

# **Rapid Onset and Durable Antiretroviral Effect of Raltegravir, a Novel HIV-1 Integrase Inhibitor, as Part of Combination ART in Treatment-Naïve HIV-1 Infected Patients: 48-Week Results**

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# Protocol 004 Study Team

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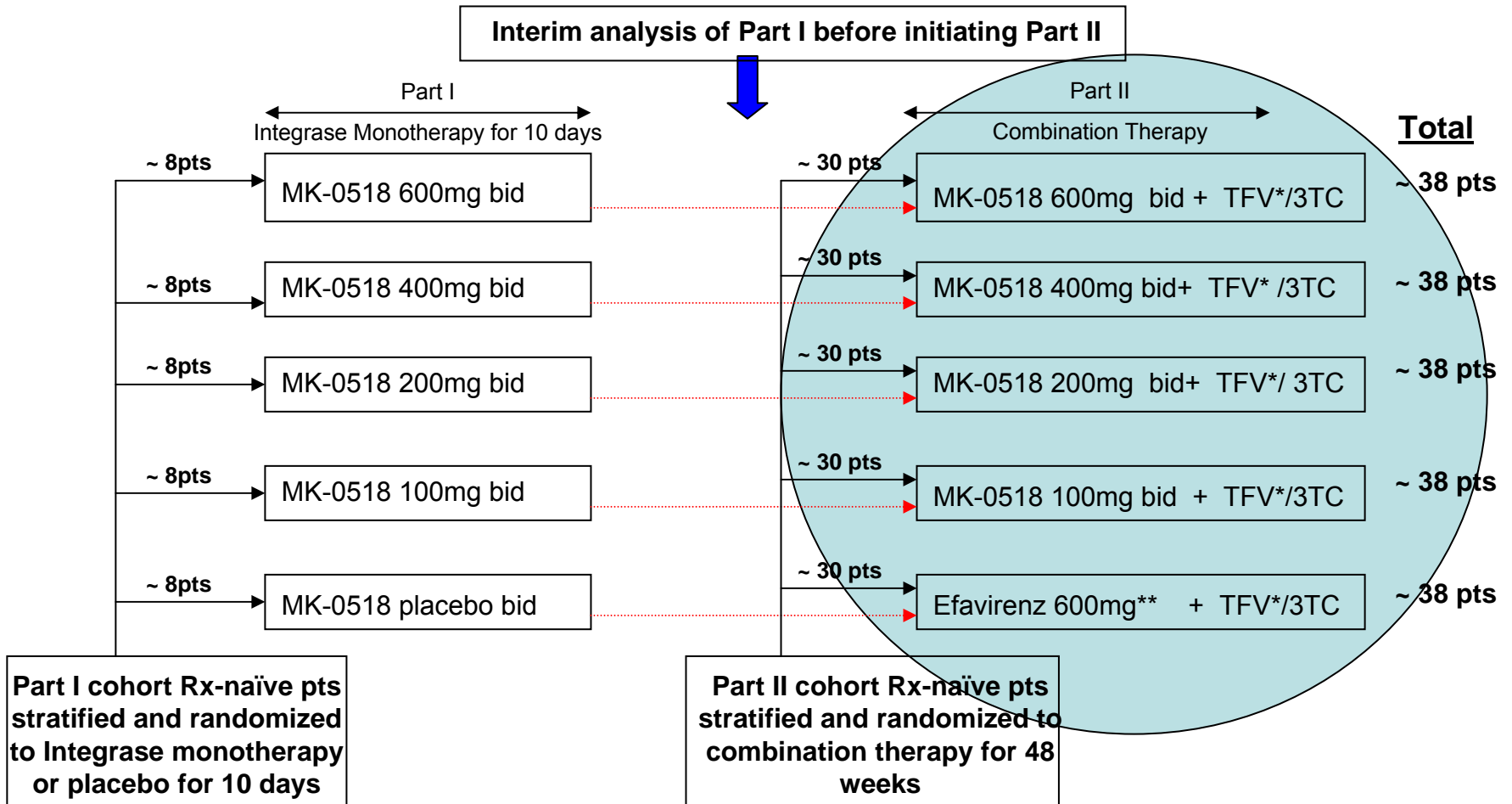
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# Raltegravir (MK-0518): HIV Integrase Strand-Transfer Inhibitor

- HIV integrase inhibition: a novel mechanism of action
- Raltegravir: potent *in vitro* activity
  - $IC_{95} = 31 \text{ nM} \pm 20 \text{ nM}$  in 50% human serum
- Metabolism primarily via glucuronidation (UGT1A1)
- Not a potent inhibitor or inducer of CYP3A4
  - Does not require “ritonavir boosting”
- In Phase I studies,
  - Doses up to 800 mg p.o. BID were generally well tolerated
  - At 100 mg BID, mean  $C_{12hr} >$  mean  $IC_{95}$
- No dose adjustment when used with other ARTs

# Protocol 004: Study Design



\*TFV = tenofovir

**HIV RNA ↓ of 1.7 – 2.2 log<sub>10</sub> copies/mL  
(Markowitz et al., JAIDS Dec 2006)**

AB104

# Protocol 004: Part II Design

- Part I patients continued at same dose in Part II (pbo→efv)
- ~150 additional patients randomized for Part II
- Key inclusion criteria
  - Susceptible to EFV, 3TC , TFV (by genotype)
  - No prior ART (<7 days allowed)
  - HIV RNA  $\geq$  5000 copies/mL
    - baseline stratification for HIV RNA  $\leq$  or  $>$  50,000 copies/mL
  - CD4  $\geq$  100 cells/mm<sup>3</sup>
- Endpoints
  - HIV-1 RNA and CD4 counts, Adverse experiences
- Hypotheses: Raltegravir + TFV/3TC
  - will be generally safe and well tolerated
  - will have antiretroviral activity similar to EFV + TFV/3TC

# Patient Baseline Characteristics

	Raltegravir mg bid*				Efavirenz * 600mg qd N=38
	100 N=39	200 N=40	400 N=41	600 N=40	
<b>Age-mean (yrs)</b>	37	34	36	37	36
<b>% Male</b>	85	73	90	73	76
<b>% Non-White</b>	82	65	66	65	68
<b>HIV RNA GM** (copies/ml) Mean (log<sub>10</sub>cp/ml)</b>	58206 (4.8)	64715 (4.8)	43083 (4.6)	57919 (4.8)	67554 (4.8)
<b>CD4 – mean (cells/mm<sup>3</sup>)</b>	314	296	338	271	280
<b>% with AIDS</b>	33	33	29	43	37

\* with TFV/3TC

\*\* geometric mean

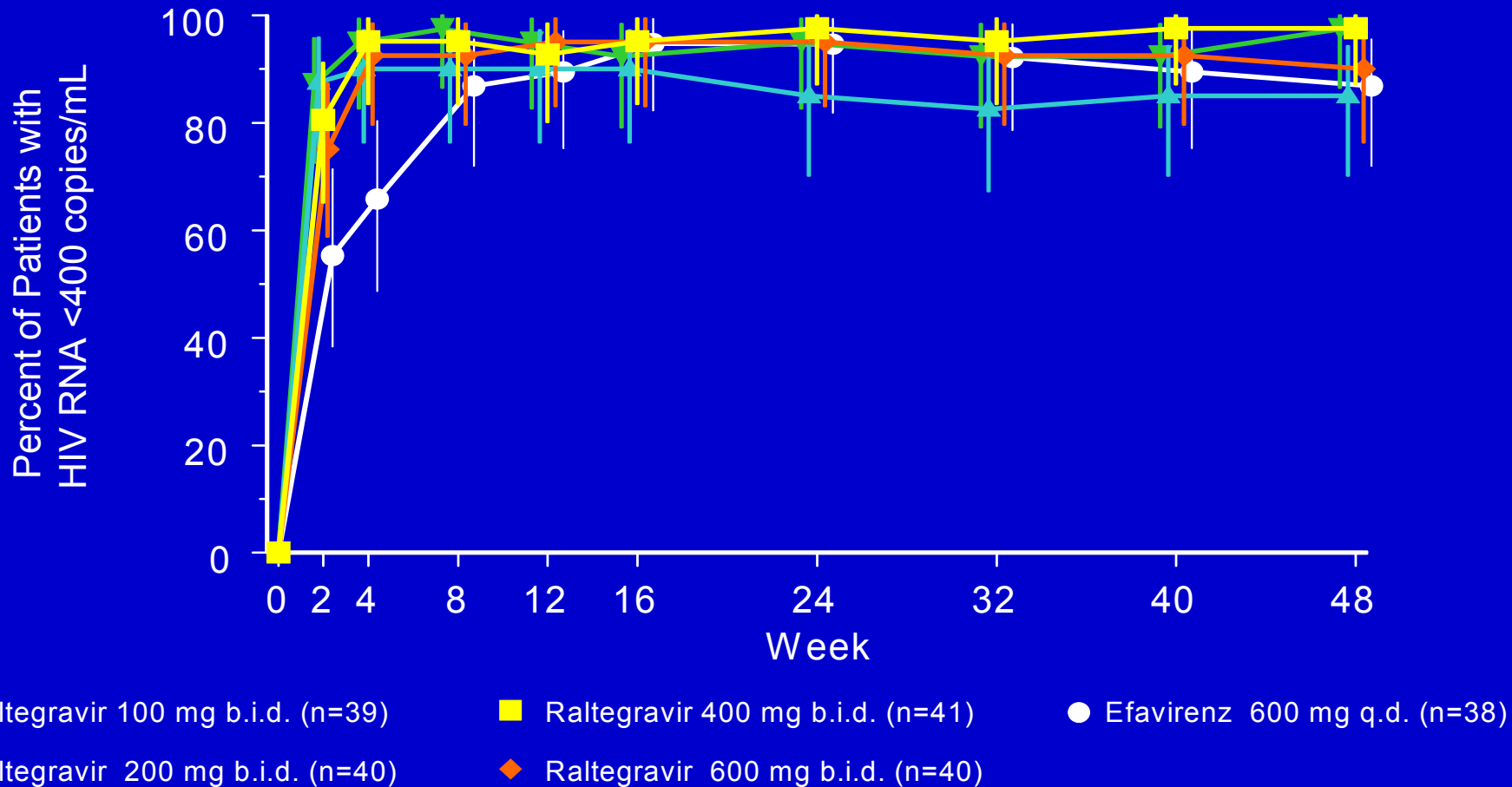
# Patient Status at Week 48

	Raltegravir*				EFV*
	100 mg n (%)	200 mg n (%)	400 mg n (%)	600 mg n (%)	n (%)
<b>Total Enrolled</b>	N = 41	N = 40	N = 41	N = 40	N = 39
Treated	39 (95)	40 (100)	41 (100)	40 (100)	38 (97)
<b>Discontinued by Wk 48</b>	0	6 (15)	2 (5)	3 (8)	3 (8)
- lack of efficacy	0	2 (5)	0	0	0
- lab AE	0	0	0	1 (3)	0
- withdrew consent	0	2 (5)	0	2 (5)	3 (8)
- lost to follow-up	0	1 (3)	2 (5)	0	0
- other reasons	0	1 (3)	0	0	0

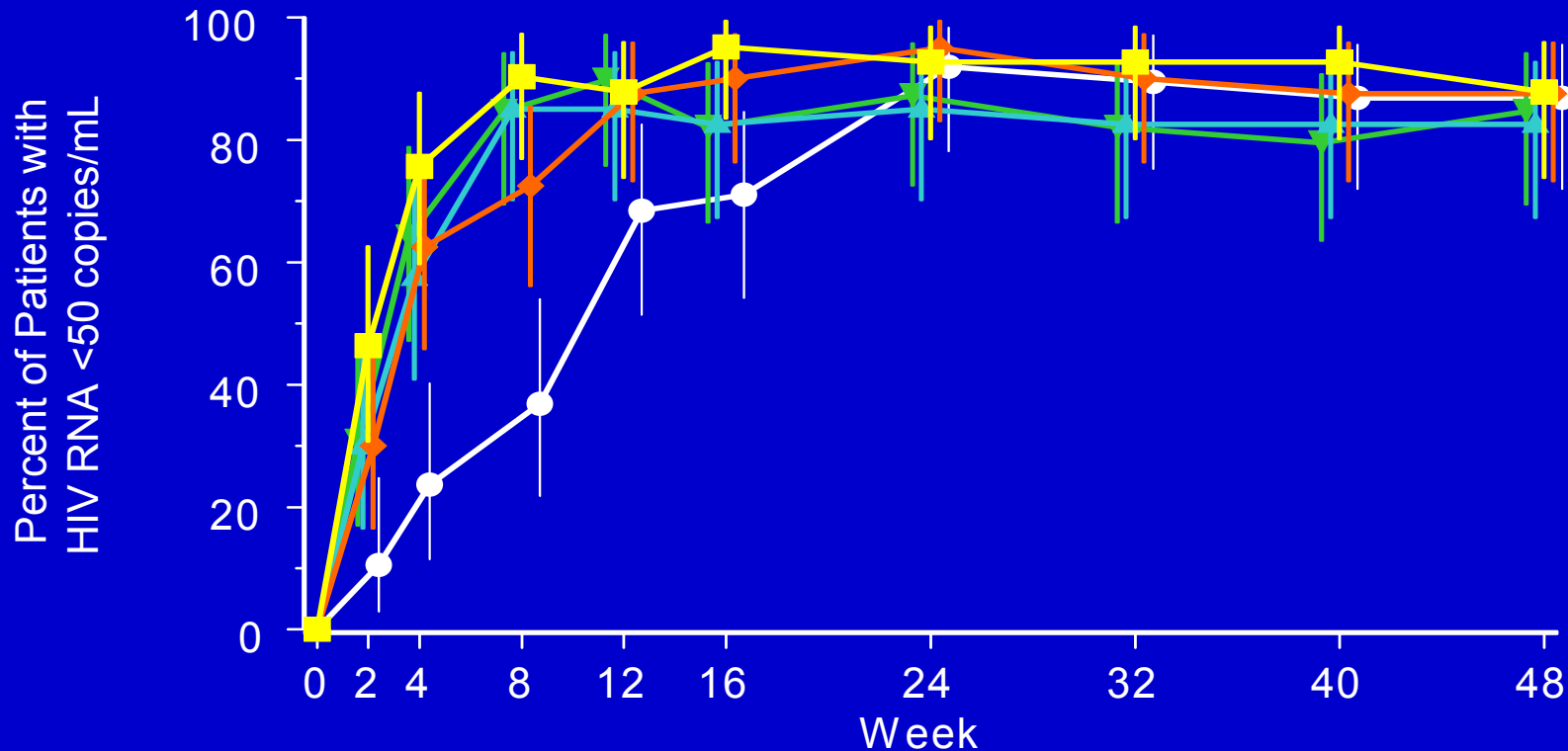
\* with TFV/3TC

n = Number of patients in each category; N = Total number of pts enrolled in each group; % = n/N

# HIV RNA <400 Copies/mL (95% CI) [Non-Completer=Failure]



# HIV RNA <50 Copies/mL (95% CI) [Non-Completer=Failure]



▼ Raltegravir 100 mg b.i.d. (n=39)

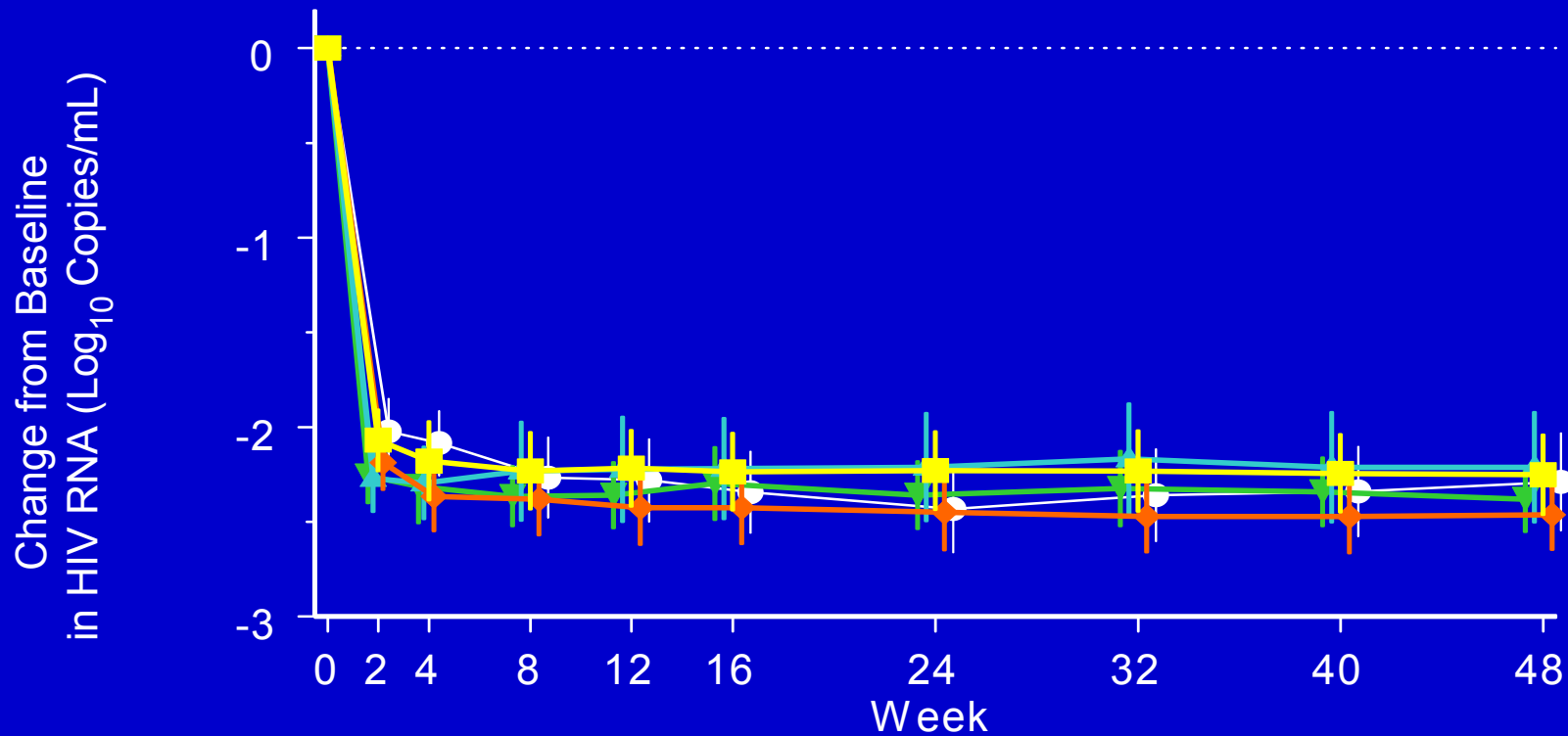
■ Raltegravir 400 mg b.i.d. (n=41)

● Efavirenz 600 mg q.d. (n=38)

▲ Raltegravir 200 mg b.i.d. (n=40)

◆ Raltegravir 600 mg b.i.d. (n=40)

# Change From Baseline in HIV RNA [Observed Failures]



▼ Raltegravir 100 mg b.i.d. (n=39)

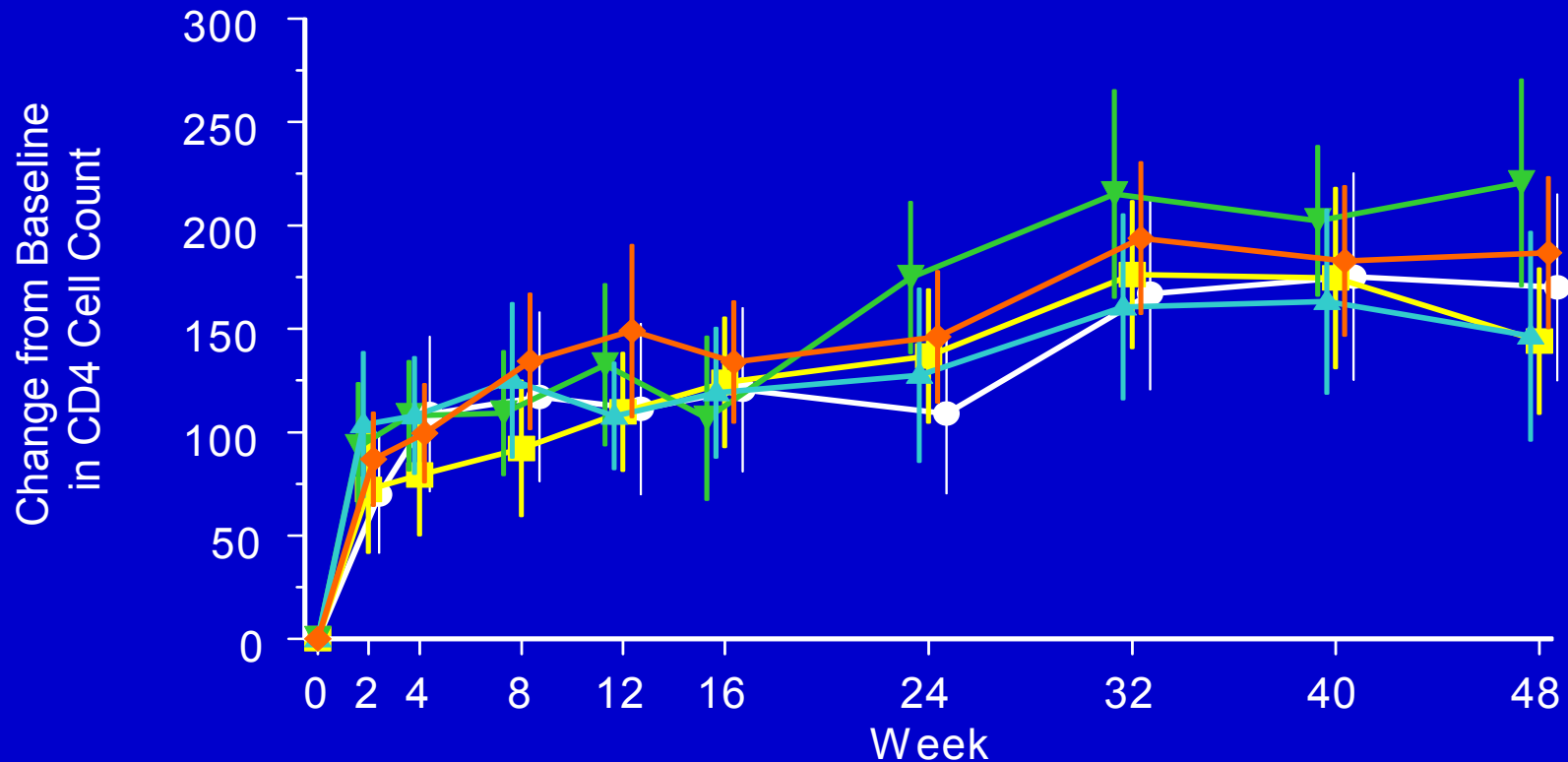
■ Raltegravir 400 mg b.i.d. (n=41)

● Efavirenz 600 mg b.i.d. (n=38)

▲ Raltegravir 200 mg b.i.d. (n=40)

◆ Raltegravir 600 mg b.i.d. (n=40)

# Change From Baseline in CD4 Cell Count [Observed Failures]



▼ Raltegravir 100 mg b.i.d. (n=39)

■ Raltegravir 400 mg b.i.d. (n=41)

● Efavirenz 600 mg q.d. (n=38)

▲ Raltegravir 200 mg b.i.d. (n=40)

◆ Raltegravir 600 mg b.i.d. (n=40)

# Virologic Failure

- Definitions: 2 measurements of HIV-1 RNA at least 1 week apart
  - Non-response:
    - >400 copies/mL at week 24 or early discontinuation, or
  - Virologic relapse:
    - >400 copies/mL after initial response to <400 copies/mL, or
    - >1.0 log<sub>10</sub> increase above nadir level.
- Resistance testing in all patients with virologic failure; performed at time of failure, compared with baseline
  - 5 of 160 (3%) in RAL group
  - 1 of 38 (3%) in EFV group

# Treatment-Emergent Mutations

Trt Grp	VF type	RAL	3TC	TFV	EFV
RAL 100	Non-response	V151I N155H D232D/N G163R/G	M184M/I/V K65K/R	K65K/R	---
	Relapse	---	M184M/I/V	---	---
RAL 200	Relapse	---	---	---	---
	Relapse	N155H	M184M/I/V	---	---
	Relapse	---	M184V	---	---
EFV	Relapse	S230S/N*	K65R	K65R	G190E

\* S230S/N is a common polymorphism not thought to affect sensitivity to integrase inhibitors. All other mutations were associated with reduced drug sensitivity. (--- indicates no mutations)

# Adverse Event Summary

## (% of patients)

	RAL 100mg	RAL 200mg	RAL 400mg	RAL 600mg	EFV 600mg
<b>Any Clinical AE</b>	80	88	88	88	90
<b>Serious</b>	5	13	0	5	5
<b>Drug-related*</b>	46	50	46	48	71
<b>Any Lab AE</b>	21	18	27	13	21
<b>Discontinued</b>	0	0	0	3	0
<b>Drug-related*</b>	8	15	10	5	8

RAL taken twice daily; EFV taken once daily; both with TFV/3TC.

\* Determined by investigator to be possibly, probably, or definitely caused by study drug regimen.

No Serious AEs were considered drug related.

# Most Common\* Drug-Related Adverse Events (% of patients)

	RAL 100mg	RAL 200mg	RAL 400mg	RAL 600mg	EFV 600mg
Diarrhea	2.6	2.5	7.3	12.5	10.5
Nausea	7.7	12.5	9.8	15.0	13.2
Dizziness	15.4	12.5	2.4	5.0	28.9
Headache	2.6	10.0	14.6	7.5	23.7
Abnormal Dreams	2.6	10.0	9.8	2.5	18.4
Insomnia	5.1	10.0	4.9	5.0	10.5
Nightmares	0	0	0	0	10.5
ALT increased	0	10.0	0	5.0	5.3

RAL taken twice daily; EFV taken once daily; both with TFV/3TC.

\* Incidence at least 5% in any treatment group; all severity levels included.

# Effect on Serum Lipids

- Total cholesterol, LDL-cholesterol, triglycerides not increased by raltegravir

Mean change from baseline (mg/dL) at week 48

	Raltegravir*		Efavirenz		RAL vs EFV
	Baseline Mean	Mean Change	Baseline Mean	Mean Change	
Cholesterol	165.9	-2.3	168.7	+20.7	P<0.001
LDL-C	103.8	-7.5	108.9	+3.0	P=0.016
Triglycerides	131.8	-1.0	127.3	+49.5	P=0.068
Total:HDL ratio	4.59	-0.59	4.72	-0.47	P=0.52

\* All raltegravir dose groups combined.

# Protocol 004: Safety Summary

- Overall AE profiles were generally similar across treatment groups
  - No dose-related toxicities
  - Drug-related clinical AEs less common with raltegravir (48%) than EFV (71%); no drug-related serious AEs
  - Neuropsychiatric symptoms\* less common with raltegravir than EFV: 8% vs 21% at wk 8  
13% vs 29% at wk 48
  - Grade 3 / 4 lab abnormalities uncommon
  - Neutral effect of raltegravir on serum lipids

\* Abnormal dreams, nightmares, depression, suicidal ideation

# Protocol 004: Conclusions

- Raltegravir is a promising new HIV integrase inhibitor with rapid and durable antiretroviral effect
- In treatment naïve patients with HIV RNA  $\geq$  5000 copies/ml and CD4  $\geq$  100/mm<sup>3</sup>, raltegravir at all doses studied for 48 weeks:
  - had potent antiretroviral activity
    - » 83-88% with HIV RNA < 50 copies/mL
    - » achieved viral suppression faster than EFV
  - was generally well tolerated