Incidence and Risk Factors of Hypophosphatemia in Patients with HIV Infection Receiving Tenofovir Disoproxil Fumarate at a Hospital Belonging to a Medical Service Department

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Abstract

Recently, the number of patients with human immunodeficiency virus (HIV) infection in Thailand tends to decrease because of more access to treatment, including the discovery and development of a combination of highly effective antiretroviral drug containing tenofovir disoproxil fumarate (TDF) and its widespread use. This is also attributed to their good efficacy and few adverse reactions. However, the nephrotoxic effect of TDF has been reported, including cases of low blood phosphate. To our knowledge, no study has investigated the incidence of hypophosphatemia caused by TDF in Thailand. This retrospective cross-sectional study aimed to estimate the incidence and risk factors of hypophosphatemia in patients receiving TDF-containing anti-HIV regimens. Data of patients with HIV infection who received TDF between July 1, 2018, and June 30, 2020, at a hospital belonging to a medical service department were reviewed. Data such as serum creatinine and serum phosphate levels were collected from medical records and electronic medical records and then transferred through a data record form. Hypophosphatemia was defined as serum phosphate value lower than 2.5 mg/dL. As a result, from 798 cases of patients with HIV infection who received TDF, 26 patients met the inclusion criteria and five patients had hypophosphatemia (19.2%), and the standard drug dose was used (300 mg/day) or was properly adjusted according to patients’ renal function. The median duration of TDF use was 10 (1–63) months. Other factors that may contribute to the development of hypophosphatemia are comorbidities and other drugs; there was one patient who used antacids longer than 1 week before onset of hypophosphatemia. This study may help develop a risk assessment tool for monitoring hypophosphatemia in patients who received TDF.

Introduction

Tenofovir disoproxil fumarate (TDF) is one of most commonly used antiretroviral medication in patients with HIV infection. Owing to its widespread application, studies have reported its side effects (1–2). The most common adverse effect of TDF is nephrotoxicity (3–6). Hypophosphatemia also occurred in most cases with TDF before nephrotoxicity was detected. Appearance can demonstrate the relationship between hypophosphatemia and nephrotoxicity (7). As a result, the use of hypophosphatemia as a monitoring tool in routine practice is limited, but results of previous studies were controversial (8). The incidence of hypophosphatemia ranged from 9–30% (5–10). To our knowledge, no study in Thailand has examined the incidence of hypophosphatemia, but only a study on the incidence of tenofovir isoproxil fumarate-induced proximal tubulopathy in patients with human immunodeficiency virus (HIV) infection found that 9.2% of patients had hypophosphatemia (5).

Therefore, this study aimed to determine the incidence of hypophosphatemia in patients with HIV infection receiving TDF and to explore the risk factors of TDF-induced hypophosphatemia.

Methods

Research design
This retrospective cross-sectional study was carried out to determine the incidence of hypophosphatemia in patients with HIV infection receiving TDF.

**Population**

The study population comprised patients with HIV infection who received TDF and visited the hospital between July 1, 2019, and June 30, 2020.

**Inclusion criteria**

- Receiving TDF at least 1 month
- Age > 18 years
- Assessment of SCr before and after 1 month of receiving TDF as baseline values
- Serum phosphate levels were monitored before and after 1 month of receiving TDF as baseline value
- Continuous monitoring of SCr and serum phosphate at least once after receiving TDF
- Antiretroviral therapy with dose modified according to renal function by considering creatine clearance

**Exclusion criteria**

- Patients who withdraw from the study or died of causes other than hypophosphatemia.
- Patients who stopped using TDF for reasons other than hypophosphatemia.

The cutoff value of hypophosphatemia was serum phosphate below 2.5 mg/dL.

**Sample size**

The sample size was calculated using the Cochrane formula (11) used in previous study (6), which found an incidence of 0.26. The following values were used to calculate the sample size: error = 0.05, Za/2 = Z0.05/2 = 1.96, P (incidence of hypophosphatemia) = 0.26, Q = 1 - P = 1 - 0.26 = 0.74, and acceptable error = 0.05.

Following substitution in the formula, \( n = \frac{(0.26)(0.74)(1.96)^2}{(0.05)^2} = 296 \) cases are needed in this study. By adding 10% as dropout rate, 326 cases should be enrolled in this study.

**Data collection**
The data collection form consisted of the following information:

- Demographic data
- Treatment information
- Laboratory information before and after receiving TDF, Scr, and serum phosphate
- Other factors that affect serum phosphate level (such as alcoholic cirrhosis, malnutrition, Crohn's disease, severe vomiting, steatorrhea, chronic diarrhea, diabetic ketoacidosis, and infection) and use of drug-induced hypophosphatemia (increase phosphate excretion: adefovir, ifosfamide, cefepime, and ceftolozane/tazobactam; increase phosphate absorption: antacid, high-dose niacin, and acetazolamide) were recorded.

For data collection, Google Forms was used via QR code (https://forms.gle/vGY3vgyTnhxFAM4y9).

**Data analysis**

The incidence of hypophosphatemia was calculated using the following formula:

\[
\text{Incidence of hypophosphatemia} = \frac{\text{Patientswhohadhypophosphatemia} \times 100}{\text{Allrecruitedpatients}}
\]

Factors associated with hypophosphatemia were analyzed by multivariate regression with level of significance set at 0.05.

This study was approved by the ethics committee of Silpakorn University, Nakhon Pathom, Thailand (REC 631012–1205118), and the local hospital.

**Results**

**Demographic data**
A total of 26 patients were recruited, and most of the patients were male (76.9) with median weight of 59 kg. The median duration of using TDF was 28.5 months. The median serum creatinine and serum phosphate levels at baseline were 0.8 mg/dL and 4.1 mg/dL, respectively. Only one patient had concomitant drug that can cause hypophosphatemia (Table 1).

**Incidence of hypophosphatemia**

In the data collection, 798 patients with HIV infection received TDF. However, 774 patients did not meet the inclusion criteria. Approximately 50% of these patients did not have serum phosphate measurement at baseline. Therefore, 26 patients were recruited, of which five patients had hypophosphatemia (Fig. 1). The calculated incidence is 19.2 and median duration of receiving TDF until hypophosphatemia occurred is 10 months as presented in Table 2

**Cases of hypophosphatemia**

Table 3 summarizes data of five patients who received TDF and developed hypophosphatemia.

All patients did not have comorbidity. The suspected comedication that could have caused hypophosphatemia was not identified, except in patient 2 who received antacid with TDF for 8 weeks, following which hypophosphatemia occurred. All patients took 300 mg of TDF at bedtime, or the dose was adjusted according to their renal function. The serum phosphate level returned to normal values in patients 1, 3, and 4 within 1 week, 3 days, and 1 month, respectively, without any intervention.

**Discussion**

**Incidence of hypophosphatemia**

The incidence of hypophosphatemia in this study was similar to that in a previous study (6) of 145 patients with HIV infection, which also reported a relationship between nephrotoxicity and increase risk of severe renal tubular damage despite normal serum creatinine level. The mean duration of using TDF until hypophosphatemia occurred was $11 \pm 9$ months, and the incidence of hypophosphatemia was 26%. Hypophosphatemia could be explained by the mechanism of TDF that induces renal tubular damage by decreasing mitochondria function, which leads to Fanconi syndrome and disrupted phosphate absorption because of phosphaturia (10, 12).

**Risk factors of hypophosphatemia**

Previous studies have investigated risk factors of hypophosphatemia (13–17), and factors are classified as comorbidity factors and comedication factors (15–17). Comorbidities that affect serum phosphate levels are alcoholism, malnutrition, Crohn's disease, severe vomiting, steatorrhea, diabetic ketoacidosis, and sepsis. Comedications that influence serum phosphate level include adefovir, ifosfamide, cefepime, and ceftolozane/tazobactam which can increase phosphate excretion. Nevertheless, some medications
interfere with phosphate absorption, such as antacids, high-dose niacin, and acetazolamide (15–17). In this study, only one patient had one risk factor; the patient was also taking antacid. Given the small sample size, this study could not use statistical methods to evaluate or explore significant factors that influence hypophosphatemia. Although nearly all cases did not have evidence of risk factors that increase the risk of hypophosphatemia, undetermined risk factors may have existed, such as poor nutrition status which is not usually evaluated in routine practice.

This study has some limitations. First, data may have been insufficient and incomplete owing to the retrospective collection of data. Therefore, the calculated incidence and onset of events were only estimated from existing data. To confirm this value, a prospective study is warranted. Second, given the small sample size, further statistical analysis was not performed to determine significant factors associated with hypophosphatemia regardless of TDF.

**Declarations**

**Acknowledgement**

The researchers thank the kind cooperation of all staffs. In addition, the researchers acknowledge the financial support of the Faculty of Pharmacy, Silpakorn University.

**Conflict of interest**

The authors declared that they have no conflict of interest.

**Ethical approval**

This study was approved by the Ethics committee of Silpakorn University, Nakhon Pathom, Thailand, and the local hospital (REC 631012-1205118).

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**References**


Tables

Table 1. Demographic data (n = 26)
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (SD)</td>
<td>46.65 (13.23) years</td>
</tr>
<tr>
<td>Range</td>
<td>21 - 70 years</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>- Male (%)</td>
<td>20 (76.9)</td>
</tr>
<tr>
<td>- Female (%)</td>
<td>6 (23.1)</td>
</tr>
<tr>
<td>Weight [median (IQR)]</td>
<td>59.0 (48.5-73.6) kg</td>
</tr>
<tr>
<td>Range</td>
<td>32.3 - 95 kg</td>
</tr>
<tr>
<td>Duration of using TDF, [Median (IQR)]</td>
<td>28.5 (18.3-64.0) months</td>
</tr>
<tr>
<td>Range</td>
<td>2-102 months</td>
</tr>
<tr>
<td>serum creatinine baseline [Median, (IQR)]</td>
<td>0.8 (0.7-1.0) mg/dL</td>
</tr>
<tr>
<td>Range</td>
<td>0.41 - 2.14 mg/dL</td>
</tr>
<tr>
<td>Serum Phosphate baseline [Median, (IQR)]</td>
<td>4.1 (3.6-4.7) mg/dL</td>
</tr>
<tr>
<td>Range</td>
<td>1.1 - 5.6 mg/dL</td>
</tr>
<tr>
<td>Number of patients who use concurrent drugs that caused hypophosphatemia</td>
<td></td>
</tr>
<tr>
<td>- Antacid</td>
<td>1 (3.8)</td>
</tr>
</tbody>
</table>

**Table 2.** Incidence of hypophosphatemia and duration

<table>
<thead>
<tr>
<th>Include patients (cases)</th>
<th>26</th>
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<tbody>
<tr>
<td>Patients with hypophosphatemia (cases)</td>
<td>5</td>
</tr>
<tr>
<td>Incidence of hypophosphatemia</td>
<td>19.2</td>
</tr>
<tr>
<td>Median duration of receiving TDF until hypophosphatemia occurred (range) in month</td>
<td>10 (1-63)</td>
</tr>
</tbody>
</table>

**Table 3.** Characteristics of patients with HIV infection who developed hypophosphatemia
<table>
<thead>
<tr>
<th>Factors</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
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</thead>
<tbody>
<tr>
<td>Comorbidity</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Medication</td>
<td>-</td>
<td>Antacid for 8 weeks</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Phosphate (mg/dL)</td>
<td>4.4</td>
<td>2.7</td>
<td>3.5</td>
<td>4</td>
<td>3.7</td>
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<tr>
<td>Scr (mg/dL)</td>
<td>0.8</td>
<td>0.9</td>
<td>0.86</td>
<td>0.72</td>
<td>0.82</td>
</tr>
<tr>
<td>Visit 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Serum Phosphate (mg/dL)</td>
<td>2.1</td>
<td>1.9</td>
<td>2.4</td>
<td>2.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Scr (mg/dL)</td>
<td>1.15</td>
<td>1.8</td>
<td>0.75</td>
<td>0.58</td>
<td>1.18</td>
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<tr>
<td>Dosage adjustment</td>
<td>-</td>
<td>TDF 300 mg q 48 hr</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Monitoring</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Serum Phosphate (mg/dL)</td>
<td>3.1</td>
<td>-</td>
<td>2.7</td>
<td>2.0 then 3.1</td>
<td>-</td>
</tr>
<tr>
<td>Scr (mg/dL)</td>
<td>1.01</td>
<td>-</td>
<td>0.95</td>
<td>2.0 then 3.1</td>
<td>-</td>
</tr>
</tbody>
</table>

**Figures**
Patients with HIV infection who received TDF (n = 798)

Did not meet the inclusion criteria
(n = 774); >50% had no baseline
serum phosphate measurement

Patients with HIV infection who received TDF who met
the inclusion criteria (n = 26)

Normal serum phosphate
n = 21

Hypophosphatemia
(serum phosphate < 2.5 mg/dL (n = 5)

**Figure 1**

The incidence of hypophosphatemia investigational process