

**Reply to: Efficacy of adjunctive sertraline for the treatment of HIV-associated cryptococcal meningitis**

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We read the recently published paper of Joshua Rhein and colleagues with great interest. In this paper sertraline plasma concentrations and the minimum inhibitory concentrations (MICs) for sertraline were measured to determine the probability of achieving therapeutic sertraline concentrations in the brain in patients with cryptococcal meningitis.<sup>1</sup> As mentioned by Joseph Jarvis and colleague no clear dose-response relationship between the sertraline dose and early fungicidal activity was found.<sup>2</sup> In the study of Joshua Rhein and colleagues, fluconazole concentrations and MICs of fluconazole were not measured. A currently accepted breakpoint for fluconazole against *Cryptococcus neoformans* is  $\leq 2$  mg/liter.<sup>3</sup> In addition, it has been demonstrated that when fluconazole is used in the treatment of cryptococcal meningitis an area under the concentration-time curve over 24-h divided by the MIC of at least 389 is associated with a favourable outcome.<sup>3</sup> However, it is predicted that monotherapy with 1,200 mg of fluconazole per day results in sufficient drug exposure in only two-thirds of patients; this proportion will be considerably lower when 800 mg fluconazole per day is used.<sup>3</sup> Therefore, we would encourage the authors to determine fluconazole concentrations and the in-vitro fluconazole susceptibility of the *Cryptococcus* isolates and verify if fluconazole exposure was sufficient and can help to explain their results.

We agree with the authors that further investigation of adjunctive sertraline for cryptococcal meningitis in randomised clinical trials is justified. In addition to trials in combination with amphotericin, sertraline may have a role in developing more effective wholly oral-based therapy and randomised controlled trials in combination with high dose fluconazole should be considered. Wholly oral-based therapies are desirable for resource poor settings and for treating asymptomatic antigenaemia, where they may offer cost and tolerability advantages.<sup>4</sup> Thus, better understanding and optimization of exposure to fluconazole and adjunctive sertraline could lead to a promising treatment of cryptococcal meningitis.

To achieve this, dried blood spot (DBS) sampling could be used to determine individual patient drug exposure and thus tailor the dose of oral drugs in relation to the MIC of their isolate. We have shown that DBS sampling (based on simple finger prick blood collection) has high sample stability allowing accurate determination of fluconazole drug concentrations.<sup>5</sup> Additionally there is little biohazard risk during transportation of the samples. With a full oral regimen, a new treatment regimen may be ready for evaluation in a randomized controlled trial for cryptococcal meningitis in resource limited settings.

We declare no competing interests.

#### References

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