



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

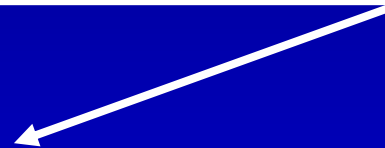
Kityo C, Walker AS, Lutwama F, Ssali F, Nalumenya R, Tumukunde D, Kawiya J, Munderi P, Reid A, Gilks CF, Gibb DM, Khoo S
on behalf of the **DART** Trial Team



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



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 ($\mu\text{g}\cdot\text{h}/\text{ml}$)		
4 <u>capsules</u> (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 $\mu\text{g}\cdot\text{h}/\text{ml}$) was substantially lower than the 90 $\mu\text{g}\cdot\text{h}/\text{ml}$ expected in Caucasian adults receiving 400/100 BD without NNRTIs
 - Mean RTV AUC was also lower than expected



Lopinavir C₁₂

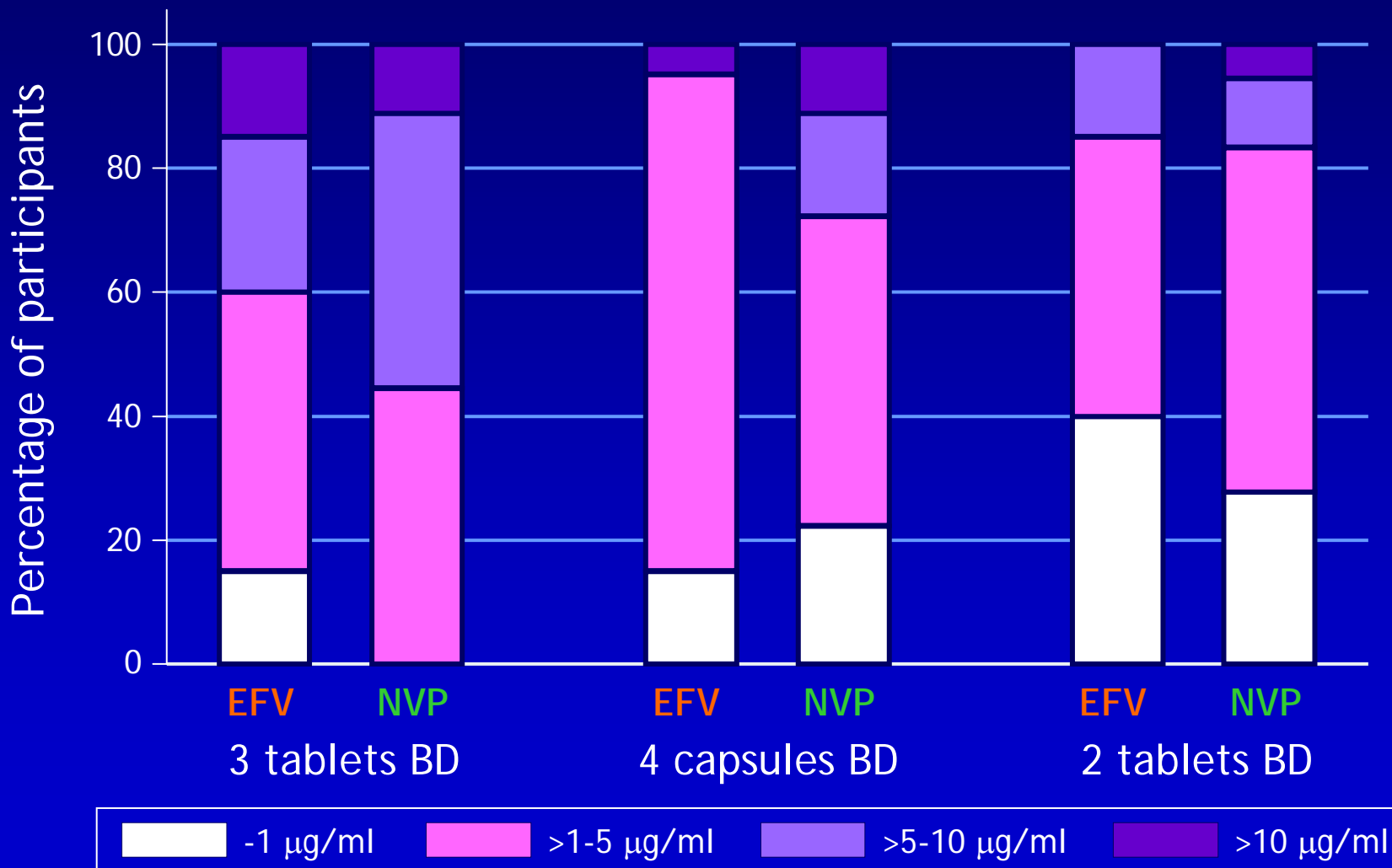


	EFV (N=20)	NVP (N=18)
Mean (sd) C ₁₂ (µg/ml)		
4 <u>capsules</u> (533/133 mg) BD	2.7 (2.4)	3.9 (2.4)
2 tablets (400/100 mg) BD	2.5 (2.5)	2.7 (2.6)
3 tablets (600/150 mg) BD	4.7 (4.1)	6.2 (2.9)
GMR 2 tabs vs 4 caps (90% CI)	0.62 (0.39, 0.98) p=0.08	0.80 (0.57, 1.12) p=0.26
GMR 3 tabs vs 4 caps (90% CI)	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 C₁₂ significantly higher with 600/150 mg tablets, and marginally lower with 400/100 mg tablets

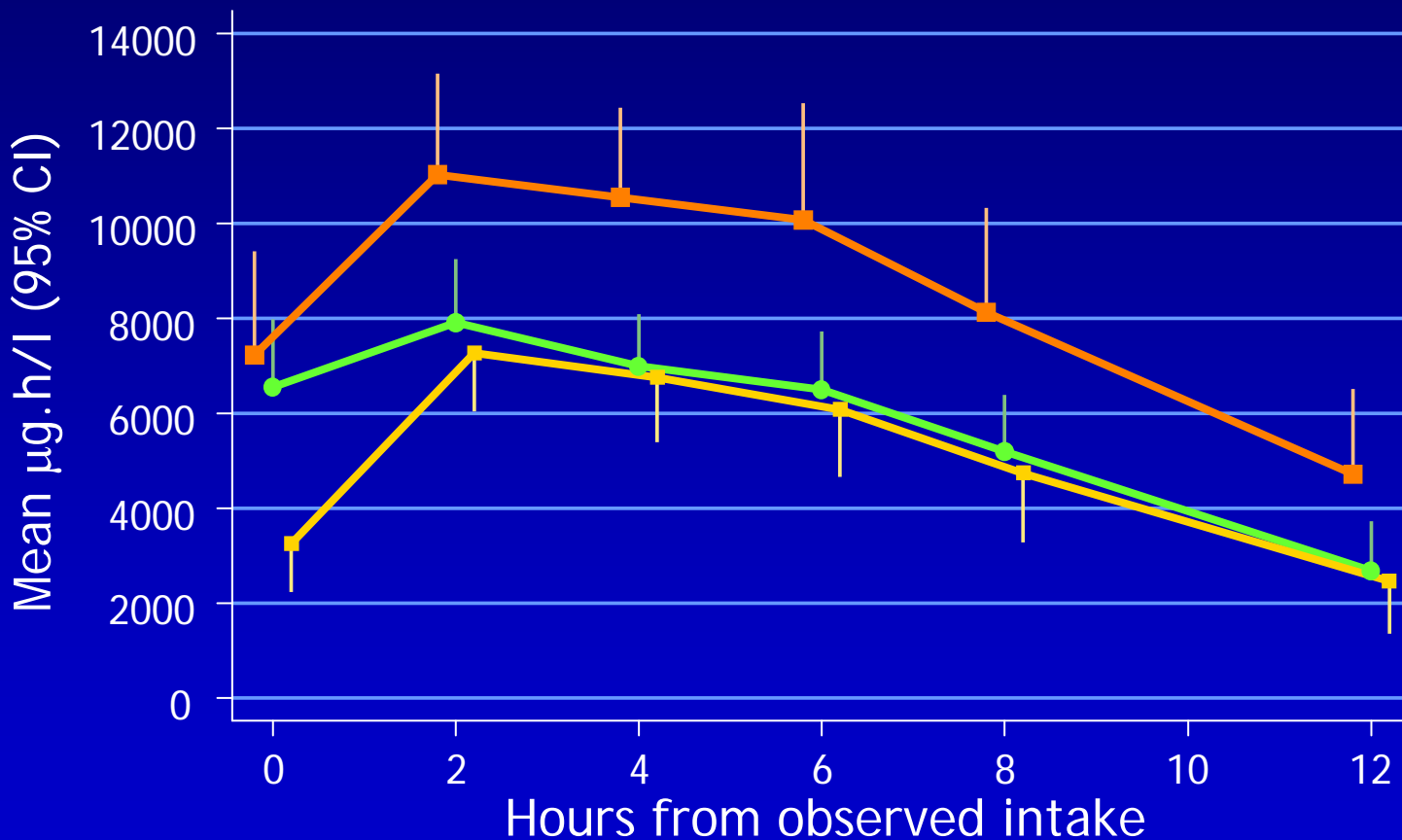


Lopinavir C₁₂

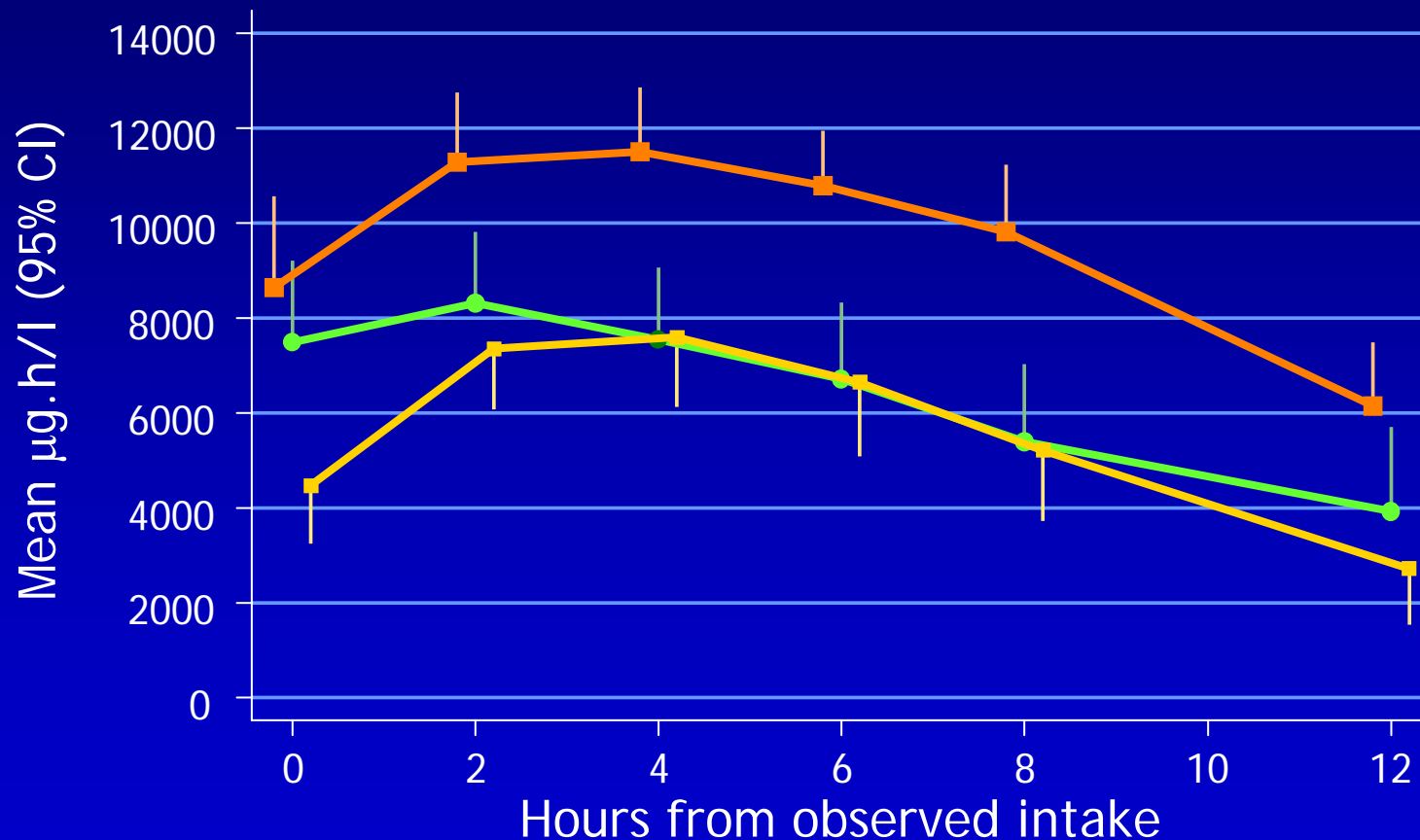




Plasma concentration-time profile: lopinavir with efavirenz



Plasma concentration-time profile: lopinavir with nevirapine



—■— 3 tablets BD —●— 4 capsules BD —■— 2 tablets BD



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 EFV¹
- This dosage is the most recent SPC recommendation



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



Acknowledgments



- **We thank all the patients and staff from all the centres participating in the DART trial.**
- **Joint Clinical Research Centre, Kampala, Uganda:** P Mugenyi, C Kityo, F Ssali, D Tumukunde, T Otim, J Kabanda, H Musana, J Akao, H Kyomugisha, A Byamukama, J Sabiiti, J Komugyena, P Wavamunno, S Mukiibi, A Drasiku, R Byaruhanga, O Labeja, P Katundu, S Tugume, P Awio, A Namazzi, GT Bakeinyaga, H Katabira, D Abaine, J Tukamushaba, W Anywar, W Ojiambo, E Angweng, S Murungi, W Haguma, S Atwiine, J Kigozi.
- **Infectious Diseases Institute (formerly the Academic Alliance) Makerere University, Mulago, Uganda:** E Katabira, A Ronald, A Kambungu, F Lutwama, A Nanfuka, J Walusimbi, E Nabankema, R Nalumenya, T Namuli, R Kulume, I Namata, L Nyachwo, A Florence, A Kusiima, E Lubwama, R Nairuba, F Oketta, E Buluma, R Waita, H Ojiambo, F Sadik, J Wanyama, P Nabongo.
- **MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda:** H Grosskurth, P Munderi, G Kabuye, D Nsibambi, R Kasirye, E Zalwango, M Nakazibwe, B Kikaire, G Nassuna, R Massa, K Fadhiru, M Namyalo, A Zalwango, L Generous, P Khauka, N Rutikarayo, W Nakahima, A Mugisha, J Todd, J Levin, S Musingo, A Ruberantwari, P Kaleebu, D Yirell, N Ndembi, F Lyagoba, P Hughes, M Aber, A Medina Lara, S Foster, J Amurwon, B Nyanzi Wakh.
- **University of Zimbabwe, Harare, Zimbabwe:** A Latif, J Hakim, V Robertson, A Reid, E Chidziva, R Bulaya-Tembo, G Musoro, F Taziwa, C Chimbetete, L Chakonza, A Mawora, C Muvirimi, G Tinago, P Svovanapasis, M Simango, O Chirema, J Machingura, S Mutsai, M Phiri, T Bafana, M Chirara, L Muchabaiwa, M Muzambi.
- **The AIDS Support Organisation (TASO), Uganda:** R Ochai, D Muhweezi.
- **Imperial College:** C Gilks, K Boocock, C Puddephatt, D Winogron, J Bohannon.
- **MRC Clinical Trials Unit:** J Darbyshire, DM Gibb, A Burke, D Bray, A Babiker, AS Walker, H Wilkes, M Rauchenberger, S Sheehan, L Peto, K Taylor, M Spyer, A Ferrier, B Naidoo, D Dunn, R Goodall.
- **Independent DART Trial Monitors:** R Nanfuka, C Mufuka-Kapuya.
- **Trial Steering Committee:** I Weller (Chair), A Babiker (Trial Statistician), S Bahendeka, M Bassett, A Chogo Wapakhabulo, J Darbyshire, B Gazzard, C Gilks, H Grosskurth, J Hakim, A Latif, C Mapuchere, O Mugurungi, P Mugenyi; Observers C Burke, S Jones, C Newland, S Rahim, J Rooney, M Smith, W Snowden, J-M Steens.
- **Data and Safety Monitoring Committee:** A Breckenridge (Chair), A McLaren (Chair-deceased), C Hill, J Matenga, A Pozniak, D Serwadda.
- **Endpoint Review Committee:** T Peto (Chair), A Palfreeman, M Borok.
- **Funding:** DART is funded by the **UK Medical Research Council**, the **UK Department for International Development (DFID)**, and the **Rockefeller Foundation**. **GlaxoSmithKline**, **Gilead** and **Boehringer-Ingelheim** donated first-line drugs for DART, and **Abbott** provided LPV/r (Kaletra/Aluvia) as part of the second-line regimen for DART.