First-Line Raltegravir (RAL) + Darunavir/ Ritonavir (DRV/r) is Non-inferior to Tenofovir/ Emtricitabine (TDF/FTC) + DRV/r: The NEAT 001/ANRS 143 Randomised Trial

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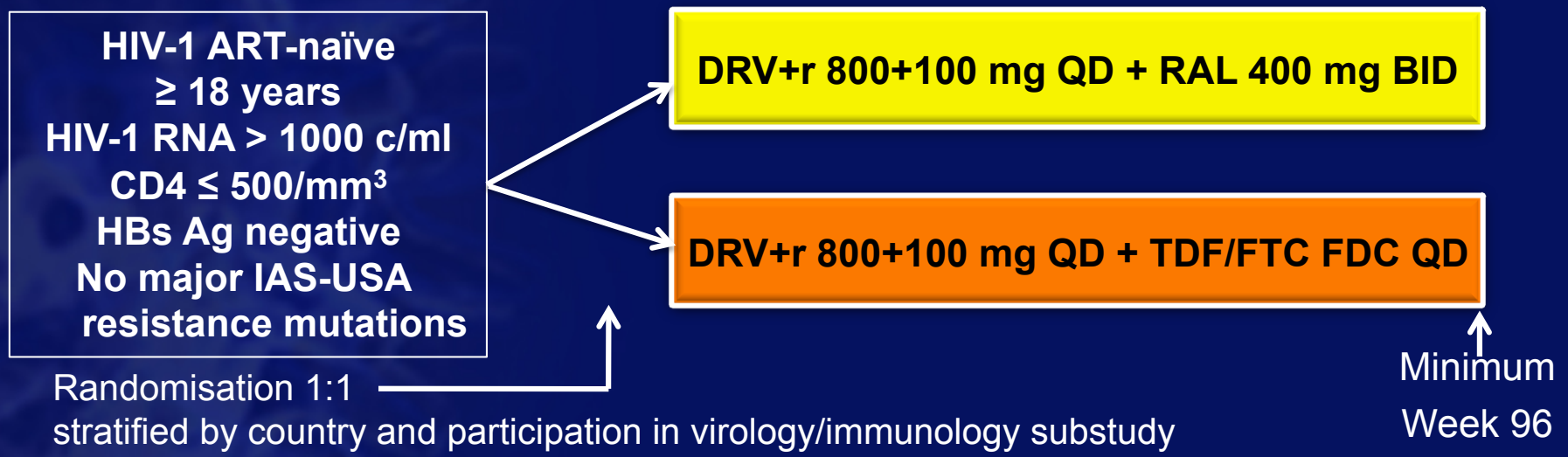
Disclosure

François Raffi

- Has served as a member of data monitoring committees for Janssen-sponsored clinical trials
- Received research grants awarded to his institution from Gilead Sciences and Janssen
- Has served as a consultant or received speaking honorarium from Abbvie, Bristol Myers Squibb, Gilead Sciences, Janssen, Merck, MSD and ViiV Healthcare

NEAT 001/ANRS 143 study design

- Phase III, randomised, open-label, multicenter, parallel-group, non-inferiority, strategic trial
- 78 sites, 15 countries (Austria, Belgium, Denmark, France, Germany, Great Britain, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Spain, Sweden)



- Composite virological and clinical primary endpoint (6 components)

Endpoints

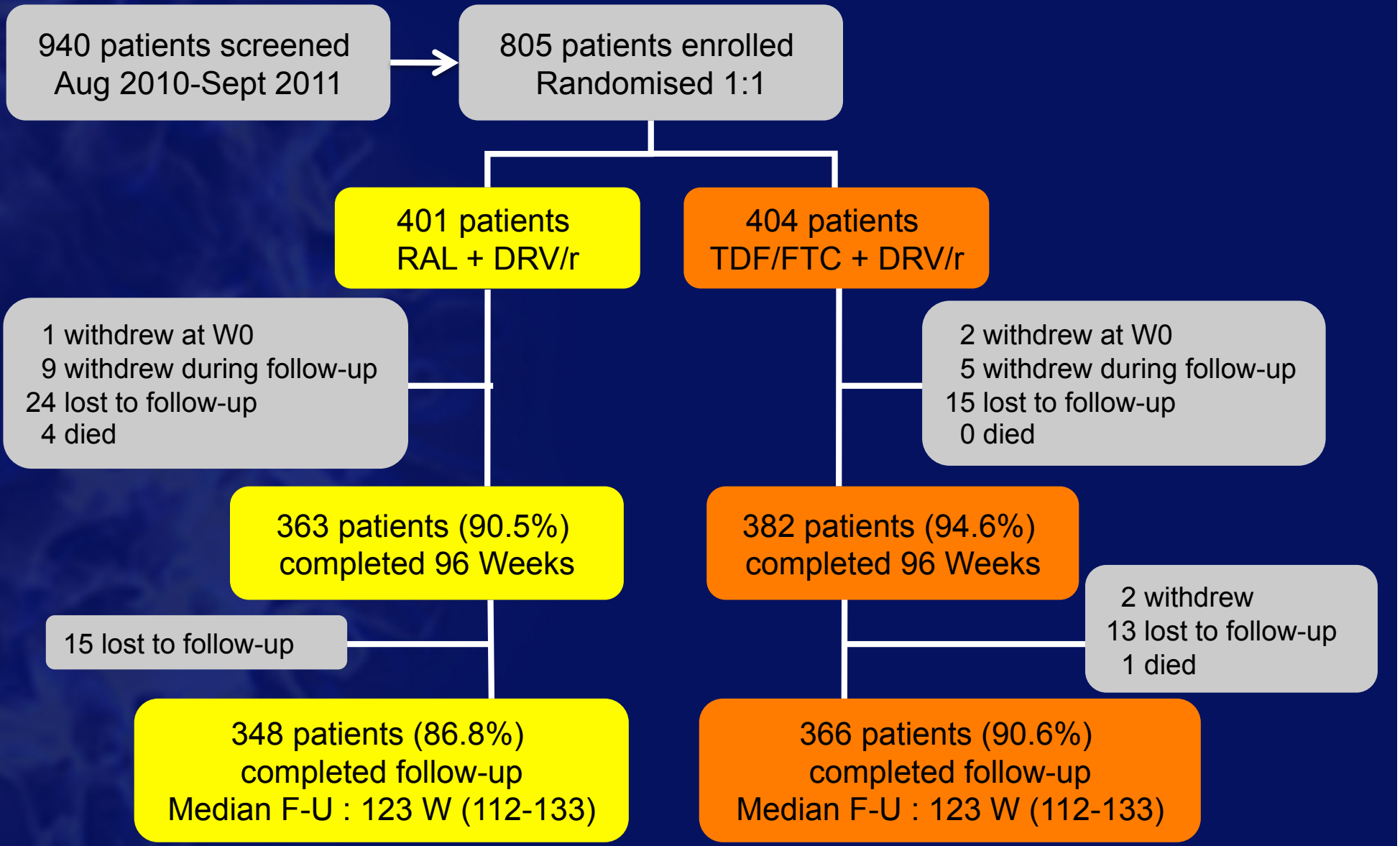
- Primary endpoint : Time to failure, as the first occurrence of any of the following components:
  - Virological
    - V1. change of treatment before W32 because of insufficient virologic response
      - HIV-1 RNA reduction < 1 $\log_{10}$ c/ml by W18*
      - or HIV-1 RNA ≥ 400 c/ml at W24*
    - V2. HIV-1 RNA ≥ 50 c/ml at W32*
    - V3. HIV-1 RNA ≥ 50 c/ml at any time after W32*
  - Clinical
    - C1 death due to any cause
    - C2. any new or recurrent AIDS defining event**
    - C3. any new serious non AIDS defining event**
- All patients followed-up until last patient reached W96, events recorded until end of F-U
- Non-inferiority margin: absolute difference of at most 9% for the failure rate of RAL vs. TDF/FTC by W96 (estimated by Kaplan-Meier methods) in the ITT analysis
- Major secondary endpoints: safety, changes in CD4 and HIV RNA, genotypic resistance

* confirmed by a subsequent measurement ; ** confirmed by the Endpoint Review Committee

Baseline Characteristics

		RAL + DRV/r n=401	TDF/FTC + DRV/r n=404
Gender	Male	88%	89%
Age	Median (y)	37	39
Ethnic group	Caucasian	82%	82%
	Black	13%	12%
	Asian	2%	2%
	Other	2%	4%
HIV CDC clinical stage	B	12%	13%
	C	5%	5%
Baseline HIV-1 RNA	Median (log_{10} c/ml)	4.78	4.75
	≥ 100,000 c/ml	36%	32%
	≥ 500,000 c/ml	6%	5%
Baseline $CD4^+$	Median (cells/mm^3)	340	325
	< 200 cells/mm^3	15%	16%
Hepatitis coinfection	HCV serology positive	4%	4%

Patient disposition during follow-up



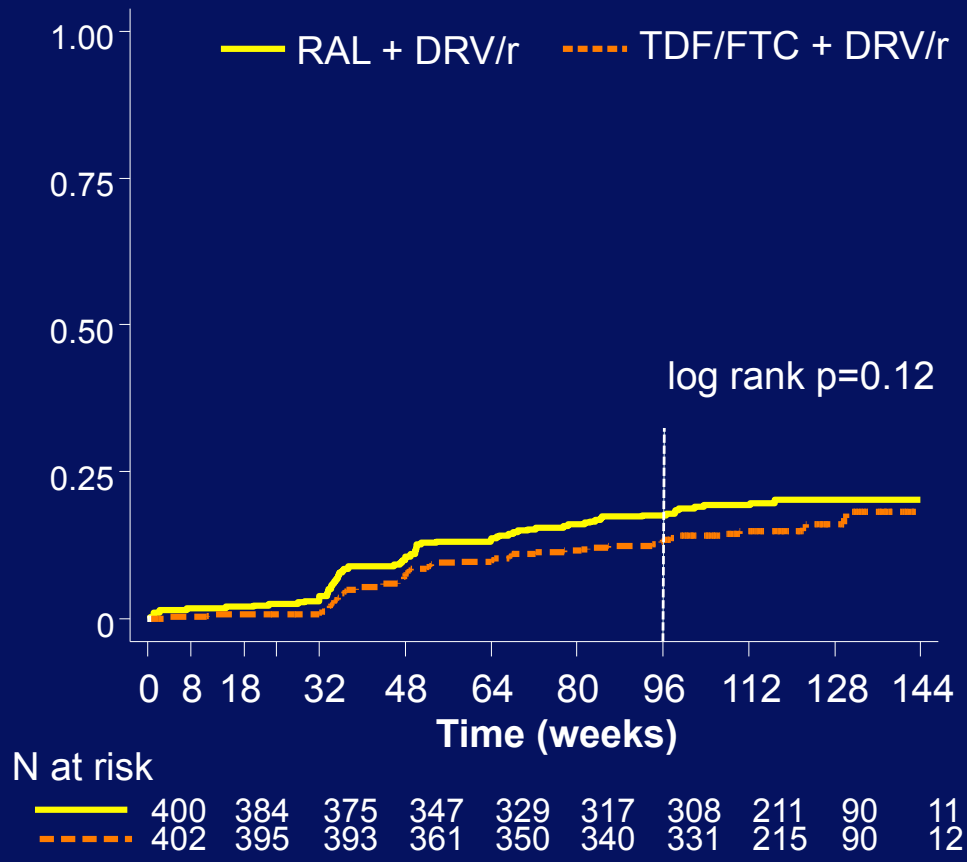
Primary analysis: time from randomisation to primary endpoint

Primary endpoint

	RAL + DRV/r	TDF/FTC + DRV/r
N	401	404
N with primary endpoint	76 (19%)	61 (15%)
V1. Regimen change for insufficient response		
< 1 log_{10} c/ml HIV RNA reduction W18*	1	0
HIV RNA ≥ 400 c/ml W24*	1	0
V2. HIV RNA ≥ 50 c/ml at W32*	27	28
V3. HIV RNA ≥ 50 c/ml after W32*	32	22
C1. Death	3	1
C2. AIDS event	5	3
C3. SNAIDS event	7	7

** confirmed by a subsequent measurement*

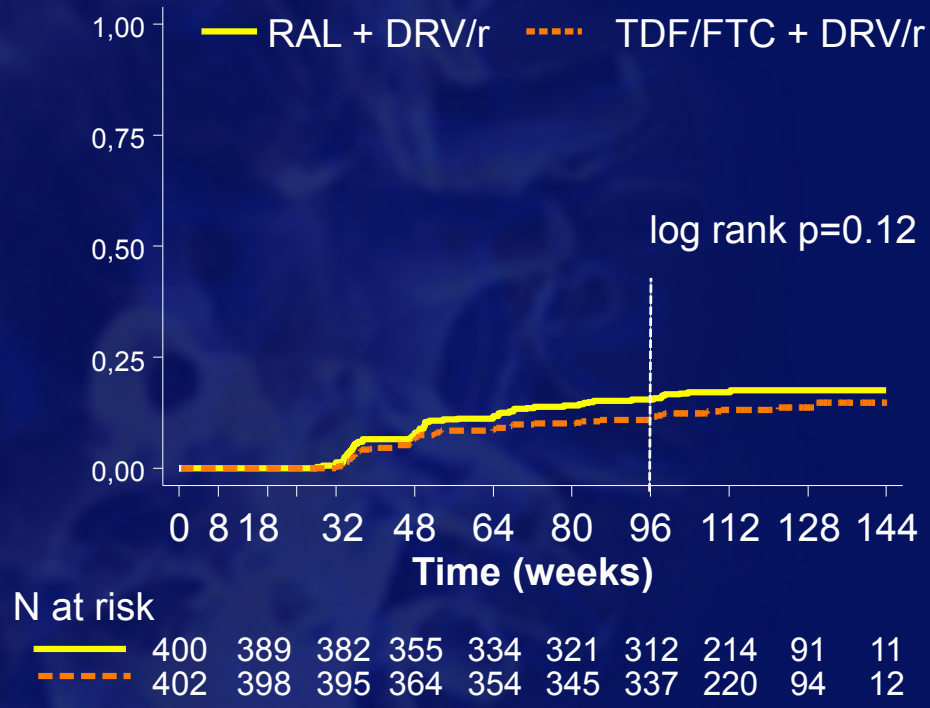
Probability of reaching primary endpoint



Estimated proportion reaching primary endpoint at W96
RAL: 17.4% vs TDF/FTC: 13.7%
Adjusted difference: 3.7% (95% CI: -1.1, 8.6%)

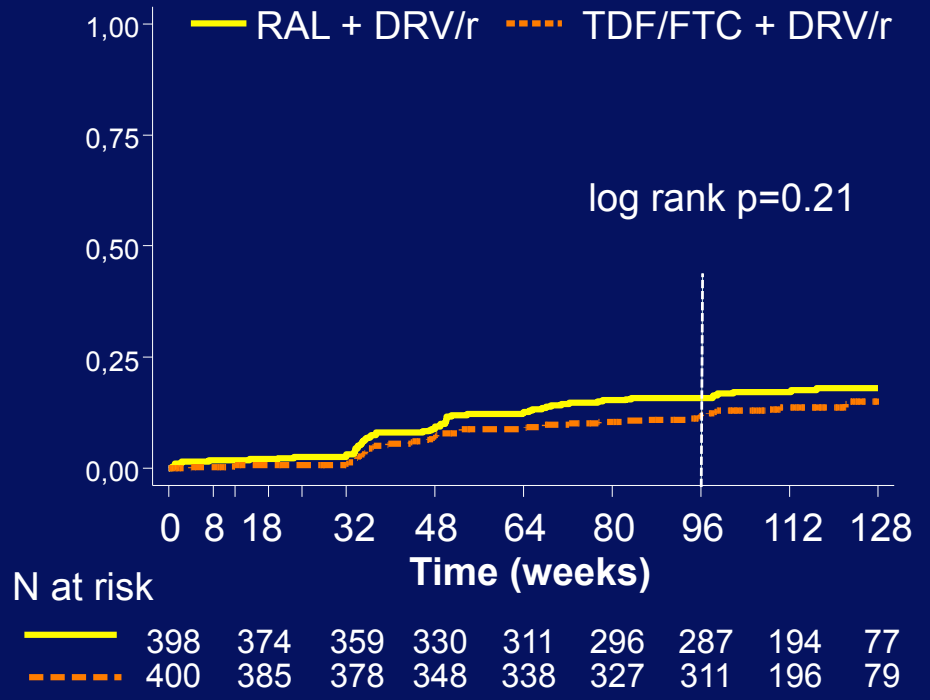
Primary endpoint: Sensitivity/secondary analysis

Sensitivity analysis : Time to virological failure as measured by virological components in primary endpoint



Estimated proportion reaching endpoint at W96
RAL: 15.4% vs TDF/FTC: 11.8%
Adjusted difference: 3.6% (95% CI: - 0.8, 8.1%)

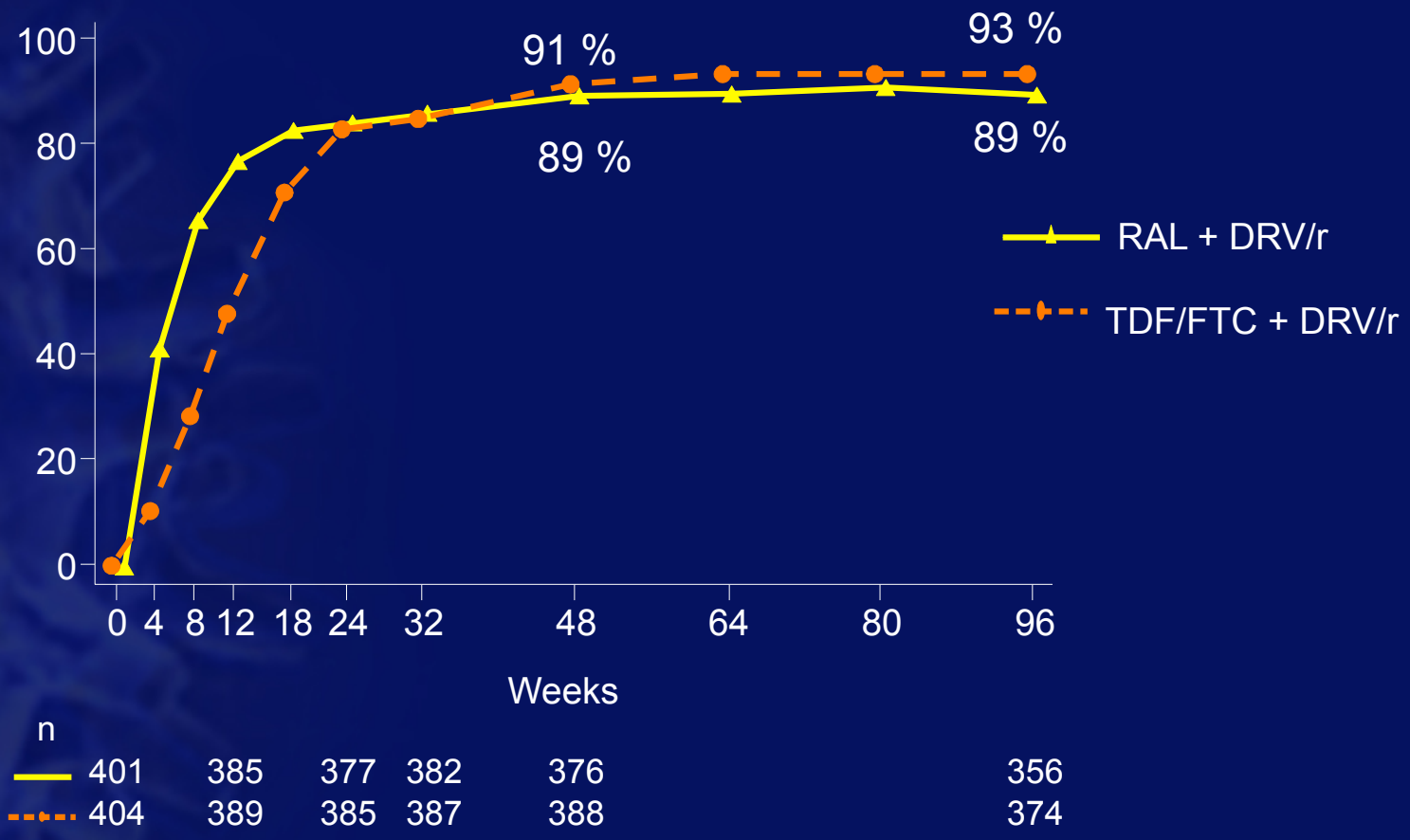
Secondary analysis : Time to primary endpoint with the addition of discontinuation of any component of randomised regimen for any reason as an endpoint



Estimated proportion reaching endpoint at W96
RAL: 22.8% vs TDF/FTC: 19.5%
Adjusted difference : 3.3% (95% CI: - 1.9, 8.4%)

HIV-1 RNA < 50 c/ml

Percentage of participants with available data

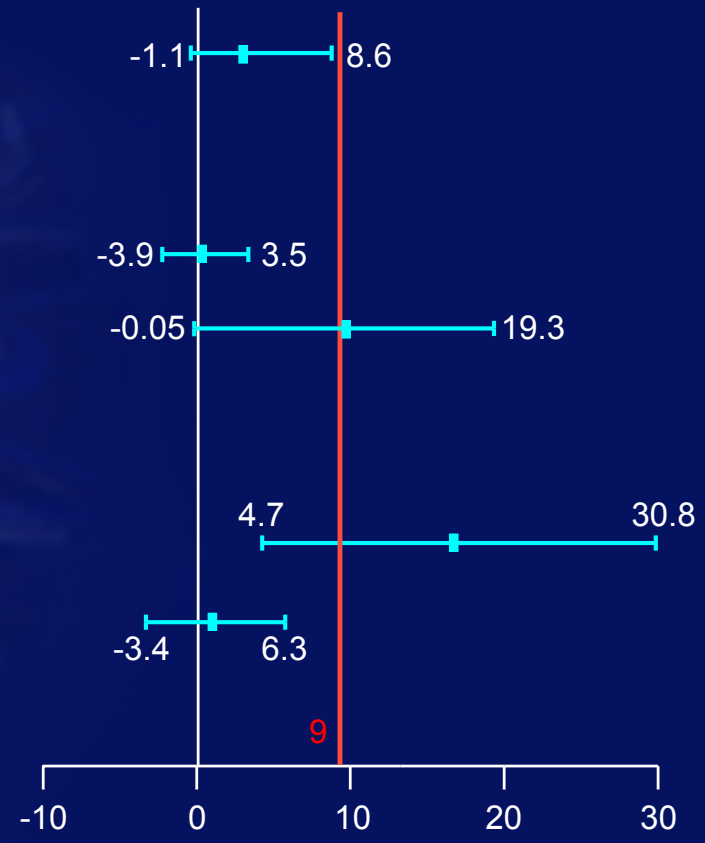


	Mean (95% CI) Change From Baseline CD4⁺ Cell Count (cells/mm³)				
		W48		W96	
RAL + DRV/r		+ 197	(184, 210)	+ 267	(250, 285)
TDF/FTC + DRV/r		+ 193	(180, 206)	+ 266	(249, 283)

Primary endpoint at W96 by baseline characteristics

Overall analysis: RAL + DRV/r non inferior to TDF/FTC + DRV/r

		RAL + DRV/r	TDF/FTC + DRV/r
Overall	n = 805	17.4 %	13.7 %
Baseline HIV-1 RNA			
< 100,000 c/ml	n = 530	7 %	7 %
≥ 100,000 c/ml	n = 275	36 %	27 %
			p = 0.09*
Baseline CD4+			
< 200/mm^3	n = 123	39.0 %	21.3 %
≥ 200/mm^3	n = 682	13.6 %	12.2 %
			p = 0.02*



Difference in estimated proportion (95% CI) RAL – TDF/FTC; adjusted

* Test for homogeneity

Virological failure during follow-up and resistance data

	RAL + DRV/r n=401	TDF/FTC + DRV/r n=404
Protocol-defined virological failure (PDVF), n	66	52
Number of PDVF who met criteria for genotype testing (HIV RNA > 500 copies/ml at or after W32)	33	9
Number of patients with single unconfirmed value of HIV RNA > 500 copies/ml at or after W32 (meeting criteria for genotype testing)	3	6
Genotype done, n	28/36	13/15
Major resistance mutations, n	5	0
NRTI	1 (K65R)	0
PI	0	0
INI	5 (N155H)*	-

* 1 additional patient with T97A

Protocol-defined virological failure change of any component of the initial randomised regimen before W32 because of confirmed insufficient virological response, defined as HIV-1 RNA reduction < 1 $\log_{10}$ copies/ml by W18 or HIV-1 RNA ≥ 400 copies/ml at W24 ; failure to achieve virological response by W32 (confirmed HIV-1 RNA ≥ 50 copies/ml at W32) ; confirmed HIV-1 RNA ≥ 50 copies/ml at any time after W32

According to the protocol, genotypic testing was carried out by local laboratories when patients had a single VL > 500 copies/ml at or after W32.

Safety and tolerability

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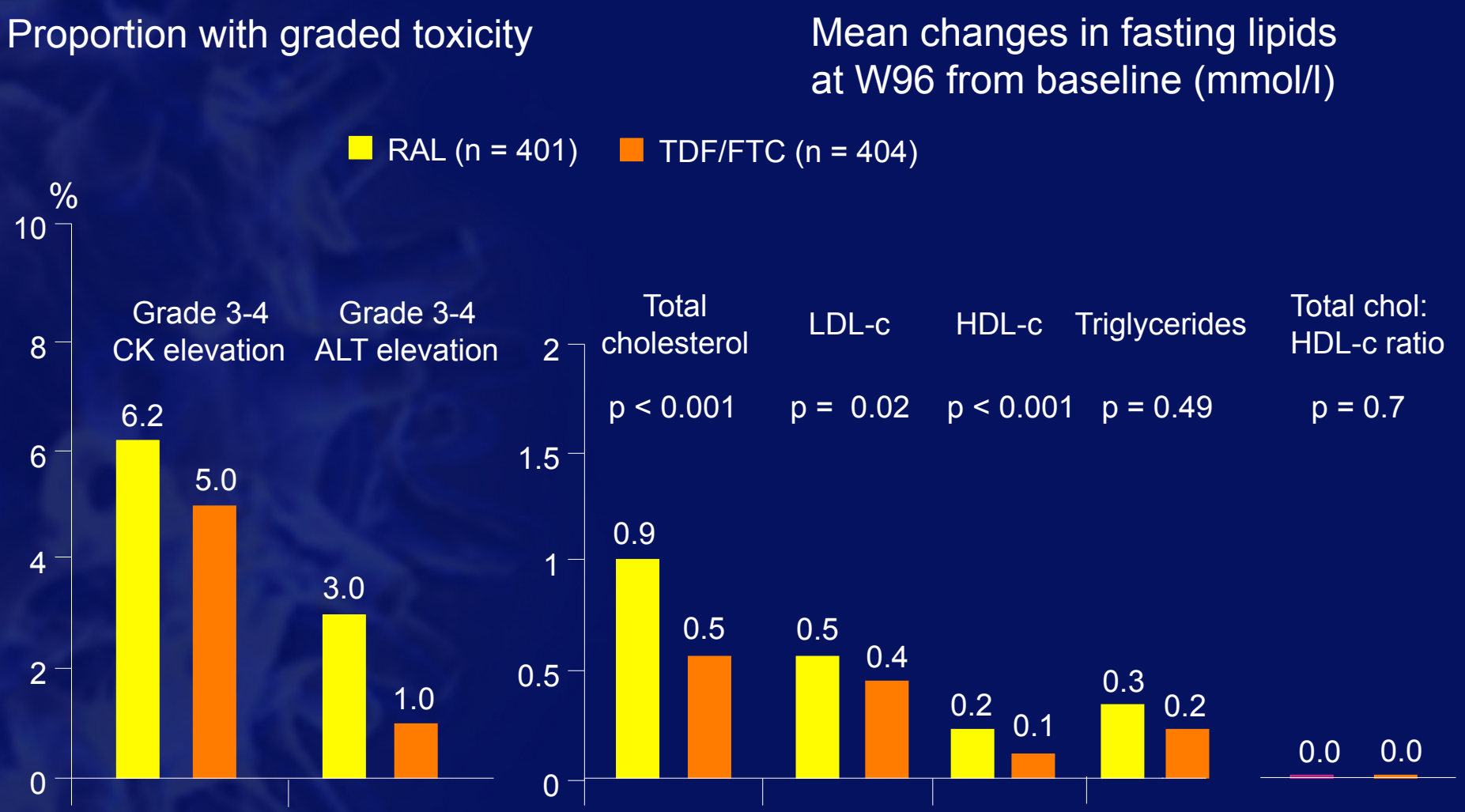
		RAL + DRV/r	TDF/FTC + DRV/r	p value (log rank)
SAE, n		89 (73 patients)	75 (61 patients)	
Type	Fatal, n	4*	1**	
	Life-threatening, n	8***	4****	
	Hospitalisation, n	67	60	
	Other medical condition, n	10	10	
Incidence rate (/100 py)		10.2	8.3	0.17
Incidence rate (/100 py)				
Grade 4 AEs		2.1	1.0	0.09
Grade 3 or 4 AEs		9.6	7.4	0.16
Grade 3 or 4 treatment-modifying AEs		1.0 $	0.6 $	0.53
Any Grade treatment-modifying AEs		4.2	4.2	0.84

* Burkitt's lymphoma, DRESS syndrome, melanoma, suicide attempt ; ** morphine overdose
*** CK increase (n = 5), hepatitis, Hodgkin, pancreatitis ; **** CK increase (n = 2), myocardial infarction, γGT increase
$ No trend for specific drug-related event
All differences between arms not statistically significant

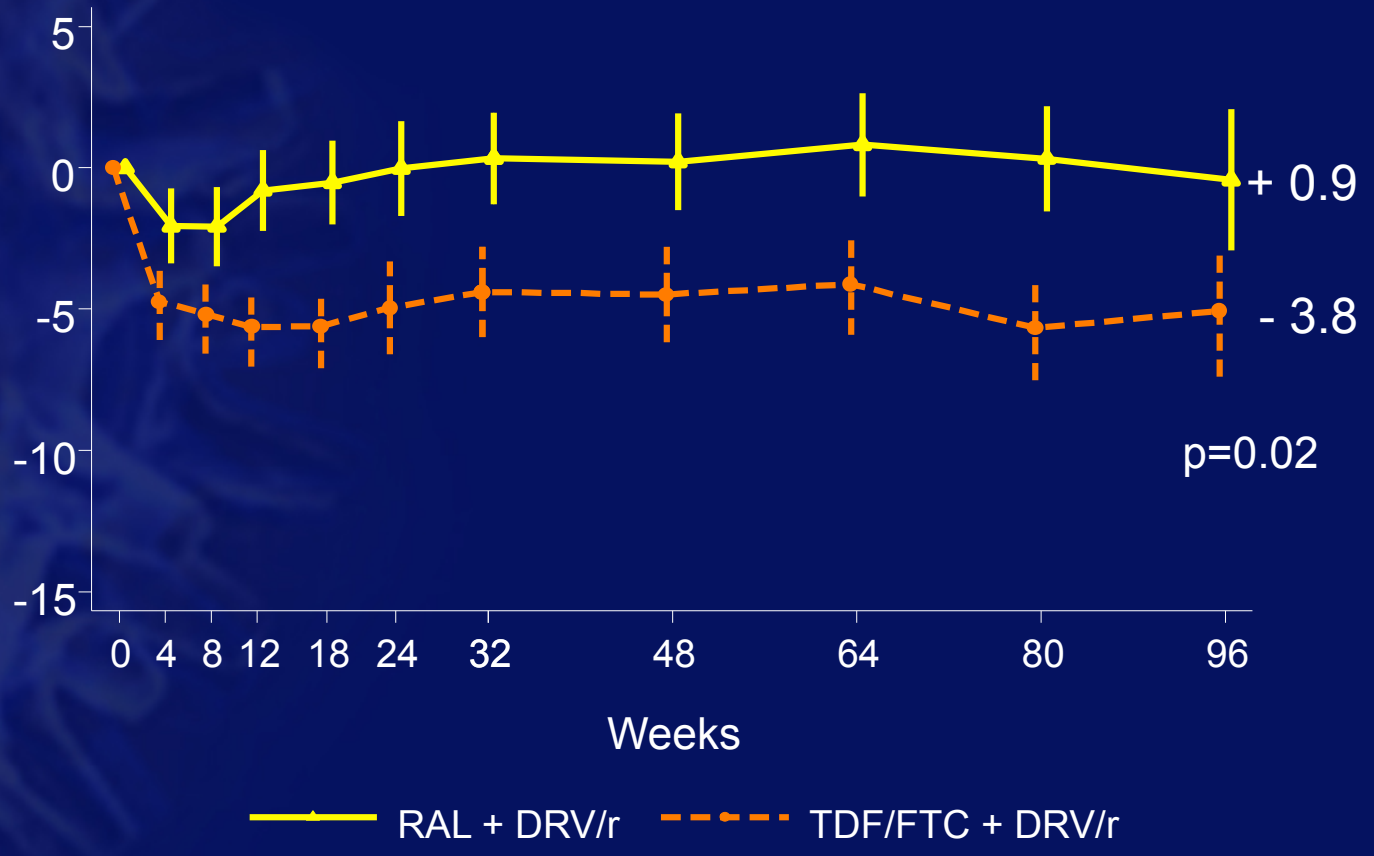
Laboratory results – W96



Renal safety

Creatinine clearance (eGFR, ml/min [Cockroft-Gault formula]

Mean (95% CI) change from baseline



No grade 2-4 creatinine elevation in either arm

NEAT 001/ANRS 143 Conclusions

In this well powered, open-label randomised study

- Overall twice daily RAL was well tolerated and had comparable efficacy to once daily TDF/FTC, when co-administered with once daily DRV/r, over 96 weeks in first-line ARV therapy
  - Primary endpoint incidence over 96 weeks was 17.4 % (RAL) vs. 13.7 % (TDF/FTC); adjusted absolute difference was 3.7%
  - The upper 95% CI of 8.6% was below the pre-specified non-inferiority margin
  - In a planned subgroup analysis of the outcome for patients with low CD4 (<200/mm^3) RAL + DRV/r was inferior to TDF/FTC + DRV/r
- Comparable safety between the 2 strategies
  - Similar rate of SAE, Grade 3-4 AE, AE leading to treatment modification
- Treatment-emergent resistance was seen in 5/28 (RAL) vs. 0/13 (TDF/FTC) patients with available genotype at failure

➔ RAL + DRV/r represents an alternative option to TDF/FTC + DRV/r for first line therapy, particularly in patients with CD4 > 200/mm^3

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