

Pharmacology

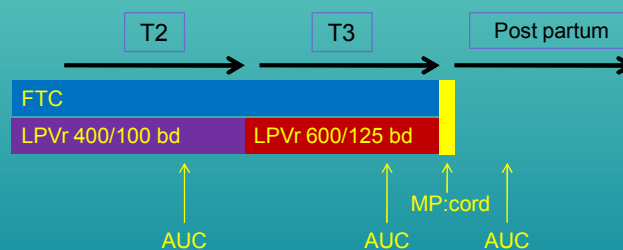
- PK in pregnancy
- Drug interactions
- New formulations
- Odds & Sods

PK in pregnancy – Optimal dosing of LPVr

#628 Bouillon Pichault et al. Population PK in pregnant women showed that 400/100 is enough to reach levels > 1000 ng/mL for naïve patients but may not be sufficient in PI-pre-treated pregnant women

#629 PACTG 1026 (Best et al)

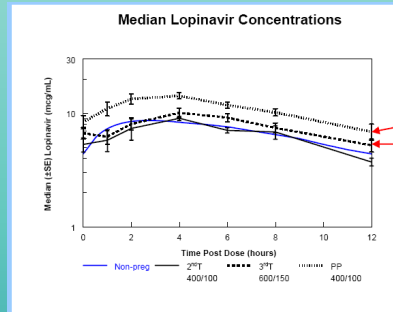
Prospective open label study of LPVr tablets in pregnant mums (n=21)
Dose escalation in 3rd trimester to iii tablets bd



Results

- LPV/r 600/150 mg BID (n=21) provided adequate exposure during the 3rd trimester;

- FTC 200 mg OD (n=18) was 12% lower than postpartum



Standard, Post partum
High dose, 3rd trimester

PK in Pregnancy – Safety of ATVr

#624 AI 424182

- Relative to data in non-pregnant historical controls, ATV AUC and C_{min} in the 3rd trimester were **reduced by 40% and 21%**
- All women had an ATV C_{min} > 150 ng/mL
- Ritonavir concentrations were also reduced
- 4 week postpartum data suggest that ATV PK remains different from the non-pregnant state (evaluation at 8 wks planned)
- **Increasing ATV/r dose to 400/100 mg OD indicated (planned)**
- Good tolerability and no drug-related discontinuations
- No evidence of pathologic neonatal jaundice and no medical intervention required, consistent with Ripamonti et al. (n = 17), and Natha et al. (n = 26), CROI 2007
- All 10 infants had negative HIV DNA PCR at birth

ATV in pregnancy: impact on neonatal hyperbilirubinemia

- Retrospective single centre cohort study, n = 9 (including 1 twin pair)
- Fetal unconjugated hyperbilirubinemia correlated to maternal bilirubin plasma concentration at delivery, suggesting placental transfer of unconjugated bilirubin
- Hyperbilirubinemia in the neonates was not sufficient to be harmful
- [ATV] in neonatal cord blood were within therapeutic levels, confirming previously described placental transfer (Ripamonti et al. CROI 2007)

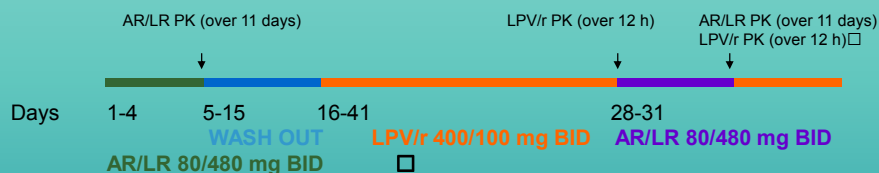
Ferreira et al. # 625

Pharmacology

- PK in pregnancy
- **Drug interactions**
- New formulations
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Drug interactions between antimalarials and LPV/r in H.V.

- Coartem (artemeter/lumefantrine, AR/LR) is used in > 60 countries
- AR and LR metabolized by CYP3A4; AR induces CYP3A4 and LR inhibits CYP2D6



| Analyte | GM 95% CI | AR/LR | AR/LR + LPV/r | Mean % change | p value |
|-----------|---------------------------------------|------------------------|------------------------|---------------|---------|
| LR (n=10) | C_{max} ($\mu\text{g/mL}$) | 12.5 (9.1-17.2) | 17.4 (9.8-30.7) | 82% | 0.1141 |
| | C_{last} ($\mu\text{g/mL}$) | 0.29 (0.22-0.39) | 0.92 (0.52-1.63) | 298% | 0.0051 |
| | AUC ($\mu\text{g}\cdot\text{h/mL}$) | 440.7 (333.6-582.1) | 1035.5 (589.2-1820) | 193% | 0.0069 |

- Safe; LPV and r unchanged; AR concentrations pending

German et al. # 132

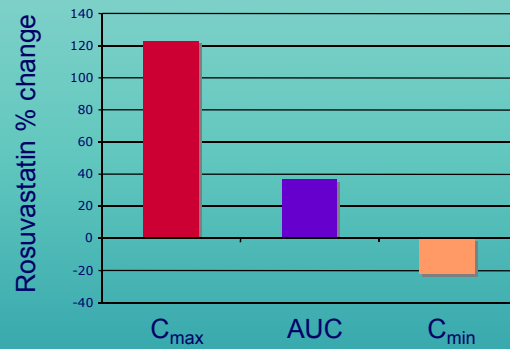
LPV/r 500/125 mg BID + EFV approximate the PK exposure of LPV/r 400/100 mg BID administered alone in H.V.

| LPV/r + EFV vs. LPV/r alone | C_{max} ($\mu\text{g/mL}$) | AUC ₁₂ ($\mu\text{g}\cdot\text{h/mL}$) | C_{0h} ($\mu\text{g/mL}$) |
|-----------------------------|--------------------------------|---|-------------------------------|
| Test | 13.49 | 113.16 | 6.46 |
| Reference | 12.04 | 106.80 | 6.77 |
| T/R | 1.121 | 1.060 | 0.954 |
| 90% CI | 1.023 to 1.228 | 0.956 to 1.174 | 0.822 to 1.108 |

RTV C_{max} , AUC₁₂ and C_{0h} were 26%, 20%, and 11% higher when LPV/r was given at 500/125 mg BID with EFV

Ng et al. # 765

PK interaction between TPV/r and rosuvastatin



- TPV/r administered 500/200 mg BID to 29 H.V. for 11 days (days 3-13) and rosuvastatin as a 10 mg single dose on days 1 and 12
- Initial rosuvastatin dose with TPV/r should be 5 mg

Paul et al. # 767

Pharmacology

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Increased LPV concentrations on OD tablets compared with capsules or liquid formulations

#766 CCTG 585

open label, crossover, randomised
LPVr 800/100 od (n=17), stable on therapy

tabs vs capsules (liq vs capsules comparable)

AUC ↑ 20% (P<0.05)

Cmin ↑ 130% (P<0.05)

- Within-subject LPV exposures generally higher with the tablet
- Cmin/IC₅₀ ratio of OD tablets similar to that seen historically with BID capsule dosing, however median Cmin are lower and variability is very high

Figure 1a. Lopinavir Concentrations (Median ± IQR) Over Time

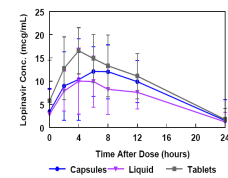
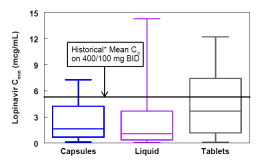


Figure 3a. Lopinavir C_{min} by Formulation



| | Capsules | Liquid | Tablets |
|-----------------------|----------|---------|---------|
| # (%) Cmin <1000ng/mL | 5 (29%) | 8 (47%) | 3 (18%) |
| Cmin/IC ₅₀ | 25 | 20 | 46 |

Long-acting TMC278, a preteral depot formulation delivering therapeutic NNRTI concentrations in preclinical and clinical settings

- Studied in 48 H.V. at 200, 400, and 600 mg administered im and sc
- Long-acting TMC278 may be a useful depot formulation since single dose gave prolonged exposure to TMC278 for several months and was well tolerated, particularly when administered im

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MVC PK in blood plasma and genital tract fluid and tissue in healthy female volunteers

| Parameters | Day 1* | | Day 7* | | |
|----------------------|------------|--------------------|------------|--------------------|-------------|
| | BP | CVF | BP | CVF | VTB*** |
| C_{max} (ng/mL) | 584 (259) | 813 (559) | 662 (242) | 1452 (1361) | 781 |
| T_{max} (h)** | 2 (1-3) | 6 (4-12) | 3 (1-4) | 6 (0-12) | 4 |
| AUC_0 (ng.h/mL) | 1991 (518) | 4655 (3661) | 2648 (798) | 9629 (7819) | 4992 |

Mean (SD)

*n = 10-12

**Median (range)

***Vaginal tissue biopsy units: ng/gm and ng.h/gm

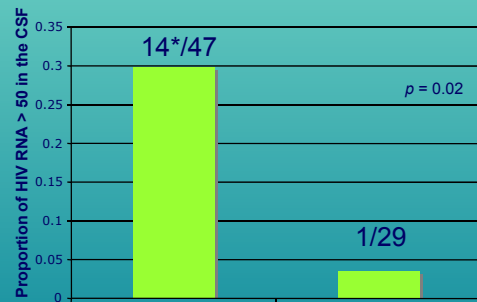
- Day 7 AUC CVF:BP = 3.9
- High variability
- Does MVC has the potential to be studied as an oral agent for HIV prophylaxis?

Dumond et al. # 135LB

Low [TFV] in CSF

- Single random plasma and CSF samples drawn within an hour from each other to determine TFV CNS penetration in HIV-pts (n = 187); time post-dose 12.3 h

| Plasma [TFV] ng/mL range | CSF [TFV] ng/mL range | CSF/plasma ratio (IQR) |
|--------------------------|-----------------------|-------------------------|
| <1 - 860 | <1 - 38.5 | 0.05 (0.02-0.20) |

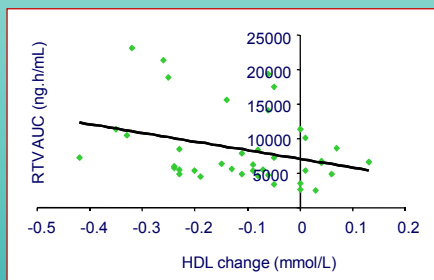


- Weak correlation between CSF and plasma [TFV]
- Results cannot be extrapolated for other compartments
- Brain concentrations not measured

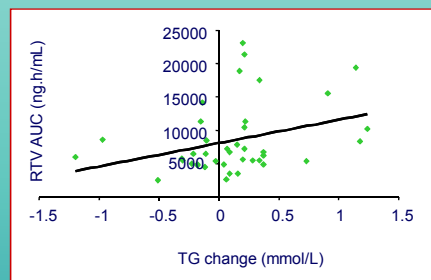
*12/14 plasma HIV RNA < 50

Best et al. # 131

Plasma exposure of 100 mg OD and Twice BID decreases HDL and CD36 expression but only BID increases triglycerides: potential impact of RTV on cardiovascular disease



Correlation between RTV AUC and decrease in HDL



Correlation between RTV AUC and increase in TG

Conclusions

- 100 mg BID RTV but not 100 mg OD RTV was associated with an increase in TG over 2 weeks in H.V.
- HDL and TG changes correlated with RTV plasma exposure
- Reduced HDL and CD36 expression were observed for both RTV dosages

Boffito et al. # 930