Short Communication: Interferon/Ribavirin Treatment for HCV Is Associated with the Development of Hypophosphatemia in HIV/Hepatitis C Virus-Coinfected Patients

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Abstract

One-third of all HIV-infected individuals in the United States are estimated to be coinfecting with the hepatitis C virus (HCV). Treatment of chronic hepatitis C in patients coinfecting with HIV is a complex problem associated with toxicities and drug interactions between HIV antiretrovirals and interferon and ribavirin. In recent HCV treatment studies, we observed a previously unreported development of hypophosphatemia in HIV/HCV-coinfecting patients treated with interferon/ribavirin (IFN/RBV). To further investigate this observation, we retrospectively reviewed 61 HIV/HCV-coinfecting patients on antiretrovirals (ARVs) during treatment with IFN/RBV as well as 154 HIV-infected patients treated with ARVs alone. We found that HIV/HCV-coinfecting patients on IFN/RBV therapy were more likely to develop frequent (57% vs. 13%, IFN/RBV-treated patients vs. no IFN/RBV; $\chi^2=0.001$) and higher-grade hypophosphatemia (67.0% Grade 2, 33.3% Grade 3 vs. 94.7% Grade 2, 5.3% Grade 3, IFN/RBV-treated patients vs. no IFN/RBV; $\chi^2<0.001$) than untreated patients. In addition, we found that the new onset of hypophosphatemia after IFN/RBV treatment initiation was followed by a diminished frequency of this toxicity upon cessation of IFN/RBV, supporting the idea that a drug-drug interaction may increase the risk of this toxicity. To understand the risks of developing this toxicity, we evaluated the association between individual ARV use and hypophosphatemia incidence. Our data suggest that concomitant tenofovir (TDF) use may be a risk factor for the development of hypophosphatemia in HIV/HCV-coinfecting patients treated with IFN/RBV. Although the etiology of this abnormality is likely multifactorial, clinicians should be aware of hypophosphatemia as a potential marker of renal toxicity in HIV/HCV-coinfecting patients being treated with IFN/RBV regimens.

HEPATITIS C VIRUS (HCV) INFECTION affects approximately 180 million people worldwide and often leads to the development of chronic liver disease.^{1,2} It is estimated that about one-third of all HIV-infected individuals are also infected with hepatitis C, likely due to shared risk factors for transmission.^{3–6} In HIV/HCV-coinfecting patients, the progression of HCV-related liver disease is accelerated and leads to an increase in morbidity and mortality.^{7–10} Thus, treatment of HCV in HIV/HCV-coinfecting patients is needed to prevent HCV-related deaths.

Complications associated with the concurrent treatment of HIV and HCV infections have emerged as a complex issue for clinicians. Treatment of HCV in HIV/HCV-coinfecting individuals with pegylated interferon- α and ribavirin (pegIFN/

RBV) is associated with decreased rates of virologic response as compared to HCV-monoinfected patients.^{11,12} In addition, treatment of HIV/HCV-coinfecting patients is further complicated by the concomitant use of certain HIV antiretrovirals (ARVs), some of which are associated with increased mitochondrial toxicities, hepatic decompensation, and anemia when used with pegIFN/RBV.^{13–15}

In recent HCV treatment studies, we observed the development of hypophosphatemia in HIV/HCV-coinfecting patients treated with IFN/RBV and wanted to determine the incidence and risk factors for the development of this toxicity. We retrospectively analyzed results from an HIV/HCV-coinfecting cohort and an HIV-monoinfected cohort. The HIV/HCV-coinfecting cohort included patients from three

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prospective, open label trials performed at the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health from 2001 to 2010. Sixty-one HIV/HCV-coinfected, treatment-naïve patients were treated with 48 weeks of weight-based ribavirin daily in addition to either pegIFN alfa-2b (1.5 µg/kg weekly), pegIFN alfa-2a (180 µg weekly), or albIFN alfa-2b (900 µg every 2 weeks) and followed every 1–2 months until at least 1 year after completion of HCV treatment. HIV treatment was provided to patients by their primary care physicians. The HIV-monoinfected cohort included 154 HIV-infected patients who enrolled in a natural history study at NIAID, National Institutes of Health outpatient clinics between 2001 to 2010. Patients were evaluated every 3 months and treated with ARV therapy in accordance with DHHS treatment guidelines. All patients gave written informed consent approved by the NIAID Institutional Review Board prior to enrollment in the treatment and natural history studies. Data from these cohorts were retrospectively analyzed for this study.

Demographic data were recorded on a standardized data collection sheet. In the HIV/HCV-coinfected group, safety laboratory tests were obtained at baseline and at least every 1–2 months throughout the course of IFN/RBV therapy, and at least every 3 months during posttreatment follow-up. Patients were evaluated for new or worsening hypophosphatemia during IFN/RBV therapy as well as for new, recurrent, or worsening hypophosphatemia for 1 year after the completion of IFN/RBV therapy. In the HIV-monoinfected group, safety laboratory tests were obtained at baseline and at least every 3 months. Patients were evaluated for new or worsening hypophosphatemia for 1 year after the initiation of ARV therapy. Patients who remained ARV naïve after enrollment or who began ARV therapy prior to enrollment were evaluated for 1 year following enrollment in the natural history study, using their screening visit as a date for baseline and the start of the 1-year follow-up period. Enrollment during the years 2001–2010 was selected as an approximate time match for the concurrently enrolling HCV/HIV-coinfected cohort in order to control for ARV prescribing trends, as new ARVs were released for use during this time.

The incidence, severity of hypophosphatemia, and percent episodes (number of hypophosphatemia events out of the total number of phosphate measurements, used in order to control for repeat measurement bias) were compared between patients treated and those not treated with IFN/RBV. In addition, within IFN/RBV-treated patients, the incidence of hypophosphatemia pretherapy and posttherapy was compared.

Hypophosphatemia was defined as serum phosphorus levels <2.5 mg/dl and graded per the 1998 DAIDS Toxicity Table as follows: Grade 2: 2.0–2.4 mg/dl, Grade 3: 1.0–1.9 mg/dl, and Grade 4: <1.0 mg/dl. For the HCV/HIV-coinfected cohort, HCV RNA concentration in plasma was measured by the VERSANT HCV RNA 3.0 Assay (Bayer Diagnostics, Puteaux, France) or Abbott Assays (Abbott Laboratories, Abbott Park, IL).

To determine if variations in tenofovir levels could predict the development of hypophosphatemia, tenofovir (TDF) plasma concentrations were measured in five HIV/HCV-coinfected patients who developed the most severe hypophosphatemia while on TDF-containing ARV regimens and IFN/RBV therapy. Testing was performed by the University of

North Carolina's Center for AIDS Research Clinical Pharmacology and Analytical Chemistry Core using frozen plasma samples. Plasma concentrations were measured at two time points: prior to the first dose of IFN/RBV and at the time of maximum hypophosphatemia while on IFN/RBV. The lower limit of quantification for the assay is 0.25 ng/ml and trough concentrations are estimated as 30–50 ng/ml.

Chi-squared analyses were used to compare the categorical values including the differences in baseline ARV regimens, incidence of hypophosphatemia, and severity of hypophosphatemia between patients who did and did not receive IFN/RBV. Student's *t*-tests were used to compare baseline demographic values such as age, CD4 count, and baseline HIV-1 viral load, as well as differences in the percentage of episodes of hypophosphatemia, and risk factors for hypophosphatemia between patients who did and did not receive IFN/RBV. Analyses were conducted using SPSS version 21 (IBM, Armonk, NY) and GraphPad Prism version 6.0a (La Jolla, CA).

Baseline demographics were similar between both groups (Table 1). However, HIV/HCV-coinfected patients undergoing IFN/RBV treatment were older (46.4 ± 8.1 vs. 40.7 ± 10.3 years, IFN/RBV vs. no IFN/RBV; $p < 0.001$) and more likely to be black (55.7% vs. 35.3% black, IFN/RBV vs. no IFN/RBV; $\chi^2 = 0.020$). In addition, HIV-monoinfected patients had slightly lower baseline CD4 cell counts (401 ± 267 cells/mm³ vs. 570 ± 274 cells/mm³, no IFN/RBV vs. IFN/RBV; $p < 0.001$) and had higher baseline HIV RNA ($38,236 \pm 97,889$ copies/ml vs. $1,144 \pm 4,386$ copies/ml, no IFN/RBV vs. IFN/RBV; $p = 0.003$), since many HIV-monoinfected patients were enrolled just prior to ARV initiation. Overall, 82% of HIV/HCV-coinfected patients and 90% of HIV-monoinfected patients received ARV therapy. Patients treated with IFN/RBV were less likely to have received regimens containing tenofovir, emtricitabine, or atazanavir, but more likely to have received stavudine.

Fifty-seven percent of IFN/RBV-treated patients had at least one episode of hypophosphatemia during treatment compared to 13.0% of patients not treated with IFN/RBV ($\chi^2 = 0.001$). In addition, IFN/RBV-treated patients had a higher percentage of episodes of hypophosphatemia (number of hypophosphatemia events out of the total number of phosphate measurements; $12.5\% \pm 15.5\%$ vs. $3.2\% \pm 11.2\%$, IFN/RBV-treated patients vs. no IFN/RBV; $p < 0.001$). Severity of hypophosphatemia was of a higher grade in those who received IFN/RBV, with treated patients more likely to experience Grade 3 hypophosphatemia (67.0% Grade 2, 33.3% Grade 3 vs. 94.7% Grade 2, 5.3% Grade 3, IFN/RBV-treated patients vs. no IFN/RBV respectively; $\chi^2 < 0.001$). Finally, the average lowest phosphate level in patients who developed hypophosphatemia was significantly lower in the IFN/RBV-treated cohort as compared to those who were not treated (2.07 ± 0.28 mg/dl vs. 2.22 ± 0.16 mg/dl, respectively; $p = 0.032$). No patients in either cohort had any documentation of clinically significant symptoms resulting from hypophosphatemia, and no patients discontinued medication as a result of hypophosphatemia.

Of 37 patients who developed hypophosphatemia during treatment with IFN/RBV, only 27% ($n = 10$) had recurrent hypophosphatemia in the 12 months following end of therapy. Thirty percent of recurrences occurred within 2 weeks of stopping IFN/RBV treatment (single episode). Seventy

TABLE 1. DEMOGRAPHICS AND CLINICAL CHARACTERISTICS OF HIV-INFECTED PATIENTS TREATED AND NOT TREATED WITH INTERFERON/RIBAVIRIN

Characteristic	IFN/RBV (n=61)	No IFN/RBV (n=154)	
Age, mean years $\pm$ SD	46.4 $\pm$ 8.1	40.7 $\pm$ 10.3	$p < 0.001$
Gender, n (% male)	51 (86.3%)	122 (79.2%)	$\chi^2 = 0.568$
Ethnicity, n (%)			$\chi^2 = 0.23$
Black	34 (38.2%)	55 (35.7%)	
White	20 (26.3%)	56 (36.4%)	
Hispanic	6 (9.8%)	35 (22.7%)	
Other	1 (1.6%)	8 (5.2%)	
CD4 cell count mean cells/mm ³ $\pm$ SD	570 $\pm$ 274	400 $\pm$ 266	$p < 0.001$
HIV-1 RNA, mean copies/ml $\pm$ SD	1,144 $\pm$ 4,386	38,236 $\pm$ 97,618	$p = 0.003$
Baseline phosphorus value	3.51 $\pm$ 0.64	3.51 $\pm$ 0.641	$p = 0.950$
Baseline GFR	106 $\pm$ 22	103 $\pm$ 36	$p = 0.597$
Baseline proteinuria	18 (36.7%)	50 (32.7%)	$p = 0.360$
Hypertension	14 (25.5%)	18 (11.8%)	$\chi^2 = 0.017$
Diabetes mellitus	10 (18.2%)	6 (3.9%)	$\chi^2 = 0.002$
Receiving ARVs	50 (82.0%)	138 (90.2%)	$\chi^2 = 0.079$
ARVs n, (%)			
Tenofovir	29 (47.5%)	110 (72.4%)	$\chi^2 = 0.001$
Emtricitabine	20 (32.8%)	84 (55.3%)	$\chi^2 = 0.002$
Abacavir	9 (14.9%)	21 (12.8%)	$\chi^2 = 0.507$
Didanosine	3 (4.9%)	3 (2.0%)	$\chi^2 = 0.228$
Stavudine	7 (11.5%)	4 (2.6%)	$\chi^2 = 0.014$
Zidovudine	8 (13.1%)	23 (15.1%)	$\chi^2 = 0.444$
Atazanavir	3 (4.9%)	41 (27.0%)	$\chi^2 < 0.0001$
Lopinavir	12 (19.7%)	20 (13.2%)	$\chi^2 = 0.161$
Efavirenz	23 (37.7%)	56 (36.8%)	$\chi^2 = 0.513$

IFN/RBV, interferon/ribavirin; GFR, glomerular filtration rate; ARVs, antiretrovirals.

percent of recurrences were less severe than the hypophosphatemia that occurred while on treatment, and 80% recurrences posttreatment occurred only once.

In HIV-infected patients who were not treated with IFN/RBV there was no association between the development of hypophosphatemia and age (42.6 $\pm$ 8.9 years vs. 40.4 $\pm$ 10.5 years, hypophosphatemia vs. no hypophosphatemia; $p = 0.17$), gender (13.2% vs. 6.3%, men vs. women with hypophosphatemia; $\chi^2 = 0.37$), CD4 count (340.8 $\pm$ 228.1 cells/mm³ vs. 408.8 $\pm$ 271.3 cells/mm³, hypophosphatemia vs. no hypophosphatemia; $p = 0.23$), or baseline glomerular filtration rate (GFR) (99.1 $\pm$ 50.4 ml/min/1.73 m² vs. 104.4 $\pm$ 29.6 ml/min/1.73 m², hypophosphatemia vs. no hypophosphatemia; $p = 0.90$). Additionally, there was no difference in the percentage of episodes of hypophosphatemia in patients with baseline proteinuria (4.0% $\pm$ 15.5% vs. 2.4% $\pm$ 8.6%, with vs. without baseline proteinuria; $p = 0.42$), or with concomitant tenofovir (TDF) use (3.9% $\pm$ 13.0% vs. 0.7% $\pm$ 3.3%, on TDF vs. not on TDF; $p = 0.116$), LPV use [2.0% $\pm$ 6.2% vs. 3.2% $\pm$ 11.8%, on lopinavir (LPV) vs. not on LPV; $p = 0.656$], or other ARV use (EFV, FTC, 3TC, ABC, RAL, ddI, d4T, NFV, ATV, NVP, AZT, SQV; data not shown).

In HIV/HCV-coinfected patients receiving IFN/RBV therapy there was also no association between the development of hypophosphatemia and age (46.6 $\pm$ 7.6 years vs. 46.2 $\pm$ 8.8 years, hypophosphatemia vs. no hypophosphatemia; $p = 0.84$), gender (58.8% vs. 50.0%, men vs. women with hypophosphatemia; $\chi^2 = 0.73$), CD4 count (565.7 $\pm$ 298 cells/mm³ vs. 576.0 $\pm$ 241.9 cells/mm³, hypophosphatemia vs. no hypophosphatemia; $p = 0.886$), or baseline GFR (104.8 $\pm$ 22.4 ml/min/1.73 m² vs. 108.5 $\pm$ 21.9 ml/min/1.73 m², hypophosphatemia vs. no hypo-

phosphatemia; $p = 0.53$). Again, there was no difference in the percentage of episodes of hypophosphatemia in patients with baseline proteinuria (4.2% vs. 2.4%, with vs. without baseline proteinuria; $\chi^2 = 0.15$), concomitant LPV use (14.2% $\pm$ 16.4% vs. 12.0% $\pm$ 15.4%, on LPV vs. not on LPV; $p = 0.66$), or other ARVs (EFV, FTC, 3TC, ABC, RAL, ddI, d4T, NFV, ATV, NVP, AZT, SQV; data not shown). Concomitant tenofovir usage was the only risk factor that exhibited a trend toward increased hypophosphatemia, with patients on concomitant TDF having more episodes of hypophosphatemia compared to patients not on TDF (16.1% $\pm$ 18.3% vs. 9.2% $\pm$ 11.7%, respectively; $p = 0.082$).

To understand the mechanism of hypophosphatemia seen in these patients we evaluated the potential for TDF toxicity as well as renal toxicity. There was no correlation between on treatment plasma TDF levels ($R^2 = 0.06$, $p = 0.89$) or the change in plasma TDF levels ($R^2 = 0.008$, $p = 0.68$) with hypophosphatemia in the five TDF and IFN/RBV-treated patients with the most severe hypophosphatemia (mean decline in phosphorus pretreatment to posttreatment was 1.6 mg/dl) who were selected for evaluation of TDF levels. In addition, among all patients who developed hypophosphatemia there was no difference in GFR from baseline to time of hypophosphatemia (103 $\pm$ 34 ml/min/1.73 m² vs. 105 $\pm$ 33 ml/min/1.73 m², $p = 0.76$, baseline vs. time of hypophosphatemia), nor was there a difference between the change in GFR between IFN-treated and untreated patients (5.7 $\pm$ 21.3 ml/min/1.73 m² vs. -3.9 $\pm$ 25.5 ml/min/1.73 m² IFN/RBV-treated vs. no IFN/RBV; $p < 0.001$). In addition, a large proportion of both IFN-treated and untreated patients who developed hypophosphatemia also had new proteinuria (68.4% of IFN-treated patients vs. 31.6% of IFN-untreated patients); this difference,

however, was not statistically significant between IFN-treated and untreated patients ($\chi^2=1$). No patients had an anion gap at baseline or at time of hypophosphatemia that could be indicative of a metabolic acidosis.

The development of hypophosphatemia was a common complication in patients receiving IFN/RBV therapy, which has not been previously reported in clinical trials.^{13,16} The new onset of hypophosphatemia after IFN/RBV treatment initiation, followed by the diminished frequency of this abnormality upon cessation, suggests that a drug toxicity is the mechanism. While the etiology is likely multifactorial, concomitant TDF may be a risk factor.

Previous trials have shown similar frequencies of laboratory abnormalities and similar adverse event profiles in HCV-monoinfected and HIV/HCV-coinfected patients treated for HCV with IFN/RBV.^{2,13} The main difference noted between the groups has been a low, but increased risk of adverse events associated with mitochondrial toxicity, as well as increased anemia in HIV/HCV-coinfected patients receiving zidovudine.^{15,16} In this study we observed high rates of new onset hypophosphatemia during treatment with IFN/RBV with diminished frequency and severity upon cessation of IFN/RBV, which has not previously been reported.

Past anecdotal reports have suggested that tenofovir is associated with the development of hypophosphatemia and have been a cause for concern due to its association with renal toxicity.^{17,18} Interestingly, we did not find an increase in hypophosphatemia in IFN-untreated patients receiving tenofovir, again suggesting that the mechanism of hypophosphatemia toxicity in our cohort is driven by IFN/RBV. However, within the group of patients who received IFN/RBV, we did find that concomitant TDF may increase the risk of developing hypophosphatemia. This is of particular concern as the standard treatment for hepatitis C now includes IFN/RBV in combination with an HCV protease inhibitor. These regimens are increasingly being used in HIV/HCV-coinfected patients, with early data showing that certain directly acting antivirals against hepatitis C can increase the plasma concentration of tenofovir by up to 30%,^{19,20} potentially worsening TDF-induced toxicities.

Tenofovir and RBV are eliminated by the kidneys, through a combination of glomerular filtration and proximal tubular secretion. Drug interactions with renal proximal tubule cell transporters have been reported to cause substantial intracellular drug accumulation,^{21,22} mitochondrial injury, and proximal tubular toxicity.²³ Clinically, this manifests as proteinuria, glycosuria, phosphaturia, hypokalemia, hypophosphatemia,²² as well as acute kidney injury, chronic kidney disease, decreased bone mineral density, or Fanconi syndrome.²¹ The increased frequency and severity of hypophosphatemia in our patients treated with IFN/RBV and concomitant TDF suggest an interaction between TDF and RBV as has been seen with other drugs in this class.^{16,24}

While a previous pharmacokinetic study in healthy volunteers did not find an interaction between TDF and RBV, TDF pharmacokinetics after only a single dose of RBV were evaluated.²⁵ Interactions between TDF and IFN/RBV will be further informed by the results of ongoing clinical trials with the use of these agents for HBV. In our study plasma TDF levels were not able to predict the development of hypophosphatemia; however, the correlation between plasma TDF concentrations and toxicity is not understood as nucleoside

reverse transcriptase inhibitors (NRTIs) are inactive until intracellular phosphorylation.²⁶ In addition, in this study plasma levels were measured during a finite time period and may have been significantly different in the past. Thus, simpler tools to measure intracellular TDF concentrations in stored samples are needed to determine predictors of TDF toxicity. In addition, we did not see a change in GFR in patients who developed hypophosphatemia; however, a large proportion of patients did develop new onset proteinuria suggesting kidney toxicity as a mechanism in both groups.

Limitations of this study include the retrospective design and unknown correlation of plasma levels of TDF with the development of associated toxicities. In addition, our control group for the development of hypophosphatemia is time-matched ARV-treated HIV-monoinfected patients. HIV/HCV-coinfected or HCV-monoinfected control patients were unavailable and may have served as better control groups; however, this is unlikely to alter our results, as hypophosphatemia has not been attributed to HCV infection. In both groups, duration of ARV therapy prior to enrollment in an NIH study was not known and thus we were not able to determine if cumulative exposure to ARVs may have impacted renal function. Finally, while our data suggest that TDF may be a risk factor for hypophosphatemia, its etiology is clearly multifactorial, and we were not able to determine the risk induced by IFN/RBV treatment alone.

In conclusion, we have found that hypophosphatemia is a common complication of IFN/RBV therapy in HIV/HCV-coinfected patients and is likely multifactorial, but may include drug-drug interactions, particularly between ribavirin and TDF. The clinical significance of this toxicity is unclear; however, clinicians should be aware of hypophosphatemia as a potential marker of renal toxicity in HIV/HCV-coinfected patients receiving IFN/RBV.

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