

Week 48 Analysis of Once-Daily (QD) Trizivir (TZV) and Tenofovir DF (TDF) in Antiretroviral Naïve Subjects (COL40263)

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Introduction

- This pilot, open-label, multicenter study evaluating a QD regimen of TZV + TDF (3 pills daily) is based on data supporting QD dosing of ABC + 3TC (DeJesus 2004, Gazzard 2003) and early data from clinical investigations into ZDV QD dosing (Ruane 2004).
- Data suggest that ZDV has increased activity against virus with K65R (Ait-Khaled 2002). Therefore, a ZDV-containing regimen combining TZV + TDF could provide a higher genetic barrier to resistance as well as being a more potent regimen.

Objective

- To evaluate the safety and efficacy of a simple three tablet once-daily TZV+TDF regimen in antiretroviral naive subjects over 48 weeks.

Methods

- Open-label, single-arm, multicenter study
- Antiretroviral-naïve adults
- HIV-1 RNA >30,000 copies/mL
- Target ≥40% with baseline VL ≥100,000 copies/mL
- No CD4 restriction
- Primary endpoints:
 - % of subjects with HIV-1 RNA <50 c/mL at Week 48
 - % of subjects with grade 3 or 4 adverse events and laboratory toxicities
- Other endpoints:
 - % of subjects with HIV-1 RNA <400 c/mL
 - CD4+ lymphocyte response
 - Development of phenotypic and genotypic resistance in virologic non-responders
 - Fasting lipids
 - Change from baseline in fat distribution and bone density by whole body DEXA
 - Change from baseline in mitochondrial DNA in PBMC by PCR
- Analysis Populations
 - The Intent-to-Treat (ITT) population included all subjects enrolled in the study who completed at least the baseline study visit.
 - The Safety population included all subjects enrolled in the study who had taken at least one dose of TZV and TDF.
- Analysis Methods for Virologic Endpoints
 - Missing=Failure (ITT M=F): Subjects who have missing values at a timepoint were considered failures.
 - As-Treated (AT): Data collected after permanent discontinuation of the baseline regimen are excluded.
- Definition of Virologic Non-Response
 - Confirmed HIV-1 RNA ≥400 c/mL at or after week 24
 - Subjects meeting definition are withdrawn from study

Baseline Characteristics

Median age (range)	38 (20-57)
CDC Classification, n (%)	
A or Asymptomatic	91 (74%)
B or Symptomatic	20 (16%)
C or AIDS-defining illness	12 (10%)
HIV Risk Factor, n (%)	
Homosexual contact	79 (64%)
Heterosexual contact	40 (33%)
Injectable drug use	6 (5%)
Occupational exposure	2 (2%)
Transfusion	2 (2%)
Other	1 (<1%)
HIV-1 RNA	
Median, log ₁₀ c/mL (range)	5.08 (4.08-6.53)
<100,000 c/mL, n (%)	51 (41%)
≥100,000 c/mL, n (%)	72 (59%)
CD4	
Median, cells/mm ³ (range)	222 (20-857)
<200 cells/mm ³ , n (%)	55 (45%)
≥200 cells/mm ³ , n (%)	68 (55%)
Fasting Lipid Profile:	
LDL, n=108	
Median, mg/dL (range)	96 (12-187)
HDL, n=108	
Median, mg/dL (range)	38 (13-78)
Triglycerides, n=109	
Median, mg/dL (range)	109 (43-323)
Total Cholesterol, n=109	
Median, mg/dL (range)	162 (63-270)

*Subjects could indicate more than 1 HIV risk factor

Subject Accountability

Number of subjects discontinuing study through week 48	52 (42%)
Primary reasons for discontinuation, n	
Adverse event*	14 (27%)
Lost to follow-up	13 (25%)
Virologic non-response	12 (23%)
Consent withdrawn	5 (10%)
Protocol violation	5 (10%)
Other	3 (6%)

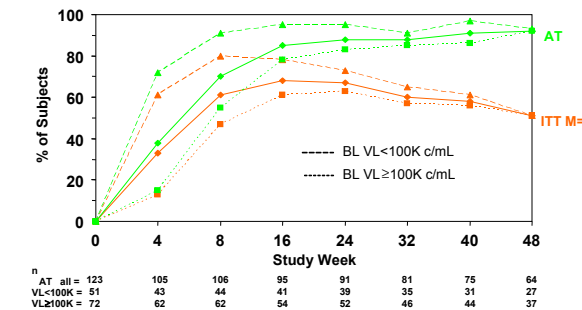
*Adverse events leading to study discontinuation were abacavir hypersensitivity reaction (8), nausea/vomiting (1), nausea/vomiting/headache (1), cancer (1), mood swings (1), abnormal liver function test (1), and positive syphilis test (1).

Efficacy Results Through Week 48

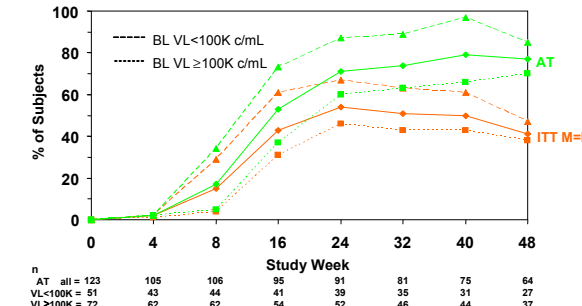
% with Plasma HIV-1 RNA <50 c/mL	
ITT M=F	41% (51/123)
AT	77% (49/64)
% with Plasma HIV-1 RNA <400 c/mL	
ITT M=F	51% (63/123)
AT	92% (59/64)
Virologic Non-Responders*	11% (14/123)
Baseline VL <100,000 c/mL	14% (2/14)
Baseline VL ≥100,000 c/mL	86% (12/14)

*Resistance data from virologic non-responders to be presented in Poster H-1068, Thursday, Sept 22

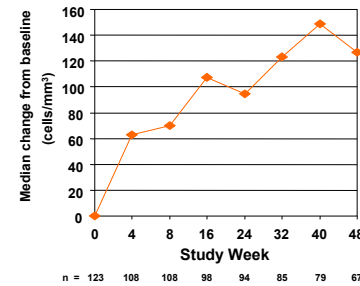
HIV-1 RNA <400 c/mL



HIV-1 RNA <50 c/mL

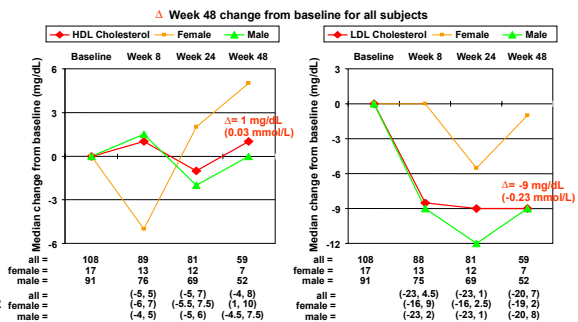
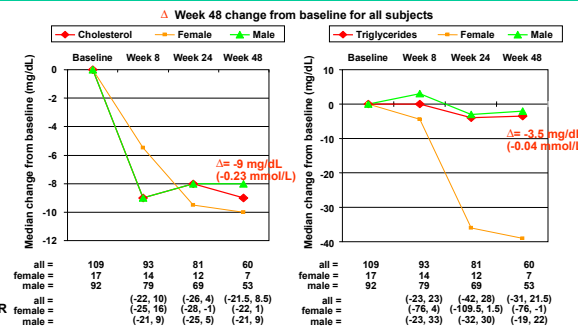


CD4+ Cell Count Changes (ITT obs)

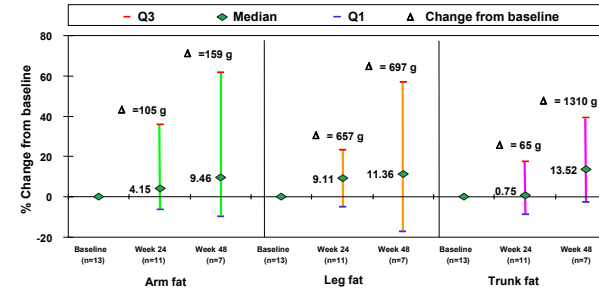


- ### Safety
- 18 subjects (15%) experienced grade 3 or 4 adverse events
 - 14 subjects (11%) experienced treatment-emergent grade 3 or 4 laboratory abnormalities
 - 11 (9%) subjects experienced treatment-related adverse events leading to premature discontinuation from study: abacavir hypersensitivity (8), nausea/vomiting/headache (1), nausea/vomiting (1), mood swings (1)
- ### Suspected ABC Hypersensitivity Results
- Suspected ABC hypersensitivity occurred in 8 subjects (6.5%): 3 female and 5 male (3 whites; 2 hispanics; 3 blacks)
 - All cases of suspected ABC hypersensitivity reaction occurred within the first 3 weeks of study drug administration.
 - All cases resolved without sequelae after discontinuation of ABC.

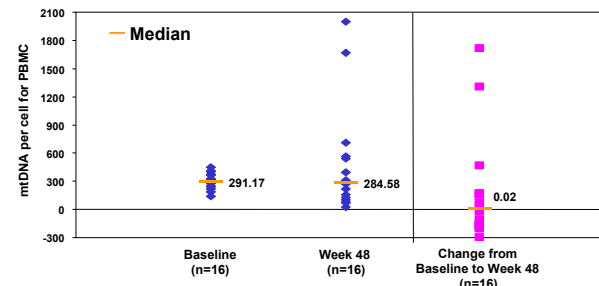
Fasting Lipid Changes



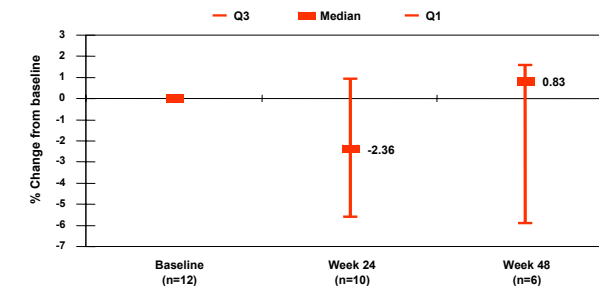
Body Composition Changes by Dexa



Mitochondrial DNA in PBMC



Lumbar Bone Mineral Density (BMD) Changes



Metabolic Changes at Week 48

- Fasting total cholesterol, LDL-cholesterol, and triglycerides values decreased from baseline to week 48, while HDL-cholesterol changes were minimal.
- Gender-related and ethnic group differences (data not shown) in lipid parameters were observed but might not be representative due to the small sample sizes.
- Arm, leg, and trunk fat increased from baseline to week 48 in a subset of patients.
- Mitochondrial DNA levels in PBMC were unchanged from baseline to week 48 in a subset of patients.
- Lumbar BMD was relatively stable in a subset of patients.

Lipid Changes with ABC and TDF

	ΔFrom BL to 48 weeks (ABC+3TC+ZDV)+TDF COL40263, Cohen et al., 2005	ΔFrom BL to 96 weeks (ABC+3TC+ZDV) ESS40002, Kumar et al., 2003
Triglycerides	-3.5 mg/dL (-0.04 mmol/L) n=60	75.2 mg/dL (0.85 mmol/L) n=44
Total Cholesterol	-9 mg/dL (-0.23 mmol/L) n=60	11.9 mg/dL (0.31 mmol/L) n=44
LDL C	-9 mg/dL (-0.23 mmol/L) n=59	-8 mg/dL (-0.21 mmol/L) n=44
HDL C	1 mg/dL (0.03 mmol/L) n=59	4.6 mg/dL (0.12 mmol/dL) n=44

	ΔFrom BL to 144 weeks (TDF+3TC+EFV) GS-903, Gallant et al. 2004
Triglycerides	1 mg/dL (0.01 mmol/L) n=170
Total Cholesterol	30 mg/dL (0.78 mmol/L) n=170
LDL C	14 mg/dL (0.36 mmol/L) n=169
HDL C	9 mg/dL (0.23 mmol/dL) n=168

Discussion

- In ART-naïve subjects, TZV + TDF QD provided virologic suppression for subjects who remained on therapy.
- The virologic response rates at 48 weeks for the ITT M=F analysis (41% <50 c/mL and 50% <400 c/mL) were low due to the high rate of premature discontinuations.
- Unlike the poor virologic responses documented in previous studies using ABC and TDF (Farthing 2003; Jemsek 2003; Gallant 2003), only 11% of subjects discontinued the study for virologic non-response.
- The rate of suspected abacavir hypersensitivity reaction is similar to previously reported rates in clinical trials using twice-daily or once-daily dosing of abacavir.
- TZV + TDF had a favorable effect on fasting lipid parameters, suggesting a synergistic effect, but further study with longer follow-up is needed.
- Data suggest neither appendicular fat loss nor bone loss were observed in a subset of patients.

Conclusion

- TZV + TDF has potential clinical utility as a PI- or NNRTI-sparing regimen.
- Given the need for simple regimens with fewer drug interactions, a fully powered study is needed to establish the role of a quadruple NRTI regimen for initial HIV treatment for a number of reasons, including the need for additional therapeutic options for:
 - Women of childbearing potential
 - Patients with psychiatric illnesses
 - Hepatitis B or C co-infected patients
 - Patients on TB medications with rifampin-based therapy

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