SPARTAN
Safety and Potency of Atazanavir and Raltegravir Treatment in Absence of Nucleosides and RTV

The SPARTAN Study: A Pilot Study to Assess the Safety and Efficacy of an Investigational NRTI- and RTV-Sparing Regimen of Atazanavir (ATV) Experimental Dose of 300mg BID plus Raltegravir (RAL) 400mg BID (ATV+RAL) in Treatment-Naïve HIV-Infected Subjects.

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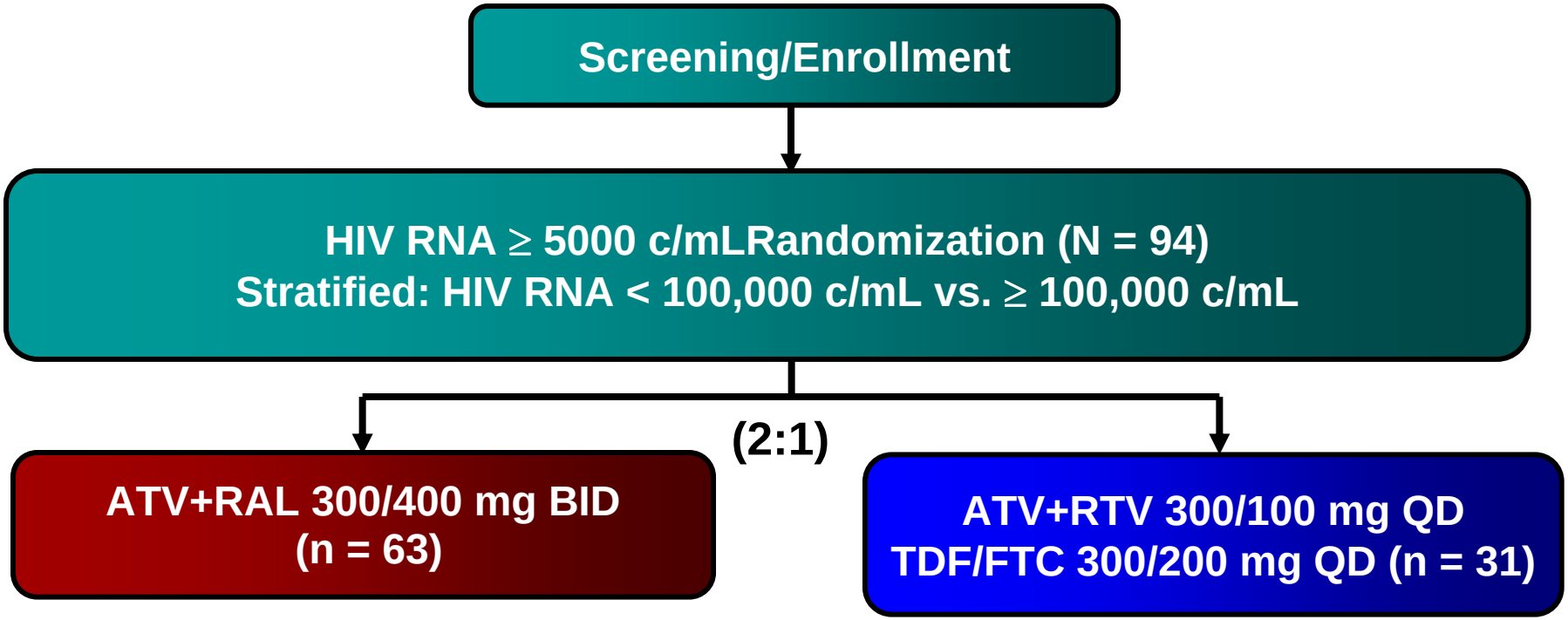
Study Design



Primary endpoint:

- **Determine the proportion of patients with HIV RNA < 50 c/mL at week 24**

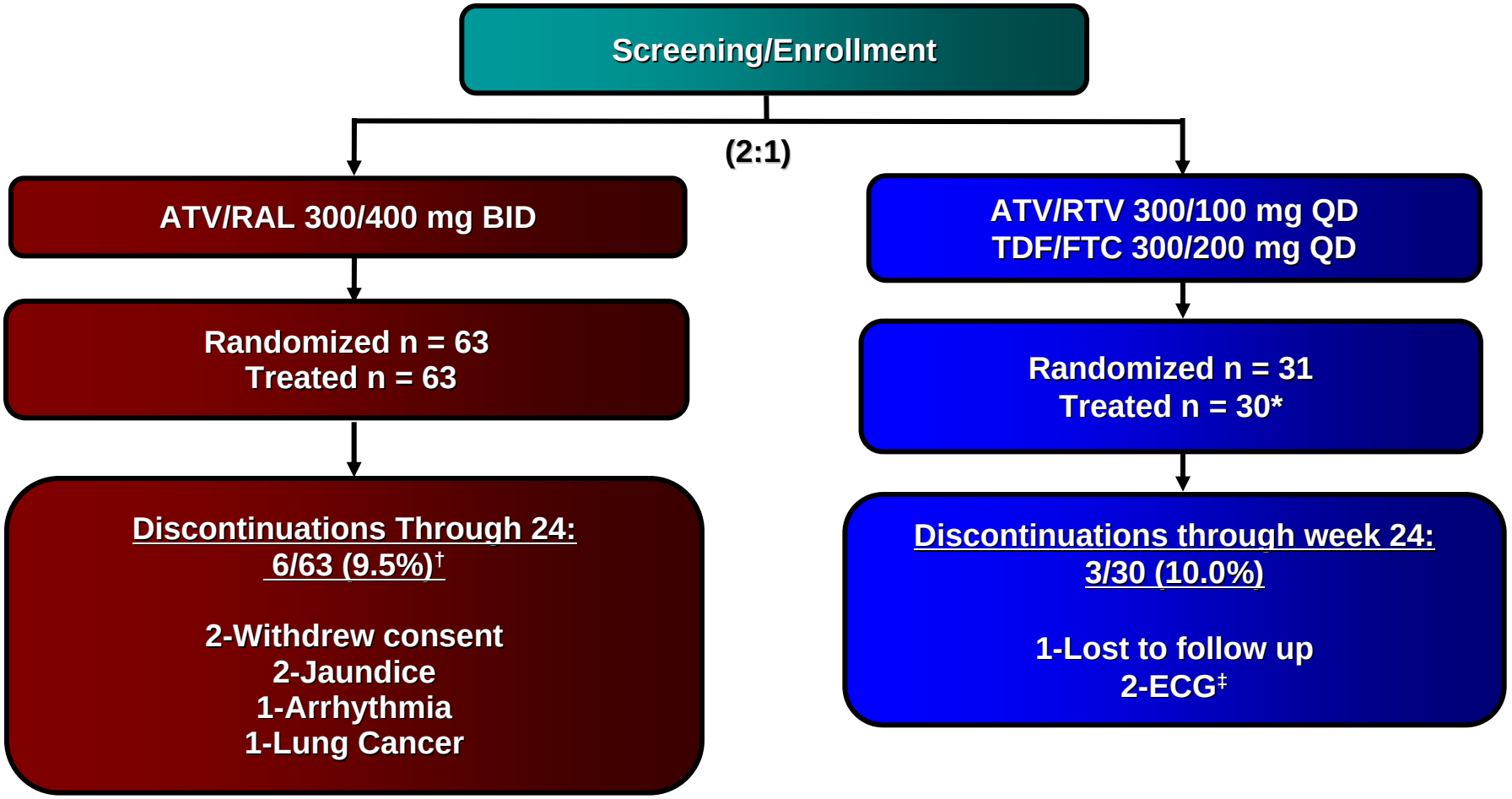
Secondary endpoints:

- **Change from baseline in CD4 cell counts at weeks 24, 48 & 96**
- **Safety through weeks 24, 48 & 96**
- **Assess pharmacokinetics of ATV+RAL experimental regimen**

Demographics

	ATV+RAL	ATV+RTV+TDF/FTC
Median Age (years)	40.0	40.5
Male n/N (%)	55/63 (87.3)	28/30 (93.3)
Race n/N (%)		
White	54/63 (85.7)	23/30 (76.7)
African American	8/63 (12.7)	6/30 (20.0)
Asian	0	1/30 (3.3)
Other	1/63 (1.6)	0
Mean BL HIV RNA $\log_{10}$ c/mL (SE)	4.9 (0.07)	4.9 (0.12)
Baseline HIV RNA < 100,000	29/63 (46.0)	17/30 (56.7)
Baseline HIV RNA ≥ 100,000	34/63 (54.0)	13/30 (43.3)
Mean CD4 cells/mm^3 (SE)	256 (14.7)	261 (24.6)

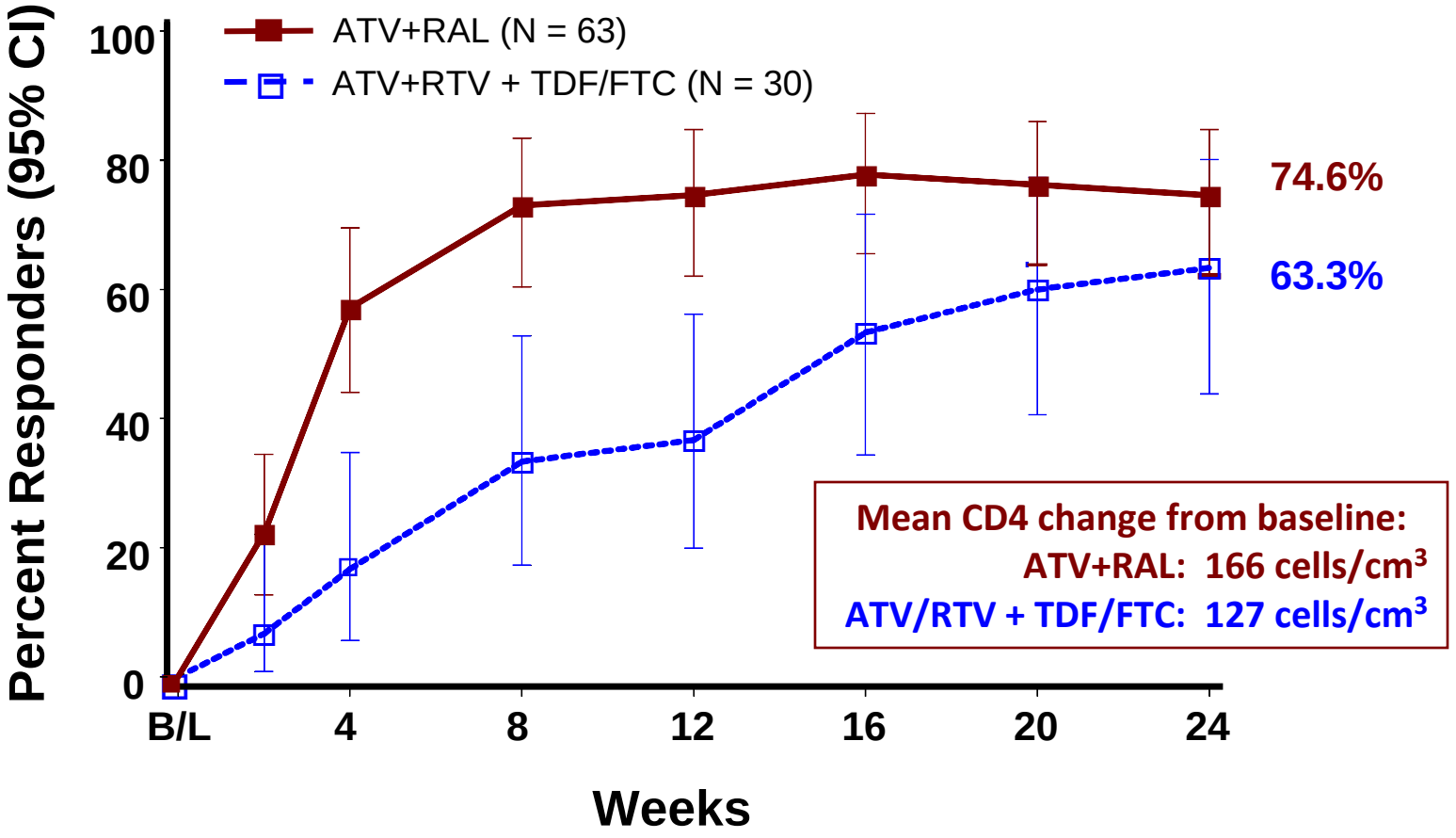
Disposition through Week 24



*One patient withdrew consent before treatment
‡Never met study criteria due to QRS prolongation

† 6/6 subjects on ATV+ RAL were undetectable (HIV RNA < 50 c/ mL) at discontinuation through week 24

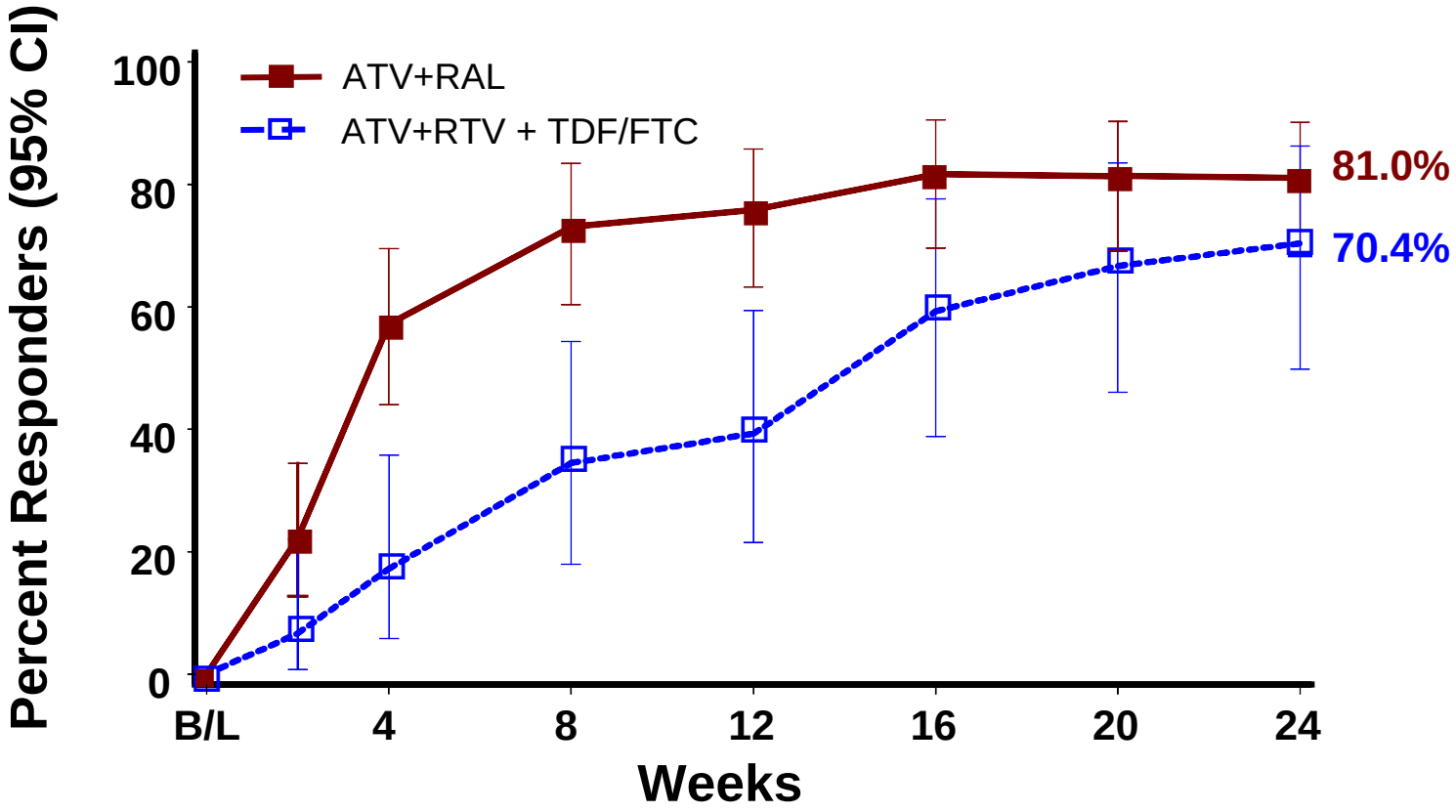
Response Rate (HIV RNA < 50 c/mL) through Week 24-CVR (NC = F)



CVR (NC = F) is a modified intent-to-treat analysis of confirmed virologic response where non-completers equal failure. Responders are:

- Subjects who achieve and maintain confirmed response (2 consecutive on-treatment HIV RNA < 50 c/mL) through the visit week without intervening virologic rebound or discontinuation
- Subjects who achieve resuppression (i.e., confirmed response after virologic rebound) at the visit week.

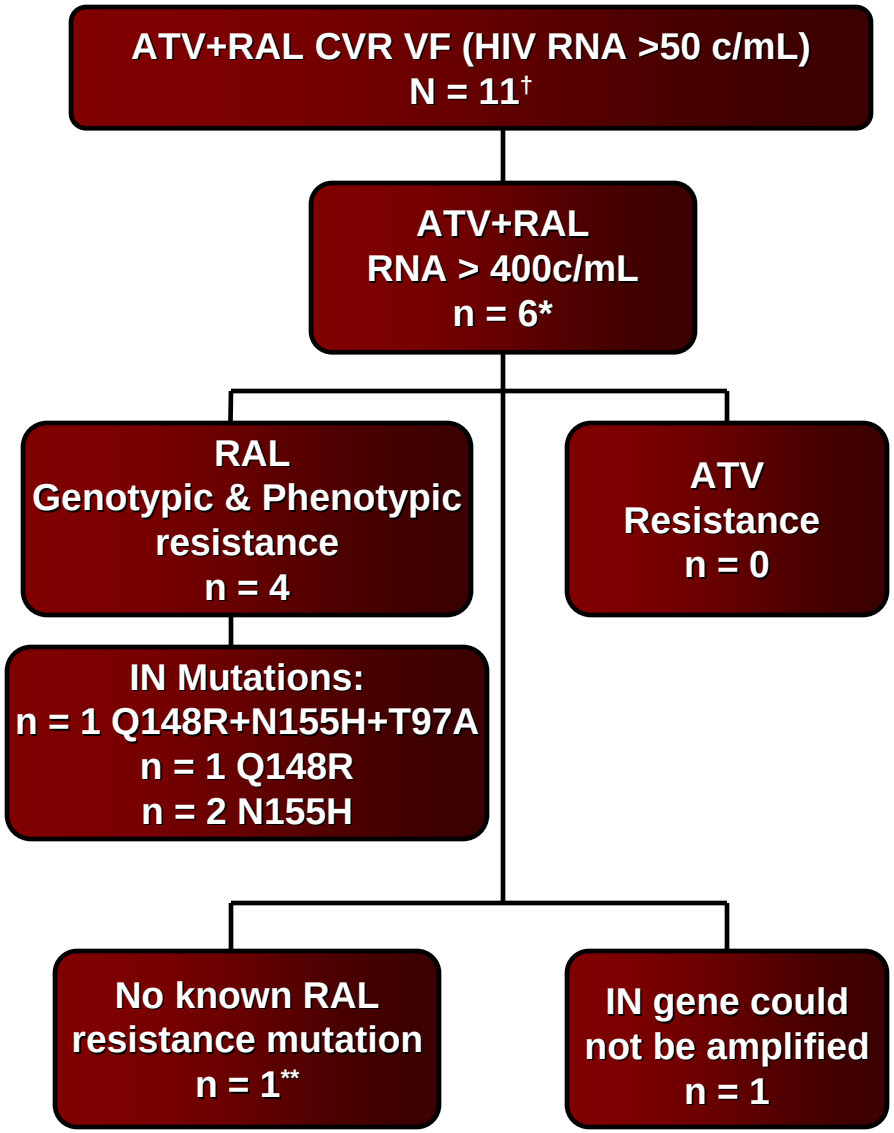
Response Rate (HIV RNA < 50 c/mL) through Week 24-CVR (NC = M)

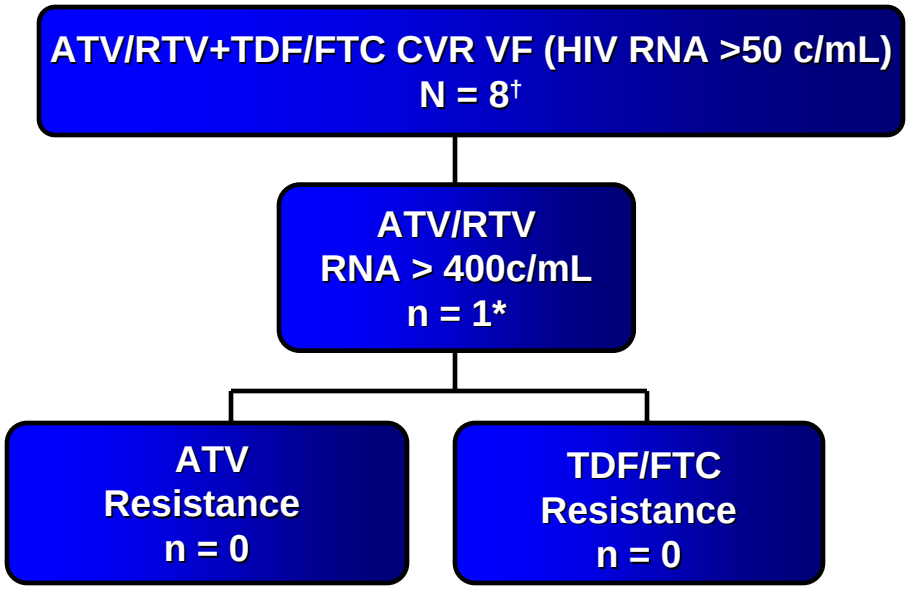


ATV+RAL: N=63	63	63	63	62	60	59	58
ATV+RTV+TDF/FTC: N=30	30	29	29	28	27	27	27

CVR (NC = M) excludes non-completers within a pre-defined visit window;
Subjects are classified as completers at week 24 if they have minimum follow-up, i.e., received at least 155 days of study therapy and have an HIV RNA measurement on or after 155 days, the lower bound of the week 24 visit window.

SPARTAN Resistance through Week 24





† 8/11 VF subjects on ATV+RAL had a baseline HIV VL>250,000
† 4/8 VF subjects on ATV/RTV +TDF/FTC had a baseline HIV VL>250,000
***** Criteria for resistance testing:
(1) Subjects with HIV RNA ≥ 400 copies/mL at or after week 24
(2) Rebound to HIV RNA ≥ 400 at any time during the study
(3) Discontinued before achieving viral suppression (HIV RNA <50) after week 8 with last HIV RNA ≥ 400
1 additional subject on ATV+RAL met criteria (2) with a wild type genotype and resuppressed at discontinuation visit
******One subject developed phenotypic resistance to RAL (BCO > 1.5) without any genotypic evidence of RAL RAMs at week 24.
Note: One additional patient at week 32 was found originally to have a major substitution (N155N/H mixture) to RAL at Week 32 but remained phenotypically sensitive to RAL. Subsequently, the contract reference lab changed the report to read "No RAL mutations detected".

Safety through Week 24

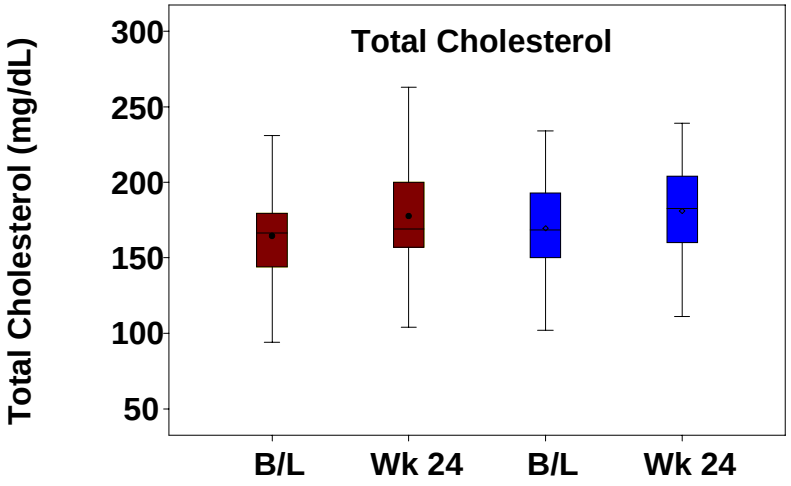
	Number of Patients	
	ATV+RAL	ATV+RTV +TDF/FTC
AEs leading to DC*	4/63 (6.3%)	0
Grade 2-4 treatment-related AEs†	19/63 (30.2%)	10/30 (33.3%)
Grade 3-4 AEs	16/63 (25.4%)	6/30 (20.0%)
Grade 3-4 total bilirubin abnormalities	38/63 (60.3%)	14/30 (46.7%)
Grade 4 total bilirubin abnormalities	13/63 (20.6%)	0
PR mean change from BL‡ msec (SE)§	17.6 (2.10)	4.9 (2.25)
QRS mean change from BL msec (SE)§	8.9 (1.02)	3.6 (1.97)

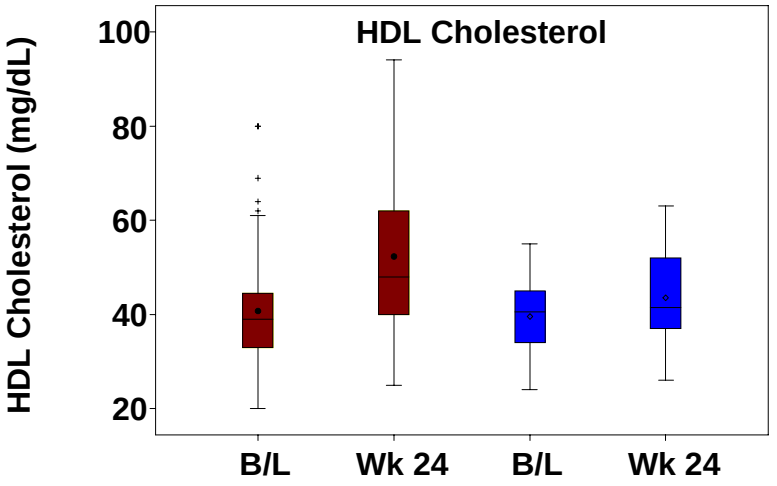
*Included arrhythmia-1, jaundice-1, jaundice and ocular icterus-1, Lung cancer-1

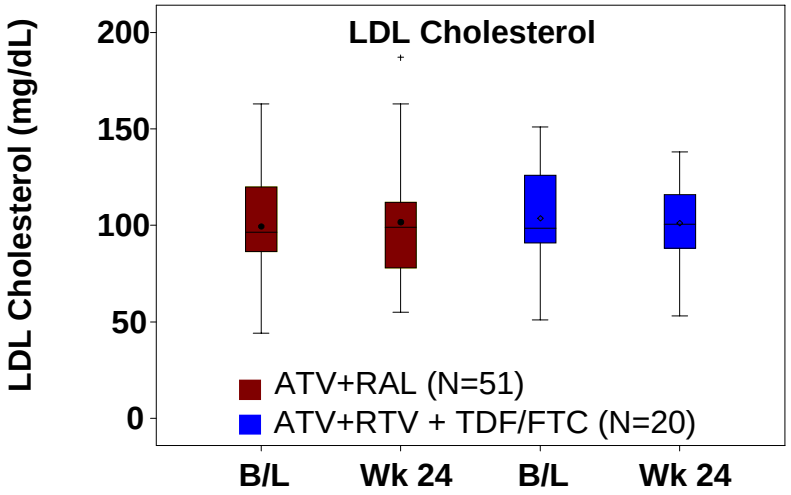
†Grade 2-4 treatment-related AE hyperbilirubinemia occurred in 19% (12/63) of subjects on ATV+RAL and 16.7% (5/30) on ATV/RTV+TVD

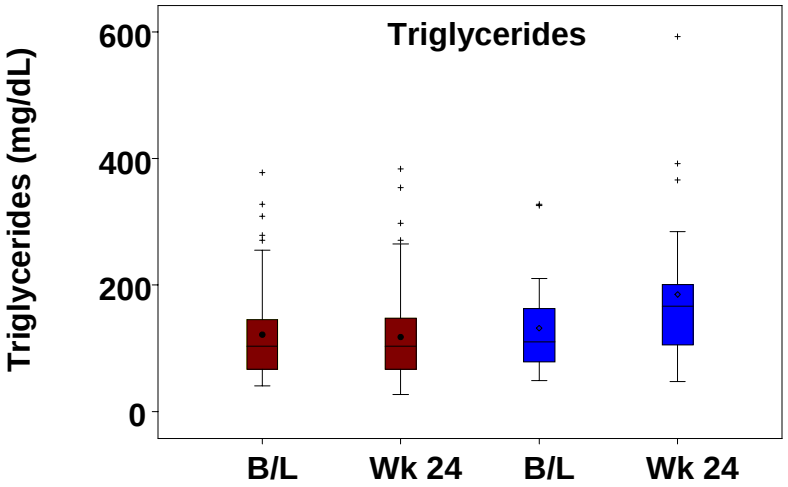
§The worst value in the visit window was used

Fasting Lipids Week 24: LOCF-Treated Subjects









Fasting Mean (SE) Total-to-HDL Chol Ratio	ATV+RAL	ATV+RTV+TDF/FTC
Baseline	4.4 (0.18)	4.4 (0.26)
Week 24	3.8 (0.21)	4.4 (0.25)

LOCF: Last Observation Carried Forward

Geometric Means of Steady State Pharmacokinetics for ATV and RAL

	ATV		RAL	
	SPARTAN* (N=13)	CASTLE (N=18)	SPARTAN* (N=13)	Historical (N=6)
C_{max} (ng/mL)	3506	2897	1577	
AUC[§] (ng•h/mL)	39806	28605	6446	6900
C_{min} [†] (ng/mL)	687	526	76	68.5

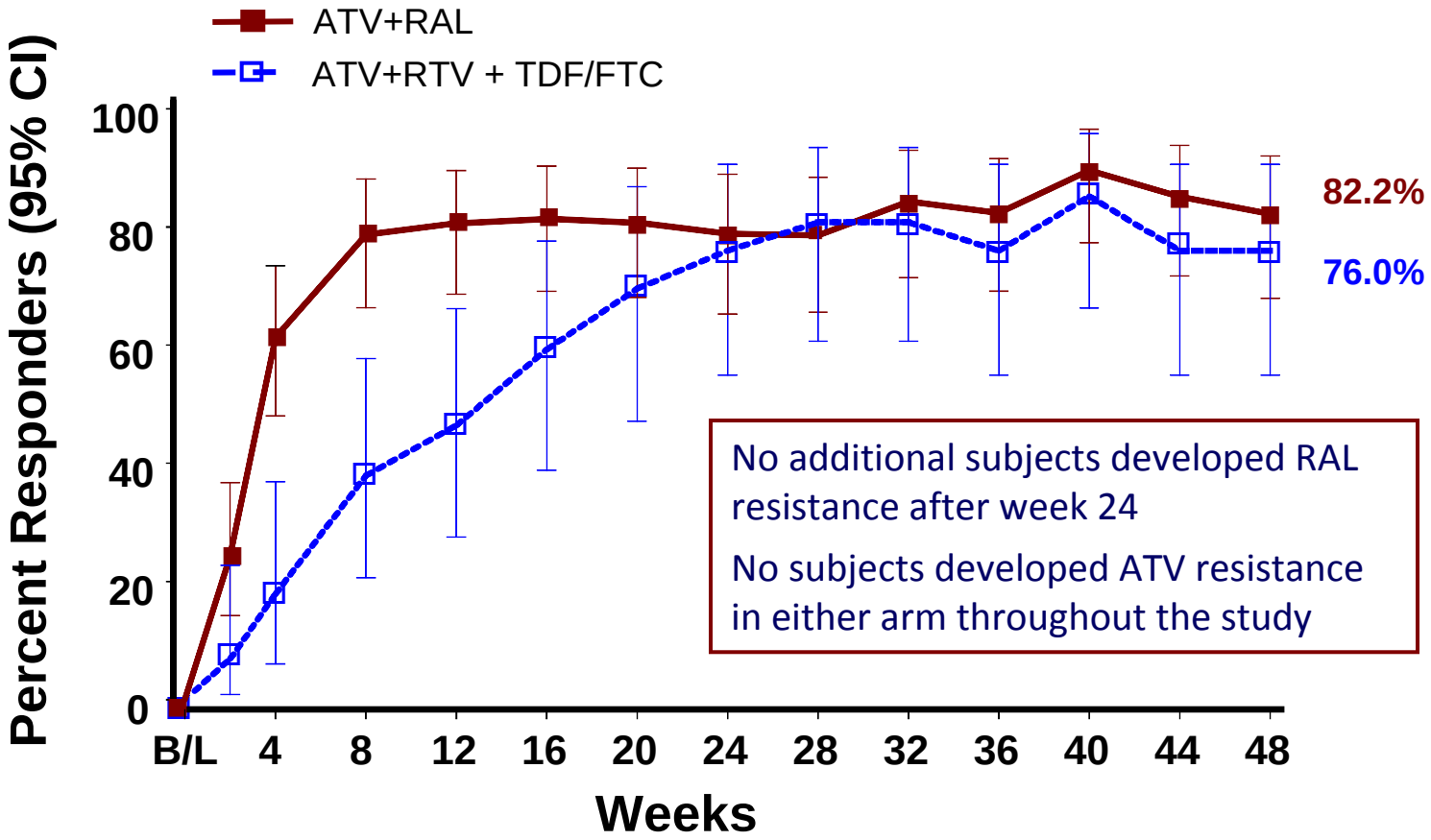
*When RAL 400 mg BID was dosed with ATV 300 mg BID

[§]ATV AUC is normalized to AUC(0-24), RAL AUC is AUC(0-12)

[†]C_{min} : Defined as C12 (12 hours post the AM dose) for SPARTAN and RAL, and C24 for ATV in CASTLE

- **ATV exposures (24 hour AUC and C_{min}) are higher than those observed in CASTLE for ATV+RTV + Truvada**
- **RAL overall exposures are comparable to historical data**

Response Rate (HIV RNA < 50 c/mL) through Week 48 VR-OC



ATV+RAL: N=63	62	62	61	62	59	57	52	56	51	51	48	47	45
ATV+RTV+TDF/FTC: N=30	29	28	29	28	27	23	25	26	26	25	27	25	25

Week 48 CD4 mean change from baseline: ATV+RAL: 235 cells/cm^3 ; ATV/RTV+TDF/FTC: 197 cells/cm^3

VR-OC is an on-treatment method. It classifies subjects as responders according to a single on-treatment HIV RNA measurement < 50 c/mL closest to the planned visit and within a pre-defined visit window. The denominator is based on subjects with an on-treatment HIV RNA measurement in that visit window.

Conclusions through week 24

- **Response rates (HIV RNA < 50 c/mL) for ATV+RAL at primary endpoint (week 24) were consistent with current standard of care**
- **There were no new or unexpected safety signals for ATV 300mg BID**
  - **Grade 4 Hyperbilirubinemia rates are higher than with ATV/RTV**
- **There were no new or unexpected safety signals for RAL 400mg BID**
- **Through week 24, 4 patients on ATV+RAL developed genotypic and phenotypic resistance to RAL**
- **No subjects developed ATV resistance in either arm throughout the study**
- **ATV exposures were higher for ATV + RAL 300/400 mg BID regimen than those observed with ATV300/RTV100 mg plus TDF/FTC**
- **RAL overall exposures were comparable to historical data**

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