



# TRANSLATING DATA INTO DOSING RECOMMENDATIONS IN PREGNANCY

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## IMPORTANT NOTE:

- Pharmacokinetic (PK) data must be interpreted alongside all of the other pertinent information. PK studies (when available) cannot be evaluated in a vacuum.

# Strength of Evidence

- Most of the time, the data will be insufficient!
- How robust is the literature so far?
  - Preliminary analysis? Published?
  - Confirmatory studies?
- Sample size?
- Population studied?

<sup>1</sup>Cressey TR, et al. Br J Clin Pharmacol. 2013 Sep;76(3):475-83.

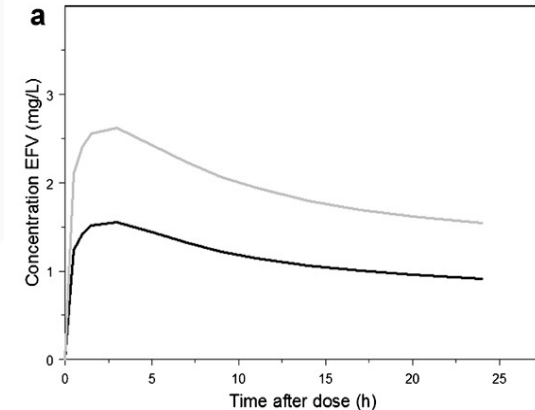
<sup>2</sup>Mulligan N, et al. AIDS. 2018 Mar 27;32(6):729-37.

<sup>3</sup>Bartelink IH, et al. J Clin Pharmacol. 2014 Feb;54(2):121-32.

## Median (Range) Body Weight in kg during Pregnancy and Postpartum

Time Point	Cressey TR <sup>1</sup>	Mulligan N <sup>2</sup>
2 <sup>nd</sup> Trimester	59.0 (48.0 - 84.0)	81.8 (46.8–138.5)
3 <sup>rd</sup> Trimester	60.5 (50.0 - 85.0)	84.9 (51.4–141.1)
Postpartum	55.0 (44.0 - 81.0)	79.2 (45.9 – 145)

## Efavirenz Concentrations during Pregnancy by Nutritional Status<sup>3</sup>



# Study Design

**TABLE IV**

*Proportionate decline of anticonvulsant levels in pregnancy*

AED	Total (%)	Free (%)
Carbamazepine	42***	28
Phenytoin	56***	31
Phenobarbital	55***	50***

\*\*\* Significantly different from baseline  $P \leq 0.005$ .

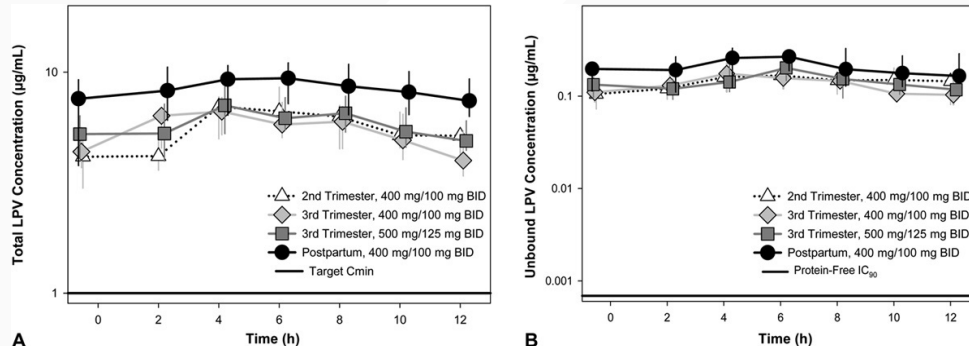


Table: Yerby MS, et al. Epilepsy Res 1990 Apr;5(3):223-8.

Figure: Patterson KB, et al. J Acquir Immune Defic Syndr 2013 May 1;63(1):51-8.

- Opportunistic or new start?
- Type of sampling?
  - Intensive? Sparse? TDM?
  - Absorption lag captured?
- Control group?
- For highly bound drugs, what was measured?

# Pharmacodynamics (Therapeutic Window)

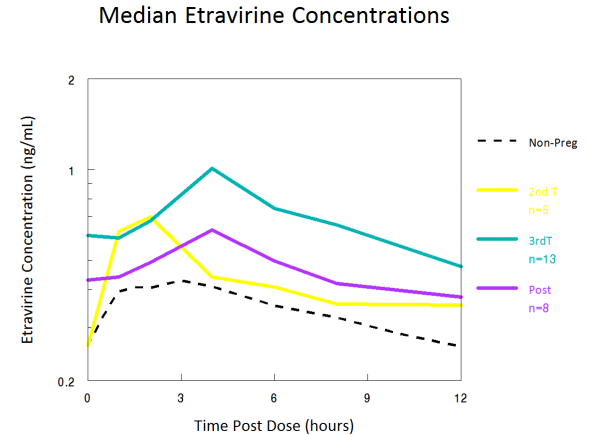
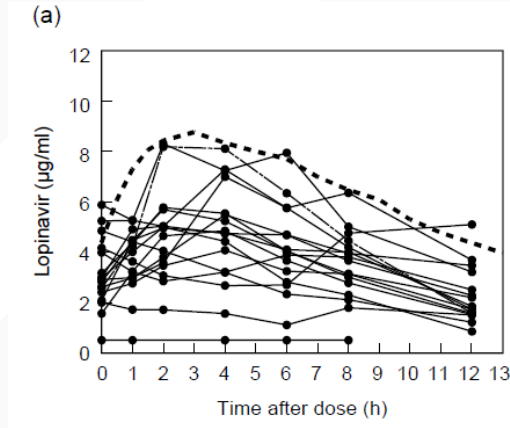
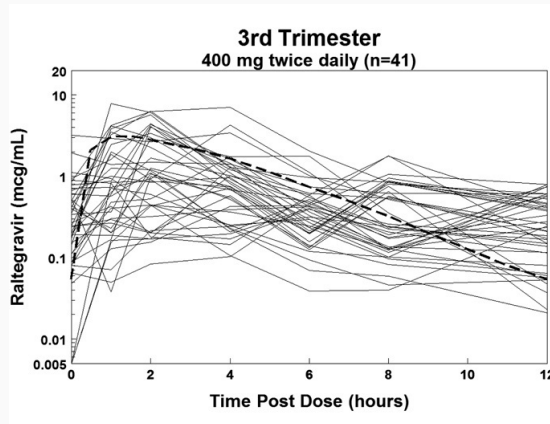
Parameter	Dolutegravir <sup>1</sup>	Elvitegravir <sup>2</sup>
AUC – 2T vs. PP	37% lower	24% lower
AUC – 3T vs. PP	29% lower	44% lower
Median Cmin	11-14 x ↑ than EC <sub>90</sub>	Below EC <sub>95</sub>

Is altered exposure clinically significant?

<sup>1</sup>Mulligan N, et al. AIDS. 2018 Mar 27;32(6):729-37.

<sup>2</sup>Momper JD, et al. AIDS. 2018;32:2507-16.

# Pharmacodynamics (Therapeutic Window)



Is altered exposure clinically significant & predictable?

What if a “therapeutic range” is undefined?

Raltegravir: Watts HD, et al. J Acquir Immun Defic Syndr. 2014;67(4):375-81.

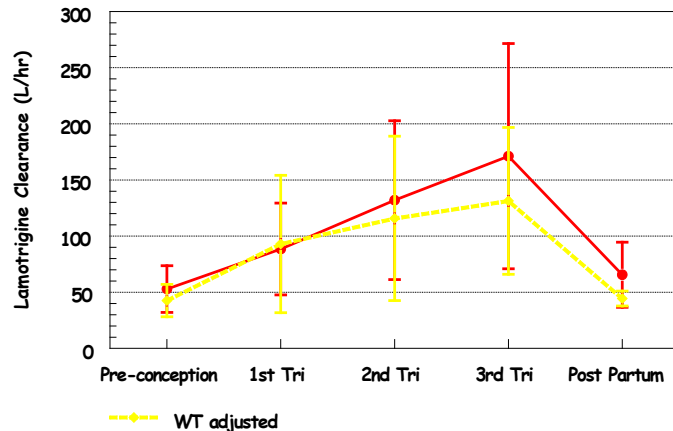
Lopinavir: Stek A, et al. AIDS. 2006;20:1931-9.

Etravirine: Mulligan N, et al. Front. Pharmacol. 2016;7:239.

TABLE V

*Period of pregnancy with greatest decline in anticonvulsant levels*

AED	Trimester	Percent total decline
CBZ total	3	52
free	3	83
PHT total	1	66
free	1	102
PB total	1	80
free	1	98



## Timing?

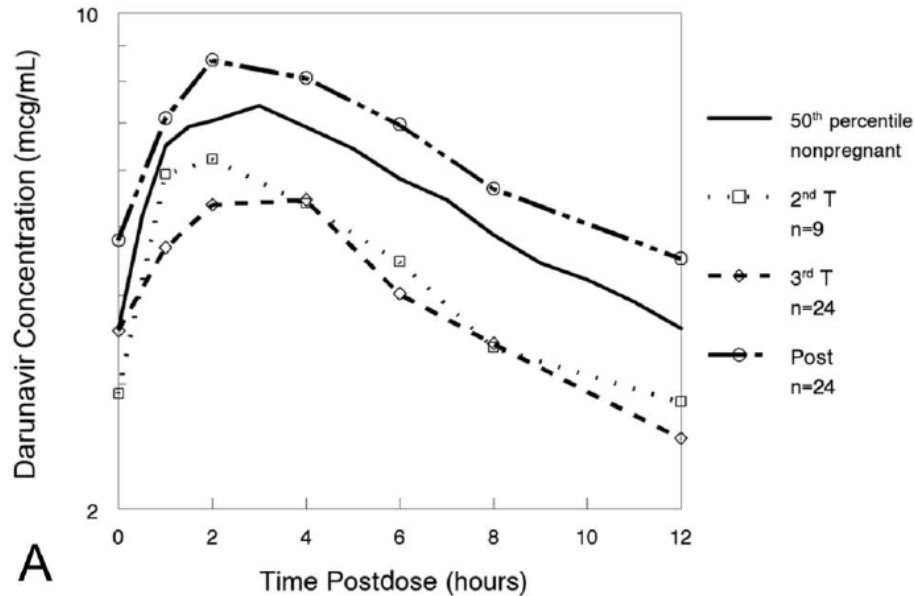
- When during pregnancy should you make a dose or regimen change?
- When should you change back?
- Integrate postpartum physiology knowledge along with lactation considerations

Yerby MS, et al. Epilepsy Res 1990 Apr;5(3):223-8.

Pennell PB, et al. Neurology 2004;62:292-5.

# Practicalities

## INCREASED Dose during Pregnancy vs. Standard Dose Postpartum



- Can the dose actually be altered?
- What is the risk of non-adherence?
- Any data for the altered dose?





# Pros/Cons of Dose Changes

- Potential repercussions of being too low or too high?
  - Bad toxicity to avoid?
  - Impact on disease progression?
  - Higher risk for bad pregnancy outcomes?
- Risks of changing therapy mid-pregnancy?
- Option for increased monitoring?
  - Could a rapid change be implemented?



# Alternatives, What to Recommend?

- Cannot recommend an altered dose until we STUDY that altered dose...
- Alternatives to recommend aside from dose changes:
  - What other treatment options are available?
  - How interchangeable are they?
  - Availability of other agents? Cost? Tolerability? Storage requirements?
- Dose recommendations DEPEND on the circumstances:
  - New start?
  - Already on and tolerating?
  - Pre-conception?
  - Current agent not well-tolerated or not working optimally?

# What Gets Into the Label?

## 2.5 Dosage Recommendations in Pregnancy

Administer 400/100 mg of KALETRA twice daily in pregnant patients with no documented lopinavir-associated resistance substitutions.

- Once daily KALETRA dosing is not recommended in pregnancy [*see Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)*].
- There are insufficient data to recommend dosing in pregnant women with any documented lopinavir-associated resistance substitutions.
- No dosage adjustment of KALETRA is required for patients during the postpartum period.
- Avoid use of KALETRA oral solution in pregnant women [*see Use in Specific Populations (8.1)*].

### Pregnancy

The  $C_{12h}$  values of lopinavir were lower during the second and third trimester by approximately 40% as compared to post-partum in 12 HIV-infected pregnant women received KALETRA 400 mg/100 mg twice daily. Yet this decrease is not considered clinically relevant in patients with no documented KALETRA-associated resistance substitutions receiving 400 mg/100 mg twice daily [*see Use in Specific Populations (8.1)*].

- While not a requirement, often only company-sponsored studies are included in prescribing information (Example: Lopinavir/ritonavir)
- Ability to adequately assess data quality is important (meet data standards)

- Label: 1 study, n=12, naïve only
- Treatment Guidelines: > 15 studies, hundreds of patients, including PK of increased doses, unbound concentrations, treatment naïve & experienced, influence of covariates (race, weight) lactation information, and even a randomized efficacy study in pregnancy



# THANK YOU!