainty in the effect of estimate on further research) using the GRADE approach for outcomes in the review

### **IMPLICATIONS OF RESEARCH**

Further trials must be conducted in Low and Middle Income Nations with high TB transmission as well as include vulnerable populations as outlined above. In addition the review authors also suggest pharmacovigilance for monitoring adverse events and resistance to rifamycins. More trials and implementation research are needed to explore various approaches of active case finding and measures to enhance adherence to treatment.

### **SO WHAT IS THE BOTTOMLINE?**

Shorter prophylactic rifampicin-based regimens did not have higher success in preventing active TB in at-risk HIV-negative people in comparison to currently used isoniazid based regimens. It is expected that shorter regimens might have better treatment completion rates and fewer adverse effect profiles. However the evidence is of low-moderate quality and might not be applicable to nations with high TB transmission settings.

### **REFERENCES**

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