18th Annual Conference of the
British HIV Association (BHIVA)

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Elvitegravir/Cobicistat/Emtricitabine/Tenofovir DF (Quad) has Noninferior Efficacy and Favorable Safety Compared to Efavirenz/Emtricitabine/Tenofovir DF in Treatment Naïve HIV-1 Infected Subjects

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Background

- A single-tablet regimen of efavirenz, emtricitabine and tenofovir DF (EFV/FTC/TDF) is a preferred initial HIV-1 regimen [1-3]
- The efficacy and safety of coformulated EVG/COBI/FTC/TDF ("Quad") was comparable to EFV/FTC/TDF in a Phase 2 study [4]
  - elvitegravir (EVG): potent once-daily HIV integrase inhibitor (150 mg)
  - cobicistat (COBI): pharmacoenhancer lacking HIV activity (150 mg)
  - emtricitabine (FTC)/tenofovir DF (TDF): approved, preferred first line NRTI combination (200 mg/300 mg) [1-3]

[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
[4] Cohen C, et al, AIDS 2011;25 (6):F7-12

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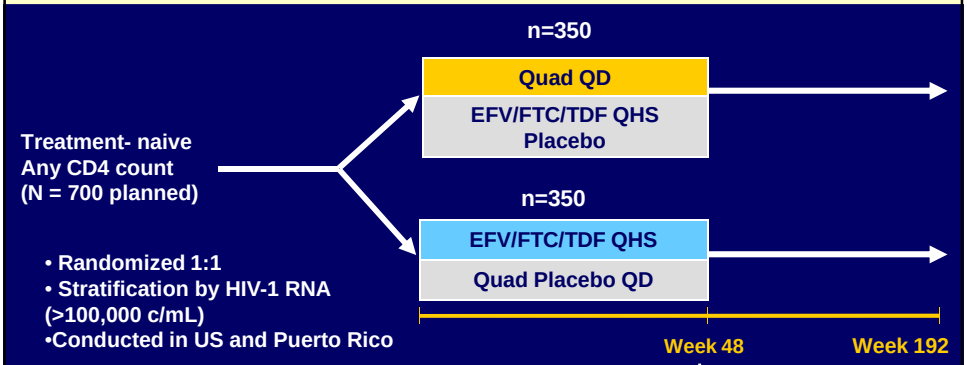
Study Design
236-0102



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

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Baseline Characteristics
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Characteristic	Quad (n=348)	EFV/FTC/TDF (n=352)
Age (years), Mean	38	38
Male (%)	88%	90%
Non-white (%)	39%	36%
Black or African descent (%)	31%	26%
Asymptomatic HIV Infection (%)	83%	84%
HBV – HCV seropositive (%)	1% - 5%	3% - 4%
HIV-1 RNA (log_{10} copies/mL), Median	4.75	4.78
>100,000 (%)	34%	33%
CD4 count (cells/mm^3), Mean (%)	391	382
≤200 cells/mm^3	12%	14%
200 to ≤350	32%	27%
351 to ≤500	32%	39%
>500	23%	20%

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Subject Disposition Through Week 48
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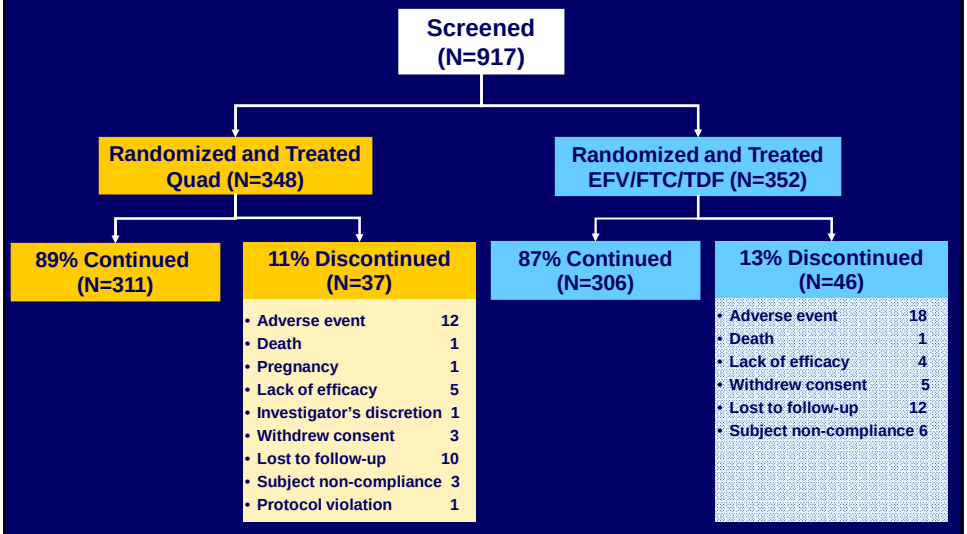

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Primary Endpoint: HIV-1 RNA < 50 copies/mL
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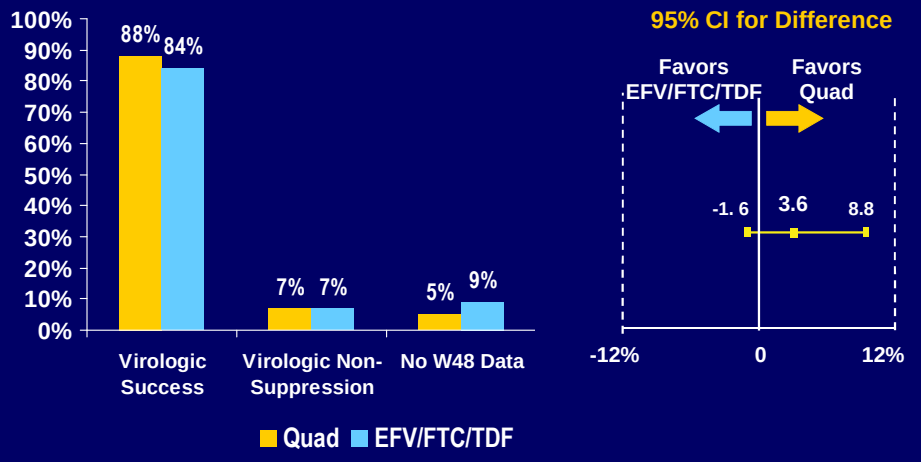
Quad was non-inferior to EFV/FTC/TDF at Week 48



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Subjects HIV-1 RNA < 50 copies/mL (ITT M = F)
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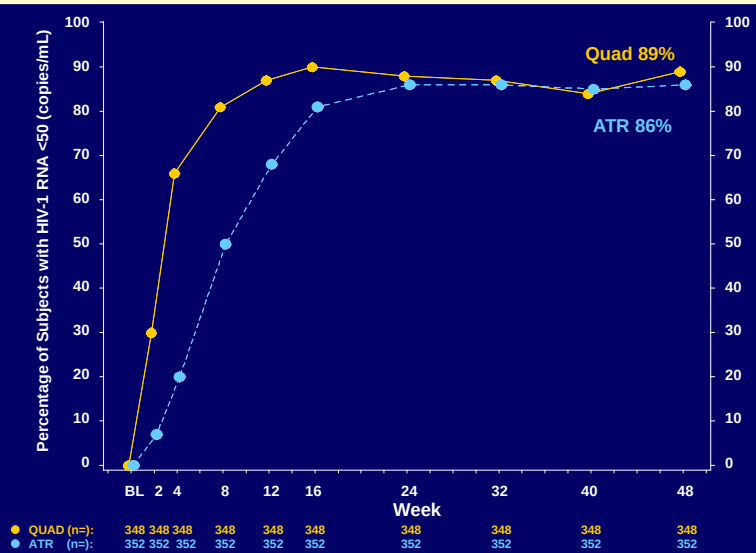

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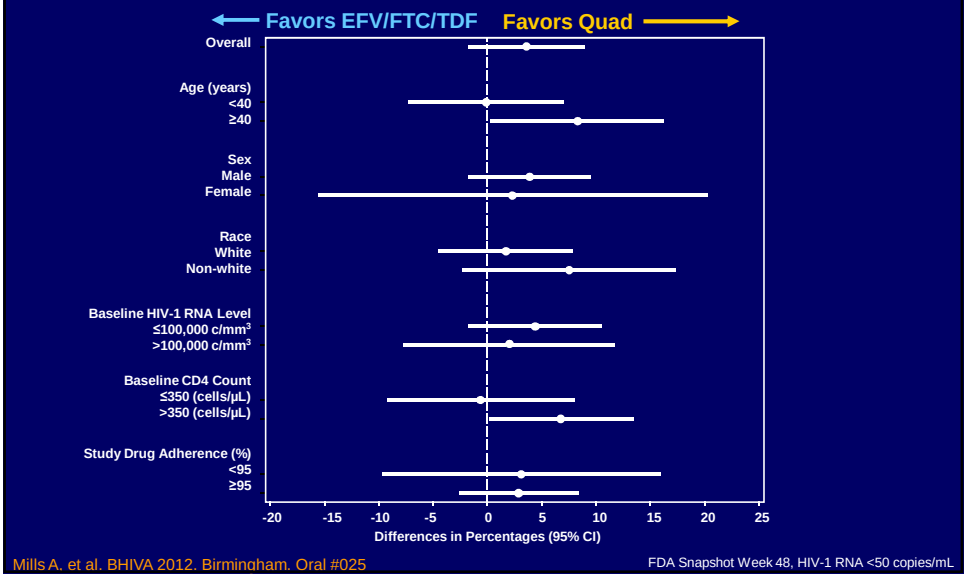
Percent Difference in Response by Subgroups 236-0102



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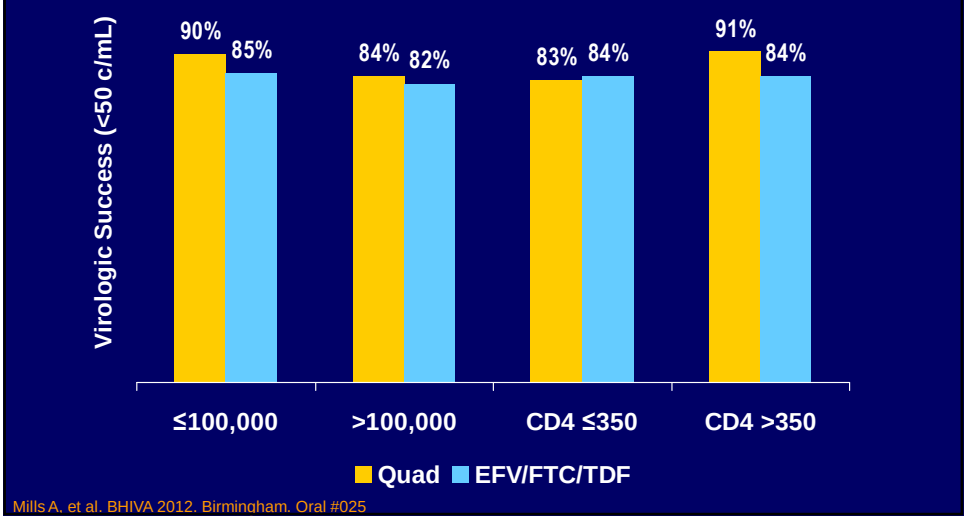
FDA Snapshot Week 48, HIV-1 RNA <50 copies/mL

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



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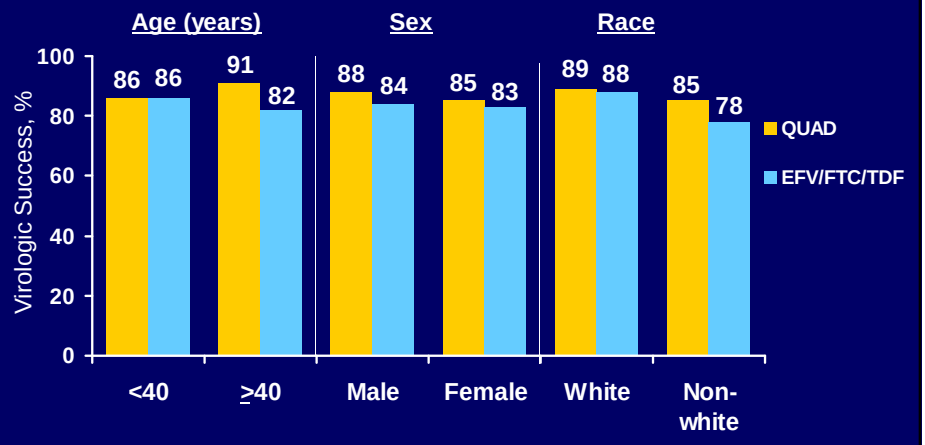
Efficacy by Baseline Demographics
236-0102



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Mean Change from Baseline in CD4 Count
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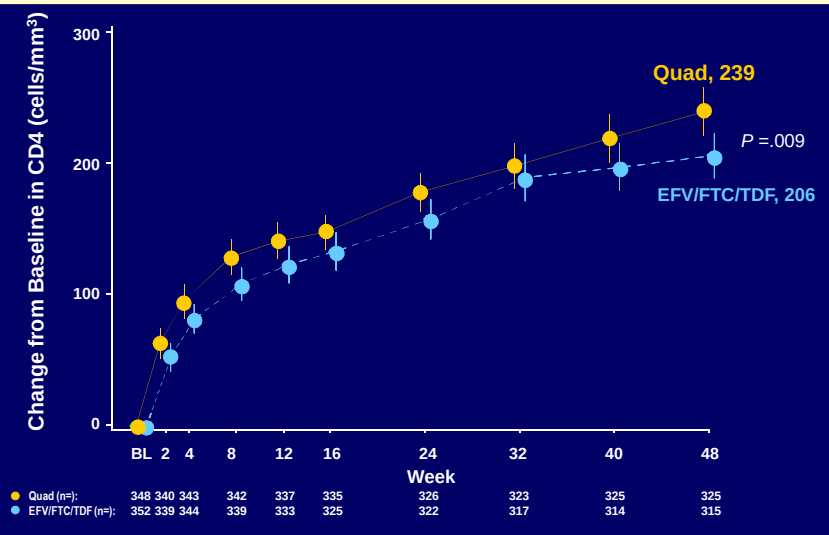

[a] Anova *P* value.

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Integrase & NNRTI Resistance Through Week 48
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	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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Common Adverse Events
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	Quad (n=348)	EFV/FTC/TDF (n=352)
Treatment Emergent Adverse Events in ≥ 10% of subjects (%)		
Diarrhea	23%	19%
Nausea *	21%	14%
Abnormal Dreams ^	15%	27%
Upper Respiratory Infection	14%	11%
Headache	14%	9%
Fatigue	12%	13%
Insomnia *	9%	14%
Depression	9%	11%
Dizziness ^	7%	24%
Rash #	6%	12%

* $p < 0.05$
^ $p < 0.001$
# $p=0.009$

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Discontinuations due to Adverse Events
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	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%

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Grade 3 and 4 Laboratory Abnormalities
236-0102

Grade 3-4 Labs *	Quad (n = 348)	EFV/FTC/TDF (n = 352)
Creatine Kinase	5%	11%
AST	2%	3%
ALT	1%	3%
GGT	2%	5%
Neutrophils	2%	3%
Amylase	2%	2%
Hematuria	2%	1%

*>5 subjects in any treatment group

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Change from Baseline in Serum Creatinine[1]
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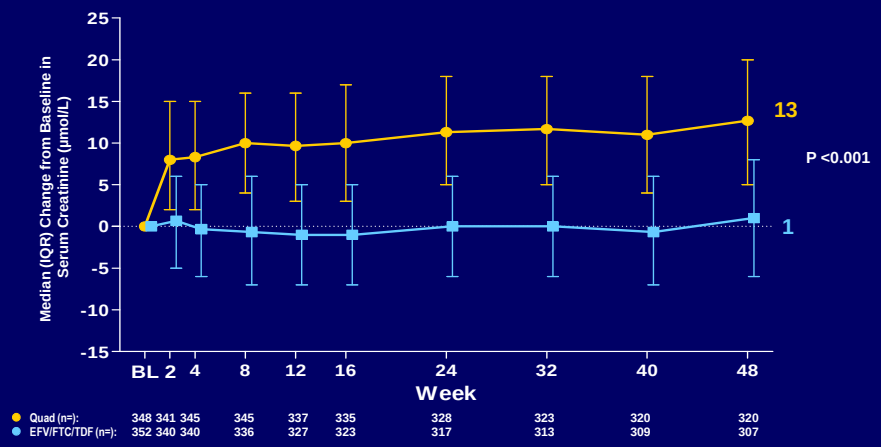

- Increase in serum Cr consistent with MATE-1 inhibition of Cr secretion by COBI[2]

1. Mills T, et al. BHIVA 2012. Birmingham. Oral #025
2. Lepist E-I, et al. ICAAC 2011. Chicago. # A1-1724

Change from Baseline in Fasting Lipids through Week 48
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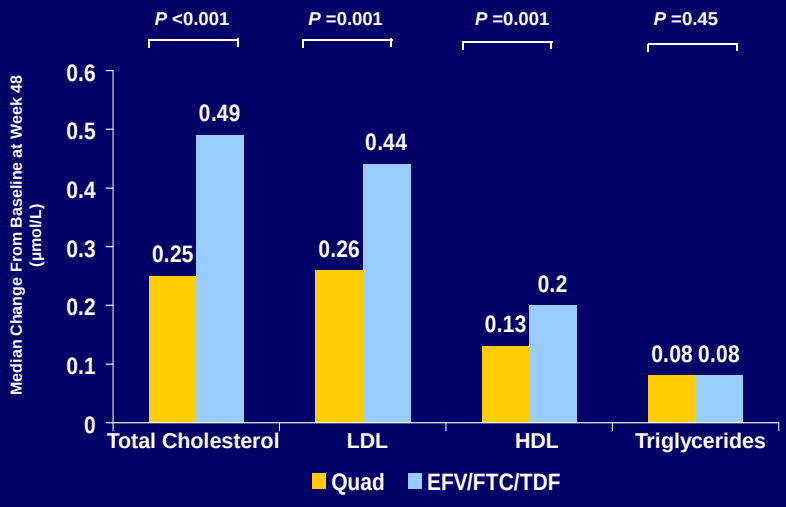

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Conclusions
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- **Quad demonstrates non-inferior efficacy to EFV/FTC/TDF – first fully-powered study comparing one tablet daily HIV regimens**
  - 88% vs 84%, respectively
  - Non-inferiority virologic suppression consistent across protocol-specified subgroups, including HIV-1 RNA >100,000 copies/mL at baseline
- **Quad was well tolerated**
  - Similar low-rates of treatment discontinuation
  - Fewer reports of abnormal dreams, insomnia, dizziness, and rash
  - Higher rate of nausea (Grade 1)
  - Median 13 µmol/L increase in serum creatinine
    - Consistent with COBI inhibition of Cr renal transporter MATE-1
  - 1.4% discontinuing due to renal events
  - Smaller increases in total cholesterol and LDL

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Summary

- **Quad also non-inferior to ATV/r in the Phase 3 Study 236-0103 (Orkin et al, oral presentation #026)**
  - Quad 90% vs. ATV/r 87% virologic success (95% CI for difference -1.9% to 7.8%)
  - 0.3% of subjects in both arms discontinued due to renal events
- **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)**

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