



# The Brazilian Journal of INFECTIOUS DISEASES

[www.elsevier.com/locate/bjid](http://www.elsevier.com/locate/bjid)



## Letter to the Editor

# Protease inhibitors and azolic antifungals in HIV patients with histoplasmosis: a clinical pharmacokinetics perspective



Dear Editor,

A previous *in vitro* investigation found that a synergistic effect might occur, when using itraconazole (ITRA) and ritonavir (RTV) against *Histoplasma capsulatum*,<sup>1</sup> where an interesting mechanism of action was proposed. However, relevant pharmacokinetic (PK) issues were under explored. Herein, this letter attempts to deepen a clinical PK discussion not performed by Brillhante and colleagues.<sup>1</sup>

Firstly, the *in vitro* model<sup>1</sup> did not account for drug penetration in macrophages, given that *Histoplasma* spp. are found as intracellular microorganisms after innate immunity recognition and phagocytation.<sup>2</sup> Secondly, one should recognize the potential CYP3A4 competitive inhibition when using RTV and an azolic agent. By combining them, we expect an elevated plasma concentration of the azolic agent,<sup>3</sup> as RTV has higher affinity to the aforementioned phase 1 enzyme, but not the opposite.<sup>1</sup> The association of both drugs is a possible scenario<sup>4</sup> when treating multiple drug resistant HIV infected patients. Whether non-CYP3A4 substrates are unavailable, clinicians should attempt to monitoring hepatic enzymes and random ITRA steady state serum concentrations (>1 µg/mL) after 7–15 days.<sup>3</sup>

Finally, the previous report<sup>1</sup> discussed that using both drugs might be clinically possible by “reducing itraconazole dose”. For several reasons,<sup>5</sup> there is no evidence on lowering ITRA doses: (a) it has an erratic gastrointestinal absorption and food composition and gastric pH might influence drug’s bioavailability (cyclodextrin-containing formulations are preferred); (b) ITRA has non-linear PK, thus, dose reductions may lead to unpredictable serum levels (zero order kinetics is dependent on enzyme saturation).

## REFERENCES

1. Brillhante RS, Caetano ÉP, Riello GB, et al. Antiretroviral drugs saquinavir and ritonavir reduce inhibitory concentration values of itraconazole against *Histoplasma capsulatum* strains *in vitro*. *Braz J Infect Dis*. 2016;20:155–9.
2. Porta A, Maresca B. Host response and *Histoplasma capsulatum*/macrophage molecular interactions. *Med Mycol*. 2000;38:399–406.
3. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2007;45:807–25.
4. Nacher M, Adenis A, Aznar C, et al. How many have died from undiagnosed human immunodeficiency virus-associated histoplasmosis, a treatable disease? Time to act. *Am J Trop Med Hyg*. 2014;90:193–4.
5. Prentice AG, Glasmacher A. Making sense of itraconazole pharmacokinetics. *J Antimicrob Chemother*. 2005;56 Suppl 1:i17–22.

Lucas Miyake Okumura

Hospital de Clínicas de Porto Alegre, Divisão de Farmácia Clínica, Porto Alegre, RS, Brazil

E-mail address: [lucasokumura@yahoo.com.br](mailto:lucasokumura@yahoo.com.br)

Received 17 February 2016

Accepted 3 March 2016

1413-8670/© 2016 Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<http://dx.doi.org/10.1016/j.bjid.2016.03.006>

Available online 16 April 2016

## Conflicts of interest

The author declares no conflicts of interest.