

**Progesterone level changes after cART  
exposure *in vitro* and *in vivo* are possibly linked  
to adverse birth outcomes**



IHPREG  
INTERDISCIPLINARY  
HIV PREGNANCY  
RESEARCH GROUP

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# Antiretroviral therapy in pregnancy

Increasing number of women getting pregnant while on ARVs

Safe for women, no birth defects in babies

**BUT**

low conception rate, miscarriage,  
small for gestational age, pre-term babies

Mechanism unknown

# HIV drugs influence sex steroids

PIs alter sex steroid hormone levels (contraceptive drugs!)

- Enzyme inhibition (CYP19A aromatase)
- Cholesterol metabolism

## Progesterone

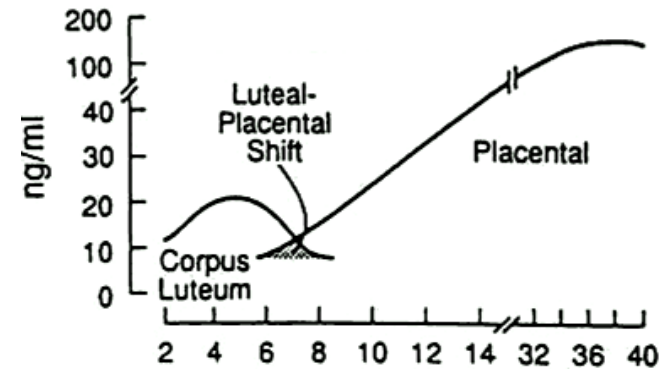
Needed to maintain pregnancy

- Proliferation of blood vessels
- Development of uterine lining, etc.

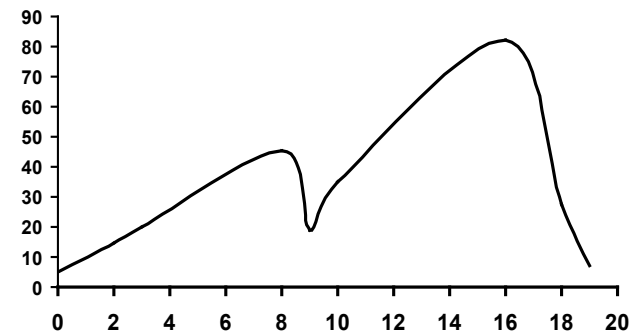
Synthesis:

- Ovaries (corpus luteum)
- Humans: placenta after week 8

**Decreased levels: low birth weight,  
preterm delivery**



Progesterone (ng/mL)  
in pregnant mice



# Questions

- Does PI-containing ART affect
  - Progesterone synthesis?
  - Rate of adverse birth outcomes?
  - Are adverse birth outcomes associated with progesterone level changes?

# 1. ART drugs effect on progesterone synthesis?

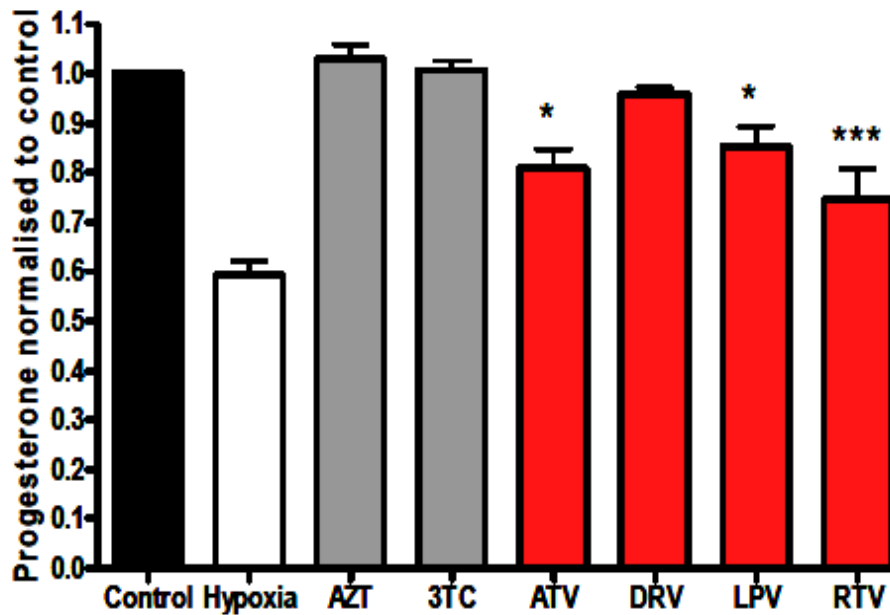
## **Cellular model:**

BeWo (human Chorioblastoma) cells

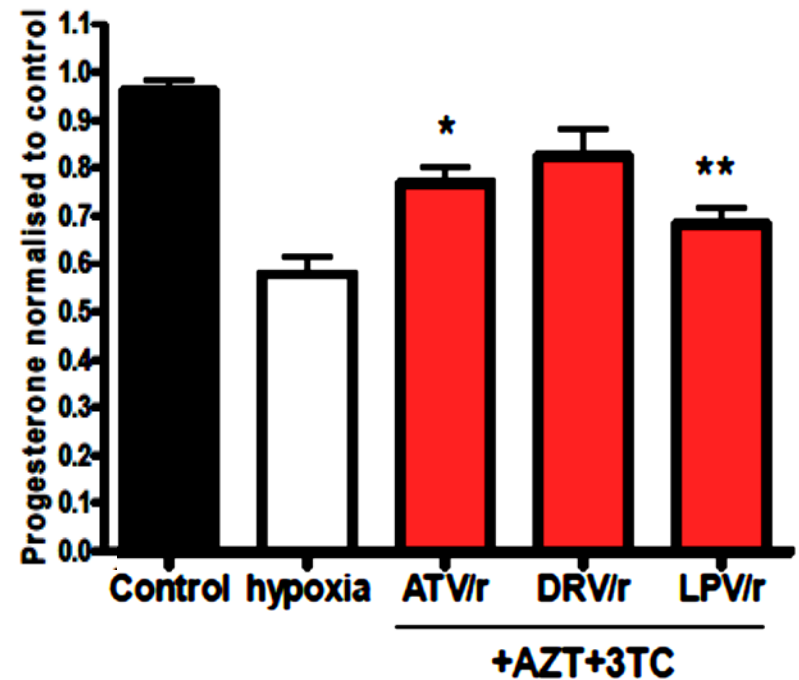
- Model for third trimester placenta
- Produces progesterone
  
- Exposed to human plasma equivalent levels
  - NRTIs: AZT, 3TC (Combivir)
  - PIs: LPV, DRV, ATV, RTV
  - Individually and in clinically relevant combinations
- Positive control: hypoxia (1% oxygen)
  
- Progesterone levels measured by immunoassay

# LPV, ATV, RTV inhibited progesterone production

## Individual drugs



## Combinations



# cART on birth outcomes and progesterone in pregnancy?

## **Mouse model:**

- C57 Black6 mice
- Pregnant, not infected
- Exposed to human-equivalent doses of cART:
  - Combivir+Kaletra
  - water control
- Followed throughout gestation Day 0- day 18

# Outcome measurements

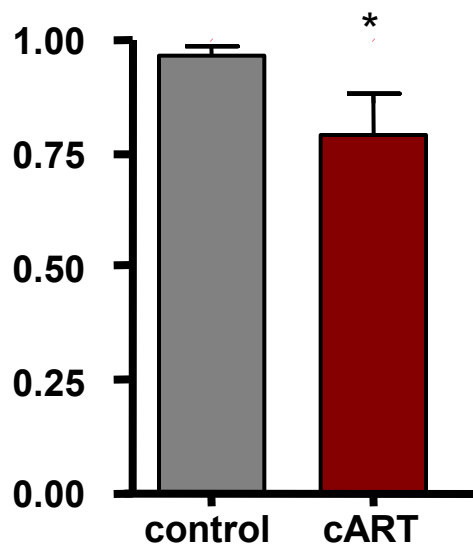
- Adverse events in pregnancy
  - pregnancy loss
  - fetal outcomes: viability, weight
  - placental weight: marker of placental development
- Progesterone levels in maternal blood (EIA)

Statistics: ANOVA, Pearson correlation

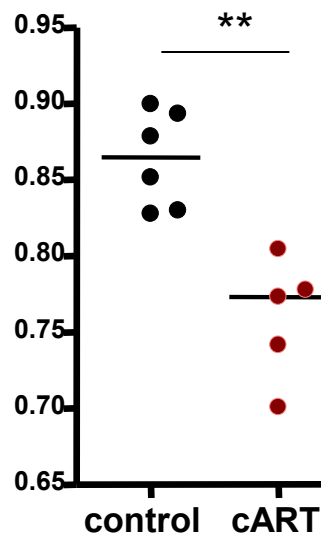


# Adverse pregnancy outcomes; fetal loss, lower fetal and placental weight

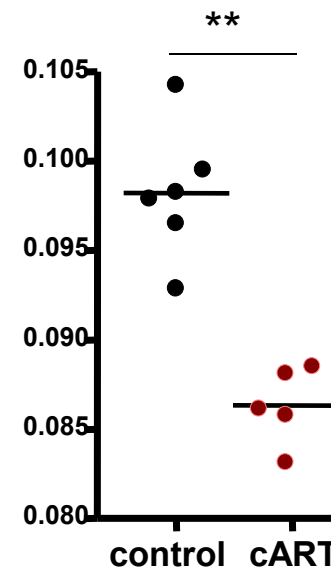
~30% increase in early pregnancy loss



Ratio of viable pups

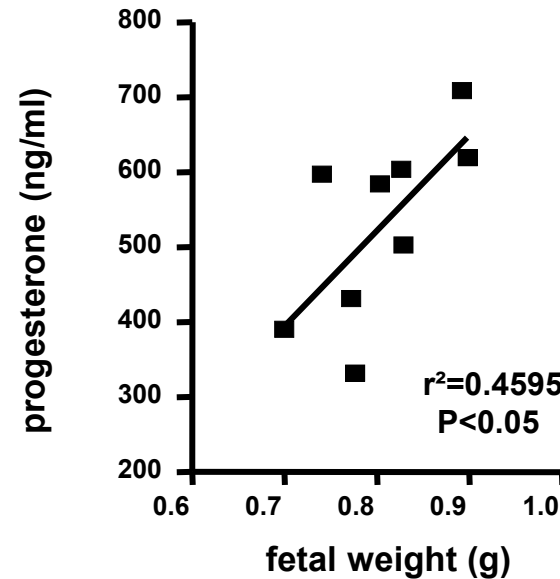
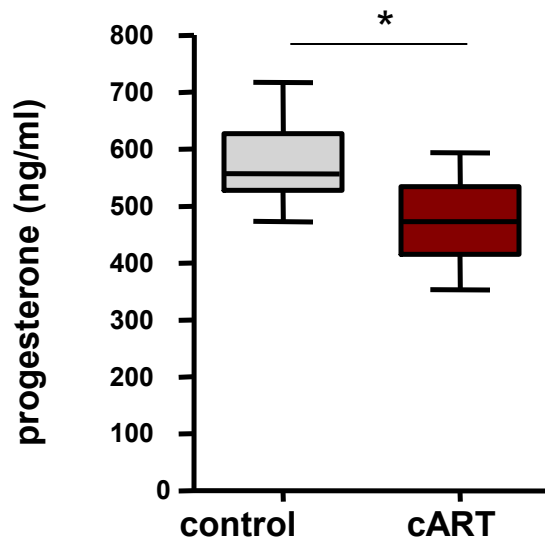


Fetal weight (g)



Placental weight (g)

# Lower progesterone levels after cART exposure - correlation with fetal weight



Placental weight decrease –PG independent

**Progesterone decreased, fetal and placental weight decreased  
Pregnancy loss and fetal death**

# Questions

- Does PI-containing ART affect
  - Progesterone synthesis? **YES**
  - Rate of adverse birth outcomes? **YES**
  - Are adverse birth outcomes associated with progesterone level changes? **YES – some of them**

# Adverse events: maternal or fetal effect?

Progesterone has dual role in pregnancy

1. Early phase (pre-implantation)

Preparing the maternal body: uterine lining development, build up blood supply

2. Later phase (post-implantation)

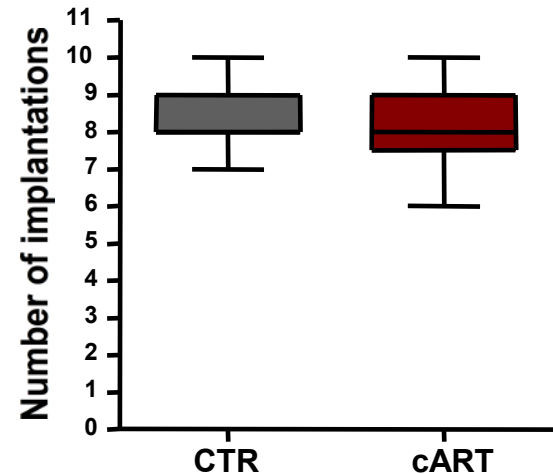
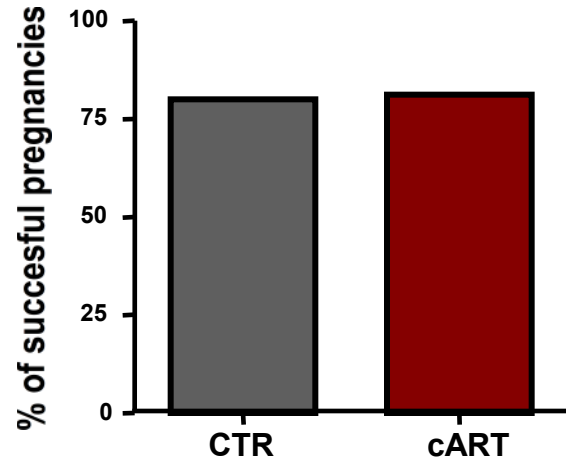
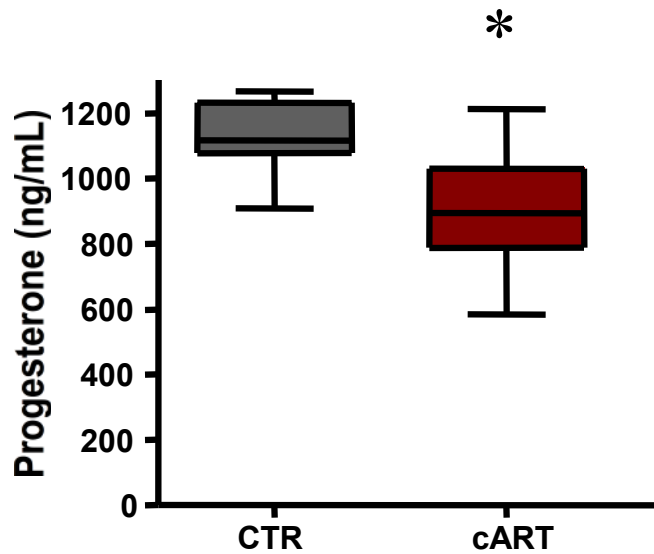
Direct effect on fetal and placental development

# Mouse model

Combivir+Kaletra or water

- Pre-implantation exposure: Day 0-6  
Outcomes: number of pregnancies, number of implantations/female, progesterone levels
- Post-implantation: Day 6-13  
Outcomes: number of pregnancies, number, weight of fetuses, placentae, progesterone levels

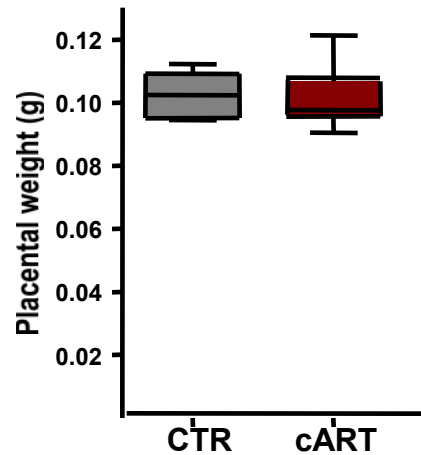
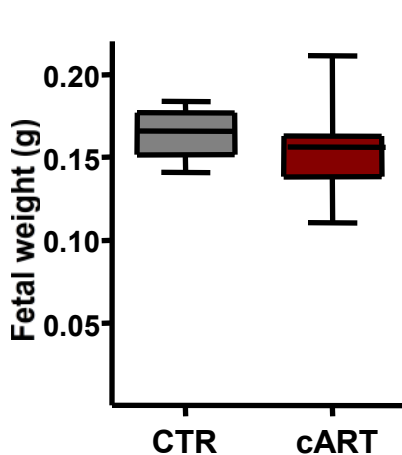
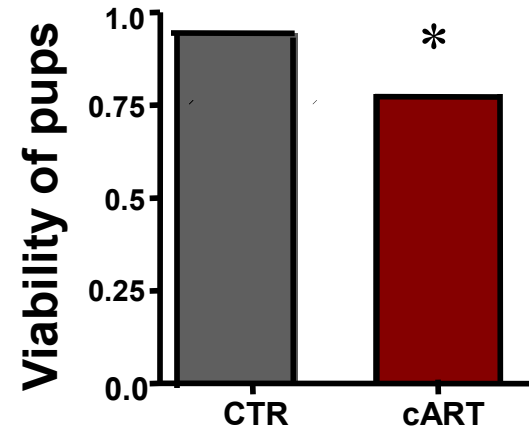
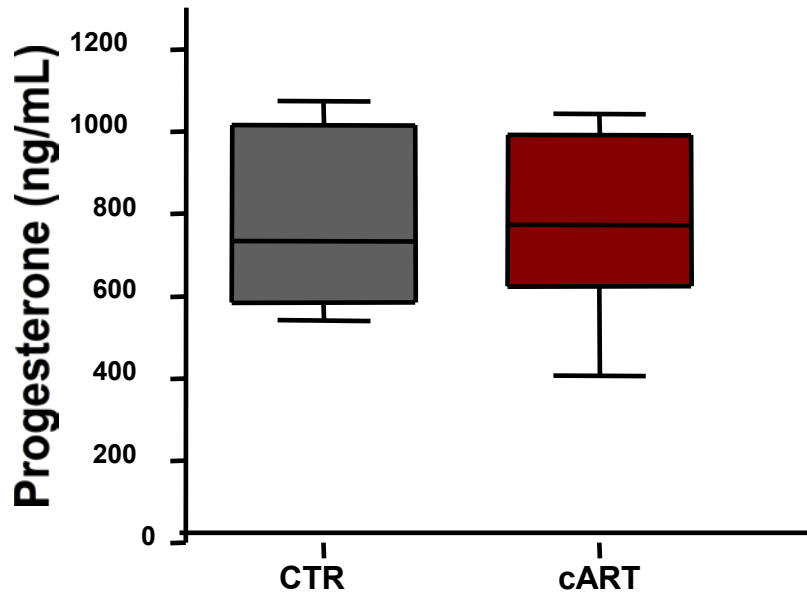
# 1. Pre-implantation period



Progesterone levels decreased

Number of successful pregnancies,  
implantation unaffected

## 2. Post-implantation period



- No change in progesterone levels
- Fetal and placental weight comparable to controls
- **But not viability**

# Summary

## ARV-associated adverse pregnancy outcomes

- 1. Progesterone-dependent mechanism:**  
Pre-implantation period seems crucial  
Fetal weight
- 2. Progesterone-independent mechanisms:**  
Direct drug effect on fetus  
Fetal viability



# Future plans

- Fate of implants exposed pre-implantation only
- Benefits of progesterone supplementation
- Compare different drug combinations
- Investigate correlations between progesterone levels and birth outcomes in humans – AAHP study participants

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