Update on HIV Drug Resistance

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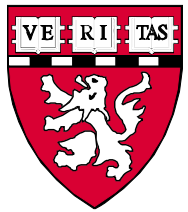


Learning Objectives

Upon completion of this presentation, learners should be better able to:

- **Review resistance patterns to newest antiretroviral drugs**
- **Discuss implications of drug resistance on sequencing of antiretroviral regimens**

Off-Label Disclosure

- Etravirine is not approved for use in treatment-naïve patients

Etravirine and Rilpivirine

Etravirine

- **TMC125 identified through screening for activity against NNRTI-resistant viruses (K103N)**
- **In vitro passage experiments suggested high genetic barrier to resistance**
- **Known and novel NNRTI resistance mutations identified through in vitro passage experiments**
  - L100I, Y181C, G190E, Y318F
  - V179I/F
- **Data from DUET and phase 2 trials identified 17 clinically significant ETV resistance mutations**

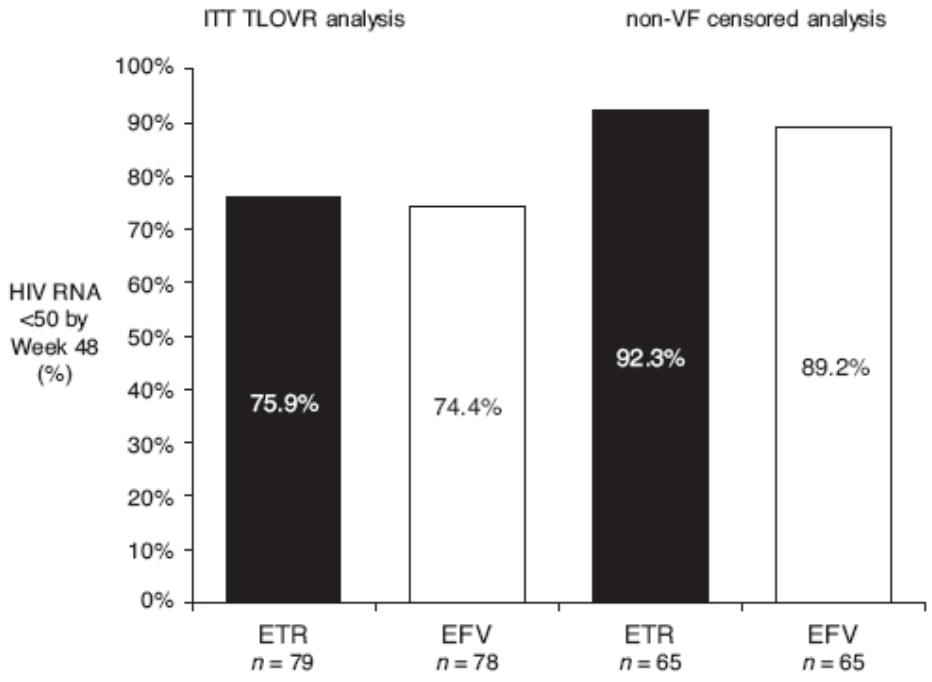
DUET-1 and -2: Etravirine resistance-associated mutations

- **ETV mutations (n=17) weighted based upon impact on response (weight factor)[1]:**
  - 3.0: Y181I/V
  - 2.5: L100I, K101P, Y181C, M230L
  - 1.5: V106I, V179F, E138A, G190S
  - 1.0: V90I, A98G, K101E/H, V179D/T, G190A
- **Most common resistance mutations emerging at ETV failure in DUET trials:**
  - V179F/I and Y181C/I[2,3]

1. Vingerhoets J, et al. AIDS 2010; 2. *Intelence* [package insert]; 2008. 3. Marcelin AG et al Antiviral Ther 2012

Phase 2 pilot study of ETR in treatment-naïve patients (SENSE)

- **ART-naïve patients randomized to ETR (400 mg QD; N=79) or EFV (N=78) plus 2 NRTI[1]**



[1]Gazzard et al AIDS 2011

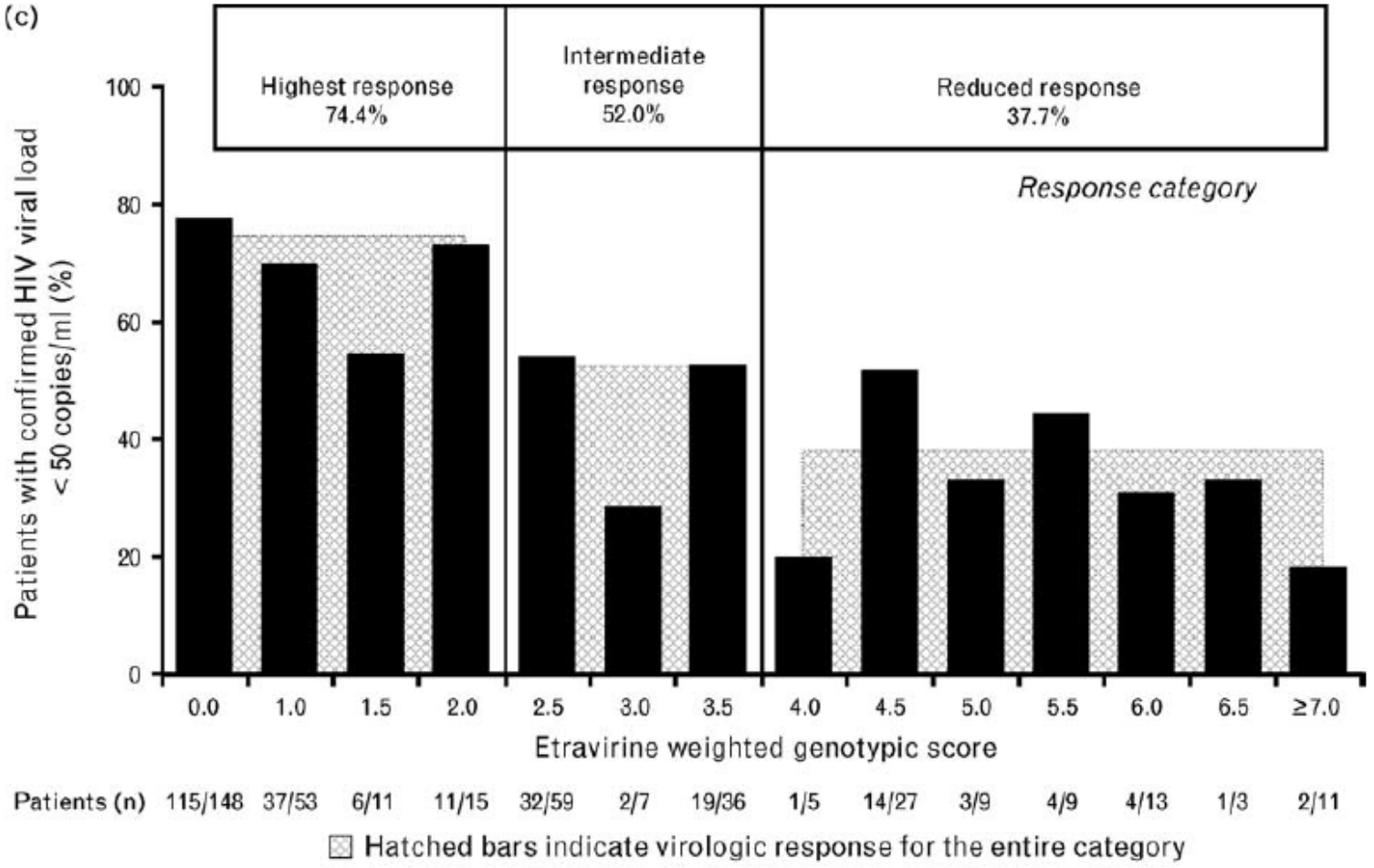
NNRTI resistance in SENSE

Table 2. Virological failures by treatment arm: HIV RNA levels and detection of genotypic resistance (IAS-USA or Bennett lists).[1]

Patient	HIV RNA					Resistance mutations
	Baseline	Week 24	Week 36	Week 48	FU	
Etravirine arm ($n=4$)[a]						
1	122 000	<50	<50	**700**	124	None
2	78 800	<50	100, **104**	<50	<50	None
3	178 000	<50	**85**	68	<50	None
4	118 000	<50	**114**	<50	50	None
Efavirenz arm ($n=7$)						
1	48 900	<50	**104**	<50	**10700**	None
2	3160	<50	**1350**	240, 62	<50, **73**	None
3	397 000	123	111	<50	**81**	None
4	3 810 000	107	129	56	<50	Not amplified
5	240 000	<50	<50	**2180**	Missing	V106I + M184I
6	82 800	<50	**72**	<50	**81600**	K103N
7	412 000	33400	**51 800**	**26 100**	Discontinued	K103N + M184V + P225H

[1]Gazzard et al AIDS 2011

DUET-1 and -2: Predictors of ETV Response and Resistance at Failure



Vingerhoets J et al. AIDS 2010

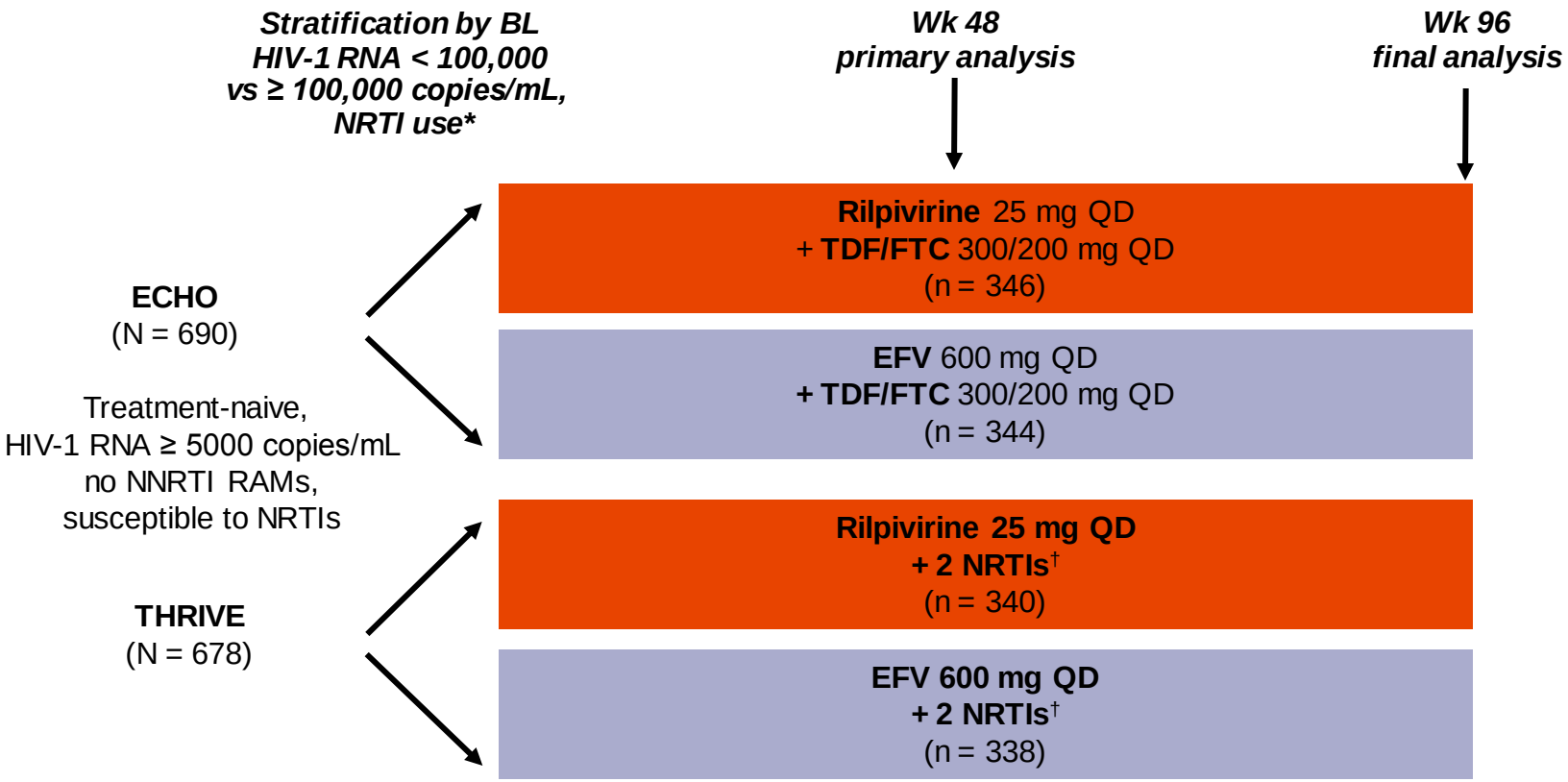
Rilpivarine (TMC278)

- **Like etravirine, selected by screening for compounds active against viruses with K103N**
- **Similar activity profile as etravirine**
  - Unaffected by K103N
  - Modest effect of Y181C
- **Slow to select resistance in vitro**

Azijn et al. Antimicrob Agents Chemother 2010

ECHO, THRIVE: Rilpivirine (TMC278) vs EFV in Treatment-Naive Patients

- **Randomized, double-blind phase III trials**



*THRIVE only. †Selected by investigator from ABC/3TC, TDF/FTC, ZDV/3TC.

Cohen C, et al. Lancet 2011

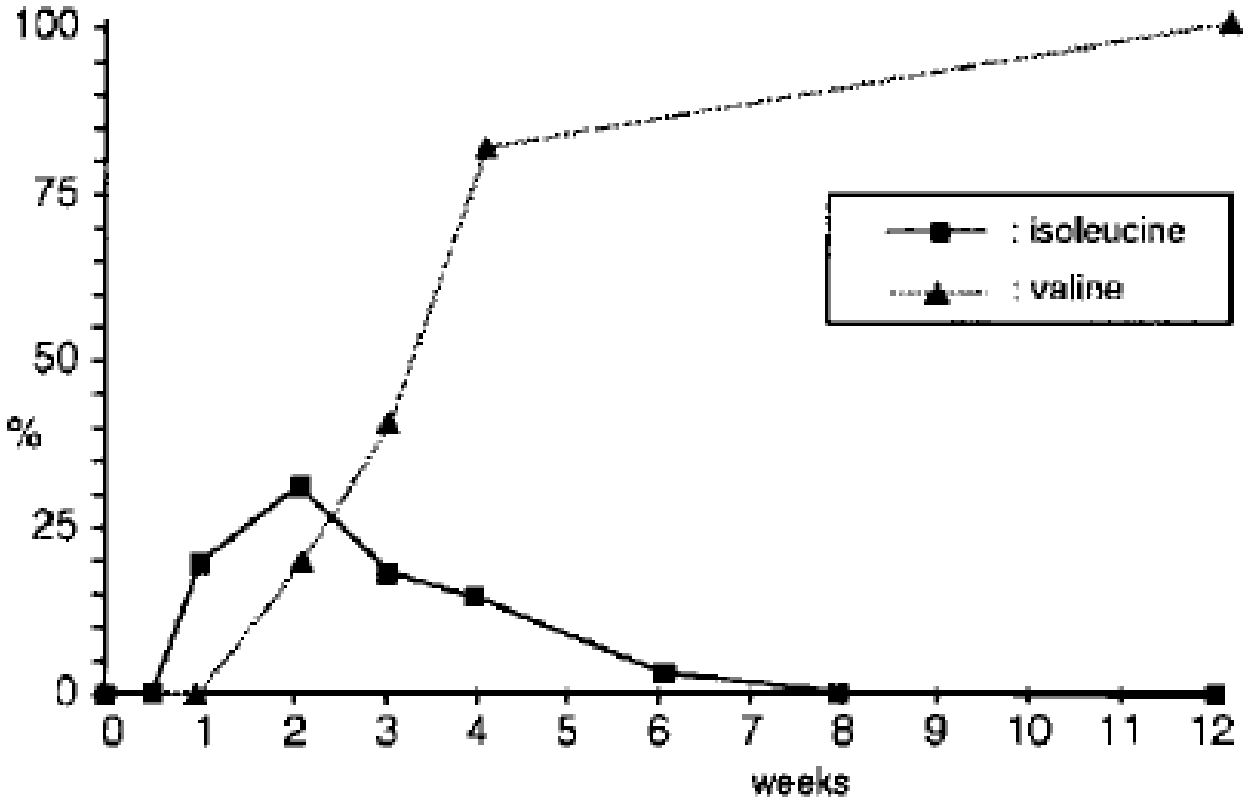
Drug resistance in ECHO and THRIVE

	TMC278 N=686	EFV N=682
Virologic failure with resistance data, n	62	28
No NNRTI[1] or NRTI[2] RAMs	29%	43%
Emergent† NNRTI[1] RAMs	63%	54%
– Most frequent NNRTI RAM	E138K	K103N
Emergent† NRTI[2] RAMs	68%	32%
– Most frequent NRTI RAM	M184I	M184V

- 31/62 (50%) of TMC278 failures were phenotypically resistant to TMC278
  - Of these, 90% were phenotypically cross-resistant to etravirine

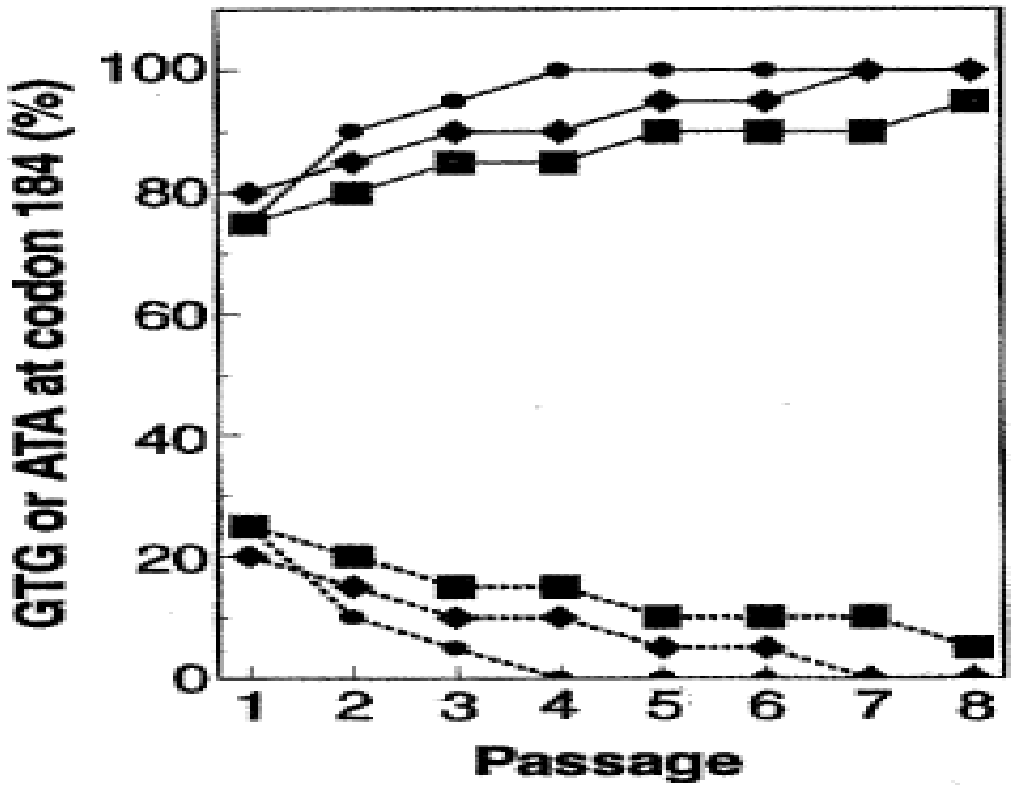
Molina et al Lancet. 2011
Cohen et al Lancet 2011

Early emergence of M184I in patients receiving 3TC monotherapy



Schuurman et al J Infect Dis 1995

M184V is fitter than M184I



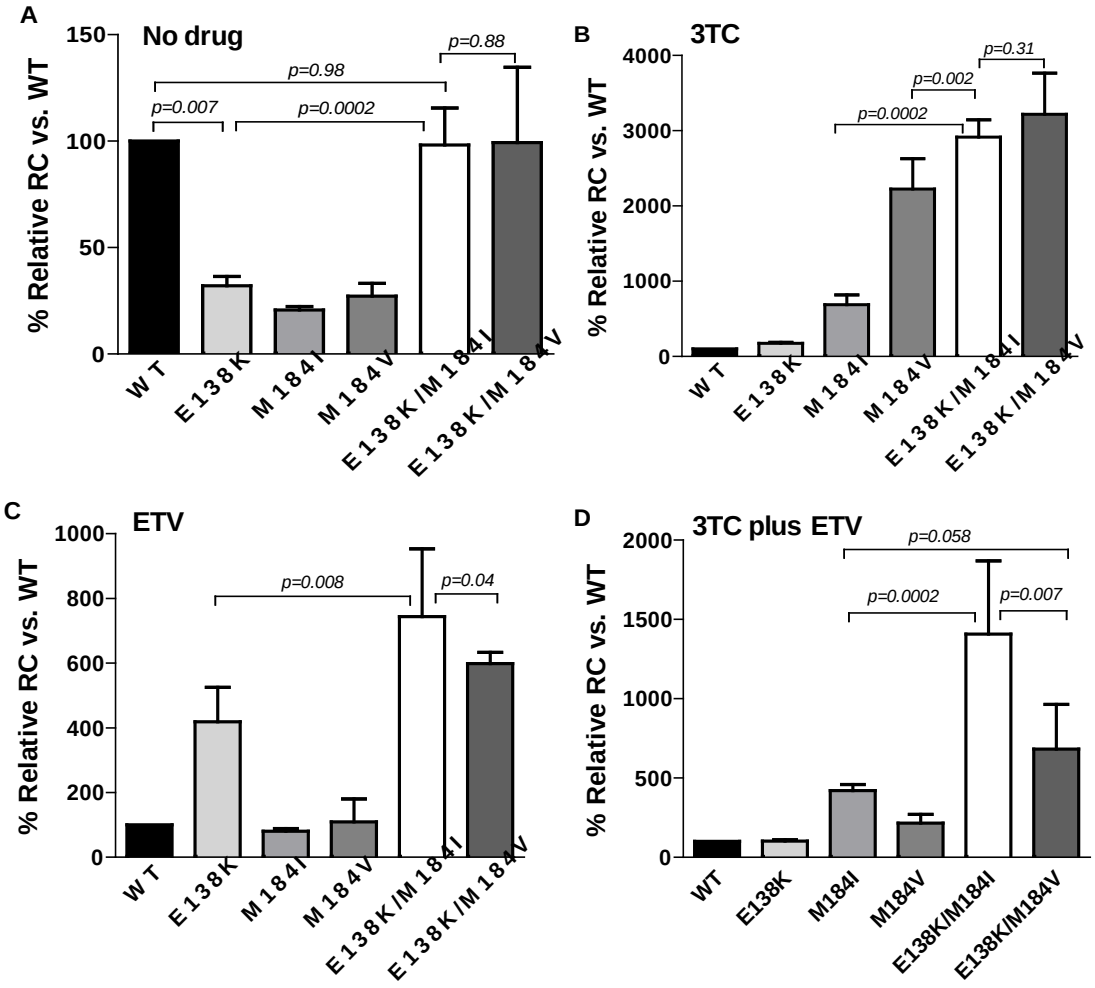
M184V

(■)no inhibitor
(◆) 3TC
(●) FTC

M184I

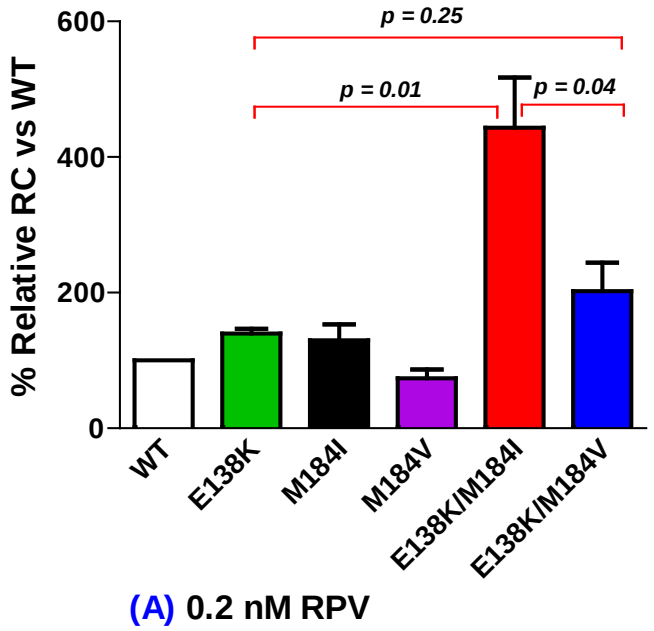
Larder et al Science 1995

Replication capacity of E138K and M184I mutants in presence of ETV and/or 3TC

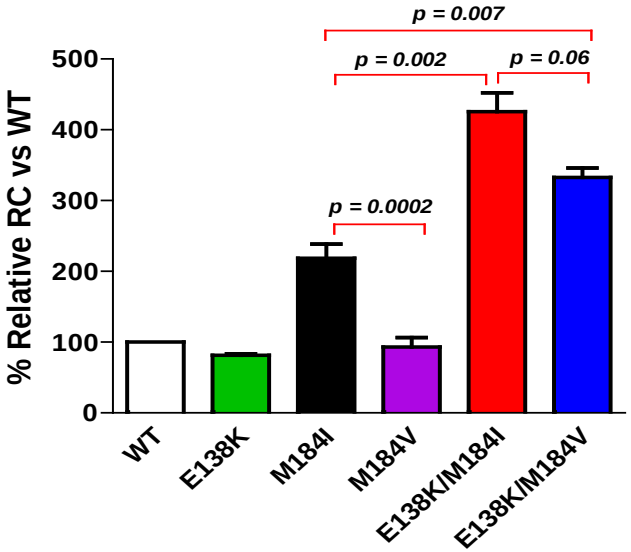


Hu and Kuritzkes, J Virol 2011

Replication capacity of E138K and M184I mutants in presence of RPV and 3TC



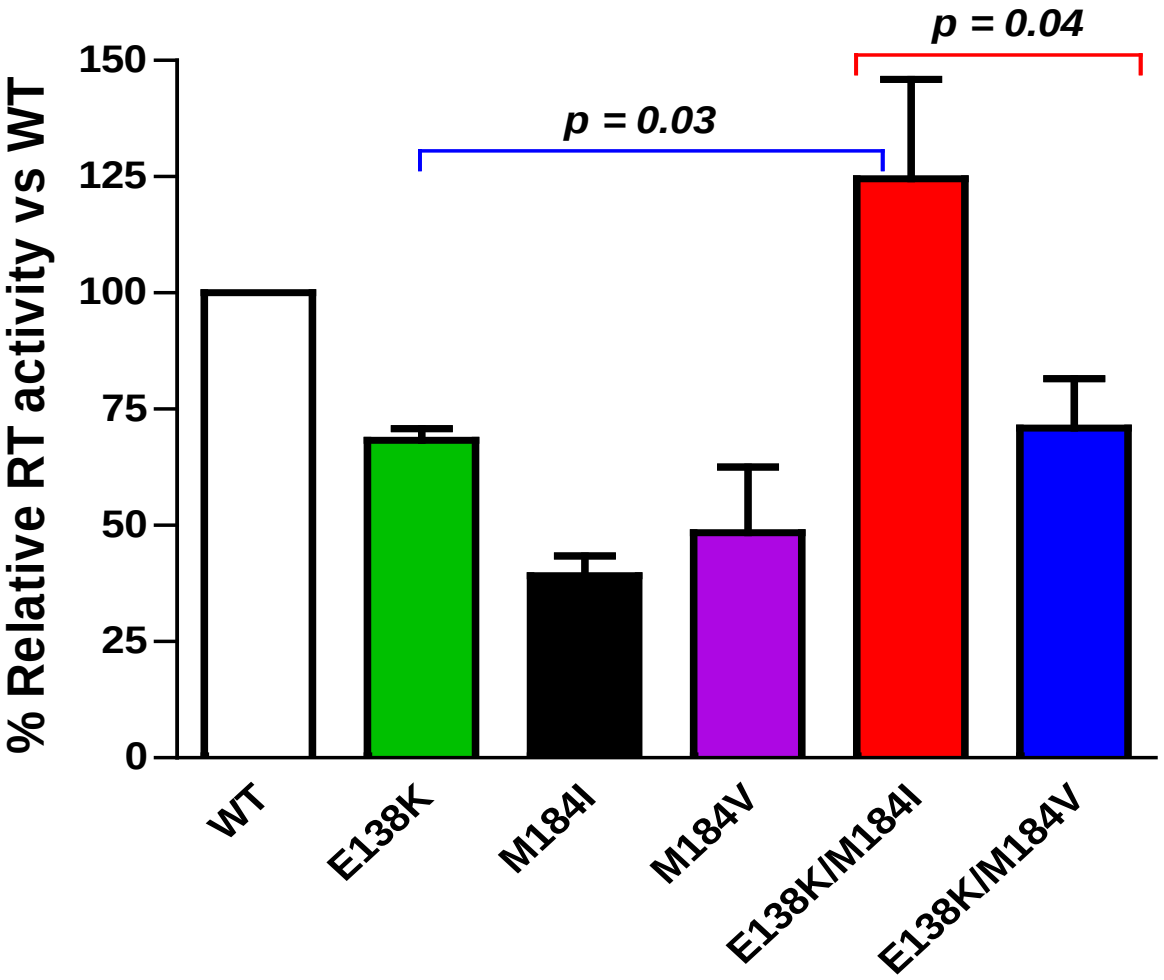
(A) 0.2 nM RPV



(B) 0.08 nM RPV + 8 μM 3TC

Hu & Kuritzkes 19th CROI, Seattle, WA 2012

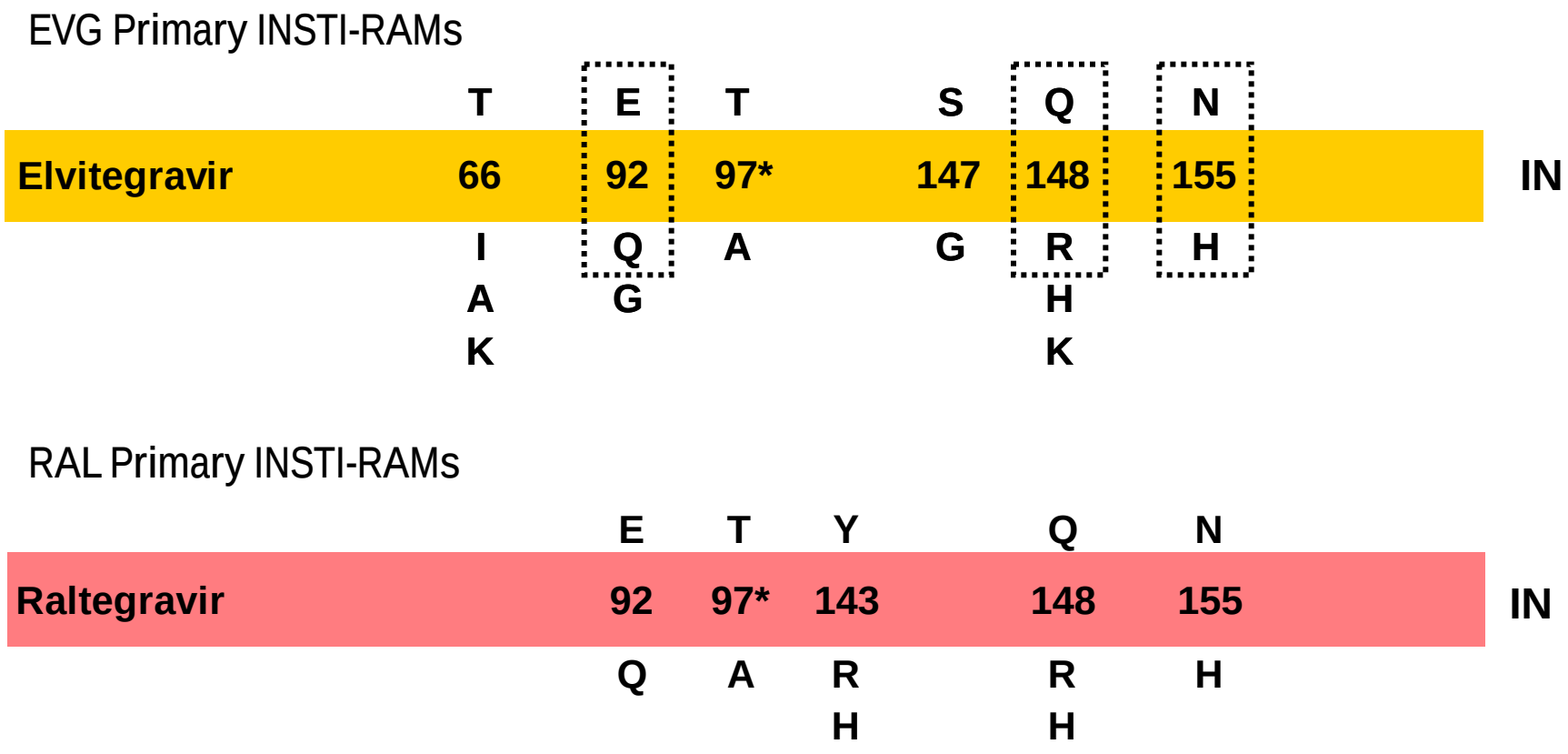
Virion-associated RT activity of HIV-1 wild-type and mutant viruses



Hu and Kuritzkes, J Virol 2011

Elvitegravir

Primary Integrase Strand Transfer Inhibitor (INSTI) Resistance-Associated Mutations (RAMs)

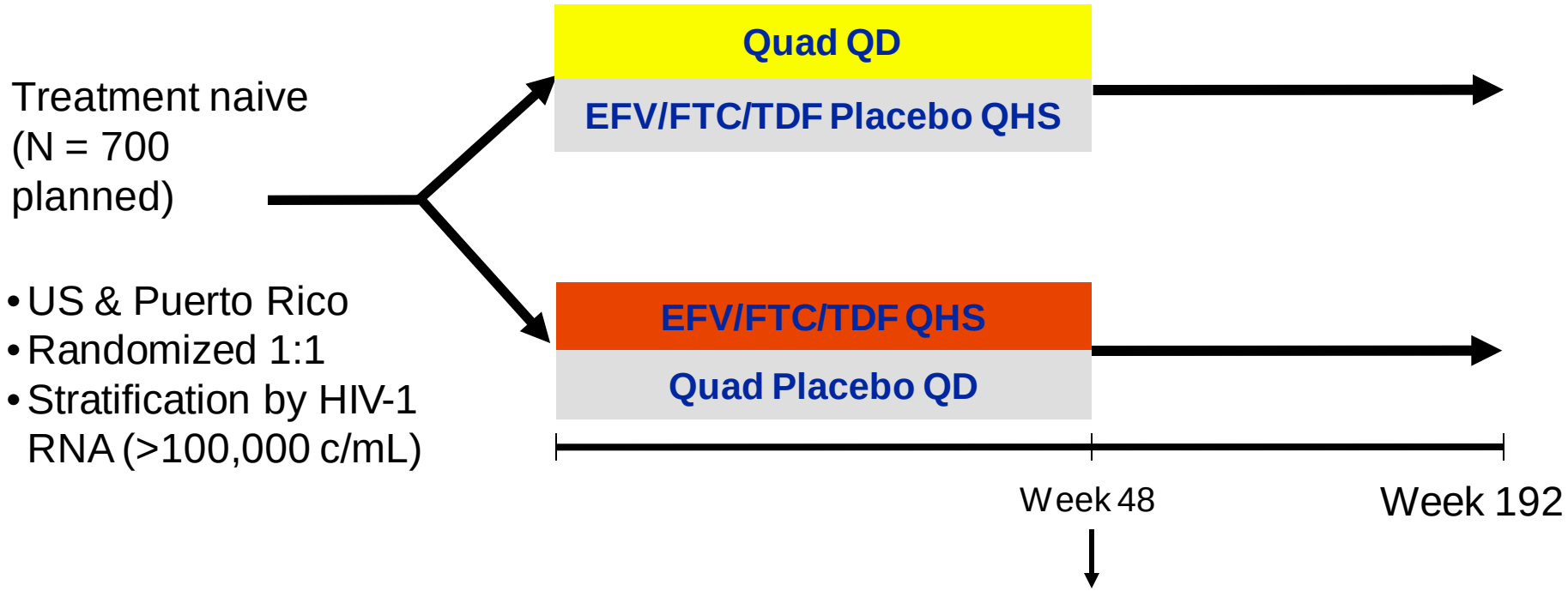


Cross-study clinical development of INSTI-RAMs

*** T97A may require additional mutations for resistance**

Abram et al Antiviral Ther 2012; 17 (Suppl 1):A11.

Study Design 236-0102

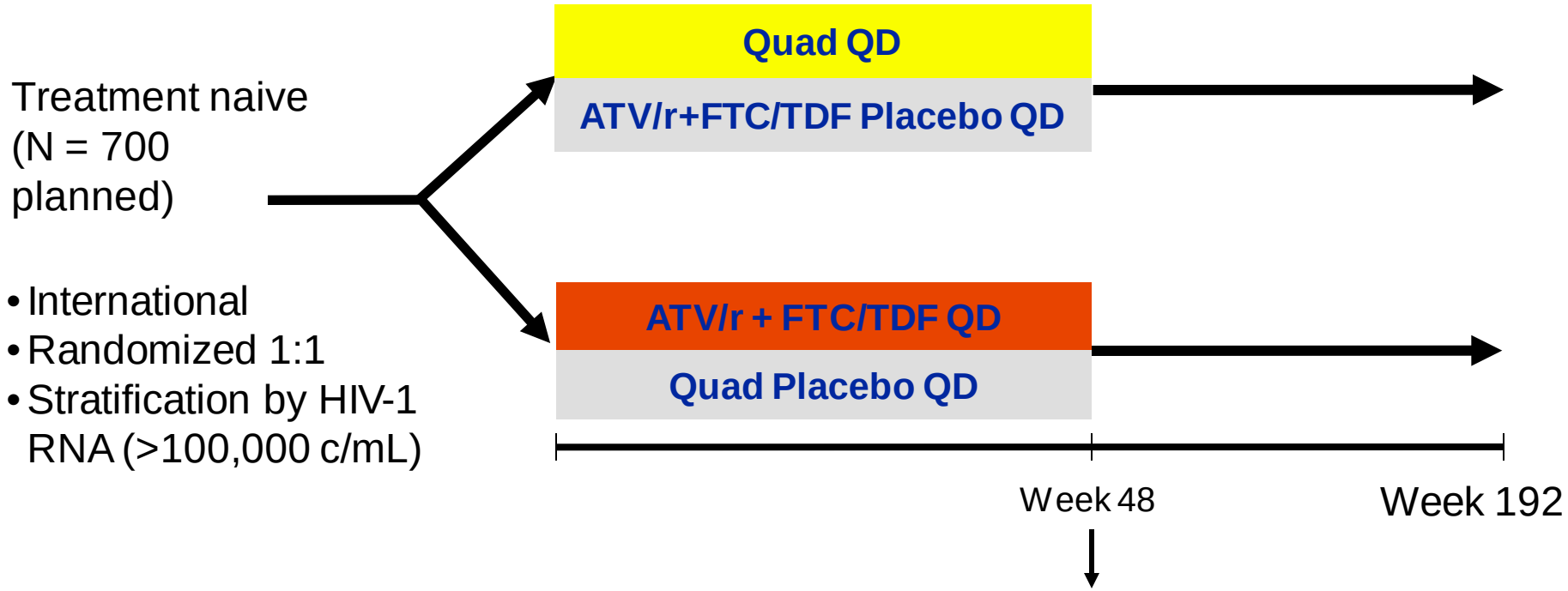


Primary Endpoint: Proportion with HIV-1 RNA < 50 c/mL at Week 48

- FDA snapshot analysis, 12% non-inferiority margin
- HIV-1 RNA: Amplicor HIV-1 Monitor Test, version 1.5

Sax P, et al. CROI 2012; Seattle. Poster 101LB

Study Design 236-0103

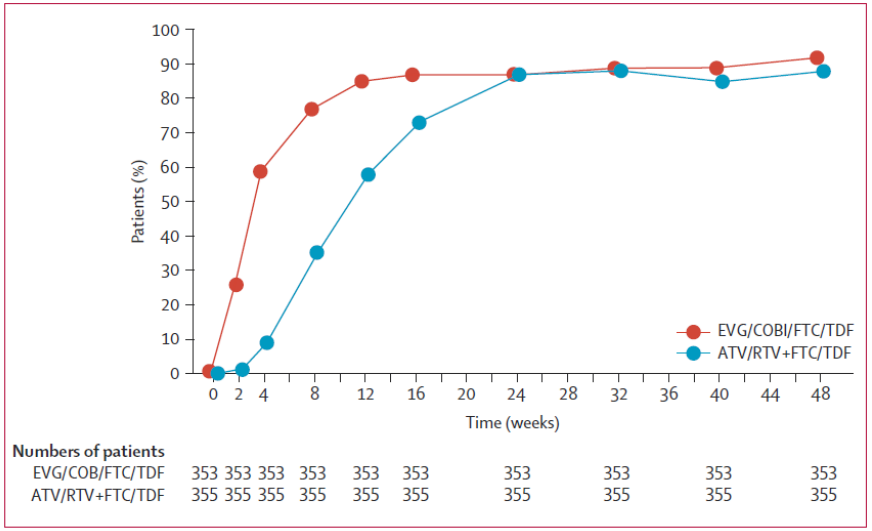


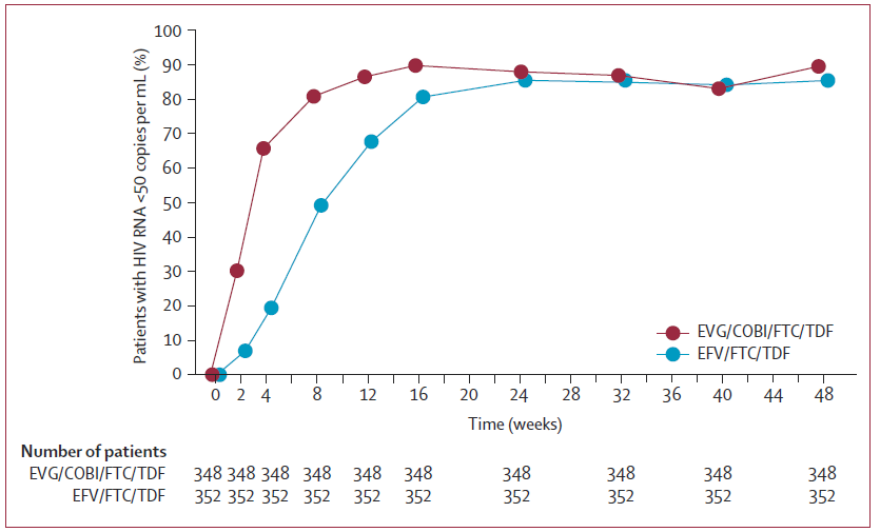
Primary Endpoint: Proportion with HIV-1 RNA < 50 c/mL at Week 48

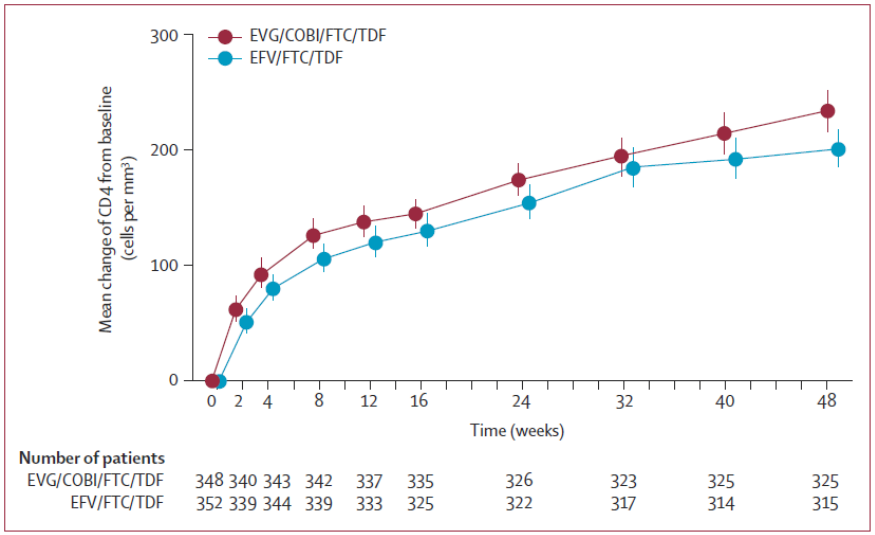
- FDA snapshot analysis, 12% non-inferiority margin
- HIV-1 RNA: Amplicor HIV-1 Monitor Test, version 1.5

DeJesus E, et al., CROI 2012; Seattle. Poster 627.

236-0102 and 236-0103: Results







Sax et al Lancet 2012; DeJesus et al Lancet 2012

QUAD Virologic Failures with EVG Resistance show RAL Cross-resistance (>biological cut-off)

INSTI	Virology Patient										
	1	2	3	4	5	6	7	8	9	10	11
EVG	>198	149	111	54	51	44	36	36	28	23	5.6
RAL	28	6.2	3.8	6.0	12	3.6	3.0	11	3.3	8.7	1.8

Biological Cut-Offs: EVG 2.5; RAL 1.5

Mead fold change value for EVG was >67-fold
Mean fold change value for RAL = 7.9-fold

White et al Antiviral Ther 2012; 17 (Suppl 1):A12.

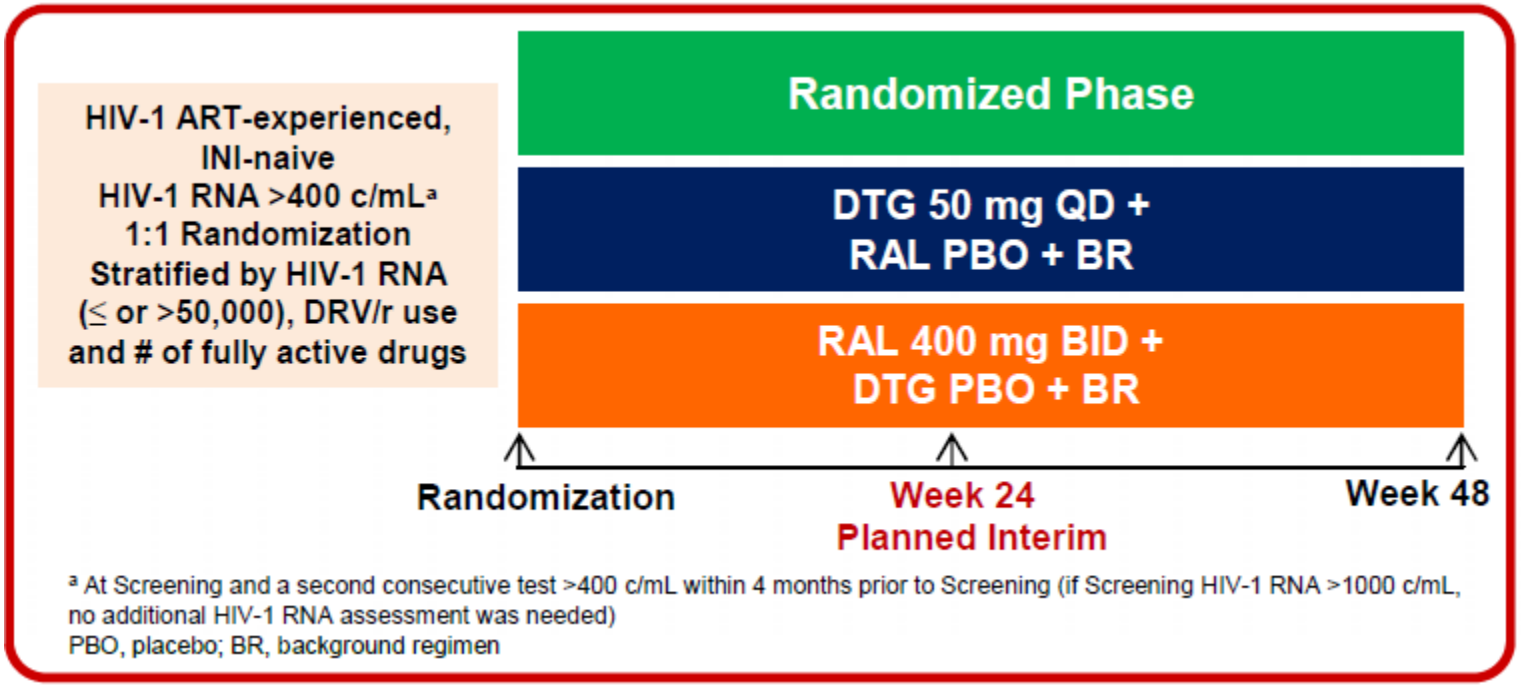
Dolutegravir

VIKING study results

Variable	Cohort I, DTG 50 mg Once Daily (n = 27)	Cohort II, DTG 50 mg Twice Daily (n = 24)
Efficacy at day 11		
Primary end point, no. (%)	21 (78)	23 (96)
Plasma HIV-1 RNA level, log_{10} copies/mL		
Baseline, mean (SD)	4.40 (0.79)	4.38 (0.74)
Day 11, mean (SD)	2.94 (1.01)	2.62 (0.78)
Change from baseline, mean (SD)	−1.45 (0.77)	−1.76 (0.54)
Model-adjusted change, mean (SD)	−1.45 (0.08)	−1.76 (0.09)
Adjusted treatment difference, mean (95% CI)[a]	−0.32 (−0.57 to −0.06)[b]	
Efficacy at week 24		
HIV-1 RNA load, copies/mL, no. (%)[c]		
<50	11 (41)	18 (75)
<400	14 (52)	20 (83)
<50, by baseline PSS to OBR at day 11		

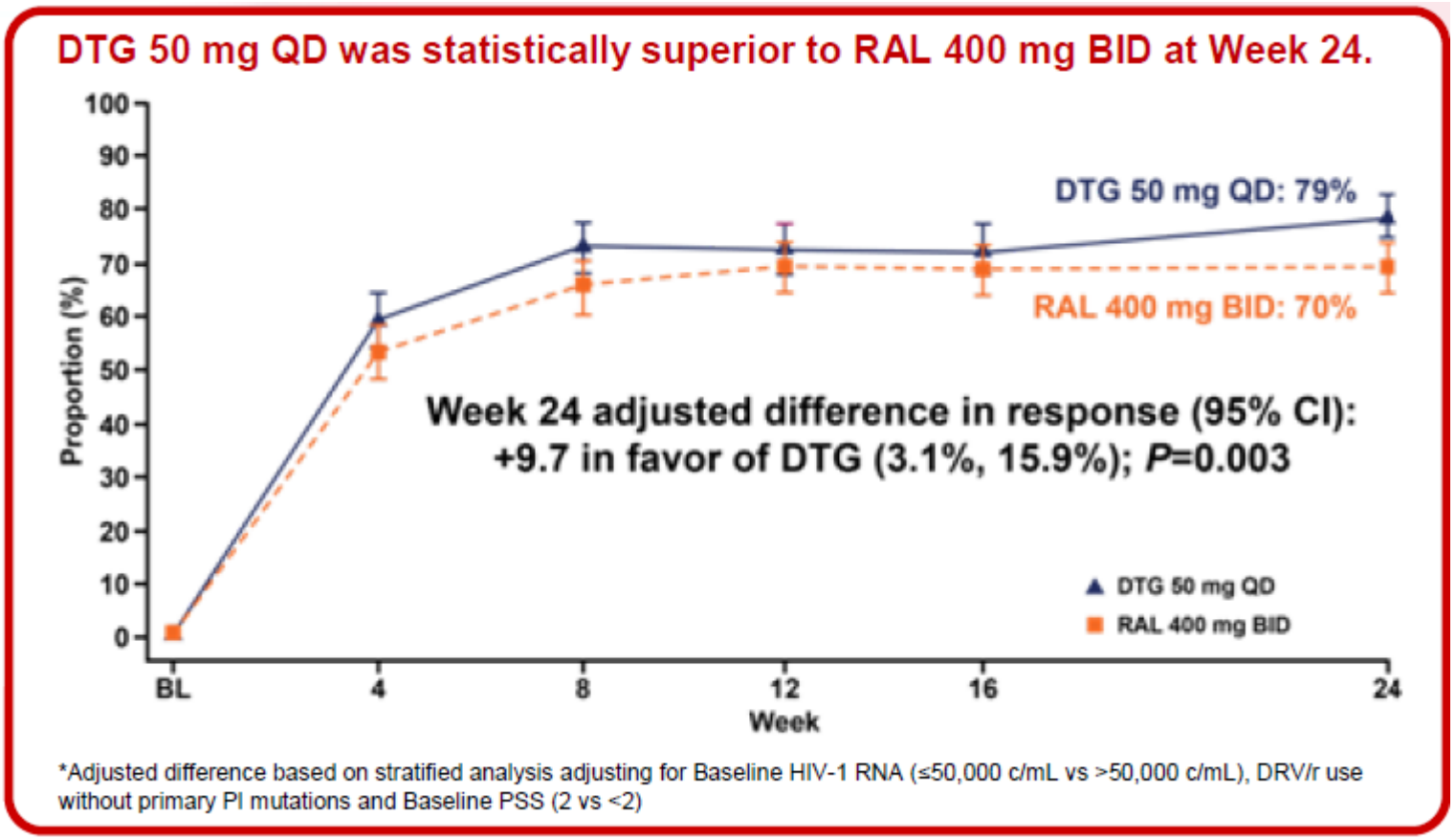
Eron et al J Infect Dis 2013

SAILING study design



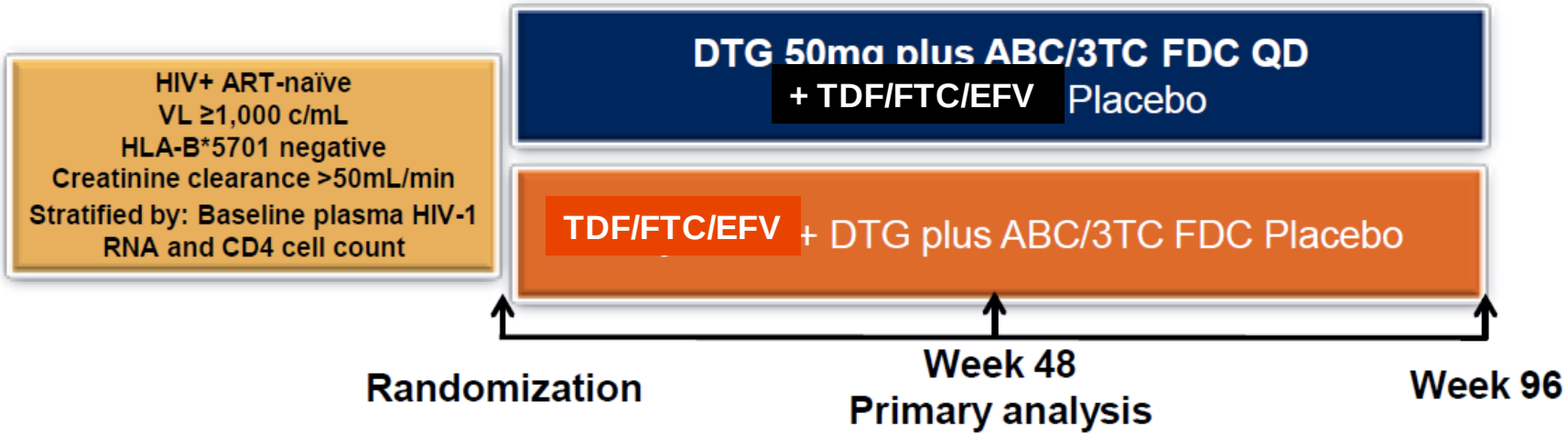
Pozniak et al, 20th CROI, 2013; Abstract, 179LB

SAILING study results



Pozniak et al, 20th CROI, 2013; Abstract, 179LB

SINGLE study design

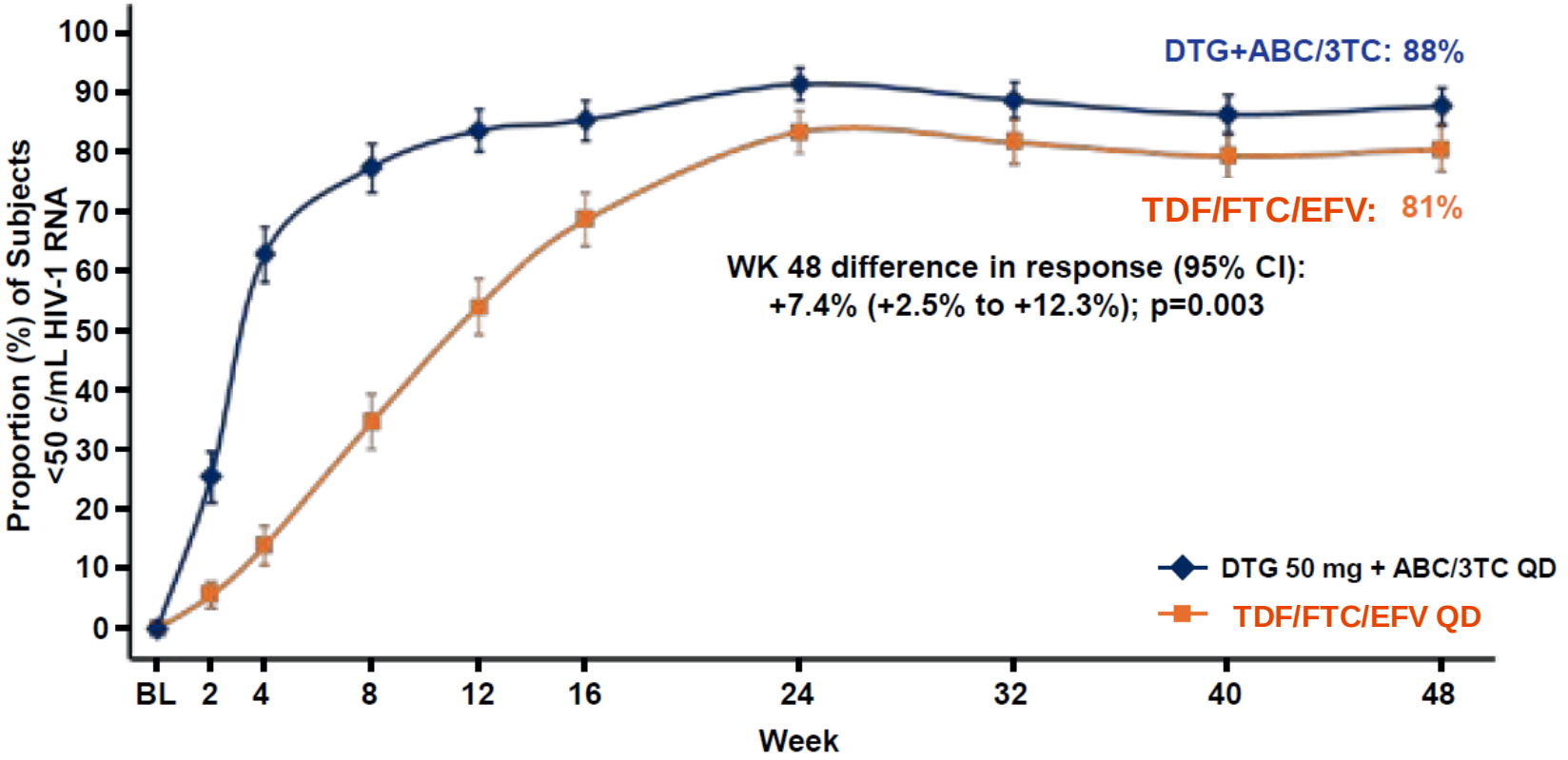


Primary endpoint:
Proportion with HIV-1 RNA <50 c/mL at Week 48, FDA snapshot analysis, -10% non-inferiority margin with pre-specified tests for superiority

Secondary endpoints:
Tolerability, long-term safety, immunologic, health outcome and viral resistance

Walmsley et al ICAAC 2012

SINGLE: primary endpoint analysis



- DTG 50mg +ABC/3TC QD was statistically superior to TDF/FTC/EFV at week 48 (primary endpoint)
- Subjects receiving DTG +ABC/3TC achieved virologic suppression faster than TDF/FTC/EFV, median time to HIV-1 RNA <50c/mL of 28 days (DTG +ABC/3TC) vs 84 days (TDF/FTC/EFV; p<0.0001)

Walmsley et al ICAAC 2012

SINGLE: Resistance at virologic failure

	DTG 50mg +ABC/3TC QD (N=414)	TDF/FTC/EFV (N=419)
Subjects with PDVF	**18 (4%)**	**17 (4%)**
PDVF genotypic population	**11**	**9**
PDVF Genotypic (RT Results at Baseline and PDVF)	**9**	**9**
NRTI tmt-emergent major mutations	0	1(K65R)
NNRTI tmt-emergent major mutations	0	4 (K101E, K103N, G190A)*
PDVF Genotypic (IN Results at Baseline and PDVF)	**7**	**7**
INI-r tmt-emergent major substitution	0**	0

* n=1 with K101E, n=1 with K103N, n=1 with G190A and n=1 with K103N+G190A
**E157Q/P polymorphism detected with no significant change in IN phenotypic susceptibility

Walmsley et al ICAAC 2012

Implications for ART sequencing*

- **Etravirine unlikely to be useful as "salvage" NNRTI following rilpivirine failure**
  - Impact of E138K on efavirenz and nevirapine uncertain
- **Raltegravir and elvitegravir cannot be used sequentially**
- **Dolutegravir likely to be active in setting of limited raltegravir and elvitegravir resistance**
- **Utility of raltegravir and elvitegravir after initial dolutegravir failure uncertain**

*Opinion of Daniel R. Kuritzkes, MD, expert.