ARV Therapies and Therapeutic Strategies

INDEPENDENT REPORTING ON IAS 2017

COMPREHENSIVE EXPERT REVIEW AND DISCUSSION OF KEY PRESENTATIONS

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PHARMACOKINETICS, PHARMACODYNAMICS AND PHARMACOGENOMICS OF EFAVIRENZ 400MG ONCE-DAILY DURING PREGNANCY AND POSTPARTUM

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Abstract TUPDB0203LB

BACKGROUND, OBJECTIVES, METHODS

Background

- ENCORE-1 showed no difference between efavirenz 400mg (EFV400) and efavirenz 600mg = EFV400 is non-inferior to the standard dose[1]
- ARV dose reductions may translate into greater benefits for more individuals as reaching higher Ns of patients and compensate for finite global manufacturing capacity and increasing demand
- WHO clinical guidelines recommend EFV400 as alternative first-line agent, with a disclaimer that no data on EFV400 during the third trimester of pregnancy (TT) exist

Objectives

- To investigate EFV400 PK, efficacy and CYP2B6 pharmacogenetics in WLWH during TT and post-partum (PP)

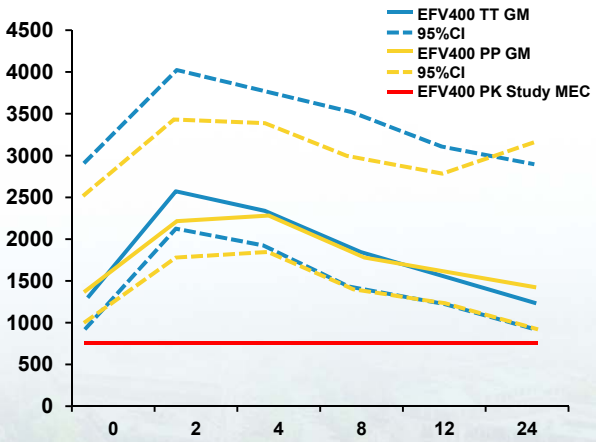
Methods

- WLWH on TDF/FTC/EFV600 with an undetectable VL switched to TDF/FTC/EFV400
- Weekly TDM, 10-14 h post dose, and bi-weekly VL
- Steady-state PK profiles and polymorphisms of interest in CYP2B6 (516C>T and 938T>C) were assessed

1 Puls et al Lancet 2014

RESULTS: PK PARAMETERS AND PROFILES

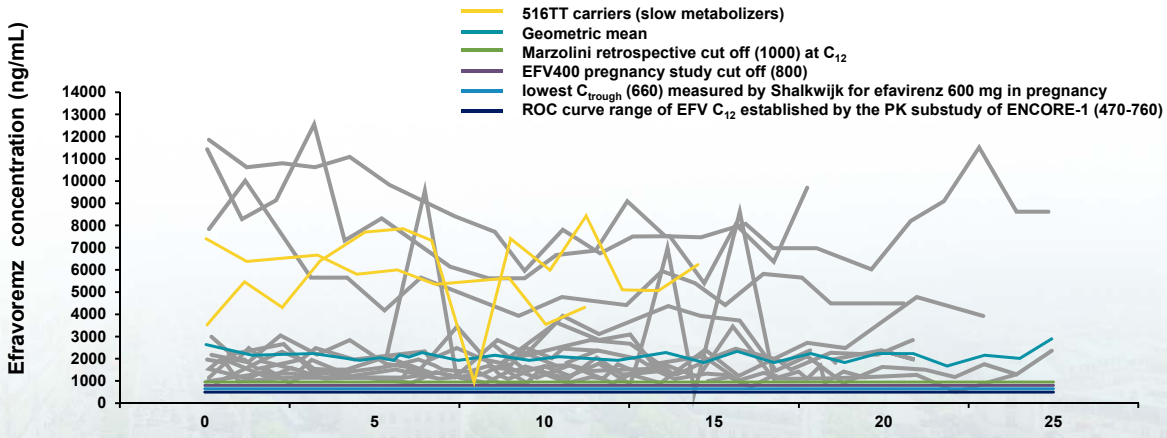
	EFV GM (95% CI)		GM (90% CI)
PK parameter	**TT**	**PP**	**TT/PP**
C_{max}	2751 (2301-4043)	2790 (2222-4170)	0.93 (0.80-1.08)
ng/mL			
CV%	142	147	
C_{trough}	1205 (897-2681)	1469 (973-3121)	0.73 (0.60-0.89)
ng/mL			
CV%	78	85	
AUC_{0-24}	39941 (31082-72568)	43168 (33012-72028)	0.84 (0.72-0.99)
ng.h/mL			
CV%	97	121	



C_{max}, C_{trough} and AUC in TT were 7%, 27% and 16% lower compared to PP but within ranges of those measured for EFV600 during TT by Schalkwijk et al. (2016) and those measured in ARV-naïve patients on EFV400 in ENCORE-1 (Dickinson et al. 2015)

Lamorde M, et al; 9th IAS, Paris, France, July 23-26, 2017; Abst. TUPDB0203LB.

RESULTS: TDM, PGX AND TARGET CONCENTRATIONS



All subjects maintained a VL<50 (all new-borns HIVneg), suggesting that EFV400 can be used in pregnant WLWH

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PHARMACOKINETIC MODELLING OF DARUNAVIR/RITONAVIR DOSE REDUCTION (800/100 MG TO 400/100MG ONCE DAILY) CONTAINING REGIMEN IN VIROLOGICALLY SUPPRESSED HIV-INFECTED PATIENTS AS MAINTENANCE TREATMENT: ANRS-165 DARULIGHT SUB-STUDY

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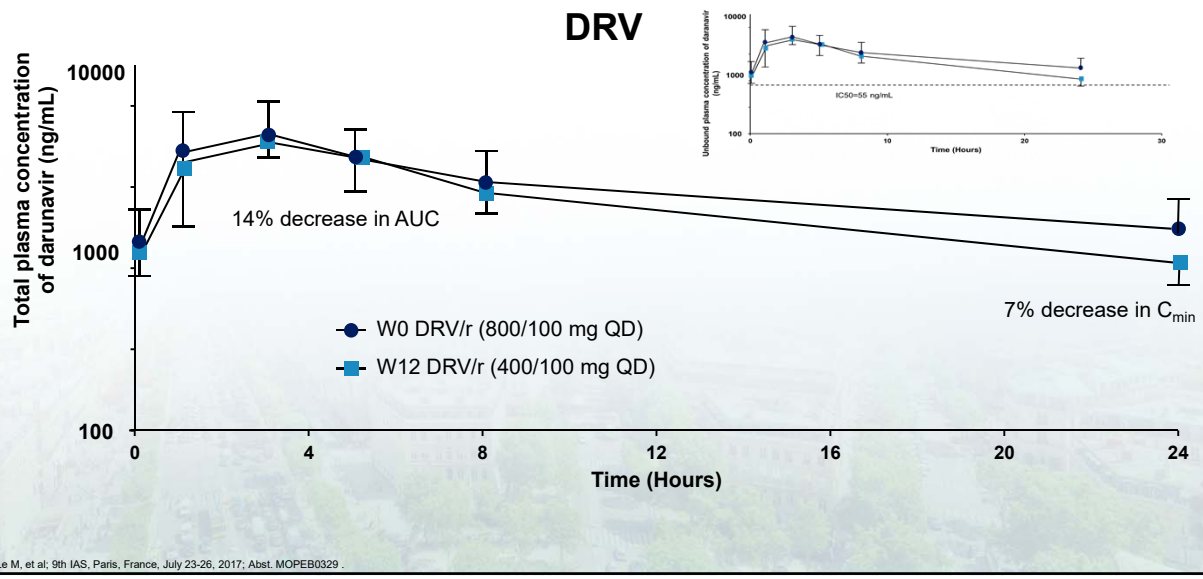
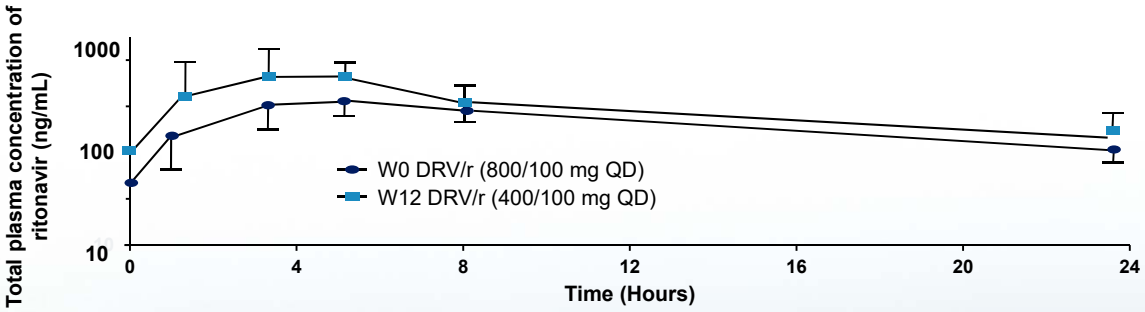
Abstract MOPEB0329

ANRS-165 DARULIGHT SUB-STUDY: RESULTS



Le M, et al; 9th IAS, Paris, France, July 23-26, 2017; Abst. MOPEB0329 .

ANRS-165 DARULIGHT SUB-STUDY: RESULTS



PK parameters	AUC WO (ng.h/mL)	AUC W12 (ng.h/mL)	C_{max} W0 (ng/mL)	C_{max} W12 (ng/mL)	C_{min} W0 (ng/mL)	C_{min} W12 (ng/mL)	$T_{1/2}$ W0 (h)	$T_{1/2}$ W12 (h)
Median	4350	6171	386	578	44	54	6.1	6.3
IQR25	3652	4514	301	442	26	42	5.4	5.4
IQR75	6545	6854	470	649	51	78	7.5	8.0
GMR (IC90%)	1.22 (1.03-1.44)		1.22 (1.03-1.44)		1.40 (1.11-1.77)		1.04 (0.93-1.17)	
P-value	NS (p=0.09)		0.02		0.01		NS	

Le M, et al; 9th IAS, Paris, France, July 23-26, 2017; Abst. MOPEB0329 .

CONCLUSIONS

- In HIV-1 infected patients, switch from DRV/r 800/100mg QD to 400/100mg QD = no significant different DRV and RTV exposure in both blood and seminal plasma
- Consistent with maintenance of virologic efficacy through 48 weeks
- Modification of the balance « inducer/inhibitor » between DRV & RTV with dose reduction