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The impact of switching to raltegravir based therapy on efavirenz-related CNS toxicity:

a phase IV open label pilot study

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EFV-related CNS toxicities: the main driver of poor adherence

- Central Nervous System (CNS) adverse events (AEs) common on EFV-based regimens[1,2]
- Most are transient
- Some experience ongoing severe AEs
- New evidence emerging of direct CNS toxic effects of EFV[3]
- Drug-related toxicity difficult to differentiate from other causes

[1]Waters L et al. *AIDS* 2011;25:65-71
[2] Scourfield A et al. *AIDS* 2012; 26:1399-1401
[3] Tovar-Y-Romo LB et al. *J Pharmacol Exp Ther* 2012; 343:696-703.

STARTMRK – comparison of toxicity profiles*

	RAL Group (N = 281)		EFV Group (N = 282)	
	n	(%)	n	(%)
Gastrointestinal Disorders	57	(20.3)	81	(28.7)
Diarrhoea	14	(5.0)	27	(9.6)
Flatulence	10	(3.6)	14	(5.0)
Nausea	25	(8.9)	29	(10.3)
General Disorders	28	(10.0)	47	(16.7)
Fatigue	12	(4.3)	25	(8.9)
Nervous System Disorders	51	(18.1)	140	(49.6)
Dizziness	22	(7.8)	99	(35.1)
Headache	26	(9.3)	40	(14.2)
Somnolence	3	(1.1)	21	(7.4)
Psychiatric Disorders	52	(18.5)	87	(30.9)
Abnormal Dreams	19	(6.8)	37	(13.1)
Insomnia	21	(7.5)	23	(8.2)
Nightmare	8	(2.8)	15	(5.3)
Skin And Subcutaneous Tissue Disorders	16	(5.7)	63	(22.3)
Rash	3	(1.1)	23	(8.2)

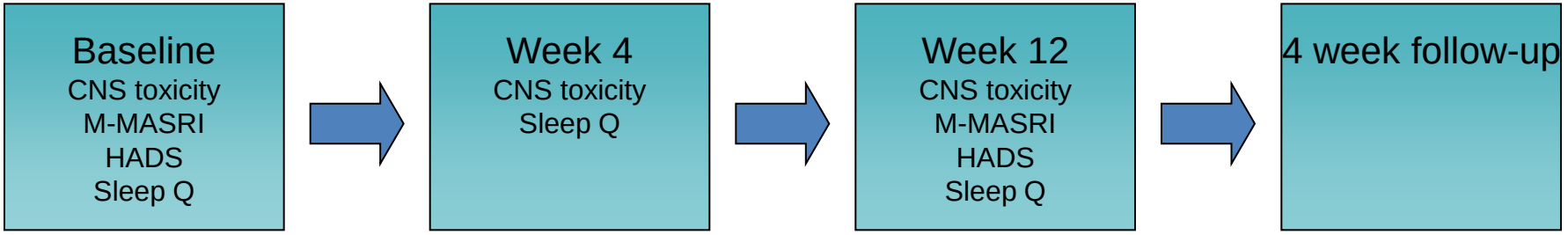
*Adapted from: Long-Term Safety and Efficacy of Raltegravir-Based Versus Efavirenz-Based Combination Therapy in Treatment-Naïve HIV-1 Infected Patients: *Final 5-Year Double-Blind Results From STARTMRK. AIDS 2012.* **Poster #LBPE19**

Objectives

- To assess the impact of switching from EFV-based cART to RAL-based cART on CNS toxicity
- To assess the impact of EFV-RAL switch on lipid profile
- To assess the ongoing efficacy of RAL at maintaining virologic suppression

Methods

- HIV-1 infected individuals virologically suppressed on EFV-based cART



- At all visits
  - FBC
  - Biochemistry
  - Lipids
  - CD4, VL

Questionnaire scoring

- CNS toxicity questionnaire
  - 10 items based on EFV SPC
  - DAIDS grading system
  - Converted to % of 100
  - Low score = low CNS toxicity
- HADS
  - 14 items: 7 anxiety, 7 depression
  - Converted to % of 100
  - Low score (≤7/21 for A or D): unlikely A or D
- Sleep questionnaire
  - 19 standardised items
  - Converted to % of 100
  - Low score = better quality sleep

Endpoints

- Primary
  - Rate of neuropsychiatric & CNS toxicity after 4 wks of RAL (measured by proportion with any grade 2-4 CNS toxicity , CNS toxicity score and sleep quality questionnaire)

- Secondary
  - Rate of neuropsychiatric & CNS toxicity after 12 wks of RAL
  - Change in CD4 from B/L to wk 12
  - Proportion of patients with VL <50 copies/mL & <400 copies/mL at wks 4 & 12
  - Change in fasting lipids from B/L to wk 4 & wk 12
  - Proportion of patients with grade 2-4 laboratory AEs from B/L to wk 12
  - Proportion of patients with grade 2-4 non-CNS AEs from B/L to wk 12
  - Change in adherence (M-MASRI) from B/L to wk 12
  - Change in CNS toxicity (HADS) from B/L to wk 12
  - Change in inflammatory markers from B/L to wk 4 & wk 12 (*pending*)

Endpoints

- Primary
  - **Rate of neuropsychiatric & CNS toxicity after 4 wks of RAL** (measured by proportion with any grade 2-4 CNS toxicity , CNS toxicity score and sleep quality questionnaire)

- Secondary
  - **Rate of neuropsychiatric & CNS toxicity after 12 wks of RAL**
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  - Proportion of patients with grade 2-4 laboratory AEs from B/L to wk 12
  - Proportion of patients with grade 2-4 non-CNS AEs from B/L to wk 12
  - Change in adherence (M-MASRI) from B/L to wk 12
  - **Change in CNS toxicity (HADS) from B/L to wk 12**
  - Change in inflammatory markers from B/L to wk 4 & wk 12 (*pending*)

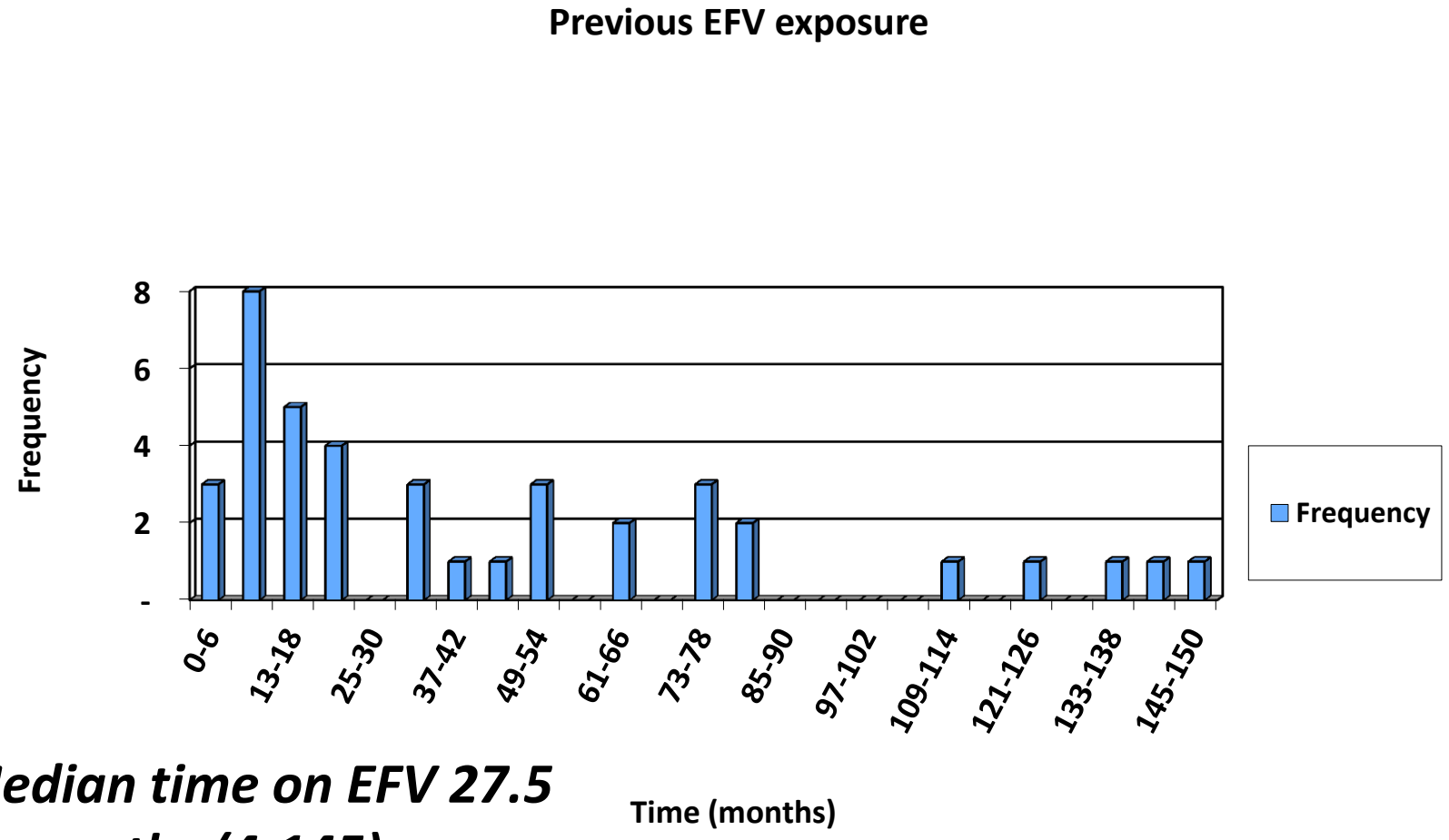
Results

- 40 patients enrolled
- 38 male
- 2 female
- Mean age 43 (range 29-62) years

Baseline regimen

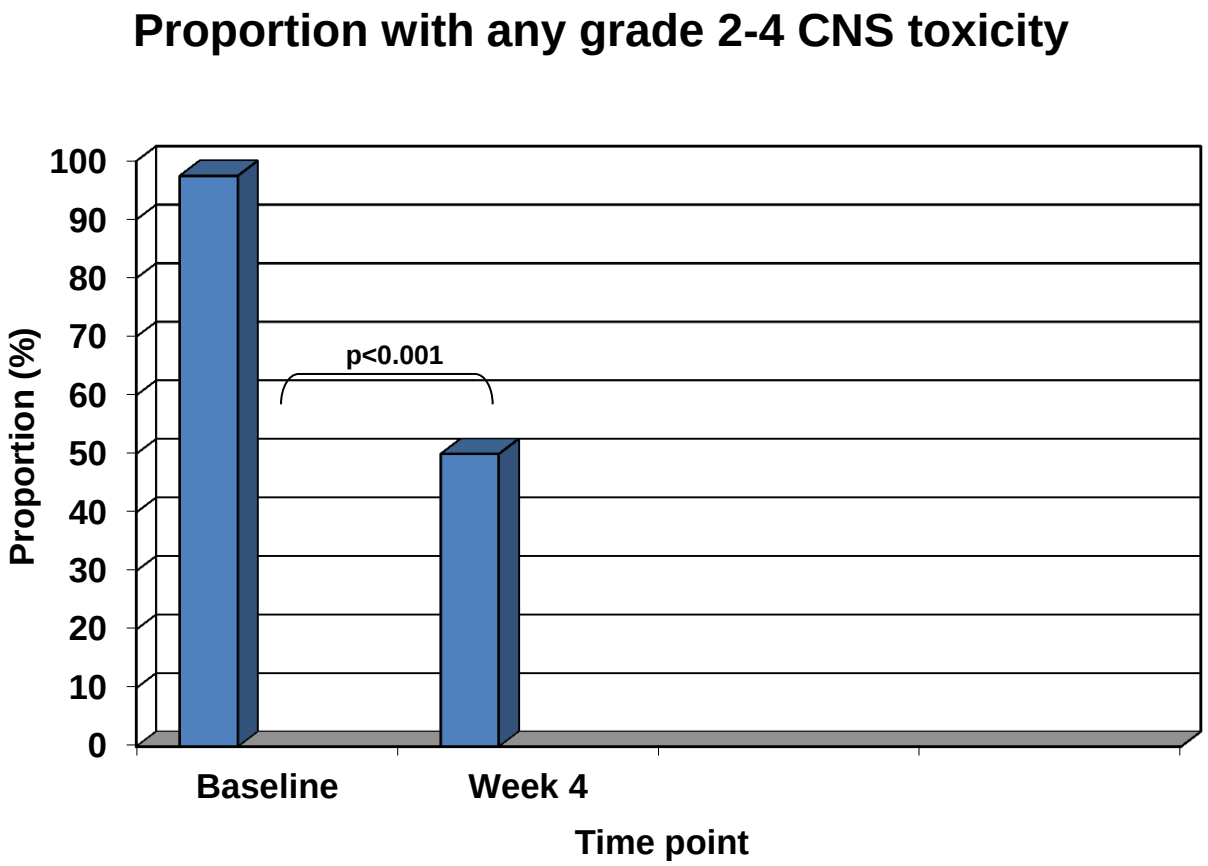
Regimen	Number (%)
TDF/FTC + EFV	40 (100%)
Other	0

Results – median time on EFV

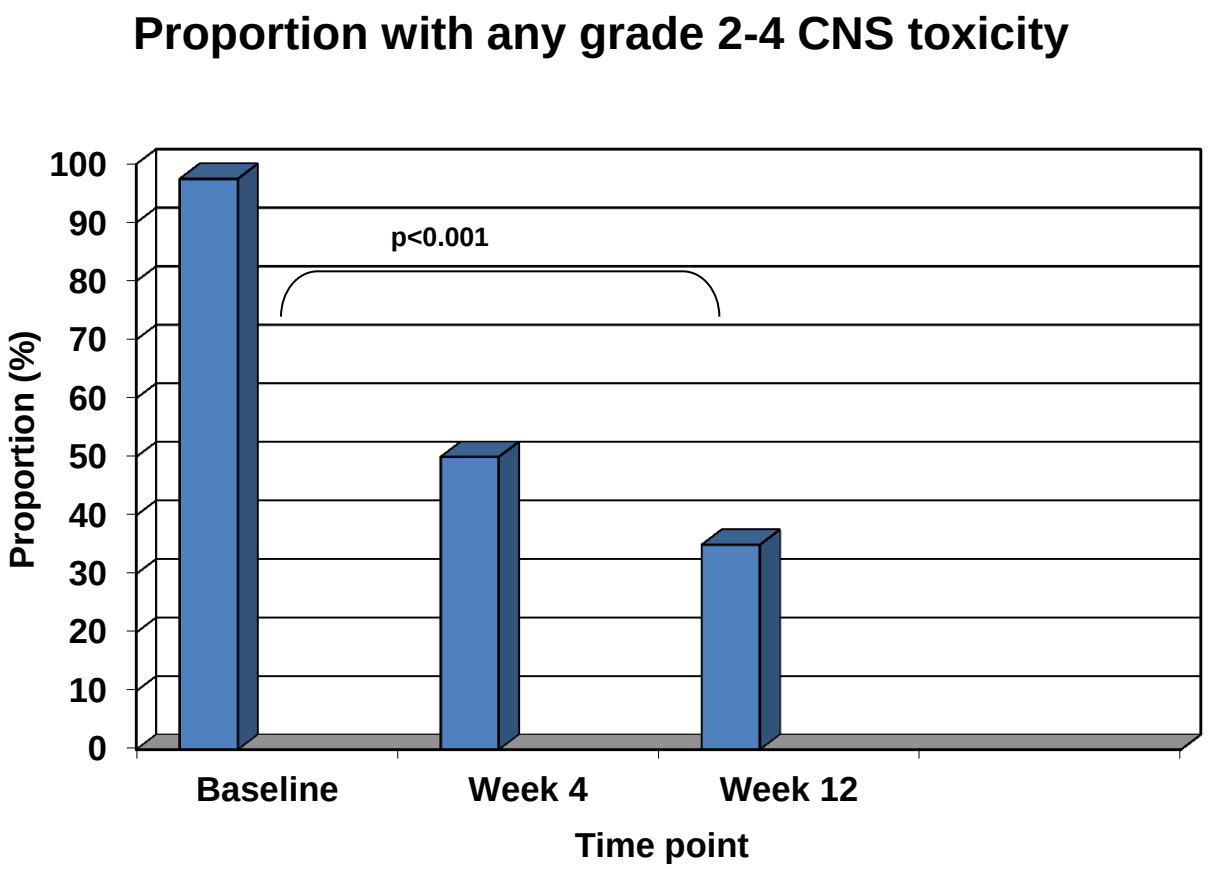


Median time on EFV 27.5 months (4-145)

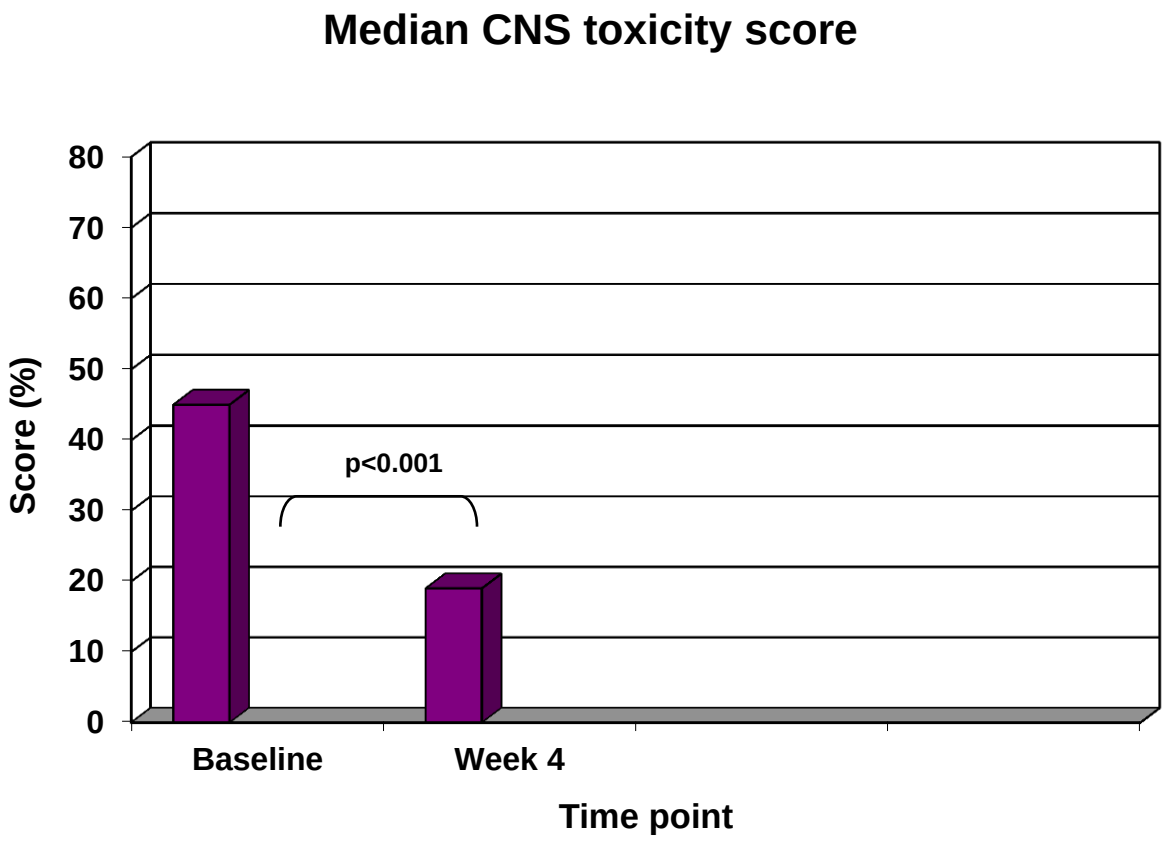
Results – proportion with any grade 2-4 CNS toxicity



Results – proportion with any grade 2-4 CNS toxicity



Results – CNS toxicity scores



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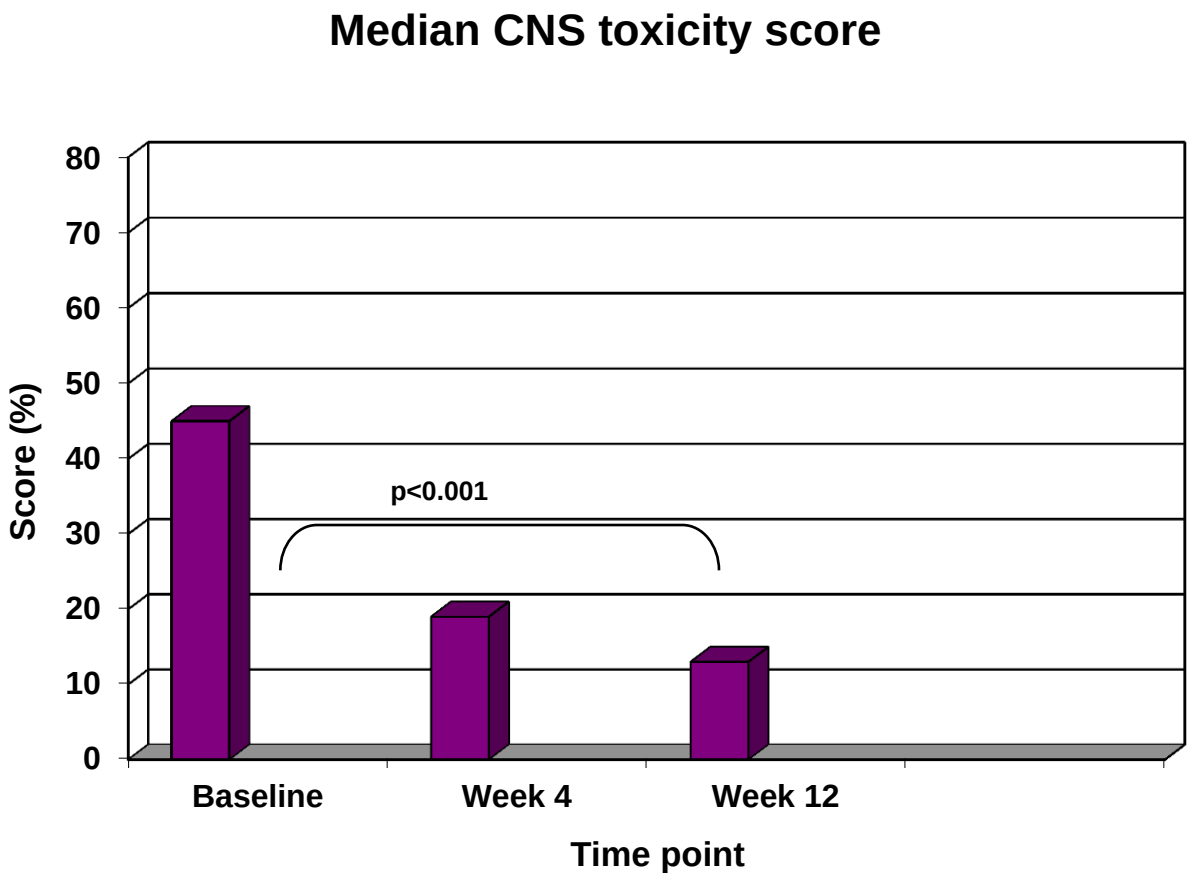
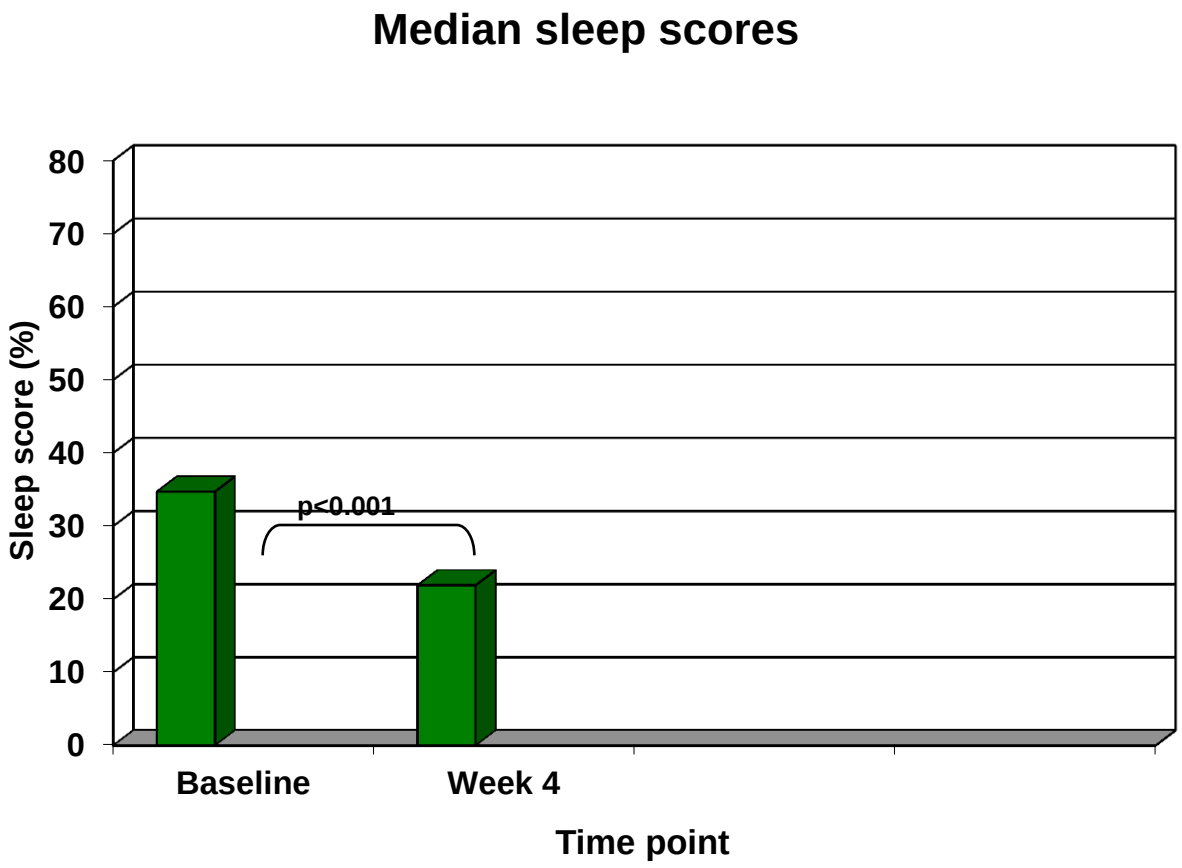


Results – sleep scores (SQ)



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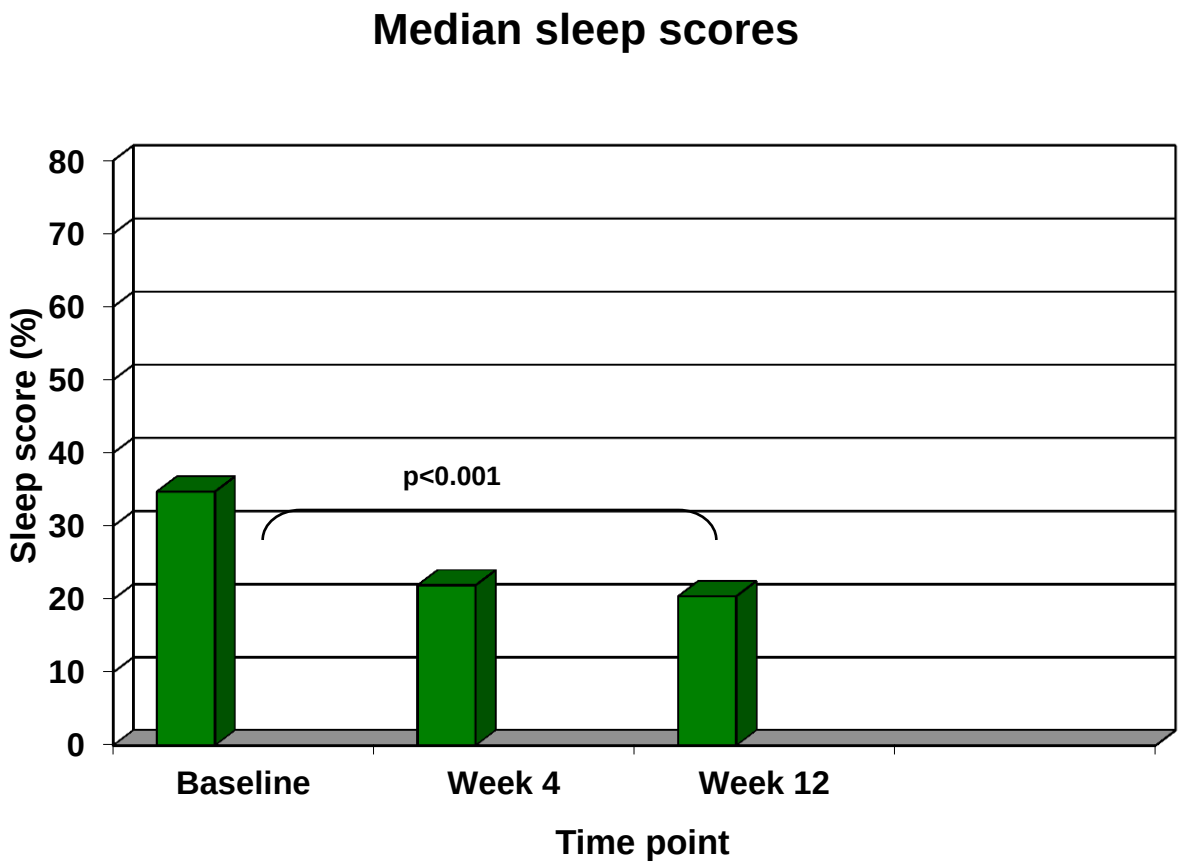
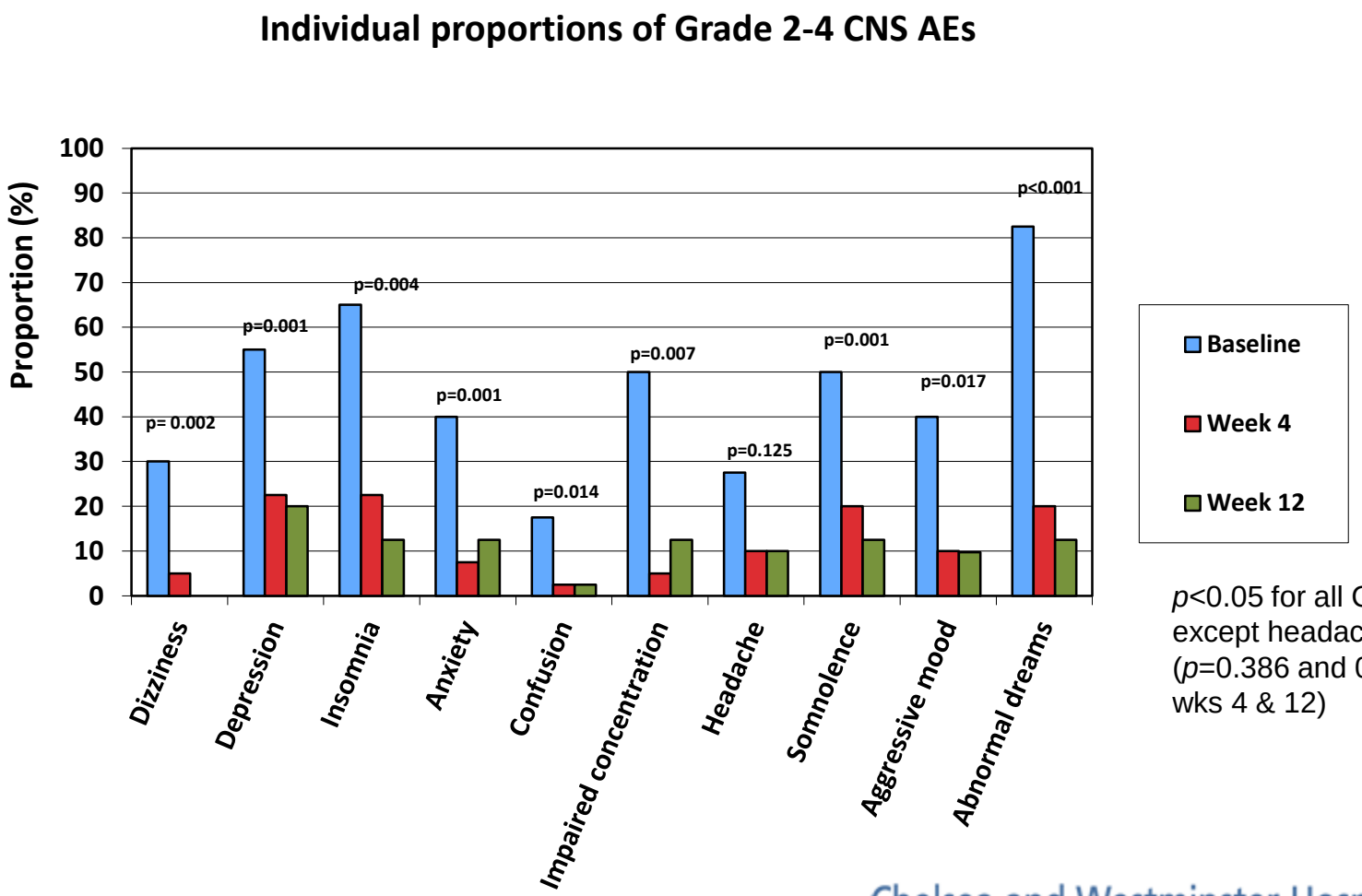


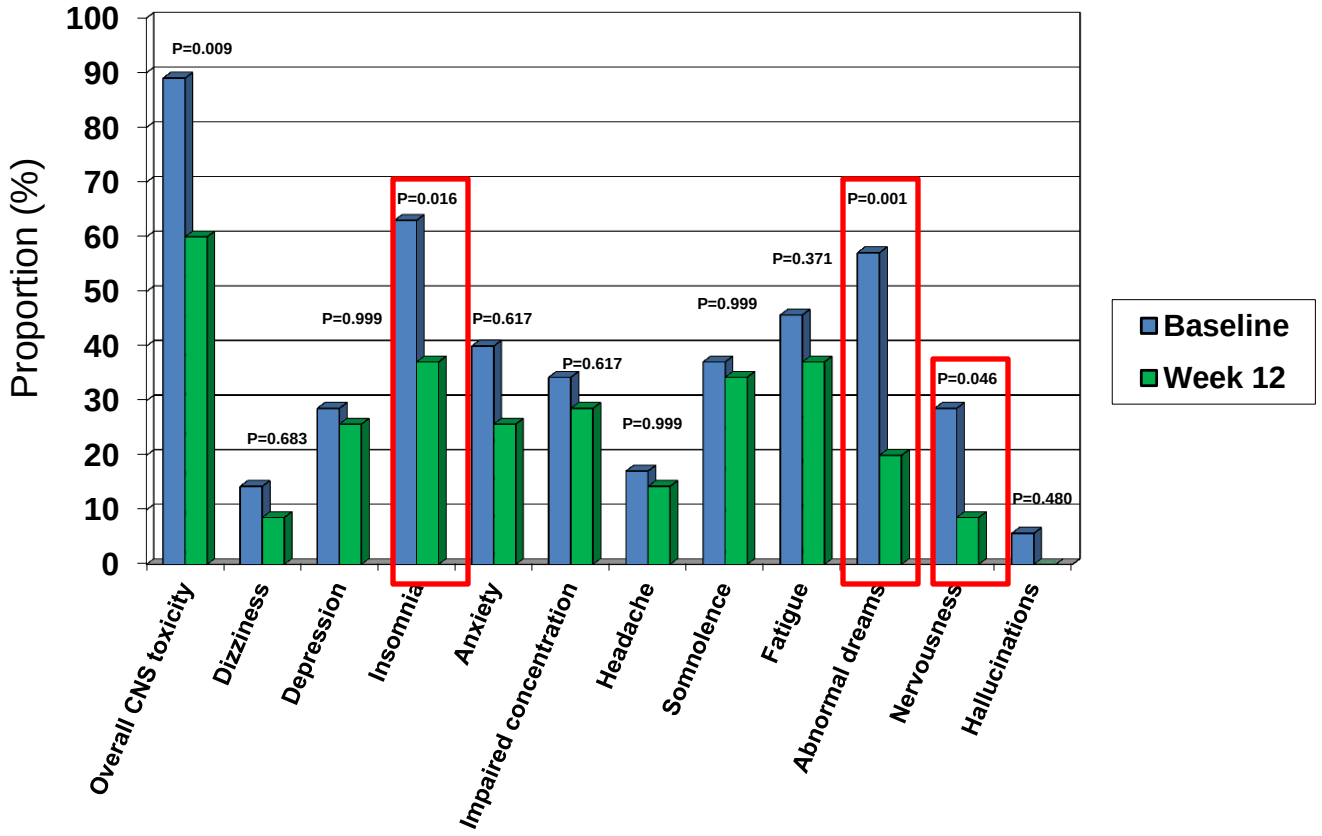
Results – CNS toxicity scores



p<0.05 for all CNS AEs except headache (*p*=0.386 and 0.125 at wks 4 & 12)

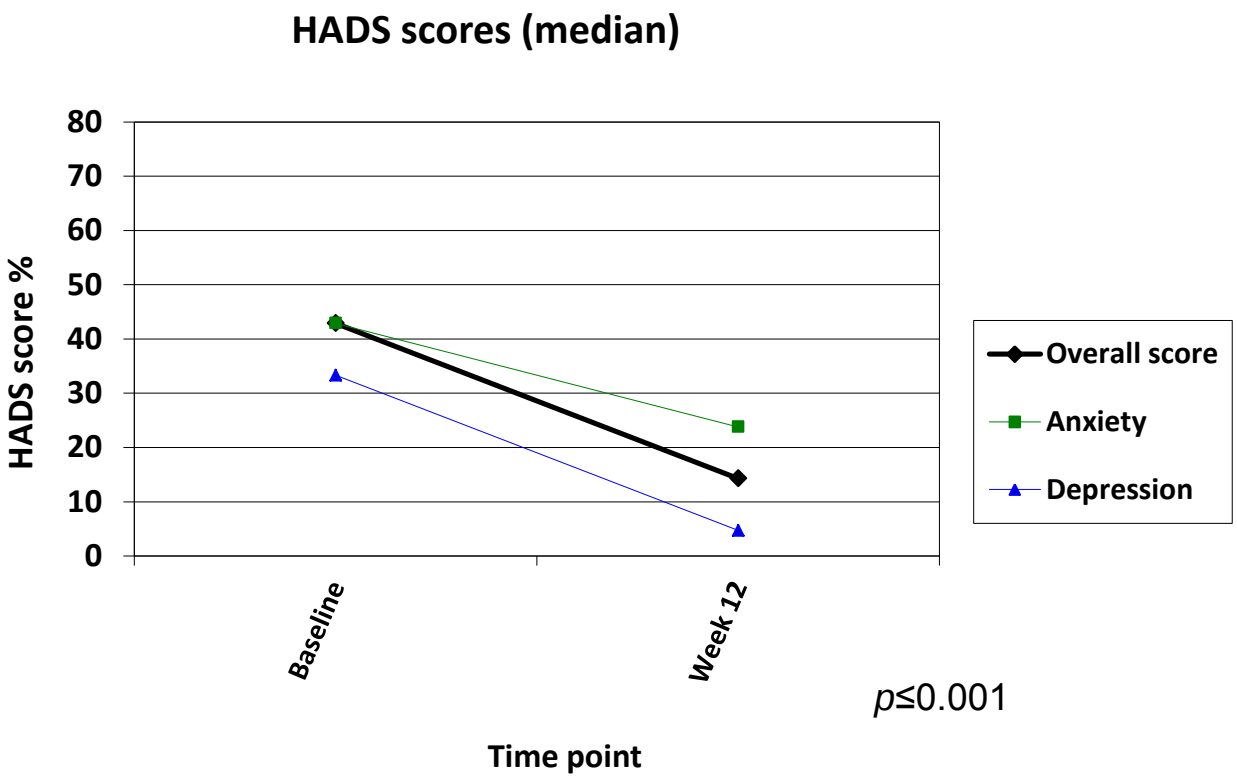
Comparison with EFV-ETR switch study

CNS grade 2-4 toxicity change from baseline on 12 weeks of ETR



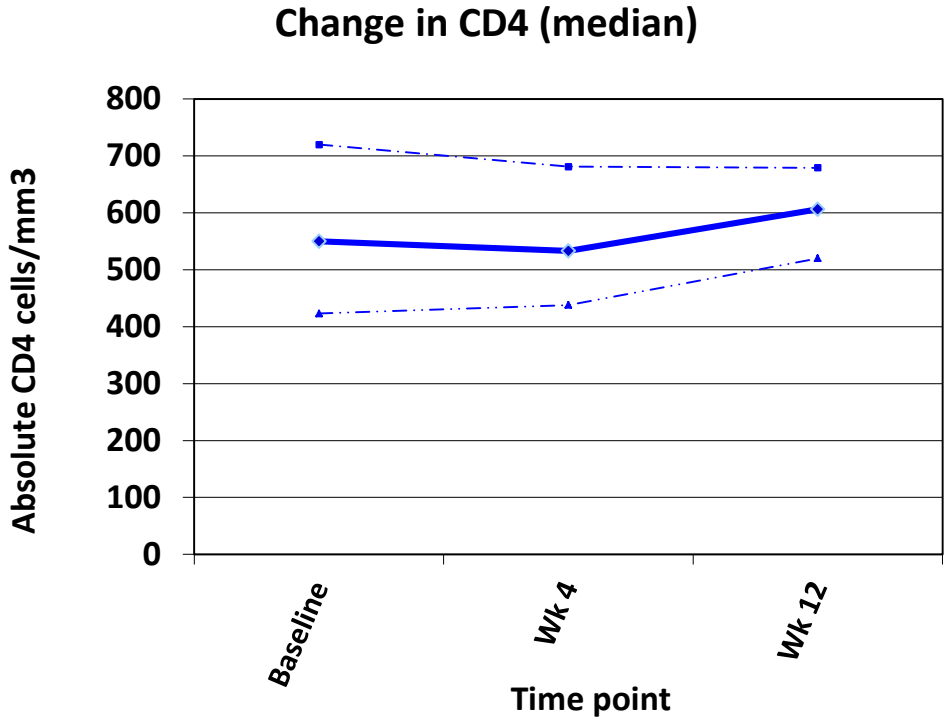
*Adapted from: Waters L et al. A phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine. *AIDS* 2011;25:65-71

Results – HADS scores



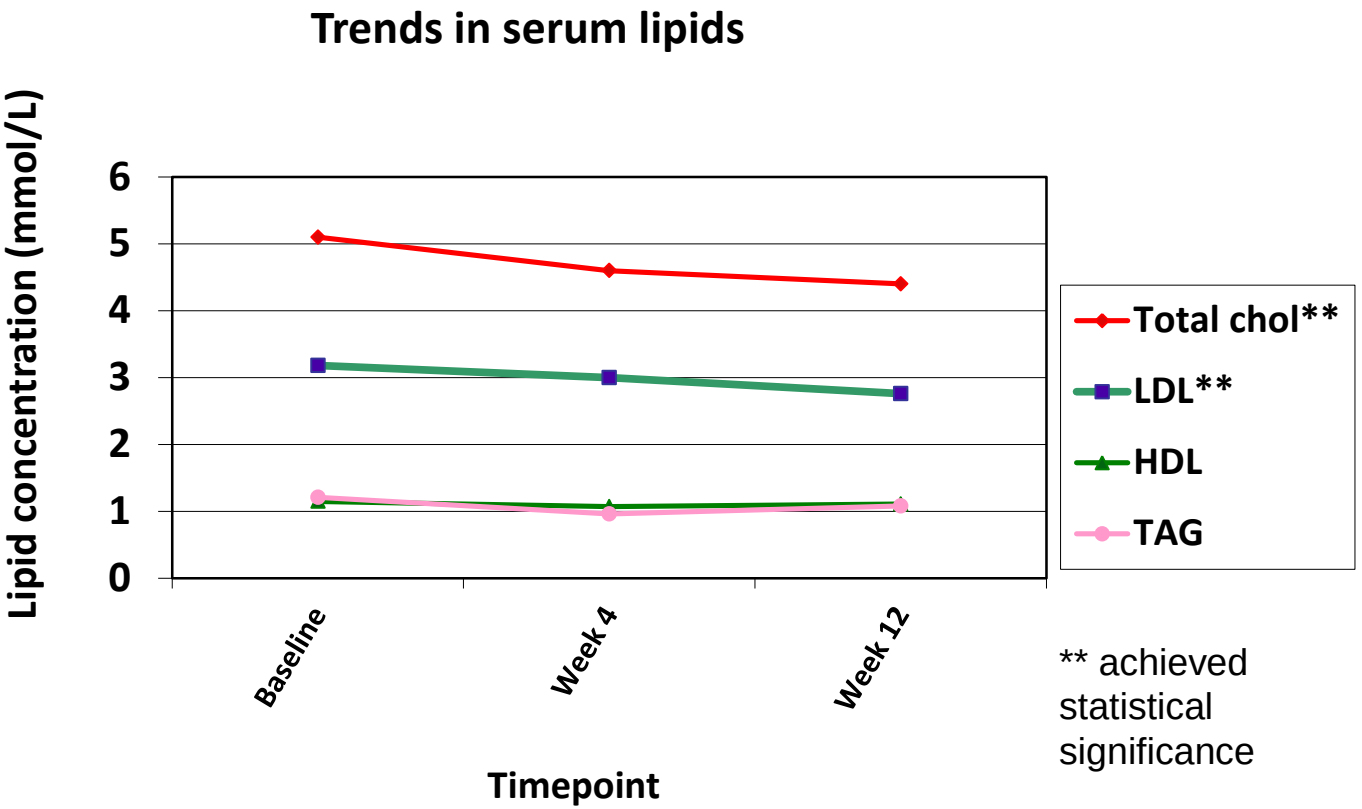
Results - change in CD4 and viral load suppression

All subjects maintained virologic suppression to wk 12



p=0.188 to wk 12

Results – change in lipids



** achieved statistical significance

Conclusions

- Switching EFV to RAL results in significant improvement of CNS AEs
- Virologic suppression is maintained
- Important to identify individuals with EFV toxicity as switching to alternative agents may result in better tolerability of cART, adherence* and quality of life

Acknowledgements

- MSD: financial support for this study
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- SSAT

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