Pharmacokinetics, Pharmacodynamics and Safety of ARVs during Pregnancy

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Outline

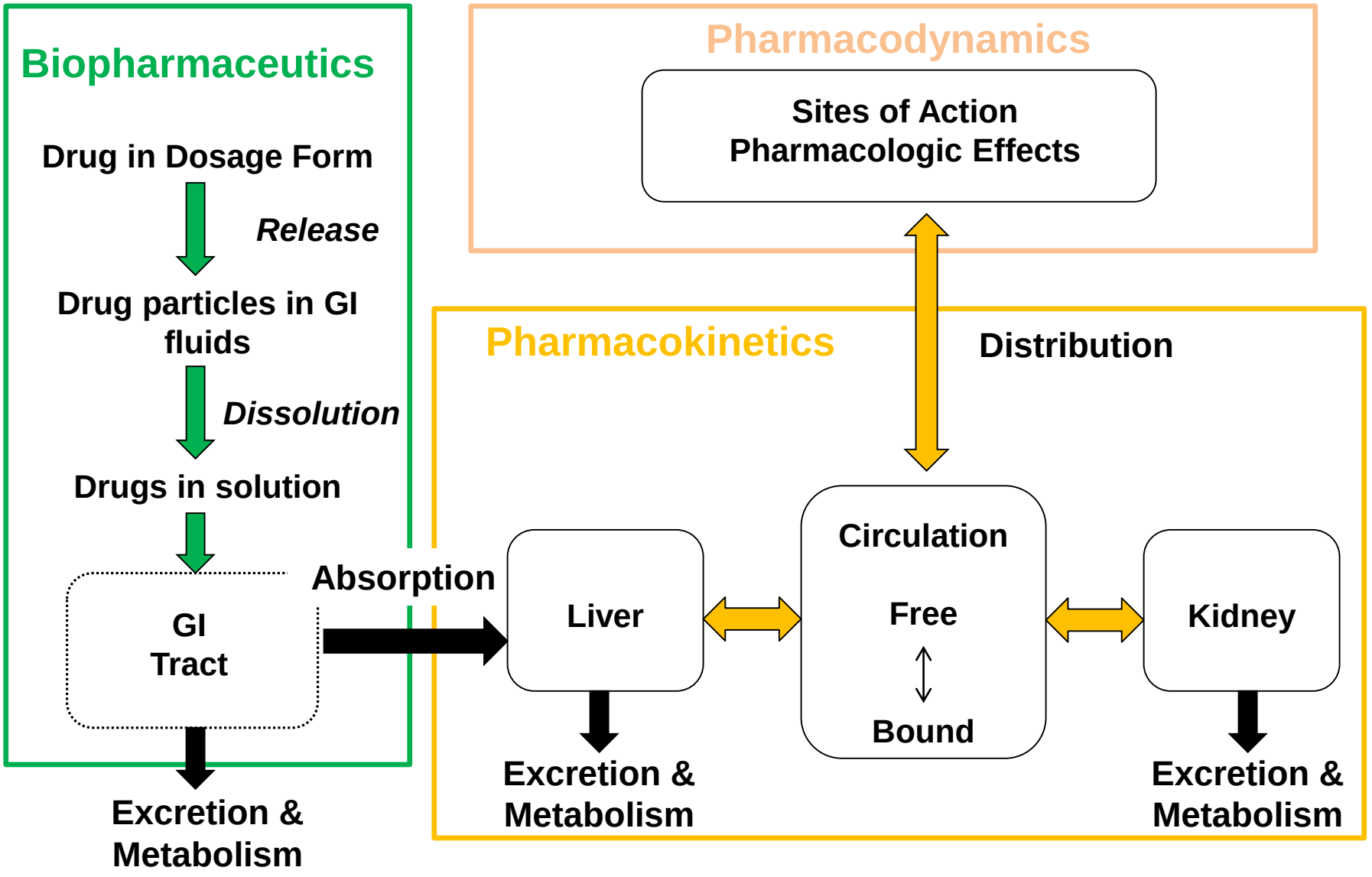
- Considerations in Pregnancy – Brief Review
- Summary of PK in Pregnancy Across Drug Classes
- Questions about Study Design in Pregnancy
- Infant Washout PK Studies
- Infant Safety & Additional Comments

Considerations for Therapy during Pregnancy

- Does the dose need to be altered?
- What are appropriate target exposures?
  - Are they different for the mother as compared to the fetus?
- Can we gather initial infant PK data?
- What are the effects on pregnancy outcomes?
- What is the potential for short or long-term toxic effects for the fetus/infant/child (if known)?

http://www.flickr.com/photos/21560098@N06/5772919213/

Overview: ADME



Drug Absorption & Distribution in Pregnancy

A

- Decreased GI motility = Delayed drug absorption and lower peak concentrations
- Nausea and vomiting may limit tolerability
- Food intake altered
  - high fat meals frequently necessary for optimal protease inhibitor absorption

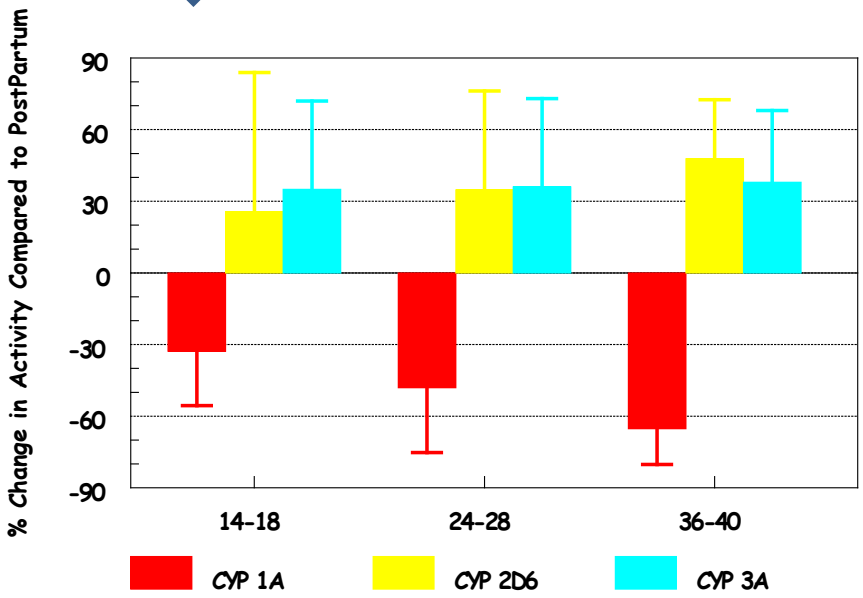
D

- Changes in body water, plasma volume and fat
  - Altered volume of distribution and peak plasma concentrations
- Protein binding changes
  - Increased free or unbound (active) drug
  - Increased clearance, lower total drug concentrations
- Transporter changes
  - Largely unknown

Drug Metabolism & Excretion in Pregnancy

M

- Metabolic activity may increase or decrease
  - ↑ CYP 2D6, 3A, 2C9, UGT 1A4
  - ↓ CYP 2C19



E

- Increased cardiac output, GFR, renal plasma flow
  - Increased elimination, lower trough concentrations for renally-cleared drugs
- Transporter changes
  - Largely unknown
  - Cholestasis in pregnancy may be result of changes in transport activity

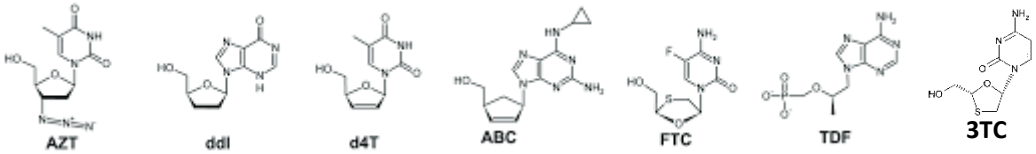
Tracy TS, Venkataramanan R, Glover DD, Caritis SN. Temporal changes in drug metabolism (CYP1A2, CYP2D6, and CYP3A activity) during pregnancy. Am J Ob Gyn 2005;192:633-9.

Table 1. PK of NRTIs in Pregnancy

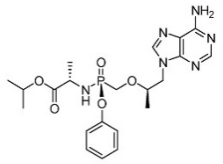
Drug Name	1° Elimination Pathway(s)	PK Disposition in Pregnancy	Dosing Recommendation	Cord / Maternal Ratios
Abacavir	UGT & Alcohol dehydrogenase	Insignificant changes	Standard doses	1.0
Didanosine	Renal (metabolites)	Not significantly altered	Standard doses	0.38
Emtricitabine	Renal (unchanged)	Exposure moderately lowered	Standard doses	1.2
Lamivudine	Renal (unchanged)	22% higher clearance	Standard doses	0.86
Stavudine	Renal (unchanged)	Similar to non-pregnant	Standard doses	1.0 – 1.3
Tenofovir alafenamide	Cathepsin B, CES1	???	???	???
Tenofovir disoproxil fumarate	Renal (unchanged)	20 – 40% lower exposure in pregnancy	Standard doses	0.6 – 1.03
Zidovudine	UGT2B7	Not significantly altered	Standard doses	0.8

Adapted from: Best BM. Clinical pharmacology of anti-infectives during pregnancy. In: Mattison DR, editor. Clinical Pharmacology during Pregnancy. London: Academic Press; 2013. p. 173 – 200. and Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf

NRTIs – Summary



- Generally higher clearance and lower exposure during pregnancy, but changes are small enough that they are not considered clinically important
  - Note: minimal CYP or UGT metabolism involved
- Active moiety, intracellular di- or tri-phosphates, have much longer half-lives; changes in plasma concentrations may not be as relevant for this drug class (but can be a rough surrogate)
- TAF – In progress, stay tuned…



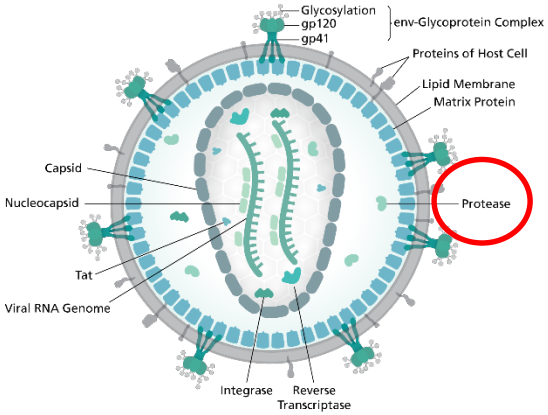
TAF (GS-7340)

Table 2. PK of PIs in Pregnancy

Drug Name	1° Elimination Pathway(s)	PK Disposition in Pregnancy	Dosing Recommendation	Cord / Maternal Ratios
ATV/rtv	CYP3A	↓ exposure	Boosted only; standard or increased doses	0.13 – 0.21
DRV/rtv	CYP3A	↓ exposure	BID only; standard doses	0.13 – 0.24
FPV/rtv	CYP3A	↓ exposure	Boosted & BID only; standard dose	0.24
IDV/rtv	CYP3A	↓ exposure	Boosted only; standard dose	0.12
LPV/rtv	CYP3A	↓ exposure, ↑ f_u	BID only; standard or increased	0.2
NFV	CYP3A, 2C19	↓ exposure	Standard dose	0.14
SQR/rtv	CYP3A	Older formulations: ↓ 500 mg tablet: ↔	Standard dose	0.0-0.3
TPV/rtv	CYP3A	No data	No data	0.4 – 1 case

Adapted from: Best BM. Clinical pharmacology of anti-infectives during pregnancy. In: Mattison DR, editor. Clinical Pharmacology during Pregnancy. London: Academic Press; 2013. p. 173 – 200. and Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lyguidelines/PerinatalGL.pdf

PIs – Summary



- Lower exposure during pregnancy
  - BID dosing recommended over QD
  - Highly protein bound: Increased free fraction may or may not overcome total exposure decreases
- PIs often alter activity of CYP, UGT, transporters
- Dosing depends on potency of agent, clinical factors of patients
- DRV/COBI & ATV/COBI…under study

Table 3. PK of NNRTIs & Enhancers in Pregnancy

Drug Name	1° Elimination Pathway(s)	PK Disposition in Pregnancy	Dosing Recommendation	Cord / Maternal Ratios
Efavirenz	CYP2B6, 3A	↓ exposure	Standard dose	0.49
Etravirine	CYP3A, 2C9, 2C19	↑ exposure	Standard dose	0.32 – 0.76
Nevirapine	CYP2B6, 3A & UGT	↔ or ↓exposure	Standard dose	0.60 – 1.02
Rilpivirine	CYP3A	↓ exposure	Individualize??	0.55 – 0.74
Ritonavir	CYP3A, 2D6	↓ exposure	Standard dose	0.05
Cobicistat	CYP3A	↓ exposure	?	0

Adapted from: Best BM. Clinical pharmacology of anti-infectives during pregnancy. In: Mattison DR, editor. Clinical Pharmacology during Pregnancy. London: Academic Press; 2013. p. 173 – 200. and Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf

NNRTIs & Pharmacoenhancers – Summary

- Each NNRTI behaves differently in pregnancy, consistent with the variety of metabolic pathways
  - Cannot generalize across class
  - Prediction becomes more difficult with more pathways involved (ETR)
- Ritonavir decreases moderately, similar to other PIs
  - Standard doses recommended, partly due to tolerability concerns
- Cobicistat – preliminary information suggests larger decreases during pregnancy

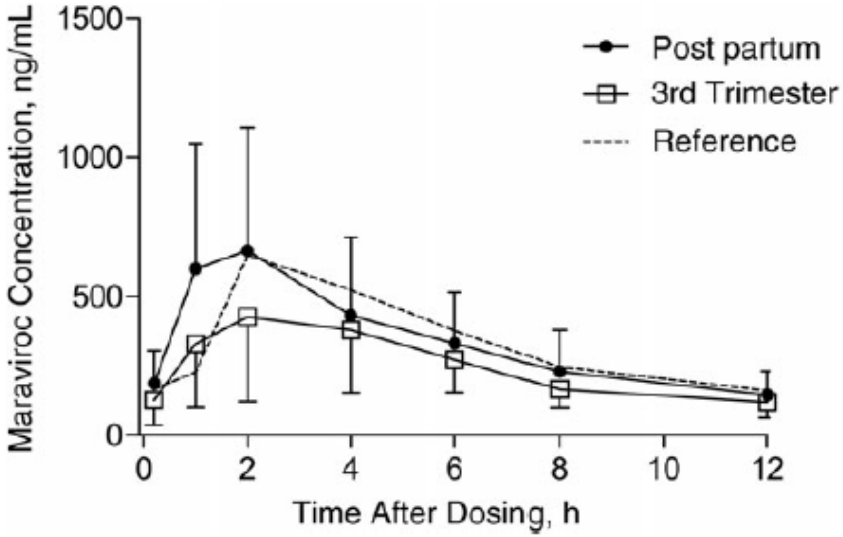
Table 4. PK of INSTIs, Entry/Fusion in Pregnancy

Drug Name	1° Elimination Pathway(s)	PK Disposition in Pregnancy	Dosing Recommendation	Cord / Maternal Ratios
Dolutegravir	UGT1A1	↓ compared to PP, still therapeutic	Standard dose	1.3
Elvitegravir	CYP3A	↓ exposure	??	1.0 – 1 case
Raltegravir	UGT1A1	↓ AUC; ↔ trough, highly variable	Standard dose	1.2 – 1.5
Enfuvirtide	Catabolism	No data	No data	minimal
Maraviroc	CYP3A	↓ exposure	Standard dose – adjusted for concomitant ARVs	0.33

Adapted from: Best BM. Clinical pharmacology of anti-infectives during pregnancy. In: Mattison DR, editor. Clinical Pharmacology during Pregnancy. London: Academic Press; 2013. p. 173 – 200. and Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf

INSTIs, Entry/Fusion Inhibitors – Summary

- For DTG and RAL (UGT 1A1) decreases in exposure during pregnancy compared to postpartum, but still therapeutic
- For EVG – substantial decreases
  - No class-specific effect
- MVC, similar decreased exposure as noted with PIs



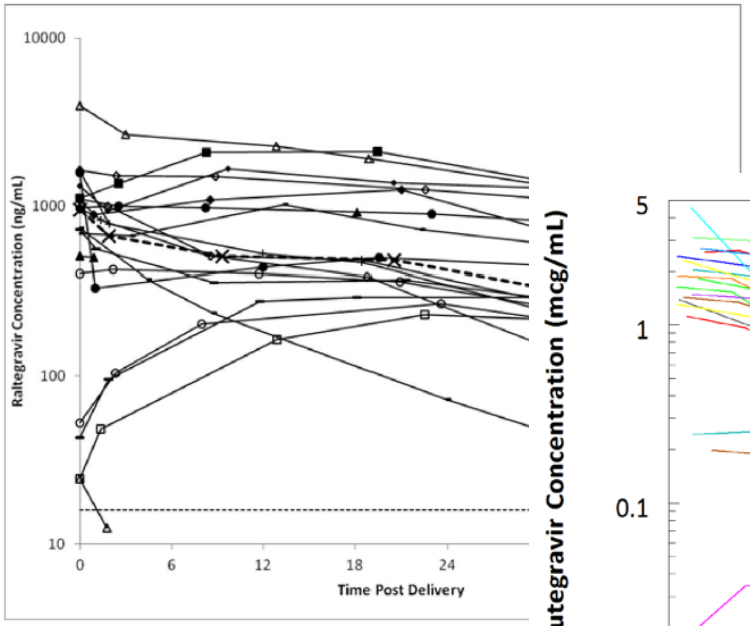
Colbers A et al. Clin Infect Dis. 2015 Nov 15;61(10):1582-9.

PK Conclusions Across Classes

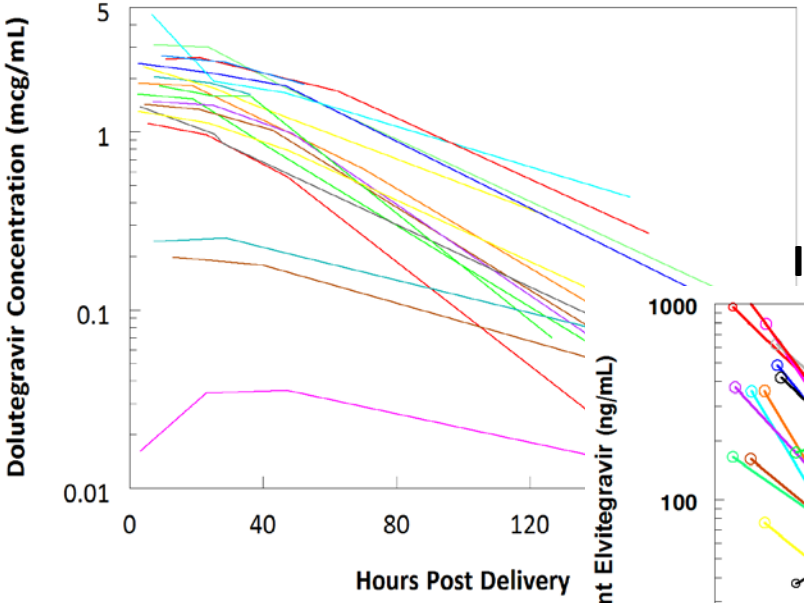
- Can we generalize across classes?
- Are all pharmacoenhancers created equal?
- Do we need to do PK studies for every new drug?
- Are opportunistic PK studies sufficient?
  - What about pharmacogenomics?
- When should efficacy studies be considered in pregnancy?
- Balance between optimal and feasible…

Are Infant Washout PK Data Useful?

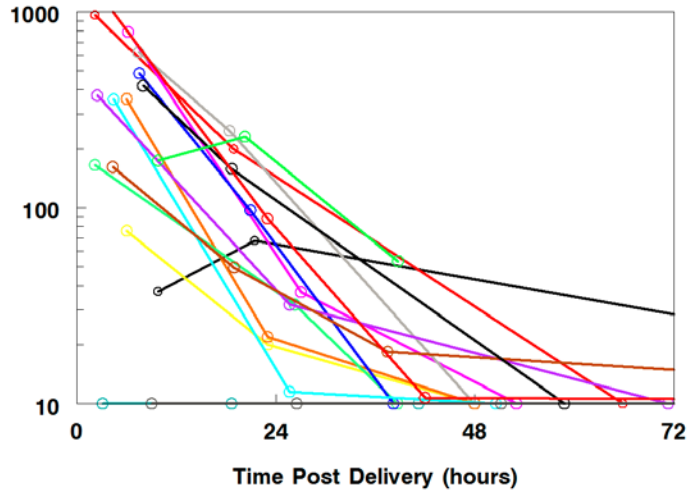
Infant Raltegravir



Infant Dolutegravir



Infant Elvitegravir



Clarke DF, et al. J Acquir Immune Defic Syndr. 2014 November 1; 67(3): 310–315.
Mulligan N et al. Poster and Themed Discussion at: CROI 2016; 2016 Feb 22 – 25; Boston, MA..
Best B, et al. Poster presented at: CROI 2017, 13-16 Feb 2017; Seattle, WA.

Safety: Pregnancy & Infant Outcomes

- In general, birth defect rate from women on ARVs is similar to rate in women not on ARVs
  - Some questions about EFV, TDF, ZDV, ATV
- ART (PIs, NNRTIs, NRTIs) may or may not increase risk of preterm delivery
  - Study results conflict; confounding is an issue
  - Data insufficient for INSTIs, Fusion/Entry Inhibitors
- Elective C-section may reduce infant infection, but not significantly in women who are suppressed/on ART – has other risks, decision must be individualized

Kennedy CE et al. Elective cesarean section for women living with HIV: a systematic review of risks and benefits. AIDS 2017 May 5, Epub.

Additional Comments

- Pharmacodynamics of ART for fetus:
  - Preventing transmission depends on control of maternal virus in systemic circulation and in genital tract; crossing the placenta for adequate pre-exposure prophylaxis in fetus; post-exposure prophylaxis for infant
  - Long-term risks of ARV exposure remain unclear
- Considerations Beyond Just PK and AEs:
  - Women taking INSTIs have lower mean fetal fraction (prenatal genetic test)
  - NIPT test may not be as effective in this population; more research is needed

Aziz A, et al "Detection of fetal fraction during noninvasive prenatal screening in HIV infected pregnant women" ACOG 2017; Abstract 21OP.

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