Randomized Comparison of Darunavir/r versus Atazanavir/r on Serum Lipids in HIV-infected Persons on Fully Suppressive Lopinavir/r or Fosamprenavir/r with High Serum Triglycerides

(Lopinavir/r or fosamprenavir/r switch to Atazanavir/R or Darunavir/r)

THE LARD STUDY

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Abstract

- **Background**- Lopinavir/ritonavir (LPV/r) and fosamprenavir/ritonavir (FPV/r) are HIV protease inhibitors (PIs), which have been associated with elevation of triglyceride (TG) levels. We designed a study to determine if switching virologically suppressed patients on a regimen containing LPV/r or FPV/r to either darunavir/r (DRV/r) or atazanavir/r (ATV/r) resulted in improved TGs while maintaining virologic suppression.
- **Methods**- Eligible patients had undetectable HIV RNA for ≥ 12 weeks, no history of PI resistance, were receiving LPV/r (n= 46) or FPV/r (n= 3) plus nucleosides, and had fasting TGs > 200 mg/dl. Patients were randomized to either once daily DRV/r (800mg/100mg) or ATV/r (300mg/100mg) while maintaining the same nucleoside backbone. The primary endpoint was the change in fasting TGs from baseline to week 24. Assessments included fasting lipids, HIV RNA, CD4 counts, adherence, quality of life assessments (QOL) and symptom assessment.
- **Results**- 66 patients were screened, 51 enrolled and 49 completed the study. 25 patients were randomized to DRV/r and 24 patients to ATV/r. 92% of subjects were male, 73% were white, with a mean age of 47. Mean baseline CD4 cell count was 569 cell/mm3 and HIV RNA was < 50 copies/mL in 88% of subjects. Baseline characteristics were similar in both arms. Mean baseline TGs were similar: 342 mg/dl (DRV/r) and 326 mg/dl (ATV/r). The two arms combined had a decline in TGs from baseline to week 24 by 113 mg/dl ($p<0.001$) with a non significant difference by arm: -126 mg/dl (DRV/r) and -99 mg/dl (ATV/r). At week 24, 48% of DRV/r and 50% of ATV/r subjects had TGs < 200 mg/dl. (Difference 2%, 95% CI: -30% to 34%.) Mean decrease in TGs was -311 mg/dl if baseline TGs ≥ 400 mg/dl (n = 13) and -41 mg/dl if baseline TGs < 400 mg/dl (n = 36). Total and HDL cholesterol decreased and LDL increased (all non significantly) and were similar in both arms. QOL was high at baseline (83%), remained high at week 24 (85%), and did not differ between treatment groups. Adherence was high: 97% vs 98%, DRV/r vs ATV/r. At week 24 there were no differences between the groups in CD4 cell counts or HIV RNA levels and virologic control was maintained. Both arms were well tolerated.
- **Conclusions**- Patients with well controlled HIV and high TGs who switched from LPV/r or FPV/r to once daily DRV/r or ATV/r had improvements in TGs, while maintaining virologic suppression and immunological control. QOL and adherence remained high.

Background

- The HIV protease inhibitors lopinavir/ritonavir (LPV/r) and fosamprenavir/ritonavir (FPV/r) have been associated with elevated triglycerides (TGs). In the KLEAN study, patients assigned to the FPV/r arm had similar rates of total, LDL, and HDL cholesterol elevations as those assigned to LPV/r at week 48; 8% in each arm had grade 3-4 TG elevations through 48 weeks[1]. Elevated lipid levels may lead to increased risks for cardiac events and may require the addition of lipid lowering medications.
- The protease inhibitors darunavir (DRV) and atazanavir (ATV) have been associated with low rates of hypertriglyceridemia. Studies comparing DRV/r or ATV/r with either LPV/r or FPV/r have demonstrated at least similar efficacy and fewer gastrointestinal side effects with the former agents. For example, the SLOAT trial demonstrated a benefit to changing from LPV/r to ATV/r in patients with undetectable viral loads[2].

1. Eron J, et al. *Lancet*. Aug 5 2006; 368(9534): 476-482.
2. Soriano V, et al. *J Antimicrob Chemother*. Jan 2008; 61(1): 200-205.

Hypothesis

- Changing from LPV/r or FPV/r to either DRV/r or ATV/r would result in lower and equivalent fasting TGs in both arms, while maintaining virologic control.

Objectives

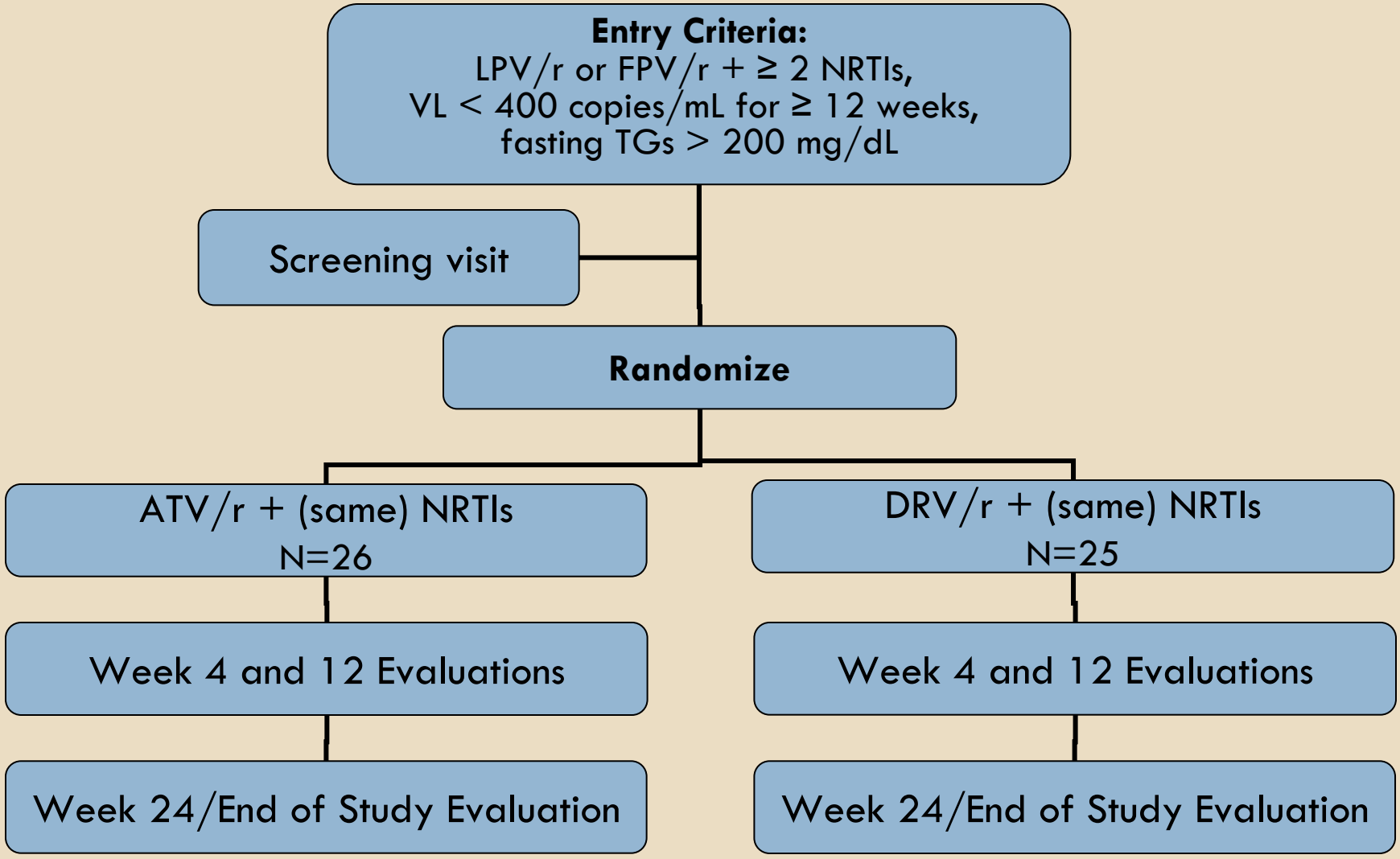
- **Primary Objective:** To compare change in fasting TGs from baseline in subjects receiving once-daily DRV/r vs. once-daily ATV/r after switching from a regimen containing either LPV/r or FPV/r.

- **Secondary Objectives:**
  - To compare:
    - cholesterol profiles (fasting total cholesterol, LDL, HDL)
    - the ability to maintain virologic suppression
    - safety/tolerability and quality of life
    - adherence
    - CD4 cell count response

Methods-1

- **Primary Eligibility Criteria**
  - Treatment with LPV/r or FPV/r + NRTIs for ≥ 12 weeks
  - Undetectable HIV viral load
  - History consistent with no protease inhibitor resistance
  - Receiving *first* protease inhibitor unless the switch to LPV/r or FPV/r was for non-virologic reasons
  - No prior use of DRV or ATV
  - Fasting triglycerides > 200 mg/dL
  - Not receiving > 20 mg/d of omeprazole or equivalent dose of proton pump inhibitor

Methods-2: Study Flow Diagram



Baseline Characteristics

	ATV/r N = 24*	DRV/r N = 25
Male, n (%)	22 (92%)	23 (92%)
Age, mean	46	48
Ethnicity, n (%)		
Caucasian	9 (38%)	12 (48%)
Hispanic	12 (50%)	7 (28%)
African-American	2 (8%)	5 (20%)
Asian	0 (0%)	1 (4%)
Other	1 (4%)	0 (0%)
CD4 Count cells/mm^3 mean (range)	554 (31-1066)	584 (249-996)
Viral Load copies/mL, median	< 50	< 50

* N=2 were randomized to ATV/r but withdrew consent at baseline. Data not included.

Baseline ARV and Concomitant Meds

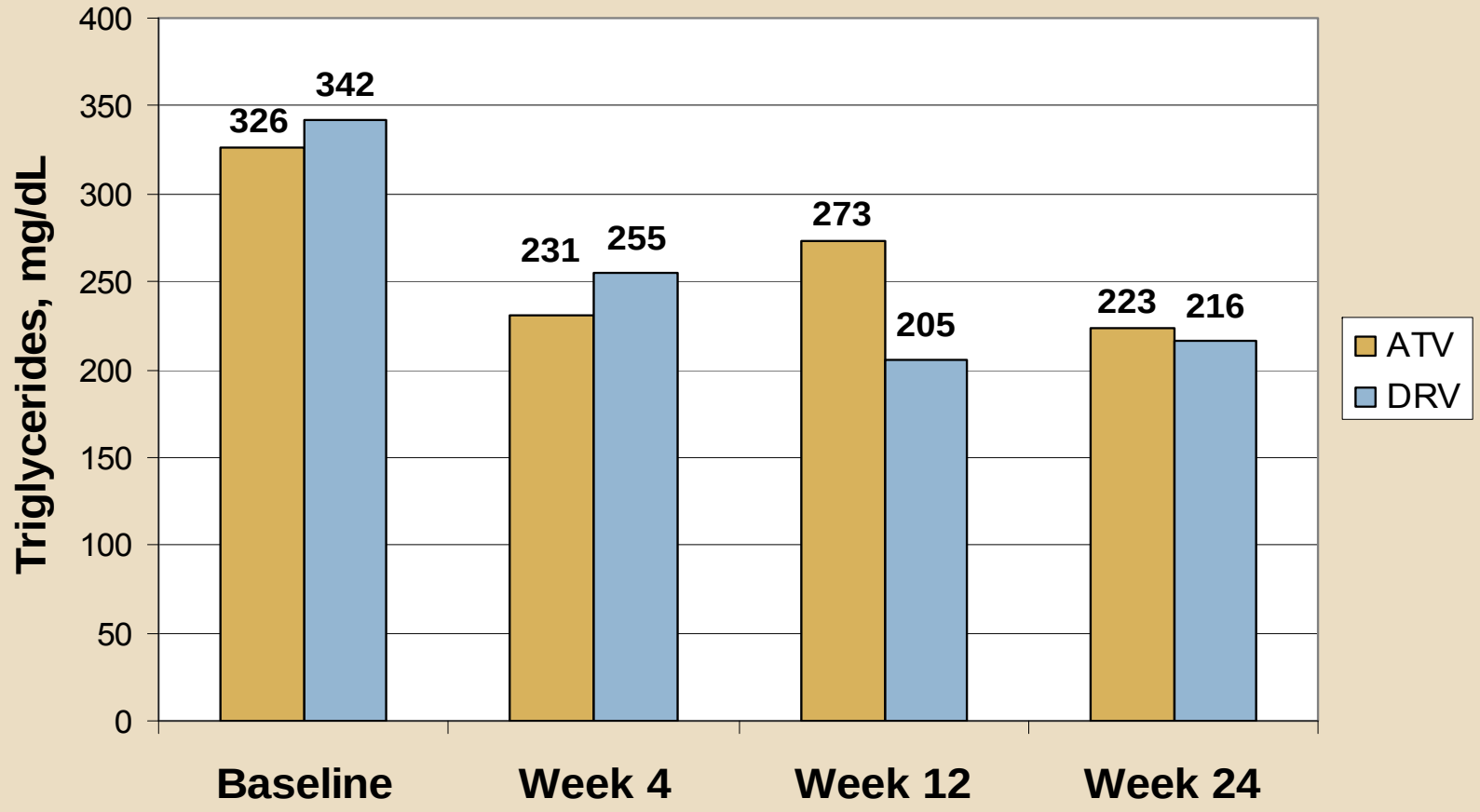
PI at Entry	ATV/r N = 24	DRV/r N = 25
LPV/r	23	23
FPV/r	1	2
NRTIs		
TDF/FTC	17	15
ABC/3TC	5	5
Other*	2	5
Lipid Lowering Meds		
Statin	3	6
Fibrate	6	5
Fish Oil	3	5
Niacin	1	0

* ABC/3TC/ZDV, ABC/3TC/TDF, ZDV/TDF/FTC, ddI/3TC, ZDV/3TC

Subjects were allowed to be on more than one lipid lowering agent.

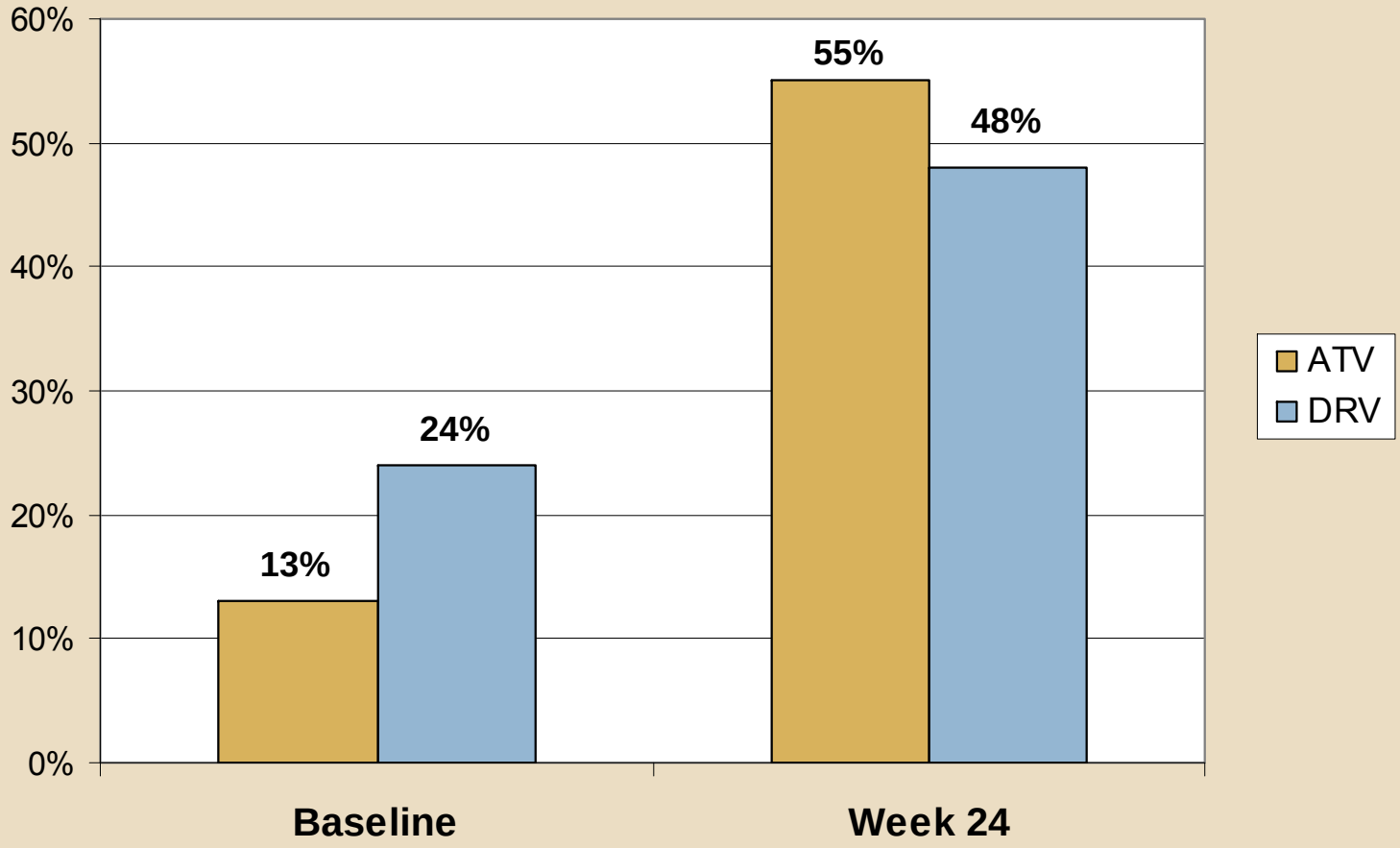
Mean Triglyceride Levels Over Time

(mg/dL)



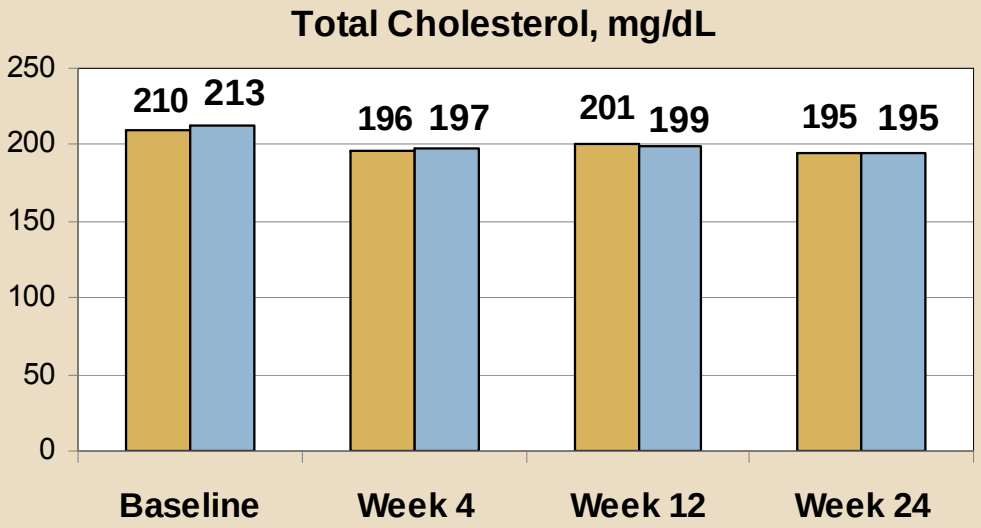
Summary: There was a significant drop in TG from Baseline to Week 24 for both ATV/r (-88 mg/dL, p=0.034) and DRV/r (-126 mg/dL, p=0.0002).

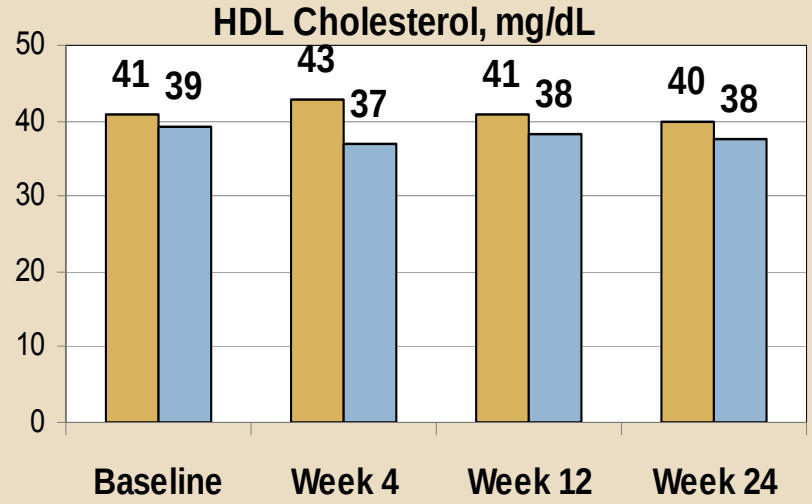
Percentage of Subjects with TGs < 200 mg/dL

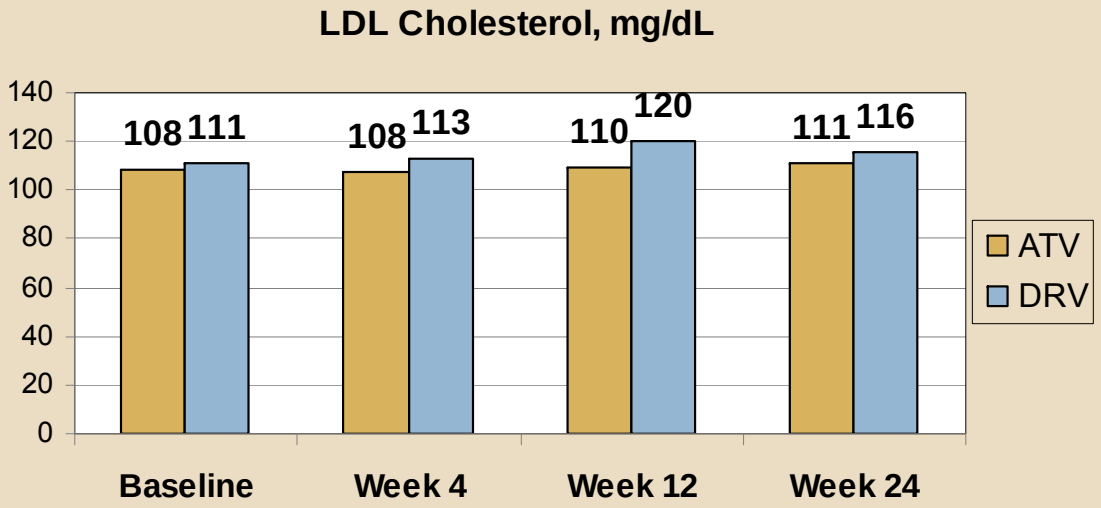


Week 24 triglycerides < 200 mg/dL were achieved in 55% of ATV/r vs 48% of DRV/r patients, (difference 7%, 95% CI: -22, +35%).

Lipid Fractions Over Time







Confirmed Viral Load < 200 copies/mL

(Discontinuation due to non-VF censored)

		ATV/r N=24*		DRV/r N=25	
		No. suppressed/ No. observations	%	No. suppressed/ No. observations	%
VL < 200	Baseline	23/23**	100%	25/25	100%
	Week 4	23/23¶	100%	25/25	100%
	Week 12	22/22†	100%	25/25	100%
	Week 24	**22/22**	**100%**	**25/25¥**	**100%**

By week 24, N=3 (N=2 on ATV/r, N=1 on DRV/r) had confirmed viral load readings > 50 copies/mL.

* N=2 randomized to ATV/r and withdrew consent at baseline. Data not included.

** N=1 with viral load missing at baseline.

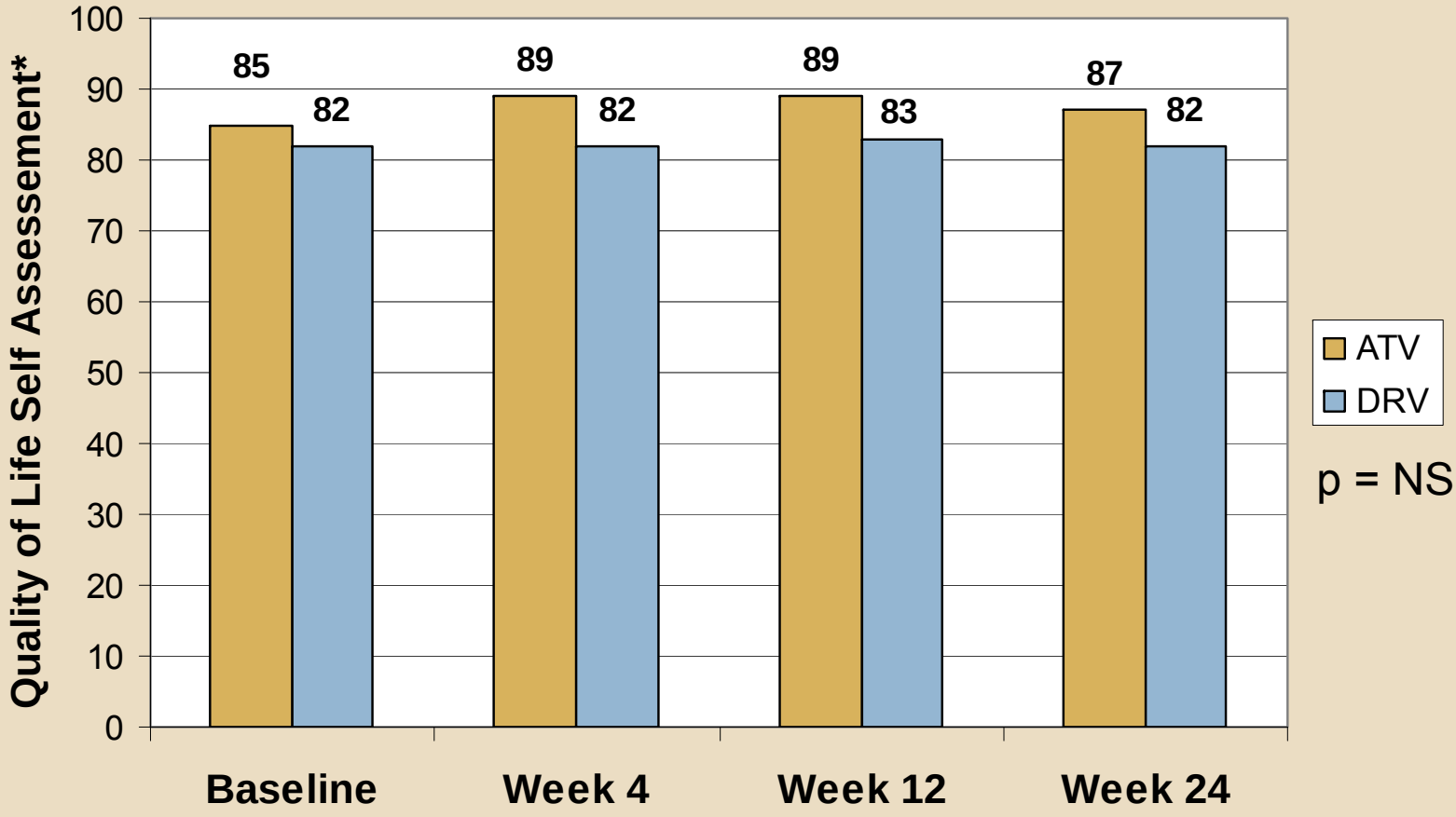
¶ N=1 discontinued due to rash prior to week 4.

† N=1 discontinued due to persistent low-level viremia prior to week 12, but did not meet the definition of virologic failure.

¥ N=1 had a viral load of 286 at week 24, but no confirmatory value was available.

Quality of Life: Mean Scores

*Question: "How would you rate your current state of health from '0' to '100'?"
0 = death or worst possible health 100 = perfect or best possible health



Results

- **Primary Endpoint:** There was a significant drop in TG from baseline to week 24 for both ATV/r (-88mg/dL) and DRV/r (-126mg/dL) arms ($p = 0.034$ and 0.0002 respectively).
  - The protocol defined sample size was 88 but study enrolled 51 - enrollment discontinued due to slow accrual. This sample size did not provide adequate power to test the hypothesis of group equivalence of no difference in the change of TG levels from baseline to week 24.

- **Secondary Endpoints:**
  - Mean CD4 counts increased in both groups: +25 on ATV/r; +12 on DRV/r
  - Mean self-reported adherence, by M-MASRI, was high in both arms:
    - 98% for ATV/r, 97% for DRV/r.

Adverse Events

	ATV/r N = 24	DRV/r N = 25
Serious AEs*	**2**	**1**
Total AEs	**47**	**46**
No. patients with AEs	**20**	**20**
Grade 2¶ and 3† AEs		
URI	5	5
Skin Rash	1	2
Erectile Dysfunction	2	0
Nausea/Vomiting	1	0
Increased Bilirubin/jaundice	1	0
Cervical Adenopathy	1	0
Pyelonephritis	0	1

* There were 2 serious AEs on ATV/r, in 2 patients (possible bowel obstruction and alcohol withdrawal/suicidal ideation). There was 1 serious AE on DRV/r (pyelonephritis).

¶ Grade 2 AEs occurring more than once on either arm reported.

† Grade 3 AEs: ATV/r: N=4 (nausea/vomiting, rash, increased bilirubin, cervical adenopathy)
DRV/r: N=1 (pyelonephritis)

LARD Study: Conclusions

- Patients with TG > 200 mg/dL on LPV/r or FPV/r demonstrated a significant decline in TG when switched to either:
  - ATV/r: -88mg/dL (p=0.034)
  - DRV/r: -126 mg/dL (p=0.0002)
  - Study enrollment had inadequate power to compare the arms for the change in triglycerides from baseline
- Similar % on ATV/r (55%) and DRV/r (48%) achieved a TG <200 mg/dL by week 24.
- Virologic suppression was maintained in both arms.
- CD4 cell counts were stable.
- Quality of life and adherence remained high in both arms.
- Drug-related adverse event rates were low in both arms.

List of Site PIs (alphabetical)

- Nicholaos Bellos MD, Dallas, TX
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- Edwin DeJesus MD, Orlando Immunology Center (OIC), Orlando, FL
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- Andrew Petroll MD, Medical College of Wisconsin Dept. of Medicine, Division of ID, Milwaukee, WI
- Frank Rhame MD, Abbott Northwestern Clinic Infectious Diseases and Travel Clinic, Minneapolis, MN
- Daniel Skiest MD, Baystate Medical Center, Springfield, MA
- Marc Tribble MD, Baylor University, Dallas, TX
- Thanes Vanig MD, Spectrum Medical Group, Phoenix, AZ

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