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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: 96-Week Follow-Up

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Abstract

Background: Raltegravir (RAL) is a 1st in class integrase strand-transfer inhibitor. Metabolic parameters, including DEXA, were compared between RAL- and efavirenz (EFV)-based regimens after 96 weeks (wk) of treatment.

Methods: Patients (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 abnormalities according to DAIDS criteria, NCEP goals, and lipoatrophy (defined as at least a 20% decrease from baseline in appendicular fat) with follow-up through 96 wk. DEXA scans were obtained on a subset of pts (n=86) at baseline and Wk 48, and on a subset of pts (n=75) at both baseline and Wk 96.

Results: At Wk 96, RAL had less impact on fasting lipids, including total, low-density lipoprotein (LDL-C) and high-density lipoprotein (HDL-C) cholesterol levels, triglycerides (trig) as well as glucose than EFV; the impact on the total:HDL-C ratio was similar (Table 1). Fat changes by DEXA appear to be similar on average at Wk 96 (Table 2).

Table 1: Mean Changes from Baseline in Lipids at Wk 96

	RAL group	EFV group	p-Value
Total Cholesterol	10 mg/dL	38 mg/dL	<0.001
LDL-C	7 mg/dL	21 mg/dL	<0.001
HDL-C	3 mg/dL	10 mg/dL	<0.001
Trig	-4 mg/dL	40 mg/dL	0.001
Total:HDL-C Ratio	-0.18	-0.04	0.192
Glc	2 mg/dL	6 mg/dL	0.025

Table 2: Body Composition Changes through 96 Weeks

	RAL group			EFV group		
Week	N	Baseline Mean (gm)	Mean % Change[1] (95% CI)	N	Baseline Mean (gm)	Mean % Change[1] (95% CI)
Arms						
0	55	1999		56	1682	
48	40	1872	23 (8, 38)	46	1701	21 (13, 29)
96	37	1976	23 (6, 41)	38	1708	24 (15, 33)
Legs						
0	55	7091		56	6072	
48	40	6949	17 (6, 28)	46	6222	17 (11, 24)
96	37	7406	17 (3, 31)	38	6272	15 (8, 23)
Appendicular						
0	55	9090		56	7754	
48	40	8821	18 (7, 30)	46	7922	18 (11, 24)
96	37	9383	18 (4, 33)	38	7980	17 (9, 25)
Trunk						
0	55	11318		56	9788	
48	40	11274	19 (6, 32)	46	9854	23 (14, 32)
96	37	12104	22 (3, 40)	38	9587	25 (15, 36)
Total						
0	55	20409		56	17542	
48	40	20095	18 (6, 30)	46	17777	20 (12, 28)
96	37	21487	20 (3, 36)	38	17567	21 (12, 30)

N = Number of patients in the treatment group.
[1]Mean % change from baseline are based on the measurements of the patients who were measured at both baseline and the time point assessed.
The DEXA re-scan (for the baseline visit) values were taken as the baselines for 7 patients and clinically deemed acceptable, when the original baseline scan readings were not available.
Note: RAL and EFV were administered with TRUVADA®

- While the majority of patients in both groups experienced modest fat gain, 3/37 pts on RAL and 2/38 pts on EFV had at least 20% appendicular fat loss (lipoatrophy).

Conclusion: Through Wk 96, RAL demonstrated minimal effects on serum lipids and glucose levels. DEXA showed minimal gains in body fat, with no patterns of fat loss in both treatment groups. Longer-term experience with RAL suggests a favorable metabolic profile in treatment-naive patients.

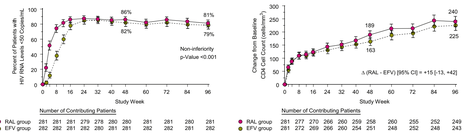
Background and Objectives

- Metabolic abnormalities have been reported with many antiretroviral therapies, characterized by lipid abnormalities, glucose intolerance, and undesirable patterns of fat gain and fat loss (lipoatrophy).
- RAL is a novel HIV-1 integrase inhibitor with potent efficacy, and a favorable safety profile.[1,2]
  - Minimal changes in lipid, glucose levels, and body composition in treatment-naïve patients have been reported through Week 48.[3]
  - The current presentation provides follow-up to Week 96.

[1]Steigbigel RT, 96-week results from Benchmrk 1&2, phase III studies of raltegravir (ral) in patients (pts) failing antiretroviral therapy (ART) with triple-class resistant HIV, 16th Annual Conference on Retroviruses and Opportunistic Infections, February, 2009.
[2]Lennox JL, et al, Raltegravir demonstrates durable efficacy through 96 weeks: results from STARTMRK, a phase III study of raltegravir (RAL)-based vs efavirenz (EFV)-based combination therapy in treatment-naive HIV-infected patients, ICAAC, [Abstract# H924B], San Francisco, CA, September 11, 2009.
[3]DeJesus E, et al, Metabolic profiles and body composition changes in treatment-naive HIV-infected patients (pts) treated with raltegravir (ral) 400 mg bid -based vs. efavirenz (efv) 600 mg qhs -based combination therapy: 48-week data, [Abstract# H1571], ICAAC, San Francisco, CA, September 11, 2009.

Overall Efficacy and Safety Results[1]

- RAL provides potent and statistically non-inferior viral suppression compared to EFV
- RAL has a numerically greater immunological effect than EFV, measured by an increase in CD4 cell counts



- RAL is generally better tolerated than EFV
  - significantly fewer overall and drug-related clinical adverse events
  - significantly lower percentages of patients with CNS side-effects

[1]Lennox JL, et al, Raltegravir demonstrates durable efficacy through 96 weeks: results from STARTMRK, a phase III study of raltegravir (RAL)-based vs efavirenz (EFV)-based combination therapy in treatment-naive HIV-infected patients, ICAAC, [Abstract# H924B], San Francisco, CA, September 11, 2009.

Overall Study Design

- Double-blind, randomized (1:1), non-inferiority study (n=563 Patients)
- 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

Metabolic Evaluation and DEXA Sub-Study Design

- We evaluated whether treatment was associated with metabolic abnormalities during extended follow-up through 96 weeks
- Treatment groups in the parent study were compared for metabolic parameters:
  - Fasting lipid and glucose abnormalities according to DAIDS criteria
  - NCEP lipid goals
  - Investigator-reported lipodystrophy AE terms
- DEXA scans were obtained on a subset of 111 patients at baseline
  - Patients at US sites were eligible.
    - Only sites with access to the necessary equipment were included.
  - Follow-up scans were performed at Week 48 and/or Week 96.
    - Fat changes over time were plotted as in: *Moyle G, et al, Body Composition changes in treatment-naïve patients treated with boosted PIs plus TDF/FTC: results from the CASTLE study through 96 weeks. Presented at 12th European AIDS Conference/EACS, 11-14 November 2009, Cologne, Germany, Abstract #LBPS11/6.*
  - Lipoatrophy was defined as ≥ 20% loss of baseline appendicular fat.

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 (or Week 96) to be included in the analysis

Results

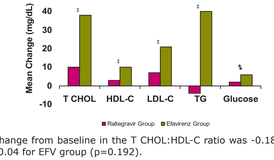
Selected Baseline Characteristics by Treatment Assignment for Participants in the Parent Study and DEXA Substudy

	All Treated Patients		Patients in the DEXA Substudy	
	Raltegravir Group (N=281)	Efavirenz Group (N=282)	Raltegravir Group (N=55)[1]	Efavirenz Group (N=57)[1]
Gender, n (%)				
Male	227 (81)	231 (82)	51 (93)	48 (84)
Female	54 (19)	51 (18)	4 (7)	9 (16)
Race/Ethnicity, n (%)				
White	116 (41)	123 (44)	34 (62)	33 (58)
Black	33 (12)	23 (8)	14 (25)	9 (16)
Asian	36 (13)	32 (11)	0 (0)	1 (2)
Hispanic	60 (21)	67 (24)	5 (9)	11 (19)
Native American	1 (0.4)	1 (0.4)	0 (0)	1 (2)
Multiracial	35 (12)	36 (13)	2 (4)	2 (4)
Region, n (%)				
Latin America	99 (35)	97 (34)	--	--
Southeast Asia	34 (12)	29 (10)	--	--
North America	82 (29)	90 (32)	55 (100)	57 (100)
Europe/Australia	66 (23)	66 (23)	--	--
Age, in years				
Mean (SD)	38 (9)	37 (10)	37 (9)	40 (10)
Median (min to max)	37 (19 to 67)	36 (19 to 71)	38 (20 to 61)	39 (21 to 67)
Weight (kg)				
Mean (SD)	72 (15)	70 (16)	83 (15)	77 (23)
Median (min, max)	72 (33 to 126)	68 (34 to 220)	81 (48 to 126)	73 (49 to 220)
BMI[2] (kg/m²)				
Mean (SD)	24 (5)	24 (5)	27 (6)	25 (6)
Median (min, max)	24 (5 to 56)	23 (14 to 62)	26 (19 to56)	25 (17 to 62)
CD4 Cell Count, cell/mm³				
Mean (SD)	219 (124)	217 (134)	236 (157)	226 (149)
Median (min to max)	212 (1 to 620)	204 (4 to 807)	231 (1 to 609)	202 (6 to 567)
Plasma HIV RNA, log_{10} copies/mL				
Mean (SD)	5.0 (0.6)	5.0 (0.6)	5.0 (0.6)	5.0 (0.6)
Median (min to max)	5.1 (3 to 6)	5.0 (4 to 6)	4.9 (4 to 6)	5.0 (4 to 6)
Plasma HIV RNA (copies/mL)				
Geometric Mean	103205	106215	90006	99834
Median (min, max)	114000 (400 to 75000)	104000 (4410 to 750000)	85700 (5310 to 750000)	112000 (44410 to 75000)
Investigator-reported History of AIDS				
Yes	52 (19)	59 (21)	10 (18)	8 (14)
Stratum, n (%)				
Screening HIV RNA level ≤50,000	75 (27)	80 (28)	16 (29)	15 (26)
Hepatitis B or C Positive	18 (6)	16 (6)	2 (4)	4 (7)
Viral Subtype n (%)				
Clade B	219 (78)	230 (82)	53 (96)	52 (91)
Non-Clade B	59 (21)	47 (17)	2 (4)	3 (5)
Missing	3 (1)	5 (2)	0 (0)	2 (4)
Baseline Plasma HIV RNA, n (%)				
≤50,000 copies/mL	79 (28)	84 (30)	19 (35)	19 (33)
>50,000 copies/mL	202 (72)	198 (70)	36 (65)	38 (67)
≤100,000 copies/mL	127 (45)	139 (49)	31 (56)	27 (47)
>100,000 copies/mL	154 (55)	143 (51)	24 (44)	30 (53)
Baseline CD4 Cell Counts, n (%)				
≤50 cells/mm³	27 (10)	31 (11)	8 (15)	9 (16)
>50 cells/mm³ and ≤200 cells/mm³	104 (37)	105 (37)	15 (27)	19 (33)
>200 cells/mm³	150 (53)	145 (51)	32 (58)	29 (51)
Missing	0 (0)	1 (0.4)	0 (0)	0 (0)

[1]There were 111 patients with DEXA scans at baseline: 86 patients were evaluable at Week 48 and 75 patients were evaluable Week 96, including 68 patients evaluable at both time points. One patient in the substudy was not scanned at baseline.
[2]The values shown for BMI were derived from 279 raltegravir recipients and 281 efavirenz recipients. Two patients in each treatment had no height measurement, so their BMI could not be calculated.

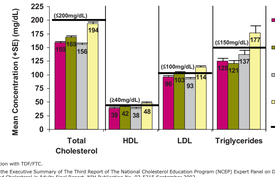
- Median baseline BMI (kg/m²) was higher in the RAL group than the EFV group overall (25.8 vs. 24.7).
- There were fewer females in the RAL group than in EFV group in the DEXA substudy [4 (7%) vs. 9 (16%)].

Mean Change from Baseline in Metabolic Parameters at Week 96



- The change from baseline in the T CHOL:HDL-C ratio was -0.18 for the RAL group and -0.04 for EFV group (p=0.192).

Fasting Lipid Levels at Baseline and Week 96
as Compared with NCEP Goals



*In combination with TDF/FTC.
†Taken from the Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Final Report. NIH Publication No. 02-5215 September 2002.

Number (%) of Patients With a Treatment Emergent Laboratory Abnormality by Treatment Group at Week 96

			Number (%)	
			RAL group (N=281) n/m (%)	EFV Group (N=282) n/m (%)
Laboratory Test (Unit)	Criteria	Grade		
Blood chemistry test				
Fasting (non-random) serum LDL-C (mg/dL)	130 - 159	Grade 1	39/271 (14.4)	47/262 (17.9)
	160 - 189	Grade 2	18/271 (6.6)	29/262 (11.1)
	≥190	Grade 3	3/271 (1.1)	17/262 (6.5)
Fasting (non-random) serum cholesterol (mg/dL)	200 - 239	Grade 1	54/276 (19.6)	64/267 (24.0)
	240 - 300	Grade 2	20/276 (7.2)	42/267 (15.7)
	>300	Grade 3	0/276 (0.0)	11/267 (4.1)
Fasting (non-random) serum triglyceride (mg/dL)	500 - 750	Grade 2	2/276 (0.7)	11/267 (4.1)
	751 - 1200	Grade 3	1/276 (0.4)	1/267 (0.4)
	>1200	Grade 4	0/276 (0.0)	3/267 (1.1)
Fasting (non-random) serum glucose test (mg/dL)	110 - 125	Grade 1	21/274 (7.7)	31/266 (11.7)
	126 - 250	Grade 2	7/274 (2.6)	11/266 (4.1)
	251 - 500	Grade 3	3/274 (1.1)	0/266 (0.0)
	>500	Grade 4	0/274 (0.0)	0/266 (0.0)

Body Composition Changes through 96 Weeks

	RAL group			EFV group		
Week	N	Baseline Mean (gm)	Mean % Change[1] (95% CI)	N	Baseline Mean (gm)	Mean % Change[1] (95% CI)
Arms						
0	55	1999		56	1682	
48	40	1872	23 (8, 38)	46	1701	21 (13, 29)
96	37	1976	23 (6, 41)	38	1708	24 (15, 33)
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Total						
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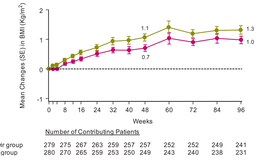
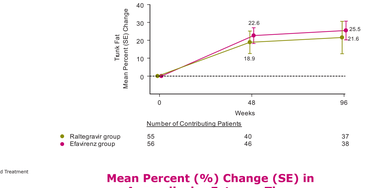
N = Number of patients in the treatment group.
[1]Mean % change from baseline are based on the measurements of the patients who were measured at both baseline and the time point assessed.
The DEXA re-scan (for the baseline visit) values were taken as the baselines for 7 patients and clinically deemed acceptable, when the original baseline scan readings were not available.
Note: RAL and EFV were administered with TRUVADA®

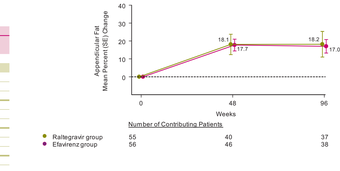
Mean Change (SE) in BMI (Kg/m²) over Time



Mean Percent (%) Change (SE) in Trunk Fat over Time



Mean Percent (%) Change (SE) in Appendicular Fat over Time



Lipoatrophy Patients at Baseline and Week 96

			Baseline						Week 96					
TRT	Patient	Gen	WT (kg)	BMI (kg/m²)	Trunk Fat (gm)	App Fat (gm)	CD4 (cells/mm³)	VL (copy/mL)	WT (kg)	BMI (kg/m²)	Trunk Fat (gm)	App Fat (gm)	CD4 (cells/mm³)	VL (copy/mL)
RAL	1	M	81	23	5604	7463	394	5640	75	21	3621	4798	577	<50
	2	M	75	29	6413	8241	67	81300	70	28	4436	6399	366	<50
	3	M	76	26	7521	6799	210	163000	68	23	4283	5312	311	<50
EFV	4	F	60	25	12413	9914	189	14400	57	24	10730	7866	299	<50
	5	M	64	21	4896	4987	170	30600	60	20	3791	3968	323	<50

Note: Lipoatrophy is defined as more than a 20% decrease from baseline appendicular fat at Week 96.

Lipoatrophy

- The majority of patients in both groups experienced modest fat gain.
- 3/37 patients on RAL and 2/38 patients on EFV had at least 20% appendicular fat loss (lipoatrophy).
  - There was no discordance between appendicular and trunk fat loss among these few patients.
  - None of the patients with lipoatrophy identified by DEXA scanning had investigator-reported lipodystrophy as an AE.

Investigator-reported Lipodystrophy

- Adverse events related to lipodystrophy (including "fat tissue increased" and "lipoatrophy") were reported by investigators in 2 patients (0.4%), both in the EFV group, through 96 weeks.
  - Both adverse experiences were of mild intensity.
    - Neither was considered serious nor resulted in discontinuation of blinded therapy.
  - Only 1 case was considered possibly related to study therapy.
  - Both patients were part of the DEXA subgroup:
    - 1 pt with Wk 48 increases: 13% trunk fat, 8% appendicular fat (no data at Wk 96)
    - 1 pt with Wk 96 increases: 8% trunk fat, 17% appendicular fat
- There were no patients in the RAL treatment group that reported clinical adverse experience terms of lipodystrophy through 96 weeks.
  - After Week 96, an AE of "lipodystrophy-acquired" was reported in 1 patient in the RAL group.

Conclusions

- At Week 96, both the RAL and EFV regimens demonstrated modest effects on serum lipids and glucose.
  - 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 the treatment groups.
- At week 96, DEXA showed small gains in body fat in both treatment groups.
- Longer-term experience with RAL suggests a favorable metabolic profile associated with minimal changes in body composition in treatment-naïve patients.

Acknowledgements

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