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## Ritonavir-boosted antiretroviral therapy with paclitaxel: will it lead to boosted toxicity?

The introduction of combination antiretroviral therapy (cART) has significantly reduced mortality among people with HIV (PWH), resulting in an increased incidence of non-AIDS related cancer and risk of drug-drug interactions (DDIs) in this aging population [1].

Taxanes are used for a variety of highly prevalent cancer types (e.g., breast cancer, prostate cancer) [2]. Concomitant use of docetaxel with ritonavir-boosted cART is not recommended, as ritonavir-boosted cART leads to an increase of docetaxel plasma concentrations and, hence, an increasing risk of toxicity [3]. Clinical implications of the concurrent use of ritonavir and another taxane, paclitaxel, have not yet been fully established, and this is currently not contra-indicated.

We present two cases describing a potential DDI with paclitaxel in HIV-infected patients, indicating that current recommendations on combining paclitaxel with ritonavir-boosted cART might need modification.

Patient 1 is a 63-year-old man tested HIV positive in 2005. As of 2019, cART consisted of darunavir 800 mg once daily (q.d.), ritonavir 100 mg q.d., lamivudine 150 mg q.d., and abacavir 600 mg q.d., achieving adequate virologic suppression. In 2019, a gastric cardia adenocarcinoma with distal esophageal metastasis was discovered. Palliative chemotherapy was started consisting of carboplatin [target AUC = 4 mg\*min/ml (Calvert)] and paclitaxel (100 mg/m<sup>2</sup>), on days 1, 8, and 15, in a 28-day cycle. cART remained unchanged as drug labels and international DDI resources currently recommend to monitor paclitaxel toxicity in case of concurrent use with ritonavir [4], and substitution to an integrase inhibitor was deemed undesirable due to psychiatric comorbidities. The first dose was completed without complications and blood count was within acceptable range (Table 1). Three days after receiving the second dose, the patient had to be hospitalized due to a severe neutropenic sepsis, caused by a nonresistant *Escherichia coli*. Despite administration of meropenem, the patient did not recover and passed away three days after admission.

Patient 2 is a 56-year-old woman, tested HIV-positive in 2000. cART consisted of lopinavir/ritonavir 800 mg/200 mg q.d. and lamivudine 300 mg q.d. She was diagnosed with HER2+ breast cancer in 2020 and chemotherapy was started. One cycle consisted of paclitaxel (80 mg/m<sup>2</sup>) once weekly and both pertuzumab (420, 840 mg loading dose) and trastuzumab (6, 8 mg/kg loading dose) every 3 weeks. After the second paclitaxel dose, the patient was hospitalized due to neutropenic fever (Table 1) and the third dose was cancelled. Cycle 2 was started 1 week later after blood count returned to normal, with 75% of the original paclitaxel dose, and was fully completed. However, rehospitalization followed and blood count showed development of a pancytopenia. Lopinavir/ritonavir was substituted for dolutegravir 50 mg because of the suspected DDI between lopinavir/ritonavir and paclitaxel. Two weeks after hospitalization, with blood counts returned to acceptable range, the third cycle was initiated with 50% paclitaxel dose reduction.

The remaining paclitaxel cycles were successfully completed, at reduced dosages (fourth cycle at 50%, fifth and sixth cycle at 60% of the original dose), without recurrent pancytopenia.

Paclitaxel is predominantly metabolized by CYP2C8 and to a lesser extent by CYP3A4, whereas ritonavir is a strong CYP3A4 and weak CYP2C8 inhibitor [5,6]. Inhibition of both metabolic pathways can reduce paclitaxel clearance and thereby increase paclitaxel exposure. Subsequently, risk of paclitaxel toxicity increases, potentially manifesting as pancytopenia [7]. Clinical implications of this DDI for treatment of Kaposi's sarcoma have been described by others. Bundow *et al.* [8] reported two cases of paclitaxel toxicity in patients receiving ritonavir-boosted cART with paclitaxel (100 mg/m<sup>2</sup> every 2 weeks). Gianfrocca *et al.* [9] reported about twofold higher paclitaxel exposure in Kaposi's sarcoma patients receiving concomitant protease inhibitors (including ritonavir), remarkably without enhanced toxicity.

**Table 1. Blood count of both patients, before and during chemotherapy with combination antiretroviral therapy.**

	Patient 1		Patient 2				Reference range
	Before first cycle	After first cycle	Before first cycle	After first cycle	After second cycle	After third cycle	
Hemoglobin (mmol/l)	7.6	<b>7.0</b>	<b>6.0</b>	<b>4.3</b>	<b>4.9</b>	<b>5.6</b>	7.5–10.0
Leucocytes (×10 <sup>9</sup> cells/l)	6.4	<b>0.42</b>	6.8	<b>0.7</b>	<b>1.7</b>	6.8	4.0–10.0
Thrombocytes (×10 <sup>9</sup> cells/l)	203	<b>97</b>	181	165	277	289	150–400

Values in bold deviate from the reference range.

However, non-AIDS related malignancies, which will occur more often due to a longer life expectancy of PWH, require higher paclitaxel dosages compared with AIDS related malignancies [9] (175–300 vs. 100 mg/m<sup>2</sup>/cycle, respectively), potentially increasing severity of paclitaxel-induced toxicity.

The above-mentioned cases provide a better understanding of the clinical relevance of the DDI between paclitaxel and ritonavir. We strongly advise to avoid the combination of paclitaxel, or another taxane, with ritonavir. Substituting to unboosted cART is preferred, as was demonstrated above in Patient 2. Although in-vitro data suggest that paclitaxel could influence metabolism of other antiretroviral drugs, including integrase inhibitors, we consider this in the absence of in-vivo data as clinically irrelevant. Pharmacokinetic data from TDM registries could be welcome to confirm this.

Strong evidence is still lacking for many DDIs between cART and chemotherapy, while the population of PWH is aging, thus more often confronted with non-AIDS related malignancies. More clinical studies in cancer patients living with HIV are needed to inform decision making around these DDIs.

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## Conflicts of interest

There are no conflicts of interest.

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## References

1. Silverberg M, Lau B, Achenbach C, Jing Y, Althoff KN, D'Souza G, *et al.* **Cumulative incidence of cancer among persons with HIV in North America.** *Ann Intern Med* 2015; **163**:507.
2. NCCN Guidelines [Internet]. National Comprehensive Cancer Network. Last updated 2021. [https://www.nccn.org/guidelines/category\\_1](https://www.nccn.org/guidelines/category_1). [Accessed 22 August 2021].
3. Rudek M, Chang C, Steadman K, Johnson MD, Desai N, Deeken JF. **Combination antiretroviral therapy (cART) component ritonavir significantly alters docetaxel exposure.** *Cancer Chemother Pharmacol* 2014; **73**:729–736.
4. Paxene, INN-Paclitaxel [Internet]. Ema.europa.eu. Last updated 22 March 2010. <https://www.ema.europa.eu/en/medicines/human/EPAR/paxene#product-information-section>. [Accessed 15 May 2021].
5. Nakajima Y, Yoshitani T, Fukushimaesaka H, Saito Y, Kaniwa N, Kurose K, *et al.* **Impact of the haplotype CYP3A4\*16B harboring the Thr185Ser substitution on paclitaxel metabolism in Japanese patients with cancer.** *Clin Pharmacol Therap* 2006; **80**:179–191.
6. Marzolini C, Gibbons S, Khoo S, Back D. **Cobicistat versus ritonavir boosting and differences in the drug–drug interaction profiles with co-medications.** *J Antimicrob Chemother* 2016; **71**:1755–1758.
7. Joerger M, Huitema A, Richel D, Dittrich C, Pavlidis N, Briasoulis E, *et al.* **Population pharmacokinetics and pharmacodynamics of paclitaxel and carboplatin in ovarian cancer patients: a study by the European organization for research and treatment of cancer-pharmacology and molecular mechanisms group and new drug development group.** *Clin Cancer Res* 2007; **13**:6410–6418.
8. Bundow D, Aboulafia D. **Potential drug interaction with paclitaxel and highly active antiretroviral therapy in two patients with AIDS-associated Kaposi sarcoma.** *Am J Clin Oncol* 2004; **27**:81–84.
9. Cianfrocca M, Lee S, Von Roenn J, Rudek MA, Dezube BJ, Krown SE, *et al.* **Pilot study evaluating the interaction between paclitaxel and protease inhibitors in patients with human immunodeficiency virus-associated Kaposi's sarcoma: an Eastern Cooperative Oncology Group (ECOG) and AIDS Malignancy Consortium (AMC) trial.** *Cancer Chemother Pharmacol* 2011; **68**:827–833.

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