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Metabolic Profiles and Body Composition Changes in Treatment-Naïve HIV-Infected Patients Treated with Raltegravir 400 mg bid-based vs. Efavirenz 600 mg qhs-based Combination Therapy: 48-Week Data

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Abstract

Background: RAL is a 1st in class integrase strand-transfer inhibitor. Metabolic parameters were compared between RAL-based and EFV-based regimens after 48 wks of treatment.

Methods: Pts were randomized in a double-blind study of RAL vs EFV, each with TDF/FTC (n=563). Groups were compared for metabolic parameters, including fasting lipid and glucose (glc) abnormalities according to DAIDS criteria, NCEP goals, and for reported lipodystrophy AE terms. DEXA scans were obtained on a subset of pts (n=76) at baseline and Wk 48, to be followed at Wk 96.

Results: At Wk 48, changes from baseline cholesterol (C), LDL-C, & triglycerides were lower in RAL vs EFV recipients (each p<0.001); HDL-C was higher in the EFV group (p<0.001). 26/281 on RAL and 42/282 on EFV had fasting serum glc of any grade (1-4); 1/26 on RAL was grade 3. AE of mild lipodystrophy were reported in 2 pts, both on EFV.

Body Composition Changes Through 48 Weeks

	RAL 400 mg bid			EFV 600 mg qhs		
Region	N	Baseline Mean (gm)	Mean % Change†(95% CI)	N	Baseline Mean (gm)	Mean % Change†(95% CI)
Arms	35	1873.08	23.33 (5.95, 40.72)	41	1724.23	18.94 (11.80, 26.07)
Legs	35	7055.66	16.31 (3.85, 28.77)	41	6305.59	15.63 (9.59, 21.67)
Appendicular	35	8928.73	17.38 (4.34, 30.42)	41	8029.83	16.09 (10.15, 22.03)
Trunk	35	11683.73	17.01 (2.87, 31.15)	41	10142.54	20.46 (11.72, 29.19)
Total	35	20612.46	16.92 (3.52, 30.32)	41	18172.37	17.98 (10.89, 25.07)

N = # of patients in the treatment group.
†Mean % change from baseline are based on the measurements of the pts who were measured at baseline and the time point assessed.
RAL and EFV were administered with TDF/FTC

Conclusion: Through wk 48 RAL demonstrated minimal effects on serum lipids and glc. DEXA showed minimal gains in body fat, with no patterns of fat loss. Early experience with RAL suggests a favorable metabolic profile in treatment-naive patients.

Overall Study Design

- Double-blind, randomized (1:1), non-inferiority study
- RAL 400 mg bid vs EFV 600 mg qhs both in combination with tenofovir/emtricitabine (TDF/FTC as Fixed Dose Coformulation)
- Key inclusion criteria
  - no prior ART
  - HIV RNA level >5000 copies/mL
  - viral susceptibility to EFV, TDF, and FTC
- Endpoints
  - Efficacy: Proportion with HIV RNA levels <50 copies/mL, change in CD4 cell counts
  - Safety/tolerability: adverse experiences; central nervous system (CNS) events; lipid changes from baseline

Background and Objectives

- Metabolic abnormalities have been reported with most antiretroviral therapies
- RAL is a novel HIV-1 integrase inhibitor with potent efficacy and a favorable safety profile
- We evaluated whether RAL treatment was associated with metabolic abnormalities
- Groups were compared for metabolic parameters:
  - fasting lipid and glucose abnormalities according to DAIDS criteria
  - NCEP goals
  - Investigator-reported lipodystrophy AE terms
- DEXA scans were obtained on a subset of patients (n=76) at baseline and Wk 48, to be followed at Wk 96
  - patients at US sites were eligible
    - Only sites with access to the necessary equipment were included

Methods

Statistical Approaches to Missing Data for the Metabolic Analyses

- Lipid Profile
  - Last Observation Carried Forward approach
    - If patients initiated or increased dosage of lipid-lowering therapy, last available lipid values prior to the use of lipid-lowering therapy were used in the analysis
- Body Composition (DEXA) and Glucose
  - Complete data set approach
    - Patients needed to have values at both baseline and week 48 to be included in the analysis

Baseline Characteristics

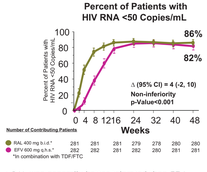
	All Treated Patients		Patients in the DEXA Sub-Study	
	RAL (N=281)	EFV (N=282)	RAL (N=54)	EFV (N=57)
Gender, n (%)				
Male	227 (81)	231 (82)	50 (92.6)	48 (84.2)
Female	54 (19)	51 (18)	4 (7.4)	9 (15.8)
Race/Ethnicity, n (%)				
White	116 (41)	123 (44)	33 (61.1)	33 (57.9)
Black	33 (12)	23 (8)	14 (25.9)	9 (15.8)
Asian	36 (13)	32 (11)	0 (0.0)	1 (1.8)
Hispanic	60 (21)	67 (24)	5 (9.3)	11 (19.3)
Native American	1 (0)	1 (0)	0 (0.0)	1 (1.8)
Multiracial	35 (12)	36 (13)	2 (3.7)	2 (3.5)
Region, N (%)				
Latin America	99 (35)	97 (34)	--	--
Southeast Asia	34 (12)	29 (10)	--	--
North America	82 (29)	90 (32)	54 (100)	57 (100)
Europe/Australia	66 (23)	66 (23)	--	--
Age, in years				
Mean (SD)	38 (9)	37 (10)	37.3 (8.9)	40.0 (10.0)
Median (min to max)	37 (19 to 67)	36 (19 to 71)	38.0 (20 to 61)	39.0 (21 to 67)
CD4 Cell Count , cell/mm³				
Mean (SD)	219 (124)	217 (134)	228.9 (149.4)	225.8 (148.9)
Median (min to max)	212 (1 to 620)	204 (4 to 807)	230.0 (1 to 573)	202.0 (6 to 567)
Plasma HIV RNA, $\log_{10}$ copies/mL				
Mean (SD)	5 (1)	5 (1)	5.0 (0.6)	5.0 (0.6)
Median (min to max)	5 (3 to 6)	5 (4 to 6)	4.9 (4 to 6)	5.0 (4 to 6)
Investigator-reported History of AIDS				
Yes	40 (14)	42 (15)	5 (9.3)	6 (10.5)
Stratum, n (%)				
Screening HIV RNA ≤50,000	74 (26)	80 (28)	15 (27.8)	5 (26.3)
Hepatitis B or C Positive	20 (7)	19 (7)	2 (3.7)	4 (7.0)
Viral Subtype n (%)				
Clade B	219 (78)	230 (82)	52 (96.3)	52 (91.2)
Non-Clade B	59 (21)	47 (17)	2 (3.7)	3 (5.3)
Missing	3 (1)	5 (2)	0 (0)	2 (3.5)
Baseline Plasma HIV RNA, n (%)				
≤50,000 copies/mL	79 (28)	84 (30)	19 (35.2)	19 (33.3)
>50,000 copies/mL	202 (72)	198 (70)	35 (64.8)	38 (66.7)
≤100,000 copies/mL	127 (45)	139 (49)	30 (55.6)	27 (47.4)
>100,000 copies/mL	154 (55)	143 (51)	24 (44.4)	30 (52.6)
Baseline CD4 Cell Counts, n (%)				
≤50 cells/mm³	27 (10)	31 (11)	8 (14.8)	9 (15.8)
>50 cells/mm³ and ≤200 cells/mm³	104 (37)	105 (37)	15 (27.8)	19 (33.3)
>200 cells/mm³	150 (53)	145 (51)	31 (57.4)	29 (50.9)
Missing	0 (0)	1 (0)	0 (0)	0 (0)

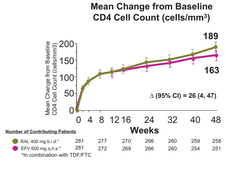
-- indicates that only participants at US sites were eligible for the DEXA sub-study.

Results

Overall Efficacy and Safety Results

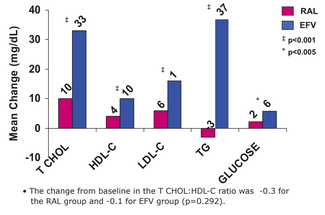
- RAL provided potent and statistically non-inferior viral suppression compared to EFV
- RAL exerted a greater immunological effect than EFV, measured by the increase in CD4 cell counts





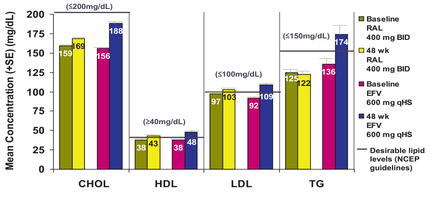
- RAL was generally better tolerated than EFV
  - significantly fewer overall and drug-related clinical adverse events
  - significantly lower percentages of patients with CNS side-effects
  - safety profile was similar in subjects with and without hepatitis B and/or hepatitis C virus co-infection
- For 96 week results, please see poster #H924b

Mean Change from Baseline in Metabolic Parameters at Week 48

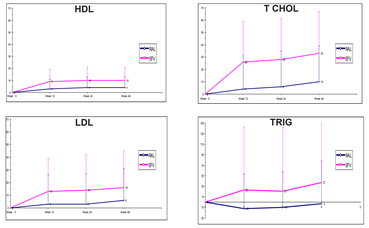


- The change from baseline in the T CHOL:HDL-C ratio was -0.3 for the RAL group and -0.1 for EFV group (p=0.292).

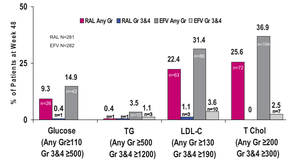
Fasting Lipid Levels at Baseline and Week 48



Mean Change from Baseline in Metabolic Parameters



DAIDS-Graded Metabolic Abnormalities at Week 48

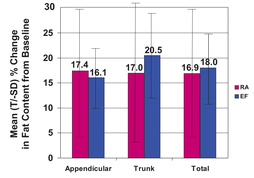


Body Composition Changes through 48 Weeks

	RAL Group			EFV Group		
		Baseline	Mean %		Baseline	Mean %
Region	N	Mean (gm)	Change†(95% CI)	N	Mean (gm)	Change†(95% CI)
Arms	35	1873	23 (6, 41)	41	1724	19 (12, 26)
Legs	35	7056	16 (4, 29)	41	6306	16 (10, 22)
Appendicular	35	8929	17 (4, 30)	41	8030	16 (10, 22)
Trunk	35	11684	17 (3, 31)	41	10143	20 (12, 29)
Total	35	20612	17 (4, 30)	41	18172	18 (11, 25)

N = # of patients in the treatment group.
†Mean % change from baseline are based on the measurements of the patients who were measured at baseline and the time point assessed.
RAL and EFV were administered with TDC/FTC as Fixed Dose Coformulation.

STARTMRK: Body Composition Changes through Week 48



Investigator-reported Lipodystrophy

- Investigator-reported lipodystrophy (including fat tissue increased and lipoatrophy) were reported in 2 patients (0.4%), both in the EFV group.
- Both adverse experiences were of mild intensity and neither were considered serious or resulted in discontinuation of blinded therapy.
- Only 1 drug-related adverse experience was reported in 1 patient (lipoatrophy) which was considered possibly related to study therapy.
- There were no patients in the RAL treatment group that reported clinical adverse experience terms of lipodystrophy.

Conclusions

- **Through week 48, both the RAL and EFV regimens demonstrated modest effects on serum lipids and glucose.**
- **At week 48, the mean changes from baseline in total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride concentrations were significantly smaller for RAL than for EFV recipients.**
  - **The change in the total cholesterol/HDL-cholesterol ratio was not significantly different between two treatment groups.**
  - **A small decline in triglycerides concentration was noted in RAL recipients.**
- **At week 48, DEXA showed minimal gains in body fat with no patterns of fat loss in both treatment groups.**
- **Early experience with RAL suggests a favorable metabolic profile and minimal body composition changes in treatment-naïve patients.**

Acknowledgements

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