

# EFFECT OF ATAZANAVIR (ATV) ON SERUM CHOLESTEROL (CH) AND TRIGLYCERIDE (TG) LEVELS IN HIV-INFECTED INFANTS, CHILDREN, AND ADOLESCENTS: PEDIATRIC AIDS CLINICAL TRIALS GROUP (PACTG) 1020A

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## ABSTRACT

**Background:** Elevation of CH and/or TG is a well-documented side effect of HAART. Treatments (trt) with minimal impact on CH/TG are needed as long-term regimens are considered. PACTG 1020A is a prospective open label, non-randomized Phase III study of ATV, in combination with 2 NRTIs, in HIV-infected children. It is designed to determine the safety, PK, & optimal dosage of ATV powder & capsules.

**Objective:** To evaluate the effect, as measured by percent change from baseline values of ATV+2NRTIs on non-fasting CH/TG at wks 24 & 48 of treatment.

**Methods:** Antiretroviral naive & experienced children with ATV pheno-susceptibility (ATV IC50 fold change < 10) and HIV-RNA > 5000 cps/mL, ages 9-12-21y are eligible. Starting dose of ATV was 310 mg/m<sup>2</sup> daily which was adjusted upward if pre-sat PK criteria were not met. At wks 24&48, percentage (%) change from baseline was assessed for TG/CH. Patients with missing baseline TG/CH were excluded in the analysis, as were early discontinuations (< 8wks). Possible effects of previous ARV exposure (exp) were tested, i.e., median % changes in TG/CH were compared for Naive vs Experienced patients (Kruskal-Wallis Test). At wks 24/48, the following are presented for TG/CH: median % change, n, 25th & 75th percentiles, p-value (Wilcoxon Matched Pairs Signed-Rank Test). Spearman Correlation evaluated if the patient's last recorded % changes in TG/CH were related to time on ATV.

**Results:** To date, 63 pts have enrolled & received ATV. Previous ARV exp had no significant effects on both TG/CH (p-values: wk 24: TG (p=.17), CH (p=.46), wk 48: TG (p=.65), CH (p=.29)). Thus, data were pooled. At baseline, median CH=139 (n=54, range 71-241); TG=115 (n=55, range 31-401). There was no significant change from baseline in TG or CH through wk 48.

	wk	Percent (%) Change from Baseline				Rate of Elevated CH	
		N	Med	[25th, 75th %]	p-value	wk ≥ 180	≥ 200
CH	24	40	2.2	[-4.0, 12.8]	.08	24	2/40
	48	32	1.6	[-4.6, 10.7]	.28	48	4/32
	24	42	-14.6	[-41.3, 36.5]	.93		
TG	48	33	10.0	[-27.6, 30.2]	.44		

Spearman Corr showed that there were no significant association between TG/CH changes & the time on ATV (TG: n=55, r=.20, p=.14; CH: n=54, r=.08, p=.54).

**Conclusions:** At 24&48 wks, trt with ATV in combination with 2 NRTIs had no significant effect on serum CH or TG. This offers a potential advantage of ATV-containing regimens, awaiting further safety & dosing info from 1020A.

## BACKGROUND

- Combination therapy (CT) has resulted in significant improvement in survival, and decreased morbidity, among the HIV-infected pediatric population.
- With treatment success has come awareness of long-term side effects of antiretroviral medications.
- One of the common side effects of CT noted among HIV-infected adults, and to a smaller extent in HIV-infected children and adolescents, has been the lipodystrophy syndrome.
- Part of the lipodystrophy syndrome has been a significant elevation of serum TG and CH levels, with, in adults, a possible increased risk of heart disease.
- ATV is a novel PI, FDA approved for use in adults. Adult data suggests ATV has a minimal impact on serum TG and CH.

## METHODS

### P1020A STUDY DESIGN

- Phase III study of ATV, in combination with 2 NRTIs, in HIV-infected children, Naive and Experienced;
- Designed to determine the Safety, PK, & optimal dosage of ATV powder & capsules;
- Eight (8) Groups based on Age/Formulation
- Part A - ATV (Completed Domestic Accrual); Groups 1-4
- Part B - ATV + Ritonavir (RTV) boosting; Groups 5-8

### DOSING

- Starting dose of ATV: 310 mg/m<sup>2</sup> daily
- Adjusted if pre-sat PK criteria were not met

### SUBJECTS & ELIGIBILITY

- ARV Naive & Experienced children
- Experienced: ATV Phenotypic Susceptibility; ATV IC50 Fold Change < 10
- HIV-RNA > 5,000 cps/ml
- Ages 9-12 years – 21 years

### STATISTICAL METHODS

- Analyses were performed on stage A (domestic) patients who received ATV with no RTV boost.
- Weeks 24, 48: calculated TG and CH percentage (%) change from baseline.
- Patients excluded: (i) with missing baseline TG/CH; and (ii) early discontinuations (< 8wks)
- Possible effects of previous ARV exp were tested (using Kruskal-Wallis), i.e., Naive vs Experienced  
 → baseline TG/CH  
 → median % changes in TG/CH at wks 24, 48
- Weeks 24, 48: Overall median % change, n, 25th & 75th percentiles, p-value (Wilcoxon Matched Pairs Signed-Rank Test).
- Spearman Correlation: patient's last recorded % changes in TG/CH were related to time on ATV.
- Frequency tables showing # of patients with CH ≥ 180, CH ≥ 200 at baseline, weeks 24, 48

### BASELINE DEMOGRAPHICS

Total Accrued n=63

ON RX: n=32 (median=128 weeks); OFF RX: n=31 (median=26 weeks)

Gender	Male 32 (51%); Female 31 (49%)
Race	White 9 (14%); Black 28 (44%); Hispanic 26 (41%)
Drug History	Exp 53 (84%); Naive 10 (16%)
Age (yrs)	median=10; Range (0, 20)
CD4 Count*	median=427; Range (0, 1511)
CD4 %*	median=20; Range (0, 46)
Log <sub>10</sub> RNA	median=4.6; Range (3.5, 6.5)

\* (1) patient with missing value

## RESULTS

### CHOLESTEROLS

Table 1

#### Baseline Cholesterol Naive vs Experienced

(excluding patients with 4 missing baseline & 5 early disc)

ARV History	n	median	min	max
Experienced	40	139	71	241
Naive	5	129	115	158

Kruskal-Wallis Test: p-value = 0.48

Table 3

#### Cholesterol % Change From Baseline

##### Naive vs Experienced

Week	ARV History	N	Median	p-value
24	Experienced	37	3.0	.46
	Naive	3	0.0	
48	Experienced	30	1.9	.29
	Naive	2	-3.5	

Note: ARV drug history did not have significant effects on CH % changes from baseline. Thus, data were pooled.

Table 5

#### Overall Rates of Elevated Cholesterol Levels

Week	≥ 180	≥ 200
0	4/54 (7%)	2/54 (4%)
24	3/40 (8%)	1/40 (2%)
48	4/32 (12%)	1/32 (3%)

#### Time on ATV and Last Recorded % Changes in TG/CH

TG:	n=55	r = 0.20	p-value = 0.14
CH:	n=54	r = 0.08	p-value = 0.54

Note that only a very small proportion of patients had elevated CH at weeks 24 and 48.

### TRIGLYCERIDES

Table 2

#### Baseline Triglyceride Naive vs Experienced

(excluding patients with 3 missing baseline & 5 early disc)

ARV History	n	median	min	max
Experienced	50	109.5	31	401
Naive	5	119.0	104	226

Kruskal-Wallis Test: p-value = 0.30

Table 4

#### Triglyceride % Change From Baseline

##### Naive vs Experienced

Week	ARV History	N	Median	p-value
24	Experienced	38	-18.3	.17
	Naive	4	28.8	
48	Experienced	31	10.0	.85
	Naive	2	-8.7	

Note: ARV drug history did not have significant effects on TG % changes from baseline. Thus, data were pooled.

Table 6

#### Triglycerides and Cholesterol Week 24, 48

	Percent (%) Change from Baseline				
	wk	N	Median	[25th, 75th %]	p-value
CH	24	40	2.2	[-4.0, 12.8]	.08
	48	32	1.6	[-4.6, 10.7]	.28
TG	24	42	-14.6	[-41.3, 36.5]	.93
	48	33	10.0	[-27.6, 30.2]	.44

NOTE: No significant change from baseline in TG or CH through wk 48.

### Cholesterols

- The median baseline CH were not significantly different for Naive (129) versus Experienced (139) patients (p-value=0.48 (Table 1)).
- At both weeks 24 and 48, Kruskal-Wallis test results showed that there was not sufficient evidence to say that the median CH percent changes from baseline significantly differed for Naive versus Experienced patients (Table 3). Thus, the data were pooled for all patients, regardless of their previous drug experience (Table 6).
- Pooled CH Results**
- At week 24, the median CH percent change from baseline was 2.2% (25th Percentile=-4.05, 75th Percentile=12.75), (p-value=0.08, Wilcoxon Matched Pairs Signed-Rank Test).
- At week 48, the median CH percent change from baseline was 1.6% (25th Percentile=-4.6, 75th Percentile=10.7) (p-value=0.28, Wilcoxon Matched Pairs Signed-Rank Test).

### Triglycerides

- The median baseline TG were not significantly different for Naive (119) versus Experienced (109.5) patients (p-value=0.30 (Table 2)).
- At both weeks 24 and 48, Kruskal-Wallis Test results showed that there was not sufficient evidence to say that the median TG percent changes from baseline significantly differed for Naive versus Experienced patients (Table 4). Thus, the data were pooled for all patients, regardless of their previous drug experience (Table 6).
- Pooled TG Results**
- At week 24, the median TG percent change from baseline was -14.6% (25th Percentile=-41.3, 75th Percentile=36.5), (p-value=0.93, Wilcoxon Matched Pairs Signed-Rank Test).
- At week 48, the median TG percent change from baseline was 10% (25th Percentile=-27.6, 75th Percentile=30.2), (p-value=0.44, Wilcoxon Matched Pairs Signed-Rank Test).

## CONCLUSIONS

- At 24 and 48 weeks of therapy, treatment with ATV in combination with 2 NRTIs had no significant effect on serum TG or CH levels.
- ATV is an important addition to the PI class of ARV agents, and with its lack of effect on serum lipids should be considered for patients at increased risk of cardiovascular disease.
- ATV's effect on TG/CH, when boosted by RTV, in pediatric HIV-infected patients is currently under investigation.