

Healthcare Professional Newsletter

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Rifabutin dosing with protease inhibitors

Rifabutin is a rifamycin derivative that is used in the treatment of tuberculosis when rifampicin cannot be used due to drug interactions (e.g. with ritonavir-boosted atazanavir or darunavir), or occasionally in patients with disseminated non-tuberculous mycobacterial infections. Rifabutin is a much weaker enzyme inducer than rifampicin. Unlike rifampicin, rifabutin is metabolised by a cytochrome P450 enzyme (CYP3A), and its concentrations can be affected by concomitant drugs that induce or inhibit CYP3A. Ritonavir-boosted protease inhibitors markedly inhibit CYP3A, necessitating a reduction in the dose of rifabutin. Previously the recommended dose of rifabutin when given with protease inhibitors was 150 mg three times a week. A recent pooled analysis of pharmacokinetic studies¹ has recommended a dose of 150 mg daily when given with protease inhibitors, as this better matches the exposure of the usual dose of 300 mg daily when used without inhibiting or inducing drugs.

However, rifabutin's main active metabolite 25-O-desacetyl rifabutin is increased about tenfold when given with protease inhibitors compared with the usual dose of 300 mg daily. The 150 mg daily rifabutin dose with protease inhibitors might therefore increase the risk of toxicity (especially uveitis, neutropaenia, and hepatitis), which is related to the concentrations of rifabutin and its 25-O-desacetyl rifabutin metabolite.

A retrospective Indian study² reported higher cure rates in patients on atazanavir-ritonavir treated with rifabutin 150 mg daily than with 150 mg thrice weekly for tuberculosis. However, there were more patients in the transferred out/unknown follow up group in the thrice weekly dosing group, which could have accounted for the difference in cure, no toxicity data were presented, and tuberculosis was almost always diagnosed clinically. Therefore there is no good clinical evidence supporting the use of daily dosing.

Despite the lack of good clinical evidence, the new US guidelines³ now recommend rifabutin 150 mg daily when given with protease inhibitors (at least during the intensive phase of therapy), in view of the risk of rifamycin resistance emerging on therapy. AfA endorses these new guidelines with careful monitoring for toxicity: regular laboratory monitoring of ALT, neutrophil count, and clinical monitoring for ocular toxicity.

References

1. Hennig S, Svensson EM, Niebecker R, et al. Population pharmacokinetic drug–drug interaction pooled analysis of existing data for rifabutin and HIV PIs. *J Antimicrob Chemother* 2016; 71: 1330–1340
2. Jenks JD, Kumarasamy N, Ezhilarasi C, et al. Improved tuberculosis outcomes with daily vs. intermittent rifabutin in HIV-TB coinfecting patients in India. *Int J Tuberc Lung Dis* 2016;20(9):1181–1184
3. <https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/325/tb>

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Drug-drug interactions involving second generation NNRTIs

Second generation NNRTIs (etravirine and rilpivirine) are increasingly being used in clinical practice in South Africa – etravirine in third-line ART regimens and rilpivirine in first or third-line regimens. It is important for clinicians to be aware of potential drug-drug interactions involving these drugs that may contra-indicate their use in certain settings.

Rilpivirine is metabolised mainly by cytochrome P450 iso-enzyme CYP3A4. Thus its concentrations may be affected by drugs that induce or inhibit this iso-enzyme. Of importance, rifampicin which is a potent inducer of CYP3A4, will reduce concentrations of rilpivirine significantly. Thus rilpivirine should not be used while patients are on treatment with rifampicin or other strong inducing drugs (e.g. phenytoin, phenobarbital, carbamazepine) and for 2 weeks after stopping the inducing drug. Rilpivirine does not itself act as a significant inducer or inhibitor of the metabolism of other drugs.

Etravirine is also mainly metabolised by CYP3A4, thus its concentrations are also affected by drugs that induce or inhibit CYP3A4. Like rilpivirine it should not be used in patients on strong enzyme-inducing drugs like rifampicin. Etravirine, however, also acts as an inducer of CYP3A4 and the glucuronide conjugating enzyme UGT1A1, and therefore has the potential to reduce the concentrations of other drugs such as:

- Atazanavir/ritonavir which should not be co-administered with etravirine because trough concentrations of atazanavir are reduced by 38% with potentially reduced efficacy (atazanavir/ritonavir also increases exposure to etravirine).
- Etravirine significantly reduces concentrations of dolutegravir. This effect is mitigated by the inhibitory effect of boosted protease inhibitors. Thus when a boosted protease inhibitor (e.g. darunavir/ritonavir) is used in third line then dolutegravir and etravirine can be co-administered. However, the combination of dolutegravir and etravirine should not be used without a boosted protease inhibitor.

We have not provided an exhaustive list of drug interactions with second generation NNRTIs here. Clinicians are urged to consult a database (e.g. <http://www.hiv-druginteractions.org>) when co-prescribing other drugs with rilpivirine or etravirine to check for potential interactions.

AfA Clinical Guidelines Booklet

The 11th edition is now available. Please send us an email (afa@afadm.co.za) with your postal address or phone 0860 100 646 if you would like us to send you a free copy. Alternatively, the guidelines can be downloaded from the AfA website (www.aidforaids.co.za) and the updated App will be available shortly



Pure Red Cell Aplasia in HIV

Pure Red Cell Aplasia (PRCA) is most commonly an acquired, rare disorder presenting with often profound anaemia due to abnormal production of red blood cells. This is manifested in the bone marrow by a virtual absence of red blood cell precursors and in peripheral blood by a marked reduction in the reticulocyte production index. Characteristically, the patient presents with symptoms related to anaemia such as fatigue, exercise intolerance and breathlessness.

In the setting of HIV, PRCA is most commonly due to coinfection with parvovirus B19, which is also the cause of Hydrops Fetalis in neonates, Fifth Disease (slap-cheek syndrome) in children, and arthritis and/or arthralgia, which is more common in adults than children, and more often seen in women. Parvovirus B19 destroys proerythroblasts by attaching to the blood globoside (group P antigen) receptor, resulting in their destruction. Characteristic bone marrow morphology shows presence of giant proerythroblasts. Until the advent of parvovirus B19 PCR, diagnosis relied on bone marrow morphology coupled with serology for B19. However, serology missed a number of cases and it is now standard practice to diagnose by testing for the viral DNA by PCR. There is no specific antiviral treatment for Parvovirus B19. Treatment is generally supportive with red blood cell transfusion and effective antiretroviral therapy. Patients who do not settle spontaneously should be discussed with a haematologist, with a view to intravenous immunoglobulin therapy.

The other main cause of PRCA in the setting of HIV is secondary to lamivudine (3TC) therapy, which was first described by Weitzel et al in 1999. This is increasingly recognized and responds to supportive care and discontinuation of lamivudine. There are as yet no published reports of emtricitabine (FTC) causing PRCA. However, there are a number of anecdotal reports of PRCA caused by emtricitabine, including AfA patients. Isoniazid too, is a recognized cause of PRCA and should be investigated as part of the differential diagnosis of PRCA in any patient who is on isoniazid prophylaxis or treatment for tuberculosis.

Reference

Weitzel, T., Plettenberg, A., Albrecht, D., Lorenzen, T. & Stoehr, A. Severe anemia as a newly recognized side effect caused by lamivudine. *AIDS* 1999;13:2309–2311

Aid for AIDS is delighted to announce

- We have been appointed as the HIV disease manager for SAMWUMED as of 01 January 2017
- LMS Medical Fund (previously known as the Liberty Medical Scheme) has amalgamated with Bonitas Medical Aid, effective 01 October 2016