APPENDIX A

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Thecontentissolelytheresponsibilityoftheauthorsanddoesnot necessarilyrepresent the official viewsofthe National Institutes of Health.

Conflicts of Interest

JHS is Director of an ultrasound lab that receives research funding from Gilead. He receives royalties from the Wisconsin Alumni Research Foundation for intellectual property related to carotid ultrasound and vascular age (technology not used in this study).

TTB has served as a consultant for Bristol-Myers Squibb, GlaxoSmithKline, Merck, Abbott, Gilead, ViiV Healthcare and has received research funding from Merck and GlaxoSmithKline.

GAM has served as a consultant, speaker, and has received research funding from Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Merck, and Tibotec. She also chaired a Data and Safety Monitoring Board for a Pfizer-funded study.

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JH Stein – conception, design, obtained funding, conduct of study, data analysis, draft of manuscript, critical revision of manuscript

HJ Ribaudo - design, conduct of study, data analysis, critical revision of manuscript

HN Hodis – design, conduct of study, critical revision of manuscript

TT Brown – design, conduct of study, critical revision of manuscript

TTT Tran - data analysis, critical revision of manuscript

Mingzhu Yan - conduct of study, critical revision of manuscript

Elizabeth Lauer-Brodell - conduct of study, critical revision of manuscript

T Kelesidis - data analysis, critical revision of manuscript

GA McComsey - design, conduct of study, critical revision of manuscript

MP Dube – conduct of study, critical revision of manuscript

RL Murphy - conduct of study, critical revision of manuscript

JS Currier - conception, design, obtained funding, conduct of study, data analysis, critical revision of manuscript

Participating Sites

ThefollowingAIDS Clinical Trials Units participated inthisstudy:103- BethIsrael DeaconessMedical CenterACTGCRS 6;107-Brigham andWomen'sHospital Therapeutics ACTG CRS 5; 201-JohnsHopkins UniversityCRS 11;401- NY University HIV/AIDS CRS 11;601- UCLACARE CenterCRS 8; 603- Harbor-UCLA Med.Ctr.CRS 24;801-UCSF AIDS CRS 4;1001–Universityof Pittsburgh CRS 4; 1101–University ofRochesterACTG CRS 4;1108- Trillium Health ACTGCRS 8;1201 -USC CRS 30;1401-UniversityofWashingtonAIDS CRS 18; 1601-DukeUniversityMedical CenterAdultCRS 3;2101-WashingtonUniversity Therapeutics CRS 23;2301- OhioState University AIDS CRS 9; 2401- Univ.ofCincinnati CRS 28;2501- CaseWestern ReserveCRS 12;2503-MetroHealthCRS 1;2701- NorthwesternUniversity CRS 23;2702- Rush UniversityMedical CenterACTG CRS 8;3201- Chapel HillCRS 15;3652-Vanderbilt TherapeuticsCRS 17;5802- Ponce de Leon Center CRS 3; 6101- UniversityofColorado Hospital CRS 40; 31473-HoustonAIDS ResearchTeamCRS 10;31477-NewJerseyMedical School-Adult Clinical Research CenterCRS 9.

SUPPLEMENTAL MATERIAL

Supplement Table 1. Baseline Characteristics of A5260s subjects and A5257 subjects not enrolled in A5260s study

Characteristic [1]	A5260s subjects (N=328)	A5257 subjects not enrolled in A5260s [2] (N=665)	P-Value
Sex			<0.001*
M	294 (90%)	494 (74%)	
F	34 (10%)	171 (26%)	
Age, years	36 (28-45)	37 (28-45)	0.97**
Race/ethnicity			0.001*
Non-Hispanic White	144 (44%)	241 (36%)	
Non-Hispanic Black	105 (32%)	293 (44%)	
Hispanic	65 (20%)	117 (18%)	
Asian/Other/More than one race	13 (4%)	12 (2%)	
10 year risk of hard coronary heart disease (%)			0.20*
Low (<6%)	289 (88%)	598 (91%)	
Medium/High (≥6%)	39 (12%)	61 (9%)	
HIV-1 RNA, $\log_{10}$ copies/ml	4.5 (4.0-5.1)	4.7 (4.3-5.2)	<0.001**
CD4+ cell count, /mm³	349 (203-455)	277 (114-392)	<0.001**
Systolic blood pressure, mm Hg	117 (108-125)	118 (109-127)	0.08**
Diastolic blood pressure, mmHg	74 (68-80)	75 (68-82)	0.34**
Fasting total cholesterol, mg/dL	155 (133-179)	152 (133-175)	0.25**
Fasting triglycerides, mg/dL	102 (70-146)	104 (74-144)	0.75**
Fasting high-density lipoprotein cholesterol, mg/dL	38 (31-45)	37 (30-45)	0.54**
Fasting non-HDL cholesterol, mg/dL	115 (96-139)	114 (95-133)	0.28**
Calculated fasting low-density lipoprotein cholesterol, mg/dL	92 (74-115)	92 (73-110)	0.28**
Body mass index, kg/m²	25 (22-28)	25 (22-28)	0.59**
Waist circumference, cm	88 (81-98)	88 (81-97)	0.78**

Characteristic [1]	A5260s subjects (N=328)	A5257 subjects not enrolled in A5260s [2] (N=665)	P-Value
Metabolic syndrome	44 (13%)	136 (21%)	0.006*
Current smoker	124 (38%)	247 (37%)	0.84*

[1] Medians (first and third quartiles) or number (%).
[2] Subjects included only those from the same clinical sites meeting A5260s eligibility criteria.
All lipid panel measures are from samples that were tested in local labs.
**Chi-Square Test; **Wilcoxon Test.*

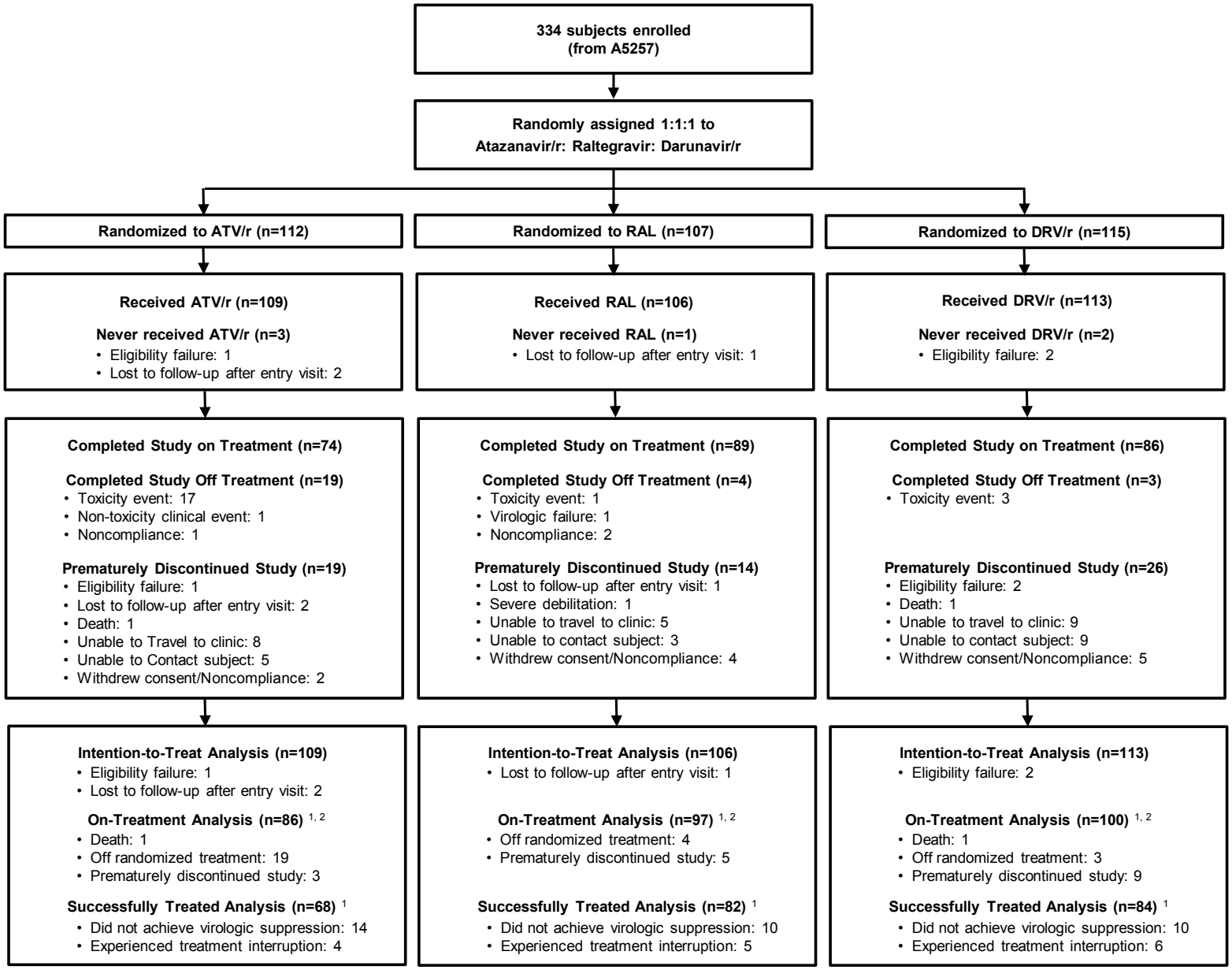
Supplement Table 2. Bilirubin-Adjusted Treatment Effects on Common Carotid Artery Intima-Media Thickness Progression in Successfully Treated Population

	Difference in Annual Rate of IMT Change (μm/year)		Adjusted Treatment Group Differences in Annual Rate of Change (μm/year)					
			ATV/r vs. DRV/r		ATV/r vs. RAL		DRV/r vs. RAL	
Bilirubin level at week 4 [1]		***p***		***p***		***p***		***p***
Continuous (mg/dL)	1.66	0.22	-8.04	0.010	-6.70	0.026	1.34	0.55
Week 4 > vs. ≤0.6	-2.19	0.42	-3.82	0.24	-2.97	0.32	0.85	0.71
Week 4 > vs. ≤0.8	5.26	0.14	-10.07	0.009	-8.50	0.019	1.57	0.49
Week 4 > vs. ≤1.0	2.55	0.48	-7.56	0.040	-6.30	0.07	1.26	0.58
Bilirubin level at week 24 [1]								
Continuous (mg/dL)	1.02	0.42	-7.94	0.013	-5.85	0.06	2.09	0.35
Week 24 > vs. ≤0.6	-1.67	0.50	-4.94	0.11	-3.33	0.23	1.60	0.48
Week 24 > vs. ≤0.8	2.20	0.44	-7.94	0.015	-5.67	0.06	2.27	0.32
Week 24 > vs. ≤1.0	1.77	0.58	-7.60	0.027	-5.50	0.09	2.11	0.35

IMT = intima-media thickness

[1] *Analyses adjusted for screening HIV-1 RNA level and Framingham risk scores, baseline common carotid artery intima-media thickness (μm) and time by treatment interaction.*

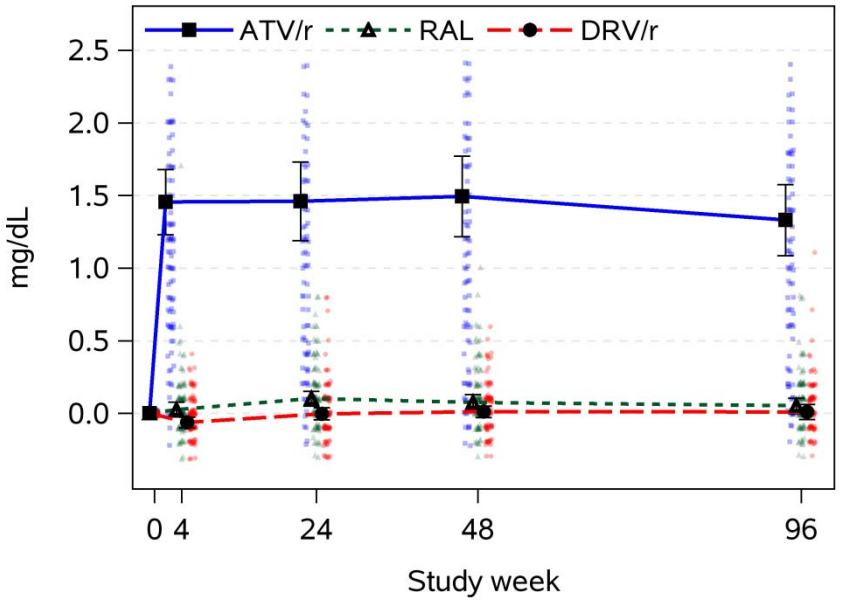
Supplement Figure 1. CONSORT Diagram



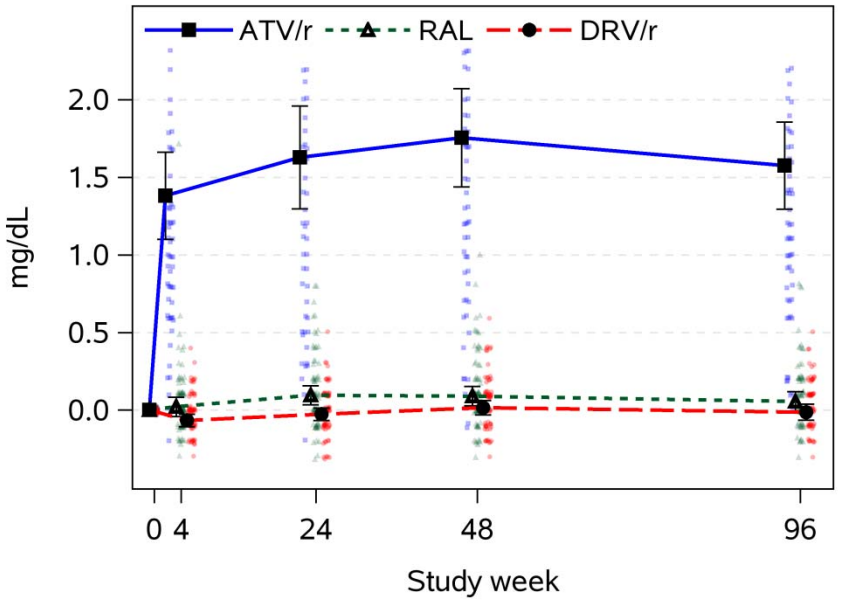
[1] The on-treatment analysis population is a subset of the ITT analysis population. Similarly, the successfully treated analysis population is a subset of the on-treatment analysis population. [2] The on-treatment analysis population Includes subjects who remained on randomized treatment despite prematurely discontinuing substudy follow-up.

Supplement Figure 2. Change in Total Bilirubin Levels from Baseline among Successfully Treated Population

(a) Intention to treat



(b) Successfully treated



Point estimates and error bars give mean and 95% confidence intervals, respectively.
ATV/r = Atazanavir/Ritonavir
DRV/r = Darunavir/ Ritonavir
RAL = Raltegravir