Changes in Body Composition with Ritonavir-Boosted and Unboosted Atazanavir Treatment in Combination with Lamivudine and Stavudine: A 96-Week Randomized, Controlled Study

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This 96-week, open-label, randomized study assessed changes in body composition in treatment-naive patients infected with human immunodeficiency virus type 1 who were treated with either atazanavir or ritonavir-boosted atazanavir, in combination with stavudine and lamivudine. Both treatment groups had similar increases in trunk fat, but patients treated with ritonavir-boosted atazanavir had a significantly lower incidence of lipoatrophy.

Changes in body composition, often associated with dyslipidemia and insulin resistance, are well-recognized adverse effects of antiretroviral therapy that can cause significant psychological morbidity [1]. Atazanavir (ATV) is less likely to cause dyslipidemia and other adverse metabolic effects, compared with other protease inhibitors [2, 3], and switching from an existing protease inhibitor to ATV or ATV boosted with ritonavir (RTV) can improve plasma lipid profiles [4, 5]. ATV appears to have a minimal impact on body composition (as measured using CT and dual-energy x-ray absorptiometry [DEXA]), with effects comparable to those of efavirenz at 48 weeks of treatment [6]. However, the effect of adding low-dose RTV to an ATV treatment regimen on body composition changes is unknown.

The present study compared the RTV-boosted and unboosted forms of ATV head-to-head in the presence of the same nucleoside reverse-transcriptase inhibitor (NRTI) backbone (lamivudine and extended-release stavudine). The 48- and 96-week efficacy and safety results, including lipid level results, have previously been published [7, 8]; this report describes the changes in body composition from baseline to week 96 of treatment.

Methods. This study was a phase 4, randomized, open-label, multicenter study designed to assess the efficacy and safety of ATV treatment when boosted with low-dose RTV in HIV-infected, antiretroviral therapy–naive patients. Study design and procedures have been published elsewhere [8]. Patients with HIV RNA levels ≥2000 copies/mL (Roche Amplicor) at screening and who had no or limited prior antiretroviral therapy were eligible for inclusion. Patients were excluded if they had previously received 30 days of NRTI therapy, 7 days of non-NRTI therapy, or any antiretroviral therapy within 30 days before screening. There were no restrictions on CD4 cell count. Patients were randomized 1:1 to receive 1 of the following 2 regimens:

1. ATV (300 mg once daily), RTV (100 mg once daily), lamivudine (300 mg once daily), and extended-release stavudine (100 mg once daily) (hereafter, “ATV300/RTV”)
2. ATV (400 mg once daily), lamivudine (300 mg once daily), and extended-release stavudine (100 mg once daily) (hereafter, “ATV400”)

Body composition was assessed at baseline and at weeks 24, 48, 72, and 96 by using cross-section CT and DEXA. For patients with paired scans at baseline and at subsequent time points, CT was used to quantify visceral adipose tissue, subcutaneous adipose tissue, and total adipose tissue, and DEXA was used to assess trunk fat, limb fat, and total body fat.

Analyses were based on observed values. CT and DEXA parameters were summarized using measured values, changes from baseline, and percentage changes from baseline at each scheduled visit through week 96 by treatment regimen. The magnitude of mean percentage changes from baseline to week 96 for each CT and DEXA parameter was assessed using 95% CIs and P values calculated by Student’s t test. Treatment regimens were compared using the difference in mean percentage changes, with 95% CIs and P values calculated by Student’s t test. In a post hoc analysis, regimens were compared using the difference in percentages of patients with lipoatrophy, defined as ≥20% loss of limb fat [9] from baseline to week 96, with 95% CIs and P values calculated using a normal approximation to the binomial distribution.
Table 1. Changes in body composition from baseline to weeks 24, 48, 72, and 96 of treatment among patient groups receiving 2 different drug regimens.

<table>
<thead>
<tr>
<th>Measure</th>
<th>ATV300/RTV</th>
<th>ATV400</th>
<th>ATV300/RTV</th>
<th>ATV400</th>
<th>ATV300/RTV</th>
<th>ATV400</th>
<th>ATV300/RTV</th>
<th>ATV400</th>
<th>Difference estimate</th>
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<td>All</td>
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<td>28</td>
<td>34</td>
<td>28</td>
<td>29</td>
<td>33</td>
<td>19.5–47.0</td>
<td>32 (19.7–44.5)</td>
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<tr>
<td>Men</td>
<td>6</td>
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<td>34</td>
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<td>26</td>
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<tr>
<td>Women</td>
<td>7</td>
<td>6</td>
<td>29</td>
<td>36</td>
<td>26</td>
<td>40</td>
<td>38</td>
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<td>16</td>
<td>12</td>
<td>12</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>–1.6 to 19.4</td>
<td>2 (–7.2 to 12.4)</td>
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<tr>
<td>Men</td>
<td>16</td>
<td>13</td>
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<td>8</td>
<td>–2</td>
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<td>–2</td>
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<td>Women</td>
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<td>23</td>
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<td>18</td>
<td>19</td>
<td>15</td>
<td>12</td>
<td>17</td>
<td>8.0–27.5</td>
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<tr>
<td>Men</td>
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<tr>
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<td>28</td>
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<td>30</td>
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<tr>
<td>Trunk fat</td>
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<td>17</td>
<td>12</td>
<td>15</td>
<td>17</td>
<td>19</td>
<td>16</td>
<td>3.6–29.7</td>
<td>14 (3.1–25.0)</td>
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<tr>
<td>Limb fat</td>
<td>18</td>
<td>21</td>
<td>2</td>
<td>–3</td>
<td>–7</td>
<td>–12</td>
<td>–9</td>
<td>–19.4 to 3.4</td>
<td>–17 (–25.5 to –7.6)</td>
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<tr>
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<td>7</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>–6.2 to 15.6</td>
<td>–1 (–9.3 to 9.0)</td>
</tr>
</tbody>
</table>

**NOTE.** ATV300/RTV, a regimen of atazanavir (300 mg once daily) boosted with ritonavir (100 mg once daily) plus lamivudine (300 mg once daily) and extended-release stavudine (100 mg once daily); ATV400, a regimen of atazanavir (400 mg once daily) plus lamivudine (300 mg once daily) and extended-release stavudine (100 mg once daily); SAT, subcutaneous adipose tissue; TAT, total adipose tissue; VAT, visceral adipose tissue.

a Primary end point.

b Respective numbers of ATV300/RTV and ATV recipients with available data are as follows: week 24 of treatment, 74 and 88 patients; week 48 of treatment, 68 and 85 patients; week 72 of treatment, 64 and 77 patients; and week 96 of treatment, 56 and 62 patients.

c Respective numbers of ATV300/RTV and ATV recipients with available data are as follows: week 24 of treatment, 22 and 27 patients; week 48 of treatment, 17 and 22 patients; week 72 of treatment, 14 and 19 patients.

d Respective numbers of ATV300/RTV and ATV recipients with available data are as follows: week 24 of treatment, 52 and 61 patients; week 48 of treatment, 47 and 53 patients; and week 96 of treatment, 42 and 43 patients.

e Respective numbers of ATV300/RTV and ATV recipients with available data are as follows: week 24 of treatment, 74 and 88 patients; week 48 of treatment, 68 and 85 patients; week 72 of treatment, 64 and 77 patients; and week 96 of treatment, 56 and 62 patients.

**Results.** A total of 200 patients were randomized (95 to receive ATV300/RTV and 105 to receive ATV400), and 199 were treated. Paired baseline and 96-week CT or DEXA data were available for 60 patients in the ATV300/RTV treatment group and 69 patients in the ATV400 treatment group. A total of 35 patients discontinued the study across both treatment groups. The main reasons for missing CT or DEXA data were the patient’s decision not to participate or problems with the scanning equipment.

Baseline demographic characteristics for patients with paired baseline and 96-week CT or DEXA data were comparable between treatment groups and were comparable to those of the study population as a whole (data not shown) [8]. The mean patient age was 37 years for the ATV300/RTV treatment group and 36 years for the ATV400 treatment group. The majority of patients were male: 73% of the ATV300/RTV treatment group and 68% of the ATV400 treatment group. Mean HIV RNA levels were similar between groups: 4.91 log_{10} copies/mL for the ATV300/RTV treatment group and 4.90 log_{10} copies/mL for the ATV400 treatment group. Baseline CT and DEXA data were also similar between the treatment groups.

Increases in visceral adipose tissue from baseline to week 96 were statistically significant in both treatment groups: 33% for the ATV300/RTV treatment group and 32% for the ATV400 treatment group (table 1). Total adipose tissue also significantly increased from baseline to week 96: 17% for the ATV300/RTV treatment group and 11% for the ATV400 treatment group. Subcutaneous adipose tissue increased in both treatment groups, but the change from baseline to week 96 was not significant. Overall, there were no statistically significant differences between the ATV300/RTV and ATV400 regimens in terms of their effects on visceral adipose tissue, subcutaneous adipose tissue, or total adipose tissue at week 96. Most of the changes in visceral adipose tissue and total adipose tissue occurred during the first 48 weeks of therapy. The mean increase in subcutaneous adipose tissue from baseline to week 48 was 12% for both treatment groups. By week 96, the increase from baseline had reduced to 8% in the ATV300/RTV treatment group and 2% in the ATV400 treatment group, indicating that some of the subcutaneous abdominal fat acquired in the first year was lost during the second year.
percentage changes in visceral adipose tissue, subcutaneous adipose tissue, and total adipose tissue than did men (table 1). The difference between sexes was most pronounced for subcutaneous adipose tissue in the ATV300/RTV treatment group; the percentage change in subcutaneous adipose tissue (from baseline to week 96) was a 2% increase for men and a 29% increase for women. Corresponding values for men and women in the ATV400 treatment group were −2% and 11%. For both women and men, changes in subcutaneous adipose tissue at week 96 represented a reduction from the changes at week 48, except for women receiving the ATV300/RTV regimen, for whom the week 96 change was slightly increased from the week 48 change.

There was no statistically significant increase in total body fat from baseline to week 96 for either treatment group (table 1). Significant increases in trunk fat were seen from baseline to week 96 for both treatment groups; limb fat decreased in both groups, although the change from baseline was only significant in the ATV400 treatment group (−17%; 95% CI, −25.5% to −7.6%; P < .001). There were no significant differences between the ATV300/RTV and ATV400 treatment groups in the changes in trunk fat, limb fat, or total body fat.

Trunk fat increased from baseline to week 24 in the ATV300/RTV and ATV400 treatment groups (mean percentage change, 13% and 17%, respectively) and remained relatively stable thereafter (table 1). In contrast, initial gains in limb fat (from baseline to week 24, 18% for the ATV300/RTV treatment group and 21% for the ATV400 treatment group) were followed by losses at each successive time point, such that mean values at week 96 were less than those at baseline.

Women experienced greater increases in trunk fat than did men after 48 and 96 weeks of therapy in both treatment groups. In a comparison of paired baseline and 96-week values, the ATV400 regimen was associated with loss of limb fat loss regardless of sex. However, women receiving ATV300/RTV experienced limb fat gain, whereas men receiving ATV300/RTV experienced limb fat loss, whereas men receiving ATV300/RTV experienced limb fat loss.

The percentage of patients with >20% limb fat loss from baseline increased modestly among patients receiving ATV300/RTV, from 21% at week 48 to 29% at week 96, but the increase was greater among patients receiving ATV400, from 30% at week 48 to 49% at week 96. The difference between treatment groups was significant at week 96 (P < .05). Changes in body mass index and waist-to-hip ratio between baseline and week 96 were negligible and were similar between treatment regimens (data not shown).

Discussion. To our knowledge, this is the first study to compare the boosted and unboosted forms of the same protease inhibitor (ATV) head-to-head in the presence of the same NRTI backbone (lamivudine and extended-release stavudine). Both treatment groups had similar increases in visceral adipose tissue and total adipose tissue between baseline and week 96, with most gains occurring during the first year of therapy. Subcutaneous adipose tissue did not show significant change between baseline and week 96 in either treatment group, but analyses at intervening time points showed that there was a gain in subcutaneous adipose tissue from baseline to week 48, followed by a loss in subcutaneous adipose tissue.

DEXA-measured limb fat values mirrored this pattern, with increases from baseline to week 24, followed by decreases through week 96. This pattern is consistent with that seen in previous studies [10, 11], with gains in limb fat in the first 12–24 weeks of treatment followed by progressive losses during the next 72–84 weeks. In our study, neither the ATV300/RTV nor the ATV400 regimen was associated with important changes in body weight, body mass index, waist circumference, or waist-to-hip ratio at week 96.

We found differences between men and women in terms of changes in body composition. Women had greater increases in visceral adipose tissue, subcutaneous adipose tissue, total adipose tissue, and trunk fat at week 96, compared with men. Additionally, women tended to lose less limb fat than did men. This pattern in women has been previously described [12].

The novel aspect of this trial is that it allowed direct comparison of body fat changes between patients receiving the boosted form and patients receiving the unboosted form of the same protease inhibitor, a comparison not possible before now. Our observation that the ATV300/RTV regimen was associated with a lower incidence of lipoatrophy at week 96, compared with unboosted ATV400 regimen, suggests that low-dose RTV may have a protective effect against peripheral fat loss, although this concept requires further study. Body composition changes found in the present study were comparable to the findings of other studies involving treatment-naive patients. These results suggest that the use of RTV-boosted ATV is not associated with a greater risk of body fat changes, compared with unboosted ATV, and may be associated with a lower incidence of lipoatrophy.

Acknowledgments

We thank PAREXEL for their editorial support in preparation of this manuscript. This assistance was funded by Bristol-Myers Squibb.

Financial support. Bristol-Myers Squibb.

Potential conflicts of interest. G.M. has received research grants from, is a consultant for, and serves on the speakers’ bureaus for Bristol-Myers Squibb, GlaxoSmithKline, Gilead, and Abbott. A.R., V.W., R.Y., M.M., and D.M. are employees of and own stock in Bristol-Myers Squibb.

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