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## Caveat Emptor? Meta-Analysis of Studies Comparing Self-Observed Therapy and Directly Observed Therapy for Tuberculosis

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### To The Editor

Pasipanodya and Gumbo compared self-administered therapy (SAT) with directly observed therapy (DOT) to determine the proportion of cases with microbiologic failure, relapse, and acquired drug resistance among a pooled cohort of 12 482 persons with tuberculosis from 10 independent studies [1]. The concept of DOT first emerged as a potential therapeutic alternative to resource-intensive hospitalization [2]. Shortly after the introduction of oral antibiotics and during a time when the prevalence of tuberculosis exceeded the availability of hospital beds, well-organized, provider-supervised ambulatory care became the only viable option [2, 3]. However, it was unclear if such therapy could achieve the same success rate as long-term hospitalization. Randomized trials from the late 1950s demonstrated similar patient outcomes to those of hospitalization [3, 4], and thus resources began to shift away from sanatorium-era approaches to clinic-based approaches that have since evolved into the accepted standard of practice for tuberculosis management with DOT. Today similar resource restrictions have forced tuberculosis programs to rethink this strategy and consider less resource-intensive alternative approaches. The polarizing debate and controversy about DOT efficacy is not new [5, 6] and Pasipanodya and Gumbo are not the first to use meta-analysis to seek evidence for consensus [7, 8].

Unfortunately, this analytic approach suffers from some potential methodological problems. First, the strength and validity of any meta-analysis is determined by criteria used to select the available pooled cohort. There are practical impediments to conducting well-designed studies on DOT efficacy. The chief among these is an ethical issue. An essential component of human research protection in clinical trials is the participant's ability to withdraw from a study at any time with no loss of privileges or rights. Unlike other illnesses evaluated by randomized trials, tuberculosis is a public health problem that affects others in the community through respiratory transmission. As a result, physicians and laboratories in

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many areas are legally required to report the identity of persons with tuberculosis to health authorities. To prevent tuberculosis transmission, persons with tuberculosis who are noncompliant with treatment can face loss of personal liberty. Randomization to a study treatment that, if not followed, can result in loss of liberty and legally mandated treatment or isolation by public health authorities is problematic. Moreover, the studies with a randomized design that did meet the authors' selection criteria included patients who had to make heroic efforts to receive DOT by reporting to a clinic during working hours. There was no support or incentives for transportation, nor financial provisions made for the income loss due to missed work. This type of DOT may result in work absence and income loss, thus potentially creating financial hardship for any enrolled patient, especially in developing countries. Second, 6 of 10 studies used sputum smear microscopy for diagnosis and clinical follow-up and were not tested for drug-resistant tuberculosis by culture prior to randomization [9–14]. Therefore, persons with drug-resistant tuberculosis had an equal chance of assignment in each arm. As such, it would follow that poor treatment outcomes associated with drug-resistant tuberculosis (ie, increased acquired drug resistance, failure, relapse, and death) would bias the comparison to the null. Third, 3 of 10 studies included both new and retreatment cases prior to randomization [15–17]. In a similar way to drug-resistant tuberculosis, persons with previous tuberculosis treatment are at higher risk of poor outcome, including increased acquired drug resistance, default, failure, relapse, and death. Fourth, for 3 of 10 studies there was a strong potential for bias induction; that is, persons with known risk factors for noncompliance were selected nonrandomly to the DOT arm, and conversely persons without known risk factors were selected nonrandomly to the SAT arm or crossed over treatment arms during the study, thus biasing the potential outcomes to the null [12, 14, 16].

Due to these ethical and methodological issues, we do not agree that these data support “shifting away resources” from DOT. Moreover, we contend that the societal savings of preventing secondary transmission and acquired drug-resistant tuberculosis, when properly managed through community-based DOT, are greater than the programmatic cost of DOT delivery. Although SAT may be less resource intensive, it is not equal to the cost-benefit potential of DOT-based programs—buyer beware.

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