First Do No Harm—Adverse Events, Drug Intolerance, and Hepatotoxicity: How Can We Not Justify Directly Observed Therapy for Treating Tuberculosis?

To the Editor—Pasipanodya and Gumbo use meta-analysis to question the evidence base used to justify directly observed therapy (DOT) for persons with tuberculosis from 10 selected studies [1]. On the basis of this analysis, the authors suggest that self-administered therapy (SAT) and DOT are statistically equivalent regarding the proportion of tuberculosis cases with microbiologic failure, relapse, and acquired drug resistance. Despite these results and the authors' recommendation to divert resources away from DOT, tuberculosis programs should be mindful of other important aspects of tuberculosis care, that is, early identification of medication-related toxicity and a poor clinical response. Adverse events may negatively affect a person's ability to adhere to treatment and when not quickly recognized lead to serious toxicity, organ damage, and death. Early response lessens the possibility of serious toxicity, minimizes treatment interruptions, encourages patient trust, and facilitates implementation of treatment modifications. The net result is a reduction in the likelihood of patient default or loss to follow-up [2]. The reported incidence of antituberculosis drug–induced hepatotoxicity, a serious and potentially fatal adverse reaction, varies between 2% and 28% in some high-risk populations [3]. Unfortunately, Pasipanodya and Gumbo narrowly focused their analysis on limited outcome comparisons between SAT and DOT, although some of their selected studies reported adverse events and tuberculosis-related deaths. We feel strongly that these are essential elements for a fair comparison of the 2 approaches. Importantly, most studies selected for meta-analysis included a protocol to change from SAT to DOT following an adverse event, making it impossible to determine the magnitude of this effect, and up to 32% of the participants of these studies experienced treatment-related adverse events and as many as 3% required termination of treatment [4]. Tuberculosis-related death is the ultimate adverse event, and reflects programmatic failure. Two of the selected studies reported 29 tuberculosis-related deaths; all (100%) received SAT [5, 6]. Although it was not explicitly stated, had these patients received provider-administered DOT, clinical deterioration might have been discovered earlier and death averted.

Under the current economic environment, many tuberculosis programs are debating the costs and benefits of DOT. This cost-benefit analysis must include not only traditionally evaluated programmatic costs but also less easily measured costs resulting from drug toxicity, ongoing transmission from failure to complete treatment, and tuberculosis-related deaths. DOT is a patient supportive means to ensure treatment is taken properly and completed, which maintains real-time ability to assess treatment response and drug-related toxicity. This aspect of DOT is even more important as tuberculosis disproportionately affects those with limited access to healthcare, which may critically delay assessment of drug toxicity. Finally, there have been a number of well-designed peer-reviewed studies that have shown that DOT reduces relapse and drug resistance and increases completion of tuberculosis treatment [6, 7]. When all aspects of tuberculosis care including the considerations outlined above and the totality of available epidemiologic trials are considered, we do not find Pasipanodya and Gumbo's results to be sufficient to support their broad recommendation that program resources be diverted away from DOT.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Barbara J. Seaworth, Lisa Y. Armitige, and David E. Griffith

University of Texas Health Science Center, Tyler

References

1. Pasipanodya JG, Gumbo T. A meta-analysis of self-administered vs directly observed therapy effect on microbiologic failure, relapse, and acquired drug resistance in tuberculosis patients. Clin Infect Dis **2013**; 57:21–31.
2. Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. Expert Opin Drug Saf **2006**; 5:231–49.
3. Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. J Gastroenterol Hepatol **2008**; 23:192–202.
4. Tuberculosis Research Centre. A controlled clinical trial of oral short-course regimens in the treatment of sputum-positive pulmonary tuberculosis. Int J Tuberc Lung Dis **1997**; 1:509–17.
5. Ormerod LP, Horsfield N, Green RM. Tuberculosis treatment outcome monitoring: Blackburn 1988–2000. Int J Tuberc Lung Dis **2002**; 6:662–5.
6. Jasmer RM, Seaman CB, Gonzalez LC, Kawamura LM, Osmond DH, Daley CL. Tuberculosis treatment outcomes: directly observed therapy compared with self-administered therapy. Am J Respir Crit Care Med **2004**; 170:561–6.
7. Weis SE, Slocum PC, Blais FX, et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. N Engl J Med **1994**; 330:1179–84.

Correspondence: Barbara J. Seaworth, MD, Heartland National TB Center, 2303 SE Military Dr, San Antonio, TX 78223 (barbara.seaworth@dshs.state.tx.us).

Clinical Infectious Diseases 2013;57(7):1063–4

DOI: 10.1093/cid/cit432