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Making up the difference: ensuring the bioequivalence of fixed-dose combinations for tuberculosis

Gustavo E. Velásquez[1,2], **Geraint R. Davies**[3], and **Carole D. Mitnick**[2,4,5]

[1]Division of Infectious Diseases, Brigham and Women's Hospital, Boston, MA, USA

[2]Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA

[3]Institutes of Infection and Global Health and Translational Medicine, University of Liverpool, Liverpool, UK

[4]Division of Global Health Equity, Brigham and Women's Hospital, Boston, MA, USA

[5]Partners In Health, Boston, MA, USA

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In this issue of the *Journal*, Court and colleagues report the results of an open-label crossover study of three rifampin (RMP) containing formulations licensed in South Africa: the four-drug fixed-dose combination (FDC) Rifafour e-275 (Sanofi); the two-drug FDC Rimactazid (Sandoz); and the single-drug referent Rimactane (Sandoz). The four-drug FDC had an average 22% (90% confidence interval 11-31%) reduction in RMP bioavailability compared to the referent, while the two-drug FDC was bioequivalent.[1]

The study points to FDC formulation as an important determinant of RMP bioavailability; this had been documented previously, but was thought to be resolved.[2] The present study pointedly affirms recent, incidental findings of suboptimal RMP peak plasma concentrations (C_{max}) in patients receiving the recommended 10 mg/kg RMP dose in high-dose RMP treatment-shortening trials that use four-drug FDCs. The HIRIF Phase II, blinded, randomized, placebo-controlled, dose-ranging clinical trial (ClinicalTrials.gov NCT01408914) administered a four-drug FDC (Macleods Pharmaceuticals), with additional placebo and/or RMP capsules donated by Sanofi. Only 33% of those in the 10 mg/kg arm achieved a C_{max} of >8 mg/L, compared with 72% in the 15 mg/kg arm and 81% in the 20 mg/kg arm.[3] Similarly, in the PanACEA HIGHRIF1 and HIGHRIF2 trials (ClinicalTrials.gov NCT01392911 and NCT00760149), four-drug FDCs manufactured by Sandoz resulted in a geometric mean RMP C_{max} of <8 mg/L in the control arms.[4,5]

Correspondence to: Gustavo E. Velásquez, MD, MPH, Department of Global Health and Social Medicine, Harvard Medical School, 641 Huntington Avenue, Boston, MA 02115, USA. Tel: (+1) 617.432.1707. Fax: (+1) 617.432.2565. gvelasquez{at}bwh.harvard.edu.

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The study by Court et al. is a call to action to review dosing recommendations and the process for ensuring continued bioavailability of products sold by the Global Drug Facility (GDF) and/or prequalified by the World Health Organization (WHO). In South Africa, based on these results, local authorities are working with drug manufacturers to resolve the issue. More broadly, the WHO last issued guidance on the use of FDCs in 2002.[6] Given that FDCs are currently recommended over separate drug formulations for the treatment of drug-susceptible tuberculosis,[7] the present paper and other accumulated evidence indicate the importance of timely review of dosing recommendations and periodic reassessment of bioavailability for FDCs that carry WHO's label of prequalification and/or that are sold by the GDF. Compromised RMP plasma exposure, and any attendant worsening of treatment outcomes and/or drug resistance,[8,9] is an unacceptable tradeoff for the benefit of reduced pill burden conferred by FDCs. Revised guidelines should consider management recommendations for countries using formulations that may have been associated with low concentrations in rigorous, representative studies such as the one published in this issue of the *Journal*. Court et al., using simulations to predict RMP exposures by WHO-recommended dosing weight bands, suggest for South Africa either routine addition of a supplemental four-drug FDC tablet for patients with low weight (30-54 kg) or of a supplemental 150 mg single dose of RMP for patients in all weight bands. Given the accumulating evidence that higher RMP doses are safe,[4,5,10,11] routine RMP supplementation may be required until and unless the bioequivalence of four-drug FDCs can be assured.

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