Safety and efficacy of tenofovir alafenamide in liver transplant recipients: A single center experience

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Abstract
Background: Tenofovir disoproxil fumarate (TDF) is frequently used for treatment of and prophylaxis against reactivation of hepatitis B virus (HBV) after liver transplant (LT). Because TDF can lead to renal impairment and a decrease in bone mineral density (BMD), the prodrug tenofovir alafenamide (TAF) may be considered a viable alternative with fewer adverse effects. Only limited information is available about the use of TAF for LT recipients. We report a European single-center experience with TAF as treatment for LT patients.

Methods: This retrospective analysis involved 29 LT recipients receiving standard immunosuppressants (mainly calcineurin inhibitors). Demographic and clinical data were documented at baseline upon switch to TAF and at various time points thereafter.

Results: None of the patients experienced HBV reactivation after the switch to TAF. Liver and renal function remained stable. Drug levels of immunosuppressive agents did not change significantly after the switch. After 1 year, 22 patients were still taking TAF; two patients had been lost to follow-up; one patient had died; and four patients had discontinued therapy because of TAF-related adverse effects. No serious adverse effects were reported.

Conclusions: Tenofovir alafenamide exhibits high antiviral efficacy and a good safety profile for LT recipients. Still, the safety and tolerability of TAF for organ transplant patients should be evaluated in larger cohorts.

KEYWORDS
hepatitis B virus, liver transplantation, tenofovir alafenamide

1 | INTRODUCTION

Nucleotide analogues (NAs) are the most important agents used to treat chronic hepatitis B virus (HBV) infection.\(^1,2\) The NA tenofovir is frequently used because of its high efficacy and barrier to resistance.\(^3,4\) The prodrug tenofovir disoproxil (TDF) has been used most frequently, although it carries potential concerns related to adverse effects, particularly a decrease in bone mineral density (BMD) and impairment of renal function. The prodrug tenofovir alafenamide (TAF) was approved for HBV patients in 2017.\(^5\) For this

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMD, bone mineral density; CI, confidence interval; eGFR, estimated glomerular filtration rate; EVR, everolimus; HBV, hepatitis B virus; Ig, immunoglobulin; LT, liver transplant; MELD, Model for End-Stage Liver Disease; MMF, mycophenolate mofetil; NA, nucleotide analogue; TAC, tacrolimus; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

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https://doi.org/10.1111/tid.13522
patient group, the antiviral efficacy of TAF is equal to that of TDF, but the plasma stability of TAF is known to be better, resulting in more efficient delivery to hepatocytes. Therefore, TAF can achieve therapeutic concentrations at lower dosages, thereby reducing the potential for adverse effects.

Chronic HBV infection is still one of the most important causes of liver cirrhosis and consecutive liver transplant (LT) in the world. In many countries, allocation for LT is based on the Model for End-Stage Liver Disease (MELD) score, which uses the serum creatinine level as a measure of renal dysfunction. For this reason, many LT patients exhibit impaired renal function at the time of transplant. After LT, most patients must maintain lifelong immunosuppression, which frequently involves the administration of calcineurin inhibitors. The most frequently used such immunosuppressant is tacrolimus (TAC), which can be associated with a variety of adverse effects, including severe nephrotoxicity.

After patients with chronic HBV undergo LT, or after the transplantation of a liver from an HBV-positive donor, prophylaxis against HBV recurrence is recommended for most patients. Reactivation prophylaxis is mostly achieved by the administration of NAs and HBV immunoglobulin (Ig). TDF is applied for a large percentage of LT patients, but impaired renal function evokes limitations, since TDF is eliminated by renal clearance and accumulates in these patients. Additionally, TDF is associated with low but still clinically significant nephrotoxicity. In the case of renal insufficiency, TDF dosing must be adjusted to renal function; thus, patients may take TDF every other day or every third day, for example, a dosing schedule resulting in variable and possibly insufficient serum levels of the antiviral drug. Furthermore, irregular intake of medication may impair medication adherence.

TAF can be considered a viable alternative for prophylaxis against HBV reactivation because there is no need for dosage adjustment related to renal function. This more regular dosing results in reliable and stable serum levels and may be associated with fewer adverse effects.

Although TAF is established as a treatment for HBV patients, the availability of data regarding the efficacy and safety of administering TAF to LT recipients is still limited. Here, we present our experience with 29 patients treated with TAF for prophylaxis against HBV recurrence after LT.

2 | MATERIALS AND METHODS

2.1 | Patients

This study retrospectively analyzed data from 29 patients who were treated with TAF as prophylaxis against HBV recurrence. One patient began TAF treatment directly after LT. Three patients had not previously been treated with NAs but began reactivation prophylaxis with TAF because of insufficient HBV antibody (anti-HBs) titers. The remaining 25 patients were switched from another NA to TAF. TAF was administered at a dosage of 25 mg once daily. Demographic and clinical data were documented. Renal function was determined by the estimated glomerular filtration rate (eGFR) as measured by the Modification of Diet in Renal Disease equation. Additionally, clinical findings (adverse effects, cause of therapy interruption) were documented at baseline (initiation of TAF treatment) and every 3 months thereafter for the first year (months 3, 6, 9, and 12). The analysis was conducted in accordance with the Helsinki Declaration of 1975 and was approved by the ethics committee of the University Hospital Essen.

2.2 | Statistical analysis

Nominal data were displayed as absolute numbers and relative proportions and were analyzed by the chi-square ($\chi^2$) test and Fisher’s exact test. Metric variables are depicted as medians and ranges and are displayed as boxplots with medians and 95% confidence intervals (CIs). Metric variables were analyzed by t test or ANOVA, as stated. All tests were two-sided, and statistical significance was assigned at the level of $P \leq .05$. Statistical analyses were performed with SPSS 24.0 (IBM SPSS Statistics; IBM Corporation), and figures were created with Graphpad Prism 5 (GraphPad Software, Inc).

3 | RESULTS

3.1 | Study cohort

Demographic data, baseline characteristics, and median laboratory values are depicted in Table 1. In total, the study included 29 patients who were treated with TAF as prophylaxis against HBV recurrence (Figure 1). The cohort consisted of 21 men (72%) and 8 women (28%) with a median age of 54 years. The median MELD score at the time of transplant was 16. The median time between LT and TAF initiation was 8 years. All patients exhibited impaired renal function (elevated serum creatinine level, impaired eGFR) at the time of therapy conversion, and most patients suffered from renal insufficiency grade 3 (62%, Table 1). Liver function was stable before the switch to therapy with TAF. Before the switch, most patients were being treated with an NA: entecavir (38%), lamivudine (28%), or TDF (14%). For most patients, immunosuppressive therapy consisted of monotherapy with TAC (45%), combination therapy with TAC and mycophenolate mofetil (31%), or combination therapy with TAC and everolimus (EVR) (17%). Three patients (10%) were also receiving treatment with prednisolone (Table 1).

Most patients (19, 66%) underwent LT because of HBV infection. The remaining patients received prophylactic treatment because they had received a LT from an anti-HBc-positive donor (Table 1). Most patients (22, 76%) completed 1 year of HBV prophylaxis with TAF. Four patients (14%) discontinued therapy because of adverse effects (headache/fatigue, two patients; nausea/vomitus/diarrhea, two patients); three of these patients experienced these adverse effects 4 weeks after the initiation of TAF therapy, whereas the other experienced the adverse effect 3 months after initiation. All four patients resumed therapy with their previous medications.
Baseline characteristics

| Characteristic | Median [range] |
|----------------|----------------|
| Leucocytes/nL  | 5.55 [2.77-8.66] |
| Hemoglobin, g/dL | 12.6 [7.3-17.6] |
| Serum creatinine, mg/dL | 1.65 [0.88-3.44] |
| Cystatin C, mg/L | 1.93 [0.97-4.23] |
| eGFR, mL/min/1.7 | 44 [19-86.8] |
| Bilirubin direct, mg/dL | 0.2 [0.1-0.9] |
| AST, U/L | 18 [6-52] |
| ALT, U/L | 22 [9-47] |
| INR | 1.01 [0.94-2.3] |
| CRP, mg/dL | 0.4 [0.4-1.9] |

Indication for liver transplant n [%]

| Indication for liver transplant | n [%] |
|---------------------------------|-------|
| HBV | 19 [66] |
| HBV/HDV | 6 [21] |
| HBV/HCV | 3 [10] |
| HCV | 1 [3] |
| Alcoholic liver disease | 6 [21] |
| Others | 3 [10] |
| HCC | 9 [31] |
| HCC/HBV | 8 [28] |
| HCC/Alcoholic liver disease | 1 [3] |

HBV medication n [%]

| HBV medication | n [%] |
|----------------|-------|
| Entecavir | 11 [38] |
| Lamivudine | 8 [28] |
| Tenofovir disoproxil fumarate | 4 [14] |
| Adefovir | 1 [3] |
| No NUC treatment | 5 [17] |

Immunosuppressive medication n [%]

| Immunosuppressive medication | n [%] |
|------------------------------|-------|
| Tacrolimus monotherapy | 13 [45] |
| Tacrolimus + MMF | 9 [31] |
| Tacrolimus + everolimus | 5 [17] |
| Cyclosporine monotherapy | 1 [3] |
| Cyclosporine + everolimus | 1 [3] |
| Additional prednisolone therapy | 3 [10] |

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; INR, international normalized ratio; LT, liver transplant; MELD, Model For End-Stage Liver Disease; MMF, mycophenolate mofetil; NUC, nucleos(t)ide analogue; TAF, tenofovir alafenamide.

3.2 No significant impact of TAF on immunosuppressive medication

To assess the effects of TAF on immunosuppressive medications, alterations in serum levels of the various immunosuppressants (TAC, cyclosporine A [CsA], EVR) and the applied dosage were analyzed every 3 months for 1 year. The trough levels of the three immunosuppressants did not differ significantly at any timepoint after TAF initiation. In addition, the administered dosages of the immunosuppressants were adjusted only marginally, with no statistically significant differences (Figure 2). Regarding the decline in the administered dosage of CsA, it has to be mentioned that there were only two patients treated with CsA in this study, of whom one had stable dosage and serum levels and the other one had high serum level at the starting point of the study, resulting in consecutive decline of the administered CsA dosage over time.

3.3 TAF does not impair liver or renal function

The serum levels of aspartate aminotransferase, alanine aminotransferase (ALT), direct bilirubin, creatinine, cystatin C and the eGFR were documented at various timepoints after the switch to TAF. Within the first year after TAF initiation, no statistically significant changes in liver function or renal function values were observed. No episodes of graft rejection occurred. Regarding the medians of parameters of kidney function, neither the serum levels of creatinine, nor of cystatin C or the eGFR did differ significantly over time (Figure 3). On the other hand, the proportion of patients with various grades of renal insufficiency did differ slightly over time without showing significant changes (P ≤ .974). Overall, the grade of renal insufficiency worsened for five patients and improved for two (Table 2).

4 DISCUSSION

Although treatment with TAF is well-established for HBV infection, data addressing the safety and feasibility of TAF for LT recipients are scarce. The current study analyzed data from 29 LT patients to
determine the effects of switching HBV recurrence prophylaxis from any NA to TAF. Switching to TAF resulted in no clinically significant effects on either transplant or kidney function. We found no significant alterations in trough levels of immunosuppressants. After the switch, none of the monitored patients exhibited seroconversion of HBsAg. However, four patients discontinued TAF therapy because of adverse effects.

One of the most important questions concerning the administration of TAF to LT recipients is the possibility of pharmacological interactions with the immunosuppressive medications taken by these patients, because changes in serum levels of these agents could have different and partially severe implications. TAF is not an inhibitor of CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 and is metabolized only minimally by CYP3A4. However, because TAF is transported by P-glycoprotein and by breast cancer resistance proteins (BRCP), drug-drug interactions are possible. Some agents, such as carbamazepine and midazolam, have been reported to interact with TAF, but interactions with immunosuppressive agents have not yet been reported. We observed no statistically significant alterations in serum levels of TAC, EVR, or CSA or in the dosages administered. Sripongpun et al administered TAF to 56 LT patients for at least 48 weeks and observed no changes in the serum levels of the immunosuppressants, although all of their patients were treated with TAC. To the best of our knowledge, no other published studies have analyzed serum levels of immunosuppressants in LT patients after the administration of TAF. Additionally, no drug-drug interactions between TDF and TAC have been reported.

![Figure 1](image-url) Patients switched to tenofovir alafenamide. Study schema. The number of liver transplant patients switched to tenofovir alafenamide is depicted as absolute numbers and relative proportions.
FIGURE 2  Influence of switch to tenofovir alafenamide on serum levels of immunosuppressive medications. The serum levels (gray) of the immunosuppressive medications tacrolimus (TAC, A), cyclosporine A (CsA, B), and everolimus (EVR, C) are displayed as boxplots with medians and 95% CIs at the time of the switch to tenofovir alafenamide (baseline, B) and at 3, 6, 9, and 12 mo after the switch. The dosages (black) of the immunosuppressive medications are depicted as medians.

FIGURE 3  Influence of switch to tenofovir alafenamide on hepatic and renal function. Liver function is displayed as boxplots with medians and 95% confidence intervals (CIs) showing laboratory values of aspartate aminotransferase (AST, A), alanine aminotransferase (ALT, B) and direct bilirubin (C) at the time of the switch to tenofovir alafenamide (baseline, B) and at 3, 6, 9, and 12 mo after the switch. Renal function is depicted as boxplots with medians and 95% CIs of serum levels of creatinine (D), cystatin C (E), and estimated glomerular filtration rate (eGFR) as determined by the modification of diet in renal disease score (F) at baseline (B) and at 3, 6, 9, and 12 mo after the switch. Variables were analyzed with one-way ANOVA with the statistical significance assigned at the level of $P \leq .05$. 
The risk of HBV recurrence after LT is strongly reduced by the administration of NAs and of HB Ig; the risk is now estimated to be 5%. 22 Tenofovir is a potent NA used to treat LT patients, and TAF has been found to be non-inferior to TDF in suppressing viral replication among non-LT patients. 9 Regarding LT patients, Sripongpun et al switched a cohort of 11 patients to the administration of TAF for 48 weeks, and all of these patients had undetectable serum HBV DNA levels throughout the study. 19 Additionally, the study of Saab et al did not show any HBsAg seroconversions in a group of 30 LT patients receiving TAF monotherapy, too. 23 However, to the best of our knowledge, there are no other reports regarding efficacy of TAF for LT patients. None of our patients exhibited seroconversion of HBsAg with stable serum levels of anti-HBs one year after the switch to TAF, a finding implying that TAF efficiently suppresses HBV in LT patients for this period of time. Although there is no evidence that TAF is more efficient than TDF, it’s effectiveness can be considered non-inferior, but it may have advantages in feasibility because it requires no dose adjustment with regard to kidney function. Therefore, TAF achieves stable NA levels with a lower estimated risk of reactivation over the long term, better patients’ compliance, and presumably fewer adverse effects. Because one of the main adverse effects of TDF is a decrease in BMD and resulting osteoporosis, it would be interesting to study BMD levels of patients switched from TDF to TAF. These variables were not part of the current study but should be analyzed in future studies.

Tenofovir alafenamide is known to be associated with less deterioration of kidney function than is TDF in non-LT patients. 6,8,9 Renal safety is always an important problem for LT recipients; renal insufficiency is common among these patients because of MELD-based selection, liver-associated kidney problems before LT, and the nephrotoxic effects of calcineurin inhibitors. 12,13 Previous studies of TAF administration to LT patients found stable 23 or even slightly ameliorated 19 renal function, without any statistically significant differences. We did not observe any statistically significant differences in eGFR or serum creatinine levels in our cohort 1 year after the initiation of TAF administration. Still, five patients exhibited worsening of renal function, whereas two exhibited improved renal function. Because our study lacked a control group, our findings cannot be compared to those of studies involving non-LT patients; nevertheless, the stability of renal function can still be considered a positive aspect, in particular with regard to the nephrotoxicity associated with immunosuppressive medications. On the other hand, TAF has been reported to reduce ALT activity in both non-LT 6 and LT 19 patients, a finding that is not reflected in our observations, since ALT levels did not change significantly over time.

Four of our patients (14%) discontinued therapy because of adverse events: two patients (8%) reported headaches and fatigue, and two (8%) experienced gastrointestinal symptoms (nausea, vomiting, and diarrhea). The overall rate of adverse events were comparable to that found in studies involving non-LT patients: for example, Buti et al reported that 14% of their patients experienced headache, 6% experienced fatigue, and 5% experienced nausea 9. Although these symptoms were not serious, it is still interesting that the rate of discontinuation of therapy in our study is quite high in comparison to that found in a study involving non-LT patients (1%). 9 Because the other studies involving LT patients did not report adverse events associated with TAF treatment, further evaluation is needed. One patient died during the study, but this event was deemed to be unrelated to TAF administration because the patient had been experiencing multiple severe diseases for years.

Of course, our study has some limitations. As it is the case for almost all retrospective analyses, potential bias cannot be excluded, and the lack of a control group impedes the interpretation of the data. Still, our study contributes an analysis regarding administration of TAF to a homogenous, single-center cohort of LT patients, including safety, efficacy, and possible interactions with immunosuppressive medications, and data concerning this questioning are still scarce. For this reason, our study can be beneficial for LT patients in whom switch of therapy is planned. However, long-term prospective studies are needed for careful assessment of the administration of TAF to LT patients. In particular, those studies should compare long-term impairment of renal function of patients receiving TAF with that of patients receiving TDF.

In conclusion, switching LT patients to HBV therapy and prophylaxis with TAF is effective in suppressing viral replication and is safe because it neither influences serum levels of immunosuppressants nor impairs graft function. In addition, adverse events in LT patients are neither more severe nor more frequent than those reported in non-LT patients.

**CONFLICT OF INTEREST**

All the authors declare no conflict of interest.

**ACKNOWLEDGMENT**

Open access funding enabled and organized by Projekt DEAL.

**AUTHORS’ CONTRIBUTIONS**

JRA, KS, AA, KW, and KH conceived and designed the experiments and gathered the data; JRA, KS, and KH analyzed the data; KH and HW contributed to materials and resources; JRA, KS, and KH wrote and edited the paper.
REFERENCES

1. European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-398.
2. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560-1599.
3. Kittinos KM, Corsa A, Liu Y, et al. No detectable resistance to tenofovir disoproxil fumarate after 6 years of therapy in patients with chronic hepatitis B. Hepatology. 2014;59(2):434-442.
4. Zoulim F, Locarnini S. Optimal management of chronic hepatitis B patients with treatment failure and antiviral drug resistance. Liver Int. 2013;33(Suppl 1):116-124.
5. De Clercq E. Role of tenofovir alafenamide (TAF) in the treatment and prophylaxis of HIV and HBV infections. Biochem Pharmacol. 2018;153:2-11.
6. Agarwal K, Brunetto M, Seto WK, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol. 2018;68(4):672-681.
7. Agarwal K, Fung SK, Nguyen TT, et al. Twenty-eight day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. J Hepatol. 2015;62(3):533-540.
8. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1(3):196-206.
9. Chan HL, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1(3):185-195.
10. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet. 2015;386(10003):1546-1555.
11. Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2015 annual data report: liver. Am J Transplant. 2017;17(Suppl 1):174-251.
12. Sharma P, Bari K. Chronic kidney disease and related long-term complications after liver transplantation. Adv Chronic Kidney Dis. 2015;22(5):404-411.
13. Issa N, Kukla A, Ibrahim HN. Calcineurin inhibitor nephrotoxicity: a review and perspective of the evidence. Am J Nephrol. 2013;37(6):602-612.
14. Kearney BP, Flaherty JF, Shah J. Tenofovir disoproxil fumarate: clinical pharmacology and pharmacokinetics. Clin Pharmacokinet. 2004;43(9):595-612.
15. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, et al. Tenofovir nephrotoxicity: 2011 update. AIDS Res Treat. 2011;2011:354908.
16. Kearney BP, Yafe K, Shah J, Zhong L, Flaherty JF. Pharmacokinetics and dosing recommendations of tenofovir disoproxil fumarate in hepatic or renal impairment. Clin Pharmacokinet. 2006;45(11):1115-1124.
17. Scott LJ, Chan HLY. Tenofovir alafenamide: a review in chronic hepatitis B. Drugs. 2017;77(9):1017-1028.
18. European Medicines Agency. Vemlidy 25 mg film-coated capsules: summary of product characteristics. 2019. http://www.ema.europa.eu/Sripongpun P, Mannalithara A, Kwo PY, Kim WR. Potential benefits of switching liver transplant recipients to tenofovir alafenamide prophylaxis. Clin Gastroenterol Hepatol. 2020;18(3):747-749.
19. Chittick GE, Zong J, Begley JA, Alianti JR, Sorbel JJ, Blum MR. Pharmacokinetics of emtricitabine/tenofovir disoproxil fumarate and tacrolimus at steady state when administered alone or in combination. Int J Clin Pharmacol Ther. 2008;46(12):627-636.
20. Jimenez-Perez M, Saez-Gomez AB, Mongil Poce L, Lozano-Rey JM, de la Cruz-Lombardo J, Rodrigo-Lopez JM. Efficacy and safety of entecavir and/or tenofovir for prophylaxis and treatment of hepatitis B recurrence post-liver transplant. Transplant Proc. 2010;42(8):3167-3168.
21. European Association for the Study of the Liver. EASL clinical practice guidelines: liver transplantation. J Hepatol. 2016;64(2):433-485.
22. Saab S, Song D, Challita YP, et al. Long-term outcomes with oral therapy in liver transplant recipients with hepatitis B. Clin Transplant. 2019;33(2):e13740.

How to cite this article: Rashidi-Alavijeh J, Straub K, Achterfeld A, Wedemeyer H, Willuwe K, Herzer K. Safety and efficacy of tenofovir alafenamide in liver transplant recipients: A single center experience. Transpl Infect Dis. 2021;23:e13522. https://doi.org/10.1111/tid.13522