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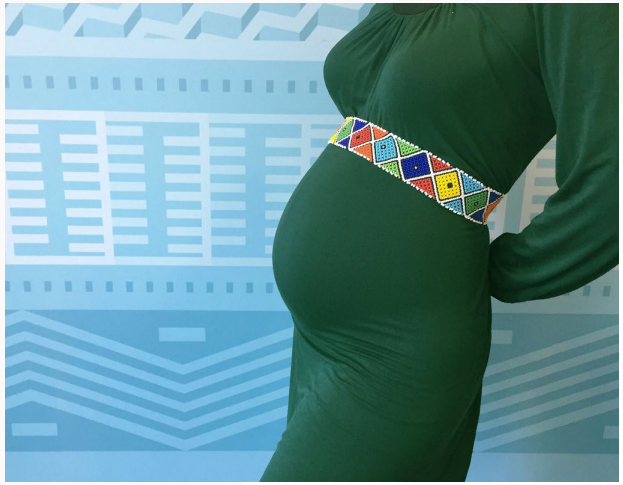

TRANSLATING DATA INTO DOSING RECOMMENDATIONS IN PREGNANCY

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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.

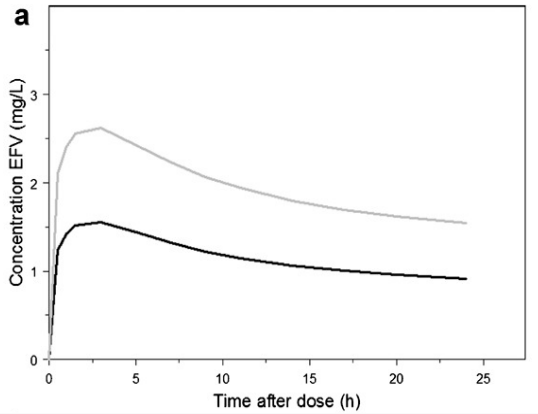
Strength of Evidence

- 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?

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

Time Point	Cressey TR[1]	Mulligan N[2]
2nd Trimester	59.0 (48.0 - 84.0)	81.8 (46.8–138.5)
3rd 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[3]



[1]Cressey TR, et al. Br J Clin Pharmacol. 2013 Sep;76(3):475-83.
[2]Mulligan N, et al. AIDS. 2018 Mar 27;32(6):729-37.
[3]Bartelink IH, et al. J Clin Pharmacol. 2014 Feb;54(2):121-32.

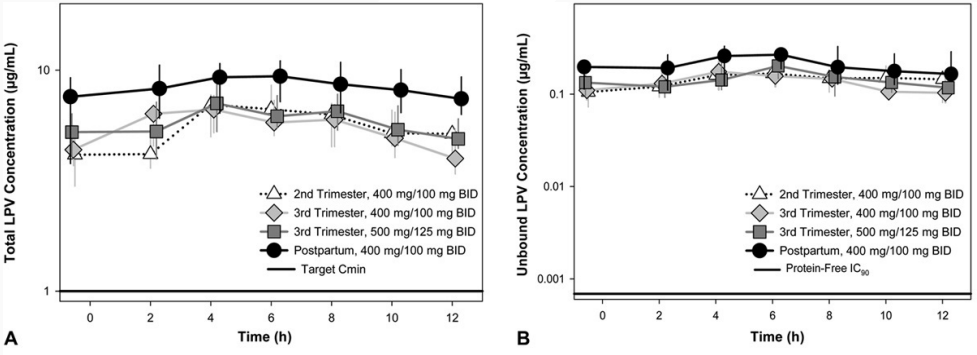
Study Design

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 $P \leq 0.005$.



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

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.

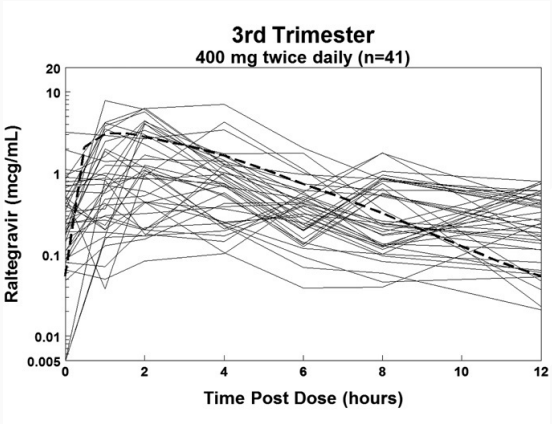
Pharmacodynamics (Therapeutic Window)

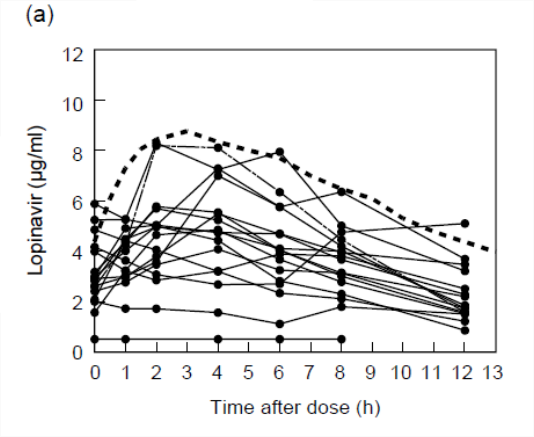
Parameter	Dolutegravir[1]	Elvitegravir[2]
AUC – 2T vs. PP	37% lower	24% lower
AUC – 3T vs. PP	29% lower	44% lower
Median Cmin	11-14 x ↑ than EC_{90}	Below EC_{95}

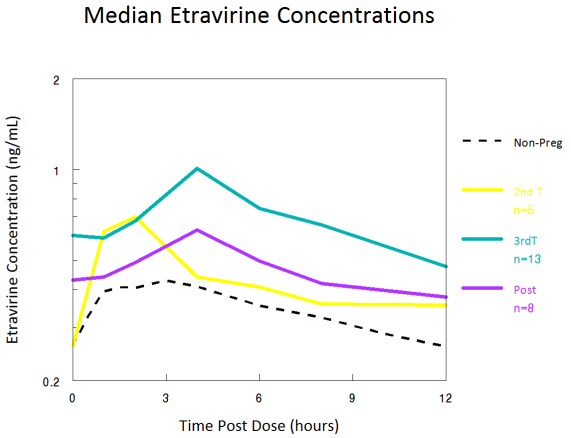
Is altered exposure clinically significant?

[1]Mulligan N, et al. AIDS. 2018 Mar 27;32(6):729-37.
[2]Momper JD, et al. AIDS. 2018;32:2507-16.

Pharmacodynamics (Therapeutic Window)







Is altered exposure clinically significant & predictable?

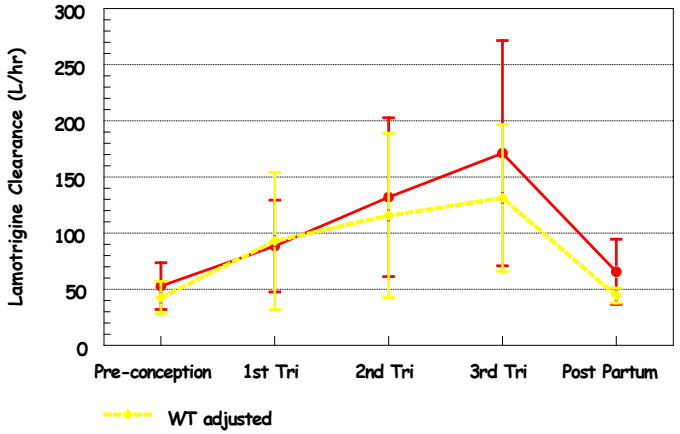
What if a “therapeutic range” is undefined?

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



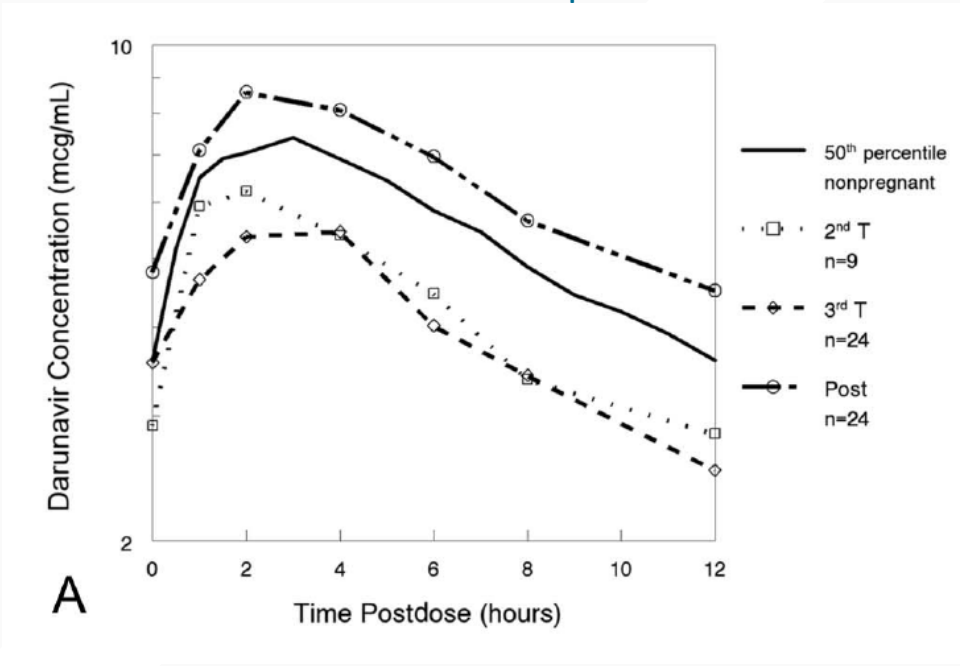
Timing?

- 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



Eke AC, et al. J Acquir Immun Defic Syndr. 2020 Apr 1;83(4):373-80.

- 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)]*.

- 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

- 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)


THANK YOU!
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