

## EDITORIAL

### Standard Antituberculous Treatment Regimens Need Urgent Revision

One-third of the world's population is currently infected with *Mycobacterium tuberculosis*. The risk of progression from infection to disease in immunosuppressed population particularly HIV infected is much higher. If left untreated, each person with active TB may infect 10 to 15 people every year, reinforcing the public health priority of controlling TB through adequate treatment. Patients with a previous history of TB treatment are a major concern for TB programs throughout the world because these patients are at a much higher risk of harboring TB that is resistant to the drugs most frequently used, resulting in poorer treatment outcomes and significant complications. More than 1 million people in over 90 countries need to be “re-treated” after failing, interrupting, or relapsing from previous TB treatment.

Management of patients who have been previously treated for tuberculosis (TB) has been a cause of much debate. In 1991, the World Health Organization (WHO) recommended the use of the “category II retreatment regimen” for all patients with a prior history of TB treatment. The category II regimen added one drug (streptomycin) to the first-line agents and extended treatment to 8 months. Every year, 10-20% of people with TB in countries like Pakistan are started on a standardized five-drug retreatment regimen [(2 SHERZ/ 1 RHEZ/ 5 RHE) meaning 2 months of streptomycin (S), isoniazid (H), ethambutol (E), rifampicin (R) and pyrazinamide (Z); 1 month of R, H, E and Z; and 5 months of R, H and E] as recommended by the WHO.

WHO surveillance data suggest that the retreatment regimen is successful in about 70% of patients, but retrospective studies that have evaluated the regimen's efficacy showed variable treatment responses with success rates ranging from 26% to 92% with worse outcomes observed among patients who failed or relapsed after their initial treatment episode. These studies have generally assessed outcomes at the completion of the retreatment regimen, while recurrence rate in this group is infrequently studied.

In spite of the fact the WHO guidelines are followed for more than three decades in over 90 countries, there is growing concern that the recommended regimens for National programs are leading to amplification of drug resistance and poor treatment outcomes. WHO TB treatment guidelines published in 2010, recommend DST guided treatment for only previously treated patients. In Pakistan a large population of TB patients is being treated under DOTS strategy. They are receiving standard four drugs in Intensive Phase and two drugs in Continuation Phase; without ever being supported by DST. Those who have resistance to one of the drug in continuation phase (WHO Cat-I) actually receive one drug. In the study published in the current issue of Pakistan Journal of Chest Medicine<sup>7</sup> the prevalence of MDR/XDR was higher in DOTS group compared with non-DOTS group.

The published data show that the retreatment regimen is only effective in compliant patients who have either largely sensitive or mono-resistant TB, resulting in acceptable clinical outcomes on completion of TB therapy. In countries like Pakistan where prevalence of primary as well as post primary MDR is reported as 3 and 21 % respectively; the successful outcome of primary treatment (current Cat-I) is likely to be much lower than expected and in any control trial the treatment failure and relapse rate will remain high as has been reported from southern Punjab in this issue.

In this country we need to identify only two clinical categories, susceptible and resistant. In Primary (Cat-I) treatment patients may be treated empirically with standard four drugs followed by three drugs. Those who do not complete or default should complete the regimen (Retreatment of Cat-I). Those who have completed the full course and have Relapse or Failed treatment must

have DST before retreatment is started; or in case of non access to the facility, may be treated empirically as MDR TB. Previous treatment outcome and current clinical behavior of the disease process assessed from history can be used to predict the likelihood of MDR-TB and adverse outcomes in patients undergoing retreatment .The experience from Georgia is an important example of how category II treatment can be successfully removed from NTP guidelines in settings where it is of limited utility.

The results from prospective studies including one published in current issue provide sufficient evidence that the standard retreatment approach to TB, as implemented in low- and middle-income countries is inadequate. A consensus among pulmonologists on a modified strategy, access to rapid diagnostics for TB drug resistance, and availability of second-line TB treatment is urgently needed

### **For Further Reading:**

- 1- Saeed W, Naseem A, Ahmed J. Retrospective audit of patients treated for MDR-TB in retreatment category. *J Ayub Med Coll.* 2009; 21(2): 94-8.
- 2- Kritski AL, Luis Sergio Rodrigues LS, Andrade MK, et al. Retreatment Tuberculosis Cases: Factors Associated with Drug Resistance and Adverse Outcomes. *Chest.* 1997; 111(5):1162-1167.
- 3- Jones-López EC, Ayakaka I, Levin J, Reilly N, Mumbowa F, Dryden-Peterson S et al. Effectiveness of the standard WHO recommended retreatment regimen (category II) for tuberculosis in Kampala, Uganda: a prospective cohort study. *PLoS Med.* 2011; 8(3): e1000427. doi:10.1371/journal.
- 4- Kelly E Dooley KE, Lahlou O, Ghali I, et al. Risk factors for tuberculosis treatment failure, default, or relapse and outcomes of retreatment in Morocco. *BMC Public Health* 2011, 11:140.
- 5- Mak A, Thomas A , Granado MD, Zaleskis R, Mouzafarova N, Menzies D. Influence of Multidrug Resistance on Tuberculosis Treatment Outcomes with Standardized Regimens, *Am J Respir Crit care Med.*2008; 178:306-312.
- 6- Jennifer Furin, Medea Gegia Carole Mitnick et al. Eliminating the category II retreatment regimen from national tuberculosis program guidelines: the Georgian experience, *Bulletin of the World Health Organization* 2012; 90:63-66.
- 7- Shahzad MI, Ayyaz S, Humayun GM et al A comparison of drug resistance pattern in category-I failure versus category-I relapse pulmonary TB patients attending a tertiary care hospital in south Punjab, Pakistan. Is who category-II ATT regimen appropriate? *Pak J Chest Med* 2013.....