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Adrenal dysfunction in HIV-exposed uninfected infants receiving ritonavir-boosted lopinavir, an HIV protease inhibitor, for the prevention of breastfeeding HIV transmission. An ANRS 12174 substudy.

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Background: We recently demonstrated that both ritonavir-boosted lopinavir (LPV/r) and lamivudine (3TC, a nucleoside analogue) given to breastfed infants can reduce the risk of post natal HIV transmission (ANRS 12174 trial; Nagot, Lancet 2016). In another setting we previously showed the occurrence of adrenal dysfunction in newborn perinatally exposed to LPV/r leading to acute adrenal insufficiency in premature babies (Simon, JAMA 2011).

Objective and hypotheses: Within the ANRS 12174 trial, the administration, randomly assigned, of LPV/r as a monotherapy prophylaxis up to one year in exposed uninfected infants, as compared to 3TC, offered a unique opportunity to study the potential adrenal impact of LPV/r in infants.

Main results: 96 infants (LPV/r: 49, 3TC: 47) samples were analyzed. A marked increase of dehydroepiandrosterone (DHEA) was observed in LPV/r exposed infants as compared to 3TC (median [IQR]): 3.0 [1.6-4.8] vs 1.4 [0.5-3.5] at W6 and 0.4 [0.0-0.8] vs 0.1 [0.0-0.3] ng/mL at W26 respectively, both p<0.001). In infants with high DHEA level at W6 (> 5ng/ml (n=11), other adrenal hormones were also significantly increased as compared with 38 with DHEA < 5 (table).

	DHEA < 5 (n=38)	DHEA > 5 (n=11)	P
17-OH-Pregnenolone	3.4	7.7	<0.01
Delta4-Androstenedione	0.15	0.28	<0.01
Corticosterone	1.3	4.9	0.01
Cortisol	5.6	12.3	<0.01
Progesterone	0.2	0.7	<0.01
Desoxycortisol	0.2	0.4	0.01

All in ng/ml except cortisol μg/dl ; no significant difference for 17-OH-Progesterone, Androstanediol, Dihydrotestosterone, Testosterone.

Conclusion/Interpretation:

- In comparison with lamivudine, LPV/r exposure during the first year of life is associated with a significant, early adrenal dysfunction sustained during exposure.
- This effect may result from the interactions between LPV/r and the immature infant's adrenal and/or an increased ACTH like effect. Further analyses on samples collected after LPV/r discontinuation will be performed.
- There was no difference in severe adverse events incidence between the two treatment groups in the entire cohort (n=1236), but subtle impact on growth and genital development are actively monitored.

Nagot N et al. Lancet. 2016 Feb 6;387(10018):566-73 ; Simon A et al. JAMA. 2011 Jul 6;306(1):70-8.
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