

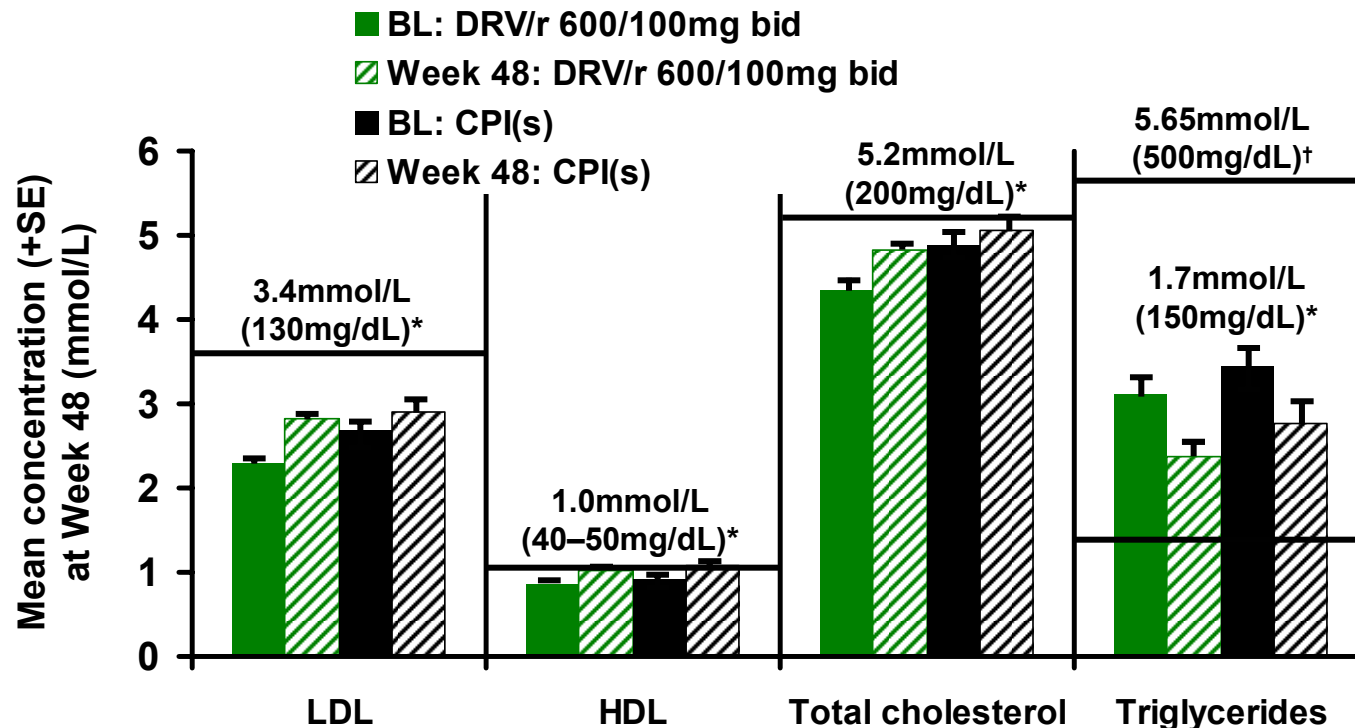
**Similar changes in metabolic parameters
of darunavir and atazanavir, each coadministered
with low-dose ritonavir
in healthy volunteers (TMC114-C159)**

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Laboratory values of interest: lipid levels at Week 48 (POWER 1 and 2)



DRV/r = darunavir with low-dose ritonavir (RTV); LDL = low density lipoprotein; HDL = high density lipoprotein

*Normal lipid levels and [†]very high triglyceride levels taken from the Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (JAMA.2001;285:2486–97) Lazzarin A, et al. 16th IAC 2006. Abstract TUAB0104

Objectives

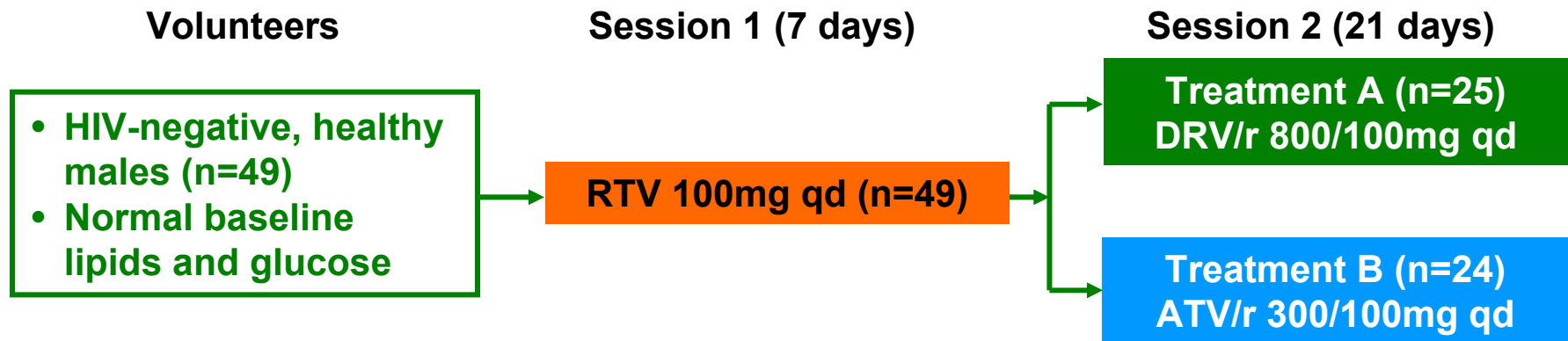
- **Primary objective**

- to assess the effects of RTV-boosted darunavir (DRV/r) qd on lipid and glucose metabolism compared with those of RTV-boosted atazanavir (ATV/r) qd

- **Secondary objective**

- to evaluate the short-term safety and tolerability of DRV/r compared with ATV/r

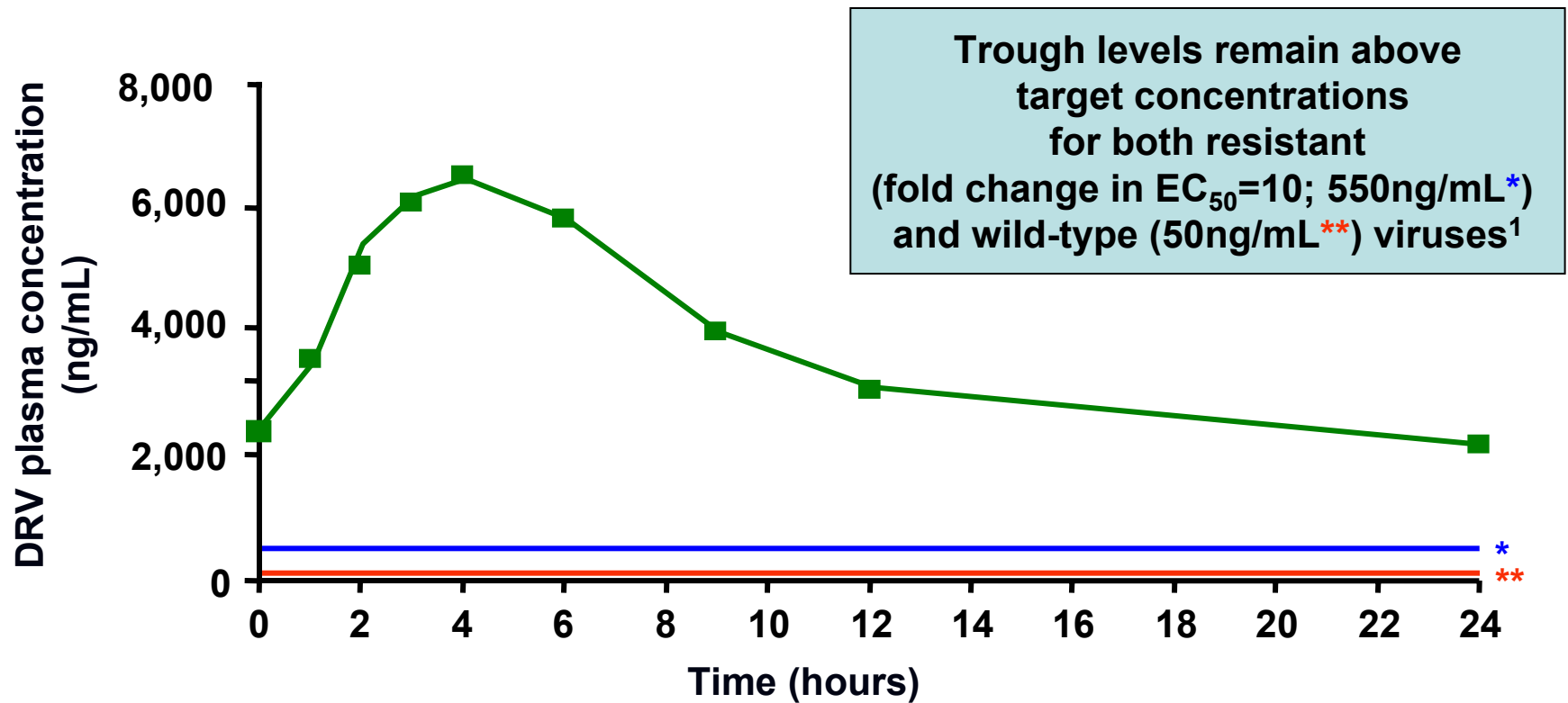
TMC114-C159: trial design



- **Setting and testing**

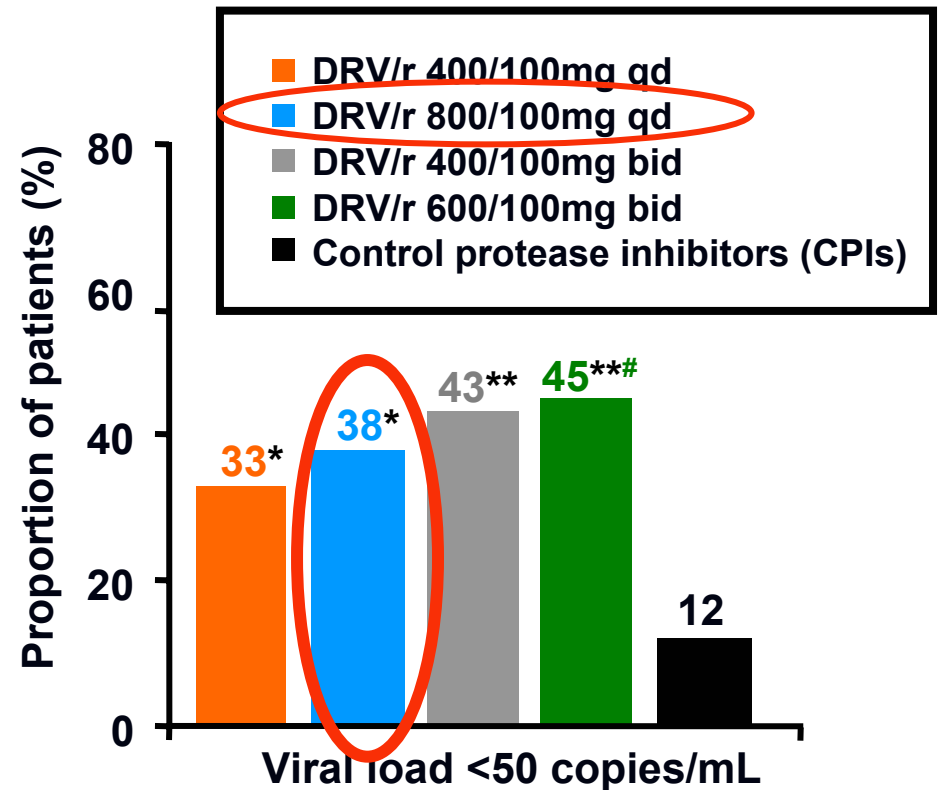
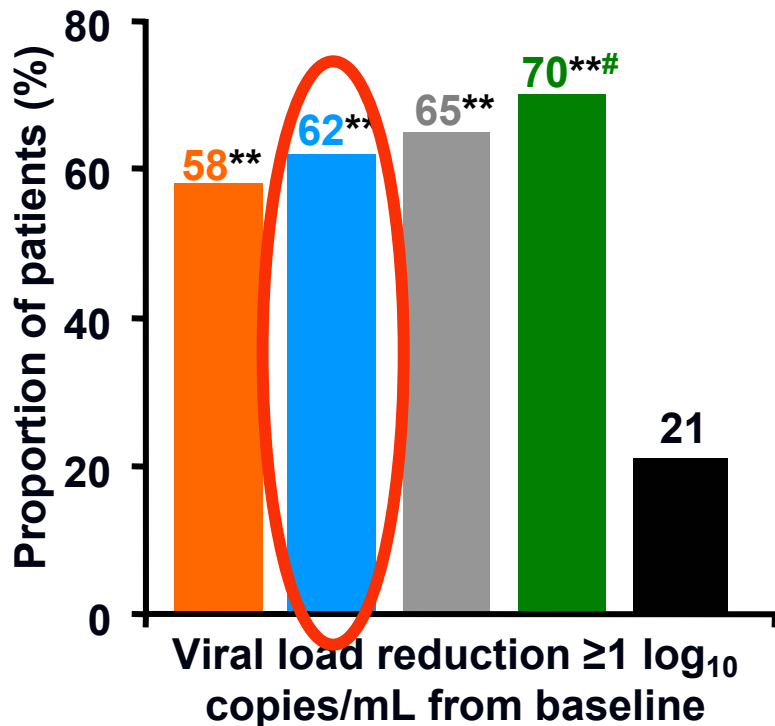
- inpatient unit
- medication was taken under fed conditions; meals were standardized for protein, fat and carbohydrate content

DRV/r 800/100mg qd: DRV plasma concentration-time profile



- DRV/r 800/100mg qd under development for use in treatment-naïve patients

POWER 1 and 2: Week 24 virologic response (ITT-TLOVR)



ITT-TLOVR = intent-to-treat, time to loss of virologic response

*p<0.05 in POWER 1¹ and 2² versus CPI(s)

**p<0.001 in POWER 1¹ and 2² versus CPI(s)

#p<0.05 in POWER 2 versus 400/100mg qd²

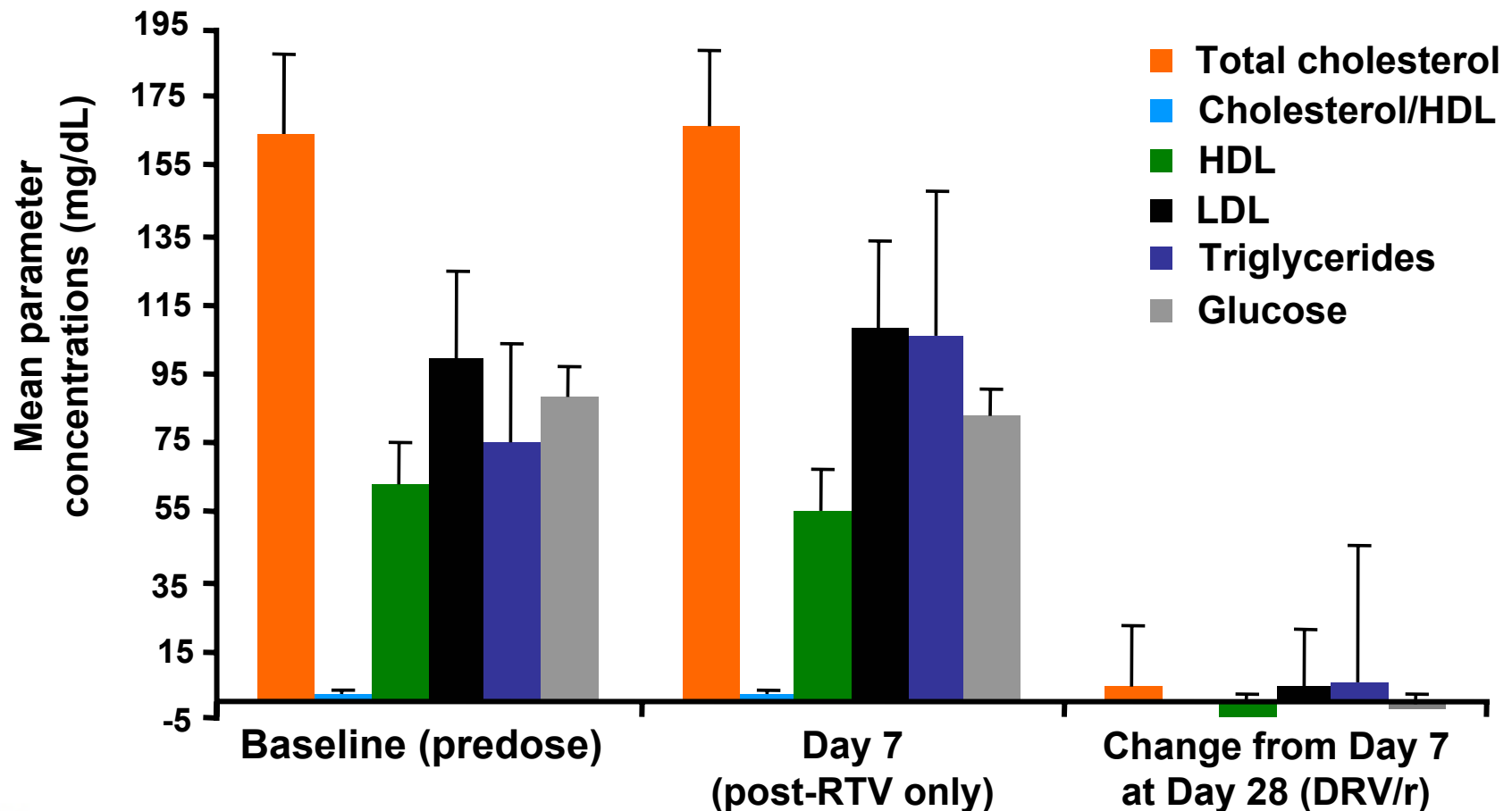
1. Katlama C, et al. 3rd IAS 2005. Abstract WeOaLB0102

2. Wilkin T, et al. 45th ICAAC, 2005. Abstract H-413

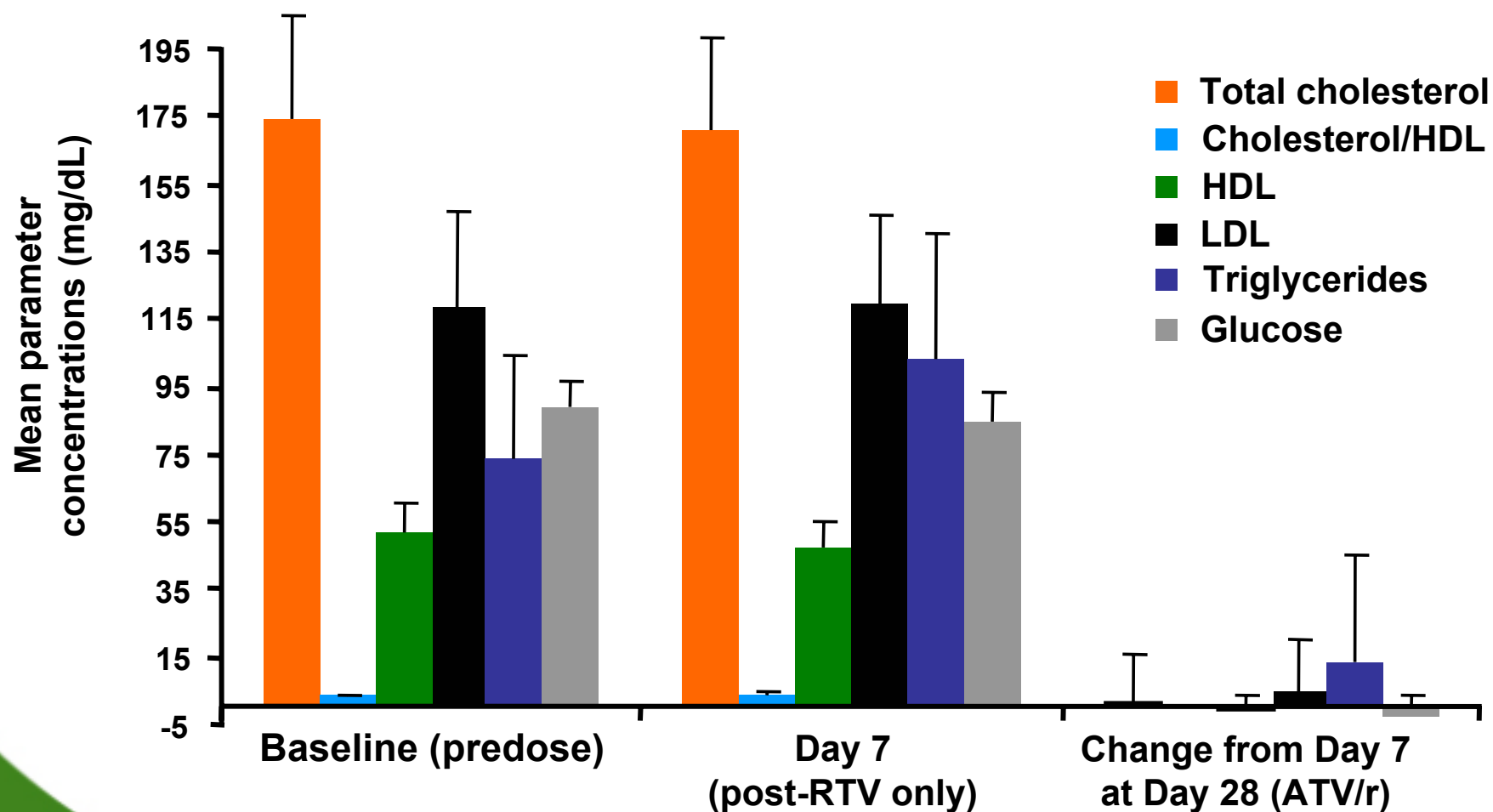
TMC114-C159: demographics and patient disposition

Demographics	DRV/r (n=25)	ATV/r (n=24)
Male, n (%)	25 (100)	24 (100)
Caucasian, n (%)	18 (72)	19 (79)
Median age, years (min; max)	25 (18; 47)	31 (18; 53)
Median weight, kg (min; max)	73 (50; 99)	73 (54; 84)
Median body mass index, kg/m ² (min; max)	23 (18; 27)	22 (19; 27)
Patient disposition, n (%)		
Completed study	22 (78)	23 (96)
Discontinued	3 (12)	1 (4)
Adverse event (AE)	2 (8)	0
Withdrew consent	1 (4)	1 (4)

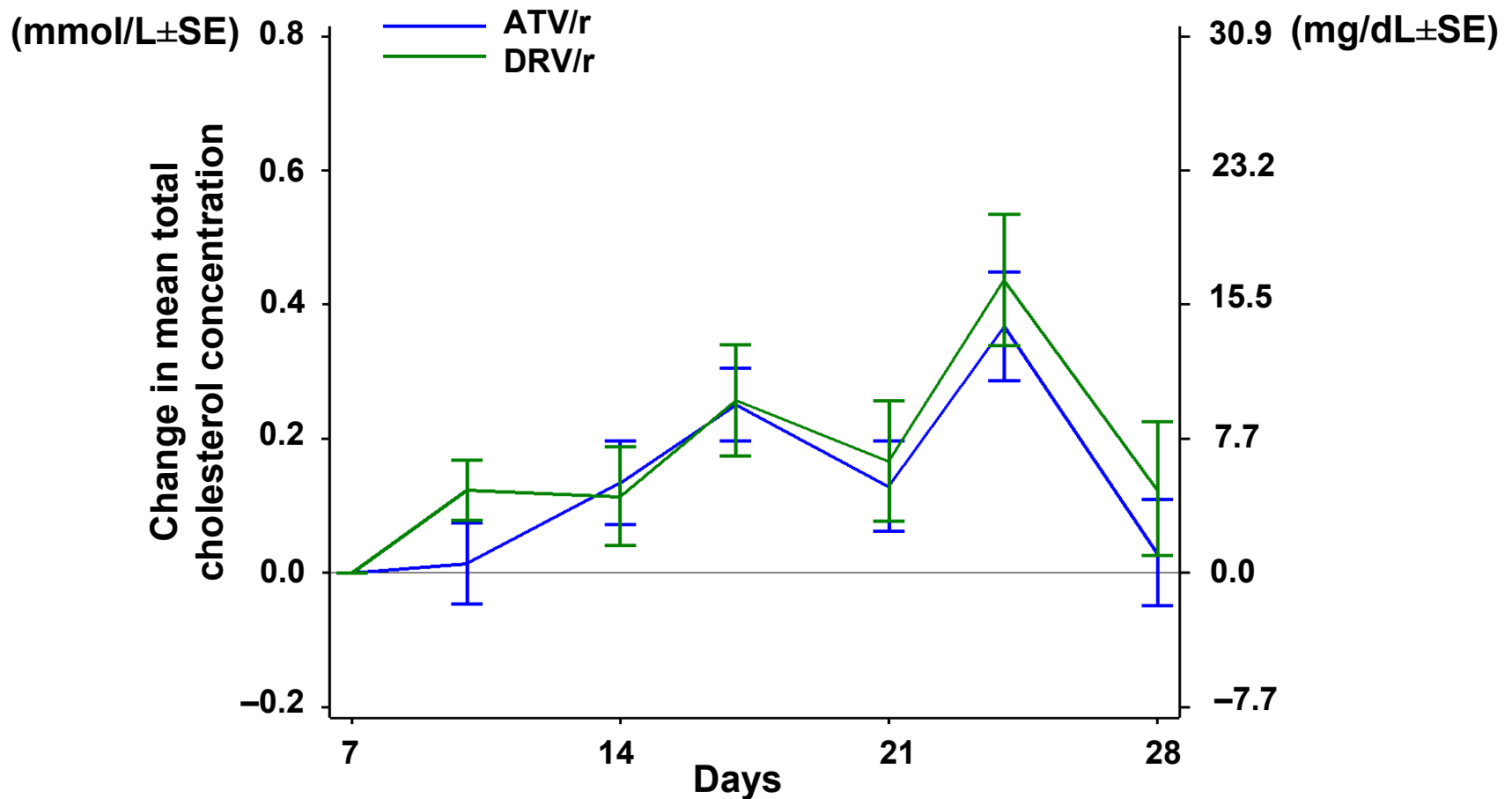
Levels of and changes in lipid and glucose parameters: DRV/r



Levels of and changes in lipid and glucose parameters: ATV/r



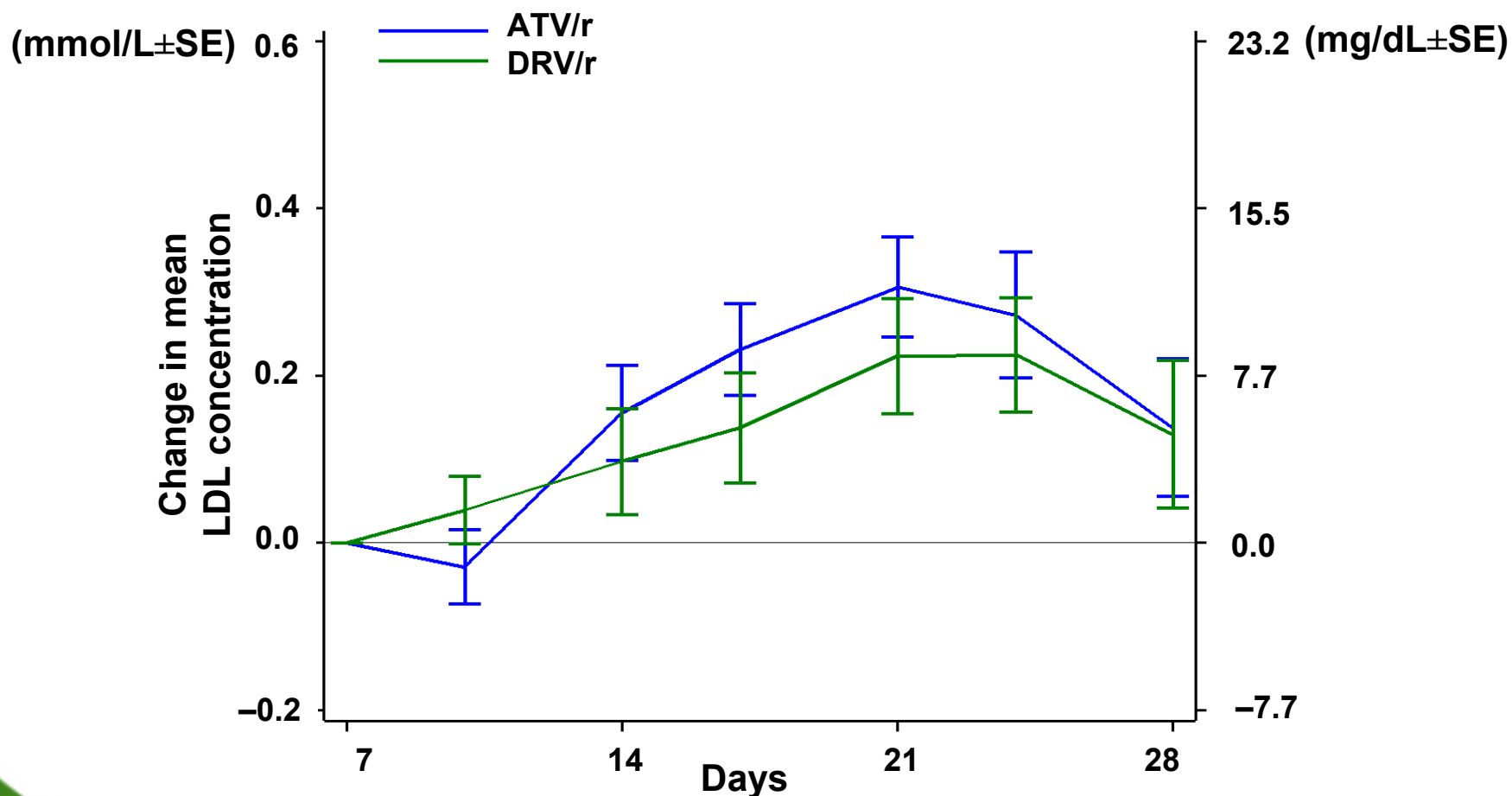
Total cholesterol: changes during treatment with DRV/r or ATV/r



ATV/r n=24	24	24	24	23	23	23
DRV/r n=25	25	25	25	23	22	22

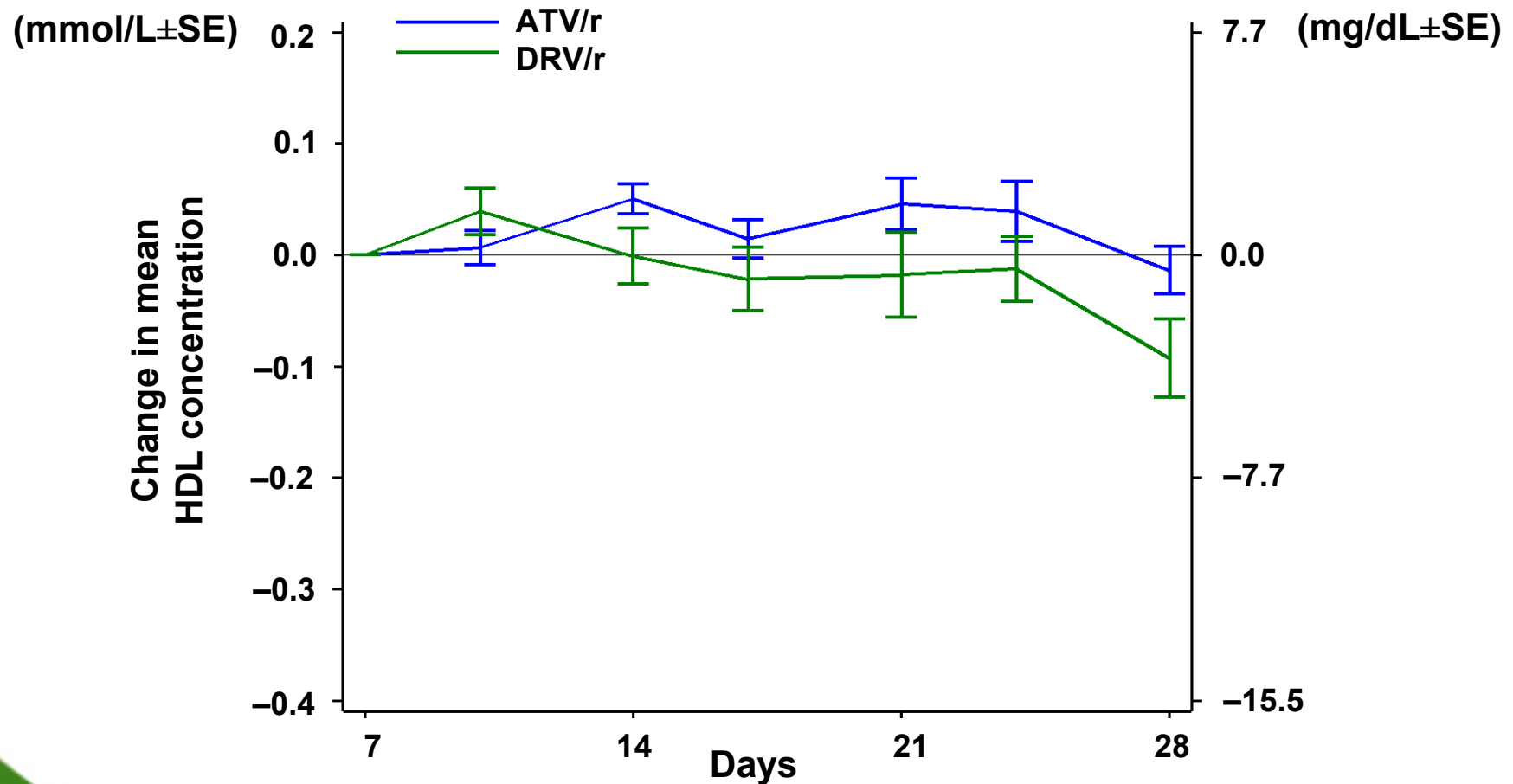
SE = standard error

LDL: changes during treatment with DRV/r or ATV/r



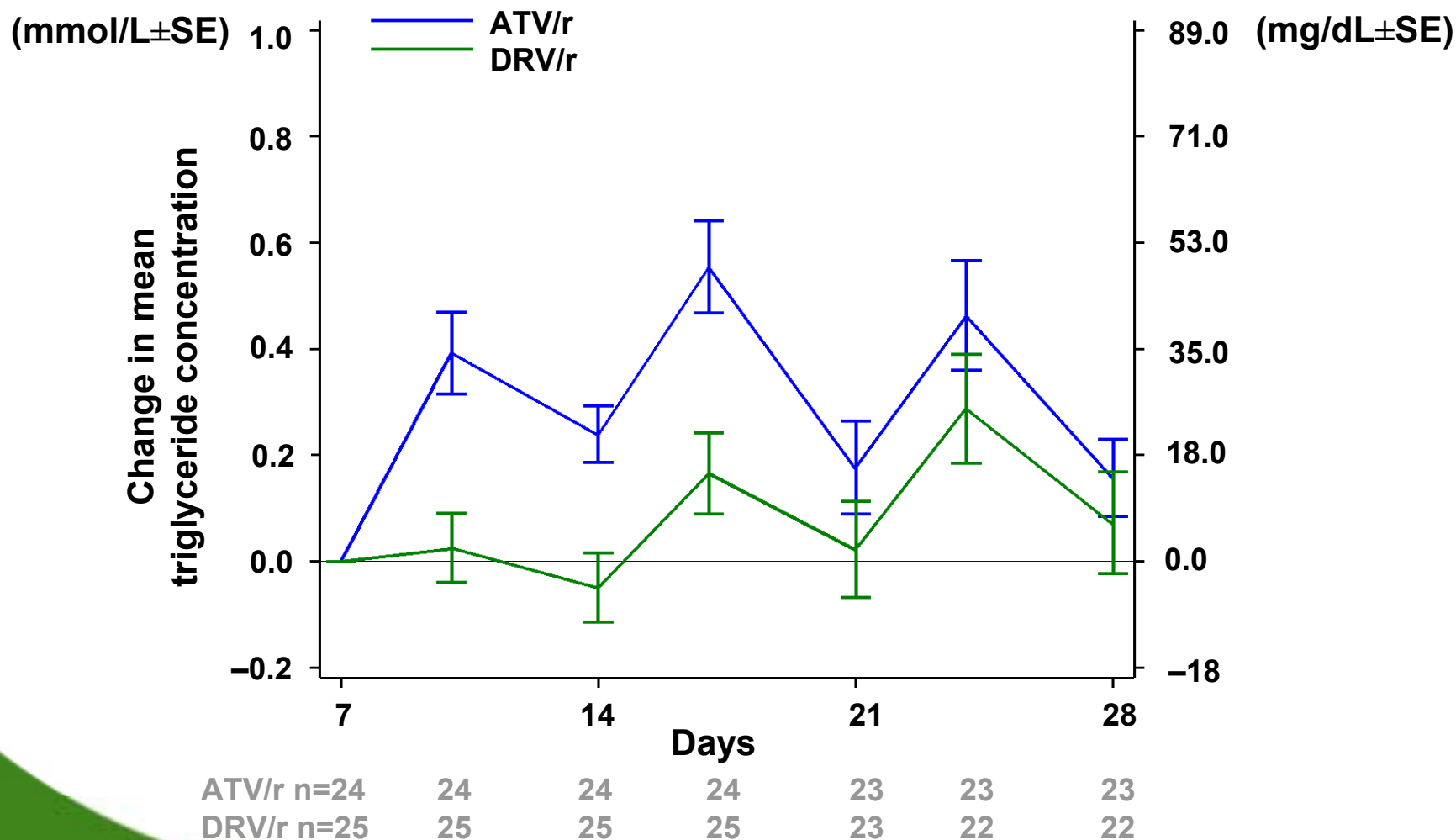
ATV/r n=24	24	24	24	23	23	23
DRV/r n=25	25	25	25	23	22	22

HDL: changes during treatment with DRV/r or ATV/r

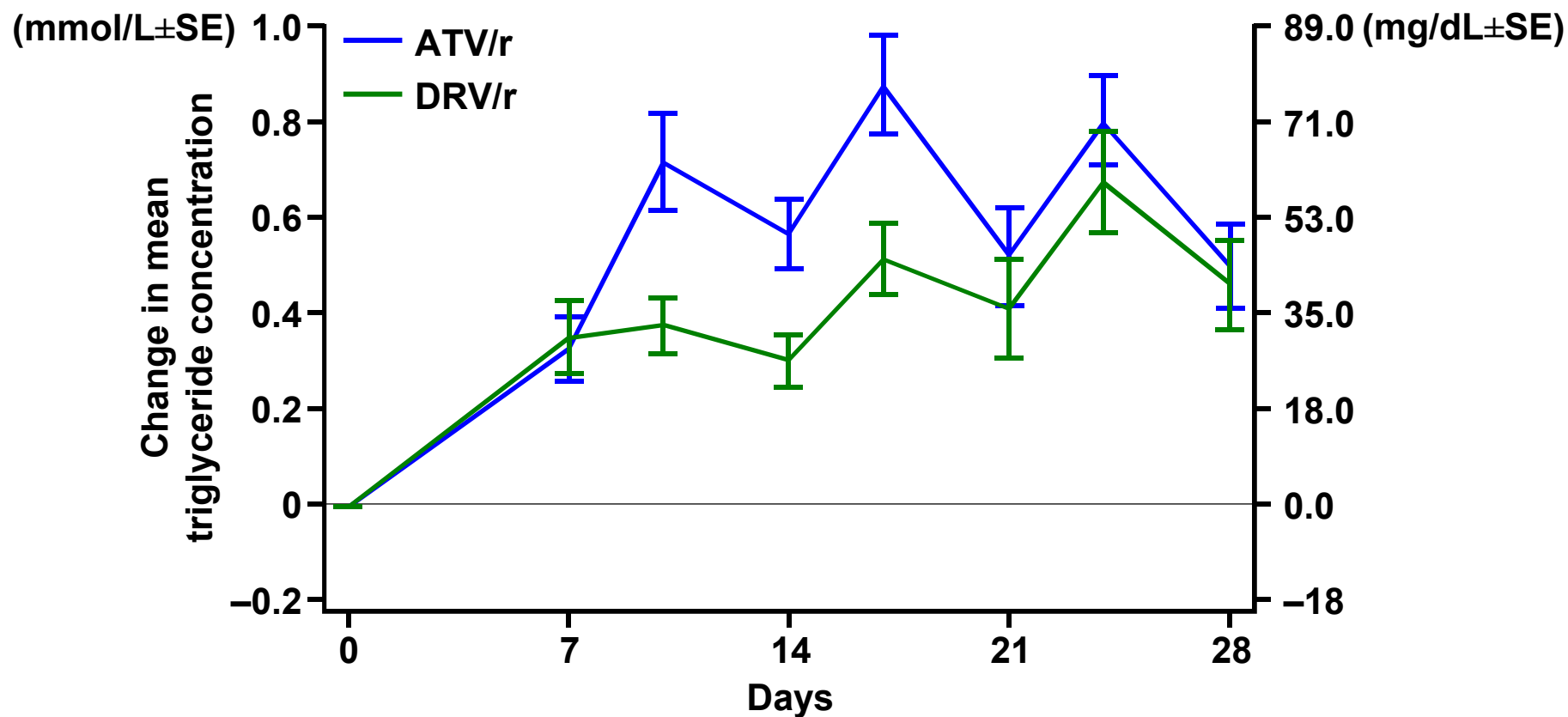


ATV/r n=24	24	24	24	23	23	23
DRV/r n=25	25	25	25	23	22	22

Triglycerides: changes during treatment with DRV/r or ATV/r

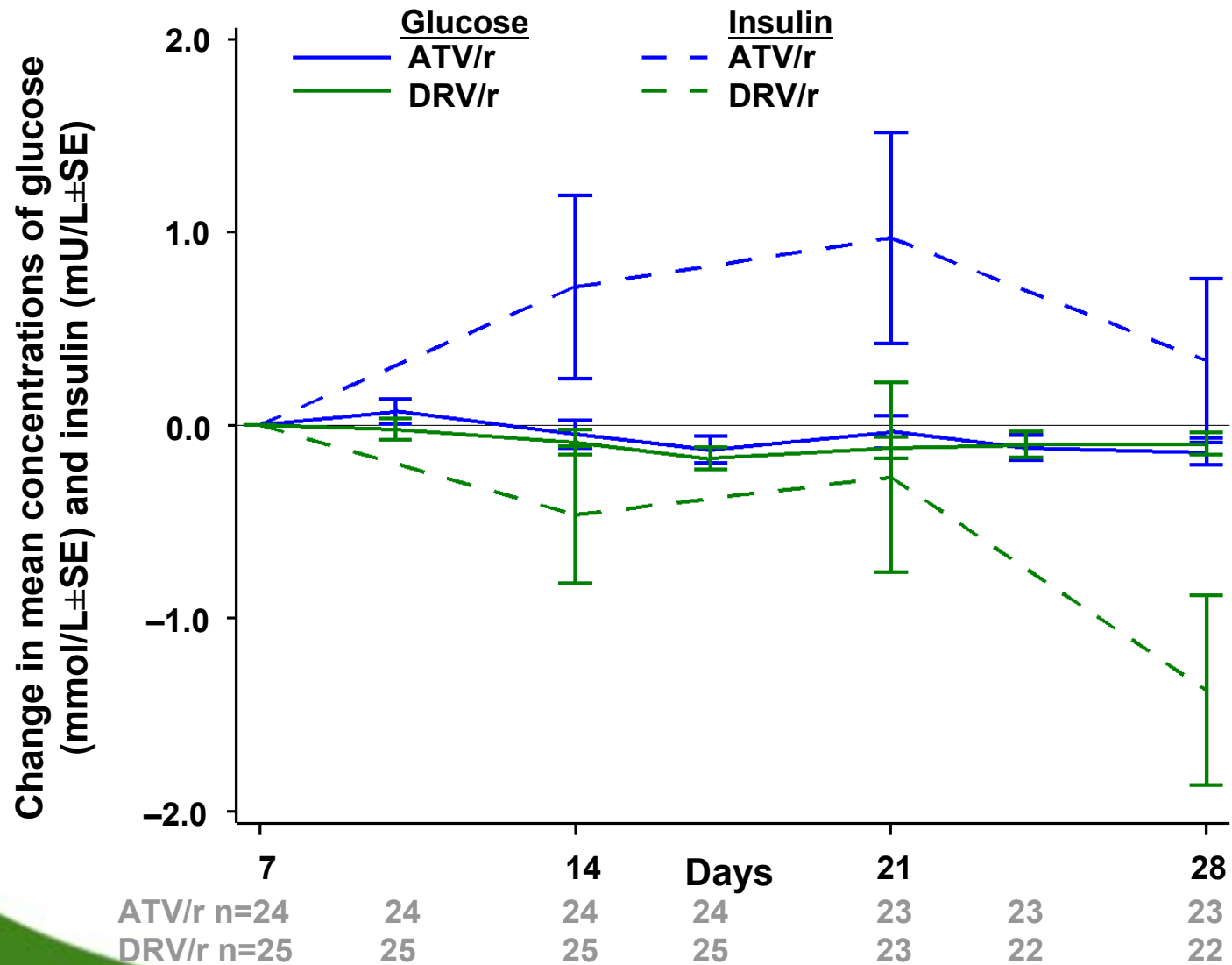


Triglycerides: changes during treatment with DRV/r or ATV/r

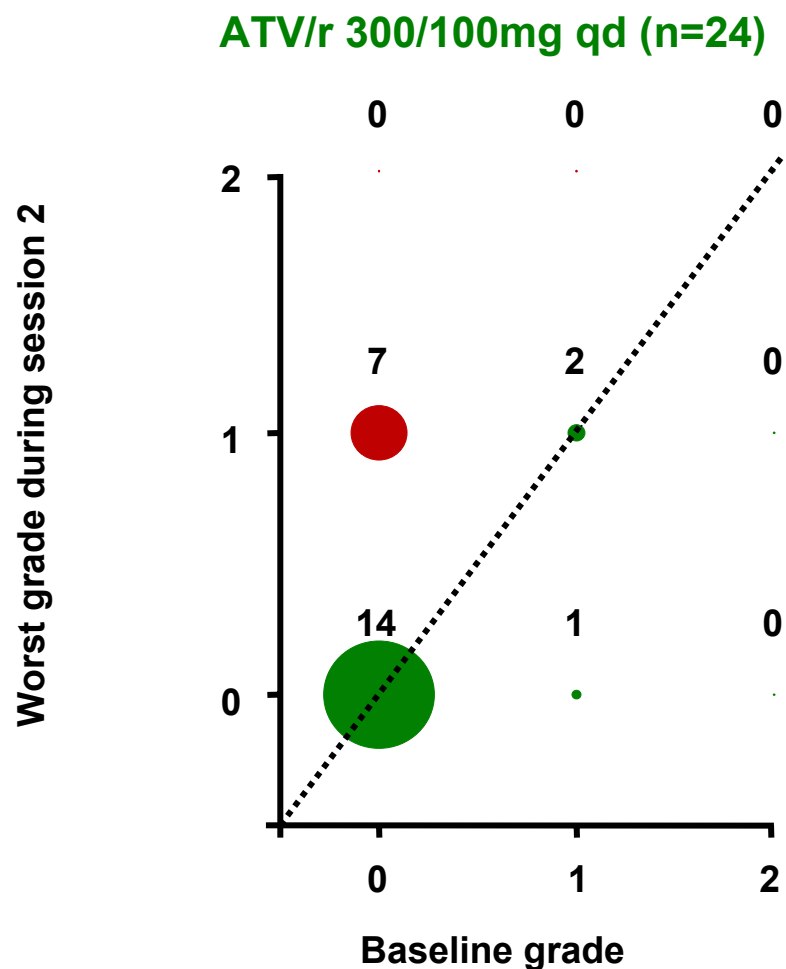
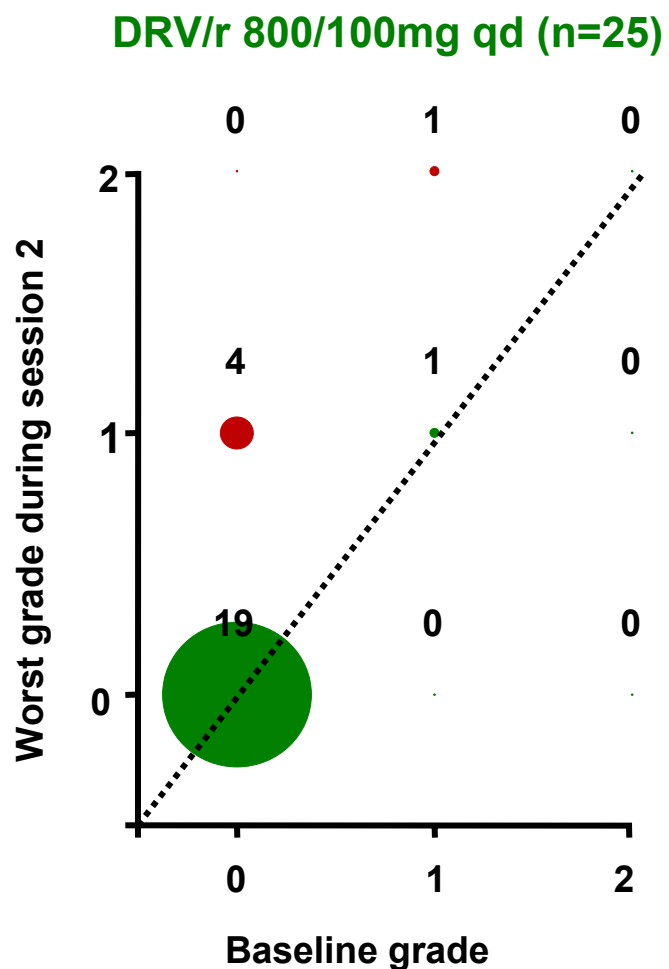


ATV/r n=	24	24	24	24	23	23	23
DRV/r n=	25	25	25	25	23	22	22

Glucose and insulin: changes during treatment with DRV/r or ATV/r

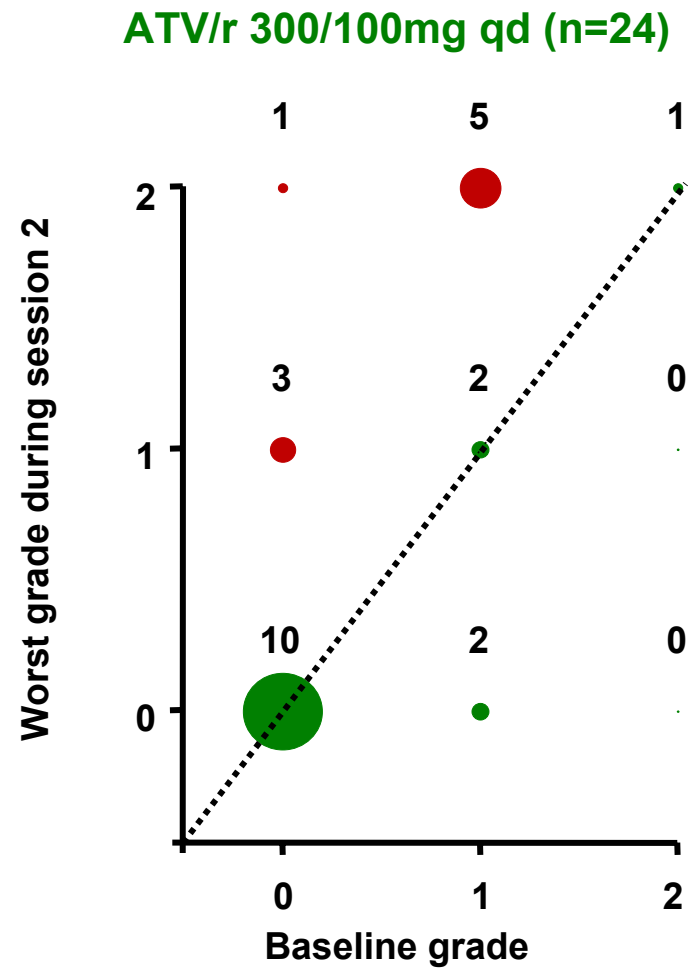
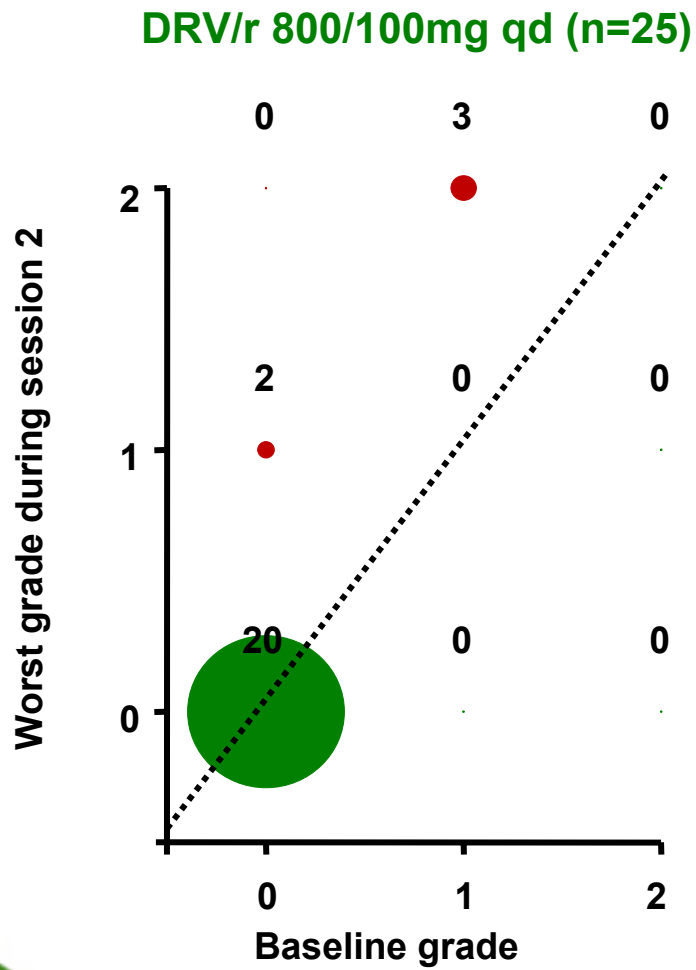


Total cholesterol grade analysis during DRV/r or ATV/r treatment



Grade 0: <200mg/dL; Grade 1: 200–239mg/dL; Grade 2: 240–300mg/dL

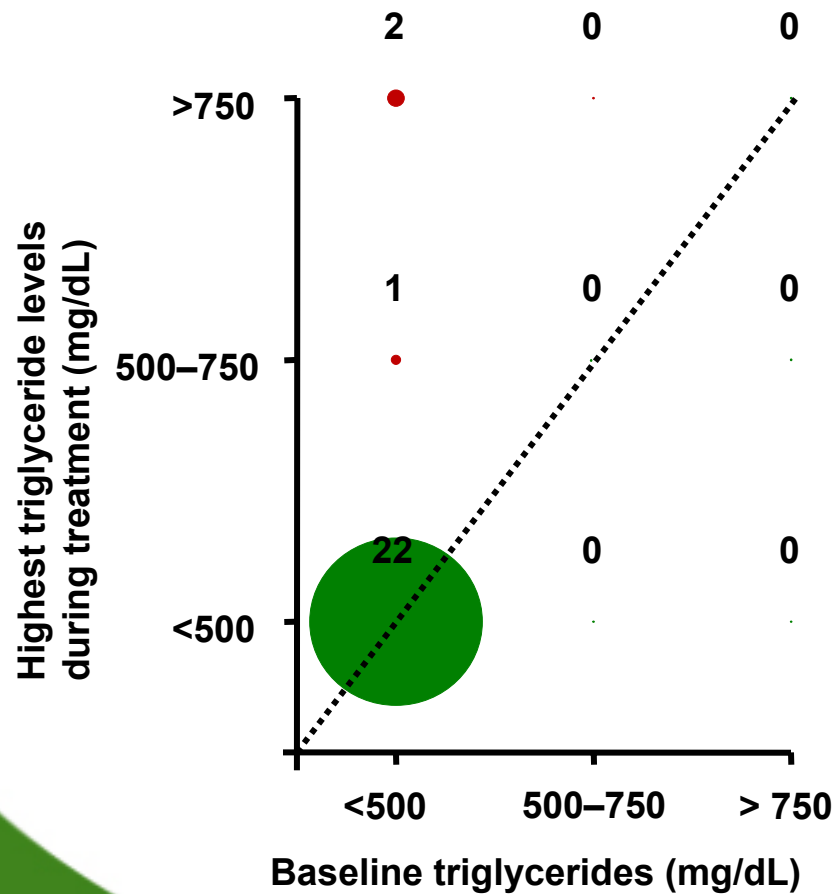
LDL grade analysis during DRV/r or ATV/r treatment



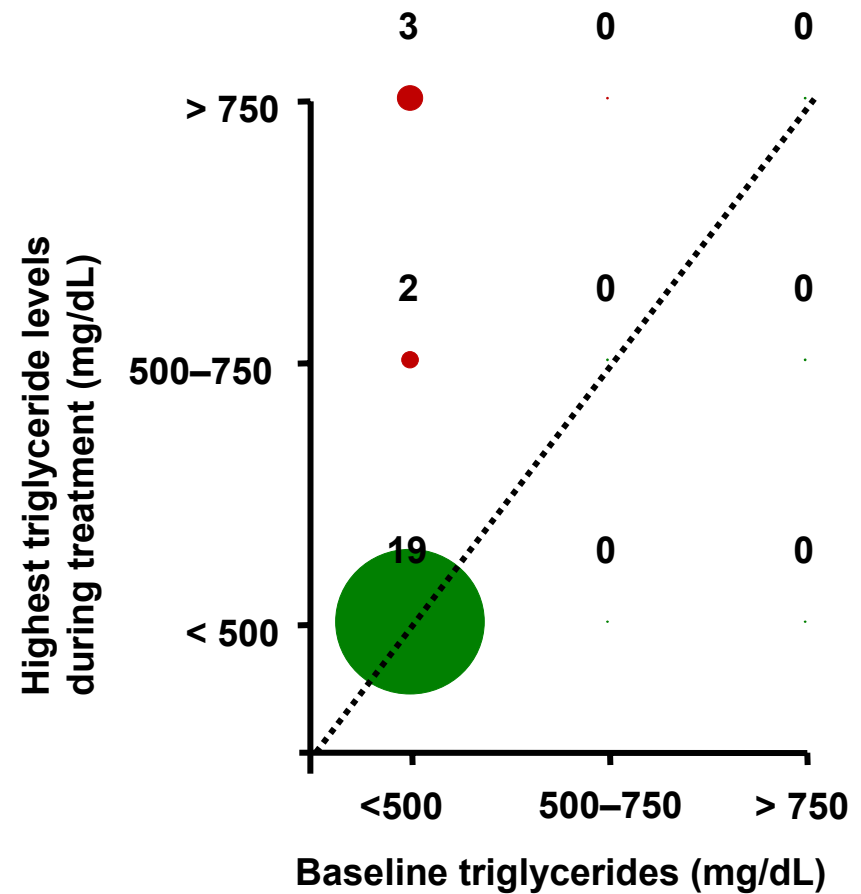
Grade 0: <130mg/dL; Grade 1: 130–159mg/dL; Grade 2: 160–190mg/dL

Triglyceride levels analysis during DRV/r or ATV/r treatment

DRV/r 800/100mg qd (n=25)



ATV/r 300/100mg qd (n=24)



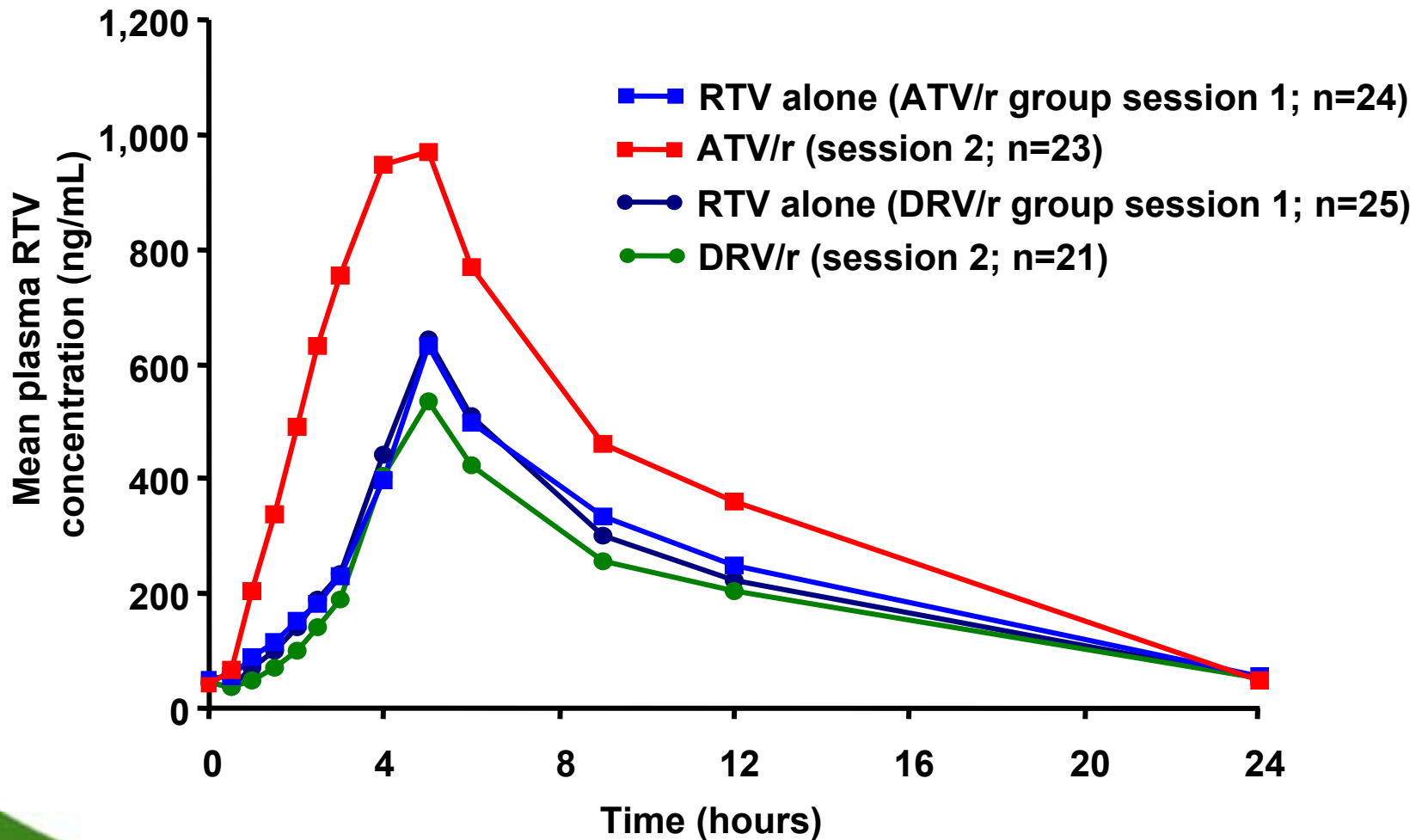
AEs* reported in ≥ 2 volunteers during Session 2

Volunteers, n (%)	DRV/r (n=25)	ATV/r (n=24)
Any AE	9 (36)	5 (21)
Headache	3 (12)	0
Diarrhea	1 (4)	2 (8)
Urticaria	2 (8)	0
Jaundice	0	2 (8)

- AEs leading to discontinuation were one case each of grade 2 and grade 3 urticaria**

***Regardless of severity or causality**

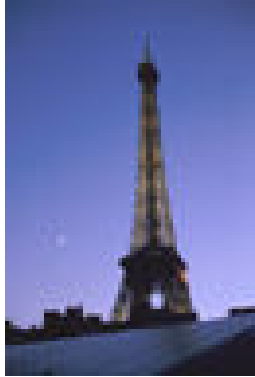
TMC114-C159: RTV pharmacokinetics



Conclusions

- **Addition of DRV or ATV to low-dose RTV resulted in small and similar changes in lipid and glucose parameters**
- **Both treatments were well tolerated with few AEs**
- **No grade 3 or 4 lipid or glucose elevations were reported during DRV/r or ATV/r treatment**
- **Low-dose RTV alone resulted in rapid increases in triglycerides in HIV-negative healthy volunteers**
- **Administration of ATV resulted in significant increases in exposure to RTV**

Acknowledgements



SGS Aster, Paris, France :

Thierry Duvauchelle, M.D, Stéphane Cardus, M.D., Didier Chassard, Brigitte Elharrar, M. Guillaume, Lionel Hovsepian, Christel Chatillon, Myriam Joseph

Tibotec C159 Study Team:

Elke Vansnick, Sara Pauwels, Viviane Robbrecht, Mathieu Bedoiseau, Richard Hoetelmans, Vanitha Sekar, Ben Van Baelen, Tony Vangeneugden, Iris Weimar, Diego Miralles, Frank Tomaka, Rudi De Greef and Ann Vandevoorde

The Volunteers



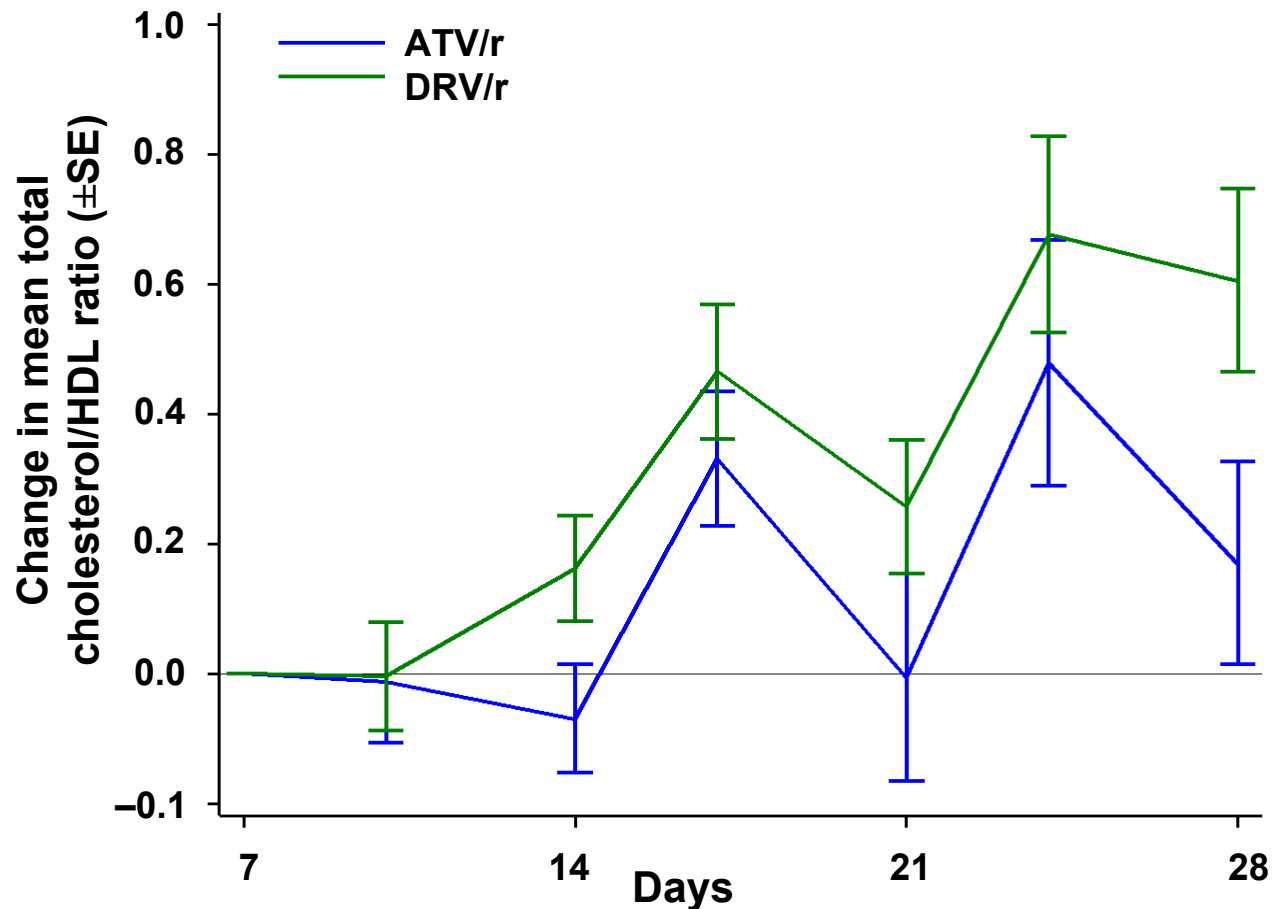
Back-up slides

Lipid analysis: worst grade during DRV/r or ATV/r treatment

Worst grade during Session 2	DRV/r baseline grade		ATV/r baseline grade		
	0	1	0	1	2
Triglycerides					
Above normal (200mg/dL)*	3*	0	5*	0	0
Total cholesterol					
Grade 1 (\geq 200–239mg/dL)	4	1	7	2	0
Grade 2 (\geq 240–300mg/dL)	0	1	0	0	0
LDL					
Grade 1 (\geq 130–159mg/dL)	2	0	3	2	0
Grade 2 (\geq 160–190mg/dL)	0	3	1	5	1
Glucose					
Grade 1 (\geq 110–125mg/dL)	1	0	0	0	0

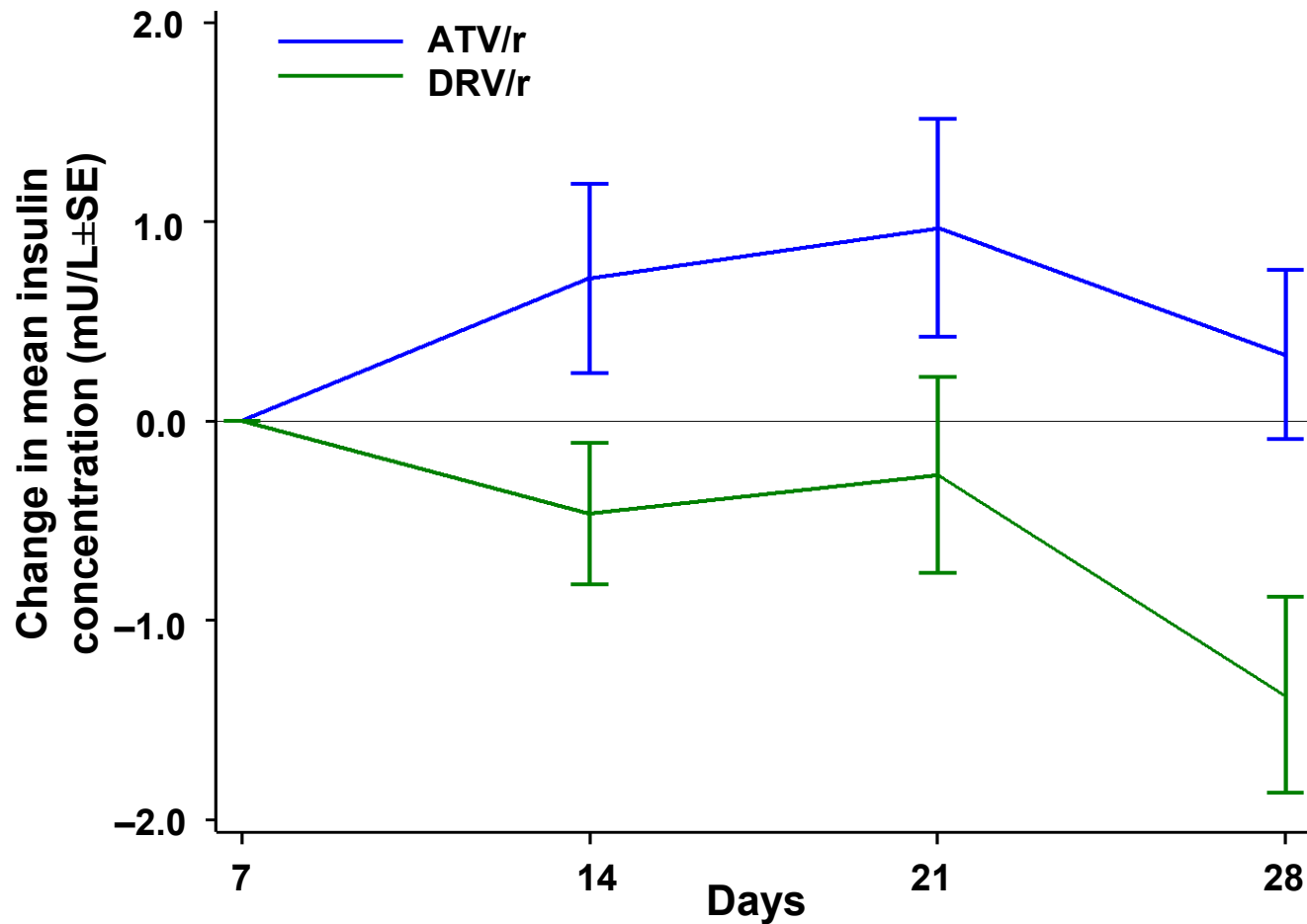
Numbers in red indicate treatment-emergent lipid changes; *below 200mg/dL at baseline

Total cholesterol/HDL ratio: changes during treatment with DRV/r or ATV/r



ATV/r n=24	24	24	24	23	23	23
DRV/r n=25	25	25	25	23	22	22

Insulin: changes during treatment with DRV/r or ATV/r



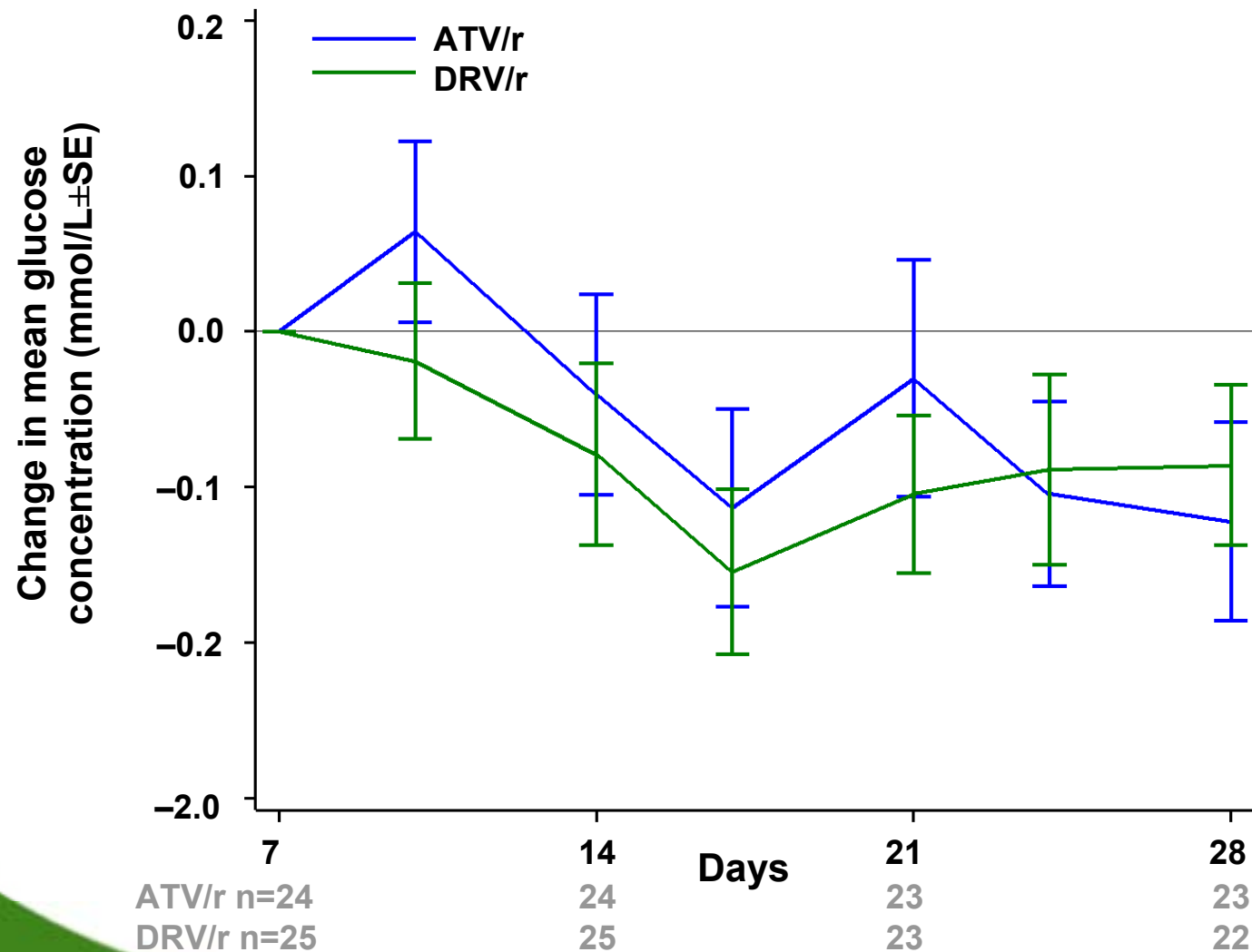
ATV/r n=24
DRV/r n=25

24
25

23
23

23
22

Glucose: changes during treatment with DRV/r or ATV/r



Mean changes in lipid and glucose parameters

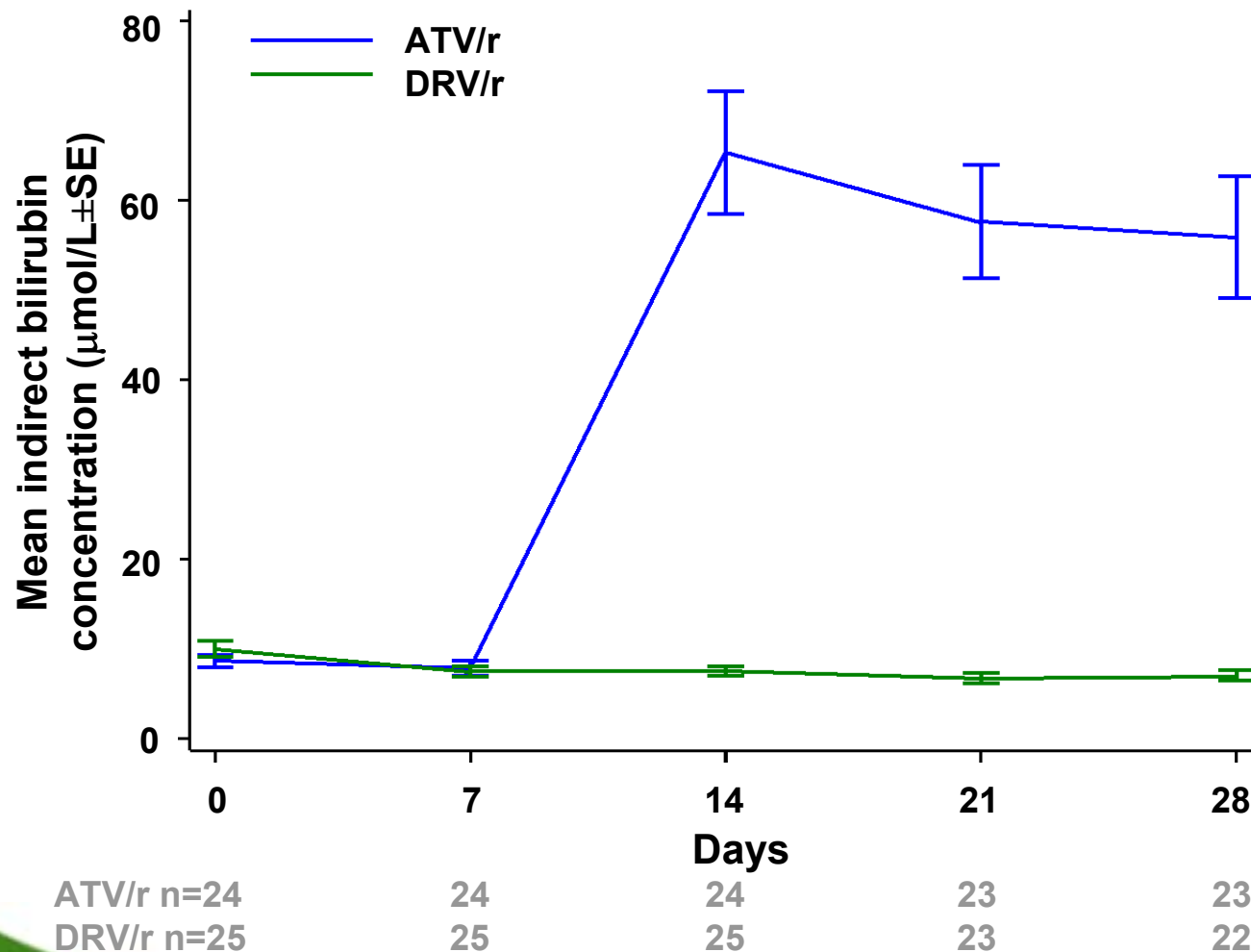
Mean, mg/dL (SD)	Baseline (predose)		Day 7 (post-RTV only)		Change from Day 7 at Day 28	
	A	B	A	B	A	B
			(RTV)	(RTV)	(DRV/r)	(ATV/r)
Total C	164 (23.7)	174 (31.1)	166 (22.2)	171 (27.1)	4.9 (18.1)	1.2 (14.7)
HDL	63 (12.7)	52 (8.3)	56 (11.5)	47 (7.7)	-3.6 (6.3)	-0.5 (4.0)
C/HDL	2.7 (0.69)	3.4 (0.72)	3.1 (0.82)	3.7 (0.70)	0.3 (0.33)	0.1 (0.37)
LDL	100 (24.5)	119 (28.2)	108 (25.6)	120 (26.1)	5.0 (16.0)	5.3 (15.3)
TGs	75 (29.2)	74 (30.0)	106 (41.3)	103 (37.8)	6.4 (39.7)	14.0 (30.8)
Glucose	89 (7.76)	89 (7.67)	83 (7.25)	83 (8.72)	-1.7 (4.83)	-2.4 (6.13)

SD = standard deviation; C = cholesterol; TGs = triglycerides

DRV/r 800/100mg qd: ARTEMIS (TMC114-C211) trial

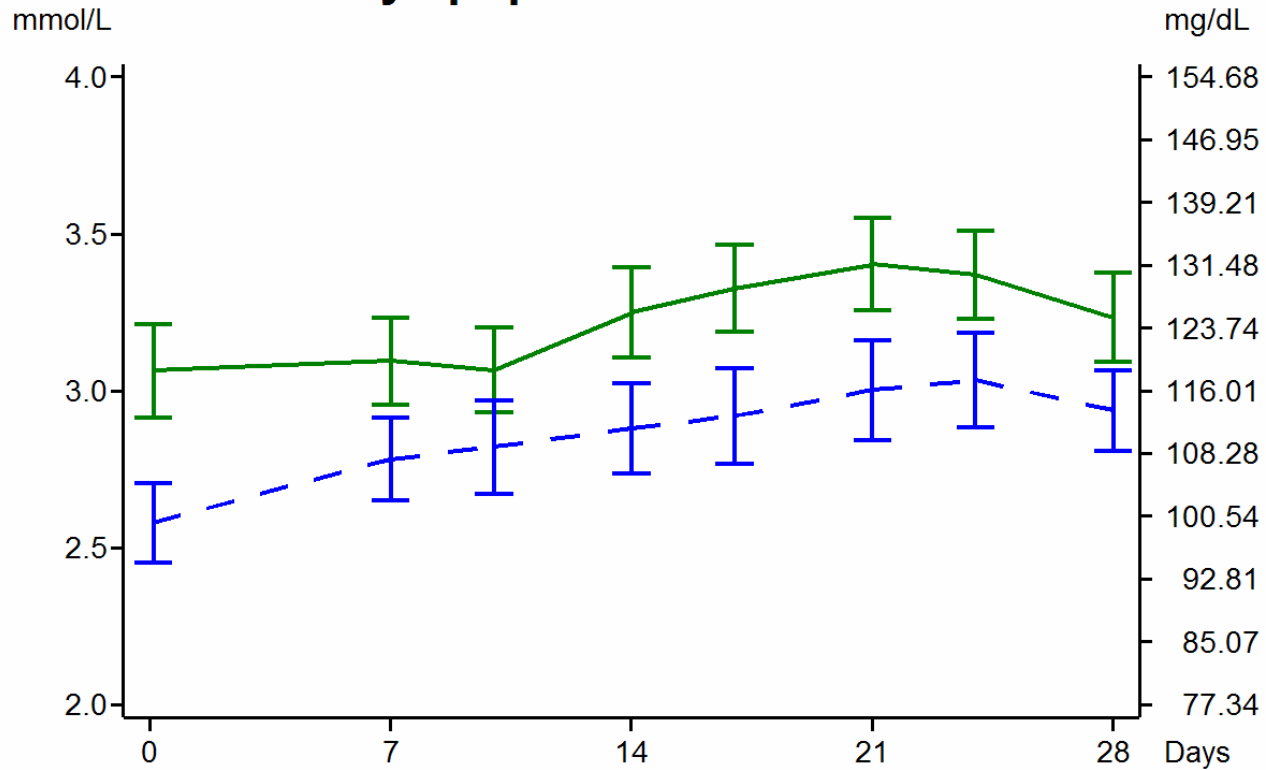
- **DRV/r 800/100mg qd is currently being evaluated in a Phase III trial**
 - 96-week, randomized, controlled, open-label trial in 660 treatment-naïve HIV-infected patients
- **Objective: to evaluate efficacy, safety and tolerability of DRV/r versus lopinavir (LPV)/r**
 - patients receive either DRV/r 800/100mg qd or LPV/r 800/200mg total daily dose
 - all patients also receive the NRTI fixed dose combination pill of tenofovir disoproxil fumarate (300mg) and emtricitabine (200mg)

Indirect bilirubin: observed changes over time from baseline to Day 28



Actual values over time: LDL

Low density lipoprotein direct

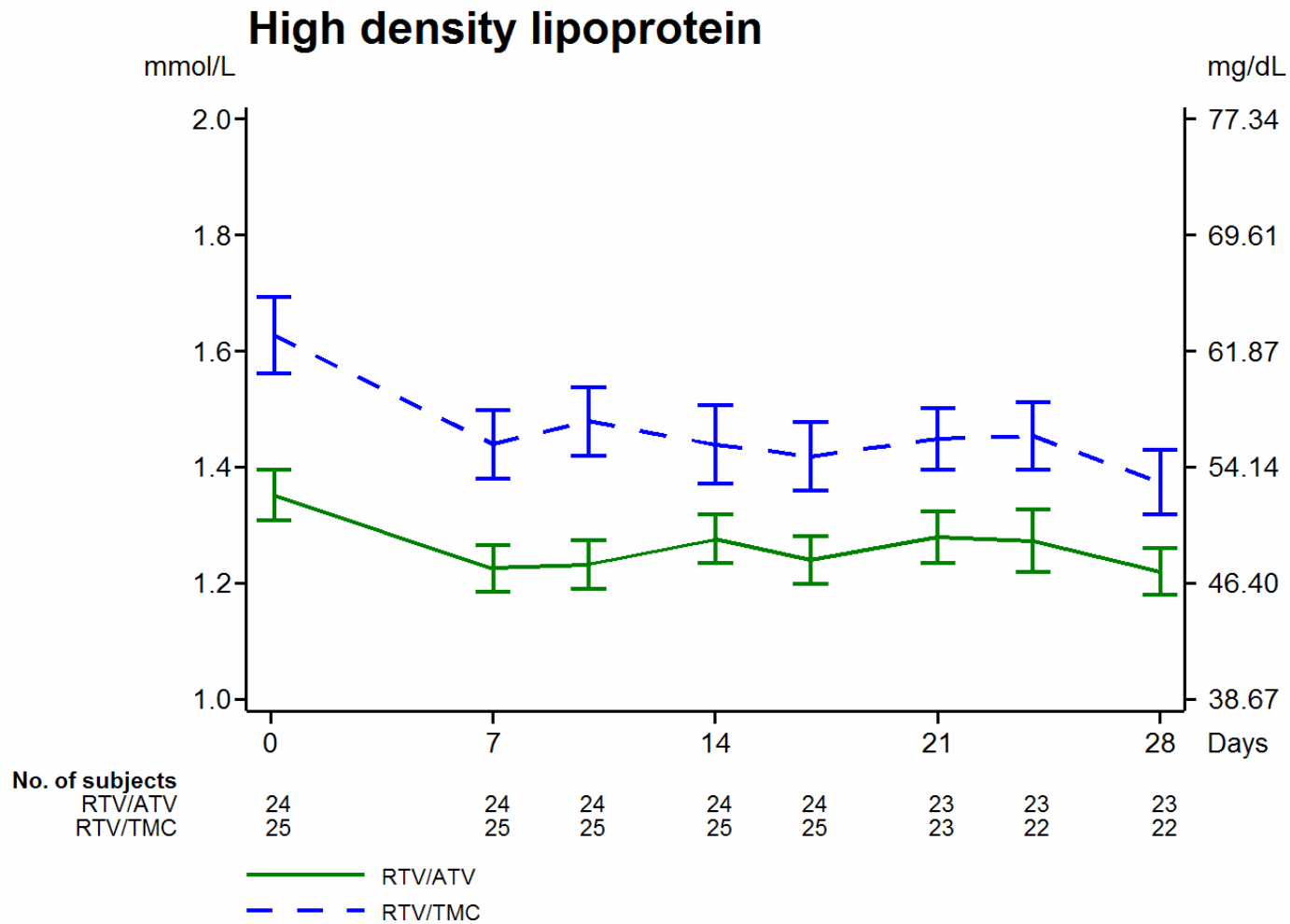


No. of subjects
RTV/ATV
RTV/TMC

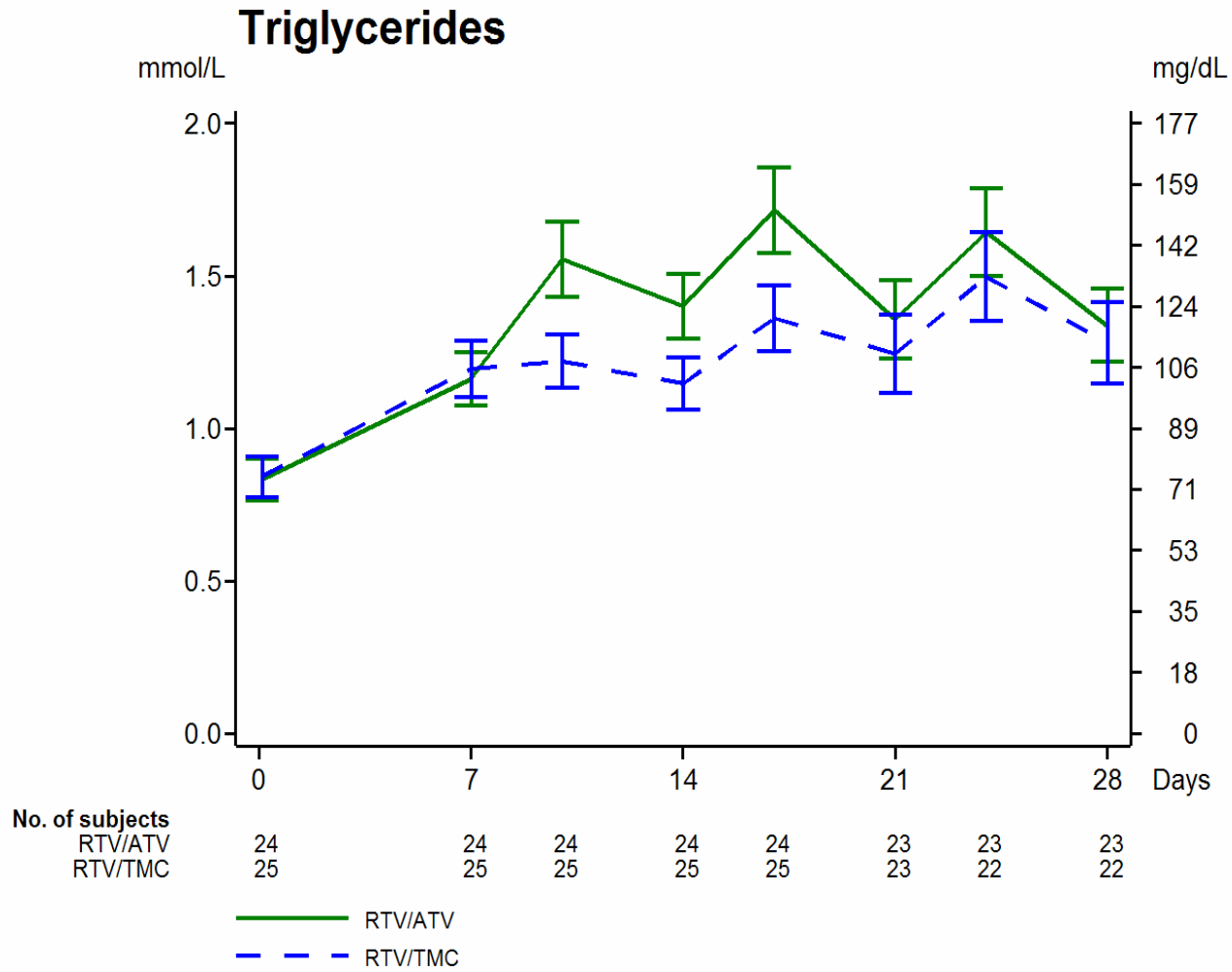
— RTV/ATV
- - RTV/TMC

24	24	24	24	24	23	23	23
25	25	25	25	25	23	22	22

Actual values over time: HDL

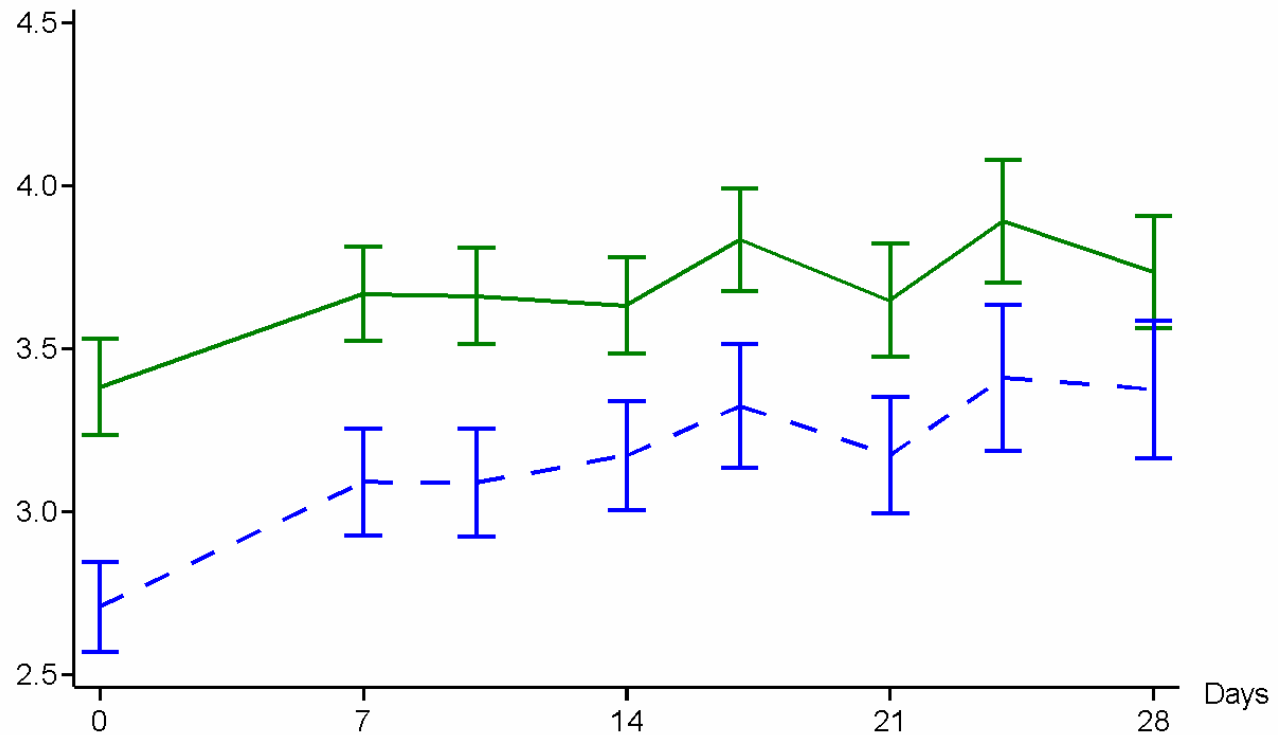


Actual values over time: triglycerides



Actual values over time: total cholesterol/HIDL

TOTAL CHOLESTROL/HDL

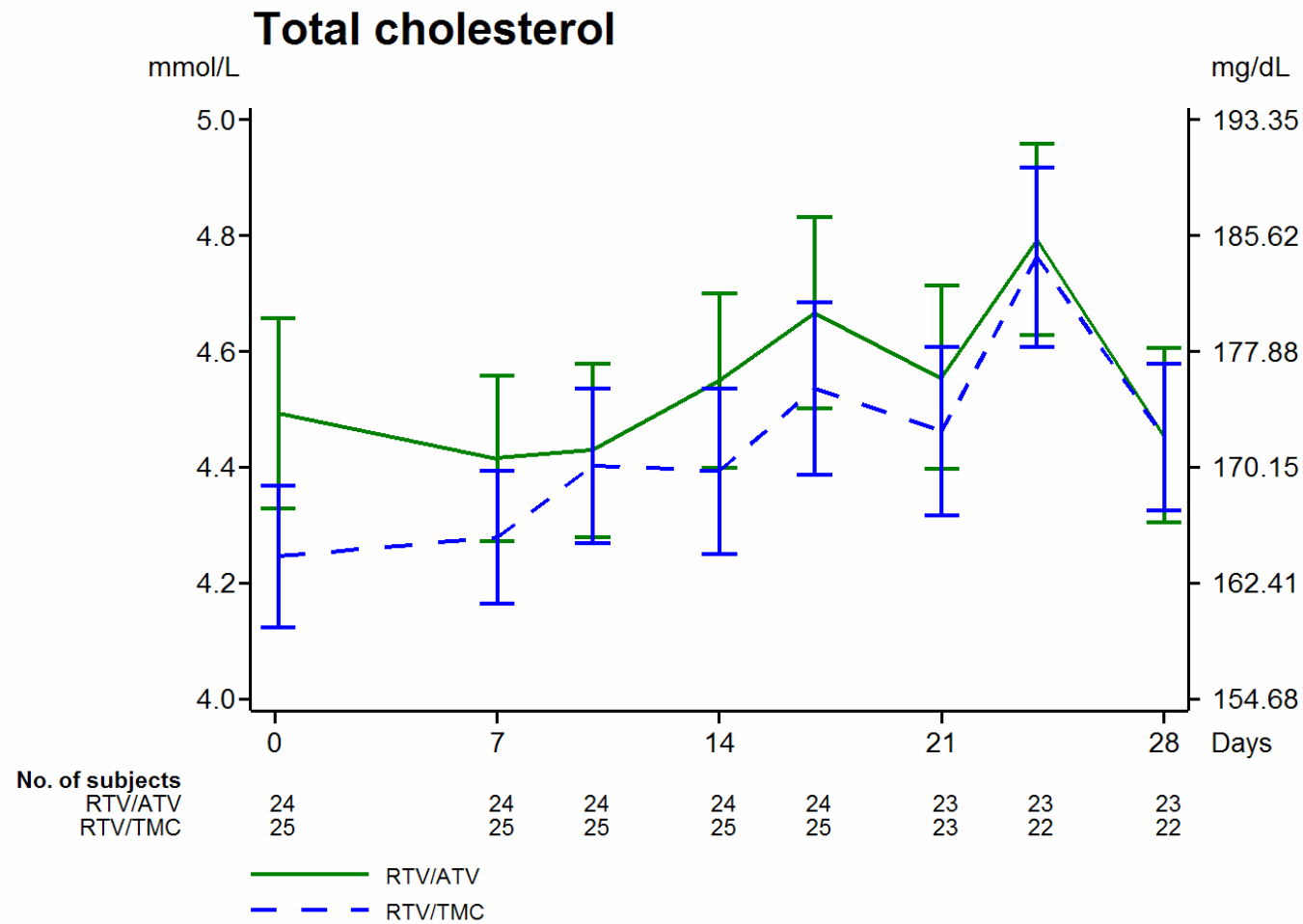


No. of subjects
RTV/ATV
RTV/TMC

— RTV/ATV
- - RTV/TMC

24	24	24	24	24	23	23	23
25	25	25	25	25	23	22	22

Actual values over time: total cholesterol



Actual values over time: glucose

