Concentrations of Nevirapine or Efavirenz when Coadministered with anti-Tuberculosis Therapy

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Background

- Highly active antiretroviral therapy (HAART) is recommended in HIV-tuberculosis (TB) co-infected patients to reduce the mortality related to TB. Although the recommended drug for tuberculosis treatment among HIV-tuberculosis coinfected patients is efavirenz, nevirapine is often used in resource limited countries.
- The present study compared concentrations (conc.) of nevirapine (NVP) or efavirenz (EFV) during coadministration with TB treatment and after discontinuation in a subgroup of patients that were enrolled in **CARINEMO trial** *(Bonnet M et al. Lancet Infect Dis 2013;13(4):303-12).*

Methods

- **Treatment**

TB drugs

Dosage: Rifampicin (R,10 mg/Kg), Isoniazid (H, 5mg/Kg), Pyrazinamide (Z, 25mg/Kg), Ethambutol (E, 15mg/Kg)
Drugs (FDC): RHZE 150mg/75mg/400mg/275mg and RH 150mg/75mg
Regimen: 2 months RHZE and 4 months RH

ARV

Lamivudine 150mg + Stavudine 30mg twice a day +
EFV 600mg once daily or
NVP 200mg twice daily **without lead-in dose**
November 2010: Stavudine replaced by Zidovudine

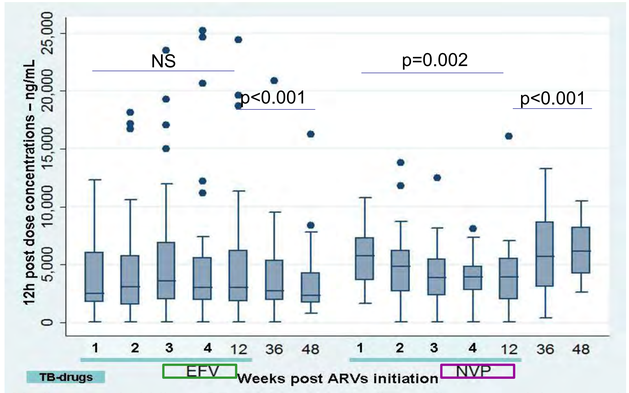
- **Sample collection**
  - Mid-dose conc. of EFV and pre-dose conc. of NVP collected at weeks (wks) 1, 2, 3, 4 and 12 after ART initiation **(on** TB drugs**)** and at wks 36 and 48 **(off** TB drugs**)**
- **Assay**
  - EFV and NVP quantified in plasma by HPLC with UV detection
  - Methods validated according to international guidelines
    - Intra- and inter-day precision and accuracy < 15%
    - LOQ 25 ng/mL for EFV and 50 ng/mL for NVP
- **Statistics**
  - Mixed models used to analyse the change in log-transformed conc. with time, time being a fixed effect in the model

Baseline characteristics

Characteristics	EFV group (n=30)	NVP group (n=32)
Age, years	34 (29-38)	36 (31-42)
Sex, male	17 (56.7)	20 (62.5)
Weight, Kg	50.9 (47.2-55.1)	51.9 (46.0-58.9)
Haemoglobin, g/dl	9.4 (8.3-10.4)	9.0 (8.1-9.8)
ALT, UI/L	28.7 (22.1-38.3)	26.4 (12.8-44.4)
Total bilirubin, mg/dl	0.5 (0.3-0.7)	0.4 (0.3-0.5)
CD4+T, cells/mm^3	91 (69-127)	106 (47-153)
HIV-1 RNA, log10 cp./ml	5.4 (5.2-6.0)	5.7 (5.3-5.9)
HBsAg, reactive	4 (13.3)	1 (3.1)
HCV antibody, reactive	1 (3.3)	1 (3.1)
Pulmonary tuberculosis	20 (66.7)	29 (90.6)

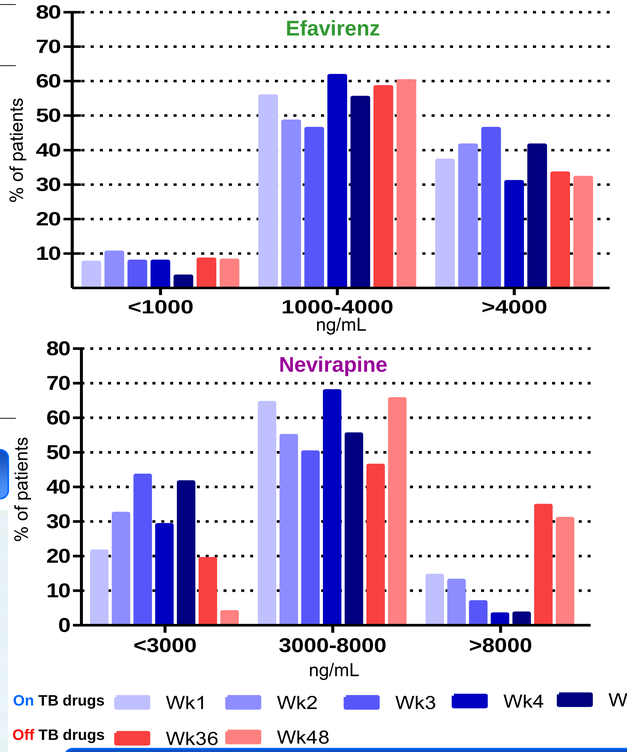
Data are n (%), median (Interquartile Range, IQR)

12h post dose plasma concentrations



Medians are bold line, IQR are boxes and adjacent lines are minimum and maximum without outliers; dots are outliers. Dotted lines are the lower targets of the therapeutic ranges (1000 ng/mL and 3000 ng/mL for EFV and NVP, respectively).

Concentrations within the therapeutic range on and off TB drugs



	EFV group		NVP group	
	Wk4 on TB drugs	Wk48 off TB drugs	Wk4 on TB drugs	Wk48 off TB drugs
Median (range), ng/mL	3004 (0-25254)	2407 (771-16247)	3888 (0-8114)	6271 (2581-10796)
Patients n (%) <BLTR*	2 (7.7)	2 (8,0)	9 (29.1)	1 (3.8)
Patients n (%) within TR*	16 (61.5)	15 (60.0)	21 (67.7)	17 (65.4)
Patients n (%) >ULTR*	8 (30.8)	8 (32.0)	1 (3.2)	8 (30.8)

*BLTR below lower limit therapeutic range, TR therapeutic range, ULTR above upper limit therapeutic range

Conclusions

- Omitting the leading dose allowed high NVP conc. at initiation of treatment; however the decrease in conc. thereafter is of concern.
- Conversely, EFV conc. was lower after discontinuation of TB treatment. These data support previous findings in South-African or Afro-American patients whose frequency of *CYP2B6* loss of function genotype is high.
- Such comparative drug-drug interaction data highlight the difference in biotransformation pathways: mainly CYP2B6 for EFV, whereas CYP2B6 and CYP3A or other CYP for NVP.
- Such different pharmacokinetic behavior of NVP and EFV when combined with rifampicin-isoniazid based antituberculosis therapy warrants further investigation in the whole CARINEMO population in relation with virological. outcome.

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