Efavirenz Pharmacokinetics with Rifampin Double Dose in TB-HIV Infected Patients

Poster · March 2018

CITATION
1

READS
152

13 authors, including:

Atwine Daniel
MSF-Epicentre Mbarara Research Centre
60 PUBLICATIONS **478** CITATIONS
SEE PROFILE

Elisabeth Baudin
Epicentre MSF
79 PUBLICATIONS **2,172** CITATIONS
SEE PROFILE

EFAVIRENZ PHARMACOKINETICS WITH RIFAMPIN DOUBLE-DOSE IN TB -HIV INFECTED PATIENTS

Daniel Atwine[1,2], Elisabeth Baudin[1], Thibaut Gelé[3], Winnie Muyindike[4], Mworozi Kenneth[1], Racheal Kyohairwe[1], Keneth Kananura[1], Dan Nyehangane[1], Patrick Orikiriza[1], Valérie Furlan[3], Anne-Marie Taburet[3], Aurélie Barrail-Tran[3], Maryline Bonnet[1,5] and the ANRS12292 Rifavirenz study group

[1]Epicentre, Paris and Mbarara, [2]Université de Montpellier, France, [3]Bicêtre hospital and UMR1184,Université Paris-Sud, France [4]Mbarara National Reference Hospital, Uganda [5]IRD UMI233/ INSERM U1175, France.

Correspondence:
maryline.bonnet@epicentre.msf.org
or daniel.atwine@epicentre.msf.org

CROI NO: 456

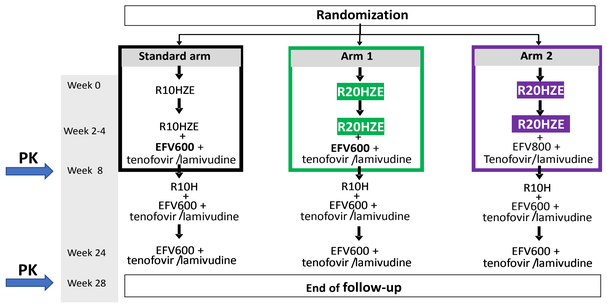
Background

- Increasing interest towards a potential reduction of TB treatment duration with use of high-dose rifampicin (R).
- Efavirenz (EFV): non-nucleoside reverse transcriptase inhibitor (NNRTI) in the first-line ART in high HIV-TB burden countries.
- Uncertainty related to its interaction with high-dose R.
- **The ANRS 12292 Rifavirenz trial evaluated EFV pharmacokinetics (PK) in Ugandan HIV/TB co-infected patients on high-dose R (20 mg/kg) as part of their standard TB treatment for the first 2 months.**

Methods

Study design: Phase 2, open-label, drug-interaction randomized controlled trial
Intervention Period: First 8 weeks of treatment.
Eligibility: New XpertMTB/RIF confirmed TB-HIV co-infected, ART-naïve, adults.
Drug regimen: Control: R10EHZ +EFV600 +TDF/3TC (R10E600)
Arm 1: R20EHZ+ EFV600 +TDF/3TC (R20E600)
Arm 2: R20EHRZ + EFV800 +TDF/3TC (R20E800)

Trial Design



Safety Monitoring

- Weekly clinical assessment
- Liver function test, full blood count at 2, 4 and 8 weeks

Pharmacokinetics

- **Sampling:** -05h; +1h; +2h; +3h; +4h; +8h; +12h; +24h post dose
- **PK parameters (WinNonLin)**: AUC, C_{12}, C_{max}, C_{24} concentrations.
- **EFV assay:** Validated HPLC, lower limit of quantitation of 0.1 µg/mL

Primary endpoint: Geometric mean ratio (GMR) of AUC and C_{24} with/without R. 90% CI compared to the bioequivalence range: 0.70 and 1.43

Results

Baseline characteristics, n=97

	R10E600 N=33	R20E600 N=31	R20E800 N=33
Males, n (%)	29 (87·9)	22 (71·0)	20 (60·6)
Age in years, median [IQR]	34·1 [29·6; 38·1]	33·4 [28·0; 36·6]	32·3 [27·8;43·1]
Weight in Kg, median [IQR]	51·9 [49·2;56·0]	53·8 [48·2;59·1]	54.1 [50·6;58·0]
Smear positive, n/N (%)	31/33 (93·9)	27/31 (87·1)	26/32 (81·3)
Hemoglobin in g/dL, median [IQR]	11·1 [9·0;12·6]	12·4 [10·7;13·8]	10·7 [9·5;12·4]
CD4 cell count/µL, median [IQR]	120 [66;252]	211 [69;334]	144 [86;367]
CD4 cell count <50, n/N (%)	7/33 (21·2)	4/27 (12·9)	4/33 (12·1)
HIV1RNA (log cps/mL), median [IQR]	5·5 [4·6 ;5·8]	5·2 [4·5;5·7]	5.1 [4·8 ;5·9]
Presence of cavities, n (%)	14 (42·4)	16 (51·6)	12 (36·4)

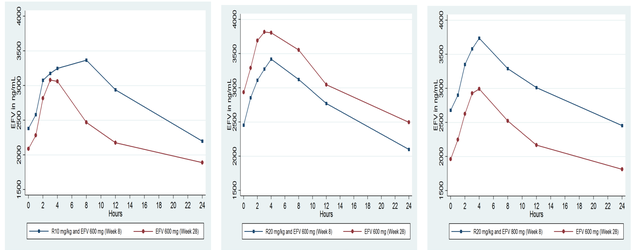
[IQR]: interquartile range

Safety

	R10E600 n=33	R20E600 n=32*	R20E800 n=33
Overall SAEs (weeks 0 to 8), n (%)	5 (15·2)	5 (15·6)	5 (15·2)
Leading to death, n (%)	1 (3·0)	1 (3·1)	1 (3·0)
Grade 3 or 4 increase ALT or AST, n (%)	2 (6·1)	2 (6·2)	2 (6·1)
CNS AE grade 2, n (%)	1 (3·0)	1 (3·1)	2 (6·2)

ALT: alanine aminotransferase ; AST: aspartate aminotransferase; CNS: central nervous system; AE: adverse event; SAE: serious adverse event (grade 3 and 4)
* 1 Patient exposed but excluded from the PK and efficacy analysis because latterly confirmed as HIV negative

EFV exposure on and off TB drugs per arm

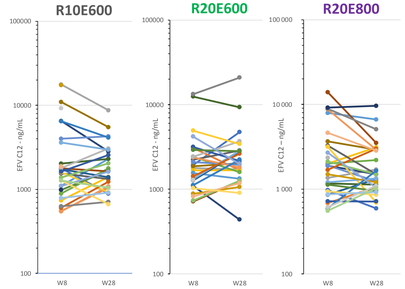


EFV PK parameters, n=87 patients*

	EFV PK parameters as median (range) EFV+R (week 8)	EFV alone (week 28)	GMR [90% CI] EFV+R/EFV
Control group (C): R10E600, n=29 patients			
C24-ng/mL	1077 (233; 9407)	1137 (324; 8049)	**0.92 [0.79**; 1.08]
AUC-µg.h/mL	40.2 (13.4; 314.5)	38.9 (14.3; 214.3)	**0.96 [0.84**; 1.09]
Group 1: R20E600, n=27 patients			
C24-ng/mL	1188 (498; 12212)	1496 (457;17967)	**0.83 [0.72**; 0.96]
AUC-µg.h/mL	47.5 (16.2; 308.4)	49.6 (13.4; 486.8)	**0.87 [0.75**; 1.00]
Group 2: R20E800, n=31 patients			
C24-ng/mL	1032 (214; 11555)	1028 (408; 11299)	**1.16 [0.97**; 1.39]
AUC-µg.h/mL	44.5 (12.9; 326.3)	35.2 (14.2; 265.7)	**1.12 [0.96**; 1.30]

*R10EFV600: 1 death, 1 discontinuation for toxicity, 1MDR-TB and 1 voluntary withdrawal
R20EFV600: 1 death, 1 discontinuation for toxicity, 2 lost to follow-up
R20EFV800: 1 death, 1 discontinuation for toxicity

Individual EFV mid-dose concentrations (C_{12})



Patients with subtherapeutic EFV C12 and C24

	Week	R10E600 N=28	R20E600 N=27	R20E800 N=30
C12<1000 ng/ml, n (%)	EFV+R (Week 8)	9 (32.1)	4 (14.8)	9 (30.0)
	EFV alone (Week 28)	6 (21.4)	2 (7.4)	6 (20.0)
		N=29	**N=27**	**N=31**
C24<1000 ng/ml, n (%)	EFV+R (Week 8)	14 (48.0)	12 (44.0)	13 (42.0)
	EFV alone (Week 28)	11 (38.0)	5 (18.0)	15 (48.0)

Efficacy

	R10E600	R20E600	R20E800
HIV Treatment efficacy*			
HIV1 RNA<400 copies/ml			
12 weeks after ART initiation	26/28 (92.9)	26/28 (92.9)	25/29 (86.2)
24 weeks after ART initiation	28/28 (100)	22/27 (81.5)	26/29 (89.7)
HIV1 RNA<100 copies/ml			
12 weeks after ART initiation	21/28 (75)	22/28 (78.6)	23/29 (79.3)
24 weeks after ART initiation	27/28 (96.4)	20/27 (74.1)	21/29 (72.4)
TB Treatment efficacy			
Week 8 TB Culture conversion			
Lowenstein-Jensen, n/N (%)	28/31 (90·3)	23/26 (88·5)	24/27 (88·9)
MGIT, n/N (%)	24/30 (80·0)	24/28 (85·7)	26/30 (86·7)
Treatment success	29 (87·9)	28 (90·3)	31 (93·9)

*Among patients who did not reach virological suppression at Week 28, 3 had baseline resistance and were excluded from the virological response analysis

Conclusions

- Doubling the R dose bears a minimal effect on EFV concentrations
  - Slight decrease in EFV concentration with high dose R (GMR= 0·87) compensated when EFV is increased to 800mg/day (GMR= 1·12).
  - Margins of the 90% CI of the GMR AUC or C_{24} irrespective of R dose within the predefined range [0.70 to 1.43].
- Co-administration of 20mg/Kg R and EFV (600 or 800mg) well tolerated.
- Low virological suppression at week 24 with high dose R, although all patients were on standard treatment from week 8.
- Slight increase in month-2 MGIT culture conversion with high dose R.

Acknowledgements

Medical, research team and patients at Epicentre Mbarara Research Centre
Mbarara University of Science and Technology, Uganda
Mbarara Regional Referral Hospital
National TB and Leprosy Programme, Uganda
Pharmacology Laboratory, Bicêtre Hospital, Paris, France
Agence nationale de recherches sur le sida et les hépatites virales