

Certain HIV medication associated with adrenal dysfunction in newborns of HIV-1 infected mothers

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Infants of human immunodeficiency virus 1 (HIV-1) infected mothers who were treated before and after birth with the protease inhibitor lopinavir-ritonavir were more likely to experience adrenal dysfunction, including life-threatening adrenal insufficiency in premature infants, compared with a zidovudine-based regimen, according to a preliminary report in the July 6 issue of *JAMA*.

"The HIV-1 transmission rate to [newborns](#) is now less than 1 percent for women treated during pregnancy. For pregnant women not optimally treated, as in cases of HIV diagnosis late during pregnancy or persistent [viral replication](#) at delivery, several guidelines, observational reports, and the results of a recent controlled study suggest reinforcing the postnatal phase of treatment with a combination of anti-retrovirals, as a 'postexposure prophylaxis.' The [protease inhibitor](#) lopinavir, with its pharmacological booster [ritonavir](#) (lopinavir-ritonavir), is now the ritonavir-boosted protease inhibitor most widely prescribed in children," according to background information in the article.

Lopinavir-ritonavir is licensed in the United States for HIV-infected newborns older than 14 days and in Europe for children older than 2 years. However, published data concerning its use in newborns are scarce. In April 2010, one of the centers of the French national screening program for congenital adrenal hyperplasia (CAH; a group of inherited disorders of the [adrenal glands](#)) identified a transient increase of

17-hydroxyprogesterone (17OHP; a [steroid hormone](#) produced mainly by the adrenal glands) in dried [blood spots](#) from 2 children treated at birth with lopinavir-ritonavir.

Albane Simon, M.D., of the Hopital Necker-Enfants Maiades, Assistance Publique-Hopitaux de Paris, France, and colleagues conducted a study to assess whether immediate postnatal exposure to lopinavir-ritonavir was associated with changes in adrenal function compared with standard prophylactic zidovudine treatment. The study included information from the database of the national screening for [congenital adrenal hyperplasia](#) and the French Perinatal Cohort, with a comparison of HIV-1-uninfected newborns postnatally treated with lopinavir-ritonavir and controls treated with standard zidovudine. There was an assessment of levels of 17OHP and dehydroepiandrosterone-sulfate (DHEA-S; the circulating form of a steroid produced primarily by the adrenal cortex) concentrations during the first week of treatment.

Among mother-child pairs in the Paris area enrolled in the study cohort between December 2004 and September 2008, the authors evaluated 50 HIV-1 uninfected children who received lopinavir-ritonavir just after birth, and 108 who received standard prophylaxis: zidovudine alone (n= 100), zidovudine and lamivudine (n = 6), or zidovudine and nevirapine (n = 2). Among the 50 newborns treated with lopinavir-ritonavir, 7 (14 percent) had abnormally high 17OHP results from dried blood spots (greater than 16.5 ng/mL at term or greater than 23.1 ng/mL preterm) vs. 0 of 108 controls. For children born at term, 5 of 42 newborns treated with lopinavir-ritonavir vs. 0 of 93 controls had values greater than 16.5 ng/mL.

The median (midpoint) 17OHP value for term newborns treated with lopinavir-ritonavir was 9.9 ng/mL vs. 3.7 ng/mL in controls. The difference observed in median 17OHP values between treated newborns and controls was higher in children also exposed in utero (11.5 ng/mL vs.

3.7 ng/mL) than not exposed in utero (6.9 ng/mL vs. 3.3 ng/mL). The median DHEA-S values for children born at term were 9,242 ng/mL for the treated group vs. 484 ng/mL for the controls. Consistent with the findings for 17OHP, the DHEA-S values were significantly higher only in cases also exposed in utero to ritonavir-boosted protease inhibitor.

"All term newborns treated with lopinavir-ritonavir were asymptomatic, although 3 premature newborns experienced life-threatening symptoms compatible with adrenal insufficiency, including hyponatremia (abnormally low level of sodium in the blood) and hyperkalemia, (higher than normal levels of potassium in the circulating blood; associated with kidney failure) with in 1 case, cardiogenic shock. All symptoms resolved following completion of the lopinavir-ritonavir treatment," the authors write.

"In summary, our findings of the association between lopinavir-ritonavir and transient adrenal dysfunction in HIV-1 uninfected newborns suggest that lopinavir-ritonavir and more generally ritonavir boosting should be used with caution, if at all, in [premature infants](#), and if this drug regimen is administered to full-term infants, it should be used under electrolyte monitoring. Whether more prolonged exposure of HIV-1 -infected or uninfected infants via breast milk is associated with endocrine disruption should be carefully investigated, and the apparent risk associated with prenatal ritonavir exposure also merits further evaluation."

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