

The impact of switching to etravirine on efavirenz-related CNS toxicity

Laura Waters¹, Martin Fisher², Alan Winston³, Chris Higgs¹, Wendy Holden², Lucy Garvey³, Sundhiya Mandalia¹, Nicky Perry², Nicola Mackie³ & Mark Nelson¹.

1. Chelsea & Westminster Hospital, London
2. Royal Sussex County Hospital, Brighton
3. St Mary's Hospital, London

Background

- Two NRTI + efavirenz is recommended for initial therapy of HIV infection
- Efavirenz is the preferred agent in the British guidelines
- Toxicities are the main driver of poor adherence and treatment failure

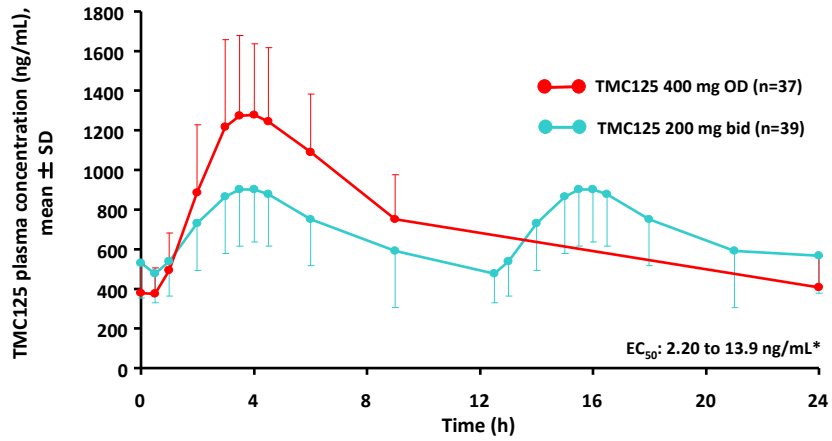
Background

- Central nervous system adverse events (CNS AE) are common on EFV-based regimens
- Most CNS AE are transient
- A significant minority of individuals experience ongoing CNS AE
- Differentiating drug AE from other causes of CNS problems can be difficult

Background

- Etravirine is a second generation NNRTI licensed for treatment-experienced HIV-1 infected patients
- Etravirine has a favourable toxicity profile
- Switching from efavirenz to etravirine is feasible in pharmacokinetic analyses

ETR steady state plasma PK profile



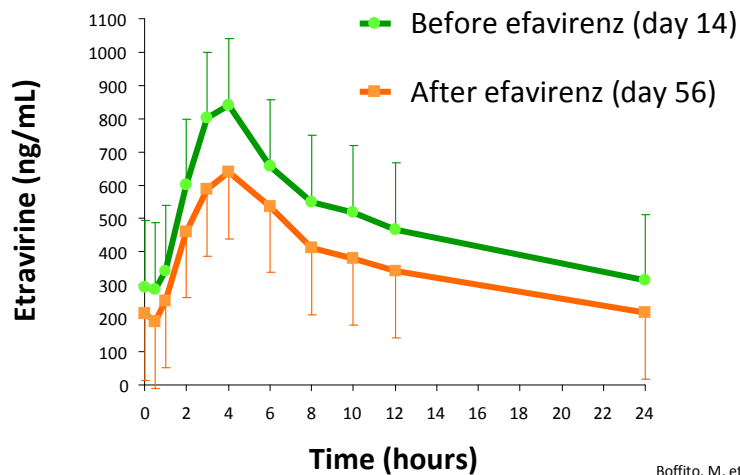
The daily systemic exposure to TMC125 with OD administration is the same as with bid administration of an equivalent dose per day

*corrected for protein binding

Schöllner-Gyüre M. 47th ICAAC, 2007. Poster A-1427. Tibotec, data on file.

ETR steady state plasma PK profile

Etravirine 400 mg once daily (n = 12) before (day 14) and after (day 56) efavirenz intake (bars = SD)



Boffito. M, et al 48th ICAAC 2008

Aim

- To assess the impact of switching from efavirenz to etravirine on CNS SE in patients with persistent CNS toxicity

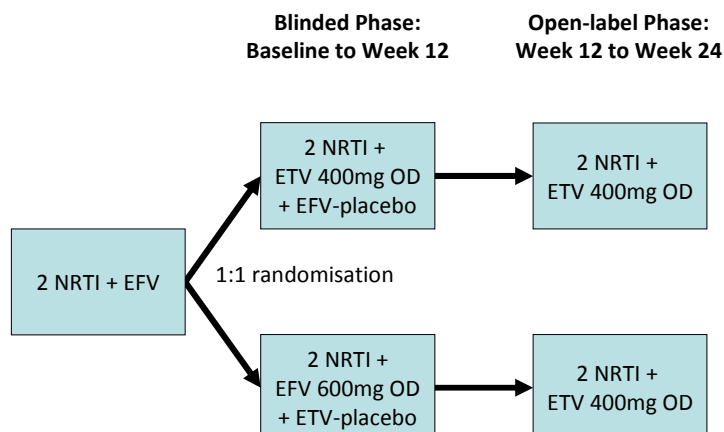
Methods

- Randomised, placebo-controlled, double-blind phase 4 study
- 3 UK study sites:
 - Chelsea & Westminster, London
 - Royal Sussex County Hospital, Brighton
 - St Mary's Hospital, London
- All patients on EFV for at least 12 weeks with CNS symptoms

Methods

- Major Inclusion Criteria:
 - Aged 18 or above
 - HIV-RNA <50 copies/ml; CD4 >50 cells/mm³
 - Stable EFV-based HAART for at least 12 weeks
 - Symptomatic toxicity associated with EFV
 - Effective birth control
- Major Exclusion Criteria:
 - Disallowed concomitant medication
 - Current ADI
 - Acute hepatitis
 - Pregnancy or breastfeeding
 - Significant medical condition or laboratory abnormality
 - Previous TMC125 or TMC278
 - Resolution of CNS toxicity before baseline

Study Design



CNS AE

- CNS AE based on DAIDS AE grading
 - 0=absent; 1=mild; 2=moderate; 3=severe; 4=life-threatening
 - 12 AE considered:
 - Dizziness •Depression •Insomnia
 - Anxiety •Pain •Impaired concentration
 - Headache •Somnolence •Fatigue
 - Abnormal dreams •Nervousness •Hallucinations

CNS Score

- Sum total of all grades of CNS toxicity
- Example:
 - Grade 1 dizziness
 - Grade 2 headache
 - Grade 2 depression
 - Grade 1 insomnia

= CNS score 6

End-Points

- Primary:
 - Change in proportion with grade 2-4 CNS AE at week 12
- Secondary:
 - Change in CNS score:
 - At weeks 12 and 24
 - Combined (both arms) after 12 weeks of etravirine
 - Median number grade 2-4 CNS AE
 - At weeks 12 and 24
 - Combined (both arms) after 12 weeks of etravirine

Secondary End-Points (cont)

- Viral suppression
- CD4 change
- Fasting lipids
- Safety and non-CNS tolerability
- Adherence (M-MASRI)
- Tolerability (HIV symptoms profile)
- Hospital anxiety and depression scale (HADS)

Statistical Analyses

- Quantitative data with hyper geometric distribution has been presented as medians with inter-quartile ranges; qualitative data has been presented as proportions.
 - Between group quantitative comparisons : Mann-Whitney U test
 - Between groups qualitative comparisons: Chi-squared test +/- Yates' correction for small numbers.
- Within subject changes over time:
 - Quantitative: Wilcoxon signed rank test
 - Qualitative: McNemar's Chi squared test (due to relatively small sample p-values presented as Yate's corrected [1]).
- All data analyses were performed in SAS V9.1; all p-values are two tailed

Agresti A (1990) Categorical Data Analysis, New York, John Wiley and Sons

Results

- 38 patients enrolled
- All male; 37 Caucasian
- Median age 43 years
- Baseline results:
 - HIV-RNA <50 copies/ml in 100%
 - Median CD4 468 (IQR 378-580)

Baseline Regimen

Regimen	Number (%)
Truvada + Efavirenz	11 (29%)
Kivexa + Efavirenz	11 (29%)
Atripla	11 (29%)
Other NRTI* + Efavirenz	5 (13%)

*Other NRTI:
ABC/TDF (3)
TDF/3TC (2)

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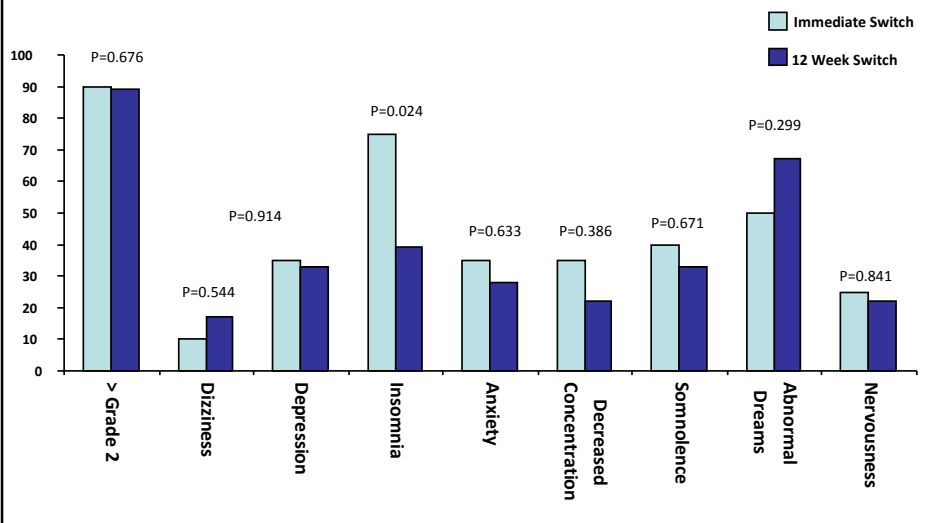
**Median prior EFV
exposure
= 21.4 months**

*Other NRTI:
ABC/TDF (3)
TDF/3TC (2)

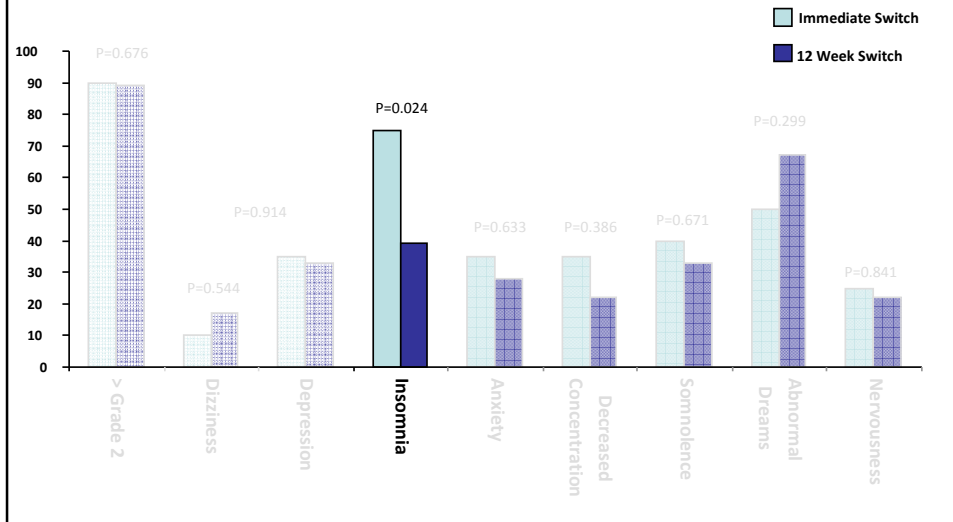
Subject Disposition

	Immediate Switch	Delayed Switch
Baselined	20	18
Completed to week 24	19	15
Lost to Follow-up	1	0
Withdrawal of consent	0	2
Adverse Event	0	1
Virological Failure	0	0

CNS Toxicity at Baseline

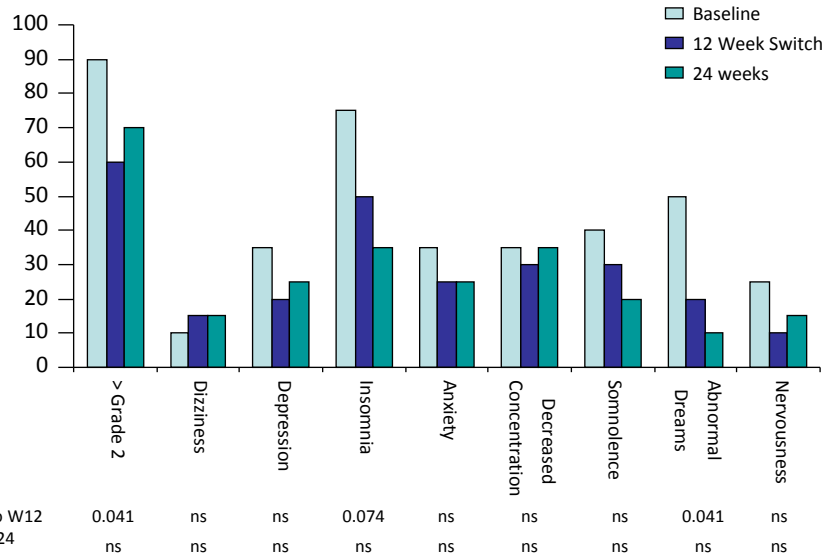


CNS Toxicity at Baseline

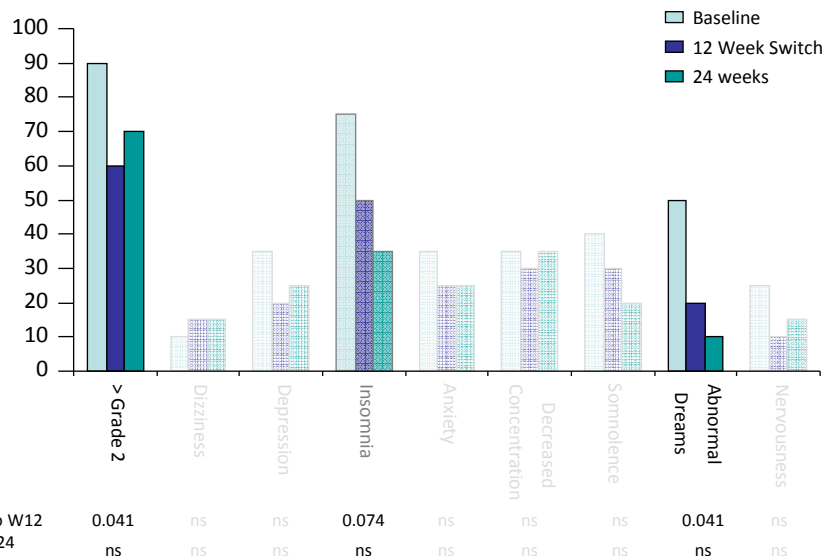


Week 24 Results

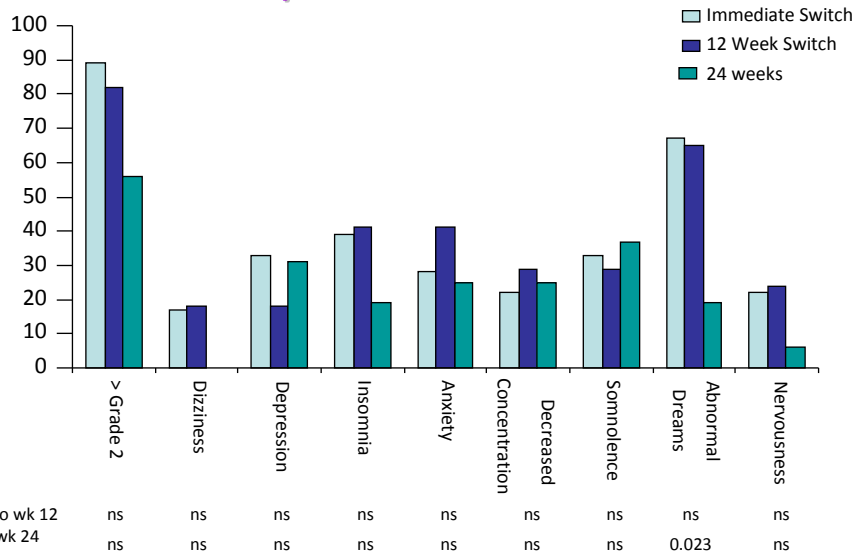
Grade 2-4 CNS Toxicity: Immediate switch arm



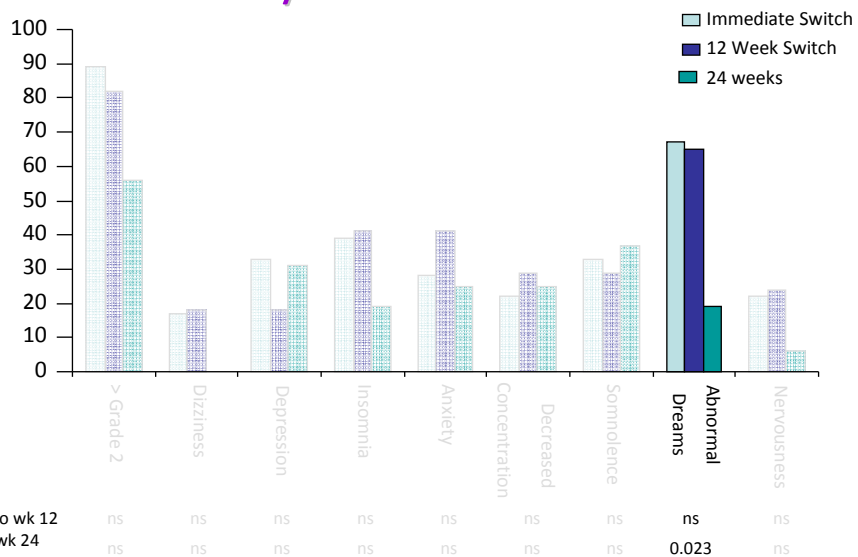
Grade 2-4 CNS Toxicity: Immediate switch arm



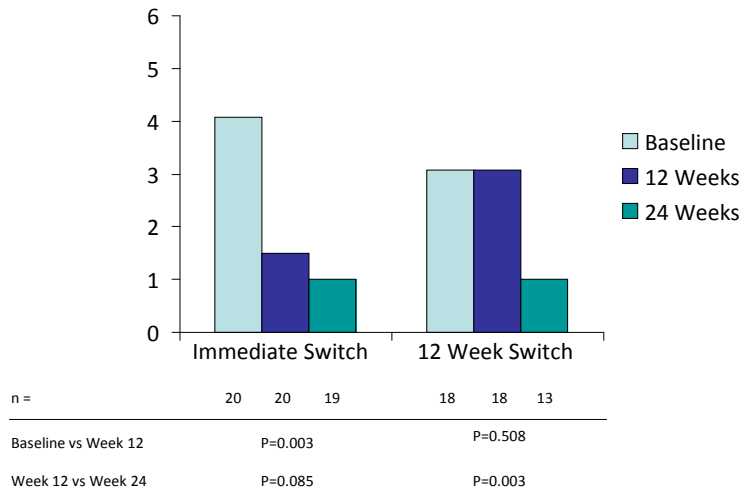
Grade 2-4 CNS Toxicity: Delayed switch arm



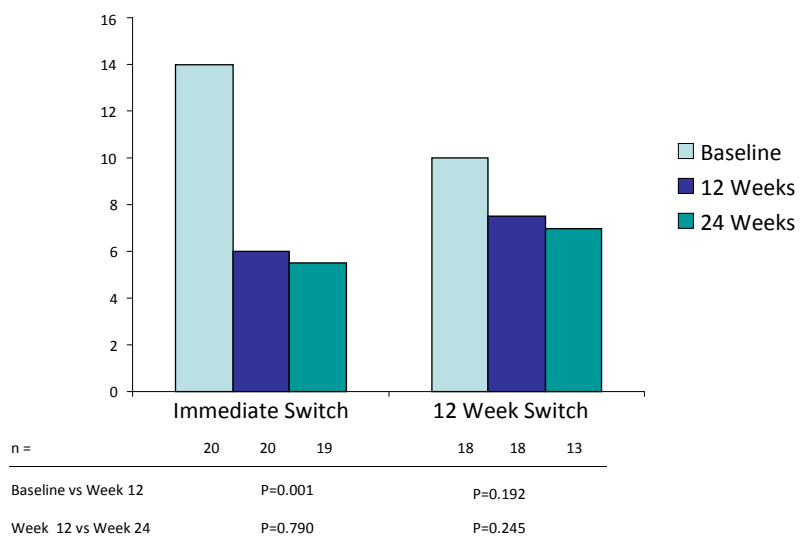
Grade 2-4 CNS Toxicity: Delayed switch arm



Median Number of Grade 2-4 CNS Toxicities

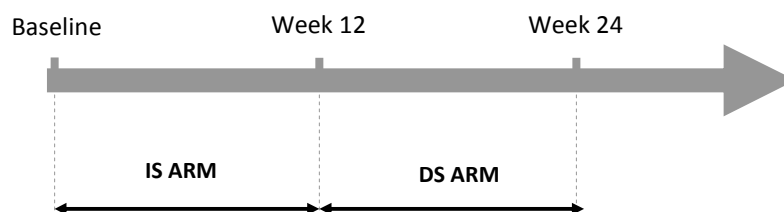


CNS Score

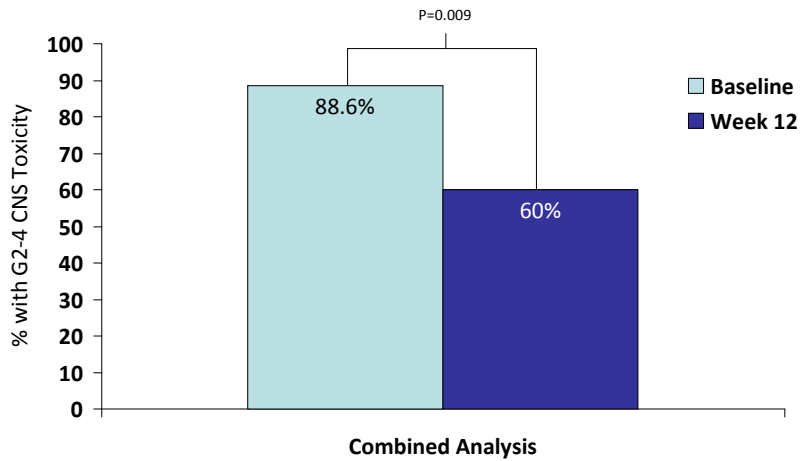


Combined Analyses: CNS Toxicity after 12 weeks of Etravirine

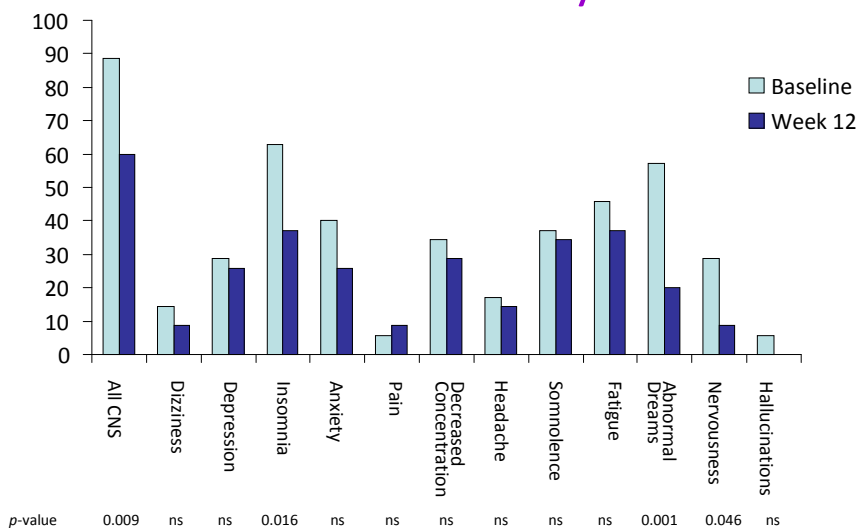
Combined Analysis



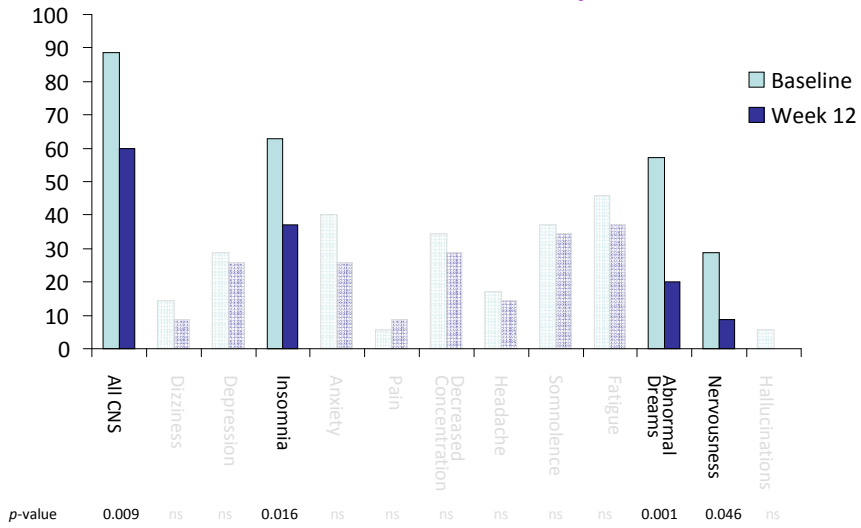
Grade 2-4 CNS Toxicity: Combined Analysis



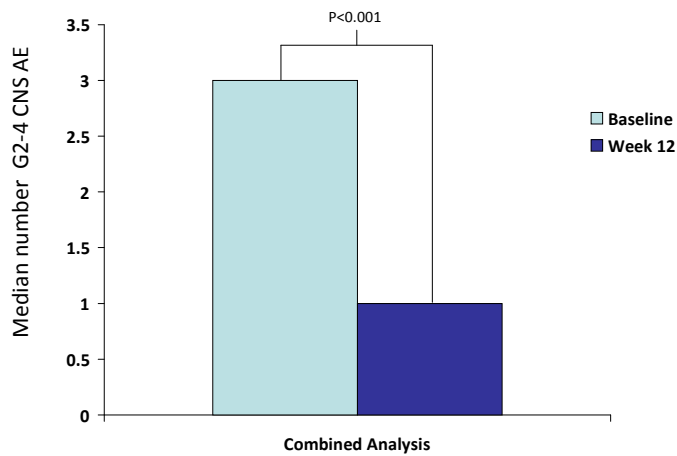
Individual Grade 2-4 CNS Toxicities: Combined Analysis



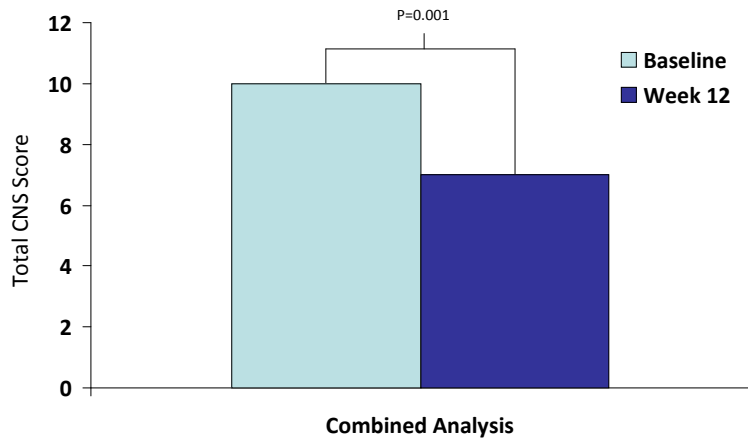
Individual Grade 2-4 CNS Toxicities: Combined Analysis



Median Number Grade 2-4 CNS AE: Combined Analysis



Total CNS Score: Combined Analysis



Conclusions

- Switching patients with CNS AE from efavirenz to etravirine resulted in significant improvements in:
 - Overall grade 2-4 CNS AE
 - Grade 2-4 insomnia, abnormal dreams, nervousness
 - Median number CNS AE
 - Total CNS score

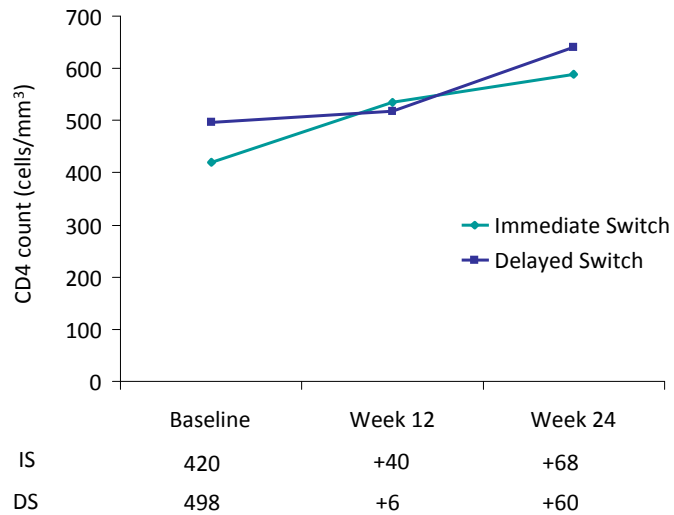
Conclusions

- Etravirine provides an effective and tolerable switch option in patients with efavirenz-related CNS AE
- The lack of improvement for some AE and some patients highlights the importance of other causes of CNS symptoms

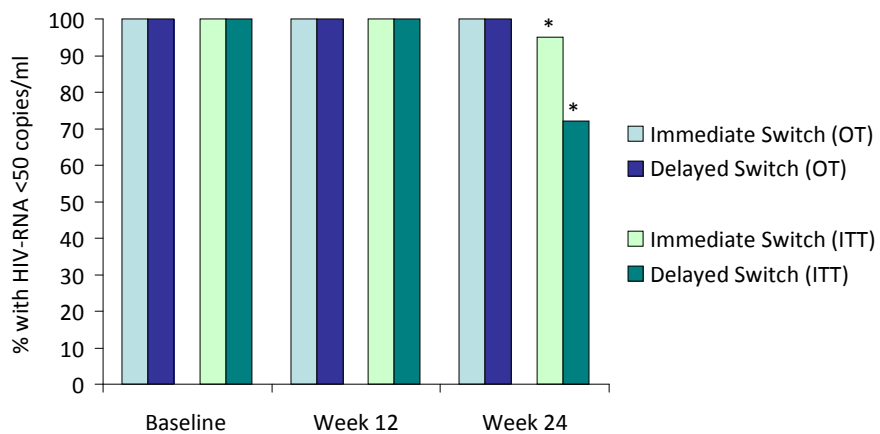
Acknowledgements

- Akil Jackson
- Paul Randell
- Andrew Scourfield
- All the patients from the 3 sites

CD4 Results



Virological Outcomes



*No discontinuations due to virological failure