APPENDIX A

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The content is solely the responsibility of the authors and does not necessarily represent the official views of the 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

The following AIDS Clinical Trials Units participated in this study: 103- Beth Israel Deaconess Medical Center ACTG CRS 6; 107- Brigham and Women's Hospital Therapeutics ACTG CRS 5; 201- Johns Hopkins University CRS 11; 401- NY University HIV/AIDS CRS 11; 601- UCLA CARE Center CRS 8; 603- Harbor-UCLA Med. Ctr. CRS 24; 801- UCSF AIDS CRS 4; 1001- University of Pittsburgh CRS 4; 1101- University of Rochester ACTG CRS 4; 1108- Trillium Health ACTG CRS 8; 1201- USC CRS 30; 1401- University of Washington AIDS CRS 18; 1601- Duke University Medical Center Adult CRS 3; 2101- Washington University Therapeutics CRS 23; 2301- Ohio State University AIDS CRS 9; 2401- Univ. of Cincinnati CRS 28; 2501- Case Western Reserve CRS 12; 2503- Metro Health CRS 1; 2701- Northwestern University CRS 23; 2702- Rush University Medical Center ACTG CRS 8; 3201- Chapel Hill CRS 15; 3652- Vanderbilt Therapeutics CRS 17; 5802- Ponce de Leon Center CRS 3; 6101- University of Colorado Hospital CRS 40; 31473- Houston AIDS Research Team CRS 10; 31477- New Jersey Medical School-Adult Clinical Research Center CRS 9.
## Supplemental Material

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>A5260s subjects (N=328)</th>
<th>A5257 subjects not enrolled in A5260s (N=665)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>294 (90%)</td>
<td>494 (74%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>F</td>
<td>34 (10%)</td>
<td>171 (26%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>36 (28-45)</td>
<td>37 (28-45)</td>
<td>0.97**</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
<td>0.001*</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>144 (44%)</td>
<td>241 (36%)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>105 (32%)</td>
<td>293 (44%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>65 (20%)</td>
<td>117 (18%)</td>
<td></td>
</tr>
<tr>
<td>Asian/Other/More than one race</td>
<td>13 (4%)</td>
<td>12 (2%)</td>
<td></td>
</tr>
<tr>
<td><strong>10 year risk of hard coronary heart disease (%)</strong></td>
<td></td>
<td></td>
<td>0.20*</td>
</tr>
<tr>
<td>Low (&lt;6%)</td>
<td>289 (88%)</td>
<td>598 (91%)</td>
<td></td>
</tr>
<tr>
<td>Medium/High (≥6%)</td>
<td>39 (12%)</td>
<td>61 (9%)</td>
<td></td>
</tr>
<tr>
<td><strong>HIV-1 RNA, log_{10} copies/ml</strong></td>
<td>4.5 (4.0-5.1)</td>
<td>4.7 (4.3-5.2)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td><strong>CD4+ cell count, /mm^{3}</strong></td>
<td>349 (203-455)</td>
<td>277 (114-392)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mm Hg</strong></td>
<td>117 (108-125)</td>
<td>118 (109-127)</td>
<td>0.08**</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure, mmHg</strong></td>
<td>74 (68-80)</td>
<td>75 (68-82)</td>
<td>0.34**</td>
</tr>
<tr>
<td><strong>Fasting total cholesterol, mg/dL</strong></td>
<td>155 (133-179)</td>
<td>152 (133-175)</td>
<td>0.25**</td>
</tr>
<tr>
<td><strong>Fasting triglycerides, mg/dL</strong></td>
<td>102 (70-146)</td>
<td>104 (74-144)</td>
<td>0.75**</td>
</tr>
<tr>
<td><strong>Fasting high-density lipoprotein cholesterol, mg/dL</strong></td>
<td>38 (31-45)</td>
<td>37 (30-45)</td>
<td>0.54**</td>
</tr>
<tr>
<td><strong>Fasting non-HDL cholesterol, mg/dL</strong></td>
<td>115 (96-139)</td>
<td>114 (95-133)</td>
<td>0.28**</td>
</tr>
<tr>
<td><strong>Calculated fasting low-density lipoprotein cholesterol, mg/dL</strong></td>
<td>92 (74-115)</td>
<td>92 (73-110)</td>
<td>0.28**</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m^{2}</strong></td>
<td>25 (22-28)</td>
<td>25 (22-28)</td>
<td>0.59**</td>
</tr>
<tr>
<td><strong>Waist circumference, cm</strong></td>
<td>88 (81-98)</td>
<td>88 (81-97)</td>
<td>0.78**</td>
</tr>
<tr>
<td>Characteristic</td>
<td>A5260s subjects (N=328)</td>
<td>A5257 subjects not enrolled in A5260s (N=665)</td>
<td>P-Value</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------------</td>
<td>-----------------------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>44 (13%)</td>
<td>136 (21%)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Current smoker</td>
<td>124 (38%)</td>
<td>247 (37%)</td>
<td>0.84*</td>
</tr>
</tbody>
</table>

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

| Bilirubin level at week 4 † | 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                   |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                  |
| 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 †

| 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
†† 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

334 subjects enrolled (from A5257)

Randomly assigned 1:1:1 to Atazanavir/r: Raltegravir: Darunavir/r

Randomized to ATV/r (n=112)

Completed Study on Treatment (n=74)
- Toxicity event: 17
- Non-toxicity clinical event: 1
- Noncompliance: 1

Completed Study Off Treatment (n=19)
- Eligibility failure: 1
- Lost to follow-up after entry visit: 2

Prematurely Discontinued Study (n=19)
- Eligibility failure: 1
- Lost to follow-up after entry visit: 2
- Death: 1
- Unable to travel to clinic: 8
- Unable to contact subject: 5
- Withdrew consent/Noncompliance: 2

Received ATV/r (n=109)
- Never received ATV/r (n=3)
  - Eligibility failure: 1
  - Lost to follow-up after entry visit: 2

Intention-to-Treat Analysis (n=109)
- Eligibility failure: 1
- Lost to follow-up after entry visit: 2

On-Treatment Analysis (n=86) 1, 2
- Death: 1
- Off randomized treatment: 19
- Prematurely discontinued study: 3

Successfully Treated Analysis (n=68) 1
- Did not achieve virologic suppression: 14
- Experienced treatment interruption: 4

Intention-to-Treat Analysis (n=106)
- Lost to follow-up after entry visit: 1

On-Treatment Analysis (n=97) 1, 2
- Off randomized treatment: 4
- Prematurely discontinued study: 5

Successfully Treated Analysis (n=82) 1
- Did not achieve virologic suppression: 10
- Experienced treatment interruption: 5

Randomized to RAL (n=107)

Completed Study on Treatment (n=89)
- Toxicity event: 1
- Virologic failure: 1
- Noncompliance: 2

Completed Study Off Treatment (n=4)
- Eligibility failure: 1
- Lost to follow-up after entry visit: 1

Prematurely Discontinued Study (n=14)
- Eligibility failure: 1
- Lost to follow-up after entry visit: 1
- Severe debilitation: 1
- Unable to travel to clinic: 5
- Unable to contact subject: 3
- Withdrew consent/Noncompliance: 4

Received RAL (n=106)
- Never received RAL (n=1)
- Lost to follow-up after entry visit: 1

Intention-to-Treat Analysis (n=106)
- Lost to follow-up after entry visit: 1

On-Treatment Analysis (n=97) 1, 2
- Off randomized treatment: 4
- Prematurely discontinued study: 5

Successfully Treated Analysis (n=82) 1
- Did not achieve virologic suppression: 10
- Experienced treatment interruption: 5

Randomized to DRV/r (n=115)

Completed Study on Treatment (n=86)
- Eligibility failure: 1
- Death: 1
- Unable to travel to clinic: 9
- Unable to contact subject: 9
- Withdrew consent/Noncompliance: 5

Completed Study Off Treatment (n=3)
- Eligibility failure: 1
- Lost to follow-up after entry visit: 1

Prematurely Discontinued Study (n=26)
- Eligibility failure: 2
- Death: 1
- Unable to travel to clinic: 9
- Unable to contact subject: 9
- Withdrew consent/Noncompliance: 5

Received DRV/r (n=113)
- Never received DRV/r (n=2)
- Eligibility failure: 2

Intention-to-Treat Analysis (n=113)
- Eligibility failure: 2

On-Treatment Analysis (n=100) 1, 2
- Death: 1
- Off randomized treatment: 3
- Prematurely discontinued study: 9

Successfully Treated Analysis (n=84) 1
- Did not achieve virologic suppression: 10
- Experienced treatment interruption: 6

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

RAL = Raltegravir