

Sustained Antiretroviral Efficacy of Raltegravir as part of Combination ART in Treatment-Naive HIV-1 infected patients: 144-week data

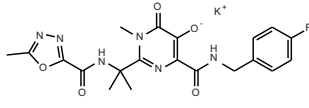
E. Gotuzzo¹, B.-Y. Nguyen², M. Markowitz³, F. Mendo⁴, W. Ratanasuwana⁵, C. Kovacs⁶, G. Prada⁷, J. Morales-Ramirez⁸, C. Crumpacker⁹, C. Lu², D. Brown², R. Isaacs², K. Strohmaier², R. Danovich², H. Tepler², and the Protocol 004 Part II Study Team

¹Hospital Nacional Cayetano Heredia, Lima, Peru; ²Merck Research Laboratories, West Point, PA, United States; ³Aaron Diamond AIDS Research Center, New York, NY, United States; ⁴Hospital Nacional Edgardo Rebagliati, Lima, Peru; ⁵Siriraj Hospital, Bangkok, Thailand; ⁶Canadian Immunodeficiency Research Collaborative, Toronto, Canada; ⁷Fundación Santafé de Bogotá University Hospital, Bogotá, Colombia; ⁸Clinical Research Puerto Rico, Inc., San Juan, Puerto Rico; ⁹Beth Israel Deaconess Medical Center, Boston, MA, United States

Background

In Vitro Activity of Raltegravir (MK-0518)

- Potent *in vitro* activity
 - IC₅₀ (Mean ± SD) = 31 nM ± 20 nM in 50% NHS
 - Active against:
 - Multi-drug resistant HIV-1
 - CCR5 and CXCR4 HIV-1
 - HIV-1 resistant to raltegravir remain sensitive to other antiretroviral classes
 - Additive/synergistic *in vitro* with NRTIs, NNRTIs, PIs, and enfuvirtide



Methods

Protocol 004: Part II Design

- Key inclusion criteria
 - Susceptible to EFV, TDF, 3TC
 - No prior ART
 - HIV RNA ≥ 5000 copies/mL; CD4 ≥ 100 cells/mm³
- Hypotheses: Raltegravir (RAL) + TDF/3TC
 - will be generally well tolerated, with similar antiretroviral activity vs efavirenz + TDF/3TC
- Endpoints
 - HIV RNA, CD4 counts, Adverse experiences
 - Exploratory: CNS adverse experiences and lipids
- Timepoints: 24 wk primary, 48 and 96 wk secondary
 - 48 week data presented AIDS 2007
 - 96 week data presented AIDS 2008
- Current presentation is 144 week update
 - 0-48 wks RAL given at doses of 100, 200, 400 or 600 mg b.i.d.
 - doses could not be differentiated at 48 wk
 - After 48 wk, all RAL groups received 400 mg b.i.d.
 - Therefore all RAL data post 48 wk shown as single RAL group (N=160)

Results

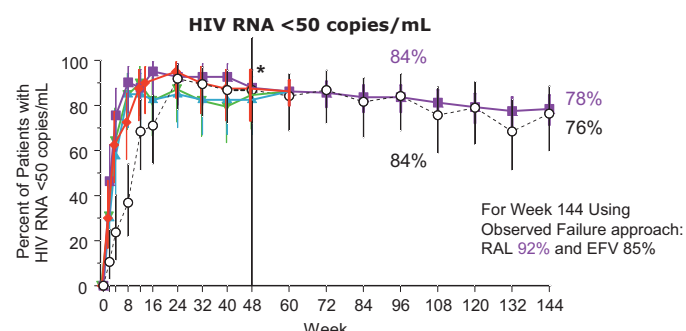
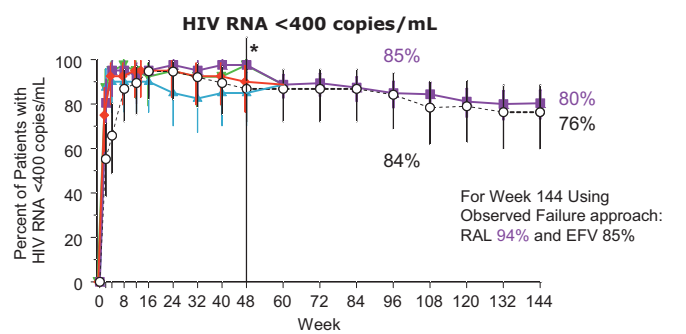
Baseline Characteristics/Patient Status

	RAL*	EFV*
# Patients Treated	N = 160	N = 38
Age-mean (yrs)	36	36
% Male	80	76
% Non-White	69	68
HIV RNA copies/ml** (log ₁₀ cp/ml)	55266 (4.7)	67554 (4.8)
CD4-mean (cells/μl)	305	280
% with AIDS*	34	37
Discontinuations by Week 144†	36 (23%)	10 (26%)

* Defined as history of clinical diagnosis of AIDS at baseline, * With TDF/3TC, ** geometric mean † RAL/EFV (# of patients); Lack of efficacy (4/2), AE (4/1), withdrew consent (9/4), Loss-to-follow up (6/1), Other reasons (13/2)

Protocol 004: 144 week Efficacy Summary

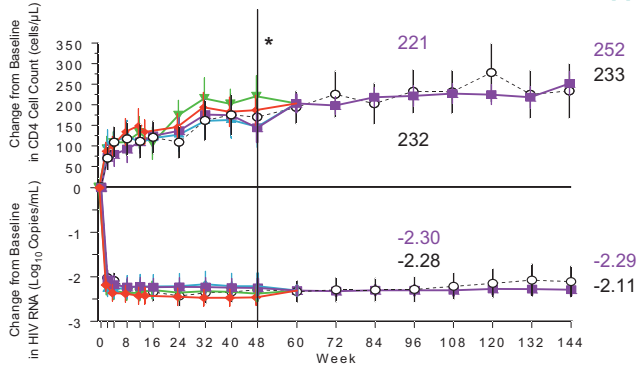
Percent of Patients with Virologic Suppression [Non-Completer=Failure]



Number of Contributing Patients

Week	Raltegravir 100 mg b.i.d. (n=39)	Raltegravir 200 mg b.i.d. (n=40)	Raltegravir 400 mg b.i.d. (n=41)	Raltegravir 600 mg b.i.d. (n=40)	Efavirenz 600 mg q.d. (n=38)
0	39	40	41	40	38
8	39	40	41	40	37
16	39	40	41	40	38
24	39	40	41	40	38
32	39	40	41	40	38
40	39	40	41	40	38
48	39	40	41	40	38
56	39	40	41	40	38
64	39	40	41	40	38
72	39	40	41	40	38
80	39	40	41	40	38
88	39	40	41	40	38
96	39	40	41	40	38
104	39	40	41	40	38
112	39	40	41	40	38
120	39	40	41	40	38
128	39	40	41	40	38
136	39	40	41	40	38
144	39	40	41	40	38

Change from Baseline: CD4 and HIV RNA [Observed Failure Approach]



Week	Raltegravir 100 mg b.i.d. (n=39)	Raltegravir 200 mg b.i.d. (n=40)	Raltegravir 400 mg b.i.d. (n=41)	Raltegravir 600 mg b.i.d. (n=40)	Efavirenz 600 mg q.d. (n=38)
0	39	40	41	40	38
8	39	40	41	40	38
16	39	40	41	40	38
24	39	40	41	40	38
32	39	40	41	40	38
40	39	40	41	40	38
48	39	40	41	40	38
56	39	40	41	40	38
64	39	40	41	40	38
72	39	40	41	40	38
80	39	40	41	40	38
88	39	40	41	40	38
96	39	40	41	40	38
104	39	40	41	40	38
112	39	40	41	40	38
120	39	40	41	40	38
128	39	40	41	40	38
136	39	40	41	40	38
144	39	40	41	40	38

*After Week 48 patients in all RAL groups continued at 400 mg b.i.d. All patients received TDF/3TC

Treatment-Emergent Mutations

- After Week 96, there were 2 virologic failures on raltegravir and 1 on efavirenz

Group	VF type	RAL	3TC	TDF	EFV
RAL 100	Non-Response ¹	V151I, N155H, D232D/N, G163R/G	M184M/I/V, K65K/R	K65K/R	---
RAL 100	Relapse	Y143C ¹	M184M/I/V	---	---
RAL 200	Relapse	---	---	---	---
RAL 200	Non-Response ¹	N155H	M184M/I/V	---	---
RAL 200	Non-Response ¹	---	M184V	---	---
RAL 200/400	Relapse	---	---	---	---
RAL 600/400	Relapse*	S153S/P, R187R/G ²	---	---	---
RAL 400	Relapse*	I204I/M, A265A/V ³	---	---	---
EFV	Relapse	---	M184V	---	Y188L, K103K/N
EFV	Non-Response ¹	S230S/N ⁴	K65R	K65R	G190E
EFV	Relapse*	Could not amplify	---	---	Y188Y/H

Protocol definition of virologic failure: (1) non-response: > 400 copies/ml at week 24 or early discontinuation, (2) virologic relapse: > 400 copies/ml after initial response of < 400 copies/ml, or > 1.0 log₁₀ increase above nadir level. (Percentage of virologic failures in RAL: 8/160 (5%), and in EFV: 3/38 (7.9%).)

¹ Failure occurred after Week 96, (--- indicates no mutations)
² Mutation developed after patient was a virologic failure
³ Not known to be RAL resistance mutations – Monogram genotypic interpretation is "sensitive"
⁴ S230S/N is a common polymorphism that does not affect raltegravir sensitivity in phenotypic assays.
⁵ All four patients with Non-Response achieved >1.0 log₁₀ decrease in HIV RNA at the nadir.

Protocol 004: 144 week Safety Summary

- Overall adverse experience (AE) profiles generally similar between RAL and EFV
- Drug-related (overall) clinical AEs: RAL (54%) vs EFV (76%)
- Serious drug-related (overall) clinical AEs: RAL (0.0%) vs EFV (2.6%)
- Neuropsychiatric symptoms*:
 - Most occurred by Week 48

	RAL	EFV
Week 08	21%	42%
Week 48	31%	55%
Week 96	34%	58%
Week 144	35%	61%

- Malignancies[†]: 2.5% (4/160 pts) for RAL vs. 2.6% (1/38 pts) in EFV
- Grade 3/4 lab abnormalities uncommon
- Minimal effect of RAL on serum lipids

[†]Cases included: 1 pt with B-cell lymphoma, 2 pts with Kaposi's sarcoma, 1 pt with both basal cell carcinoma and squamous cell carcinoma (SC), 1 pt with both gastrointestinal carcinoma and SC

*Abnormal dreams, acute psychosis, adjustment disorder with depressed mood, auditory hallucination, completed suicide, concentration impaired, confusional state, delirium, depressed level of consciousness, depressed mood, depression, depressive symptom, dizziness, dysthymic disorder, hallucination, hallucination visual, insomnia, major depression, nervous system disorder, nightmare, psychotic disorder, somnolence, suicidal behavior, suicidal ideation, suicide attempt. Numbers are based upon a list of neuropsychiatric AE terms associated with efavirenz.

Most Common* Drug-Related Adverse Events (144 weeks)

	RAL (N=160) (%)	EFV (N=38) (%)
Diarrhea	6.9	10.5
Nausea	12.5	10.5
Dizziness	8.8	26.3
Headache	8.8	23.7
Abnormal Dreams	6.3	18.4
Insomnia	8.1	10.5
Nightmares	0	10.5

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

* Incidence at least 10% in either treatment group; all intensity levels included.

Percent of Patients with Grade 3/4[†] Laboratory Abnormalities

Laboratory Test	Toxicity Criteria ¹	Raltegravir ² (N = 160)		Efavirenz ² (N = 38)	
		n	(%)	n	(%)
Absolute neutrophil count	<750 cells/μL	2	(1.3)	0	(0.0)
Fasting LDL cholesterol	≥190 mg/dL	1	(0.6)	2	(5.3)
Fasting total cholesterol	>300 mg/dL	0	(0.0)	2	(5.3)
Fasting triglycerides	>750 mg/dL	1	(0.6)	3	(7.9)
Fasting glucose	>250 mg/dL	1	(0.6)	0	(0.0)
Alkaline phosphatase	>5 x ULN	1	(0.6)	0	(0.0)
Pancreatic amylase	>2 x ULN	4	(2.5)	0	(0.0)
Lipase	>3 x ULN	2	(1.3)	0	(0.0)
Aspartate aminotransferase	>5 x ULN	6	(3.8)	1	(2.6)
Alanine aminotransferase	>5 x ULN	4	(2.5)	2	(5.3)
Creatine kinase	≥10 x ULN	14	(8.8)	1	(2.6)

No grade 3 or 4 abnormalities were reported in either treatment group for the following parameters: hemoglobin, platelet count, creatinine, and total bilirubin.

¹ Division of AIDS grading scale December 2004

² RAL taken twice daily; EFV taken once daily; both with TDF/3TC

ULN – Upper Limit of Normal

Effect on Serum Lipids (144 weeks)

- LDL-cholesterol and triglycerides not increased by raltegravir
- Mean change from baseline (mg/dL) at week 144

	RAL* (N=160)		EFV (N=38)		RAL vs EFV
	Baseline Mean	Mean Change	Baseline Mean	Mean Change	
Cholesterol	166.2	+6.8	171.7	+33.5	P<0.001
LDL-C	103.8	-1.9	110.4	+10.5	P=0.015
HDL-C	38.0	+6.6	37.9	+11.7	P=0.007
Triglycerides	135.4	+1.1	131.2	+55.8	P=0.118
Total: HDL ratio	4.6	-0.5	4.6	-0.4	P=0.451

* All RAL dose groups combined; all patients received TDF and 3TC

P004 Conclusions

- At 144 weeks, RAL had sustained antiretroviral effect similar to 96 week data and to EFV (both with TDF/3TC)
 - 78% vs 76% (RAL vs EFV) with HIV RNA < 50 copies/mL
- RAL was generally well tolerated at 144 weeks:
 - Drug-related AEs appeared less frequent for RAL vs. EFV
 - RAL had minimal effect on total cholesterol, LDL-C, and triglycerides.

Acknowledgements – Protocol 004 Study Team

Investigators				Merck Research Laboratories
E. Gotuzzo	Peru	S. Little	USA	H. Tepler
M. Markowitz	USA	N. Bodsworth	Australia	B.-Y. Nguyen
F. Mendo	Peru	R. Schwartz	USA	R. Isaacs
W. Ratanasuwana	Thailand	C. Tsoukas	Canada	C. Lu
C. Kovacs	Canada	C. Workman	Australia	D. Brown
G. Prada	Colombia	R. Liporace	USA	L. Wenning
J. Morales-Ramirez	Puerto Rico	D. Baker	Australia	M. Miller
A. Afani	Chile	C. Hicks	USA	D. Hazuda
D. Cooper	Australia	K. Tashima	USA	R. Danovich
J. Perez	Chile	C. Crumpacker	USA	
S. Thitvichianlert	Thailand	P. Kumar	USA	
J. Cortes	Colombia	K. Lichtenstein	USA	
R. Steigbigel	USA	J. Santana-Bagur	Puerto Rico	
M. Bloch	Australia	S. Brown	USA	