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Inflammatory Biomarker Changes and Their Correlation with Framingham Cardiovascular Risk and Lipid Changes in Antiretroviral-Naive HIV-Infected Patients Treated for 144 Weeks with Abacavir/Lamivudine/Atazanavir with or without Ritonavir in ARIES

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Abstract

Propensity for developing coronary heart disease (CHD) is linked with Framingham-defined cardiovascular risk factors and elevated inflammatory biomarkers. Cardiovascular risk and inflammatory biomarkers were evaluated in ARIES, a Phase IIIb/IV clinical trial in which 515 antiretroviral-naive HIV-infected subjects initially received abacavir/lamivudine + atazanavir/ritonavir for 36 weeks. Subjects who were virologically suppressed by week 30 were randomized 1:1 at week 36 to either maintain or discontinue ritonavir for an additional 108 weeks. Framingham 10-year CHD risk scores (FRS) and risk category of <6% or ≥6%, lipoprotein-associated phospholipase A2 (Lp-PLA2), interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hsCRP) were assessed at baseline, week 84, and week 144. Biomarkers were stratified by FRS category. When ritonavir-boosted/nonboosted treatment groups were combined, median hsCRP did not change significantly between baseline (1.6 mg/liter) and week 144 (1.4 mg/liter) in subjects with FRS <6% (p = 0.535) or with FRS ≥6% (1.9 mg/liter vs. 2.0 mg/liter, respectively; p = 0.102). Median IL-6 was similar for subjects with FRS <6% (1.6 pg/ml) and week 144 (1.4 pg/ml) and for FRS ≥6% (2.0 pg/ml vs. 2.2 pg/ml, respectively; p = 0.099). Median Lp-PLA2 decreased significantly (p < 0.001) between baseline (197 nmol/min/ml) and week 144 (168 nmol/min/ml) in subjects with FRS <6% and with FRS ≥6% (238 nmol/min/ml vs. 175 nmol/min/ml, respectively; p < 0.001). In conclusion, in antiretroviral-naive subjects treated with abacavir-based therapy for 144 weeks, median inflammatory biomarker levels for hsCRP and IL-6 generally remained stable with no significant difference between baseline and week 144 for subjects with either FRS <6% or FRS ≥6%. Lp-PLA2 median values declined significantly over 144 weeks for subjects in either FRS stratum.

Introduction

Clinical studies suggest that many factors may be associated with an elevated risk of coronary heart disease (CHD) among HIV-infected compared with non-HIV-infected individuals.1-3 Infection with HIV has been associated with CHD-exacerbating chronic inflammation, as indicated by elevated inflammatory biomarkers4 and hypercoagulability leading to increased thrombogenesis.5,6 Due to the effectiveness of highly active antiretroviral treatment (HAART), many HIV-infected individuals are now living well beyond 50 years of age and are also developing aging-related comorbid medical conditions that may increase CHD risk, such as hypertension, diabetes, impaired kidney function, and obesity.7

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A substantial proportion of these individuals have lifestyle practices (e.g., smoking, sedentary, high-fat diet) that over time can hasten atherosclerosis and thrombosis development.7 HIV-infected patients have a higher prevalence of prolonged corrected QT interval and an increased risk for malignant arrhythmia and cardiovascular mortality.8 In addition, several non-age-related comorbid medical conditions have the potential to negatively impact cardiac status (co-infection with hepatitis B or C, intravenous drug use, cocaine use, excessive alcohol consumption). Finally, the combinations of antiretroviral agents that comprise effective HAART regimens may expose treated patients to long-term mitochondrial toxicity and drug-associated lipid elevation that have an additive adverse impact on their heart and blood vessels.9

As with HIV-negative individuals, thorough assessment of cardiovascular risk in the HIV population requires focus on traditional CHD risk factors strongly associated with worsening cardiac status, as described in the Framingham equation, and use of the readily available tool to calculate the 10-year risk of developing CHD [myocardial infarction (MI) and coronary death] that incorporates patient age, gender, total cholesterol, high-density lipoprotein (HDL)-cholesterol, smoking status, systolic blood pressure, and antihypertensive medication use.10,11 Clinical investigations have also evaluated cardiovascular risk status by assessing the predictive utility of measuring inflammation-associated biomarkers in HIV-infected patients. In particular, changes in certain biomarkers, including elevated levels of lipoprotein-associated phospholipase A2 (Lp-PLA2), interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hsCRP), have each been associated with increased cardiovascular risk.4,12

Dyslipidemic effects of antiretrovirals may potentially lead to an increased risk in CHD in HIV-infected patients. While atazanavir (ATV) has demonstrated little dyslipidemic impact as compared with certain other protease inhibitors (PIs), there are concerns regarding ritonavir (/r)-boosted PI regimens as potentially increasing CHD risk, although whether this would be associated with any change in inflammatory biomarker concentrations is unclear.13–16 Abacavir (ABC) is a generally well-tolerated nucleoside reverse transcriptase inhibitor (NRTI) that has been used in combination antiretroviral regimens since the 1990s,17 and while the majority of studies8–22 have not demonstrated an increased ABC-attributable CHD risk in the absence of confounding factors, two recent analyses of observational cohorts23,24 reported a statistically increased incidence in MI in HIV-infected patients receiving ABC-based therapy with various third agents.

To better define any underlying cardiovascular risk mechanism and to evaluate whether the use of ritonavir boosting and/or ABC use could be affecting inflammatory biomarker levels, a prospective cardiovascular risk analysis was performed in ARIES (Atazanavir, Ritonavir, Induction with Epzicom Study; EPZ108859). ARIES was a large phase IIIb/IV treatment-simplification clinical trial in which antiretroviral therapy-naive subjects who achieved virologic suppression by week 30 on a regimen of abacavir/lamivudine (ABC/3TC) plus atazanavir/ritonavir (ATV/r) were randomized to remain on their original regimen or discontinue the ritonavir component of the regimen for up to a total of 144 weeks.25–27 In this analysis, subjects had baseline assessment of their Framingham 10-year CHD risk scores and were classified as low or moderate risk groups (<6% or ≥6%). Plasma concentrations of hsCRP, IL-6, and Lp-PLA2, and fasting lipids were assessed at baseline, week 84, and week 144. These parameters were evaluated by treatment group and/or by risk group to determine whether there were any significant differences over time and if these changes were influenced by baseline risk classification or long-term inclusion of ritonavir in the HAART regimen.

Materials and Methods

Study design

ARIES was a randomized, open-label, noninferiority, multicenter study and was conducted at outpatient HIV clinics in the United States and Canada, and enrolled HLA-B5701-negative, antiretroviral-naive (≤14 days of prior NRTI and no prior PI or NNRTI) HIV-infected subjects ≥18 years old with a screening viral load ≥1000 copies/ml and any CD4+ cell level (a detailed study design has been presented elsewhere25–27). Subjects with cardiovascular disease per se could be included in this study, although subjects were excluded if they had medical conditions that investigators considered severe enough to compromise safety [diabetes mellitus, congestive heart failure, cardiomyopathy, or other cardiac dysfunction, clinically significant cardiac conduction system disease, severe first-degree atrioventricular block (PR interval >0.26 s), or second- or third-degree atrioventricular block].

The primary objective of ARIES was to evaluate the efficacy, safety, tolerability, and durability of antiviral response with ABC/3TC plus ATV/r compared to this regimen without ritonavir. Subjects were initiated on a 36-week regimen of once-daily ABC/3TC fixed-dose combination (600 mg/300 mg, Epzicom, ViiV Healthcare, Research Triangle Park, NC) plus ATV (300 mg, Reyataz, Bristol-Myers Squibb, New York, NY) and ritonavir (r) (100 mg, Norvir, Abbott, Abbott Park, IL). At week 36, subjects who had achieved a confirmed viral load <50 copies/ml by week 30 were randomized 1:1 to either ABC/3TC plus unboosted ATV 400 mg once daily (the “simplification” regimen) or to continue ABC/3TC plus ATV/r 300/100 mg once daily for 48 weeks. Subjects who remained in the study through week 84 were offered the opportunity to participate in an “extension phase” of the study, during which they were maintained on their current treatment regimen through week 144. Subjects were not required to have plasma HIV-1 RNA <50 copies/ml at week 84 to participate in the extension phase. Per protocol, subjects were required to withdraw from the study if they failed to achieve plasma HIV-1 RNA <400 copies/ml by week 30 or if they experienced confirmed HIV-1 RNA rebound ≥400 copies/ml after achieving virologic suppression to <400 copies/ml and their confirmatory viral load result was ≥2,000 copies/ml. All subjects provided written informed consent to participate in the extension phase and the study was approved by the ethics review board for each participating center. The study was conducted in accordance with Good Clinical Practice.

Framingham risk measurement

Framingham 10-year CHD risk scores were calculated at baseline, week 84, and week 144 using an algorithm that factored in baseline cardiac risk factors including sex, age,
total cholesterol, HDL-cholesterol, low-density lipoprotein (LDL)-cholesterol, smoking status, blood pressure, and diabetes history. Subjects with Framingham 10-year CHD risk scores <6% (connoting low risk, i.e., <6% chance of an MI within the next 10 years) were subclassified from subjects with risk scores ≥6% (connoting at least moderate risk, i.e., ≥6% chance of an MI within the next 10 years).28

Biomarker measurements

EDTA-containing plasma samples were collected at baseline, week 84, and week 144 for measurement of hsCRP and IL-6 concentrations and Lp-PLA2 activity. All samples were stored at −80°C until analysis by Quest Diagnostic Nichols Institute (San Juan Capistrano, CA). hsCRP concentrations were assessed by fixed-time nephelometry using a Siemens Dade Behring BN II nephelometer (Siemens Healthcare Diagnostics, Inc., Tarrytown, NY) with an intraassay coefficient of variation (CV) of 3.7%, an interassay CV of 2.8%, and reportable range of 0.2–1,100 µg/ml. IL-6 concentrations were assessed by enzyme-linked immunosorbent immunoassay (ELISA) with an intraassay CV of 7.0%, interassay CV of 11.3%, and reportable range of 0.31–5.00 pg/ml. Lp-PLA2 activity was assessed by a colorimetric activity method using a microtiter plate analyzer (CTL-US-Valencia). The assay characteristics included intraassay precision of 1.7% and interassay precision of 4.8%.

Lipid measurements

A fasting lipid panel was done at baseline and every 12 weeks thereafter through week 144. In the unboosted ATV and ATV/r groups, median fasting lipid concentrations were compared at baseline, week 84, and week 144. These median concentrations were also compared to the cut-points (maximum concentrations considered within normal limits) established by the U.S. Department of Health and Human Services National Cholesterol Education program (NCEP) guidelines.29

Statistical analysis

All analyses of Framingham CHD risk scores, biomarkers, and fasting lipids were done in the intent-to-treat-exposed population. The biomarker values were grouped by the Framingham 10-year scores in females were 0% (0–11%) at baseline, 0% (0–8%) at week 84, and 1% (0–6%) at week 144. Similarly, in the ATV/r group, 9% (13/144) of subjects at <6% risk at baseline were reclassified to ≥6% risk by week 144, while 3% (5/146) at ≥6% risk at baseline were reclassified to <6% risk by week 144.

Within each treatment regimen, median Framingham 10-year risk scores showed little change in median risk over time. The unboosted ATV group had a median (IQR) Framingham 10-year risk score of 1% (0–20%) at baseline, 1% (0–25%) at week 84, and 1% (0–31%) at week 144, while the ATV/r group had a median (IQR) Framingham 10-year risk score of 1% (0–20%) at baseline, 2% (0–31%) at week 84, and 2% (0–31%) at week 144.

In a subsequent analysis by gender, Framingham 10-year risk scores also showed little change over time. For the unboosted ATV group, females had median (IQR, Q1–Q3) Framingham 10-year scores of 0% (0–14%) at baseline, 0% (0–11%) at week 84, and 1% (0–6%) at week 144, and males had scores of 1% (0–20%) at baseline, 1% (0–25%) at week 84, and 1% (0–31%) at week 144. Similarly, in the ATV/r group, the scores in females were 0% (0–11%) at baseline, 0% (0–8%) at week 84, and 0% (0–11%) at week 144, and the scores in males were 2% (0–20%) at baseline, 2% (0–31%) at week 84, and 3% (0–31%) at week 144.

Biomarker changes in the overall population

For the overall population, biomarker changes between the start of treatment and 144 weeks were minimal (Table 2). Median hsCRP concentrations in subjects with baseline Framingham risk scores <6% did not differ significantly between baseline (1.6 mg/liter) and week 84 (1.6 mg/liter; p = 0.677) or between baseline and week 144 (1.4 mg/liter; p = 0.535). Similarly, for subjects with baseline Framingham risk scores ≥6%, median hsCRP concentrations did not differ significantly between baseline (1.9 mg/liter) and week 84 (1.7 mg/liter;
In the IL-6 analyses, median concentrations in subjects with baseline Framingham risk scores <6% (1.6 pg/ml) declined significantly \( (p < 0.001) \) at week 84 to 1.2 pg/ml, and remained marginally lower than the baseline value at week 144 (1.4 pg/ml), although this difference was not statistically significant \( (p = 0.267) \). In subjects with baseline risk scores \( \geq 6\% \), median values remained relatively stable between baseline and week 84 (from 2.0 to 1.8 pg/ml, \( p = 0.522 \)) before slightly increasing to a level that was nonsignificantly higher than baseline at week 144 (2.2 pg/ml, \( p = 0.099 \)).

Of the biomarkers, the most consistent reduction in concentrations over the entire 144-week study period occurred in Lp-PLA2 activity. Thus, in subjects with baseline Framingham CHD risk scores <6%, median Lp-PLA2 activity fell significantly from a baseline of 197 to 189 nmol/min/ml at week 84 \( (p < 0.001) \) and to 168 nmol/min/ml at week 144 \( (p < 0.001) \). Similarly, in subjects with baseline risk scores \( \geq 6\% \), median Lp-PLA2 activity decreased significantly from a baseline of 238 to 210 nmol/min/ml at week 84 \( (p < 0.001) \) and to 175 nmol/min/ml at week 144 \( (p < 0.001) \).

### Biomarker changes by treatment group

Since levels of hsCRP > 3 mg/liter have been considered by some groups to be a critical clinical cut-off for patients at “high risk” for future heart disease, the hsCRP biomarker results were evaluated by treatment group applying this cut-point. In the ATV/r-treated group for subjects with paired baseline and week 144 data, the proportion of subjects with hsCRP > 3 mg/liter at baseline was 30% (45/152 subjects) and remained similar to that observed at week 144 [34% (51/152 subjects)]. Likewise, in the unboosted ATV-treated group, the...
The proportion of subjects with hsCRP > 3 mg/liter at baseline [28% (44/159)] was virtually unchanged compared with that at week 144 [27% (43/159)]. Regardless of whether subjects in the ATV/r and unboosted ATV groups had baseline Framingham risk scores <6% or ≥6%, no significant changes were observed between baseline and week 84 or between baseline and week 144 (Table 2). There was a small but not statistically significant decline in median hsCRP levels from baseline through week 144 for both treatment groups and, similarly, there was no statistically significant change from baseline for this biomarker when evaluated by Framingham risk score for either treatment group over 144 weeks.

In the IL-6 analyses, subjects with Framingham risk scores <6% in the ATV/r and unboosted ATV groups had a significant decrease in median IL-6 concentrations at week 84 compared to baseline, which was no longer apparent at week 144 (Table 2). No other significant changes from baseline were observed at week 84 or week 144 in either treatment group regardless of baseline Framingham risk score being <6% or ≥6%.

In the Lp-PLA2 analyses, the ATV/r and unboosted ATV groups had significant decreases from baseline in Lp-PLA2 concentrations at both week 84 and week 144, and this was observed in subjects with baseline Framingham risk scores <6% as well as those with scores ≥6% (Table 2).

### Table 2. Biomarker Data

<table>
<thead>
<tr>
<th>Study visit</th>
<th>Baseline</th>
<th>Week 84</th>
<th>Week 144</th>
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<tbody>
<tr>
<td>10-Year Framingham CHD risk score</td>
<td>n</td>
<td>Median (Q1–Q3)</td>
<td>n</td>
</tr>
<tr>
<td>hsCRP (mg/liter)</td>
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<td></td>
<td></td>
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<tr>
<td>ATV and ATV/r arms combined</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6%</td>
<td>285</td>
<td>1.6 (0.6–3.4)</td>
<td>280</td>
</tr>
<tr>
<td>≥6%</td>
<td>61</td>
<td>1.9 (0.9–2.8)</td>
<td>60</td>
</tr>
<tr>
<td>All</td>
<td>346</td>
<td>1.6 (0.7–3.3)</td>
<td>340</td>
</tr>
<tr>
<td>ATV arm alone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6%</td>
<td>147</td>
<td>1.5 (0.6–3.5)</td>
<td>144</td>
</tr>
<tr>
<td>≥6%</td>
<td>31</td>
<td>1.8 (0.7–3.6)</td>
<td>30</td>
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<tr>
<td>All</td>
<td>178</td>
<td>1.6 (0.6–3.5)</td>
<td>174</td>
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<tr>
<td>ATV/r arm alone</td>
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<td></td>
</tr>
<tr>
<td>&lt;6%</td>
<td>138</td>
<td>1.6 (0.6–3.4)</td>
<td>136</td>
</tr>
<tr>
<td>≥6%</td>
<td>30</td>
<td>2.0 (1.0–2.7)</td>
<td>30</td>
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<tr>
<td>All</td>
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<td>1.6 (0.7–3.1)</td>
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<td>IL-6 (pg/ml)</td>
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<td>&lt;6%</td>
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<td>1.6 (1.0–2.5)</td>
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<td>≥6%</td>
<td>61</td>
<td>2.0 (1.3–2.6)</td>
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<tr>
<td>All</td>
<td>348</td>
<td>1.6 (1.0–2.5)</td>
<td>348</td>
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<tr>
<td>ATV arm alone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6%</td>
<td>147</td>
<td>1.6 (1.0–2.6)</td>
<td>147</td>
</tr>
<tr>
<td>≥6%</td>
<td>31</td>
<td>1.9 (1.1–3.1)</td>
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<td>1.6 (1.0–2.6)</td>
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<td>2.1 (1.4–2.6)</td>
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<td>170</td>
<td>1.6 (1.1–2.5)</td>
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<td>Lp-PLA2 (nmol/min/ml)</td>
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<tr>
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<td>203 (166–250)</td>
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<tr>
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<tr>
<td>&lt;6%</td>
<td>146</td>
<td>193 (159–224)</td>
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<td>All</td>
<td>176</td>
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<td></td>
</tr>
<tr>
<td>&lt;6%</td>
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<td>208 (170–253)</td>
<td>140</td>
</tr>
<tr>
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</tr>
<tr>
<td>All</td>
<td>168</td>
<td>212 (174–255)</td>
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</table>

*p-values from Wilcoxon signed-rank test comparing baseline and postbaseline.

CHD, coronary heart disease; hsCRP, high sensitivity C-reactive protein; IL-6, interleukin-6; Lp-PLA2, lipoprotein-associated phospholipase A2; Q1–Q3, first quartile through third quartile; ATV/r, atazanavir/ritonavir.
Triglyceride, mg/dl (median) 127, 123
LDL-cholesterol, mg/dl (median) 88, 85
HDL-cholesterol, mg/dl (median) 37, 39
Total cholesterol, mg/dl (median) 152, 153
Total cholesterol/HDL-cholesterol ratio (median) 4.15, 4.10

With a shorter period (typically 12 months) of observation.33–35 With although these studies involved smaller populations and a
from non-ABC-containing regimens to ABC/3TC regimens, antiretroviral-experienced subjects who have been switched
Similarly, in other studies a lack of significant long-term
STEAL).30,31 In these studies, when an ABC/3TC nucleoside
low cardiovascular risk. Median Framingham risk scores did
median hsCRP and IL-6 levels in the overall study population,
no significant change between baseline and week 144 in
‡ Change from BL to week 36
BL, baseline
Change from Change from Change from
BL, ATV, ATV, ATV, ATV, ATV, ATV, ATV, ATV, ATV, ATV, ATV, ATVR
ATVR
BL to week 36
BL to week 36 to week 144
BL to week 144

Total cholesterol, mg/dl (median) 152, 153
p-value 0.7626 0.4138 0.005 0.0031
HDL-cholesterol, mg/dl (median) 37, 39
p-value 0.8641 0.7269 0.8492 0.9515
LDL-cholesterol, mg/dl (median) 88, 85
p-value 0.9662 0.2490 0.1195 0.05
Total cholesterol/HDL-cholesterol ratio (median) 4.15, 4.10
p-value 0.9207 0.3532 0.0076 0.0168
Triglyceride, mg/dl (median) 127, 123
p-value 0.7550 0.7005 <0.0001 0.0001

Table 3. Change in Fasting Lipids

Lipid changes

At baseline, the ATV/r and ATV groups were similar with respect to median total cholesterol (153 vs. 152 mg/dl), LDL-cholesterol (85 vs. 88 mg/dl), HDL-cholesterol (39 vs. 37 mg/dl), total cholesterol/HDL-cholesterol ratio (4.10 vs. 4.15), and triglycerides (123 vs. 127 mg/dl) (Table 3). At week 144, the ATV/r treatment group had a significantly greater increase than the unboosted ATV treatment group in total cholesterol (p = 0.003) and LDL-cholesterol (p = 0.05), a significantly higher triglyceride concentration (p < 0.001) and lower total cholesterol/HDL-cholesterol ratio (p = 0.017), and a similar increase in HDL-cholesterol (p = 0.952). Week 144 median fasting total and LDL-cholesterol levels remained below NCEP cut-points in both groups. The median fasting triglyceride level remained below the NCEP cut-point in the ATV group but not the ATV/r group.

Discussion

The majority of subjects in ARIES had Framingham risk scores of <6% at baseline, suggesting they were at relatively low cardiovascular risk. Median Framingham risk scores did not change significantly over 144 weeks, which is consistent with the results of two shorter term studies (Bicoombo-met and STEAL).30,31 In these studies, when an ABC/3TC nucleoside backbone was compared to another nucleoside/nucleotide backbone, tenofovir/emtricitabine (TDF/FTC), no significant change in median or mean Framingham 10-year CHD risk scores over 48 and 96 weeks were observed.

Since changes in hsCRP concentrations have been previ-
Lp-PLA2 has been reported to be a better predictor of risk of coronary events than hsCRP because, unlike hsCRP, its pre-
3 mg/liter, considered by the American Heart Association
Centers for Disease Control and Prevention to be a critical
cut-off point for patients at “high risk” for future heart
disease (including MI and stroke) and an increased mortality
rate.36,37

Since it is known that low doses of ritonavir, in the absen-
care of coadministered antiretroviral drugs, can produce
elevations in lipids within 2 weeks,15 the relatively greater
elevation in fasting total cholesterol, LDL-cholesterol, and tril-
glycerides seen in subjects who remained on the ritonavir-
boosted ATV regimen compared to the unboosted ATV regi-
men was not unexpected. Similar findings also have been
reported in other studies comparing the use of ritonavir in
regimens containing ABC/3TC and ATV in antiretroviral-
naive patients.40,41 Despite the elevations in these particular
lipids for subjects receiving the ritonavir-boosted regimen, it
should be noted that median values for the ATV/r-treated
subjects remained below NCEP cutoffs for use of lipid-
lowering agents. Among the ritonavir-boosted protease in-
inhibitors, ATV/r has low lipogenicity, as evidenced by fewer
lipid increases than lopinavir/r and only small lipid eleva-
tions reported in direct comparisons in treatment-naive sub-
jects14,42 and in treatment-experienced subjects switched from
lopinavir/r to ATV/r.43,44 Unboosted ATV, relative to most
other protease inhibitors, has been documented to have little
effect on lipids,45 which is consistent with what we observed.

The median 15-mg/dl increase in HDL-cholesterol seen
both the unboosted ATV and ATV/r groups allowed the total cholesterol/HDL-cholesterol ratio to improve slightly.

In our biomarker analysis, we were also able to stratify the change in median biomarker levels over 144 weeks by treatment group. There was no significant change between baseline and week 144 in median hsCRP and IL-6 levels in the ATV or ATV/r treatment groups, or within each treatment group when stratified by the Framingham CHD risk group (<6% or ≥6%). As was seen for the overall population, the median Lp-PLA2 activity decreased significantly and consistently over the 144-week course of the study in both treatment groups and when stratified within treatment groups into <6% and ≥6% Framingham risk groups. In ARIES, subjects with low baseline CV risk demonstrated no increase in CV risk over time and no significant increase in CV-associated biomarker levels. No MIs were observed during the 144 weeks of the ARIES study. In our study, we observed no significant change in Framingham 10-year CHD risk scores, hsCRP, and IL-6 concentrations, declines in Lp-PLA2 activity (hypothesized to correlate with reductions in the atherosclerotic process36), and improvements in the total cholesterol/HDL-cholesterol ratio over 144 weeks with ABC/3TC + ATV-containing regimens. These results are consistent with those from many studies that have evaluated ABC-containing regimens and failed to observe an increase in estimated cardiac risk.18–22,26 and contrast with findings from two recent observational cohorts analyses that reported a statistically increased incidence in MI in HIV-infected patients receiving ABC-based therapy with various third agents.23,24 For our study, as with other studies, confounding risk factors such as recreational drug use or alcohol consumption may impact the findings but may be difficult to assess. Our prospective study examined only ART-naive subjects who had low cardiovascular risk, while in observational studies (where most subjects are treatment-experienced), selection and classification bias, in addition to confounding risk factors, can be more pronounced than that within a rigorous clinical study. No randomized clinical studies conducted to date have demonstrated a clear association with any type of antiretroviral therapy and CHD endpoints.47

This study focused on three cardiovascular biomarkers that previously have been associated with cardiovascular disease risk. Several other studies have examined additional biomarkers, including D-dimer, tumor necrosis factor (TNF)-α, soluble intercellular adhesion molecule-1, soluble vascular adhesion molecule-1, selectin E, selectin P, adiponectin, myeloperoxidase, amyloid A, and amyloid P, and generally showed no significant changes in median or mean values over at least 48 weeks of continuous ABC use.15,24,35

In conclusion, the majority of antiretroviral-naive subjects (81%) in this study had relatively low baseline cardiovascular risk. After initiating treatment with ABC/3TC plus ATV/r and then randomizing at week 36 to remain on ATV/r or simplify to unboosted ATV for an additional 108 weeks, cardiovascular risk status, as estimated by Framingham risk score categories (<6% and ≥6%), remained relatively stable over this period, with improvement in median HDL-cholesterol levels for both ATV- and ATV/r-treated subjects. Over 144 weeks, median biomarker levels remained stable or declined overall, with significant declines observed for Lp-PLA2 irrespective of whether ritonavir was maintained or discontinued after 36 weeks.

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