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## Itraconazole and antiretroviral therapy: strategies for empirical dosing - Author's reply

Thuy Le, Antoine Adenis, Andrew S Limper, Thomas Harrison

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- 4 Huet E, Hadji C, Hulin A, Botterel F, Bretagne S, Lévy Y. Therapeutic monitoring is necessary for the association itraconazole and efavirenz in a patient with AIDS and disseminated histoplasmosis. *AIDS* 2008; **22**: 1885–86.
- 5 Koo HL, Hamill RJ, Andrade RA. Drug-drug interaction between itraconazole and efavirenz in a patient with AIDS and disseminated histoplasmosis. *Clin Infect Dis* 2007; **45**: e77–79.
- 6 Crommentuyn KML, Mulder JW, Sparidans RW, Huitema ADR, Schellens JHM, Beijnen JH. Drug-drug interaction between itraconazole and the antiretroviral drug lopinavir/ritonavir in an HIV-1-infected patient with disseminated histoplasmosis. *Clin Infect Dis* 2004; **38**: e73–75.
- 7 Schwartz IS, Kenyon C, Lehloeny R, et al. AIDS-related endemic mycoses in Western Cape, South Africa and clinical mimics: a cross-sectional study of adults with advanced HIV and recent-onset, widespread skin lesions. *Open Forum Infect Dis* 2017; published online Aug 25; DOI:10.1093/ofid/ofx186.

### Author's reply

We thank Ilan S Schwartz and Sean Wasserman for their interest in our paper on the management of HIV-associated endemic mycoses.<sup>1</sup> Schwartz and Wasserman rightly express concern regarding the known drug–drug interaction between itraconazole and non-nucleotide reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine, which results in considerable reductions in plasma itraconazole concentrations following co-administration. NNRTIs are often included in standardised first-line antiretroviral therapy regimens in developing countries, and co-administration with itraconazole is commonly required during the consolidation and maintenance of therapy for histoplasmosis in Latin America and talaromycosis in Asia. Despite the pharmacokinetic interaction, treatment relapse is uncommon in patients who begin antiretroviral therapy with efavirenz or nevirapine. No disease relapse was observed in two talaromycosis cohorts in Taiwan (n=9)<sup>2</sup> and Thailand (n=33)<sup>3</sup> or in a histoplasmosis cohort in the USA (n=32).<sup>4</sup> NNRTI therapy was safely initiated in these cohorts, and itraconazole treatment was safely

terminated in patients who had a successful immune response to antiretroviral therapy.<sup>2–4</sup>

The pharmacokinetic interaction between itraconazole and NNRTIs has been documented in human volunteers and in histoplasmosis case reports. In the study by Huet and colleagues<sup>5</sup>—cited by Schwartz and Wasserman—efavirenz was associated with a 20–50% reduction in plasma itraconazole concentrations, but was also associated with substantial increases in the concentration of its active metabolite hydroxyitraconazole, which has similar antifungal activity. In the study by Koo and coworkers,<sup>6</sup> itraconazole concentrations were inversely correlated with urine histoplasma antigen levels in a patient who was clinically cured. None of the studies showed a correlation between low blood itraconazole concentrations and clinical response or relapse.

Well designed pharmacokinetic and pharmacodynamics studies are required to evaluate the association between itraconazole exposure and response in the treatment of endemic mycoses to assess the therapeutic range of itraconazole, and to further investigate interactions between itraconazole and antiretrovirals. Of note, such analyses are in progress for a trial in Vietnam<sup>7</sup> comparing itraconazole and amphotericin B as an initial treatment for HIV-associated talaromycosis. All patients with HIV started treatment with efavirenz and received the standard maintenance dose of itraconazole of 200 mg daily. The overall relapse rate was low at 4.0%, and 1.5% in patients who received a course of amphotericin B before itraconazole.<sup>7</sup>

We do agree that therapeutic drug monitoring for itraconazole<sup>8</sup> and protease and integrase inhibitor-based antiretroviral therapy are appropriate strategies. However, at present we would maintain that the evidence is insufficient to change the current practice for consolidation and maintenance itraconazole dosing

for HIV-related endemic mycoses in resource-limited settings where protease inhibitors and integrase inhibitors are not feasible options for first-line antiretroviral therapy and therapeutic drug monitoring is not available. Routinely increasing itraconazole dose results in a high pill burden, high costs, and potential harm in some cases. More clinical evidence must be generated to guide the management of endemic mycoses in HIV infection.

AA delivered a talk for Janssen Pharmaceutical and received diagnostic tests for research from the Centers for Disease Control and Prevention Mycotic Diseases Branch and Immuno-Mycologics. TH reports grants from Gilead Sciences, personal fees from Pfizer and Viamet, and non-financial support from Immuno-Mycologics, outside the submitted work. TL and AL declare no competing interests.

Thuy Le, Antoine Adenis,  
Andrew Limper, \*Thomas Harrison  
tharriso@sgul.ac.uk

Oxford University Clinical Research Unit, Wellcome Trust Major Overseas Programme, Ho Chi Minh City, Vietnam (TL); Centre d'Investigation Clinique Antilles Guyane, Inserm CIC1424, Centre Hospitalier de Cayenne, Cayenne, France (AA); Mayo Clinic College of Medicine, Rochester, MN, USA (AL); Institute of Infection and Immunity, St George's, University of London, London SW17 0RE, UK (TH)

- 1 Limper AH, Adenis A, Le T, Harrison TS. Fungal infections in HIV/AIDS. *Lancet Infect Dis* 2017; **17**: e334–43.
- 2 Hung CC, Chen MY, Hsieh SM, Sheng WH, Hsiao CF, Chang SC. Discontinuation of secondary prophylaxis for penicilliosis marneffeii in AIDS patients responding to highly active antiretroviral therapy. *AIDS* 2002; **16**: 672–73.
- 3 Chaiwarith R, Charoenyos N, Sirisanthana T, Supparatpinyo K. Discontinuation of secondary prophylaxis against penicilliosis marneffeii in AIDS patients after HAART. *AIDS* 2007; **21**: 365–67.
- 4 Goldman M, Zackin R, Fichtenbaum CJ, et al. Safety of discontinuation of maintenance therapy for disseminated histoplasmosis after immunologic response to antiretroviral therapy. *Clin Infect Dis* 2004; **38**: 1485–89.
- 5 Huet E, Hadji C, Hulin A, Botterel F, Bretagne S, Lévy Y. Therapeutic monitoring is necessary for the association itraconazole and efavirenz in a patient with AIDS and disseminated histoplasmosis. *AIDS* 2008; **22**: 1885–86.
- 6 Koo HL, Hamill RJ, Andrade RA. Drug-drug interaction between itraconazole and efavirenz in a patient with AIDS and disseminated histoplasmosis. *Clin Infect Dis* 2007; **45**: e77–79.
- 7 Le T, Kinh NV, Cuc NTK, et al. A trial of itraconazole or amphotericin B for HIV-associated talaromycosis. *N Engl J Med* 2017; **376**: 2329–40.

- 8 Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. *J Antimicrob Chemother* 2014; **69**: 1162–76.

## Post-migration follow-up of migrants at risk of tuberculosis

In recent Correspondence about the screening and treatment of latent tuberculosis infection in migrants who had moved from countries with a high tuberculosis burden to low-burden countries, Kayvan Bozorgmehr<sup>1</sup> reported that asylum seekers in Germany from Somalia and Iraq had very different prevalences of latent infection. He commented that “Many studies on effectiveness of tuberculosis screening treat migrants as homogenous, neglecting that this population is socially constructed and highly heterogeneous”, citing our study<sup>2</sup> as one of the examples.

In fact, we did not treat our study cohort as homogeneous: we presented analysis considering age, sex, visa category (students, settlement and dependants, work, working holiday, family reunion, other), and tuberculosis prevalence of the country of origin, and found that there were significant differences in tuberculosis risk associated with the last two variables.<sup>2</sup> This complements earlier work on the yield of latent tuberculosis infection screening in England,<sup>3,4</sup> which informed the new national screening programme in England.

We agree with Bozorgmehr that collection of detailed data is important “to develop and assess screening programmes that account for the heterogeneity in migrant populations”.<sup>1</sup> We would like to highlight that in addition to latent tuberculosis infection prevalence in different migrant groups, several other important considerations are related to the effectiveness, cost-effectiveness, and equity<sup>3–5</sup> of

tuberculosis control programmes for migrants. Addressing them requires detailed data from programmes,<sup>6</sup> including data linkage between pre-entry screening programmes,<sup>7</sup> post-migration latent tuberculosis infection screening and treatment programmes, and surveillance of active tuberculosis diagnoses.

Programmes need to ensure access to screening, promote treatment uptake in patients with diagnosed latent tuberculosis infection, and provide effective support for adherence to treatment, in ways that are culturally sensitive and cost-effective. Uncertainty in the effectiveness of latent tuberculosis infection treatment regimens<sup>8</sup> causes uncertainty in the expected impact and cost-effectiveness of screening and treatment programmes. Record linkage of large, detailed datasets from such screening programmes and surveillance of active tuberculosis diagnoses will be essential for assessing and optimising the impact of the programmes. Finally, it is important to monitor the epidemiology of tuberculosis and the performance of control programmes at the local level to ensure appropriate allocation of resources and equitable access to care.<sup>5</sup>

PJW has received research funding from Otsuka SA for a retrospective study of multidrug-resistant tuberculosis treatment in several eastern European countries. IA and ACH co-chaired the National Institute for Health and Care Excellence tuberculosis guideline development group, which considered evidence on testing and treatment of latent tuberculosis in migrant groups. RWA declares no competing interests. PJW thanks the UK National Institute for Health Research (NIHR) Health Protection Research Unit in Modelling Methodology at Imperial College London, in partnership with Public Health England (HPRU-2012-10080) and the Medical Research Council (MR/K010174/1) for funding. IA was supported by the NIHR, the Department of Health Policy Research Programme (015/0307), and the Medical Research Council. RWA thanks the Wellcome Trust for funding a research training fellowship (097980/Z/11/Z) and the NIHR for funding an academic clinical lectureship. ACH is supported by funds from the NIHR. The views expressed are those of the authors and not necessarily those of the Department of Health, Medical Research Council, NHS, NIHR, Public Health England, or Wellcome Trust.

\*Peter J White, Ibrahim Abubakar, Robert W Aldridge, Andrew C Hayward  
p.white@imperial.ac.uk

MRC Centre for Outbreak Analysis and Modelling, NIHR Health Protection Research Unit in Modelling Methodology, and Department of Infectious Disease Epidemiology, Imperial College London, London W2 1PG, UK (PJW); Modelling and Economics Unit, National Infection Service, Public Health England, London, UK (PJW); Institute for Global Health, University College London, London, UK (IA, RWA); Medical Directorate, Public Health England, London, UK (IA); and Institute of Epidemiology and Health Care, University College London, London, UK (RWA, ACH)

- 1 Bozorgmehr K. Post-migration follow-up of migrants at risk of tuberculosis. *Lancet Infect Dis* 2017; **17**: 692.
- 2 Aldridge RW, Zenner D, White PJ, et al. Tuberculosis in migrants moving from high-incidence to low-incidence countries: a population-based cohort study of 519 955 migrants screened before entry to England, Wales, and Northern Ireland. *Lancet* 2016; **388**: 2510–18.
- 3 Pareek M, Watson JP, Ormerod LP, et al. Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. *Lancet Infect Dis* 2011; **11**: 435–44.
- 4 Pareek M, Bond M, Shorey J, et al. Community-based evaluation of immigrant tuberculosis screening using interferon gamma release assays and tuberculin skin testing: observational study and economic analysis. *Thorax* 2013; **68**: 230–39.
- 5 Pareek M, Abubakar I, White PJ, et al. TB screening of migrants to low TB burden nations: insights from evaluation of UK practice. *Eur Resp J* 2011; **37**: 1175–82.
- 6 White PJ, Abubakar I. Improving control of tuberculosis in low-burden countries: insights from mathematical modeling. *Front Microbiol* 2016; **7**: 394.
- 7 Aldridge RW, Zenner D, White PJ, et al. Prevalence and risk factors for active tuberculosis in migrants screened before entry to the UK: a population-based cross-sectional study. *Lancet Infect Dis* 2016; **16**: 962–70.
- 8 Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of latent tuberculosis infection: an updated network meta-analysis. *Ann Int Med* 2017; **167**: 248–255.

## WHO delays guinea-worm disease eradication to 2020: are dogs the sole culprits?

WHO's 2007 global plan<sup>1</sup> targeted the eradication of guinea-worm disease by 2015. This objective was not met and the culprits have, apparently, been identified. In addition to the political instability that prevails in many areas of Africa, which prevents the applicability of control strategies for disease control, dogs have been considered the most serious obstacle