In HIV/hepatitis C virus co-infected patients, higher 25-hydroxyvitamin D concentrations were not related to hepatitis C virus treatment responses but were associated with ritonavir use1-4

Andrea D Branch, Minhee Kang, Kimberly Hollabaugh, Christina M Wyatt, Raymond T Chung, and Marshall J Glesby

ABSTRACT

Background: Among patients with hepatitis C virus (HCV) monoinfection, 25-hydroxyvitamin D [25(OH)D] concentrations are positively associated with a response to peg-interferon/ribavirin. Data on the relation between 25(OH)D concentrations and HCV treatment response in HIV-infected patients are limited.

Objective: The objective was to determine whether baseline 25(OH)D concentrations predict virologic response in HIV/HCV co-infected patients and to examine variables associated with 25(OH)D concentrations ≥30 ng/mL.

Design: Data and samples from 144 HCV genotype 1, treatment-naive patients from a completed HCV treatment trial were examined in this retrospective study. Early virologic response (EVR) was defined as ≥2 log10 reduction in HCV RNA and/or HCV RNA <600 IU/mL at week 12 of peg-interferon/ribavirin treatment. Baseline 25(OH)D was measured by liquid chromatography/tandem mass spectrometry.

Results: Compared with the non-EVR control group (n = 68), the EVR group (n = 76) was younger, had fewer cirrhotic subjects, had a higher proportion with the IL28B CC genotype, had a higher albumin concentration, and had a lower HCV viral load at baseline (P ≤ 0.05). The difference in baseline 25(OH)D concentrations between EVR and non-EVR patients was not statistically significant (median: 25 ng/mL compared with 20 ng/mL; P = 0.23). Similar results were found for sustained virologic response (SVR). In multivariable analysis, white and Hispanic race-ethnicity (OR: 6.26; 95% CI: 2.47, 15.88; P = 0.0001) and ritonavir use (OR: 2.68; 95% CI: 1.08, 6.65; P = 0.033) were associated with higher 25(OH)D concentrations (≥30 ng/mL).

Conclusion: Baseline 25(OH)D concentrations did not predict EVR or SVR. Because ritonavir impairs the conversion of 25(OH)D to the active metabolite, utilization of 25(OH)D may have been impaired in patients taking ritonavir. This trial was registered at www.clinicaltrials.gov as NCT00078403.

INTRODUCTION

Hepatitis C virus (HCV)5 co-infection occurs in about one-third of subjects infected with HIV in the United States and Europe (1, 2). Liver disease is now a leading cause of mortality in HIV-infected patients, and chronic HCV infection is the most common etiology (3–5). HIV/HCV co-infected patients who achieve a sustained virologic response (SVR) to HCV treatment have increased survival (6) and a reduced risk of subsequent antiretroviral-related toxicities (7); however, responses to the current standard of care—dual therapy with pegylated interferon (PEG) and ribavirin—are generally poor (8–10).

Several studies have examined viral and host factors predicting HCV virologic response (11–20). Recently, vitamin D status was proposed as a predictor of HCV treatment outcome. The hypothesis that vitamin D might improve treatment responses is based on evidence that vitamin D enhances both innate and adaptive immune responses, reduces inflammation, and retards fibrogenesis (21–27). In HCV mono-infected patients, vitamin D deficiency has been associated with poor treatment response and with more advanced liver fibrosis (28–33), although contrary findings have also been reported (34). Vitamin D supplements have been reported to improve treatment outcomes in HCV mono-infected individuals (35–37). In a study of HIV/HCV co-infected patients carried out in France (38), lower 25-hydroxyvitamin D [25(OH)D] concentrations were associated with more advanced liver fibrosis, but not with HCV treatment failure. In contrast, a study carried out in Austria showed a positive relation between 25(OH)D concentrations and response to HCV treatment (39). To our knowledge, the relation between 25(OH)D concentrations and treatment response has not been examined in HIV/HCV patients in the United States, which has a racially and ethnically diverse population.

Apart from its possible effect on treatment outcome and liver disease progression, the vitamin D status of HIV/HCV-positive

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5 Abbreviations used: ACTG, AIDS Clinical Trials Group; EVR, early virologic response; GFR, glomerular filtration rate; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; PEG, pegylated interferon; SVR, sustained virologic response; 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D.

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patients is important because vitamin D promotes the absorption of
dietary calcium and strengthens bone. HIV/HCV co-infected
patients often have low bone density (40–42) and are exposed to
antiretroviral drugs that disturb vitamin D and calcium metab-
olism; efavirenz reduces 25(OH)D concentrations (43), ribavirin
reduces serum calcium concentrations (44), ritonavir impairs
bioactivation of vitamin D (45), and tenofovir causes elevations
in parathyroid hormone that are especially pronounced in pa-
tients with 25(OH)D concentrations <30 ng/mL (46–49).

The most widely used clinical indicator of vitamin D status is
25(OH)D. This molecule is the precursor of the active metabo-
ilite 1,25-dihydroxyvitamin D [1,25(OH)2D], which is a steroid hor-
mon. The optimal concentration of 25(OH)D for an individual
is difficult to establish. The Institute of Medicine determined
that 20 ng/mL is adequate for 97.5% of healthy adults (50); however, HIV practice guidelines recommend concentrations
>30 ng/mL (51).

In this study, we examined the relation between baseline
25(OH)D concentrations and response to PEG/ribavirin treat-
ment in HCV treatment-naive patients with genotype 1 HCV
from the completed AIDS Clinical Trials Group (ACTG) A5178
study (52). We also identified factors associated with 25(OH)D
cconcentrations ≥30 ng/mL in this study group.

SUBJECTS AND METHODS

Subjects

The design of A5178 was previously described (52). Briefly, it
was a multicenter prospective trial conducted by the ACTG to
elucidate the role of maintenance PEG therapy in HCV treatment
nonresponders with HIV co-infection (52). The trial enrolled 330
subjects from August 2004 to April 2007 from 36 ACTG sites
within the United States. In Step 1, all subjects were treated with
pegylated-interferon-α 2a 180 μg/wk plus weight-based ribavirin
for 12 wk to distinguish treatment responders from nonresponders
by early virologic response (EVR), defined as a ≥2 log10 de-
crease from baseline or undetectable HCV RNA (<600 IU/mL)
at 12 wk. Patients with an EVR received a total of 72 wk of PEG/
ribavirin therapy, whereas patients without an EVR were followed
in a maintenance trial. All A5178 subjects provided written in-
formed consent, and 87% provided consent for genetic testing
through a separate protocol. The institutional review boards of all
sites participating in the parent study approved the study protocol.
Guidelines of the US Department of Health and Human Services
and those of the authors’ institutions were followed in the con-
duct of this research. The current study was a retrospective analysis
of 144 subjects with genotype 1 HCV who were treatment-naive and
who consented to IL28B genotyping as part of a separate study
(19). The study group included 47 non-Hispanic whites, 76 non-
Hispanic blacks, and 21 Hispanics (19 of whom were white and 2
of whom were black). In several analyses whites were grouped
with Hispanics, in keeping with the methods used in the parent
study. Only one Asian was eligible for the study, and this person
was excluded to reduce heterogeneity.

Vitamin D concentrations

The 25(OH)D concentration was measured centrally in base-
line serum samples by HPLC tandem mass spectrometry (Quest
Diagnostics). The interassay CV across the analytic range of
the assay is 7%. Serum samples were pristine and stored at −70°C
for 40 days until shipment on dry ice to the central repository and
ultimately the central laboratory. 25(OH)D was analyzed as a
continuous variable and as a dichotomous variable by using a
cutoff of ≥30 ng/mL (51).

Viral load tests and treatment outcomes

HCV RNA was tested by using the Roche Cobas Amplicor
assay with a lower detection limit of 600 IU/mL for the quan-
titative assay (during the first 12 wk) and 60 IU/mL for the
qualitative assay (to assess SVR). HIV RNA was tested by using
Roche Ultrasensitive HIV reverse transcriptase–polymerase chain
reaction with a lower limit of quantification of 50 copies/mL.
EVR was defined as a ≥2 log10 reduction in HCV RNA and/or
HCV RNA <600 IU/mL at week 12 by using the quantitative
assay. SVR was defined as undetectable HCV RNA at 24 wk after
treatment cessation.

Covariates

The following covariates were of interest to characterize the
study population: sex, age at enrollment, race-ethnicity (non-
Hispanic blacks vs. white and Hispanics), BMI, current or prior
intravenous drug use, cirrhosis, season when baseline sample was
collected, region of site enrollment in the United States [north,
>40°N/south, <40°N], and baseline clinical laboratory values,
including estimated glomerular filtration rate (GFR), platelet
count, alkaline phosphatase, albumin, HOMA-IR, CD4 cell count,
HIV-1 RNA concentration, HCV viral load, CD4 nadir, IL28B
genotype, use of highly active antiretroviral therapy (HAART;
defined as a combination of ≥3 antiretroviral drugs, one of which
could be ritonavir as a pharmacokinetic booster). GFR was esti-
inated by using the Chronic Kidney Disease Epidemiology Col-
aboration equation (53). HOMA-IR was calculated by using the
subject’s fasting glucose and fasting insulin concentrations:
HOMA-IR = (fasting glucose × fasting insulin)/405.

Statistical analysis

Wilcoxon’s rank-sum test was used to test differences in
continuous measures between 2 groups, including comparison
of 25(OH)D concentrations between EVRs and non-EVRs,
and Van Elteren’s test was used for stratified rank-based com-
parisons. Fisher’s exact tests were used for comparisons of
binary and categorized variables between 2 groups, except for
IL28B, for which the Cochran-Armitage trend test was used.
Logistic regression models were developed to assess factors
associated with 25(OH)D. The following factors were con-
sidered: sex, age, race, ethnicity, BMI, intravenous drug use,
cirrhosis, region, season of sample collection, use of HAART,
use of specific antiretroviral drugs (efavirenz, ritonavir, and
tenofovir), platelet counts, GFR, baseline CD4+T cell count,
HIV viral load, and IL28B genotype. The analyses were done
by using SAS (version 9; SAS Institute). A statistical signif-
icance level of 0.05, 2-sided, was used. Because of the ex-
ploratory nature of the analysis, no adjustment for multiple
testing was made.
RESULTS

Comparison of EVR and non-EVR groups

The 144 study subjects were predominantly male and non-Hispanic black and had a median age of 48 y (Table 1). Most subjects (79.2%) were receiving HAART, and 38.2% were taking ritonavir, which was used only as a pharmacologic booster. The median 25(OH)D concentration was 22.5 ng/mL [quartile 1 = 14.0; quartile 3 = 29.0]. Slightly more than half of the subjects met the criteria for EVR. Compared with the non-EVR group (n = 68), the EVR group (n = 76) was younger, had a higher percentage of non-Hispanic whites, had a lower percentage with liver cirrhosis, had a higher albumin concentration, had a lower HCV viral load, and had a higher percentage with the favorable IL28B CC genotype (Table 1).

The difference in baseline 25(OH)D concentrations between EVR and non-EVR patients was not statistically significant (P = 0.23): median of 25.0 ng/mL (quartile 1 = 13.0; quartile 3 = 30.5) compared with 20.0 ng/mL (quartile 1 = 14.0; quartile 3 = 27.5), respectively. The trends were similar between blacks (non-Hispanic) and non-blacks (whites and Hispanics). Median 25(OH)D concentrations were 19.0 and 17.0 ng/mL among EVR and non-EVR blacks, respectively, and 28.0 and 26.0 ng/mL among EVR and non-EVR non-blacks. Hence, adjustment for race-ethnicity had a lower HCV viral load, and had a higher percentage with the favorable IL28B CC genotype (Table 1).

The lack of association between 25(OH)D concentrations and ritonavir exposure (54). Ritonavir exposure was associated with higher 25(OH)D concentrations and treatment outcome further, additional analyses were performed in which 25(OH)D was analyzed as a dichotomized variable. None showed a statistically significant relation between 25(OH)D measurements and EVR or SVR.

Variables associated with 25(OH)D concentrations ≥30 ng/mL

Three of 18 variables differed significantly between the group with 25(OH)D concentrations ≥30 ng/mL (n = 35) and the group with lower values (n = 109) (Table 2). The group with higher 25(OH)D measurements had a lower percentage of non-Hispanics blacks (22.9% compared with 62.4%), more HAART users (94.3% compared with 74.3%), and, specifically, more ritonavir users (57.1% compared with 32.1%). These 3 variables were included in a multivariable logistic regression analysis (Table 3). In the multivariable analysis, a 25(OH)D concentration ≥30 ng/mL was positively associated with white and Hispanic race-ethnicity and ritonavir exposure.

DISCUSSION

We found no significant association between the baseline serum 25(OH)D concentration and EVR or SVR in this clinical trial of peg-interferon and ribavirin treatment of HIV/HCV co-infected subjects. The median value among EVRs was 25.0 ng/mL compared with 20.0 ng/mL among non-EVRs, and this difference was not statistically significant. The lack of association between serum 25(OH)D concentration and HCV virologic response was not confounded by race or any other measured covariate in this analysis. One interpretation of these results was that vitamin D status is unrelated to treatment response in HIV/HCV co-infected patients; however, there were several caveats.

The study had a relatively small sample size of 144 patients. Our study also had the limitation of being a retrospective study from a completed trial. In addition, vitamin D status was determined by a single baseline measurement of 25(OH)D. In the future, longitudinal measurements and/or genetic analysis of polymorphisms that affect 25(OH)D concentrations might provide a clearer understanding of the relation between 25(OH)D concentrations and treatment responses.

A further consideration is that 25(OH)D is only a surrogate marker of vitamin D status. Using skeletal health as the outcome, the Institute of Medicine determined that 50% of the adult population is vitamin D replete at a 25(OH)D concentration of 16 ng/mL, whereas the other 50% require up to 20 ng/mL, or more, to achieve optimal vitamin D status. If these estimates are correct, they indicate that almost 50% of the population changes from a state of vitamin D repletion to one of vitamin D deficiency as 25(OH)D concentrations fall by 4 ng/mL. As a result, 25(OH)D concentrations in the range 16–20 ng/mL are expected to have limited ability to predict vitamin D status. In future studies, measurements of additional factors that indicate vitamin D status, such as parathyroid hormone, calcium, phosphate, and markers of bone turnover, might allow patients with and without vitamin D deficiency to be distinguished more accurately than is possible when 25(OH)D is used as the sole determinant.

The need to use a combination of factors to establish vitamin D status is especially great in patients receiving HAART because antiviral drugs cause complex alterations in vitamin D and calcium metabolism. This is illustrated by published data demonstrating that parathyroid hormone elevations occur in tenofovir users who have 25(OH)D concentrations <30 ng/mL (46–49). In the current study, a different type of alteration was observed in ritonavir users. Ritonavir exposure was associated with higher 25(OH)D concentrations. A recent study of 672 HIV-positive patients found this same association between higher 25(OH)D concentrations and ritonavir exposure (54). Ritonavir blocks the activity of the 1α hydroxylase that converts 25(OH)D into its biologically active form, 1,25(OH)2D (45). Because the physiologic effects of vitamin D require adequate concentrations of 1,25(OH)2D, we propose that ritonavir (and possibly other drugs) distorts the relation between 25(OH)D measurements and vitamin D status by blocking the conversion of 25(OH)D to 1,25(OH)2D. More information about the effect of antiviral drugs on vitamin D and calcium metabolism could improve the design of future studies of the relation between vitamin D status and treatment outcome in HIV/HCV co-infected patients.

Our results add to the growing literature on 25(OH)D concentrations and virologic responses to HCV therapy (28–33, 35–37,39). Previously, an investigation in HIV/HCV co-infected patients conducted in Austria reported a positive relation between 25(OH)D concentrations and SVR (39), whereas a study conducted in France found no association (38), in keeping with our results, which were obtained in a US study group that was 52.8% black and 14.6% Hispanic. The inconsistent results across studies suggest that the effect of baseline 25(OH)D on treatment outcomes may be modest, if it exists. However, given the very high costs and toxicity of
TABLE 1  
Baseline characteristics by EVR status

<table>
<thead>
<tr>
<th>EVR status</th>
<th>Total (n = 144)</th>
<th>EVR (n = 76)</th>
<th>Non-EVR (n = 68)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male [n (%)]</td>
<td>119 (82.6)</td>
<td>66 (86.8)</td>
<td>53 (77.9)</td>
<td>0.19&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age (y)</td>
<td>48</td>
<td>47</td>
<td>49</td>
<td>0.006&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>41.5, 52.0</td>
<td>40, 50</td>
<td>44, 53</td>
<td>0.006&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Race-ethnicity [n (%)]</td>
<td>0.014&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>47 (32.6)</td>
<td>33 (43.4)</td>
<td>14 (20.6)</td>
<td>0.17&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>76 (52.8)</td>
<td>33 (43.4)</td>
<td>43 (63.2)</td>
<td>0.041&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hispanic</td>
<td>21 (14.6)</td>
<td>10 (13.2)</td>
<td>11 (16.2)</td>
<td>0.041&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.7</td>
<td>25.5</td>
<td>25.9</td>
<td>0.77&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>22.8, 29.3</td>
<td>23.0, 28.5</td>
<td>22.7, 29.6</td>
<td>0.004&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>IV drug use history [n (%)]</td>
<td>91 (63.2)</td>
<td>44 (57.9)</td>
<td>47 (69.1)</td>
<td>0.17&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cirrhosis [n (%)]</td>
<td>18 (12.5)</td>
<td>5 (6.6)</td>
<td>13 (19.1)</td>
<td>0.041&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Platelet count (10³/mm³)</td>
<td>79, 114</td>
<td>74, 124</td>
<td>79, 114</td>
<td>0.003&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>3.15</td>
<td>3.37</td>
<td>2.76</td>
<td>0.44&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>101, 113.5</td>
<td>87.1, 111.8</td>
<td>81.7, 113.8</td>
<td>0.82&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Median</td>
<td>1.76</td>
<td>5.10</td>
<td>5.51</td>
<td>1.59, 4.65</td>
</tr>
<tr>
<td>Albumin (g/dL)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>507</td>
<td>507</td>
<td>504</td>
<td>507, 504</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>380, 703</td>
<td>384, 645</td>
<td>356, 719</td>
<td>0.014&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nadir CD4 (cells/mm³)</td>
<td>247</td>
<td>205</td>
<td>258</td>
<td>0.12&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Median</td>
<td>22.5</td>
<td>25</td>
<td>20</td>
<td>0.23&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA [n (%)]</td>
<td>101 (70.1)</td>
<td>53 (69.7)</td>
<td>48 (70.6)</td>
<td>1.00&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Undetectable, &lt;50 copies/mL</td>
<td>6.54</td>
<td>6.50</td>
<td>6.60</td>
<td>0.64&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Baseline log₁₀ HCV RNA (IU/mL)</td>
<td>6.15, 6.88</td>
<td>5.88, 6.87</td>
<td>6.40, 6.89</td>
<td>0.024&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>IL28B genotype [n (%)]&lt;sup&gt;7&lt;/sup&gt;</td>
<td>35 (32.7)</td>
<td>22 (39.3)</td>
<td>13 (25.5)</td>
<td>0.62&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>TT</td>
<td>73 (50.7)</td>
<td>37 (48.7)</td>
<td>36 (52.9)</td>
<td>0.62&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Season, summer [n (%)]&lt;sup&gt;9&lt;/sup&gt;</td>
<td>114 (79.2)</td>
<td>62 (81.6)</td>
<td>52 (76.5)</td>
<td>0.54&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Antiretroviral medication use [n (%)]</td>
<td>55 (38.2)</td>
<td>31 (40.8)</td>
<td>24 (35.3)</td>
<td>0.61&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>HAART</td>
<td>22.5</td>
<td>25</td>
<td>20</td>
<td>0.61&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Median</td>
<td>14.0, 29.0</td>
<td>13.0, 30.5</td>
<td>14.0, 27.5</td>
<td>0.23&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EVR, early virologic response; GFR, glomerular filtration rate; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; IV, intravenous; Q1, first quartile (25th percentile); Q3, third quartile (75th percentile); 25(OH)D, 25-hydroxyvitamin D.

<sup>2</sup> Fisher’s exact test.

<sup>3</sup> Wilcoxon’s test.

<sup>4</sup> Total n = 142 (n = 75 for EVR and n = 67 for non-EVR).

<sup>5</sup> CKD-EPI equation.

<sup>6</sup> Total n = 70 (n = 37 for EVR and 33 for non-EVR).

<sup>7</sup> Total n = 107 (n = 56 for EVR and n = 51 for non-EVR).

<sup>8</sup> Exact Cochrant-Armitage trend test.

<sup>9</sup> June–November.
HCV treatment, even a modest beneficial effect could be clinically and economically significant if it can be obtained through the use of vitamin D supplements. With further investigation, it may be possible to identify the characteristics of patients most likely to benefit from higher 25(OH)D concentrations and from adjunctive treatment with vitamin D supplements before and during HCV treatment; moreover, given the high prevalence of bone disease in HCV-infected patients (42, 55–59), HIV-infected patients (60), and HIV/HCV co-infected patients (40, 41), it may be prudent to consider vitamin D supplements for all patients with 25(OH)D concentrations 20–30 ng/mL, regardless of the anticipated effect on HCV treatment response.

In summary, this study of 144 HIV/HCV co-infected patients did not show a significant relation between baseline 25(OH)D concentrations and EVR or SVR. Ritonavir exposure and white

### TABLE 2
Baseline characteristics by 25(OH)D concentrations

<table>
<thead>
<tr>
<th>Dichotomized 25(OH)D&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Total (n = 144)</th>
<th>&lt;30 ng/mL (n = 109)</th>
<th>≥30 ng/mL (n = 35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male [n (%)]</td>
<td>119 (82.6)</td>
<td>89 (81.7)</td>
<td>30 (85.7)</td>
<td>0.80&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age (y)</td>
<td>48</td>
<td>48</td>
<td>47</td>
<td>0.92&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Median</td>
<td>41.50, 52.00</td>
<td>32, 66</td>
<td>35, 59</td>
<td></td>
</tr>
<tr>
<td>Race [n (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black non-Hispanic</td>
<td>76 (52.8)</td>
<td>68 (62.4)</td>
<td>8 (22.9)</td>
<td>&lt;0.001&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hispanic, regardless of race</td>
<td>21 (14.6)</td>
<td>14 (12.8)</td>
<td>7 (20.0)</td>
<td>0.29&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;) Median</td>
<td>25.74</td>
<td>25.83</td>
<td>25.50</td>
<td>0.73&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>22.84, 29.33</td>
<td>23.05, 29.03</td>
<td>22.64, 30.20</td>
<td></td>
</tr>
<tr>
<td>IV drug use history [n (%)]</td>
<td>91 (63.2)</td>
<td>71 (65.1)</td>
<td>20 (57.1)</td>
<td>0.42&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cirrhosis [n (%)]</td>
<td>18 (12.5)</td>
<td>14 (12.8)</td>
<td>4 (11.4)</td>
<td>1.00&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Region, north [n (%)]</td>
<td>60 (41.7)</td>
<td>49 (45.0)</td>
<td>11 (31.4)</td>
<td>0.17&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Antiretroviral medication use [n (%)]</td>
<td>73 (50.7)</td>
<td>52 (47.7)</td>
<td>21 (60.0)</td>
<td>0.25&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Platelet count (10&lt;sup&gt;3&lt;/sup&gt;/mm&lt;sup&gt;3&lt;/sup&gt;) Median</td>
<td>206.5</td>
<td>206</td>
<td>219</td>
<td>0.25&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>159, 250</td>
<td>156, 237</td>
<td>166, 265</td>
<td></td>
</tr>
<tr>
<td>GFR (mL · min&lt;sup&gt;-1&lt;/sup&gt; · 1.73 m&lt;sup&gt;2&lt;/sup&gt;) Median</td>
<td>101.53</td>
<td>100.29</td>
<td>102.97</td>
<td>0.79&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>84.27, 113.50</td>
<td>89.38, 112.53</td>
<td>79.89, 113.68</td>
<td></td>
</tr>
<tr>
<td>Baseline CD4 count (cells/mm&lt;sup&gt;3&lt;/sup&gt;) Median</td>
<td>507</td>
<td>495</td>
<td>549</td>
<td>0.38&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>380, 703</td>
<td>384, 645</td>
<td>356, 719</td>
<td></td>
</tr>
<tr>
<td>Baseline HIV-1 RNA (copies/mL)</td>
<td>Undetectable (&lt;50)</td>
<td>101 (70.1)</td>
<td>77 (70.6)</td>
<td>24 (68.6)</td>
</tr>
<tr>
<td>IL28B genotype [n (%)]&lt;sup&gt;7&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>23 (21.5)</td>
<td>18 (22.8)</td>
<td>5 (17.9)</td>
<td>0.65&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>CT</td>
<td>49 (45.8)</td>
<td>36 (45.6)</td>
<td>13 (46.4)</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>35 (32.7)</td>
<td>25 (31.6)</td>
<td>10 (35.7)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>Cran-D-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; HAART, highly active antiretroviral therapy; IV, intravenous; Q1, first quartile (25th percentile); Q3, third quartile (75th percentile); 25(OH)D, 25-hydroxyvitamin D.
<sup>2</sup>Cutoff = 30 ng/mL.
<sup>3</sup>Fisher’s exact test.
<sup>4</sup>Wilcoxon’s test.
<sup>5</sup>June–November.
<sup>6</sup>Cran-D-EPI equation.
<sup>7</sup>Total n = 107; n = 79 for 25(OH)D < 30 ng/mL and n = 28 for 25(OH)D ≥ 30 ng/mL.
<sup>8</sup>Exact Cochran-Armitage trend test.
race were associated with 25(OH)D concentrations ≥30 ng/mL. Future studies are needed to identify methods for accurately determining the physiologic vitamin D status of patients receiving antiviral therapy for HIV to clarify the effect of the new direct-acting antiviral drugs for HCV on vitamin D and calcium metabolism.

We thank the ACTG A5178 study team, the study subjects, and the many individuals involved in the conduct and/or care of patients enrolled in this study at each of the participating institutions. The authors’ responsibilities were as follows—ADB, MJG, RTC, and MK: designed the research; MK and KH: performed the statistical analysis; ADB: wrote the first draft of the manuscript; CMW: directed the interpretation of GFR data; ADB and MG: had primary responsibility for the final content; and all authors: edited and approved the final version. The authors declared that no competing interests existed.

REFERENCES


