MRC Clinical Trials Unit

UCL

This house believes that efavirenz should remain as an option to treat HIV in the UK

Alejandro Arenas-Pinto
MRC-Clinical Trial Unit
University College London

23rd Annual Conference of the British HIV Association (BHIVA)
5th April 2017

MRC Clinical Trials Unit

UCL

This house Does not believe that efavirenz should remain as an option to treat HIV in the UK

Alejandro Arenas-Pinto
MRC-Clinical Trial Unit
University College London

23rd Annual Conference of the British HIV Association (BHIVA)
5th April 2017

Shall we keep EFV as a treatment option in the UK?

- Potency and efficacy
- Resistance profile
- Tolerability profile
- Toxicity profile

Shall we keep EFV as a treatment option in the UK?

- Potency and efficacy
- Resistance profile
- Tolerability profile
- Toxicity profile

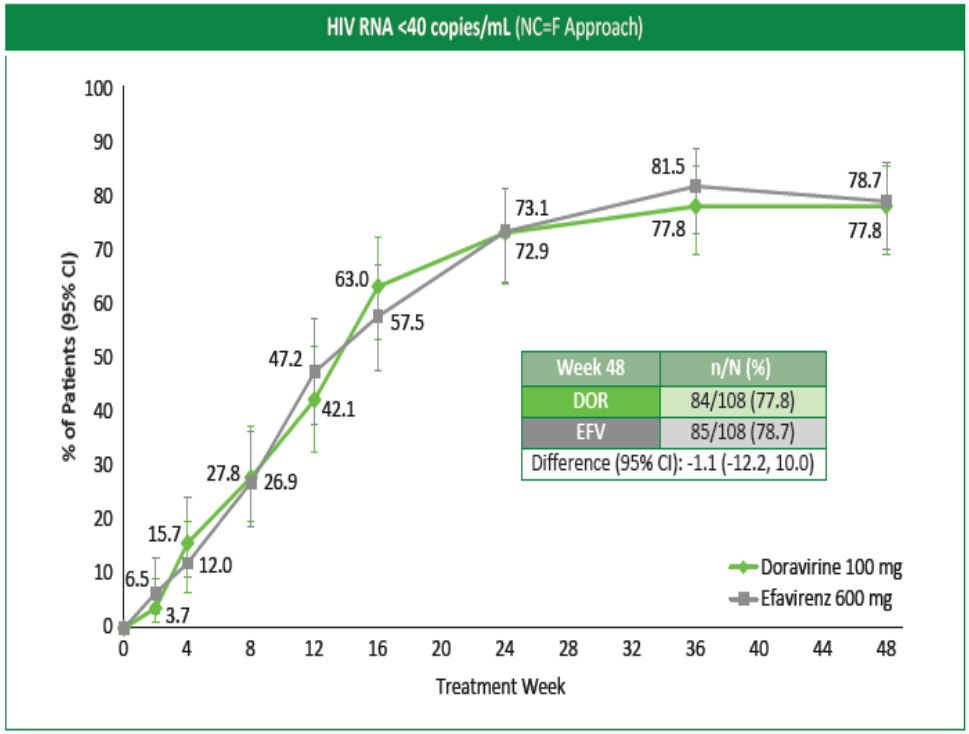
Shall we keep EFV as a treatment option in the UK?

- Potency and efficacy
- Resistance profile
- Tolerability profile
- Toxicity profile

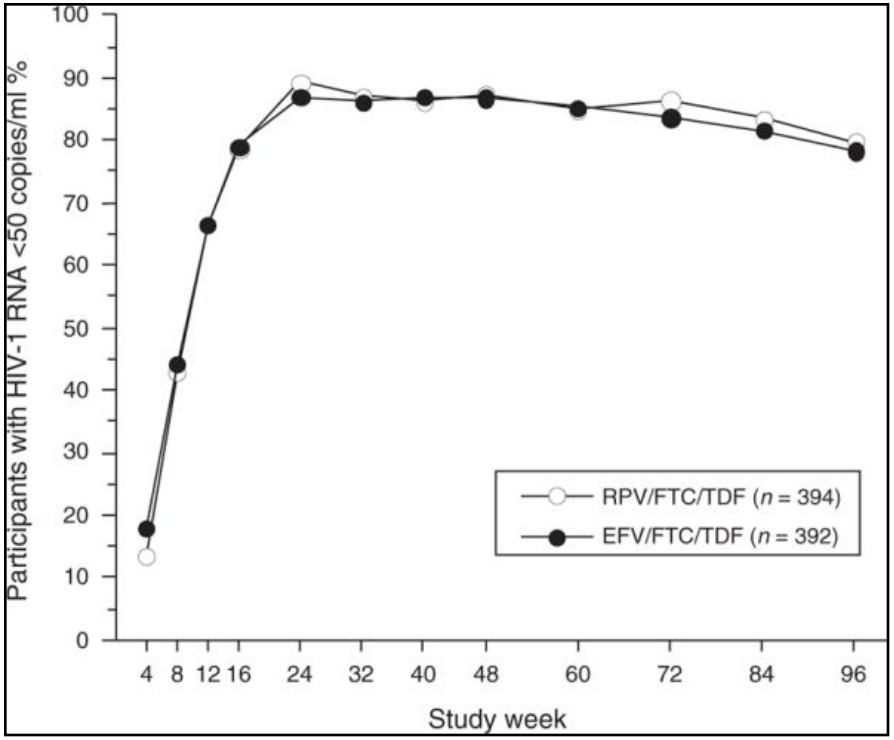
- What would be the right place for EFV in 2017?

Potency compared to other NNRTI

Doravirine vs EFV: 48 week results[1]



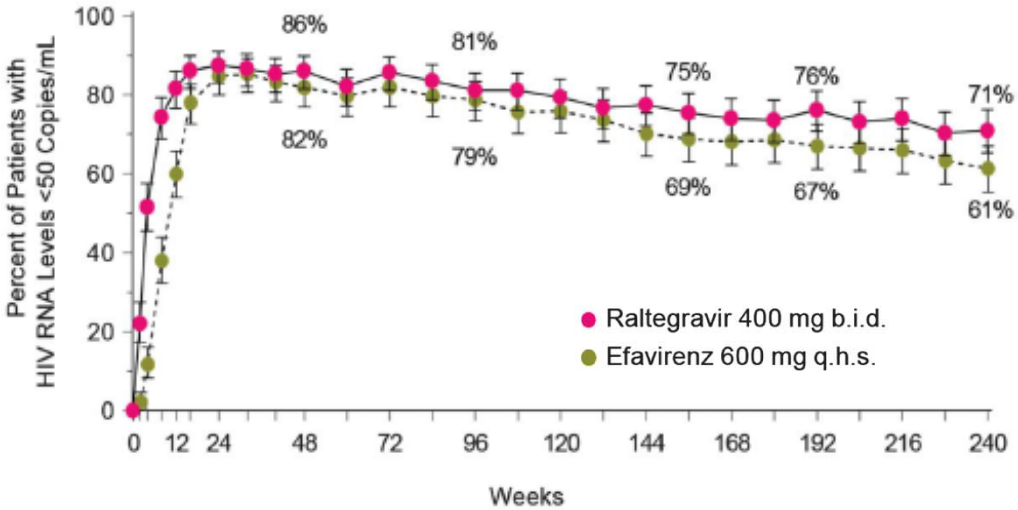
Rilpivirine vs EFV: 96 week results[2]



[1]Gatell et al. CROI 2016, Boston, MA, US (Abs 470). [2] van Lunzen et al. AIDS 2016; 30(2): 251 – 9

Potency compared to Insti

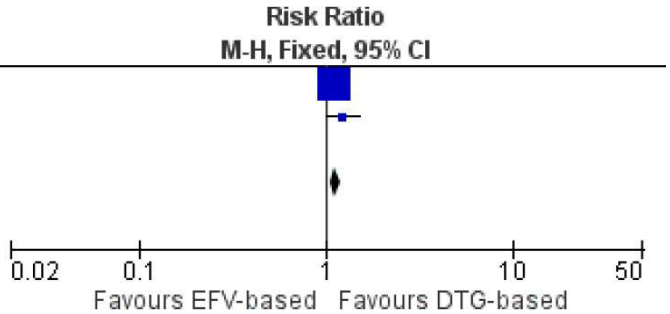
STARTMRK: EFV vs RAL in ART-naïve patients[1]



DTG + two NRTI vs. EFV + two NRTIs. Viral suppression to non-detectable (<50 copies/mL) at 96 weeks[2]

Study or Subgroup	DTG-based regimen Events	DTG-based regimen Total	EFV-based regimen Events	EFV-based regimen Total	Weight	Risk Ratio M-H, Fixed, 95% CI
SINGLE	331	414	302	419	89.2%	1.11 [1.03, 1.20]
SPRING-1	45	51	36	50	10.8%	1.23 [1.00, 1.50]
Total (95% CI)		**465**		**469**	**100.0%**	**1.12 [1.04, 1.21]**
Total events	376		338			

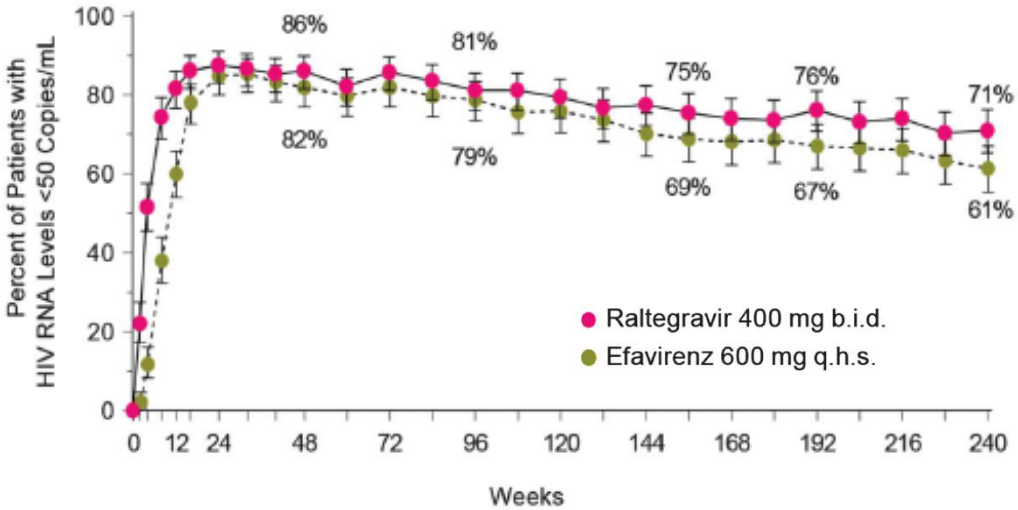
Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 3.14 (P = 0.002)



[1]Rockstroh JK et al. JAIDS 2013; 63(1): 77-854. [2] Rutherford GW, Horvath H. PLoS ONE 11(10): e0162775

Potency and efficacy

STARTMRK: EFV vs RAL in ART-naïve patients[1]

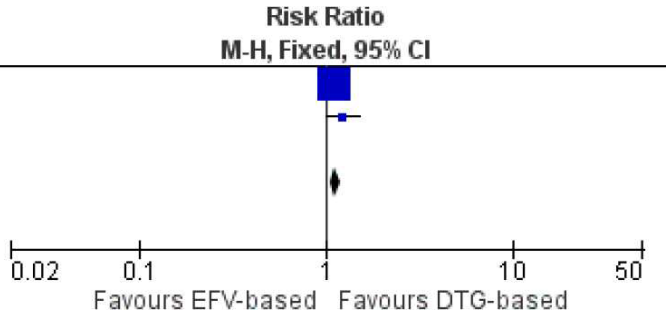


There are other options with similar or even better efficacy

DTG + two NRTI vs. EFV + two NRTIs. Viral suppression to non-detectable (<50 copies/mL) at 96 weeks[2]

Study or Subgroup	DTG-based regimen Events	DTG-based regimen Total	EFV-based regimen Events	EFV-based regimen Total	Weight	Risk Ratio M-H, Fixed, 95% CI
SINGLE	331	414	302	419	89.2%	1.11 [1.03, 1.20]
SPRING-1	45	51	36	50	10.8%	1.23 [1.00, 1.50]
Total (95% CI)		**465**		**469**	**100.0%**	**1.12 [1.04, 1.21]**
Total events	376		338			

Heterogeneity: Chi² = 0.83, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 3.14 (P = 0.002)



[1]Rockstroh JK et al. JAIDS 2013; 63(1): 77-854. [2] Rutherford GW, Horvath H. PLoS ONE 11(10): e0162775

Resistance profile

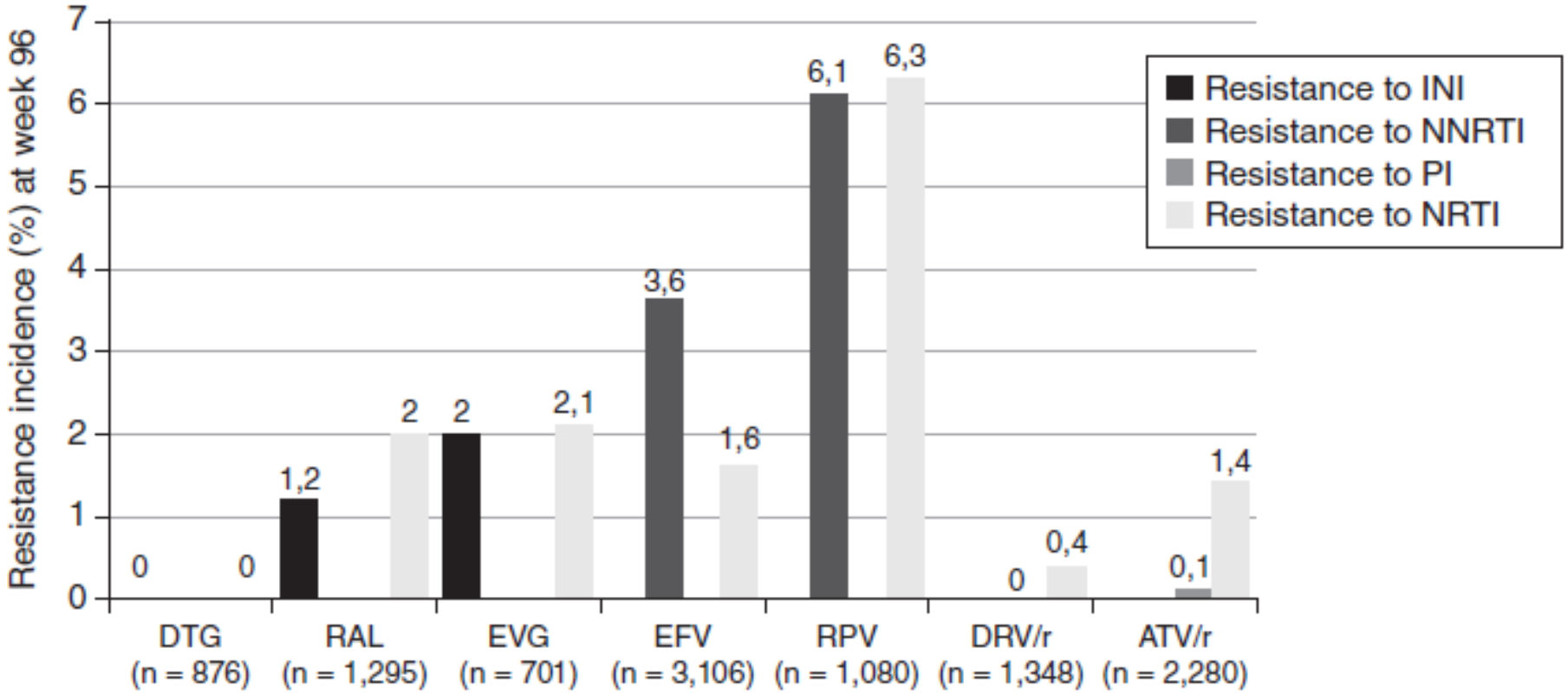


Figure 4. *Incidence of resistance at week 96 in pivotal clinical trials of antiretroviral therapy in naive patients (see text for explanation and references). II: integrase inhibitors; DTG: dolutegravir; RAL: raltegravir; EVG: elvitegravir; NNRTI: nonnucleoside reverse transcriptase inhibitors; EFV: efavirenz; RPV: rilpivirine; PI: protease inhibitors; DRV/r: darunavir/ritonavir; ATV/r: atazanavir/ritonavir.*

Llibre et al. AIDS Rev 2015; 17: 56 – 64

Resistance profile

TDR in ART-naïve patients (UK): predicted phenotypic resistance

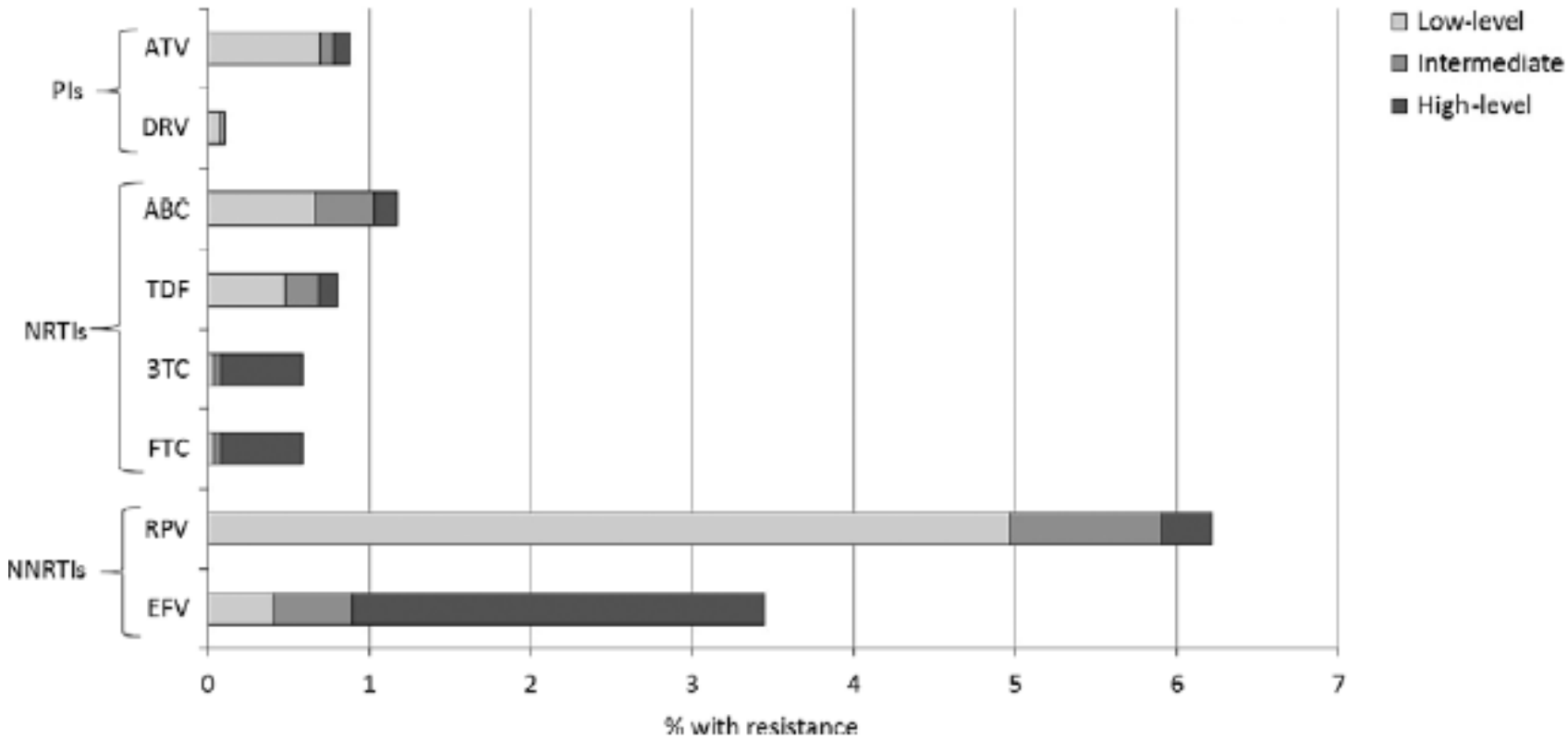


Fig. 2 Predicted phenotypic resistance (Stanford scores) for antiretroviral drugs currently recommended for first-line combination therapy in the UK, 2010–2013. 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; DRV, darunavir; EFV, efavirenz; FTC, emtricitabine; PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; RPV, rilpivirine; TDF, tenofovir.

Tostevin A et al. *HIV Med* 2017; 18: 204 – 13

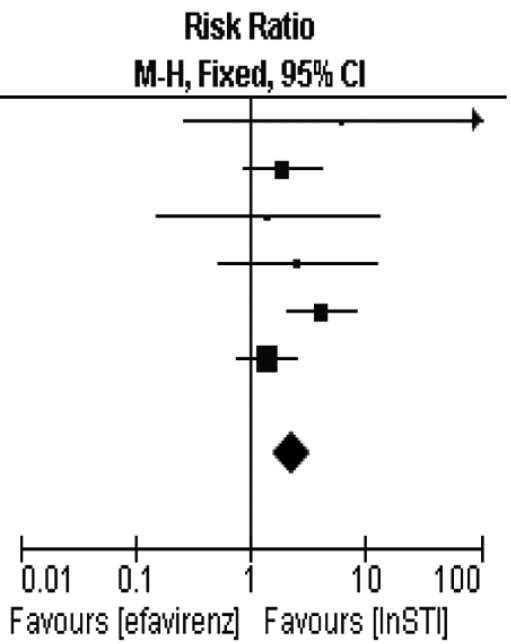
Tolerability

discontinuation of the therapy due to adverse events

Study or Subgroup	efavirenz Events	efavirenz Total	InSTI Events	InSTI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cohen 2011	1	23	0	48	0.8%	6.13 [0.26, 144.82]
Lennox 2009/2010 STARTMRK	17	282	9	281	22.7%	1.88 [0.85, 4.15]
Markowitz 2007/2009	1	38	3	160	2.9%	1.40 [0.15, 13.12]
Stellbrink 2013 SPRING-1	5	50	2	51	5.0%	2.55 [0.52, 12.54]
Walmsley 2013 SINGLE	42	419	10	414	25.4%	4.15 [2.11, 8.16]
Zolopa2013 GS-US-236-0102	24	352	17	348	43.1%	1.40 [0.76, 2.55]
Total (95% CI)		**1164**		**1302**	**100.0%**	**2.30 [1.60, 3.31]**
Total events	90		41			

Heterogeneity: $Chi^2 = 6.38$, df = 5 (P = 0.27); $I^2 = 22\%$

Test for overall effect: Z = 4.50 (P < 0.00001)



Kryst et al. PLoS One 2015; 10(5): e0124279

Can we predict tolerability?

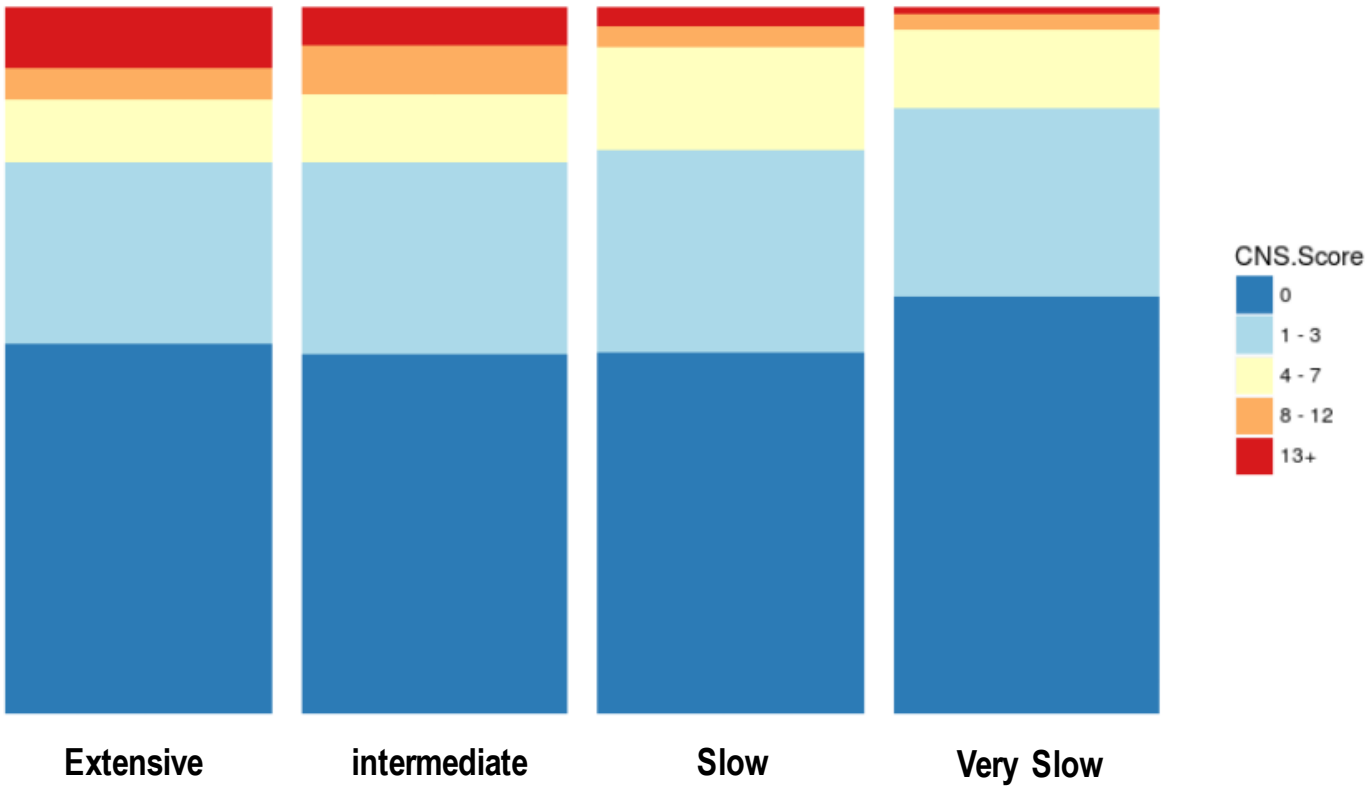
Tolerability seems to depend on the rate of EFV metabolism

Table 2 Incidence density rates of central nervous system (CNS) events according to cytochrome P450 (*CYP*) *2B6* 516 T variants

CNS events	Number of events	Cumulative time (months)	Incidence density rate (per 100 patient-years)	Confidence interval (patient-years)	*P*
CYP2B6 516 G/G	106	270	39.2	38.5–40.0	0.02
CYP2B6 516 G/T or T/T	143	260	55.0	54.1–55.9	
Total	249	530	47.0	46.4–47.5	

Gallien et al. *HIV Med* 2017 [Epub ahead of print]

Extensive EFV metabolism is associated with greater CNS toxicity



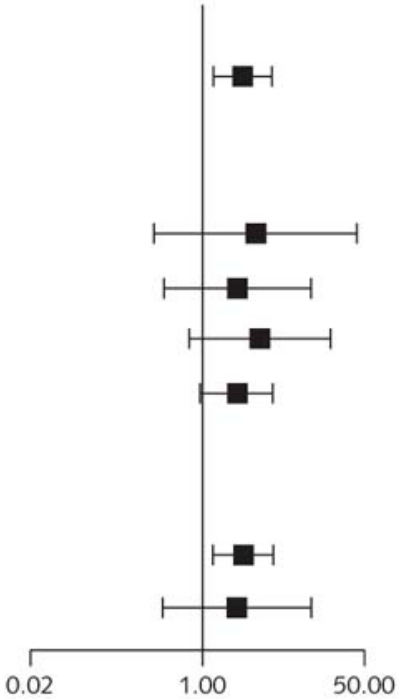
Vujkovic M et al CROI 2017. Seattle, WA, USA (Abs 384)

Serious toxicity: suicidality

- ACTG meta-analysis: 4 ART-naïve RCTs

A. ITT DSMB

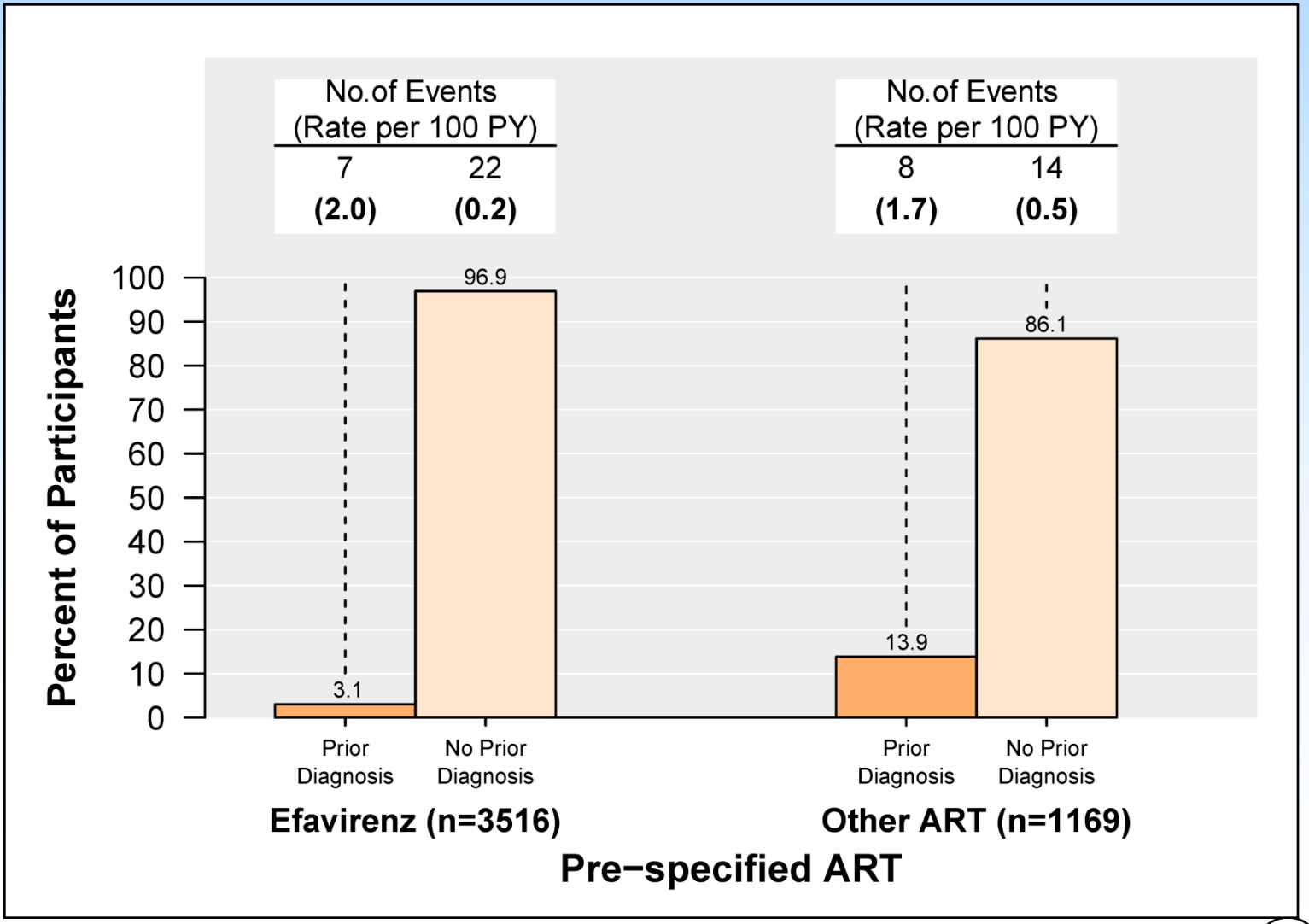
	Events/PYs (IR per 1000 PYs)				Hazard Ratio (95% CI)	*P* Value
	EFV		EFV-Free			
Variable						
Overall	47/5817	(8.08)	15/4099	(3.66)	2.28 (1.27–4.10)	0.006*
Study						0.94
A5095	6/739	(8.12)	1/364	(2.75)	3.00 (0.36–24.88)	
A5142	8/1001	(7.99)	2/510	(3.92)	2.04 (0.43–9.62)	
A5175	13/1763	(7.38)	2/889	(2.25)	3.28 (0.74–14.52)	
A5202	20/2315	(8.64)	10/2336	(4.28)	2.02 (0.94–4.31)	
Region						0.87
United States	39/4346	(8.97)	13/3354	(3.88)	2.32 (1.23–4.38)	
Multinational	8/1471	(5.44)	2/745	(2.68)	2.02 (0.43–9.53)	



Increased Suicidality With EFV-Free | Increased Suicidality With EFV

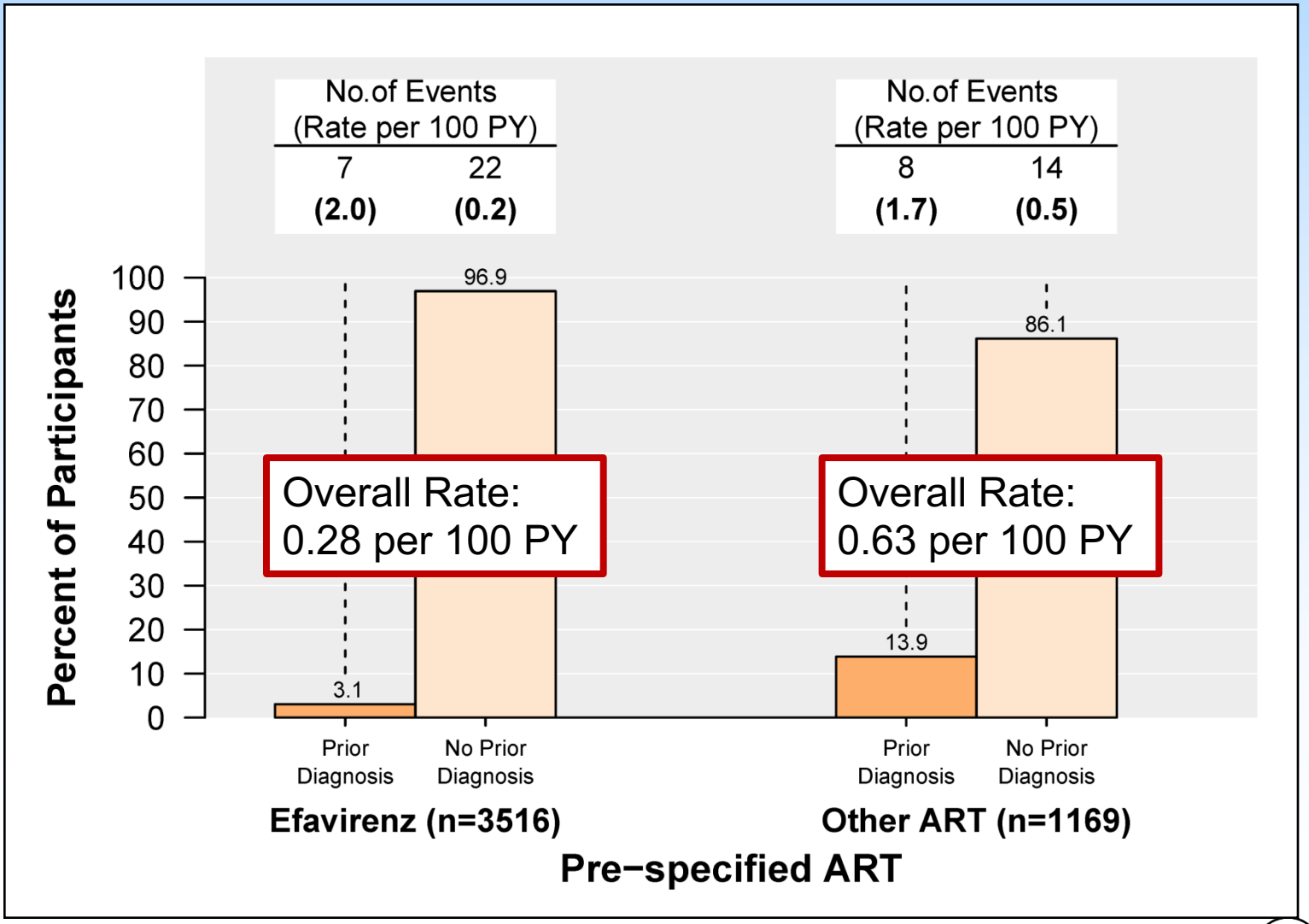
Mollan et al. *Ann Intern Med*. 2014;161(1):1-10

Suicidal behaviour by Pre-specified ART and Prior Psychiatric Diagnosis in START



Arenas-Pinto et al. AIDS 2016 Conference. Durban, SA (Abstract THAB0202)

Suicidal behaviour by Pre-specified ART and Prior Psychiatric Diagnosis in START



Arenas-Pinto et al. AIDS 2016 Conference. Durban, SA (Abstract THAB0202)

Suicidal/self harming events by randomisation arm in START

	N	Immediate ART		Deferred ART		HR[a]	95% CI	P	Int. P[b]
		Events	Rate	Events	Rate				
ITT analysis, year 1 only									
EFV pre-specified	3516	9	0.52	2	0.11	3.75	(0.8, 17.5)	0.09	0.15
Other ART pre-specified	1169	7	1.25	7	1.19	1.02	(0.4, 2.9)	0.96	
Censoring deferred arm participants at ART initiation									
EFV pre-specified[c]	3516	17	0.35	3	0.08	4.16	(1.2, 14.4)	0.02	0.05
Other ART pre-specified[d]	1137	9	0.59	8	0.69	1.04	(0.4, 2.7)	0.93	

[a] Estimated in Cox proportional hazards models, stratified by psychiatric diagnosis.
[b] Interaction between indicators for treatment group and pre-specified regimen.
[c] Of these events, 6 and 0, in the immediate vs deferred arms, respectively, occurred among 108 participants with prior psychiatric diagnoses.
[d] Of these events, 5 and 2, in the immediate vs deferred arms respectively, occurred among 162 participants with prior psychiatric diagnoses. Of the 1169 participants without EFV in the pre-specified regimen, 32 were excluded (in the immediate group, 7 never started ART, and for 25, the first ART regimen contained EFV). Follow-up in the immediate group was censored at EFV start.

Arenas-Pinto et al. AIDS 2016 Conference. Durban, SA (Abstract THAB0202)

insight

Conclusion

- EFV is a very good drug that deserves a prominent place,

Conclusion

- EFV is a very good drug that deserves a prominent place,

Not here

British HIV Association
BHIVA
CLINICAL
GUIDELINES

Conclusion

- EFV is a very good drug that deserves a prominent place,

Not here

British HIV Association
BHIVA
CLINICAL
GUIDELINES

But, there

BSHM
British Society for the History of Medicine

Acknowledgments

Many thanks to

- Prof David Dunn, MRC-CTU at UCL
- START trial team
- Insight network
- You all for your attention