Poster Number

627

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Efficacy and Safety of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir DF "Quad" Compared to Ritonavir-boosted Atazanavir plus Emtricitabine/Tenofovir DF in Treatment Naïve HIV-1 Infected Subjects

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Background

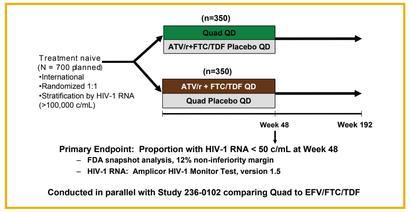
- Elvitegravir (EVG)/ cobicistat (COBI)/emtricitabine (FTC)/ tenofovir DF (TDF) has been coformulated as the first integrase inhibitor-containing single-tablet regimen "Quad"
  - EVG is a potent once-daily HIV integrase inhibitor (150 mg)
  - COBI is a pharmacoenhancer lacking anti-HIV activity (150 mg)
  - FTC/TDF is a preferred first line NRTI combination (200 mg/300 mg)[1-3]
- Recommended initial HIV regimen[1-3]
  - Efavirenz (EFV)/FTC/TDF
  - Atazanavir/ritonavir (ATV/r) + FTC/TDF
  - Darunavir/ritonavir (DRV/r) + FTC/TDF
  - Raltegravir (RAL) + FTC/TDF

1. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
2. Thompson et al. JAMA. 2010;304(3):321-333
3. EACS Guidelines for the Clinical Management and Treatment of HIV Infected Adults in Europe. Version 6.0 - October 2011

Study Design

- Randomized, double-blind, double-dummy, active-controlled, non-inferiority study
- Eligibility criteria
  - Treatment naïve
  - Genotypic sensitivity to ATV, FTC, and TDF
  - HIV-1 RNA > 5,000 c/mL
  - eGFR ≥ 70 mL/min (Cockcroft-Gault equation)
- Primary endpoint
  - HIV-1 RNA < 50 c/mL at Week 48 (Amplicor HIV-1 Monitor Test, version 1.5)
  - FDA snapshot algorithm
  - Prespecified primary analysis of non-inferiority margin 12%
- Exploratory analysis of PK/PD relationship

Figure 1. Study Design



Results

Table 1. Baseline Characteristics

Characteristic	Quad (n=353)	ATV/r + FTC/TDF (n=355)
Age (years), Mean (SD)	38	39
Male	92%	89%
Non-White	29%	22%
Black or African Heritage	20%	13%
Asymptomatic HIV Infection	81%	83%
HBV – HCV Seropositive	1% – 5%	2% – 3%
HIV-1 RNA (log_{10} copies mL), Median	4.88	4.86
HIV RNA > 100,000 c/mL	43%	40%
CD4 count (cells/mm³), Mean	364	375
< 200	15%	11%
201 to ≤ 350	35%	35%
351 to ≤ 500	35%	34%
> 500	16%	20%

Figure 2. Subject Disposition Through Week 48

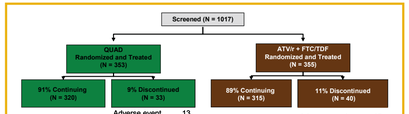


Figure 3. Primary Endpoint: HIV-1 RNA <50 c/mL

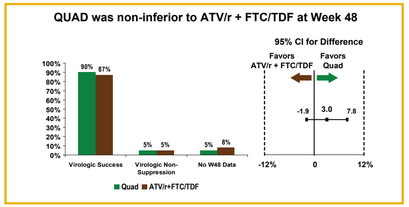
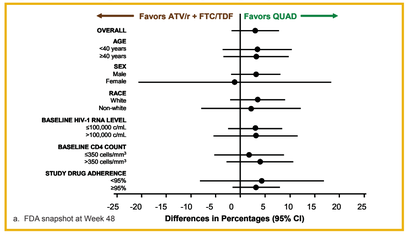
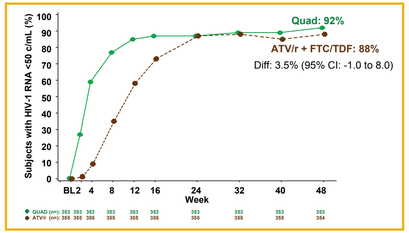


Figure 4. Virologic Success[a] by Subgroups



a. FDA snapshot at Week 48

Figure 5. HIV-1 RNA < 50 c/mL Through Week 48 (M=F)



Results (cont'd)

Figure 6. Efficacy in Baseline HIV-1 RNA and CD4 Subgroups

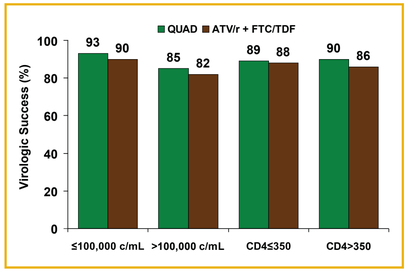


Figure 7. Efficacy by Baseline Demographics

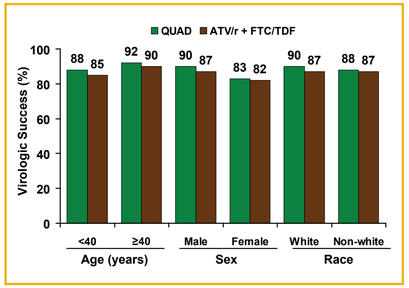


Figure 8. Mean Change from Baseline in CD4 Cells (cells/mm³)

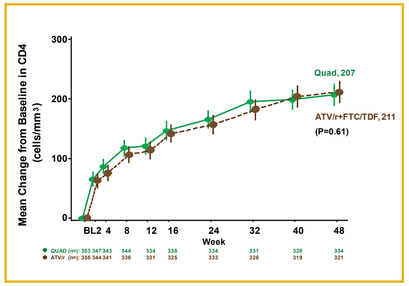


Table 2. Integrase, PI, NRTI Resistance Through Week 48

	Quad (n=353)	ATV/r + FTC/TDF (n=355)
Subjects Analyzed for Resistance[a], n (%)	12 (3)	8 (2)
Subjects with Resistance to ARV Regimen, n (%)	5 (1)	0
Any Primary Integrase-R, n	4	-
E92Q	1	-
T66I	1	-
Q148R	2	-
N155H	2	-
Any Primary PI-R, n	-	0
Any Primary NRTI-R, n	4	0
M184V/I	4	
K65R	1	

a. Subjects who experienced either suboptimal virologic response (two consecutive visits with HIV-1 RNA ≥50 c/mL and <1 log_{10} below baseline after Week 8), virologic rebound (two consecutive visits with HIV-1 RNA either ≥400 c/mL after achieving HIV-1 RNA <50, or >1 log_{10} increase from nadir), or had HIV-1 RNA ≥400 c/mL at their last visit

Figure 9. Virologic Success by EVG Exposure – Quad

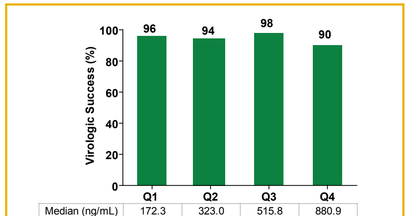


Table 3. Summary of Adverse Events (AEs)

	Quad (n=353)	ATV/r + FTC/TDF (n=355)
Grade 3 or 4 AE	13%	14%
Drug-related AE	45%	57%
SAE	7%	9%
Drug-related SAE	1%	1%
AE leading to DC of study drug	4%	5%
Death, (n)	0	1% (3)[a]

a. Causes of death included septic shock, Pneumocystis jiroveci pneumonia, and cardiopulmonary arrest after overdose of recreational drugs

Table 4. Common Adverse Events

Adverse Event[a]	Quad (n=353)	ATV/r + FTC/TDF (n=355)
Diarrhea	22%	27%
Nausea	20%	19%
Upper respiratory infection	15%	16%
Headache	15%	12%
Fatigue	14%	13%
Ocular icterus	1%	14%

a. > 10% in either treatment group

Table 5. Common Adverse Events Leading to DC

Adverse Event[a,b]	Quad (n=353)	ATV/r + FTC/TDF (n=355)
Overall	4%	5%
Diarrhea	1%	<1%
Pyrexia	1%	0%
Nausea	<1%	1%
Vomiting	<1%	1%
Fatigue	<1%	1%
Ocular Icterus	0%	1%
Jaundice	0%	1%
Dizziness	0%	1%
Drug Eruption	0%	1%

a. At least 2 subjects in either treatment group
b. One subject from each treatment group discontinued due to renal adverse event; one subject in Quad group due to blood creatinine increased, one subject in ATV/r + FTC/TDF group due to nephropathy toxic.

Table 6. Grade 3 or 4 Laboratory Abnormalities

Grade 3 or 4 labs[a]	Quad (n=353)	ATV/r + FTC/TDF (n=355)
Creatinine Kinase	6%	7%
Hematuria	4%	2%
AST	2%	3%
Amylase	2%	3%
ALT	2%	2%
Hyperbilirubinemia	1%	58%

a. At least 2% in either treatment group

Figure 10. Change from Baseline in Serum Creatinine

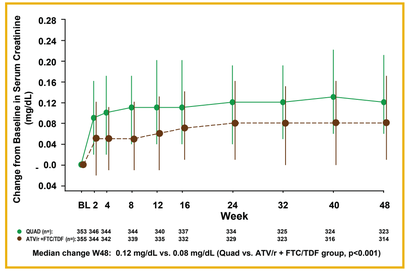


Figure 11. Change from Baseline in Fasting Lipids at Week 48

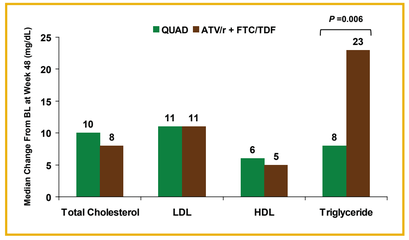
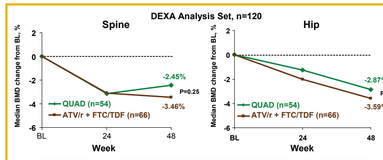


Figure 12. Bone Mineral Density (DEXA Analysis Set)



	Quad (n=353)	ATV/r + FTC/TDF (n=355)	P value
Fracture events, (n)	1% (3)	2% (6)	0.51

Conclusions

- High and comparable efficacy in Quad and ATV/r+FTC/TDF
  - Robust, durable, and consistent efficacy on all endpoints
  - High virologic suppression rates in all subgroups, including those with baseline HIV-1 RNA > 100,000 c/mL
- Quad was well-tolerated
  - Similar low rates of treatment discontinuation
  - Smaller increases in triglyceride in Quad
  - Discontinuations due to renal adverse events were 0.3% in ATV/r + FTC/TDF and 0.3% in Quad

Summary

- Study 236-0102 comparing Quad to EFV/FTC/TDF, an oral presentation on Wednesday, March 7th 10:45AM (Sax P et al. Paper #101)
- Full results of studies 236-0102 and 236-0103 submitted for peer-reviewed publication
- Health authority filings submitted in Europe, Australia, Canada, Switzerland, and the U.S. (FDA decision expected by August 27, 2012)

Study 236-0103 Investigators

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Online Expert Poster Review and Discussion

ARV Therapies and Therapeutic Strategies

Reporting From

The 19th Conference on Retroviruses and Opportunistic Infections (CROI)

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC

The Efficacy and Safety of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir DF ("Quad") Compared to Efavirenz/Emtricitabine/Tenofovir DF in Treatment Naïve HIV-1 Infected Subjects: Primary Results of Study GS-US-236-0102

Paul Sax[1], Edwin DeJesus[2], Anthony Mills[3], Andrew Zolopa[4], Calvin Cohen[5], David Wohl[6], Joel Gallant[7], Hui C Liu[8], Kirsten White[8], Erin Quirk[8], and Brian Kearney[8]

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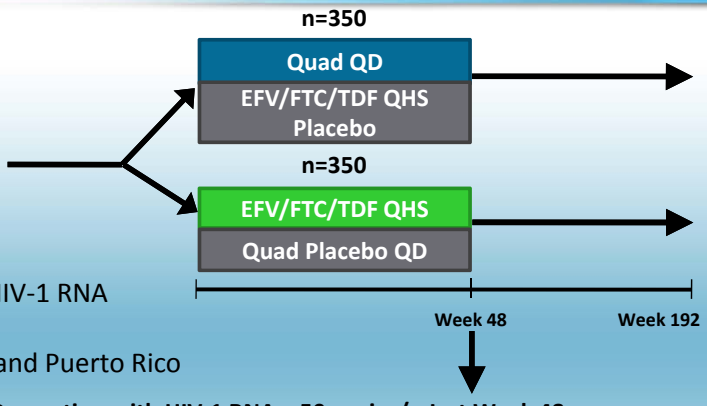
Abstract #101

Study Design: 236-0102

Treatment-Naïve
Any CD4 count
(N= 700 Planned)

- Randomized 1:1
- Stratification by HIV-1 RNA (>100,000 c/mL)
- Conducted in US and Puerto Rico



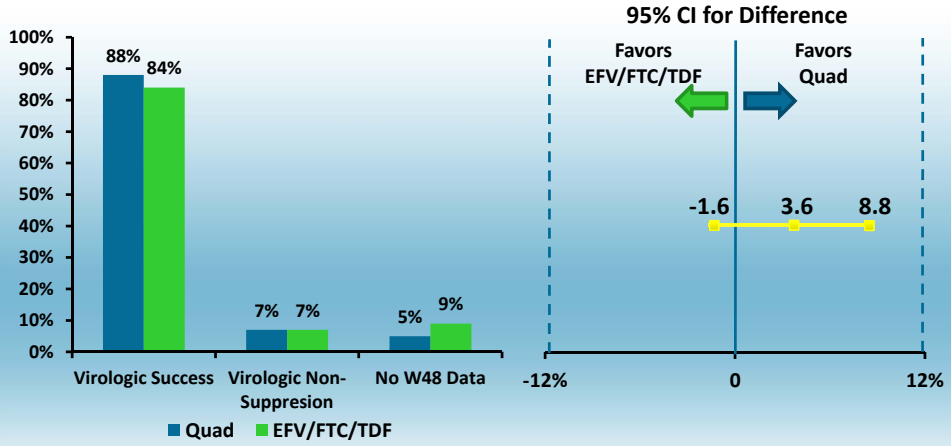
Primary Endpoint: Proportion with HIV-1 RNA < 50 copies/mL at Week 48

- FDA snapshot analysis (ITT), 12% noninferiority margin
- HIV-1 RNA: Amplicor HIV-1 Monitor Test, version 1.5

Conducted in parallel with Study 236-0103 comparing Quad to FTC/TDF + ATV/r (DeJesus et al, Poster #627)

Primary Endpoint: HIV-1 RNA < 50 copies/mL Study 236-0102

Better Recovery of CD4 in the Quad Arm: 239 vs 206 Cells/µL *P*=.009



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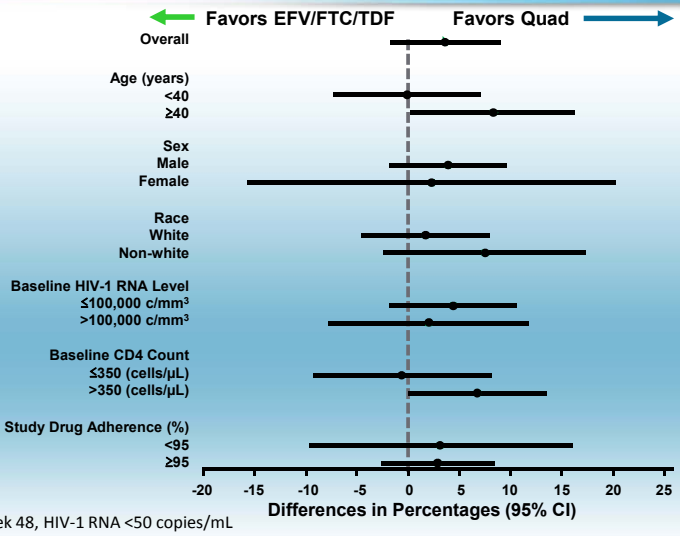
236-0102 Subgroup Analysis



FDA Snapshot Week 48, HIV-1 RNA <50 copies/mL

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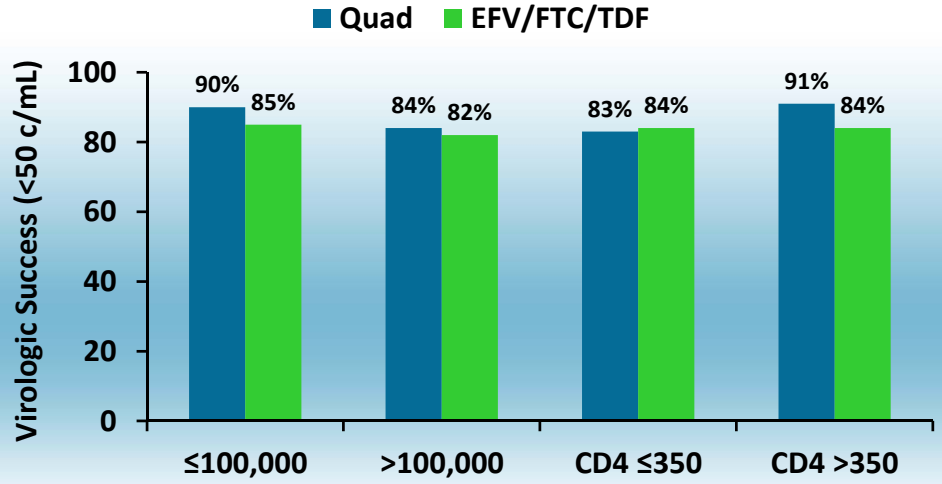
Efficacy in Baseline HIV-RNA and CD4 Subgroups Study 236-0102



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Integrase & NNRTI Resistance Through Week 48 Study 236-0102

	Quad (n=348)	EFV/FTC/TDF (n=352)
Subjects Analyzed for Resistance*, n (%)	**14 (4)**	**17 (5)**
Subjects with Resistance to ARV Regimen, n (%)	**8 (2)**	**8 (2)**
Any Primary Integrase-R, n	**7**	
E92Q	7	
T66I	1	
Q148R	1	
N155H	1	
Any Primary NNRTI-R n		**8**
K103N		7
V108I		2
Y188Y/F/H/L		1
G190A		1
Any Primary NRTI-R, n	**8**	**2**
M184V/I	8	2
K65R	3	2

*Subjects who experienced either suboptimal virologic response (two consecutive visits with HIV-1 RNA ≥50 c/mL and <1 $\log_{10}$ below baseline after Week 8), virologic rebound (two consecutive visits with HIV-1 RNA either ≥400 c/mL after achieving HIV-1 RNA <50, or >1 $\log_{10}$ increase from nadir), or had HIV-1 RNA ≥400 c/mL at their last visit.

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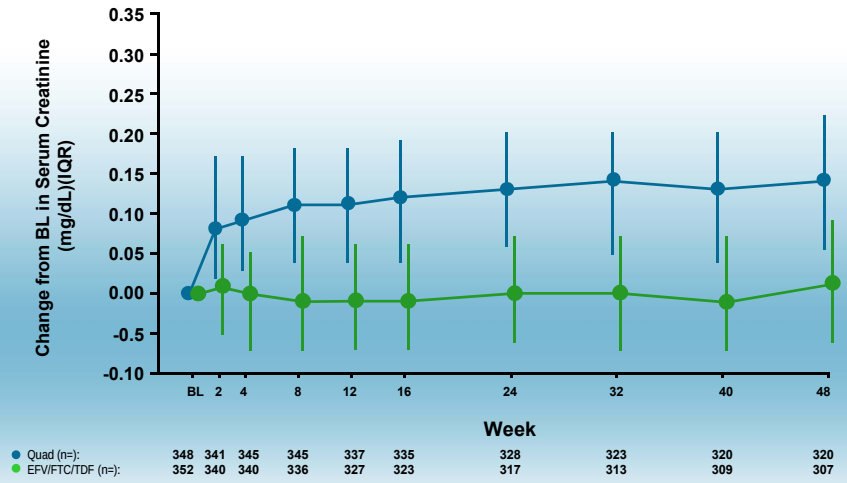
Discontinuations Due to Adverse Events Study 236-0102

	Quad (n=348)	EFV/FTC/TDF (n=352)
Discontinuations Due to AE, n (%)	4%	5%
AE leading to discontinuation in >1 subject (%)		
Rash and Drug Hypersensitivity	0	1.4%
Renal Abnormalities	1.4%	0
Depression	0.3%	0.9%
Abnormal Dreams	0	0.6%
Fatigue	0.3%	0.3%
Paranoia	0.3%	0.3%

Sax P et al. 19th CROI; Seattle, WA; March 5-8, 2012; Abst. 101.

Median Change from Baseline in Serum Creatinine



Median change at Week 48: 0.14 mg/dL vs. 0.01 mg/dL (Quad vs. EFV/FTC/TDF group, *P*<0.001)

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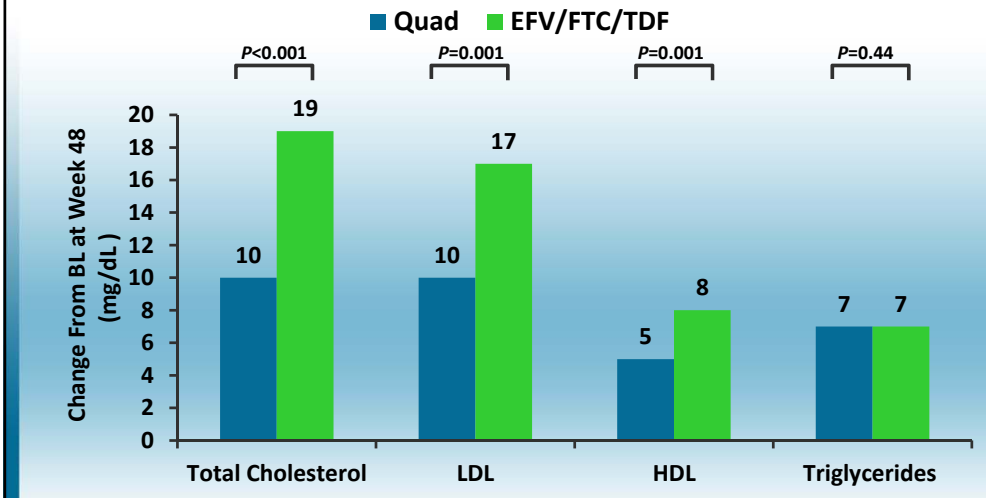
Median Change from Baseline in Fasting Lipids through Week 48 Study 236-0102



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