Impact of efavirenz and nevirapine on pharmacokinetics of lopinavir/ritonavir as capsules and tablets in African patients

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on behalf of the **DART** Trial Team

Background – LPV/r & NNRTI

	Kaletra® capsules (133/33 mg)	Aluvia® tablets (200/50 mg)
Without NNRTI	400/100mg (3 caps) BD	400/100mg (2 tabs) BD
With NNRTI	consider 533/133mg (4 caps) BD	OPTIONS 400/100mg (2 tabs) BD 600/150mg (3 tabs) BD

Previous recommendations

- USPI: 400/100mg BD, but consider 600/150 mg BD if decreased LPV/r susceptibility suspected
- Prior SPC: 600/150 mg BD + close monitoring

Background – LPV/r & NNRTI

- In healthy volunteers, compared to LPV/r 400/100 mg (2 tablets) BD alone, administering LPV/r with EFV at the following doses led to

  - 400/100 (2 tabs) BD:
    decrease in LPV AUC_{12} by 20% and C_{trough} by 27%[1]

  - 600/150 (3 tabs) BD:
    increase in LPV AUC_{12} and C_{trough} by 36%[2]

1 Klein, Glasgow 2006, #366

2 Klein EACS 2005, P4.3/2

Background – the DART trial

- DART is a large randomised controlled trial evaluating laboratory and clinical monitoring strategies for adults initiating ART
- 84% of DART participants received a 3NRTI first-line regimen (CBV/ABC or CBV/TDF)
- Patients failing a 3NRTI regimen are treated with a boosted PI (bPI)+NNRTI±NRTI regimen
  - Likely to be highly effective as it contains two new ARV classes
  - LPV/r is the commonly used bPI
- DART participants initially received LPV/r capsules 533/133 mg BD with NNRTIs: what dose of 200/50 mg LPV/r tablets should be used?

Objective and Design

- To evaluate the pharmacokinetics of LPV/r in Ugandan adults, taken as 4 capsules (533/133mg), 2 tablets (400/100mg) and 3 tablets (600/150mg) BD with NNRTIs
- Design: 3 period crossover PK study in HIV-infected patients receiving LPV/r with EFV (n=20) or NVP (n =20)
  - Patients should have been taking 3 tablets (600/150mg) BD with NNRTIs for more than 2 weeks

- 6 point PK sampling (0, 2, 4, 6, 8 and 12 hours) after observed intake with a standardised breakfast

Methods

- LPV and ritonavir (RTV) concentrations were determined by validated HPLC-tandem mass spectrometry in Liverpool
  - Limit of quantitation 103 and 26 ng/ml respectively
- 40 participants (21 EFV, 19 NVP) recruited
  - Two had very low LPV and RTV measurements at the PK day on 4 capsules (533/133 mg) BD
  - These 2 participants were excluded from analyses because this was the reference group for comparing bioequivalence

Baseline Characteristics

		EFV	NVP
Included in analysis		20	18
Women		**6 (30%)**	**13 (72%)**
Age (years)	median	41	35
Weight (kg)	median	60	64
BMI (kg/m^2)	median	23.2	24.8
Haemoglobin (g/dl)	median	13.8	13.6
Concurrent NRTIs	none	1	
	lamivudine	1	
	abacavir	4	2
	didanosine	**14**	**14**
	tenofovir DF		1
	lamivudine+tenofovir DF		1

Lopinavir AUC

	EFV (N=20)	NVP (N=18)
Mean (sd) **AUC** (μg.h/ml)		
4 capsules (533/133 mg) BD	70.2 (27.0)	76.6 (38.9)
2 tablets (400/100 mg) BD	62.6 (33.0)	68.7 (34.5)
3 tablets (600/150 mg) BD	104.3 (53.1)	114.2 (34.7)
GMR 2 tabs vs 4 caps (90% CI)	0.82 (0.68, 0.99) p=0.09	0.90 (0.77, 1.06) p=0.27
GMR 3 tabs vs 4 caps (90% CI)	1.40 (1.18, 1.65) p=0.002	1.66 (1.46, 1.88) p<0.001

- Compared to 533/133 mg capsules, mean AUC marginally lower with 400/100 mg tablets and significantly higher with 600/150 mg tabletsd

Lopinavir AUC (ctd)

- Similar results for nevirapine and efavirenz
- No effect of sex, age, weight or BMI on LPV AUC
- Similar results for ritonavir AUC

However

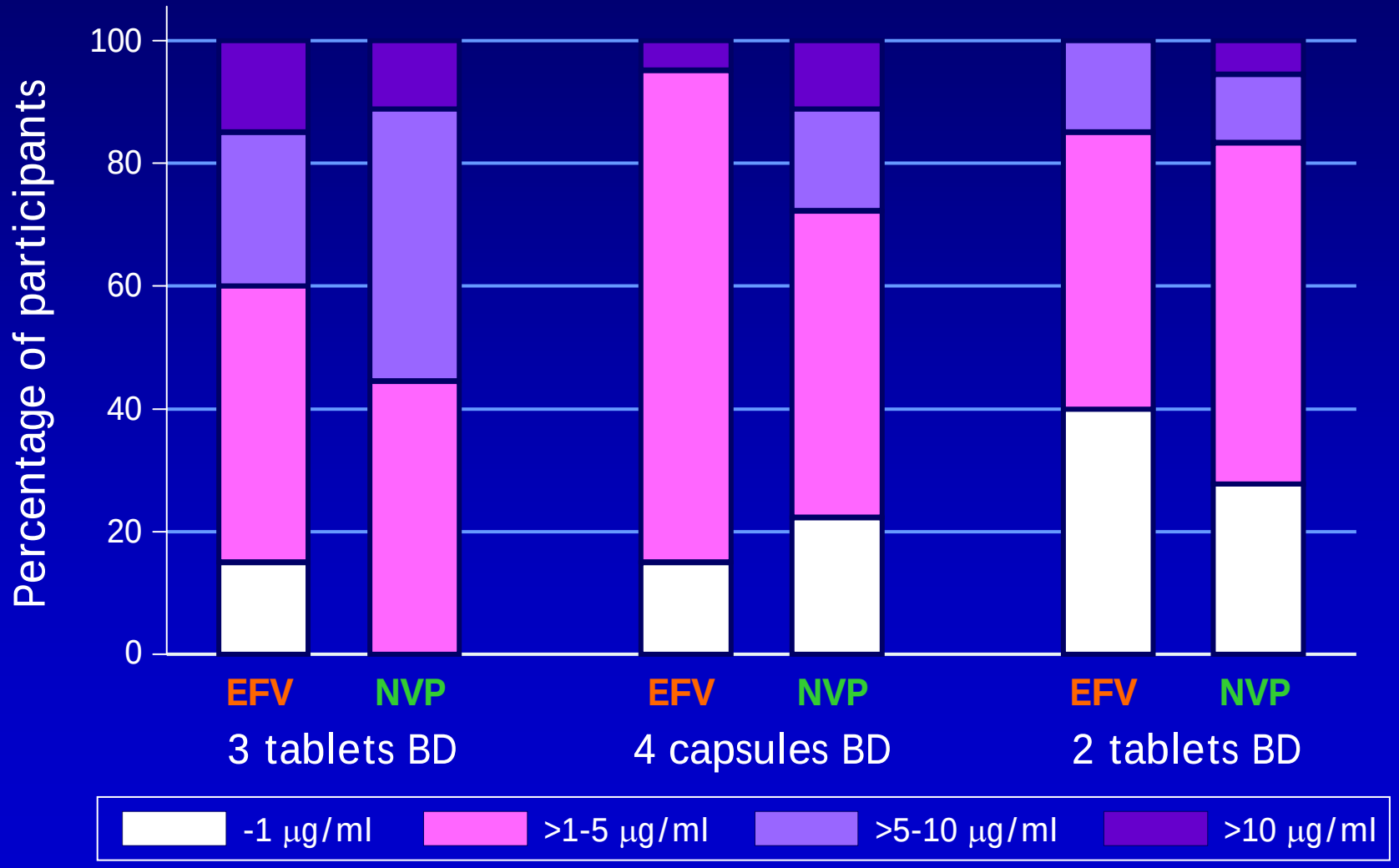
- LPV AUC variability was not reduced with tablet compared to capsule formulation as expected
- Mean LPV AUC on 4 capsules 533/133 mg BD (~70-75 μg.h/ml) was substantially lower than the 90 μg.h/ml expected in Caucasian adults receiving 400/100 BD without NNRTIs
  - Mean RTV AUC was also lower than expected

Lopinavir C_{12}

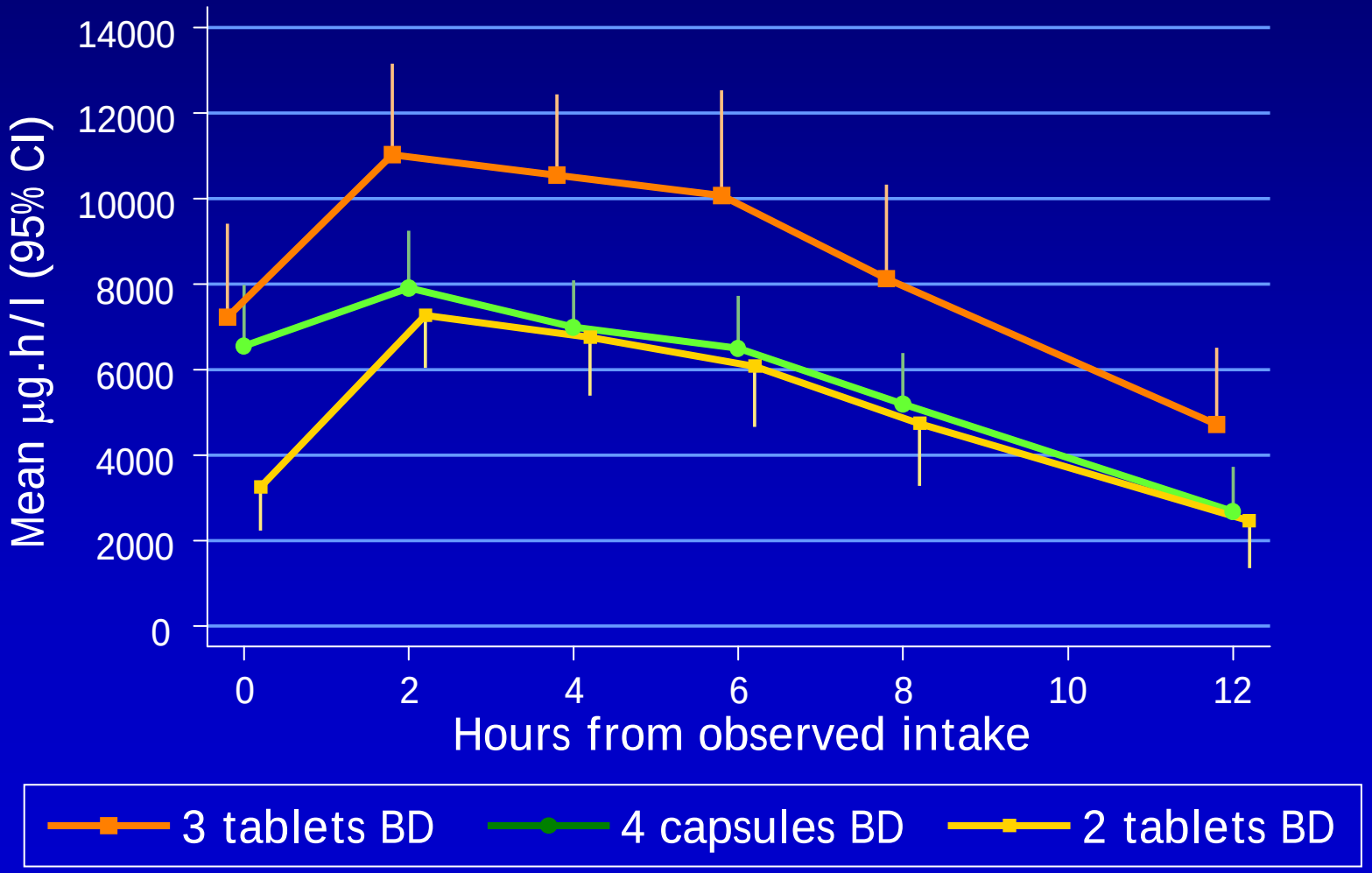
	EFV (N=20)	NVP (N=18)
Mean (sd) **C_{12}** (μg/ml)		
4 capsules (533/133 mg) BD	2.7 (2.4)	3.9 (2.4)
2 tablets (400/100 mg) BD	2.5 (2.5)	2.7 (2.6)
3 tablets (600/150 mg) BD	4.7 (4.1)	6.2 (2.9)
GMR 2 tabs vs 4 caps (90% CI)	0.62 (0.39, 0.98) p=0.08	0.80 (0.57, 1.12) p=0.26
GMR 3 tabs vs 4 caps (90% CI)	1.48 (1.09, 2.02) p=0.04	2.31 (1.64, 3.24) p=0.0005

- Compared to 533/133 mg capsules, mean C_{12} significantly higher with 600/150 mg tablets, and marginally lower with 400/100 mg tablets

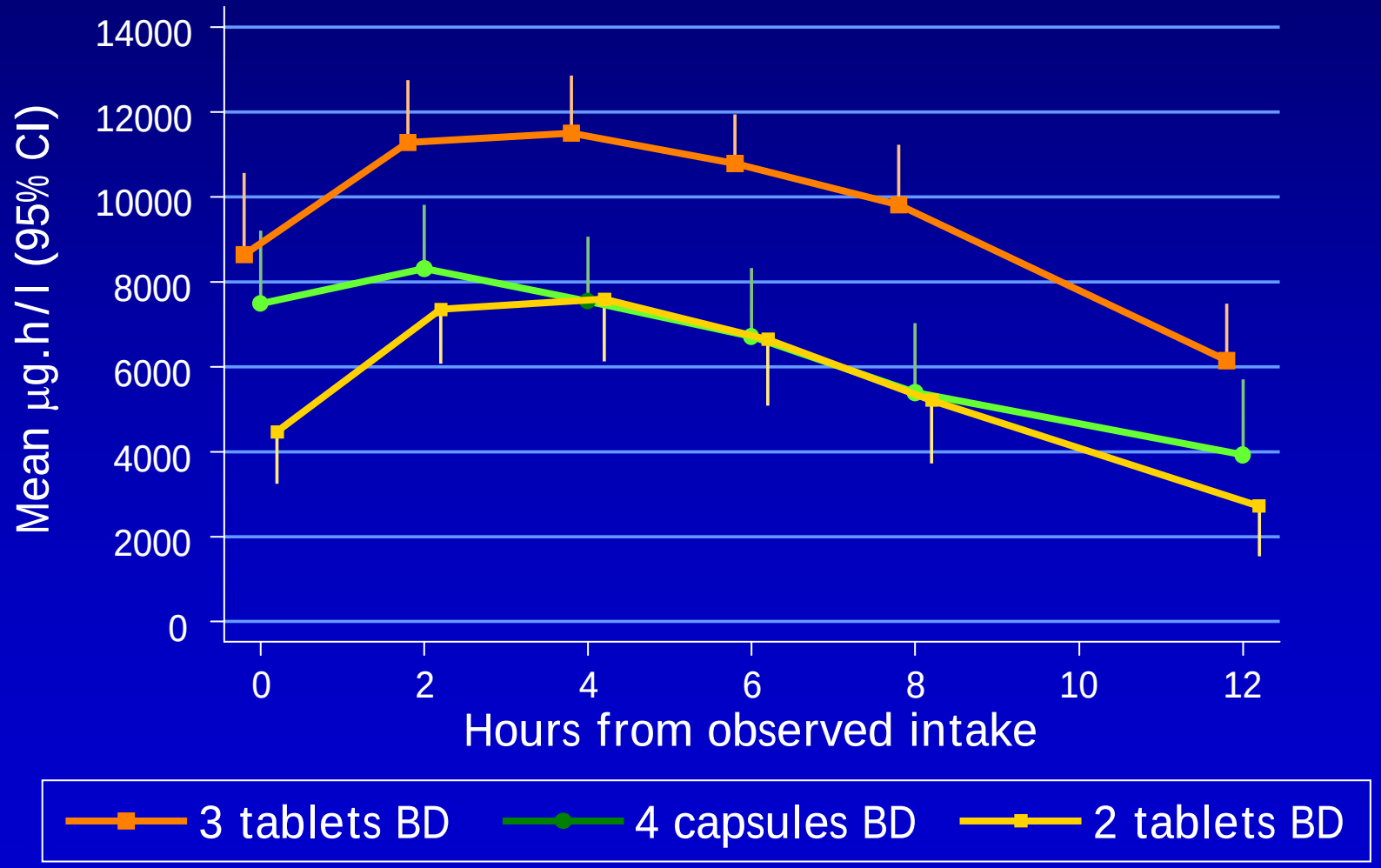
Lopinavir C_{12}



Plasma concentration-time profile: lopinavir with efavirenz



Plasma concentration-time profile: lopinavir with nevirapine



Conclusion

- When co-administered with **NVP or EFV** in HIV-infected African patients, LPV AUC and C_{12} are significantly higher with 3 tablets BD and marginally lower with 2 tablets BD compared to 4 capsules BD
  - Higher plasma levels on 3 tablets BD may lead to greater long-term toxicity
  - Low plasma C_{12} on 2 tablets BD may increase the risk of virological failure
    - However, these levels are similar to C_{trough} seen with 800/200 mg (4 tablets) QD which has shown good efficacy in patients without LPV resistance

Most recent recommendations

- LPV/r 100/25 mg (paediatric) tablet is now available
- Recent study demonstrates that LPV/r dose of 500/125 mg BD (2x200/50 mg tabs + 1x100/25 mg [half-dose] tab BD) with EFV provides similar exposure to 400/100 mg BD without EFV[1]
- This dosage is the most recent SPC recommendation

1 Ng, CROI 2008, #765

Limitations

- Only dose at time 0 was observed, not preceding dose
  - C_0 was generally slightly higher than C_{12}, which does not support non-adherence
- Lack of comparative group of African patients receiving LPV/r without NNRTIs
  - Further studies ongoing to estimate LPV and RTV PK parameters in African patients taking 2 LPV/r tablets BD without NNRTIs

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