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

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Cressey TR(^1)</th>
<th>Mulligan N(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2(^{nd}) Trimester</td>
<td>59.0 (48.0 - 84.0)</td>
<td>81.8 (46.8–138.5)</td>
</tr>
<tr>
<td>3(^{rd}) Trimester</td>
<td>60.5 (50.0 - 85.0)</td>
<td>84.9 (51.4–141.1)</td>
</tr>
<tr>
<td>Postpartum</td>
<td>55.0 (44.0 - 81.0)</td>
<td>79.2 (45.9 – 145)</td>
</tr>
</tbody>
</table>

Efavirenz Concentrations during Pregnancy by Nutritional Status\(^3\)

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Study Design

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

### Table IV

**Proportionate decline of anticonvulsant levels in pregnancy**

<table>
<thead>
<tr>
<th>AED</th>
<th>Total (%)</th>
<th>Free (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>42***</td>
<td>28</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>56***</td>
<td>31</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>55***</td>
<td>50***</td>
</tr>
</tbody>
</table>

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


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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dolutegravir&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Elvitegravir&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC – 2T vs. PP</td>
<td>37% lower</td>
<td>24% lower</td>
</tr>
<tr>
<td>AUC – 3T vs. PP</td>
<td>29% lower</td>
<td>44% lower</td>
</tr>
<tr>
<td>Median Cmin</td>
<td>11-14 x ↑ than EC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>Below EC&lt;sub&gt;95&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

Is altered exposure clinically significant?

<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?


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

Practicalities

- 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?
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 C12h 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!