



# **Impact of In-utero Exposure to Protease Inhibitor-Based Antiretroviral Drug Regimens on Developmental Milestones in Mice**

Authors: Ambalika Sarkar, Kayode Balogun, Monica S. Guzman Lenis, Sebastian Acosta, Lena Serghides\*

Affiliations: Toronto General Hospital Research Institute,  
University Health Network, Toronto, ON, Canada

Correspondence: [lena.serghides@utoronto.ca](mailto:lena.serghides@utoronto.ca)

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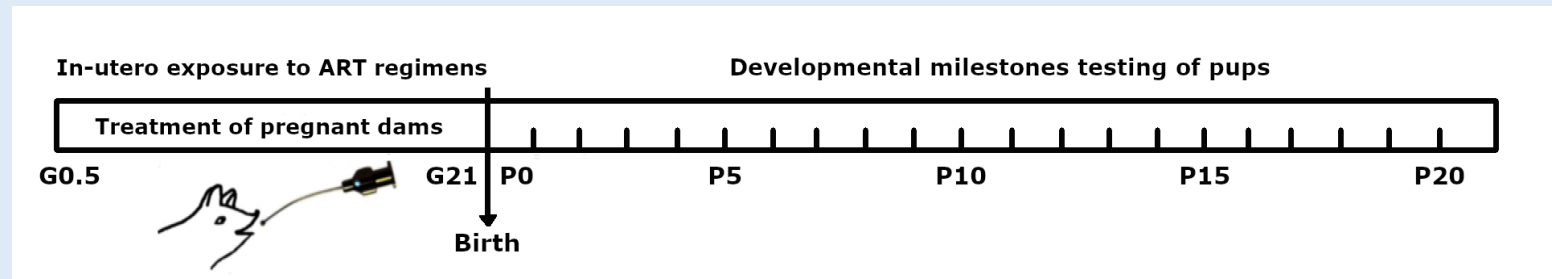
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# Abstract

**Introduction:** Antiretroviral therapy (ART) in pregnancy has dramatically reduced rates of HIV vertical transmission. Consequently, there is now a growing number of children who are born to mothers living with HIV, but are themselves not infected. Studies suggest that children exposed in-utero to ARTs may experience developmental delays compared to their peers. We investigated the effects of in-utero ART exposure on perinatal neurodevelopment in a mouse model, through assessment of **developmental milestones**. Developmental milestone tests (parallel to reflex testing in human infants) are reflective of brain maturity and are useful in predicting later behavioral outcomes.

**We hypothesized** that ART in pregnancy alters the in-utero environment for the developing fetal brain leading to altered developmental milestone outcomes in pups.

**Methods:** Pregnant dams were treated throughout pregnancy with boosted-atazanavir combined with either Kivexa (KVX); abacavir/lamivudine (ATV/r/ABC/3TC), or Truvada (TRV); tenofovir/emtricitabine (ATV/r/TDF/FTC), or water as control. Pups were assessed on a battery of tests for primitive reflexes from postnatal-day 1 (P1) to P21, including surface-righting, negative-geotaxis, cliff-aversion, rooting, ear-twitch, auditory-reflex, forelimb-grasp and air-righting, and for behaviors in the neonatal open field, and olfactory test.

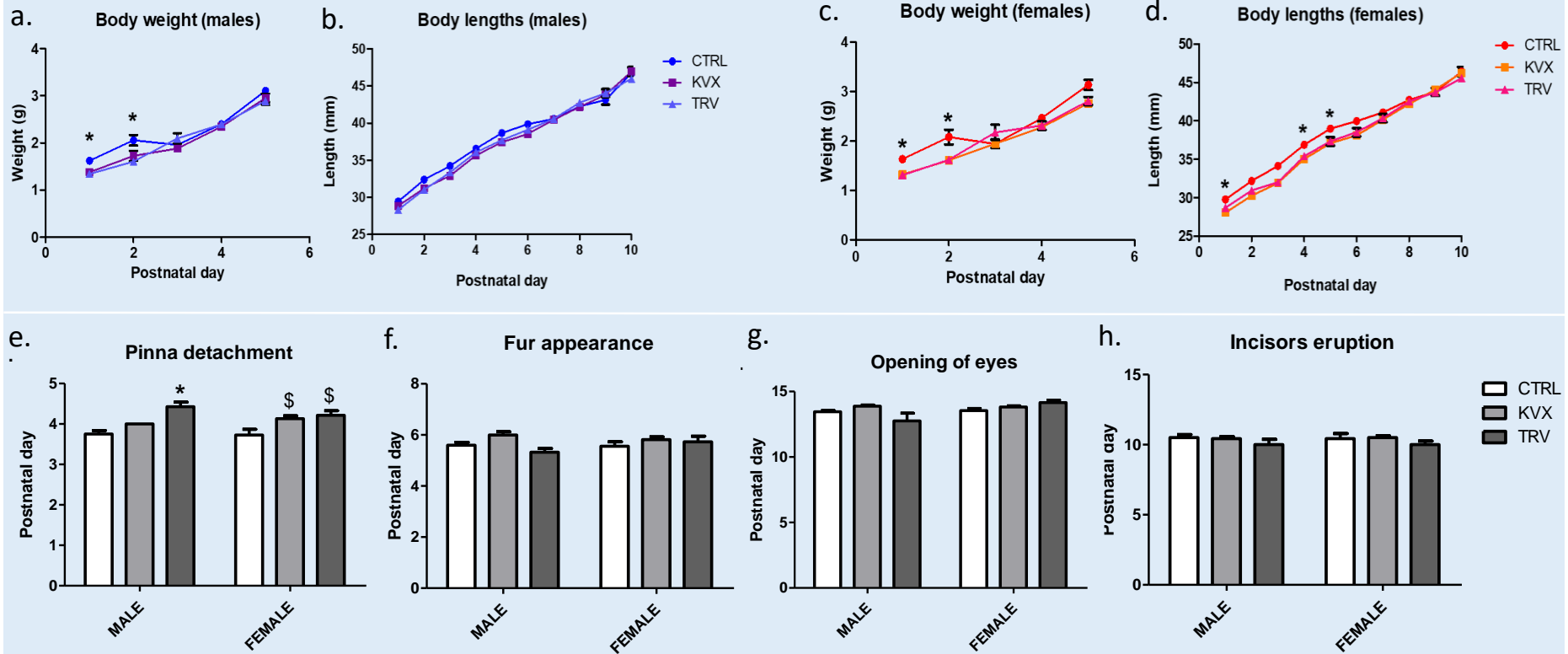


**Results:** In-utero exposure to either ART regimen significantly delayed development of negative geotaxis and cliff-aversion by 2 days compared to controls. Significant delays in development of the ear-twitch reflex and detachment of pinna were observed in the ATV/r/TDF/FTC-exposed group. Exposure to ATV/r/ABC/3TC was also associated with a deficit in olfactory response.

**Conclusions:** We show here that in-utero ART exposure delays the development of certain primitive reflexes, suggesting that ARTs could be disrupting the normal progress/maturation of the underlying neurocircuits. Our findings encourage further investigation for underlying mechanisms.

# Pups exposed in-utero to ATV/r/ABC/3TC (KVX) and ATV/r/TDF/FTC (TRV) are born small and weigh less for gestational age, and exhibit slower somatic development on certain measures

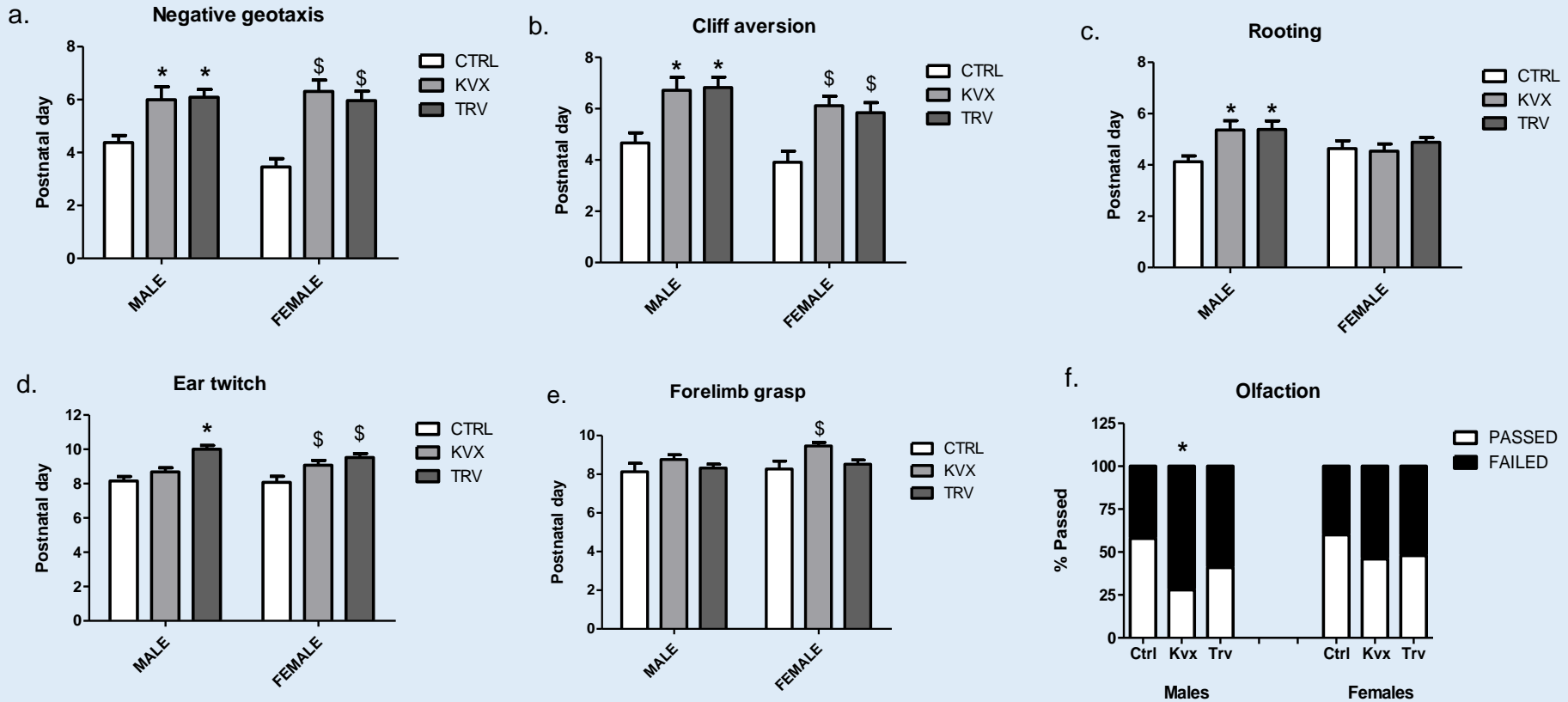
Fig. 1



**Fig 1.** Male and female pups exposed in-utero to ATV/r/ABC/3TC and ATV/r/TDF/FTC weighed significantly lower than controls on P1 and P2 (a, c). Body lengths of male pups were not different between groups across P21 (b). Body lengths of female pups exposed to ATV/r/ABC/3TC were significantly lower than that of controls on P1, P4 and P5 (d). Body lengths of female pups exposed to ATV/r/TDF/FTC were not different from that of controls across P21 (d). Exposure to ATV/r/TDF/FTC delayed pinna detachment in males and females (e). Exposure to ATV/r/ABC/3TC delayed pinna detachment in the females only (e). Fur appearance (f), opening of eyes (g) and incisors eruption (h) were not delayed in either sex by either treatment regimen. Data are mean  $\pm$  SEM (n = 11-34 pups/group). \* $p < 0.05$  compared to controls.  $\$p < 0.05$  compared to control females.

# In-utero exposure to ATV/r/ABC/3TC and ATV/r/TDF/FTC delays appearance of developmental milestones

Fig. 2



**Fig 2:** In-utero exposure to ATV/r/ABC/3TC and ATV/r/TDF/FTC significantly delayed the appearance of negative geotaxis (a) and cliff aversion (b) in male and female pups. Appearance of rooting reflex was delayed significantly in male pups exposed to either treatment regimens (c). Appearance of ear-twitch response was delayed by exposure to ATV/r/ABC/3TC in females (d) and by ATV/r/TDF/FTC in both male and female pups (d). Exposure to ATV/r/ABC/3TC significantly delayed fore-limb grasp in females (e) and disrupted olfaction in male pups (f). Data are mean  $\pm$  SEM (n = 11-34 pups/group). \* $p < 0.05$  compared to control males. \$ $p < 0.05$  compared to control females

### **Concluding remarks:**

Pups exposed in-utero to PI-based ART regimens:

- are born small and weigh less for their gestational age
- show delayed somatic development on certain measures
- demonstrate delayed appearance of several developmental milestones
- demonstrate olfactory deficits
- demonstrate deficits in development of reflexes that are dependent on somatosensory and vestibular pathways

### **Open questions:**

- What are the underlying molecular mechanisms for the observed delays and deficits?
- What are the long-term effects of developmental milestone delays on behavior?

### **Selected references:**

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### **Conflict of Interest Disclosure:**

We have no conflicts of interest