P1063: Phase I/II Safety And Efficacy Investigation of Atorvastatin for Treatment of Increased LDL Cholesterol in HIV-infected Children and Adolescents

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Primary aim

To evaluate the safety and efficacy (based on direct LDL-cholesterol levels) of escalating doses of atorvastatin in HIV-1-infected children treated with combination antiretroviral treatment regimens.

- Grade 3-4 toxicities, LDL-cholesterol at weeks 12, 24 and 48.

Secondary aims

- To evaluate changes from baseline in fasting total cholesterol, triglycerides, HDL cholesterol, ApoA1 and B, and lipoprotein (a) after initiation of atorvastatin.
- To evaluate changes from baseline in inflammatory-associated cardiac risk markers (e.g. high-sensitivity CRP) after initiation of atorvastatin.
- To describe the pharmacokinetics of atorvastatin when administered concurrently with protease inhibitors.
- To evaluate changes from baseline in plasma HIV-1 RNA levels after initiation of atorvastatin.

Study status

- Opened for enrollment in June 2009
  - Version 2.0 – May 2010- expanded age range, lowered LDL-C entry criterion, removed PI requirement
- Study closed in February 2014
- Primary manuscript in press PIDJ
- Awaiting contract for atorvastatin levels for secondary manuscript

Methods

- HIV-infected youth aged 10- <24 years
  - On stable ART
  - LDL-C ≥ 130 mg/dL for ≥ 6 months
- Started 10mg atorvastatin once daily
  - Increased to 20 mg if LDL-C decreased < 30% from baseline or was > 110 mg/dL at week 4
- Fasting lipids and safety labs at screening, entry, weeks 4, 8(safety labs only), 12, 24 and 48
- Apo A1, B, hs-CRP, IL-6 batched and run at end of the study

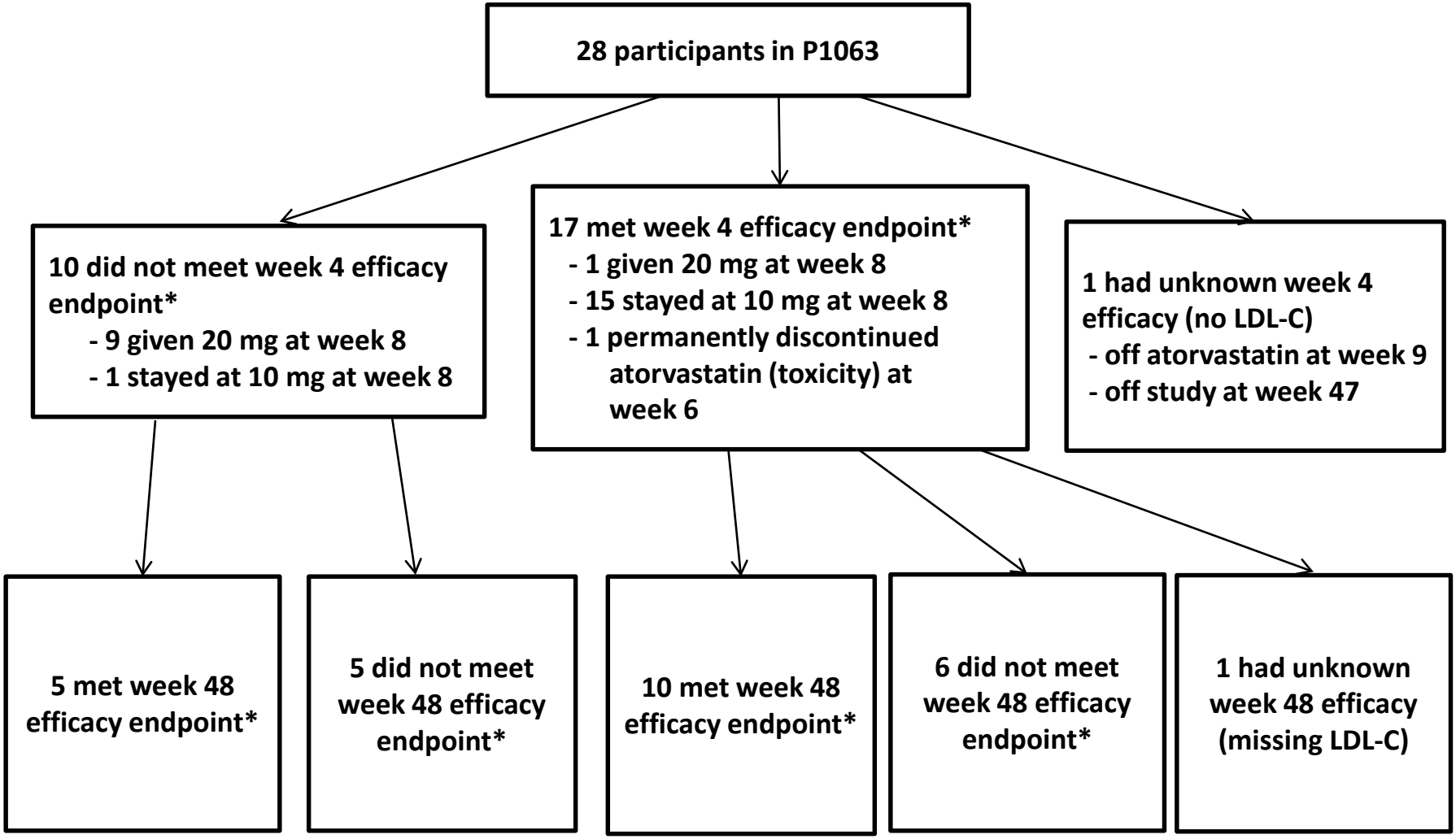
RESULTS

Baseline Characteristics N=28

		Number (%)
Age at study entry (years)	Mean (range)	17 (10-23)
Age Group	≥10 to <15 years old	7 (25%)
	15 to <19 years old	12 (43%)
	19 to <24 years old	9 (32%)
Sex	Male	9 (32%)
	Female	19 (68%)
Race/Ethnicity	White Non-Hispanic	4 (14%)
	Black Non-Hispanic	18 (64%)
	Hispanic	5 (18%)
	Asian, Pacific Islander	1 (4%)
BMI (kg/m^2) at entry	Mean (range)	25.6 (14.7-55.8)

Baseline Characteristics N=28

		Number (%)
CD4 Percent at screening	15 to <25%	2 (7%)
	≥25%	26 (93%)
HIV-1 RNA (copies/mL)	≥LLQ	8 (29%)
	<LLQ	20 (71%)
ARV regimen at entry	At least 1 PI and at least 1 NNRTI	5 (18%)
	At least 1 PI and no NNRTI	17 (61%)
	At least 1 NNRTI and no PI	4 (14%)
	Other ARV regimen	2 (7%)



*Efficacy endpoint: <110 mg/dL or ≥30% decrease in LDL-C from baseline

Safety

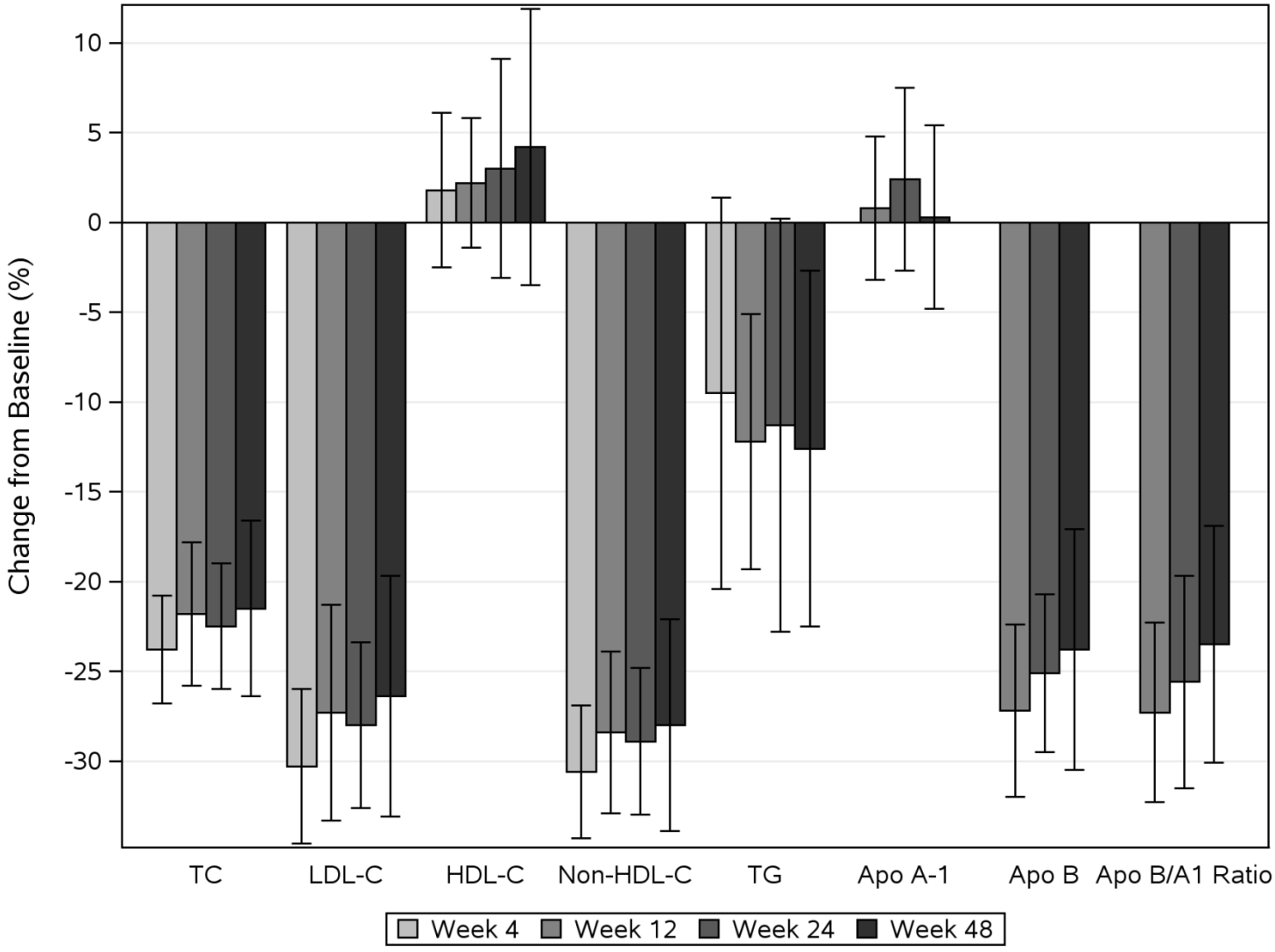
- 2 discontinued atorvastatin due to potentially related toxicity – both in the 10-15 yr age group
  - Grade 3 elevation in creatinine at week 6
  - Grade 4 ALT/AST at final study visit
- 6 non-related Grade 3 events

Lipid concentrations at baseline and changes on atorvastatin treatment

	Baseline	Wk 4	Wk 12	Wk 24	wk 48
	N=28	N=27	N=26	N=26	N=25
LDL-C (mg/dL)	162 (133, 207)	113 (74, 165) -30.3 (-34.6, -26.1)	114 (68, 179) -27.3 (-33.3, -21.4)	110 (84, 173) -28.0 (-32.7, -23.4)	115 (67, 164) -26.4 (-33.0, -19.7)
HDL-C (mg/dL)	50 (31, 77)	49 (35, 80) 1.8 (-2.5, 6.1)	50 (25, 88) 2.2 (-1.4, 5.8)	48 (36, 90) 3.0 (-3.1, 9.1)	53 (30, 84) 4.2 (-3.5, 11.9)
TC (mg/dL)	240 (179, 285)	178 (135, 235) -23.8 (-26.8, -20.8)	187 (113, 249) -21.8 (-258, -17.9)	176 (142, 261) -22.5 (-26.0, -19.0)	185 (120, 248) -21.5 (-26.4, -16.6)
Non-HDL-C (mg/dL)	186 (136, 250)	129 (86, 185) -30.6 (-34.3, -26.9)	132 (79, 181) -28.4 (-32.9, -23.9)	124 (99, 192) -28.9 (-33.0, -24.8)	130 (74, 197) -28.0 (-34.0, -22.1)
TGs (mg/dL)	124 (61, 387)	121 (38, 272) -9.5 (-20.4, 1.4)	126 (32, 390) -12.2 (-19.3, -5.1)	121 (57, 250) -11.3 (-22.8, 0.3)	111 (44, 566) -12.6 (-22.5, -2.7)

Median (Min, Max)
Mean % change (90% CI)

Mean percent change in lipid and lipoprotein concentrations from baseline during atorvastatin treatment.

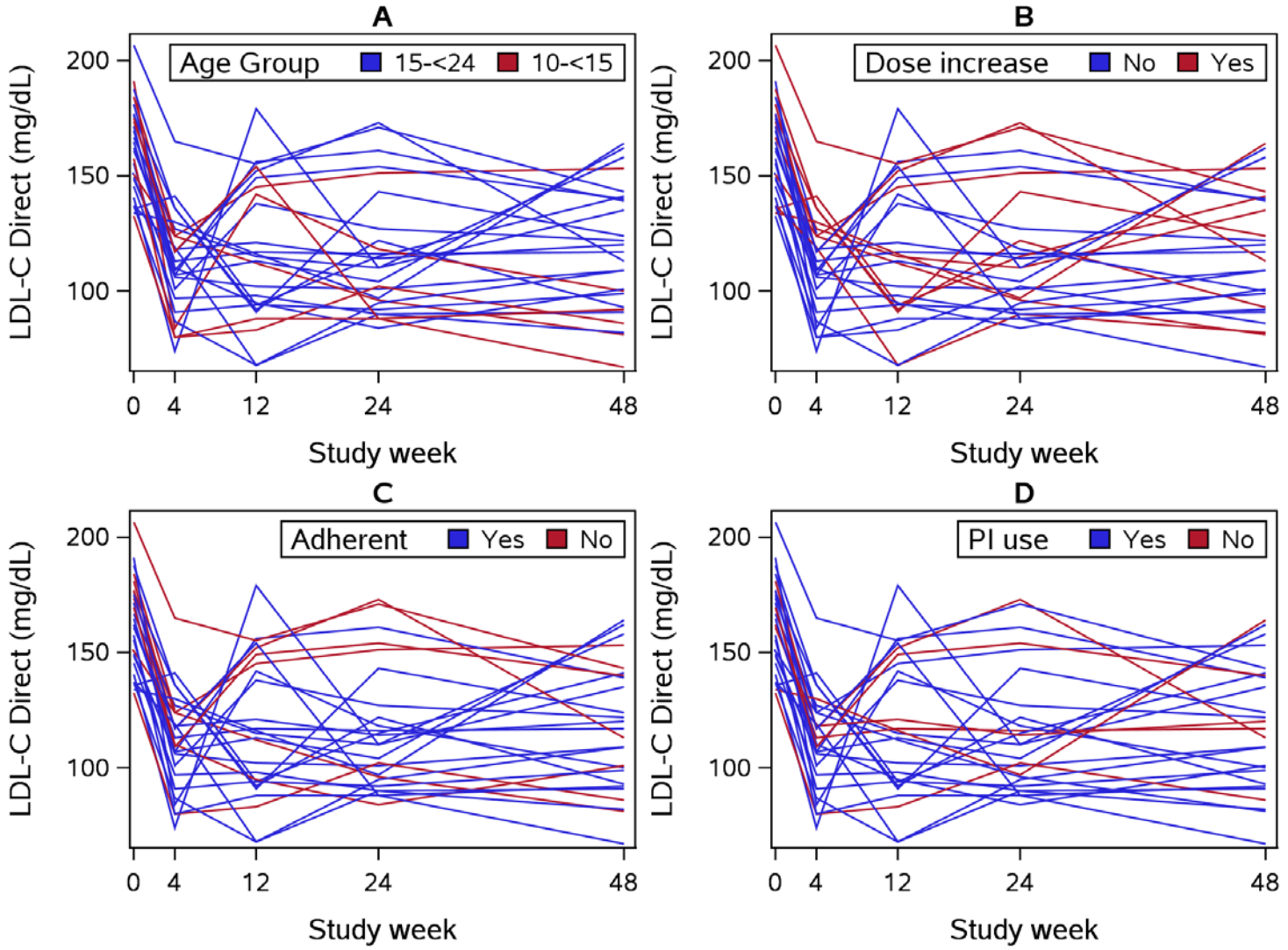


Absolute inflammatory marker concentrations before atorvastatin treatment and changes during atorvastatin treatment

	Baseline	Wk 12	Wk 24	Wk 48
	N=27	N=24	N=23	N=24
IL-6 (pg/mL)	1.66 (0.47, 7.94)	1.94 (0.51, 6.97) -1 (-32, 110)	1.36 (0.42, 4.41) -19 (-32, -5)	1.15 (0.56, 24.56) -11.5 (-34, 46)
hs-CRP (mg/L)	1.20 (0.20, 22.00)	1.00 (0.20, 20.50) 0 (-35, 44)	0.50 (0.20, 18.90) -20 (-67, 0)	0.60 (0.20, 19.30) 0 (-78, 17)

Median (Min, Max)
Median % change (90% CI)

Observed direct LDL-C concentrations over time by age group at study initiation (panel A), actual dose at week 8 (panel B), adherence assessment (panel C) and ARV treatment at study initiation (Panel D)



Conclusions

- Atorvastatin lowered TC, LDL-C, non-HDL-C and ApoB in HIV-infected youth with ART-associated hyperlipidemia
- Safety monitoring is important particularly in younger children

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