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Response to “Anti-retroviral therapy with efavirnez in HIV infected pregnant women - understanding the possible mechanisms for drug-drug interaction”

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To the editor

We appreciate the letter by Dr. Srinivas (1) suggesting potential mechanisms by which dihydroartemisinin (DHA) and piperaquine (PQ) exposure were reduced in HIV-infected pregnant women receiving efavirenz (compared with HIV-uninfected pregnant women not receiving efavirenz). Dr. Srinivas argues that DHA bioavailability may be reduced due to efavirenz promoting intestinal presystemic glucuronidation of DHA to its glucuronide metabolite, thereby reducing the oral bioavailability and exposure of DHA without affecting its elimination. We agree that this certainly is plausible in spite of others reporting efavirenz does not impact intestinal metabolism (2, 3). We completed a study of bedaquiline, an antitubercular agent, in the absence and presence of efavirenz where the alterations of metabolite formation and elimination that we observed was perhaps best explained by efavirenz induction of metabolism within the gastrointestinal tract (presystemic) as well as the liver. Even though the peak levels of parent drug did not change, the elimination of the metabolite was faster than parent drug (i.e. did not follow the elimination slope of parent drug) and thus must have been formed before the parent drug reached the central plasma compartment (4).

We also agree with Dr. Srinivas that induction of CYP3A4 by efavirenz may also influence PQ clearance, thereby leading to a reduced PQ half-life (5). This can most easily be explained by an induction of hepatic metabolism which has clearly been demonstrated for efavirenz (3).

As stated by Dr. Srinivas and as we concluded in our manuscript, we agree that these drug interactions may have critically important clinical consequences. We have recently

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CONFLICT OF INTEREST

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performed population pharmacokinetic/pharmacodynamic (PK/PD) modeling from these trials, and have estimated that maintaining a protective PQ concentration of >10.3 ng/mL was associated with 95% protection from maternal malaria and parasitemia among HIV-uninfected women given DHA-PQ (Savic et al in review). In women receiving efavirenz-based ART and standard monthly DHA-PQ as IPTp, less than 1% achieved these protective PQ levels during pregnancy (Wallender et al in review). Optimizing the dosing of DHA-PQ for chemoprevention in the setting of a drug-drug interactions will be an essential advancement in malaria control.

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References

1. Srinivas NR. Is there a differential conversion of artesunate to dihydroartemisinin in pregnant vs. post-partum patients with malaria after oral artesunate dosing? *Br J Clin Pharmacol*. 2016; 81:389–90. [PubMed: 26521664]
2. Oswald S, et al. Impact of efavirenz on intestinal metabolism and transport: insights from an interaction study with ezetimibe in healthy volunteers. *Clinical pharmacology and therapeutics*. 2012; 91:506–13. [PubMed: 22297387]
3. Meyer zu Schwabedissen HE, et al. Compartment-specific gene regulation of the CAR inducer efavirenz in vivo. *Clinical pharmacology and therapeutics*. 2012; 92:103–11. [PubMed: 22588604]
4. Dooley KE, et al. Safety, tolerability, and pharmacokinetic interactions of the antituberculous agent TMC207 (bedaquiline) with efavirenz in healthy volunteers: AIDS Clinical Trials Group Study A5267. *J Acquir Immune Defic Syndr*. 2012; 59:455–62. [PubMed: 22126739]
5. Kajubi R, et al. Antiretroviral Therapy With Efavirenz Accentuates Pregnancy-Associated Reduction of Dihydroartemisinin-Piperaquine Exposure During Malaria Chemoprevention. *Clinical pharmacology and therapeutics*. 2017; 102:520–8. [PubMed: 28187497]