HUMAN CONFIRMATION OF ORAL DOSE REDUCTION POTENTIAL OF NANOPARTICLE ANTIRETROVIRAL FORMULATIONS

Reported by Jules Levin
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WEBCAST: ***http://www.croiwebcasts.org/console/player/33376?mediaType=slideVideo&***

Summary and conclusions

- Both SDN formulations proved to be well tolerated at the studied doses, with no grade 3-4 adverse events.
- These data confirm the potential for a 50% dose reduction while maintaining therapeutic exposure, using a novel approach to formation of efavirenz and lopinavir SDNs.
- If confirmed in larger future studies, the approach has the potential for savings up to 243 million USD per year while also freeing up manufacturing capacity up to 930 tons per year.
- Further formulation development is required for future translation (e.g. co-formulation, tableting, stability).
- The approach has wide applicability to drugs from several classes for numerous indications, and other development programmes are currently ongoing for oral and long-acting SDN applications.

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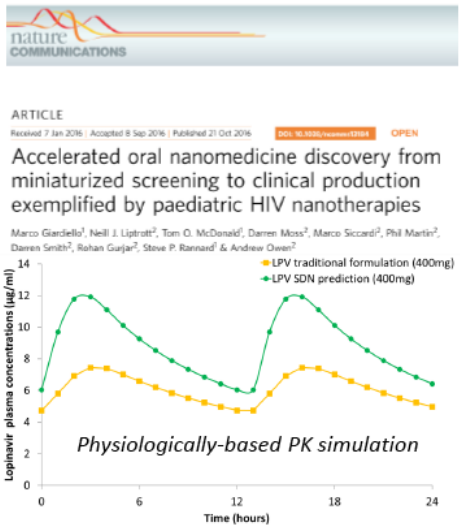
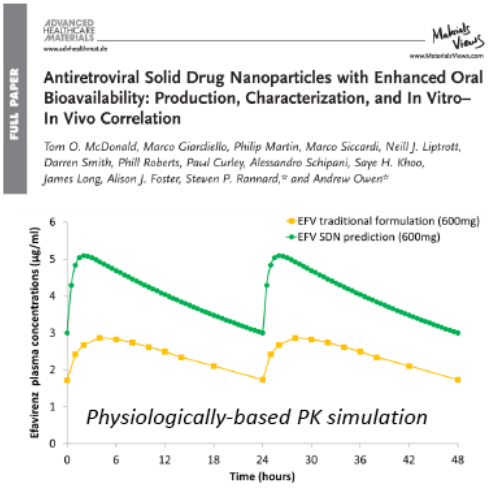
Introduction: preclinical SDN selection





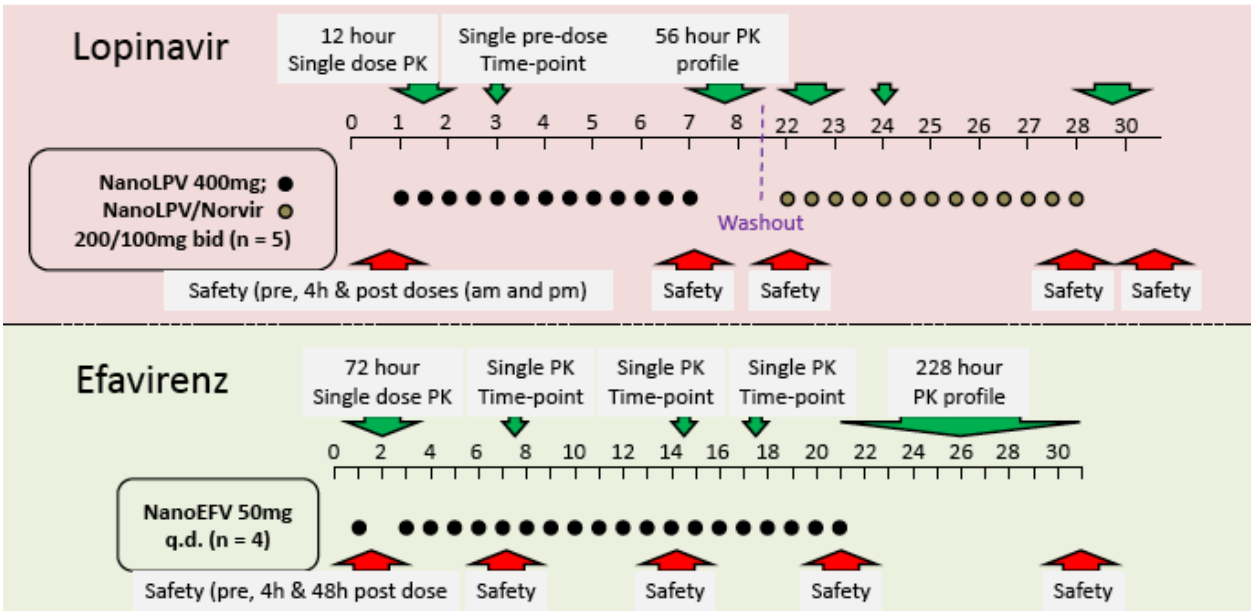
Dispersal of drugs into water may have explicit benefits for paediatric formulation without the need for organic solvents.

***In vitro*, *in silico* and *in vivo* preclinical selection of lead SDN formulations**

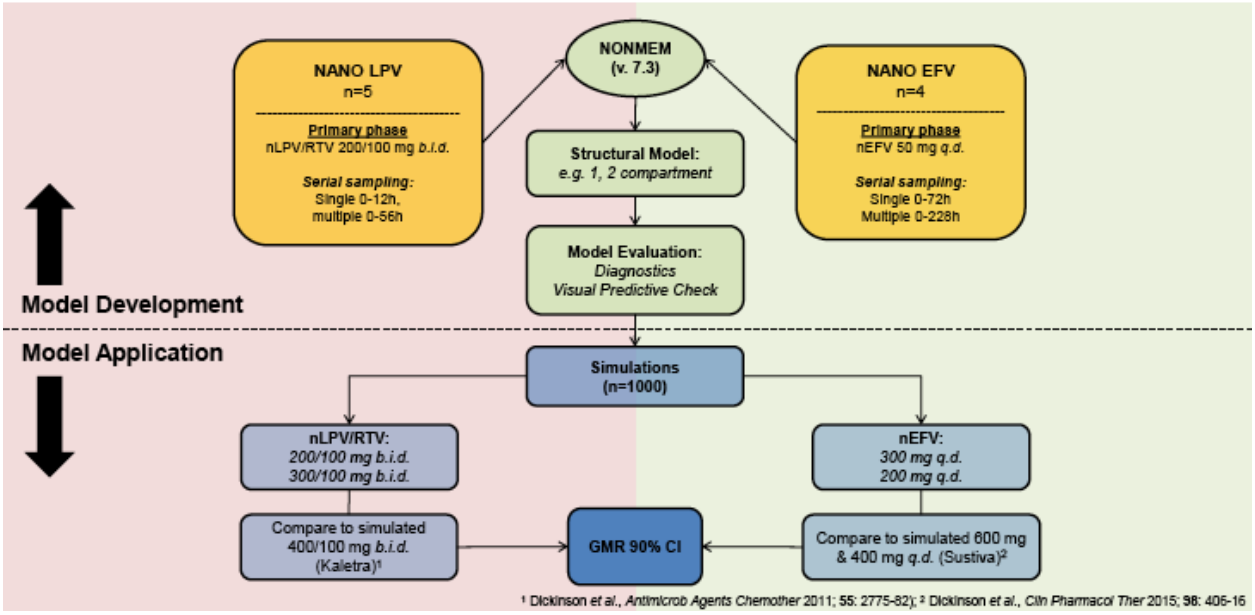
Aims

- To investigate the pharmacokinetics of lower dose lopinavir and efavirenz solid drug nanoparticle (SDN) formulations in healthy human volunteers.
- To construct population pharmacokinetic (popPK) models to describe the available data and compare pharmacokinetics to historical data with Kaletra and Sustiva.
- To investigate the multiple dosing safety and tolerability of lopinavir and efavirenz SDNs.

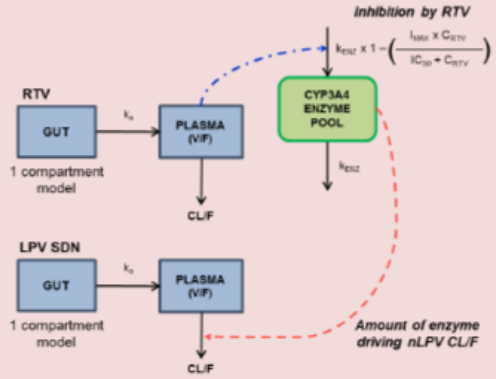
Clinical strategy (EudraCT number 2013-004913-41)



Population pharmacokinetic (popPK) modelling strategy



Lopinavir model structure and model estimates



Covariates not assessed due to small sample size

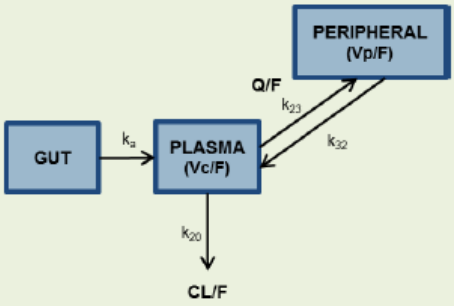
Subject	AUC_{0-12} (mg.h/L)	T_{max} (h)	C_{max} (mg/L)	C_{12} (mg/L)	Terminal Half-Life (h)
1	95.04	4	8.76	6.88	11.82
2	87.51	4	8.15	6.23	10.94
3	54.97	4	5.59	3.48	6.46
4	102.19	4	9.32	7.49	13.03
5	40.49	4	4.37	2.25	5.11

Parameter	Estimate	RSE (%)	IIV (%)	RSE (%)
Ritonavir				
CL/F (L/h)	11.0	5.4	60	47
V/F (L)	69.9	24	61	69
k_a (h^{-1})	0.926	5.6		
Lag-time (h)	0.936	2.5		
Residual Error				
Proportional (%)	52	20		
Lopinavir				
CL/F (L/h)	7.48	10	16	68
V/F (L)	31.1	8.8		
k_a (h^{-1})	0.383	8.9		
Lag-time (h)	1.43	19		
Residual Error				
Proportional (%)	38	31		
Interaction				
I_{MAX}	1 *fix*	-		
IC_{50} (mg/L)	0.437	32		
k_{ENZ} (h^{-1})	0.499	22		

RSE: relative standard error; IIV: interindividual variability; RSE% = ($SE_{ESTIMATE}$/SE) * 100

Efavirenz model structure and model estimates

2 compartment oral model, 1st order absorption



Parameter	Estimate	RSE (%)	IIV (%)	RSE (%)
CL/F (L/h)	5.14	15	30	38
V_c/F (L)	76.7	15		
Q/F (L/h)	74.2	20	34	48
V_p/F (L)	839	6.2		
k_a (h^{-1})	0.745	3.8		
Residual Error				
Proportional (%)	17	24		
Additive (mg/L)	0.009	92		

RSE: relative standard error; IIV: interindividual variability; RSE% = ($SE_{ESTIMATE}$/SE) * 100

Subject	AUC (mg.h/L)*	T_{max} (h)	C_{max} SD (mg/L)	C_{max} MD (mg/L)	Terminal Half-Life (h)
101	11.1	2.0	0.24	0.59	152.83
102	14.7	2.0	0.13	0.58	191.68
104	7.6	2.0	0.20	0.45	104.90
105	7.2	2.0	0.16	0.40	96.96

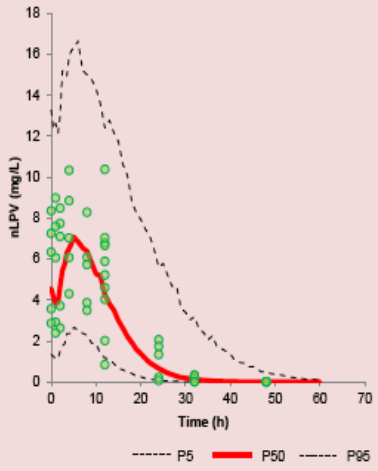
* AUC= Dose/CL

Covariates not assessed due to small sample size

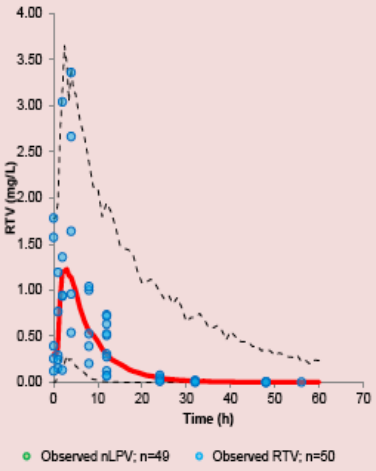
Visual predictive check for model performance

(1000 simulated volunteers; 90% Prediction Interval, P5-P95)

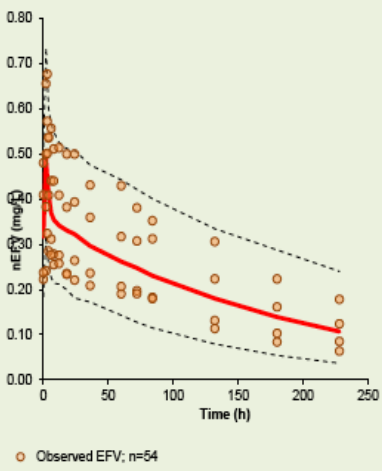
Lopinavir SDN: 94% of observations within the 90% prediction interval



Ritonavir: 96% of observations within the 90% prediction interval



Efavirenz SDN: 92% of observations within the 90% prediction interval



Simulated comparison with currently used formulations

(1000 simulated individuals; historical comparison)

Simulated LPV_{SDN}/RTV 200/100 mg to simulated LPV/RTV (Kaletra) 400/100 mg[1]

	Geometric mean		Geometric Mean Ratio
LOPINAVIR	LPV SDN 200 mg#	Kaletra 400 mg bid [1]	GMR (90% CI)*
C_{12} (mg/L)	4.16	4.02	1.04 (0.99-1.08)
AUC_{0-12} (mg.h/L)	72.35	79.07	0.92 (0.89-0.94)
C_{max} (mg/L)	10.69	9.97	1.07 (1.05-1.10)

EFAVIRENZ	EFV SDN 300 mg	Sustiva 600 mg q.d. [2]	GMR (90% CI)*
AUC_{0-24} (mg.h/L)	51.56	58.61	0.88 (0.86-0.90)
C_{12} (mg/L)	2.03	2.51	0.81 (0.78-0.83)
C_{24} (mg/L)	1.90	1.44	1.32 (1.26-1.37)
C_{max} (mg/L)	2.99	3.36	0.89 (0.87-0.91)

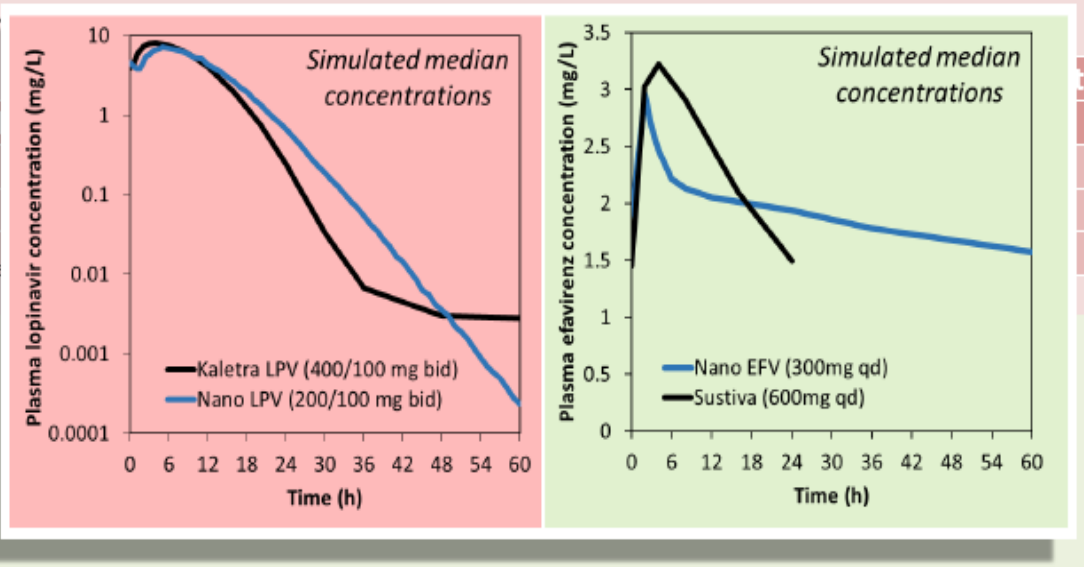
Simulated EFV_{SDN} 300 mg or 200 mg to simulated EFV (Sustiva) 600 or 400 mg

[1]Dickinson *et al.* *Antimicrob Agents Chemther* 2011; **55**: 2775-82

[2]Dickinson *et al.*, *Clin Pharmacol Ther* 2015; **98**: 406-16

Simulated comparison with currently used formulations

(1000 simulated individuals; historical comparison)



[1]Dickinson *et al.* *Antimicrob Agents Chemther* 2011; **55**: 2775-82
[2]Dickinson *et al.*, *Clin Pharmacol Ther* 2015; **98**: 406-16

Limitations

- Low sample size for LPV (n = 5) and EFV (n = 4) SDNs.
- No direct comparison within the study (relies upon historical data for conventional formulations but stage 2 ongoing).
- Dose prediction above the studied doses assumes linear pharmacokinetics (particularly relevant to EFV SDNs although linear pharmacokinetics has been demonstrated across adult doses of this drug[1]).

[1]Sustiva (efavirenz) [package insert], 2004, Bristol-Myers Squibb

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