

Appendix 1 (as supplied by authors): Drug interactions between antiretrovirals and anticonvulsants, corticosteroids and phosphodiesterase-5 inhibitors

Anticonvulsants

Many anticonvulsant agents are substrates as well as potent inducers of CYP3A isoenzymes. The main anticonvulsants to be aware of in this regard include carbamazepine, felbamate, oxcarbazepine, phenytoin, phenobarbital, and primidone. The potential exists for bi-directional interactions with most protease inhibitors, NNRTIs, and elvitegravir/cobicistat.^{1,2} In healthy volunteer studies, darunavir increased the area under the concentration–time curve (AUC) of carbamazepine by 54% with little impact on darunavir pharmacokinetics³ while a negative 2-way interaction was seen with phenytoin and lopinavir/ritonavir (lopinavir AUC ↓ 33% and phenytoin AUC ↓ 31%).⁴ A negative dual interaction between carbamazepine and efavirenz was also observed in one healthy volunteer study (efavirenz AUC ↓ 36%; carbamazepine AUC ↓ 27%).⁵ There are several case reports of patients who have experienced toxic anticonvulsant concentrations and/or subtherapeutic antiretroviral exposures with coadministration of these drugs.^{6–9} Therefore, use of these anticonvulsants in patients on a protease inhibitor, NNRTI or elvitegravir/cobicistat therapy should be avoided and agents such as valproic acid or levetiracetam considered as an alternative. If anticonvulsant treatment cannot be modified, close monitoring and measurement of anticonvulsant and antiretroviral serum-drug concentrations is recommended. Alternatively, use of a raltegravir-based antiretroviral regimen may be considered, upon consultation with an HIV specialist, in order to ensure adequate viral potency. Tiagabine and zonisamide are also CYP3A4 substrates and concentrations may be influenced by antiretroviral therapy although data are lacking.

Corticosteroids

Corticosteroids are substrates of CYP3A4, and hence are susceptible to interactions with potent CYP3A4 inhibitors such as protease inhibitors and cobicistat. In many instances, such interactions may be clinically significant, even when corticosteroids are administered via non-oral routes. There have been numerous case reports of Cushing syndrome in HIV-infected patients on both ritonavir and inhaled or intranasally administered fluticasone propionate.^{10–13} Cases of adrenal suppression and/or Cushing syndrome have been seen with coadministration of ritonavir and injectable triamcinolone as well,^{14–18} inhaled or oral budesonide,^{19–21} and even corticosteroid topical eye drops and ointment.²²

Therefore, caution is warranted when inhaled, intra-articular or even topical steroids are co-administered with ritonavir or cobicistat-based therapy. The use of inhaled fluticasone and ritonavir should be avoided if possible. Although budesonide is not contraindicated, based on these recent case reports, caution is warranted. If steroids are clearly indicated, ritonavir or cobicistat should be avoided and other antiretroviral options used, if feasible and in consultation with the patient's HIV care provider. If the combination of ritonavir or cobicistat and steroids is required, the lowest effective steroid dose should be used or inhaled or intranasal beclomethasone may be a preferred choice.¹³ Close monitoring for signs and symptoms of Cushing syndrome is recommended as symptoms typically appear after several weeks and may take months to resolve once diagnosed.

Phosphodiesterase-5 (PDE-5) Inhibitors

The phosphodiesterase type 5 (PDE5) inhibitors sildenafil and tadalafil are indicated for both treatment of erectile dysfunction and more recently, primary pulmonary arterial hypertension (PAH), which may be an HIV-related condition. Sildenafil exposures are increased 2 to 11-fold in the presence of protease inhibitors.^{2,23,24} A case report of recurrent priapism secondary to an

interaction between tadalafil and boosted fosamprenavir has been reported.²⁵ For the treatment of erectile dysfunction, significant dose reductions of sildenafil and tadalafil are necessary in the context of protease inhibitor or cobicistat therapy. According to product labelling, vardenafil is contraindicated with strong CYP3A4 inhibitors including protease inhibitors.²⁶ Given the marked effect of protease inhibitors and cobicistat on increasing sildenafil exposures, as well as the higher daily dose required for chronic treatment of PAH, sildenafil for treatment of PAH is contraindicated with all protease inhibitors as well as cobicistat.² Tadalafil may be used for treatment of PAH with appropriate dosing adjustments.² Etravirine has been shown to reduce sildenafil exposures by 57% in healthy volunteers.²⁷ The potential for similar interactions between other NNRTIs and all PDE5 inhibitors exists. Thus, close monitoring is warranted if coadministration is necessary, with dose adjustment of the PDE5 inhibitor as necessary based on response.

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