References


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Voriconazole and cobicistat-boosted antiretroviral salvage regimen co-administration to treat invasive aspergillosis in an HIV-infected patient

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Sir,

Antiretroviral (ARV) regimens to treat MDR HIV strains often require the use of a ritonavir-boosted PI, usually darunavir, in combination with other drugs.1 Aspergillosis is a serious infection in immuno-compromised patients and the drug of choice for its treatment is voriconazole2 but it shows a complex drug–drug interaction profile. Ritonavir induces the CYP3A4 isoenzyme, leading frequently to insufficient drug levels of voriconazole3 contraindicating its co-administration.4–7 Consequently, in patients with MDR HIV infections and aspergillosis, therapeutic options are limited. Cobicistat shows a theoretically better drug–drug interaction profile, due to the more selective 3A4 isoenzyme inhibition, but clinical experience with drugs other than ARVs is lacking.3,8

A middle-aged male patient with HIV since 1987, treated since the early 1990s with several ARV regimens and experienced multiple virological failures causing an MDR strain (62V/65R/101E/181C/184I mutations, conferring resistance to lamivudine/emtricitabine/didanosine/abacavir/nevirapine/efaviren/zidovudine and partial resistance to tenofovir). In 2014 he had an undetectable viral load and CD4 lymphocyte count >1000 cells/mm3, and was on 800/100 mg of darunavir/ritonavir once daily and 400 mg of raltegravir twice daily. He never developed an AIDS-related opportunistic infection. He also had a severe chronic obstructive pulmonary disease. In July 2014, he was admitted for a respiratory infection and treated with broad-spectrum antibiotics and high doses of systemic steroids with incomplete response. Then invasive pulmonary aspergillosis was diagnosed (Figure 1). The chosen antifungal drug was liposomal amphotericin B plus anidulafungin. However, the patient showed no clinical response, so the antifungal regimen was modified to 200 mg of voriconazole twice daily and the ARV regimen was changed to enfuvirtide, zidovudine, tenofovir and raltegravir at the usual doses. On this treatment, he clinically improved and was discharged. After 4 months the patient requested an ARV regimen change, due to intolerance to enfuvirtide injections. The regimen chosen then was 150/150/200/300 mg of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (co-formulated as Stribild9) once daily and 800 mg of darunavir once daily.

To check the pharmacokinetics of this drug combination, a complete 24 h pharmacokinetic curve was performed for 800 mg of darunavir once daily and 200 mg of voriconazole twice daily on this regimen, showing a darunavir Cmax of 0.2 µg/mL, Cmax of 5.9 µg/mL at 4 h and an AUC of 51.2 mg·h/mL. For voriconazole, the Cmin was 0.31 µg/mL, the Cmax was 1.92 µg/mL at 2 h post-administration and the AUC was 11.9 mg·h/L. These values represented a slight decrease in AUC for voriconazole (~20%) and for darunavir (~15%), compared with reference values. Voriconazole plasma concentrations were measured by validated reverse-phase HPLC adapted to a UV/Vis detector. The limit of quantification was 0.10 µg/mL. Elvitegravir plasma levels were not

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The results of these pharmacokinetic curves were only available later on during the clinical course and thus were not used for dose adjustments or therapeutic decisions. Voriconazole doses were adapted in real time according to \( C_{\text{min}} \) monitoring and were progressively increased to 400 mg twice daily to reach the target plasma level of 1 mg/mL.9 The patient presented good tolerance and complete clinical resolution after 9 months. Plasma HIV viral load remained consistently undetectable.

Voriconazole is metabolized by the hepatic P450 cytochrome isoenzymes CYP2C19 and, to a minor extent, CYP2C9 and CYP3A4.6 Its therapeutic window is narrow, with a high risk of side effects when serum levels are 3–5 times higher than the minimal threshold for efficacy.2 It shows a well-described drug–drug interaction profile with several ARV drugs, particularly those metabolized by the P450 cytochrome. Ritonavir is mainly a CYP3A4 isoenzyme inhibitor, but also a CYP2C19 and CYP2C9 inducer, so it decreases voriconazole levels. Then, in patients with MDR HIV infections treated with a PI and presenting with aspergillosis, therapeutic options are limited due to the contraindicated use of concomitant voriconazole and ritonavir-boosted PIs. Nevertheless, cobicistat could be an alternative in those cases, due to its higher specificity for 3A4 inhibition.8,10 However, clinical experience is extremely limited beyond cobicistat co-administration with elvitegravir and some PIs. Despite that the combination of elvitegravir/cobicistat and darunavir is not recommended for the potential reduction of darunavir plasma levels (as seen in our case), this reduction of darunavir AUC has, probably, no clinical relevance for simplification of patients virologically suppressed for long periods.

In conclusion, our case is original for several reasons. First, as far as we know, this is the first report of co-administration of cobicistat, darunavir and voriconazole (in the context of a complex ARV regimen). Second, it offers clinical insight into the efficacy of this antimicrobial regimen in a real-life setting, the maintenance of undetectable viral load and a complete clinical response to pulmonary aspergillosis. Finally, it provides evidence of the potential usefulness of this ARV combination for simplification in experienced patients, a two-pill regimen combination that could be active in patients with extensive ARV drug resistance, although more clinical experience is needed.

**Figure 1.** Clinical evolution. GA, galactomannan antigen; BAL, bronchoalveolar lavage; LAMB, liposomal amphotericin B; AFG, anidulafungin; VRC, voriconazole; DRV, darunavir; ZDV, zidovudine; TDF, tenofovir; RAL, raltegravir; T20, enfuvirtide; Stribild\(^{w}\), elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate co-formulation. Arrow: suspected nodule of pulmonary aspergillosis.

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<th>Year</th>
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<td>2014</td>
<td>LAMB + AFG therapy started</td>
<td>Antifungal regimen modified to VRC 200 mg twice daily and ART to T20, ZDV, TDF and RAL</td>
<td>The patient requests a change of ART (T20 intolerance). New ART regimen: Stribild(^{w}) + DRV</td>
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<td>2015</td>
<td>Stop of VRC after a complete resolution of symptoms, significant improvement of CT scan (image 2) and negative GA in serum</td>
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**Image 1**

**Image 2**

VRC plasma levels (\( C_{\text{min}}, \mu g/mL \))

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<th>1.18</th>
<th>0.31</th>
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**Figure 1.** Clinical evolution. GA, galactomannan antigen; BAL, bronchoalveolar lavage; LAMB, liposomal amphotericin B; AFG, anidulafungin; VRC, voriconazole; DRV, darunavir; ZDV, zidovudine; TDF, tenofovir; RAL, raltegravir; T20, enfuvirtide; Stribild\(^{w}\), elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate co-formulation. Arrow: suspected nodule of pulmonary aspergillosis.
Sir,

Ritonavir-boosted PI (PI/r) therapy of HIV infection can have adverse effects upon fasting lipids, and is associated with increased risk of myocardial infarction.1 However, only half of this increased risk is explained by fasting dyslipidaemia. Post-prandial dyslipidaemia is associated with myocardial infarction in the general population2–4 and so might contribute to PI/r-associated cardiovascular risk. We have previously shown that low-dose ritonavir monotherapy in HIV-uninfected adults can result in significant increases in post-prandial LDL cholesterol compared with the integrase strand transfer inhibitor (INSTI) raltegravir,5 which has minimal adverse lipid effects.6

Of the current generation of PI/r options, atazanavir/ritonavir does not appear to increase the risk of myocardial infarction or stroke7 and causes less carotid intimal thickening than either darunavir/ritonavir or raltegravir.8 Few clinical data are available to judge the contribution of darunavir/ritonavir to major cardiovascular events. However, darunavir/ritonavir has superior intention-to-treat efficacy compared with atazanavir/ritonavir9 and is the only PI/r recommended for initial combination ART (cART) in resource-rich settings by all major international consensus anti-retroviral guidelines.10–12

In this randomized, open-label, multicentre pilot study, we compared the post-prandial lipid effects of darunavir/ritonavir with those of raltegravir in adults initiating cART. It was hypothesized that darunavir/ritonavir would result in greater post-prandial dyslipidaemia than raltegravir.

HIV-1-infected adults (age ≥ 18 years) were enrolled if they were commencing CART (either ART naive or off ART for >6 months) and had a CD4+ lymphocyte count <0.50×10^9 cells/L and plasma viral load >10 000 copies/mL; no baseline genotypic resistance to tenofovir, emtricitabine or darunavir/ritonavir; a BMI <30 kg/m^2; were not diabetic or receiving lipid-lowering therapy; and provided written, informed consent. Pregnancy and breast-feeding were exclusion criteria. Participants were randomized 1:1 to open-label tenofovir/emtricitabine plus either darunavir/ritonavir (800/100 mg once daily) or raltegravir (400 mg twice daily) for 24 weeks. The study was approved by the institutional human research ethics committee, and conducted in accordance with international guidelines. Each participant provided written, informed consent.

Participants underwent a standardized meal challenge (energy content = 5780 kJ; 88 g of fat, 37 g of protein and 104 g of carbohydrate) at weeks 0, 4 and 24, with blood samples collected fasting, then hourly for 4 h immediately post-meal. Arterial stiffness was also measured pre- and post-meal by radial artery tonometry, and corrected for heart rate. A mixed-effects random intercept model was used to determine the change in incremental area under the curve (ΔiAUC) for all post-prandial endpoints. All analyses used the intention-to-treat method. The primary endpoint was the between-group difference in ΔiAUC for LDL cholesterol at week 24. Secondary endpoints were the between-group differences in: ΔiAUC for other post-prandial lipids and arterial stiffness; fasting lipids; and clinical and laboratory adverse events. Our previous study of post-prandial lipids in HIV-negative volunteers had identified significant differences in ΔiAUC with a sample size of 10 per group after 4 weeks. It was anticipated that 24 weeks with a sample size of 15 per group would be sufficient to detect any significant

Post-prandial lipid effects of raltegravir versus darunavir/ritonavir in HIV-1-infected adults commencing combination ART

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