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

British HIV Association
BHIVA

# Dr Chloe Orkin

Barts and The London NHS Trust

*18-20 April 2012, The International Convention Centre, Birmingham*

# Efficacy, safety and pharmacokinetic results of an ongoing international phase 3 study comparing elvitegravir/cobicistat/emtricitabine/tenofovir DF (Quad) with ritonavir-boosted atazanavir plus emtricitabine/tenofovir DF in treatment naïve HIV-1 infected subjects at 48 weeks

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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

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# Study Design
## 236-0103

- 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

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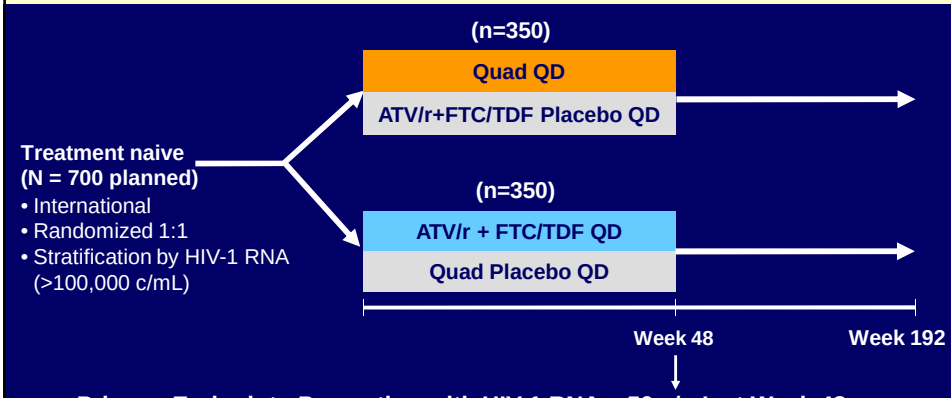
# Study Design
## 236-0103




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

- FDA snapshot analysis, 12% non-inferiority margin
- HIV-1 RNA: Amplicor HIV-1 Monitor Test, version 1.5

**Conducted in parallel with Study 236-0102 comparing Quad to EFV/FTC/TDF**

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# Baseline Characteristics
## 236-0103

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

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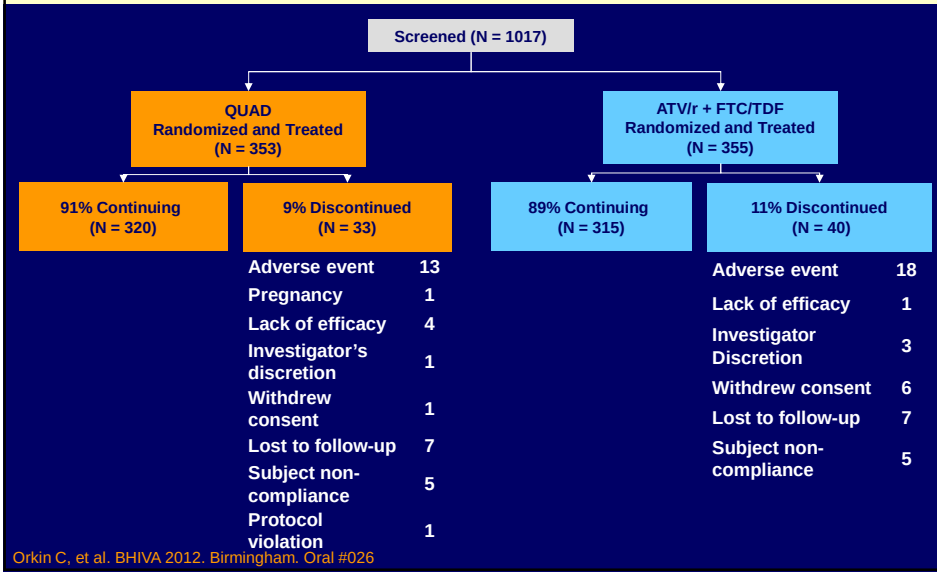
# Subject Disposition Through Week 48
## 236-0103




| | |
|---|---|
| Adverse event | 13 |
| Pregnancy | 1 |
| Lack of efficacy | 4 |
| Investigator's discretion | 1 |
| Withdrew consent | 1 |
| Lost to follow-up | 7 |
| Subject non-compliance | 5 |
| Protocol violation | 1 |

| | |
|---|---|
| Adverse event | 18 |
| Lack of efficacy | 1 |
| Investigator Discretion | 3 |
| Withdrew consent | 6 |
| Lost to follow-up | 7 |
| Subject non-compliance | 5 |

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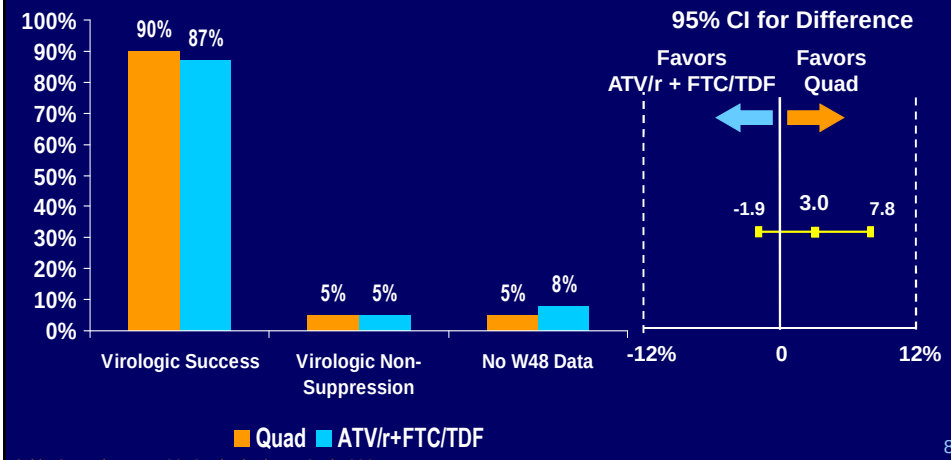
# Primary Endpoint: HIV-1 RNA < 50 c/mL
## 236-0103

### QUAD was non-inferior to ATV/r + FTC/TDF at Week 48

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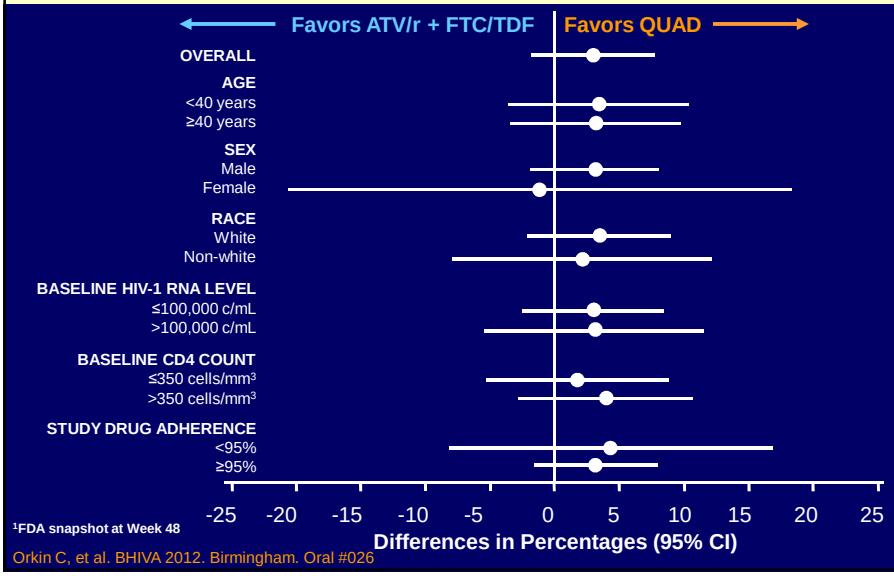
# Virologic Success[1] by Subgroups
## 236-0103




[1]FDA snapshot at Week 48

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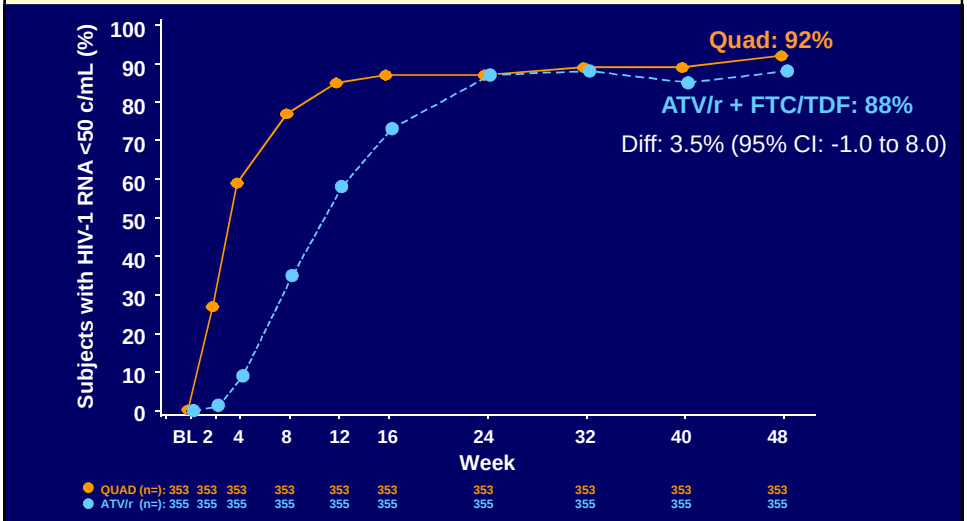
# HIV-1 RNA < 50 c/mL through Week 48 (M=F)
## 236-0103

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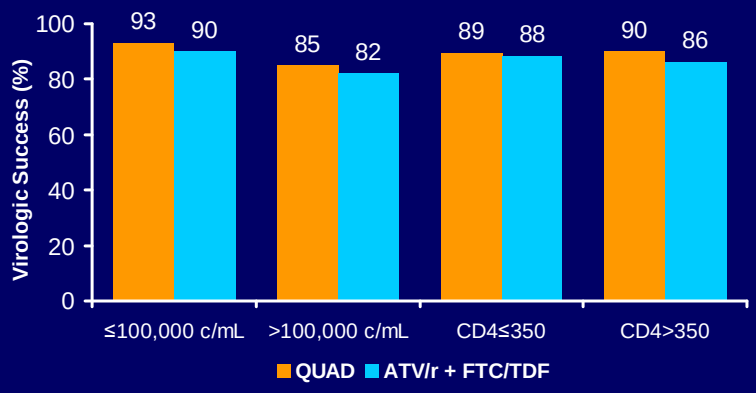
## Efficacy in Baseline HIV-1 RNA and CD4 Subgroups 236-0103

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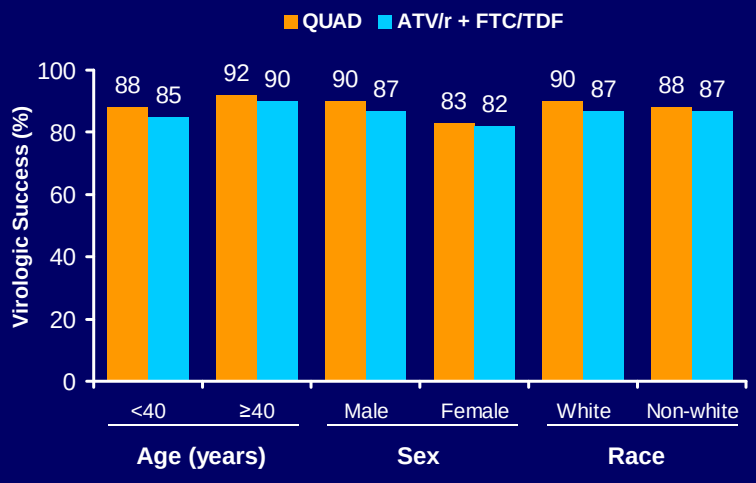
## Efficacy by Baseline Demographics 236-0103

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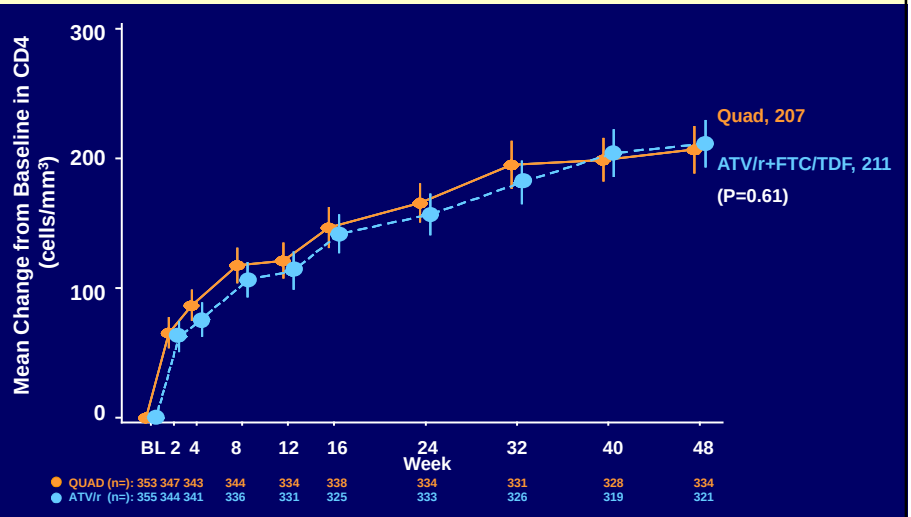
# Mean Change from Baseline in CD4 Cells (cells/mm$^3$)
## 236-0103

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# Integrase, PI, NRTI Resistance Through Week 48
## 236-0103

| | 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.

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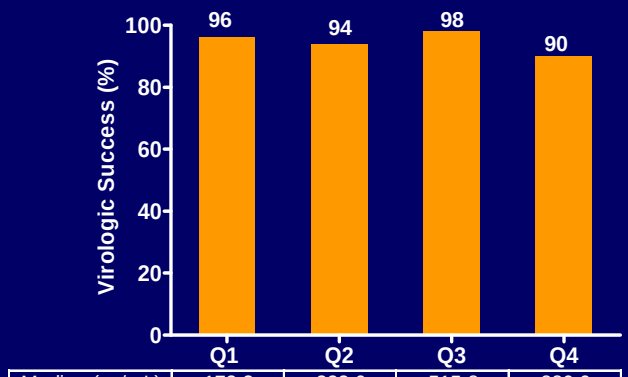
# Virologic Success by EVG Exposure – Quad 236-0103




PK/PD Analysis Set, n=192

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# Summary of Adverse Events (AE) 236-0103

| | 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.

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# Common Adverse Events (All Grades)
## 236-0103

| 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

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# Common Adverse Events Leading to DC
## 236-0103

| 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.

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# Grade 3 and 4 Laboratory Abnormalities
## 236-0103

| Grade 3 or 4 Labs[a] | Quad (n=353) | ATV/r + FTC/TDF (n=355) |
|---|---|---|
| Creatine 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

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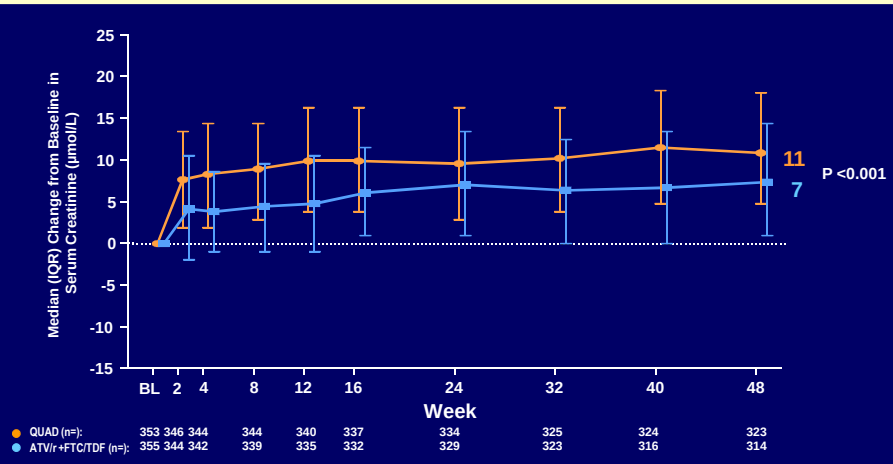
# Change from Baseline in Serum Creatinine[1]
## 236-0103




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

1. Orkin C, et al. BHIVA 2012. Birmingham. Oral #026
2. Lepist E-I, et al. ICAAC 2011. Chicago. # A1-1724

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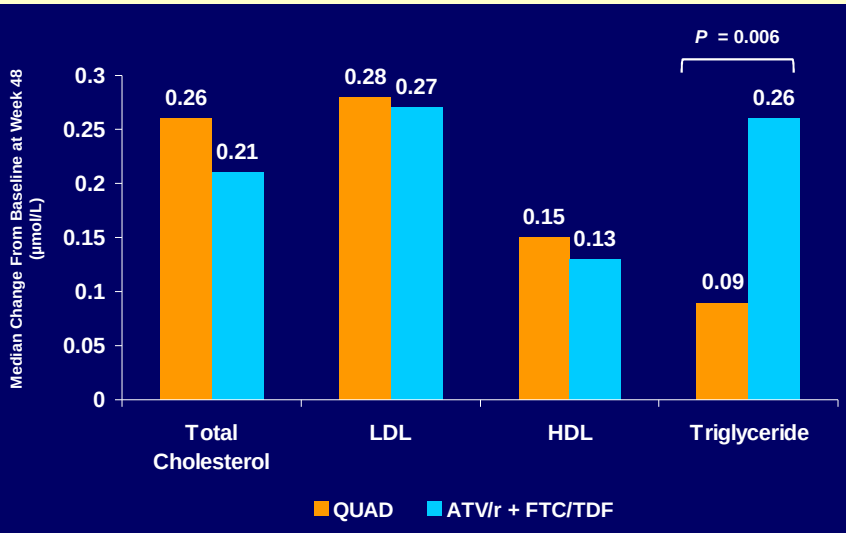
# Change from Baseline in Fasting Lipids at Week 48 236-0103

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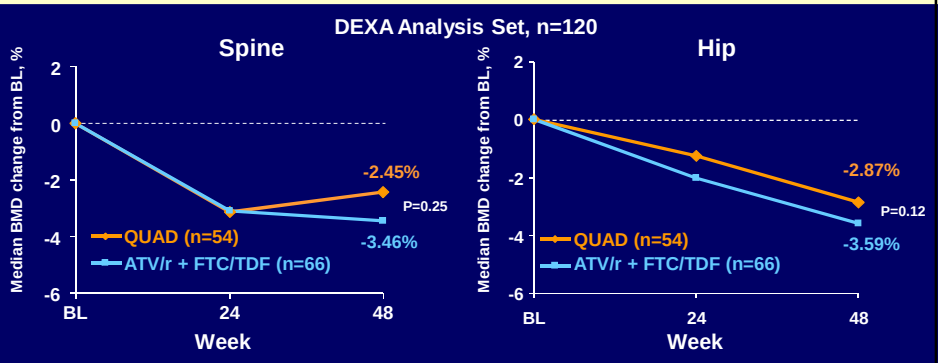
# Bone Mineral Density at Week 48 236-0103




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

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## Conclusions
### 236-0103

- 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



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## Summary

- 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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