The effects of highly active antiretroviral therapy on albuminuria in HIV-infected persons: results from a randomized trial

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Abstract

Background. Human immunodeficiency virus (HIV)-infected patients receiving highly active antiretroviral therapy (HAART) regimens, especially those containing protease inhibitors (PIs), are at increased risk for cardiovascular events. Albuminuria is a known independent predictor for the development of cardiovascular disease and may potentially increase in patients receiving PIs. Alternatively, albuminuria may improve with HAART as a result of treating renal parenchymal HIV infection. Longitudinal studies have not been performed previously addressing the effects of HAART on albuminuria.

Methods. We evaluated the effects of HAART on albumin to creatinine ratios (ACRs) during the initial 64 weeks of therapy in 68 previously untreated HIV-infected subjects, without pre-existing diagnosed diabetes or hypertension, enrolled in a randomized trial comparing PI-based (n=32) with non-PI-based (n=36) HAART regimens. We also estimated the prevalence of albuminuria, defined as an ACR ≥3.4 mg/mmol, in these subjects prior to initiation of HAART.

Results. The changes in ACR over the initial 64 weeks of therapy in those receiving PIs [0.0 mg/mmol (−0.4, 0.3)] and in those not receiving PIs [0.0 mg/mmol (−0.5, 0.3)] were not significantly different. There was also no significant difference in the change in the ACR in the group as a whole. However, albuminuria at baseline was found in seven (10%) subjects. Five of these seven subjects had substantial improvements in ACR, ranging from 45 to 95%, with HAART use; three subjects had resolution of albuminuria. ACR at baseline significantly correlated with the baseline HIV-1 RNA level (r = 0.25; P = 0.04) and negatively with CD4 cell count (r = −0.25; P = 0.04).

Conclusion. Albuminuria in HIV-infected, treatment-naive patients was found more frequently than expected and may be influenced by baseline immune status. Although we did not observe an effect of HAART on ACR during the first 64 weeks of therapy, we cannot exclude the possibility that HAART may be beneficial in those patients with significant albuminuria prior to treatment. Research in larger cohorts is required to investigate more definitively the associations between immune status, antiretroviral therapies and renal function in HIV-infected patients.

Keywords: albuminuria; antiretroviral therapy; cardiovascular disease; cardiovascular risk; HIV; protease inhibitors

Introduction

Cardiovascular disease in human immunodeficiency virus (HIV)-infected patients is increasingly prevalent in the current era of highly active antiretroviral therapy (HAART) [1]. Albuminuria is an early manifestation and independent predictor of cardiovascular events in the general population, even in the absence of diabetes or hypertension [2]. Detecting albuminuria may, therefore, identify patients at heightened risk for future cardiovascular disease.

The link between renal and cardiovascular disorders is increasingly thought to be due to systemic endothelial dysfunction [3]. Patients receiving protease inhibitor (PI)-based regimens, as opposed to non-PI-based regimens such as those incorporating non-nucleoside reverse transcriptase inhibitors (NNRTIs), may be especially at risk for cardiovascular events [4], perhaps as a result of the association between PI and endothelial dysfunction [5]. PIs, more than NNRTIs, have also
been associated with the development of the metabolic syndrome [6], which is a risk factor for vascular disease in the general population and is also associated with albuminuria [7]. Therefore, it is possible that PIs may preferentially induce albuminuria.

Alternatively, HIV can infect and disrupt the glomerular epithelium with the ensuing development of HIV-associated nephropathy (HIVAN), which may be reversed with the use of HAART [8]. Therefore, it is also possible that antiretroviral therapy, regardless of its components, may actually reduce albuminuria. In order to test these competing hypotheses, we performed a post hoc, secondary analysis of a randomized clinical trial comparing nelfinavir, a PI, with efavirenz, an NNRTI.

Subjects and methods

Study design and objectives

The primary objective of this study was to compare the effects of an antiretroviral regimen containing a PI with one containing an NNRTI on albuminuria. AIDS Clinical Trial Group (ACTG) 384 [9] was a randomized, controlled trial comparing different antiretroviral treatment strategies using the PI nelfinavir vs the NNRTI efavirenz and the nucleoside backbone combinations didanosine + stavudine vs zidovudine + lamivudine. For those in the metabolic substudy of ACTG 384 [10], urine specimens were collected at weeks 0 (entry), 16, 32, 48 and 64 and frozen at −70 °C for later analysis. These subjects were enrolled between October 1998 and November 1999. In order to isolate the effects of PIs vs NNRTIs, data from only the following four arms of this study were utilized: arm A (didanosine + stavudine + efavirenz), arm B (didanosine + stavudine + nelfinavir), arm C (zidovudine + lamivudine + efavirenz) and arm D (zidovudine + lamivudine + nelfinavir). Subjects with virological failure or a treatment-limiting toxicity on their initial regimen were then switched to an arm containing all new drugs, e.g. failing arm A subjects were switched to zidovudine + lamivudine + nelfinavir. Only those subjects with available urine samples at both weeks 0 and 64 were included in these analyses; urine samples collected in the intervening study visits in these specific subjects were also analysed. For the primary analysis, subjects in arms B and D and those in arms A and C, respectively, were pooled to form the nelfinavir and efavirenz groups.

Secondary objectives included comparing the effects of the pooled nucleoside backbone combinations (arms A and B combined vs arms C and D combined) and the four individual treatment arms on the change in albuminuria; within-group changes were also estimated. We also estimated the prevalence of albuminuria at baseline and factors associated with the baseline albumin to creatinine ratio (ACR).

Prior to enrolment, all subjects who participated in both ACTG 384 and the metabolic substudy provided written, informed consent. The human research ethics committees of each participating institution approved these studies.

Study population

To be eligible for ACTG 384 and its metabolic substudy, all subjects at entry were required to be antiretroviral treatment-naïve (<7 days of previous antiretroviral use), age > 13 years, have a serum creatinine <1.5 times the upper limit of normal at their institution’s laboratory, and not have a diagnosis of diabetes mellitus. Subjects were not eligible if they had unexplained fever or diarrhoea within 30 days of entry or were undergoing acute therapy for a serious infection or other serious medical illness.

Laboratory methods and definitions

All urine specimens were analysed in batch for urine albumin and creatinine at a central laboratory (Quest Diagnostics, Inc., Baltimore, MD). Urine albumin was measured using an immunoturbimetric assay [coefficient of variation (CV) < 5%; Kamiya Biomedical Co., Seattle, WA], and urine creatinine was measured using a modified Jaffé reaction (CV < 3%; Olympus America Inc., Melville, NY). Random urine ACRs were then calculated for each sample. An ACR ≥ 3.4 mg/mmol and < 34 mg/mmol (30–299 mg/g) defined microalbuminuria; macroalbuminuria was defined as ≥ 34 mg/mmol (300 mg/g). These gender-neutral cut-offs were used to allow baseline (week 0) comparisons with the general US population [11]. Insulin resistance was estimated using the homeostasis model assessment-insulin resistance (HOMA-IR) [12]. The glomerular filtration rate (GFR) was estimated using the simplified MDRD equation [13]. This equation was chosen to allow staging of this cohort’s baseline renal function, to allow general comparisons with other reference populations (e.g. the NHANES III cohort) and because the racial and gender demographics of this study’s population are more similar to the MDRD study population than that used to derive the Cockcroft-Gault equation; however, we acknowledge that wasting conditions such as untreated HIV infection may skew MDRD GFR estimates and, therefore, may not be as accurate.

Statistical analyses

Intent-to-treat analyses were performed for the overall group. On-treatment analyses were also completed for those who did not switch treatment arms within the first 64 weeks of the study. Unless otherwise specified, all values are presented as medians and interquartile ranges. To compare variables between treatment groups and those with and without baseline albuminuria, the Wilcoxon rank-sum test (a non-parametric version of a standard t-test) was used to compare continuous variables between groups, and Fisher’s exact test was used for comparison between groups of binary variables. The Wilcoxon signed-rank test was used for assessing within-group changes in ACR between week 0 and week 64. Spearman rank correlation was used to assess the association of week 0 ACR with other variables. Mixed-models analysis of variance was used for longitudinal modelling incorporating all observations from week 0 through week 64 and for assessing the impact of various potential confounders on change over time. All P-values were two-sided and considered statistically significant if < 0.05.

Results

There were 155 subjects randomized each (total 620) to arms A, B, C and D in the parent ACTG 384 study.
Of these, 60, 55, 50 and 44 subjects from arms A, B, C and D, respectively, were enrolled into the metabolic substudy. A total of 68 subjects (arm A, n = 15; arm B, n = 19; arm C, n = 21; arm D, n = 13), or 33% of the metabolic substudy, had both week 0 and 64 urine samples available for the current analyses. Therefore, 32 and 36 subjects, respectively, were included in the pooled nelfinavir and efavirenz groups (representing 32 and 33% of those initially randomized to receive these drugs in the metabolic substudy). Forty-nine (72%) of these (arm A, n = 10; arm B, n = 11; arm C, n = 19; arm D, n = 9) did not switch treatments during the first 64 weeks of treatment. None of the 68 subjects had documentation of physician-diagnosed diabetes, hypertension or renal disease at entry. Table 1 describes the clinical characteristics of these subjects. The baseline characteristics listed in Table 1 of the overall group of 68 subjects and of the subgroup of 49 subjects who did not switch therapies were not significantly different from those enrolled into the metabolic substudy (data not shown). There were no significant differences in baseline characteristics between the pooled nelfinavir and efavirenz groups; nor were there baseline differences between the pooled didanosine + stavudine and zidovudine + lamivudine groups or between the four individual arms in either the overall group or the subgroup remaining on stable therapy (data not shown).

Over the initial 64 week treatment period, none of the 68 in the overall group developed physician-diagnosed hypertension or developed a grade 3 or 4 serum creatinine abnormality (serum creatinine >3 times upper limit of normal at the study site’s reference laboratory; grade 1 or 2 abnormalities were not recorded). Four subjects were receiving one antihypertensive drug each at entry (nifedipine, amlodipine, enalaprilat and irbesartan) for unknown reasons. It is possible that these drugs were not used specifically for hypertension or renal disease, e.g. migraine prevention or HIV-induced cardiomyopathy.

The median changes in ACR from weeks 0 to 64 between the nelfinavir-containing regimens [0.0 mg/mmol (–0.4, 0.3)] and the efavirenz-containing regimens [0.0 mg/mmol (–0.5, 0.3)] and between the zidovudine + lamivudine group [–0.1 mg/mmol (–0.5, 0.2)] and the didanosine + stavudine group [0.1 mg/mmol (–0.3, 0.3)] were not statistically significantly different (each P > 0.2); the changes among the four individual treatment groups (data not shown) were also not significantly different (P = 0.17). The within-group changes in ACR over the initial 64 weeks of treatment for the entire group of 68 [0.0 mg/mmol (–0.5, 0.3)] and for the four individual treatment groups (data not shown) were not significant (each P > 0.2). Similar results were found for these same comparisons in the subgroup of 49 subjects who were on stable HAART during the first 64 weeks and after exclusion of those using antihypertensives. Adjustment for age, race (black vs non-black), baseline CD4 cell count and baseline HIV-1 RNA level in a mixed-models analysis of variance did not change these results. Of the four subjects using antihypertensives, which were continued without changes or additions throughout the study period, only the subject receiving irbesartan had any significant changes in ACR (Table 2).

Six (9%) subjects had microalbuminuria and one subject (1%) had macroalbuminuria at entry. These seven subjects were significantly older than those without albuminuria at entry and tended to have lower CD4 cell counts (Table 1). As shown in Table 2, the median change in ACR from entry to week 64 was not significant [–5.4 mg/mmol (–8.9, 4.3); P > 0.2], although the ACR decreased appreciably in five of these seven subjects. Three subjects had resolution of albuminuria. Only one subject with baseline albuminuria received an antihypertensive (irbesartan) at baseline and subsequently throughout the study period; this subject’s ACR declined over the first 64 weeks of treatment. Entry ACR was significantly

### Table 1. Clinical characteristics and changes in the albumin to creatinine ratio (ACR) of the overall study group

<table>
<thead>
<tr>
<th></th>
<th>Nelfinavir (n = 32)</th>
<th>Efavirenz (n = 36)</th>
<th>P</th>
<th>Baseline albuminuria</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (n = 7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No (n = 61)</td>
<td></td>
</tr>
<tr>
<td><strong>Week 0</strong></td>
<td>0.7 (0.4, 1.6)</td>
<td>0.6 (0.4, 1.4)</td>
<td>&gt;0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Week 64</strong></td>
<td>0.6 (0.5, 1.3)</td>
<td>0.5 (0.5, 0.9)</td>
<td>&gt;0.2</td>
<td>9.4 (5.9, 11.4)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td><strong>Change in ACR</strong></td>
<td>0.0 (–0.4, 0.3)</td>
<td>0.0 (–0.5, 0.3)</td>
<td>&gt;0.2</td>
<td>–5.4 (–8.9, 4.3)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td><strong>Estimated GFR</strong></td>
<td>102 (92, 113)</td>
<td>106 (97, 120)</td>
<td>&gt;0.2</td>
<td>111 (89, 116)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td><strong>CD4, ×10^6</strong> cells/l (IQR)</td>
<td>313 (108, 452)</td>
<td>232 (45, 416)</td>
<td>&gt;0.2</td>
<td>87 (43, 206)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>**HIV-1 RNA, log10 copies/ml (IQR)</td>
<td>5.1 (4.8, 5.6)</td>
<td>5.2 (4.6, 5.6)</td>
<td>&gt;0.2</td>
<td>5.4 (4.9, 5.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>**BMI, kg/m² (IQR)</td>
<td>25.9 (23.3, 27.5)</td>
<td>23.9 (21.6, 27.1)</td>
<td>&gt;0.2</td>
<td>22.9 (20.7, 25.7)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>**Glycosylated haemoglobin b, % (IQR)</td>
<td>5.4 (5.0, 5.9)</td>
<td>5.4 (5.2, 5.9)</td>
<td>&gt;0.2</td>
<td>5.8 (5.1, 6.1)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>**HOMA-IR (IQR)</td>
<td>1.4 (1.0, 2.1)</td>
<td>1.5 (1.1, 1.9)</td>
<td>&gt;0.2</td>
<td>1.2 (0.8, 1.6)</td>
<td>&gt;0.2</td>
</tr>
</tbody>
</table>

IQR = interquartile range; BMI = body mass index; GFR = glomerular filtration rate.

a All values are medians.

b To convert mg/mmol to mg/g, multiply by 8.84.
Subjects 1 and 5 switched regimens at weeks 16 and 32, respectively. Subject 6 received irbesartan throughout the study period.

$$\frac{1}{4}$$ ZDV $$+$$ 5 ddI $$+$$ 4 ZDV $$+$$ 3 ddI $$+$$ 1 ZDV

Table 2. Progression of albumin/creatinine ratios (ACRs) in the seven subjects with albuminuria (ACR $\geq$ 3.4 mg/mmol$^3$) at study entry

<table>
<thead>
<tr>
<th>Subject</th>
<th>Initial regimen</th>
<th>0</th>
<th>16</th>
<th>32</th>
<th>48</th>
<th>64</th>
<th>Percentage change from week 0 to 64</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ZDV + 3TC + EFV</td>
<td>93.0</td>
<td>66.4</td>
<td>27.3</td>
<td>N/A</td>
<td>13.8</td>
<td>$-$85%</td>
</tr>
<tr>
<td>2</td>
<td>ZDV + 3TC + NFV</td>
<td>11.4</td>
<td>1.9</td>
<td>3.1</td>
<td>5.1</td>
<td>6.3</td>
<td>$-$45%</td>
</tr>
<tr>
<td>3</td>
<td>ddl + d4T + NFV</td>
<td>9.4</td>
<td>0.7</td>
<td>0.7</td>
<td>0.5</td>
<td>30.1</td>
<td>$+$220%</td>
</tr>
<tr>
<td>4</td>
<td>ZDV + 3TC + EFV</td>
<td>9.4</td>
<td>0.8</td>
<td>1.2</td>
<td>N/A</td>
<td>0.5</td>
<td>$-$95%</td>
</tr>
<tr>
<td>5</td>
<td>ddl + d4T + NFV</td>
<td>7.4</td>
<td>2.3</td>
<td>N/A</td>
<td>1.0</td>
<td>0.6</td>
<td>$-$92%</td>
</tr>
<tr>
<td>6</td>
<td>ZDV + 3TC + EFV</td>
<td>5.9</td>
<td>N/A</td>
<td>N/A</td>
<td>0.6</td>
<td>0.6</td>
<td>$-$90%</td>
</tr>
<tr>
<td>7</td>
<td>ddl + d4T + NFV</td>
<td>3.4</td>
<td>3.5</td>
<td>2.2</td>
<td>N/A</td>
<td>7.7</td>
<td>$+$126%</td>
</tr>
</tbody>
</table>

ZDV = zidovudine; 3TC = lamivudine; ddl = didanosine; d4T = stavudine; EFV = efavirenz; NFV = nelfinavir; N/A = not available, urine not archived at this time point.

Subjects 1 and 5 switched regimens at weeks 16 and 32, respectively. Subject 6 received irbesartan throughout the study period.

*To convert mg/mmol to mg/g, multiply by 8.84.

correlated with HIV-1 RNA level ($r = 0.25$, $P = 0.04$) and inversely correlated with CD4 cell count ($r = -0.25$, $P = 0.04$); entry ACR was not significantly correlated with age, estimated GFR, body mass index, HOMA-IR or glycosylated haemoglobin.

Discussion

Albuminuria is an independent predictor of cardiovascular disease, as well as all-cause mortality, in the general population [2]. There is also emerging data that glomerular dysfunction in HIV-positive patients, manifested as both a decline in renal function and the presence of proteinuria on urine analysis, is associated with faster progression to AIDS and overall mortality [14]. To our knowledge, this is the first study in HIV-infected patients investigating and comparing the course of albuminuria after initiation of a PI-based vs an NNRTI-based antiretroviral regimen. Although changes in ACR were not found during the initial period of antiretroviral treatment in the overall cohort, albuminuria did appear to improve in the subset of subjects with the highest levels of ACR at baseline.

Endothelial dysfunction has been shown to predict the development of cardiovascular disease [15]. PI-based regimens have also been linked with endothelial dysfunction [5], and albuminuria has been associated with endothelial dysfunction in some populations [3]. Contrary to our hypothesis that albuminuria may increase during PI use, we did not find that HAART increased the ACR among treatment-naive patients during the first 64 weeks of antiretroviral therapy; nor were there differences between the pooled or individual treatment groups. It is possible that the relationship between PI use and endothelial dysfunction may be agent specific, rather than class specific. Previous studies associating PI use with endothelial dysfunction have suggested that the pro-atherogenic lipid profile seen with protease inhibitors is the underlying cause of endothelial dysfunction [5]; however, these investigations have involved primarily indinavir. In fact, nelfinavir, when compared with other PIs, such as indinavir and ritonavir-boosted combinations, may be less likely to cause low levels of high density lipoprotein-cholesterol (HDL-C) [16]. Furthermore, triglycerides appear to improve when patients switch their PI from indinavir or saquinavir plus ritonavir to nelfinavir [17]. Therefore, the results from this study may not necessarily extend to patients receiving other PI-containing regimens. Another potential explanation for the negative results of this study may lie in the fact that the risk of cardiovascular disease among HIV patients may only increase after several years of therapy [1]; therefore, it is also possible that the relatively small sample size and duration of follow-up in this study may have precluded from finding a positive association between use of antiretrovirals and albuminuria.

We also did not see an overall improvement in ACR with the use of HAART in this small study with few subjects with substantial albuminuria. It should be noted that the use of antihypertensive medications by four subjects may have precluded finding a more definitive improvement in ACR with the use of HAART. However, we did find that five of the seven subjects with baseline albuminuria had substantial improvements of 45–95% with HAART over the initial 64 weeks. This suggests that albuminuria in HIV-infected patients may initially be the result of direct renal damage by HIV that may improve with HAART [8]. Alternatively, albuminuria may indeed be related to endothelial dysfunction caused by HIV infection that, at least in the short-term, seems to improve from HAART use [18].

We found in this cohort a higher prevalence than expected of albuminuria with normal GFR in patients prior to initiation of HAART. The proportion of subjects with ‘microalbuminuria’ in our cohort (9%; age range 21–59 years) was approximately three times higher than that found in the similarly aged, non-diabetic, non-hypertensive NHANES III US population (3%) [11]. Even if the subjects receiving antihypertensives at baseline are excluded to eliminate the possibility that the cohort contains subjects truly having hypertension, diabetes or renal disease at baseline, the proportion of microalbuminurics without co-morbidity in this cohort would still be high.
HAART and albuminuria

(five out of 65, or 8%). The identification of albuminuria at baseline in this study depended on a single measurement, so misclassification is possible and may have falsely elevated the baseline prevalence of albuminuria. However, this high prevalence of microalbuminuria is corroborated by the results from a previous study [19], suggesting there truly is increased glomerular impairment in the untreated HIV population. In this study, albuminuria at baseline was associated with older age, positively correlated with HIV-1 RNA level, and negatively correlated with CD4 count. These findings are similar in direction and magnitude to those of our previous study in a different population describing dipstick-detected proteinuria in a cohort of patients at the time of HIV documentation [20], where proteinuria was also associated with older age and significantly correlated with CD4 cell count ($r = -0.20$, $P = 0.003$) and HIV-1 RNA level ($r = 0.25$, $P = 0.005$). Therefore, it seems that immune status may be associated with albuminuria in the untreated HIV population, but further research in larger cohorts is required to investigate this possibility more conclusively.

Because our primary hypothesis was that PI-based therapy would lead to systemic endothelial dysfunction, and, in turn, incipient glomerular disease, we chose to measure albuminuria, as opposed to proteinuria, as this may be a more specific measure of glomerular disease and is likely to occur earlier than overt proteinuria. However, we recognize that proteinuria is more commonly measured in clinical practice, especially when screening for HIVAN or for identifying patients with renal disease due to febrile states, which may occur frequently in the HIV population. Therefore, the results of this study may not be immediately applicable in evaluating or managing renal diseases in this special population.

In conclusion, albuminuria appears to be prevalent in the untreated HIV-infected population and may be influenced by immune status. However, we did not observe a change in ACR during the initial 64 weeks of HAART, although subjects with elevated baseline albuminuria had substantial reductions in ACR. A larger study enriched with a population likely to have more substantial albuminuria at baseline (i.e. an older African-American cohort with lower baseline CD4 cell counts) and longer duration of follow-up would perhaps find a more significant reduction in ACR with the use of HAART.

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Conflict of interest statement. S.K.G. has received speaker’s fees from Gilead Sciences, Inc.; R.A.P. has consulted for Merck and Co.; G.K.R. has consulted for or received honoraria from Bristol-Myers Squibb, Agouron/Pfizer and GlaxoSmithKline; M.P.D. has received honoraria, speaker’s and consultant’s fees, research grants, and donated drug for research purposes from Agouron/Pfizer, GlaxoSmithKline, Gilead Sciences, Inc., Bristol-Myers Squibb and Merck and Co.

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