

Switch from Efavirenz for CNS
toxicity
UK Experience

Available Antiretrovirals 2013

NRTIs

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

NNRTIs

- Efavirenz
- Nevirapine
- Etravirine
- Rilpivirine

Protease Inhibitors

- Atazanavir
- Darunavir
- Fos-Amprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

New Classes

Fusion Inhibitors

- Enfuvirtide






R5 Inhibitors

- **Maraviroc**

Integrase Inhibitors






- Raltegravir

Guideline recommendations for first-line treatment of naïve patients

	 IAS¹ <small>International Antiviral Society-USA</small>	 DHHS² <small>DEPARTMENT OF HEALTH & HUMAN SERVICES-USA</small>	 EACS³ <small>European AIDS Clinical Society</small>	 BHIVA⁴ <small>British HIV Association</small>	 WHO⁵ <small>World Health Organization</small>
NRTI					
TDF/FTC or 3TC	X	X	X	X	X
ABC/3TC	X		X		
ZDV/3TC					X
NNRTI					
EFV	X	X	X	X	X
NVP			X		X
RPV			X		
PI					
ATV/r	X	X	X	X	
DRV/r	X	X	X	X	
LPV/r			X		
II					
RAL	X	X	X	X	

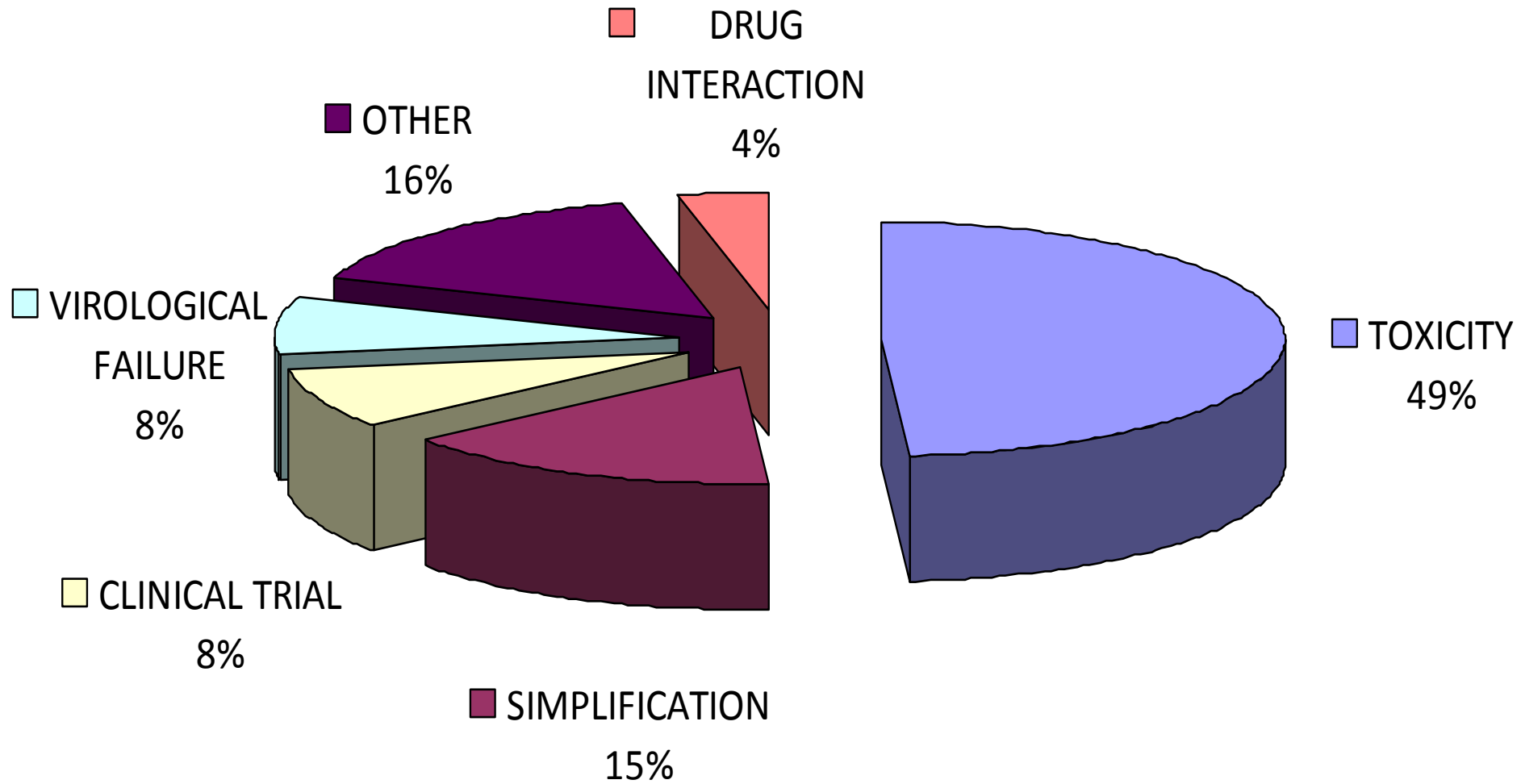
1. Thompson M, et al. JAMA 2012;308:387–402 2. <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>
3. EACS guidelines, November 2012. Available at:<http://www.europeanaidscinicalsociety.org/images/stories/EACS-Pdf/eacsguidelines-6.1.pdf>
4. http://www.bhiva.org/documents/Guidelines/Treatment/2012/hiv1029_2.pdf 5. <http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf>

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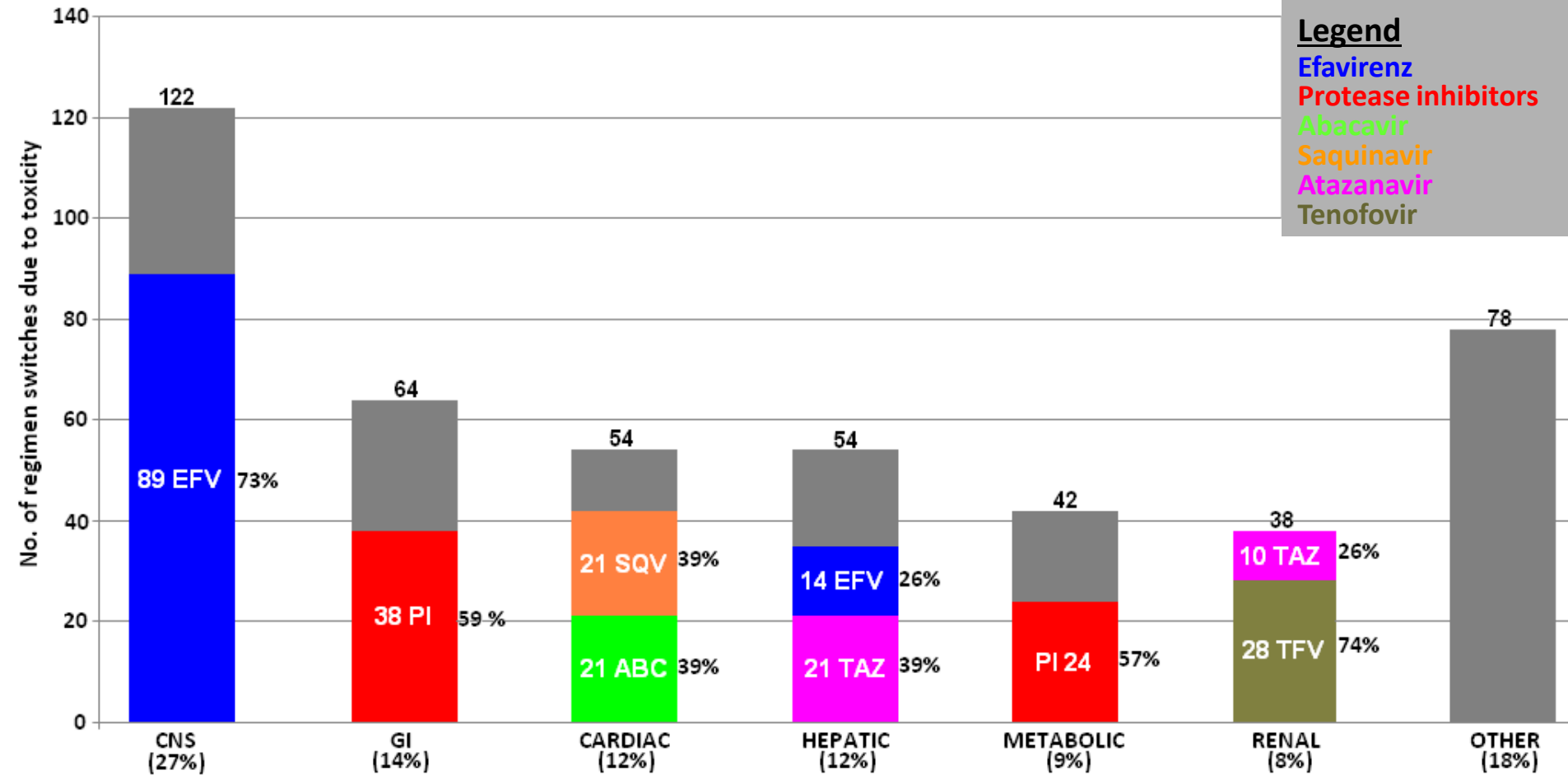
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Reasons for switching ARVs

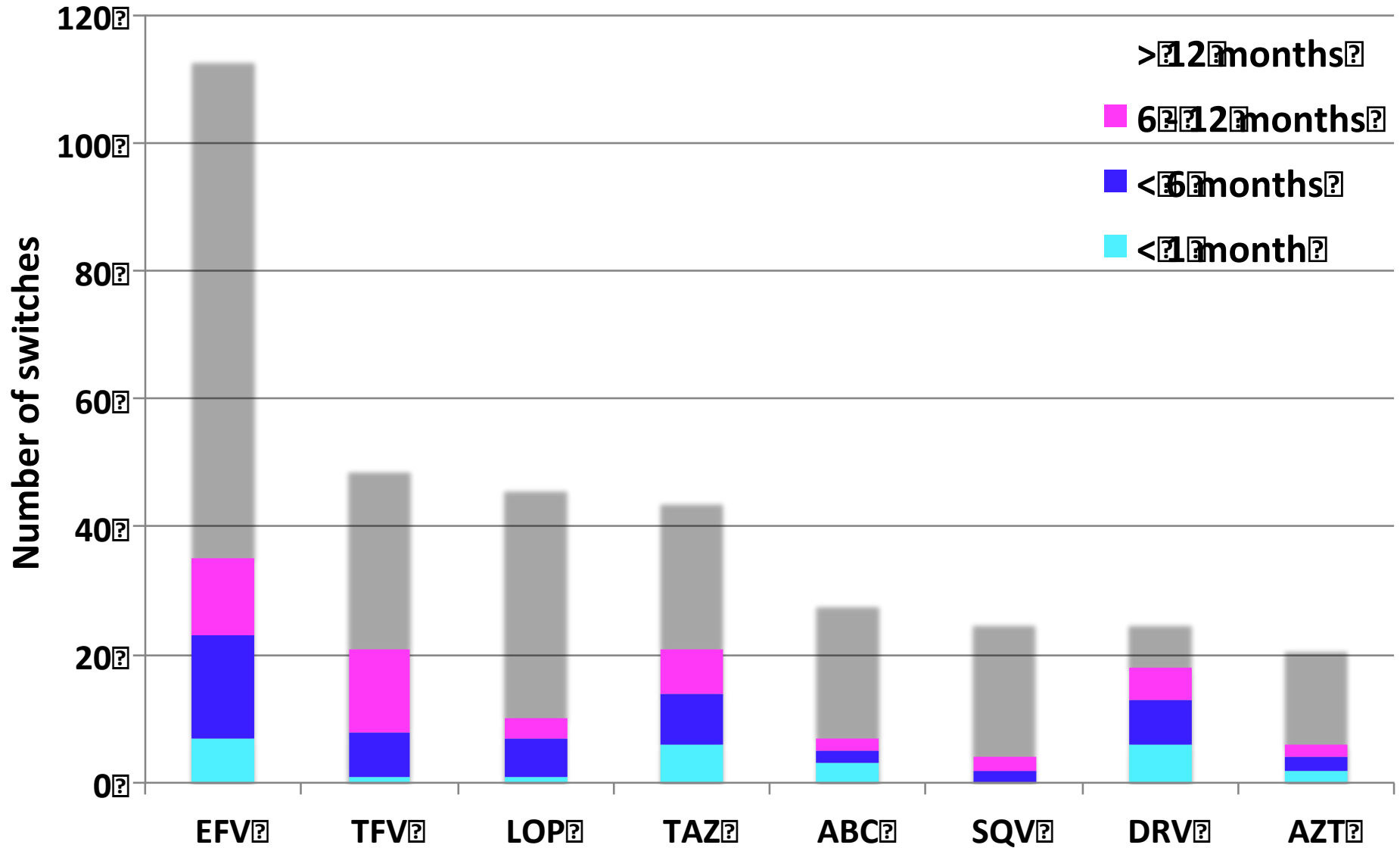


Toxicity switches

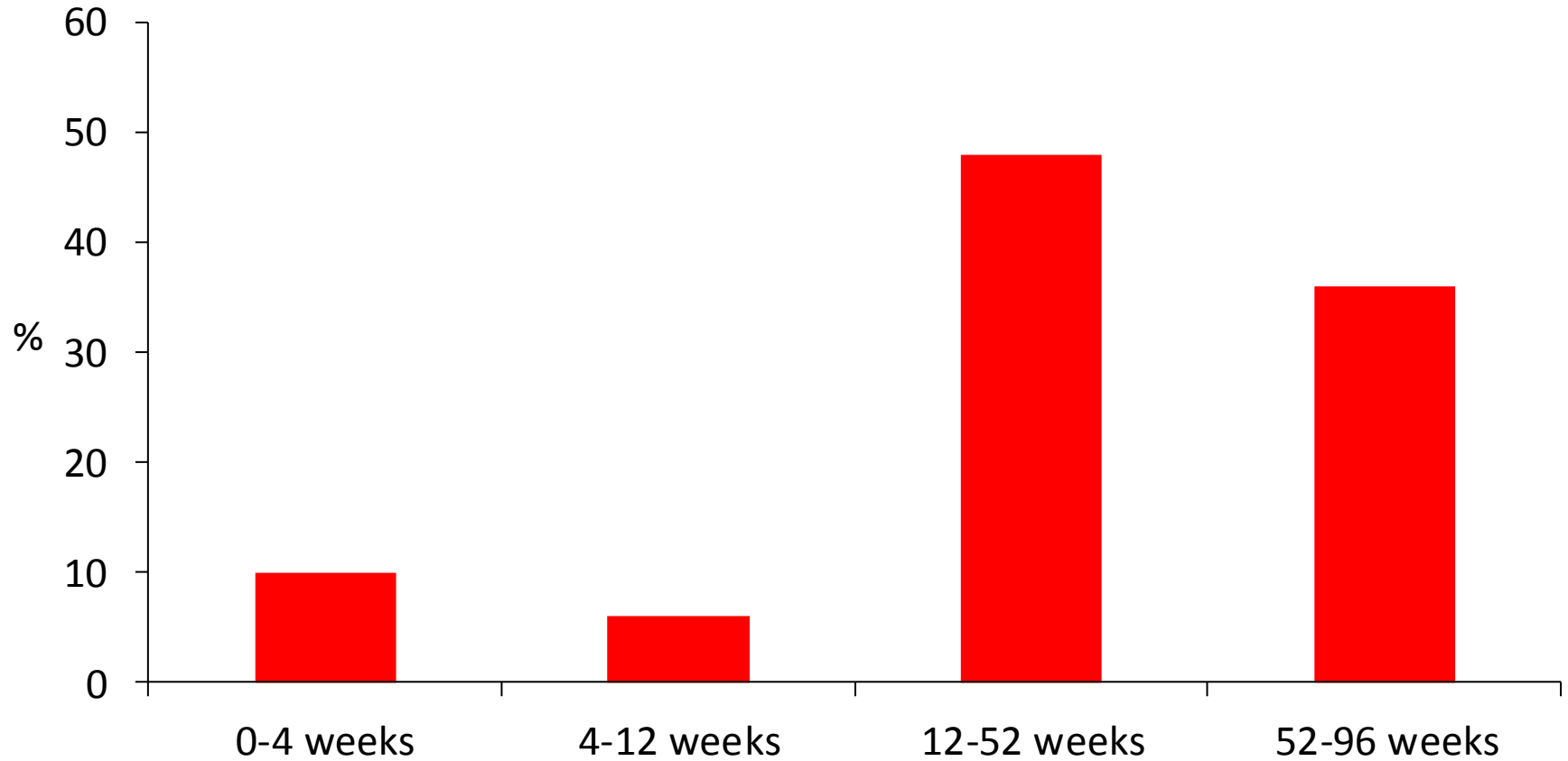
- 452 switches due to toxicity/perceived toxicity



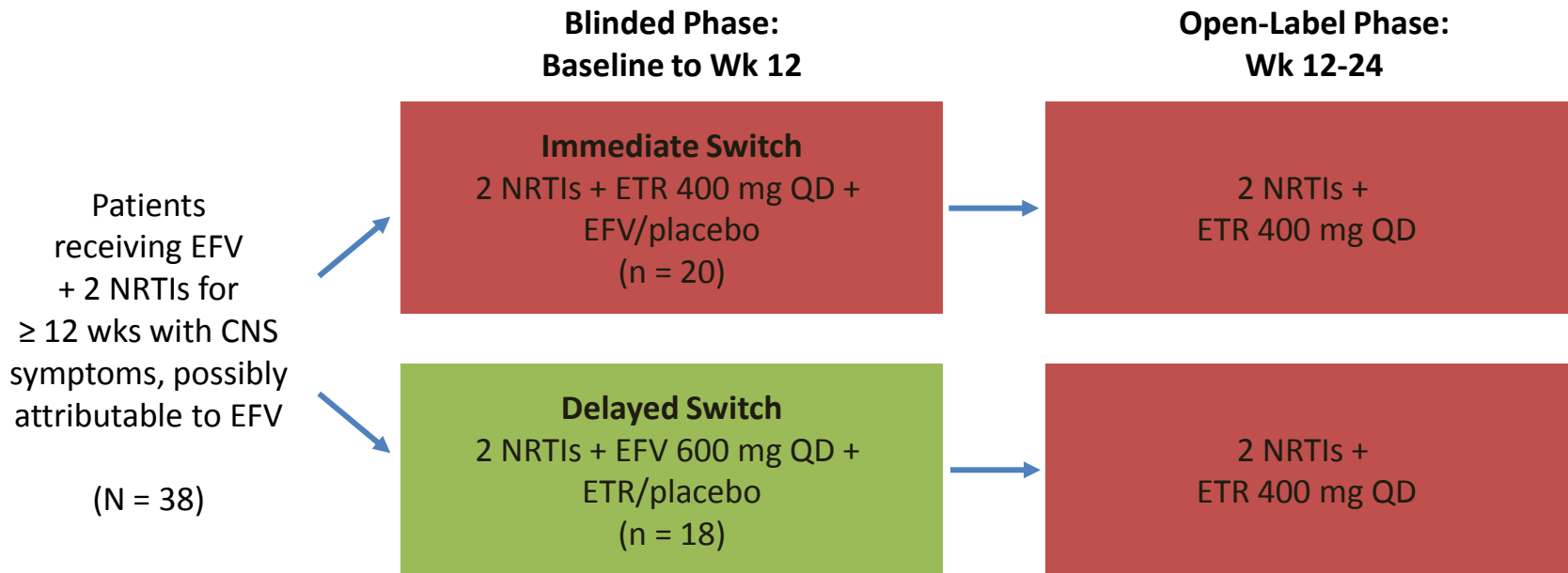
Time to toxicity switch



Time to switch for CNS toxicity

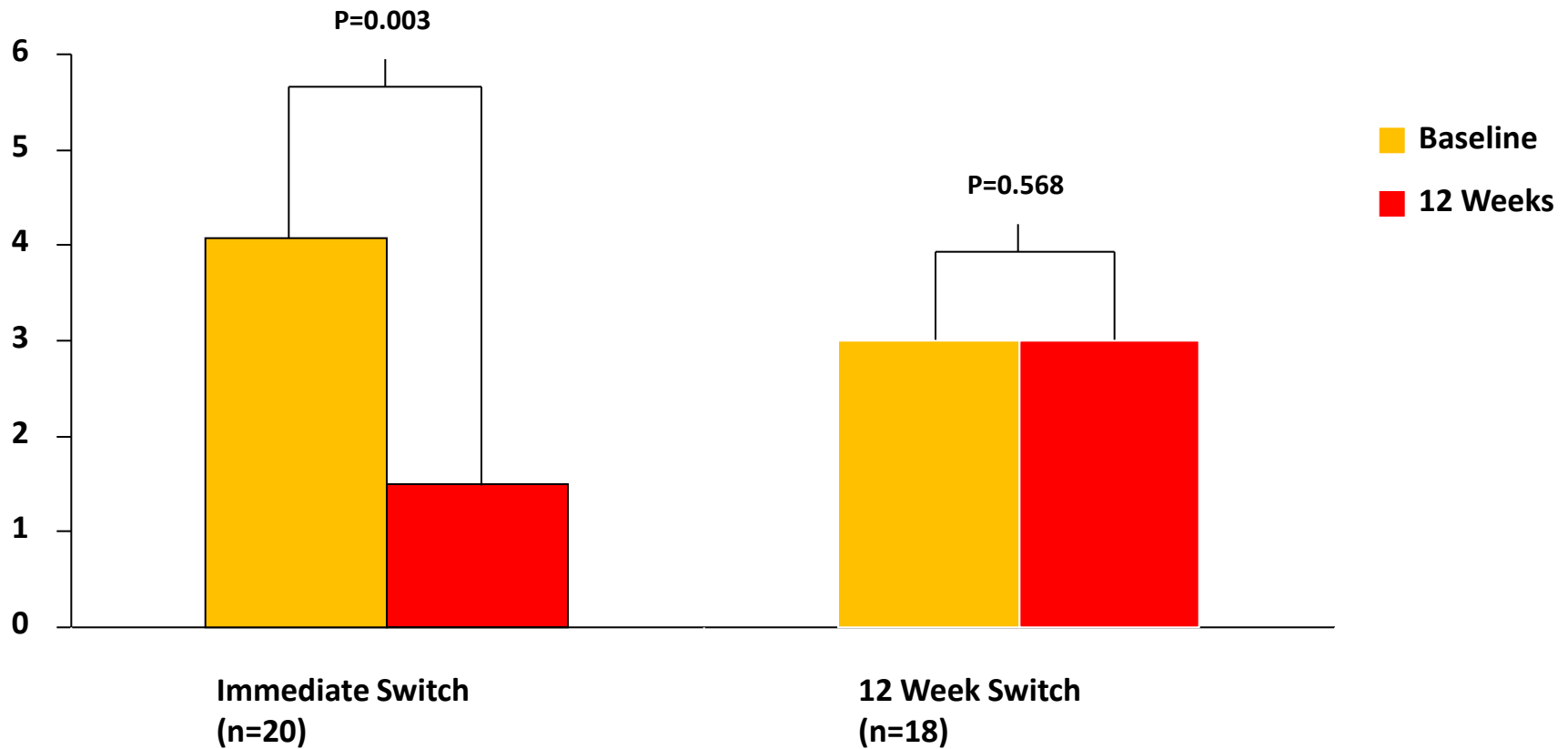


Substitution of EFV With ETR in Patients With CNS Toxicity

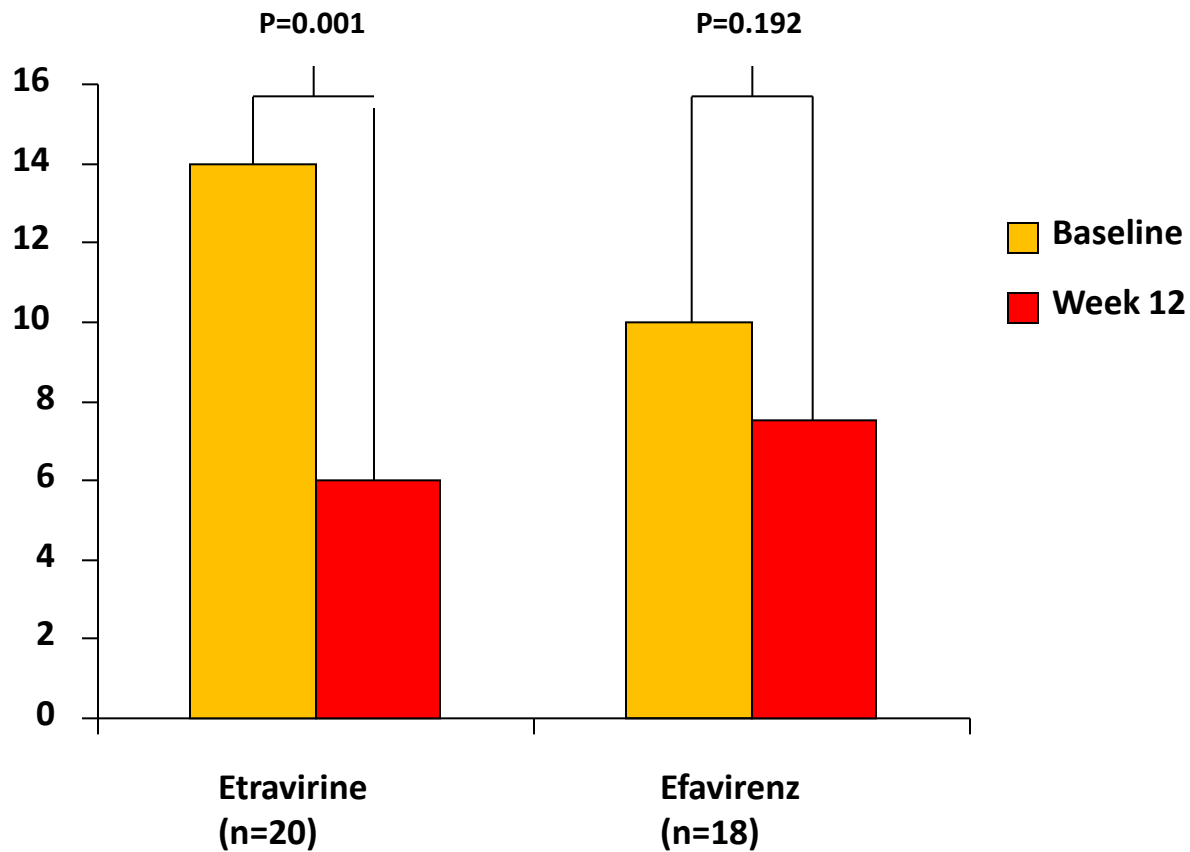


- Primary endpoint: change in % of patients with grade 2-4 CNS AEs at Wk 12
 - Secondary: change in CNS score at Wk 12, Wk 24, and for both arms combined after 12 wks of ETR; median number grade 2-4 CNS AEs at Wk 12, Wk 24, and for both arms combined after 12 wks of ETR

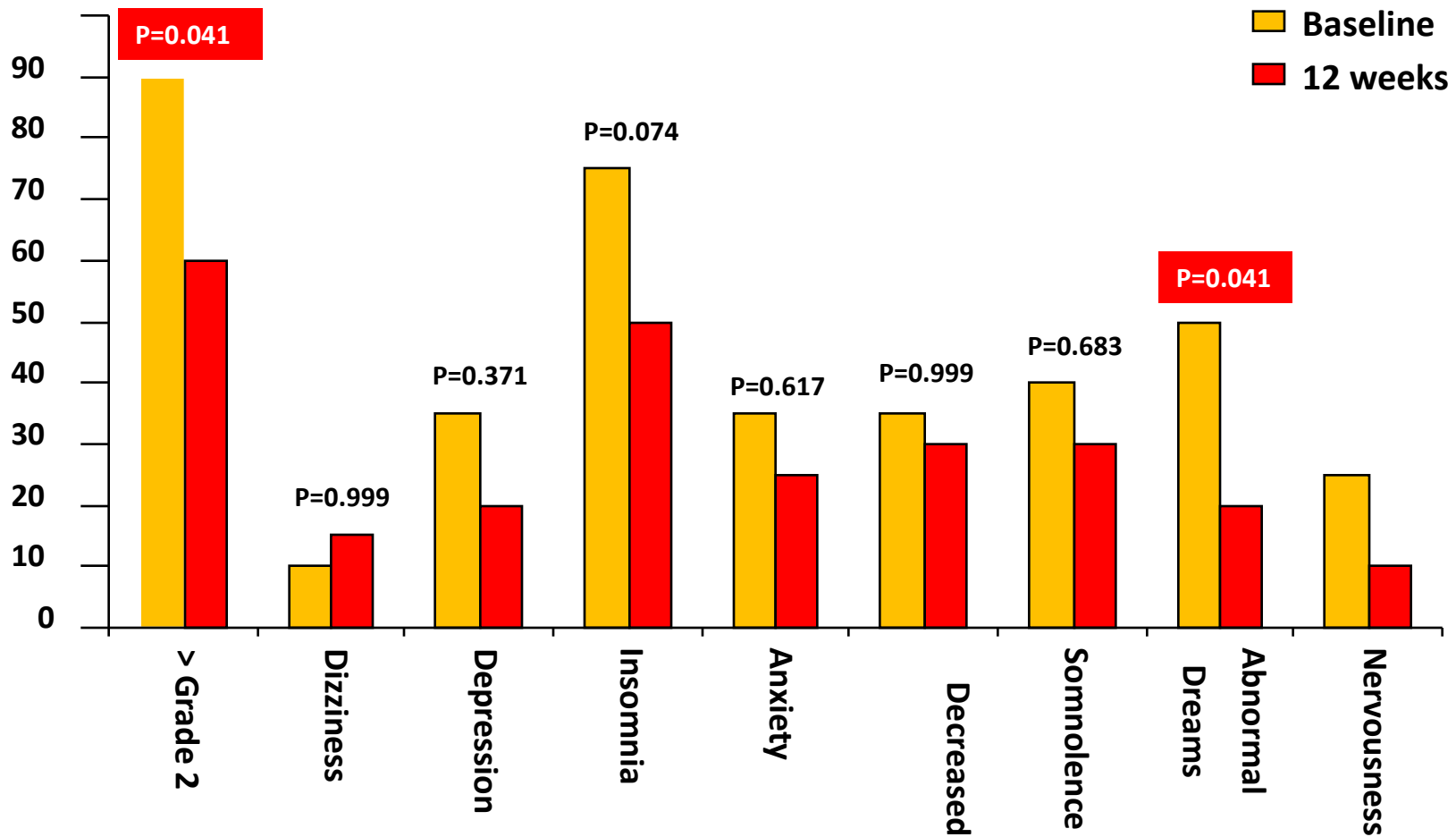
Median Number of Grade 2-4 CNS Toxicities



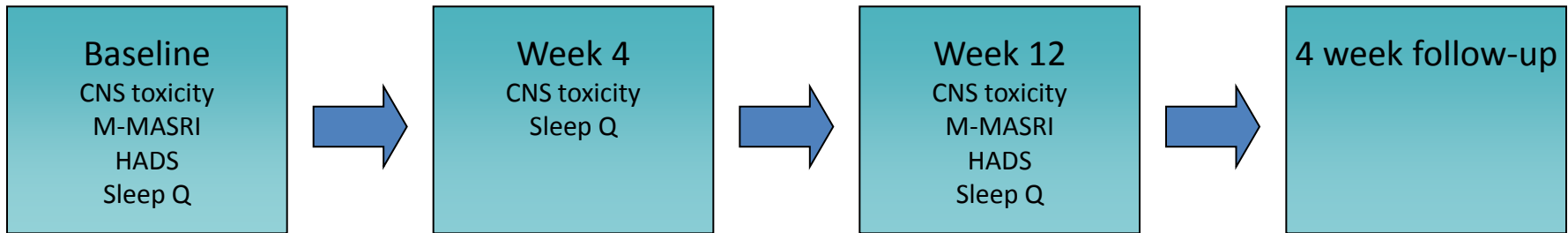
CNS Score: Baseline to Week 12



CNS Toxicity TMC125 ARM: Baseline vs Week 12

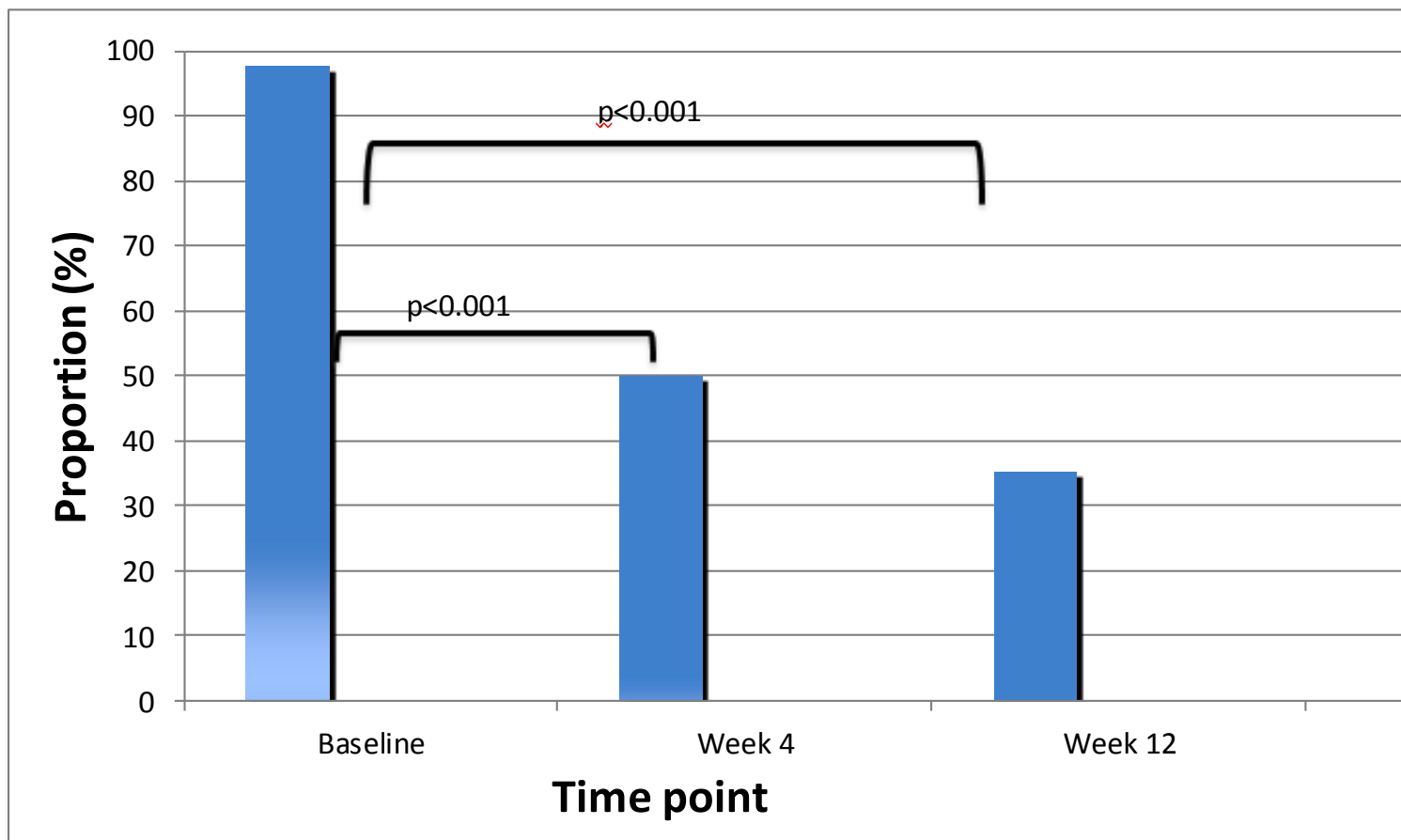


Efavirenz to Raltegravir Switch



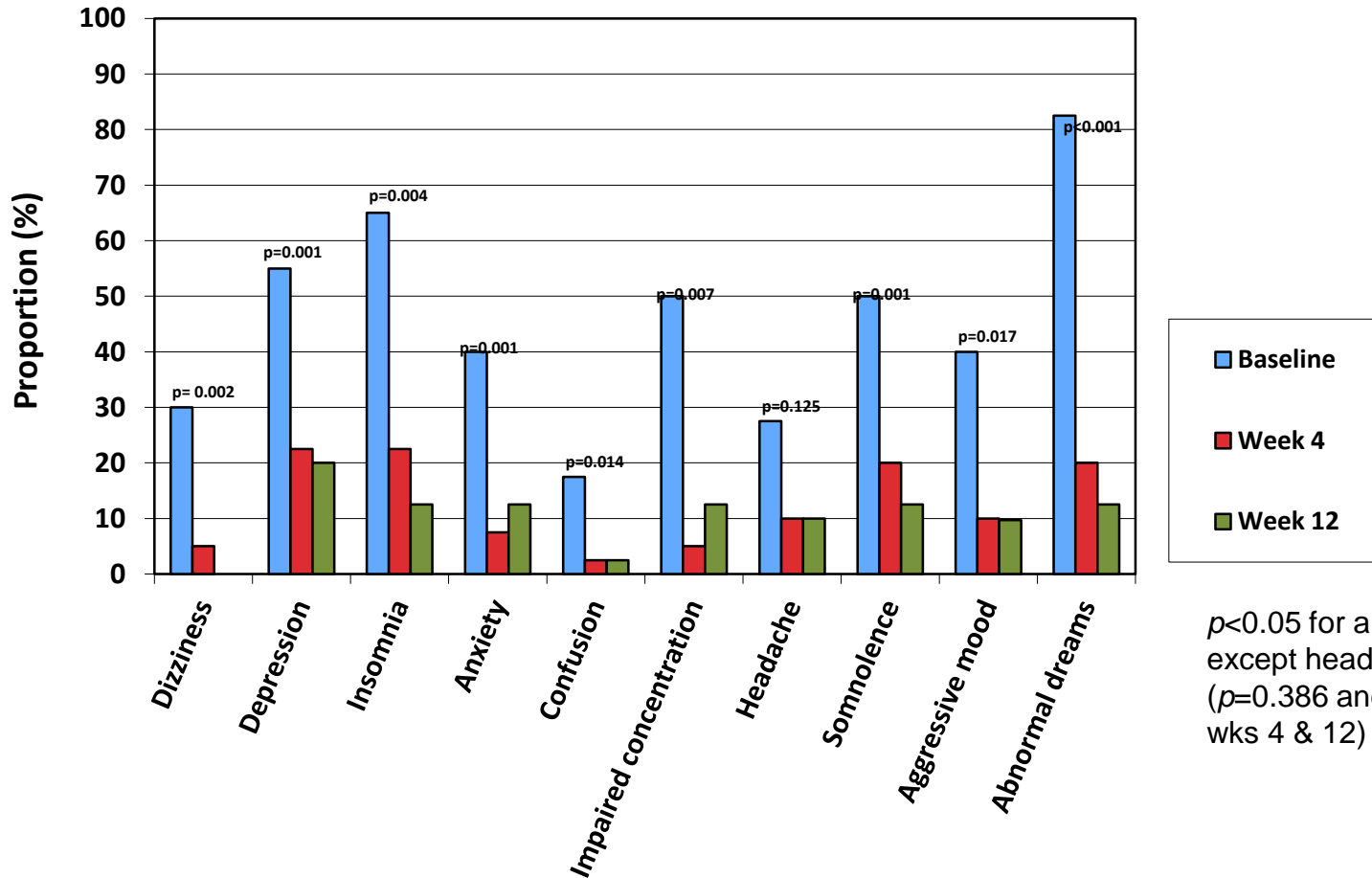
- At all visits
 - FBC
 - Biochemistry
 - Lipids
 - CD4, VL

Proportion with any grade 2-4 CNS toxicity



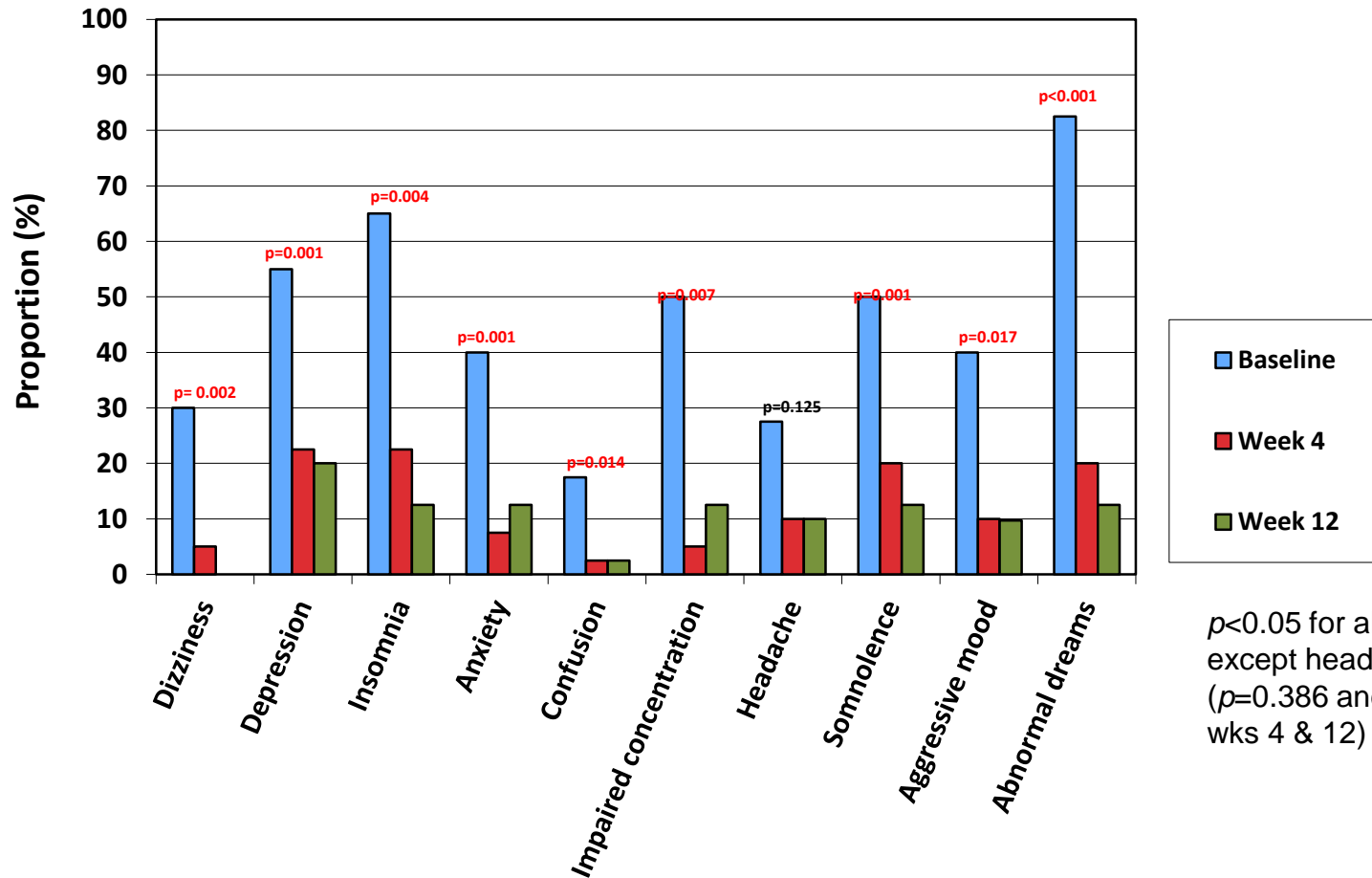
Results – CNS toxicity scores

Individual proportions of Grade 2-4 CNS AEs



Results – CNS toxicity scores

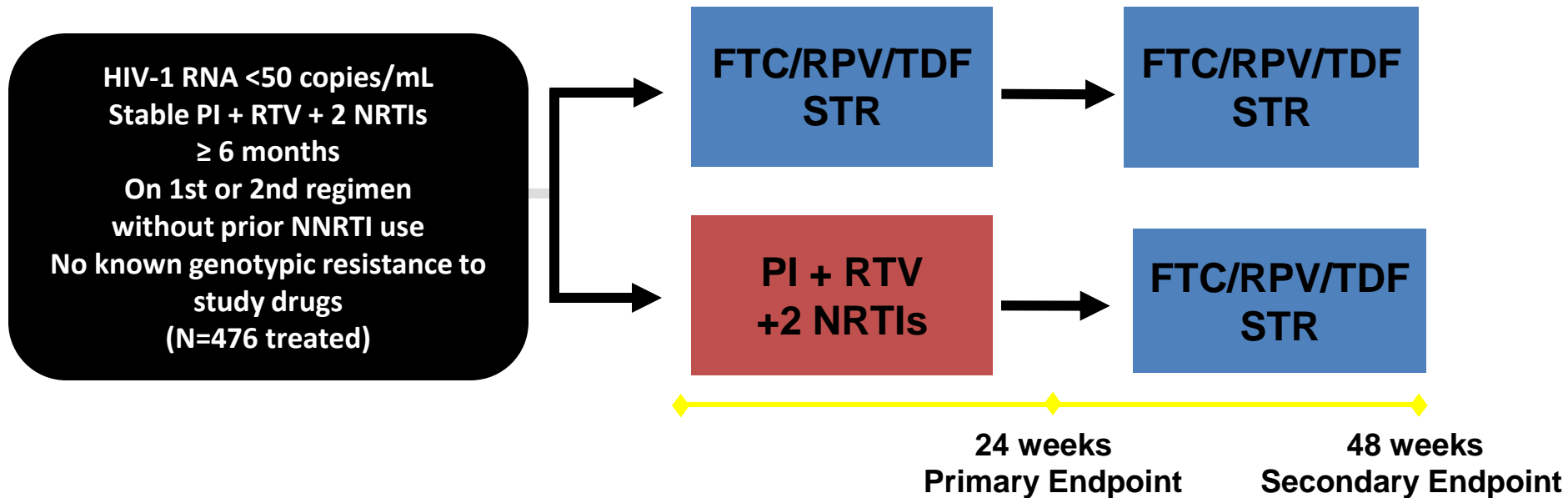
Individual proportions of Grade 2-4 CNS AEs



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

- No Virological failure
- Etravirine- multiple tablets, tablet composition
- Raltegravir – twice daily

SPIRIT Study Design



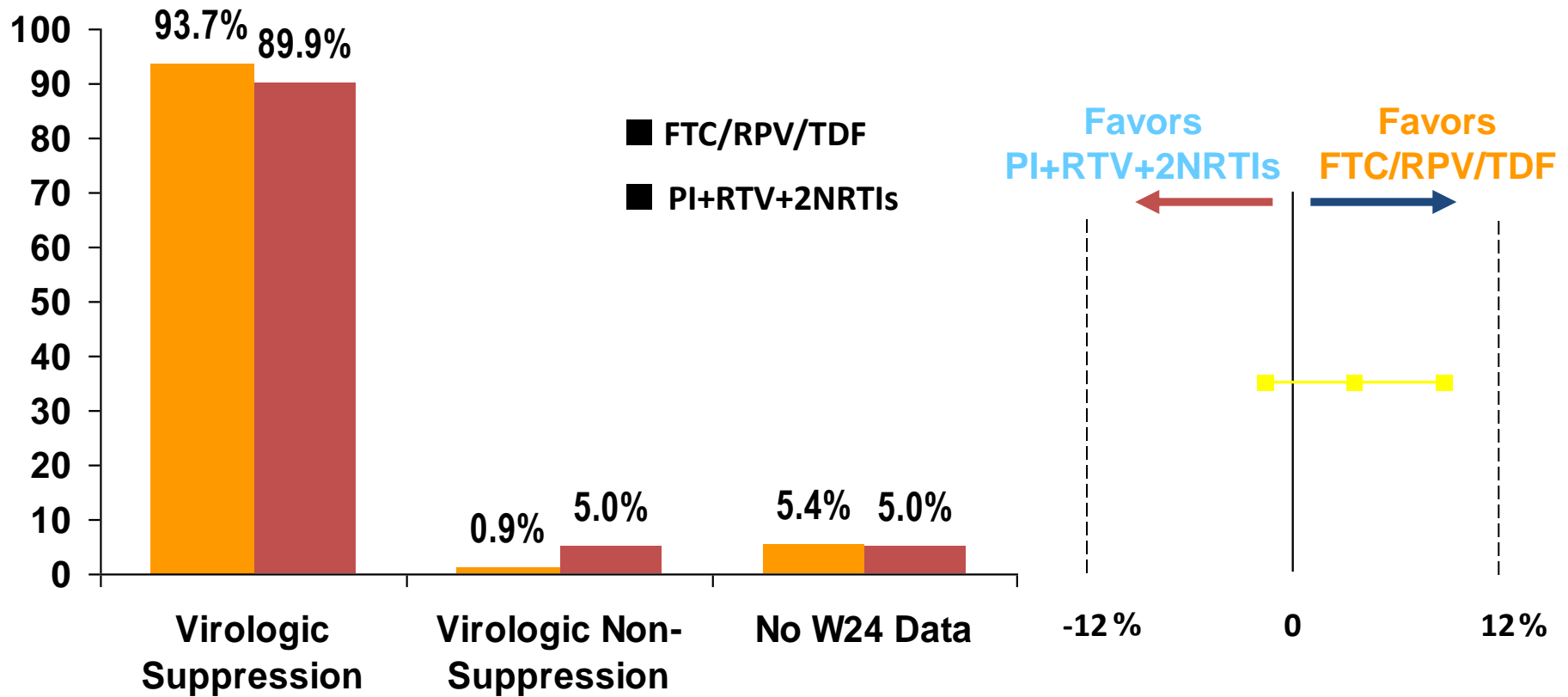
Primary Endpoint:

Non-inferiority (12% margin) to PI + RTV + 2 NRTIs by FDA snapshot analysis HIV-1 RNA <50 copies/mL at 24 weeks

Secondary Endpoints:

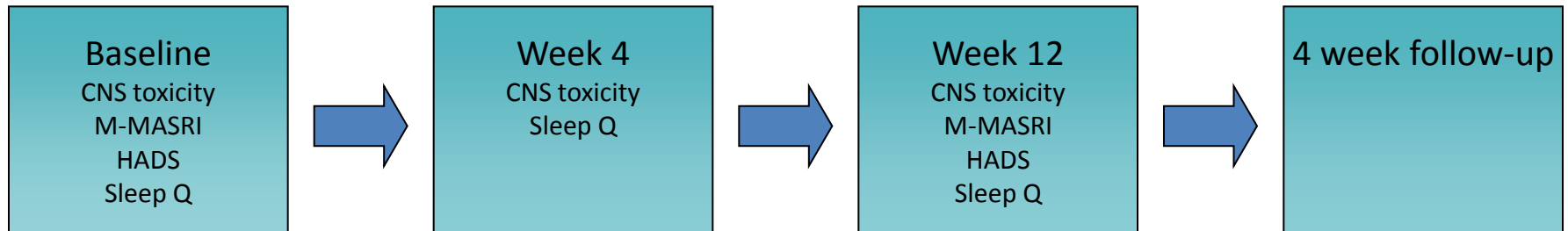
Change in fasting lipid parameters at 24 and 48 weeks
Safety and tolerability at 24 and 48 weeks
Change in CD4 cell count at 24 and 48 weeks

Primary Endpoint: Virologic Suppression at Week 24 FDA Snapshot Analysis – ITT Population



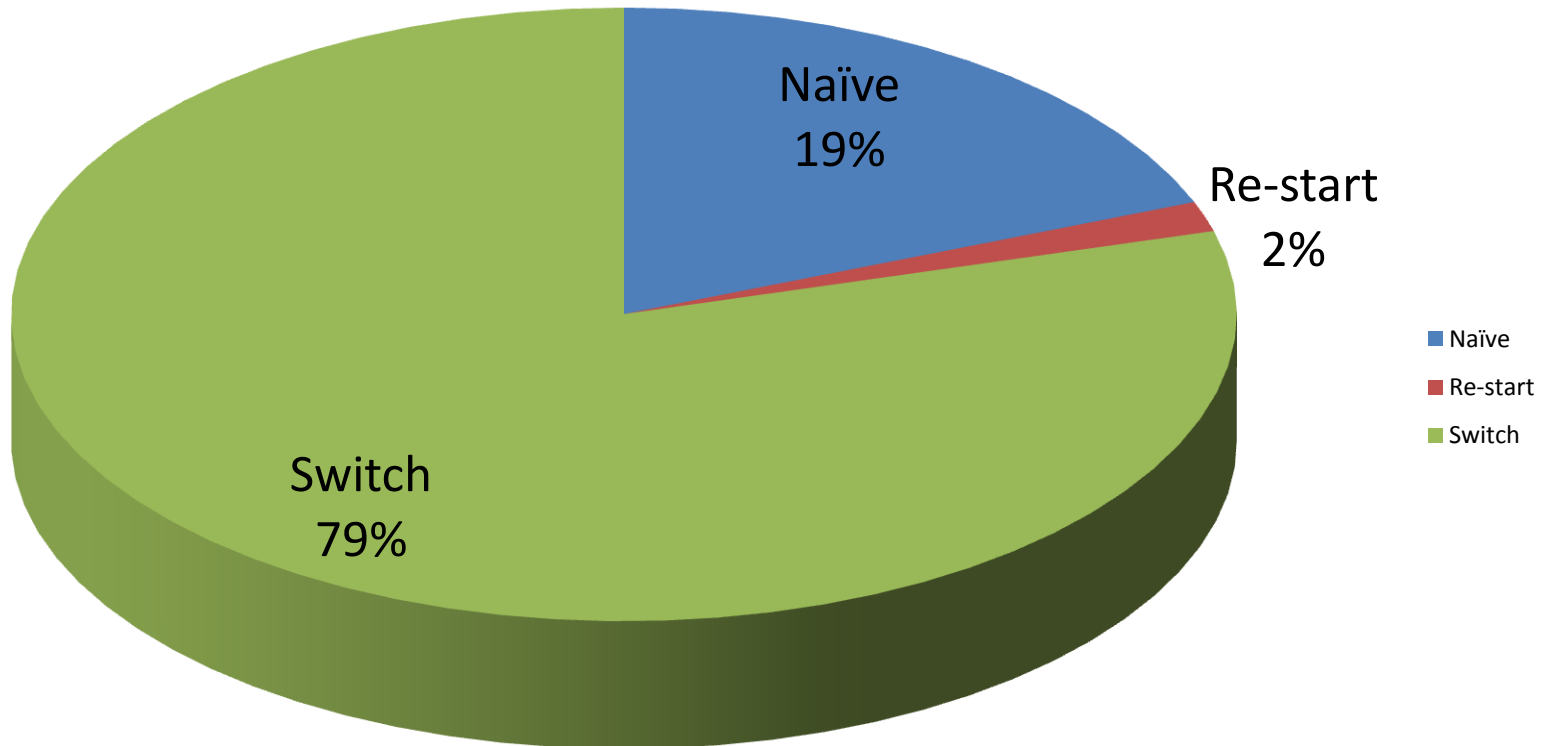
Change in CD4 count (cells/mm³) : FTC/RPV/TDF +20 vs PI+RTV +32 (p=0.28)

Atripla to Eviplera Switch



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

Patient profile



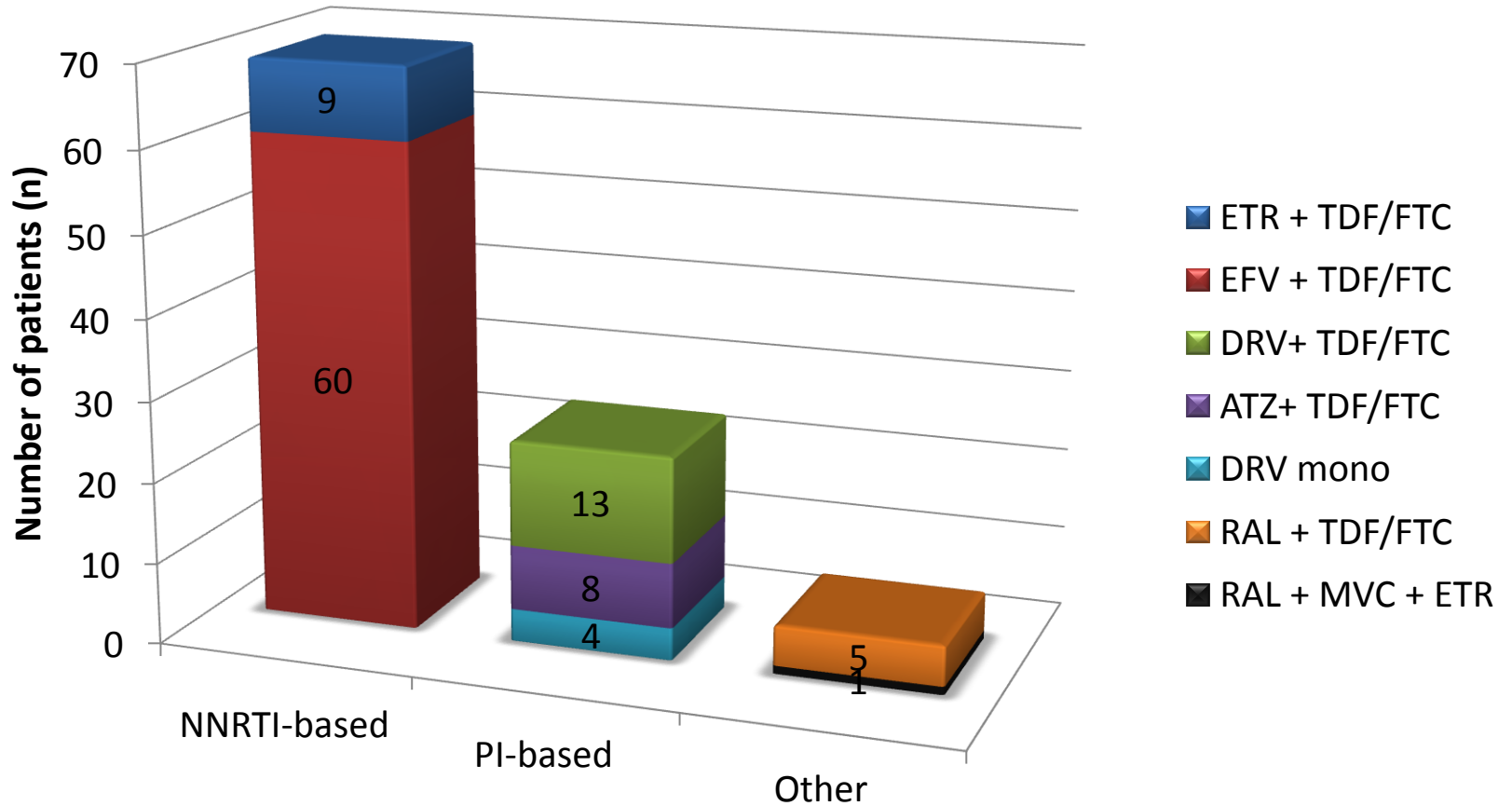
Naïve	Re-start	Switch
24	2	100

Demographic and clinical characteristics of switch patients

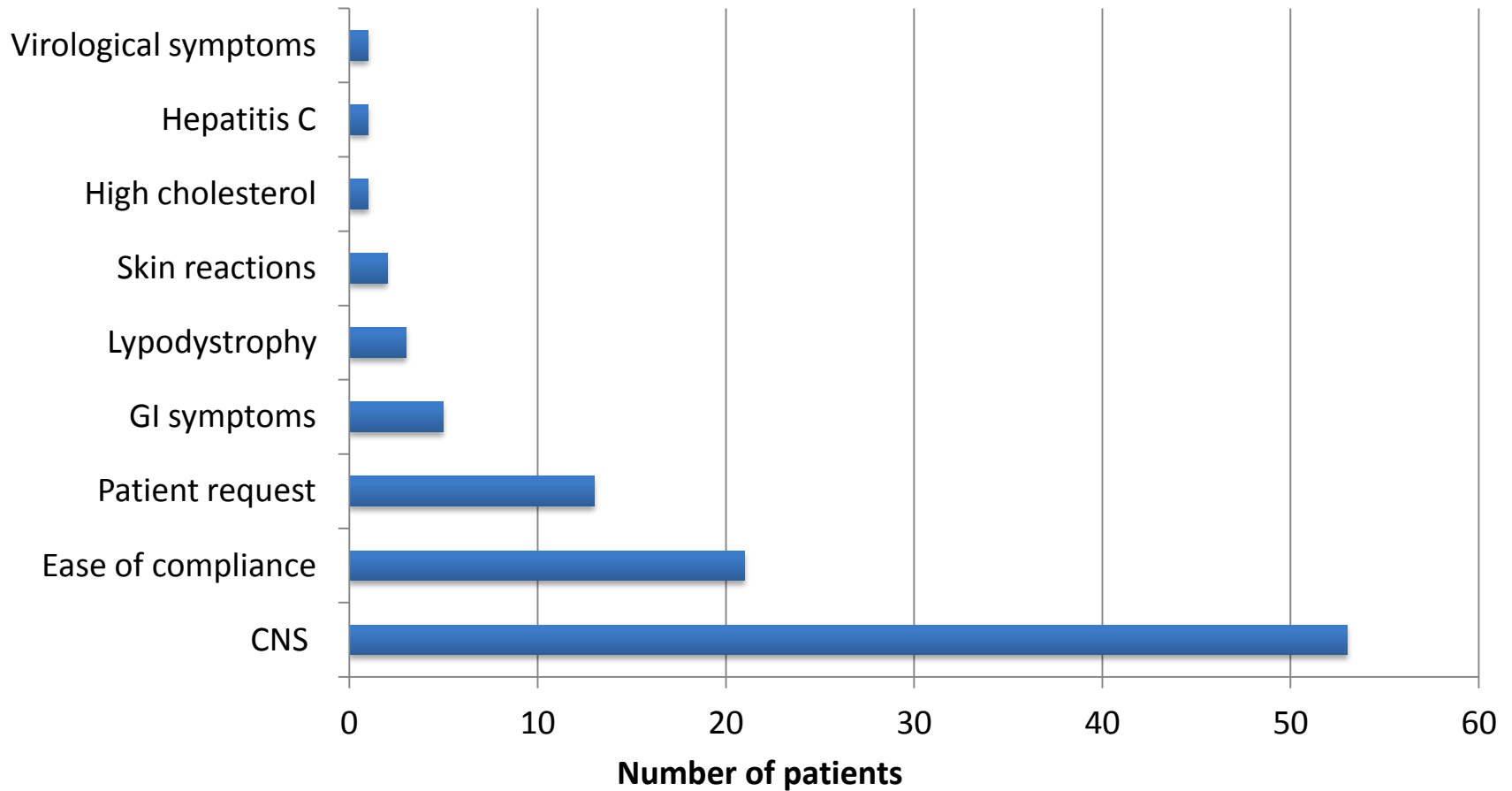
Parameter	Median (range)*
Number of patients [n (M/F)]	100 (93/7)
Age (yr)	40 (23-74)
Baseline CD4 cell count	536 (96-1586)
Overall exposure to ARVs	67 months (16-115)

*unless differently specified

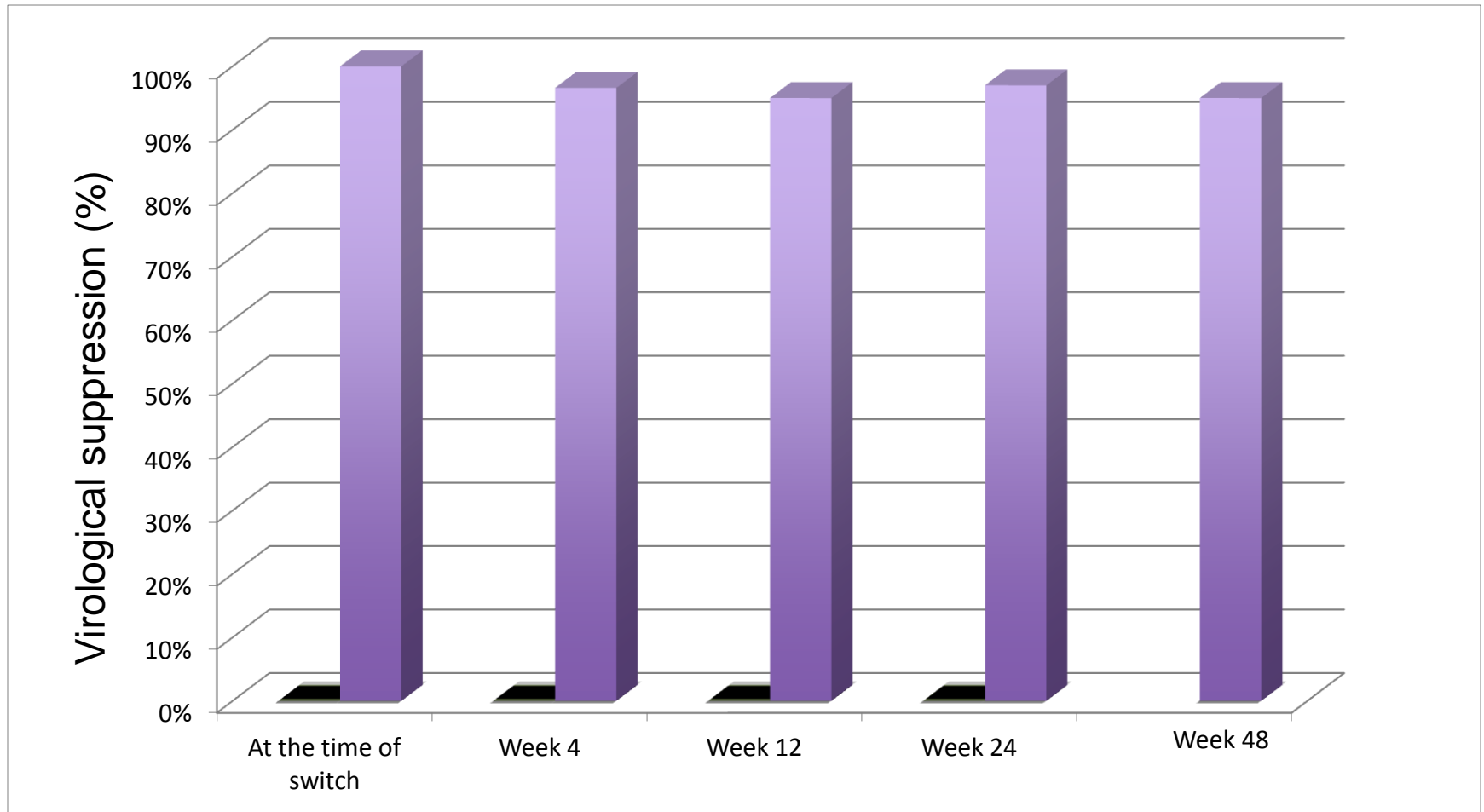
Pre-switch ARV profile



Reasons for switching to RPV



Virological suppression



n=

100

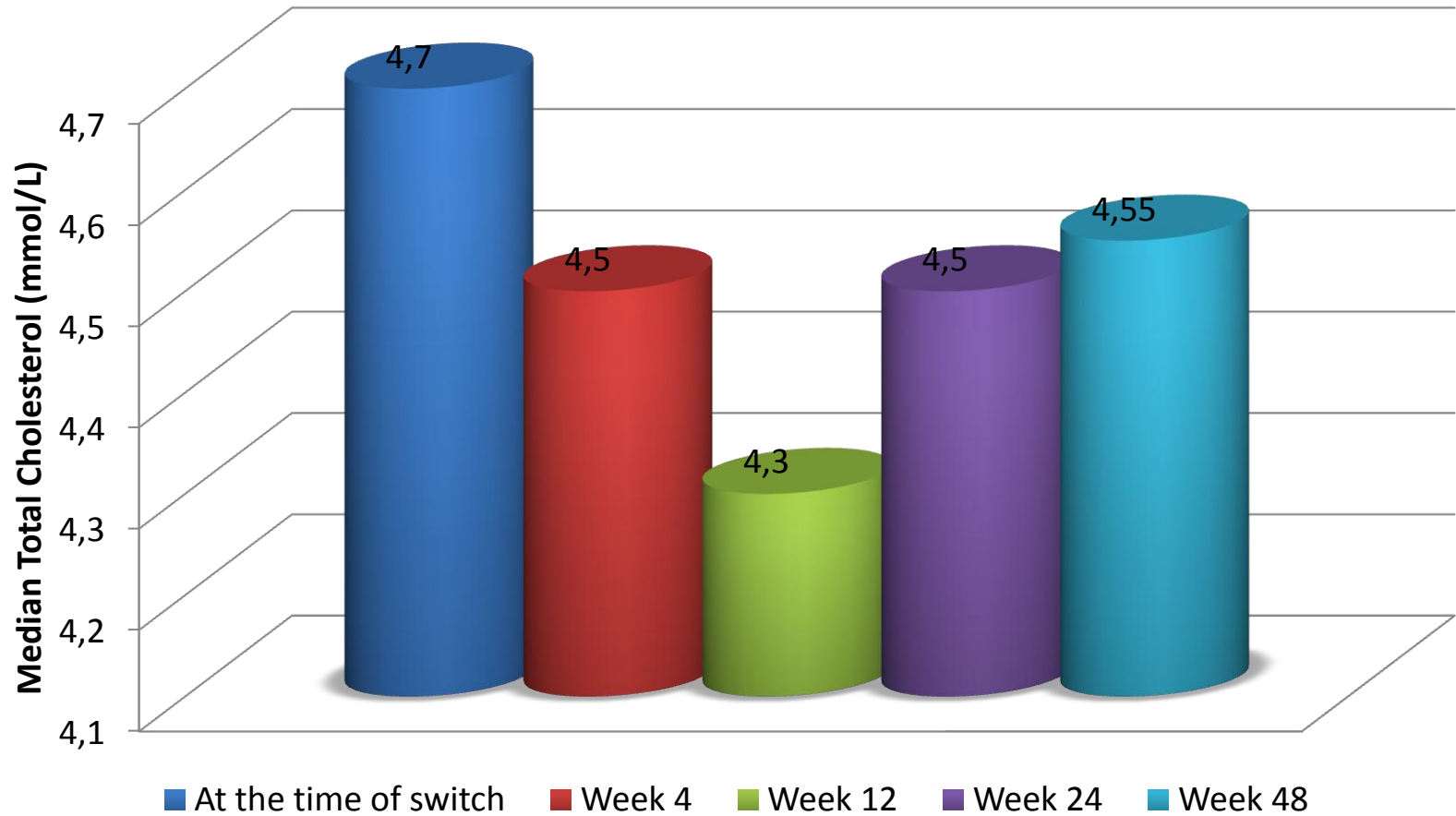
58

71

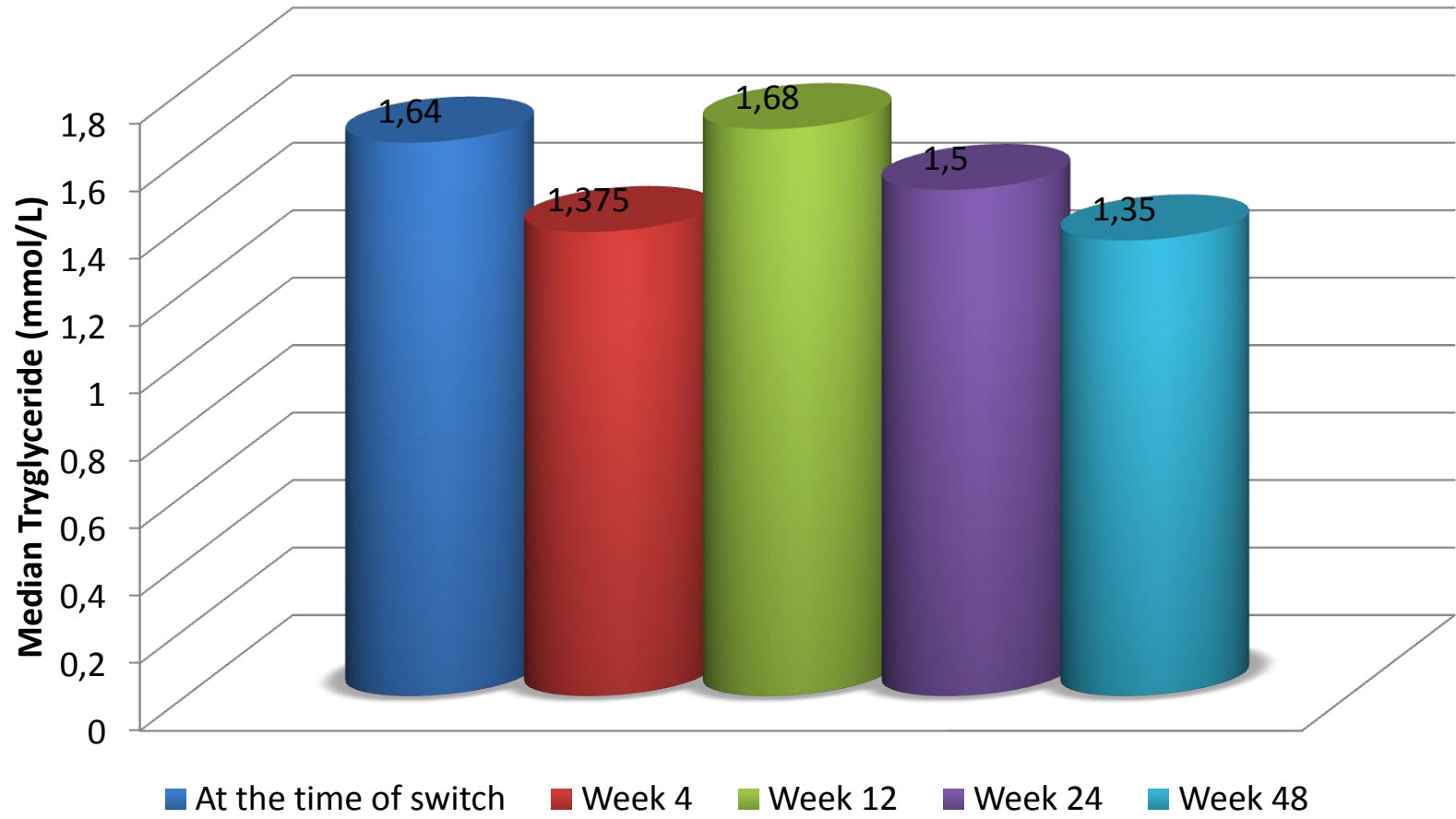
63

17

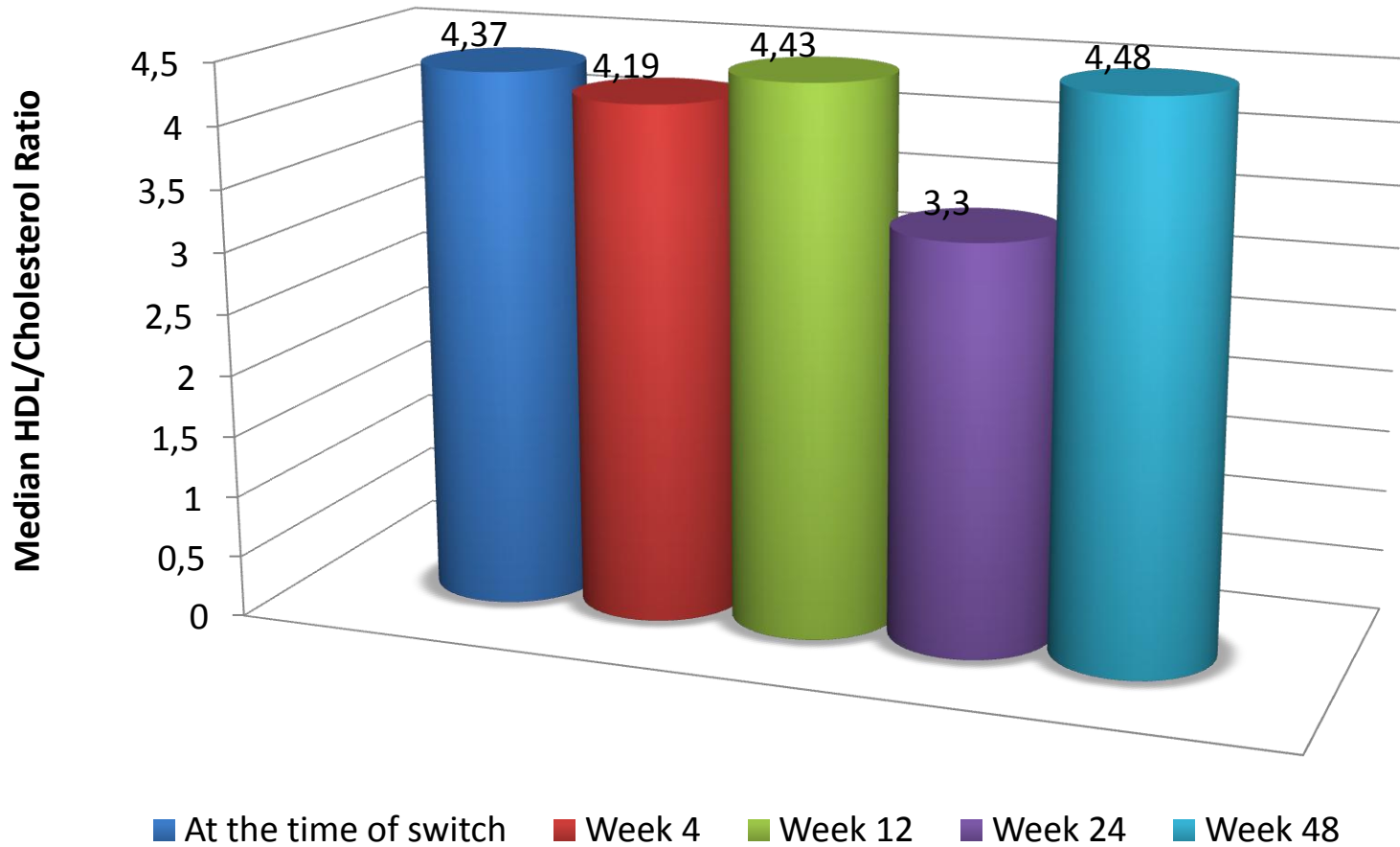
Total Cholesterol



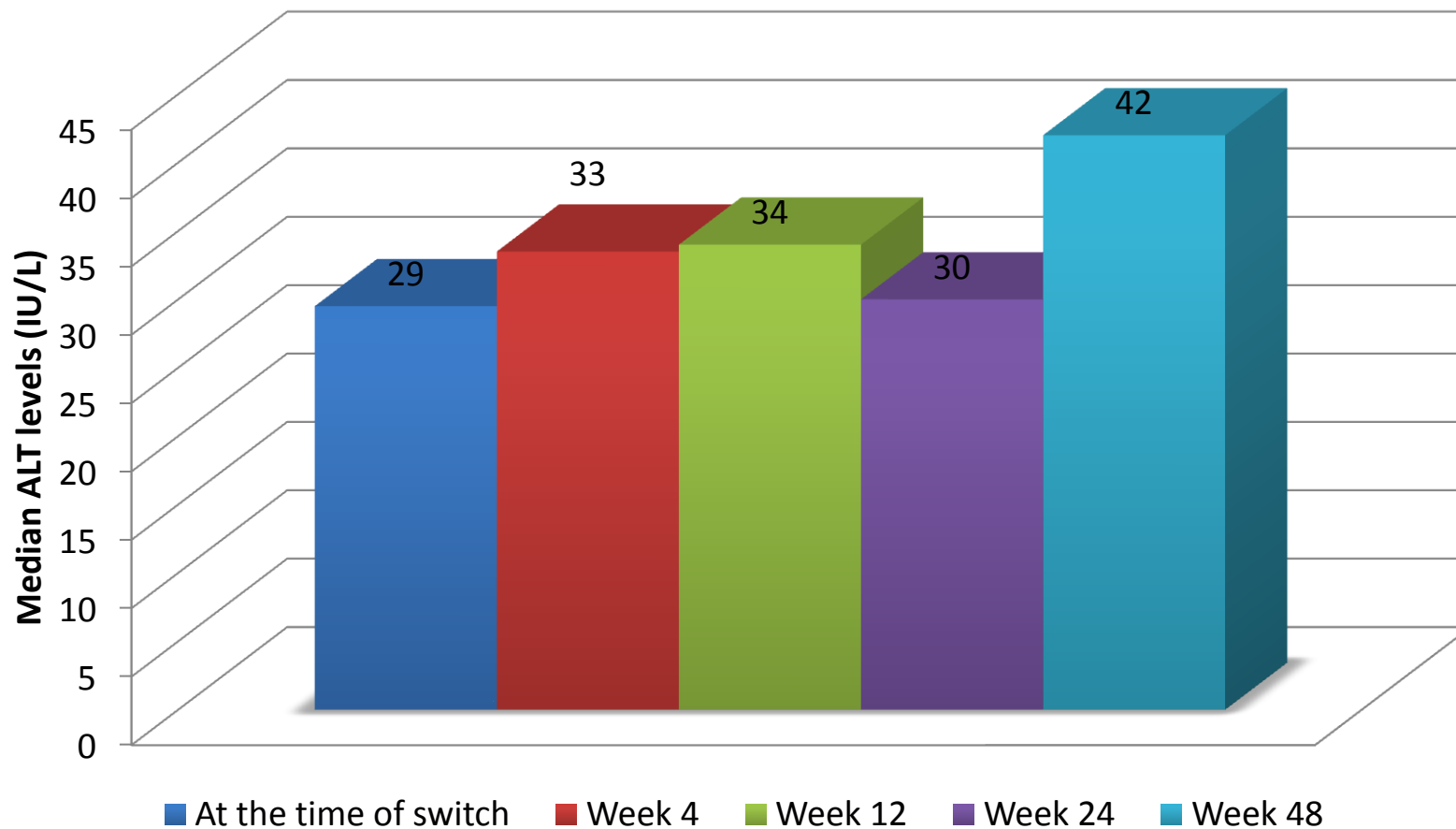
Tryglyceride



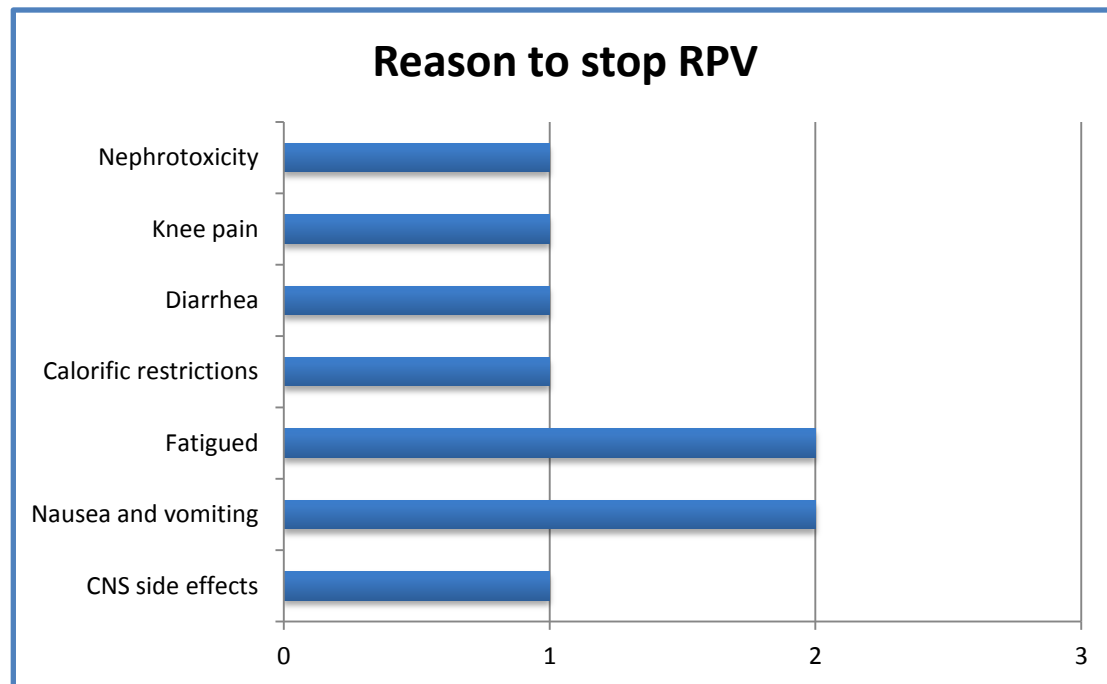
HDL/Cholesterol



ALT levels



- 9 patients switched back to their previous regimen



N of patients

- * Patient with nephrotoxicity already had deranged renal functions at the baseline
- * Patient with CNS side effects had hallucinations and vivid dream, switched back to previous regimen (DRV/rTV/TDF/FTC)

Conclusion

- Efavirenz CNS toxicity may be short and long term
- Switching from efavirenz to alternate NNRTIs or integrase inhibitors frequently is associated with resolution of potential CNS toxicities and continued virological suppression
- Newer STRS may permit continued single tablet dosing with cessation of CNS toxicity associated with Atripla