

Renal Safety of Tenofovir Disoproxil Fumarate and Entecavir in Liver Transplant Patients: A Nationwide Korean Registry Study

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Abstract

Background and aims: Tenofovir disoproxil fumarate (TDF) and entecavir (ETV) have been recommended after liver transplantation to prevent recurrence of hepatitis B virus infection. Despite its proven efficacy, the renal safety of TDF has not been established in liver transplant recipients. We aimed to compare the effects of TDF and ETV on renal function in liver transplant recipients and to evaluate risk factors for renal dysfunction after liver transplantation.

Methods: This is a retrospective, observational multicenter study of data from the Korean Organ Transplantation Registry. We included adults who underwent liver transplantation for hepatitis B virus-related complications from April 2014 to December 2017 and received TDF or ETV post-transplantation. Renal dysfunction was defined as an estimated glomerular filtration rate decline by at least 20% from baseline (1 month post-transplantation). Median duration of follow-up was 29 months (interquartile range 19–42).

Results: A total of 804 liver transplant patients were included. The cumulative probability of renal dysfunction was significantly higher in the TDF group than in the ETV group. Multivariable analysis confirmed that TDF was independently associated with an increased risk of renal dysfunction (hazard ratio = 1.47, 95% confidence interval 1.12-1.92; $P = 0.005$). Independent risk factors for renal dysfunction included older age, worse baseline renal function, and low body mass index. Renal dysfunction after liver transplantation was independently associated with increased mortality.

Conclusions: In this nationwide study, use of TDF was associated with an increased risk of renal dysfunction, when compared with ETV.

Introduction

Hepatitis B virus (HBV) infection remains one of the most important causes of severe liver disease requiring consideration of liver transplantation (LT) in the world [1, 2]. Before the advent of effective antiviral prophylaxis, HBV infection was considered a relative contraindication for LT because of poor graft outcomes associated with HBV recurrence [3]. The introduction of nucleos(t)ide analogues (NAs) and hepatitis B immune globulin (HBIG) has significantly decreased post-transplant HBV recurrence and improved long-term graft survival [4].

Combinations of HBIG and potent NAs have been recommended to prevent recurrent HBV after LT [5, 6]. Entecavir (ETV) and tenofovir disoproxil fumarate (TDF), which have greater potency and higher genetic barriers to resistance than other agents, are first-line NAs recommended by current international guidelines [7, 8]. Although TDF and ETV are generally well tolerated, renal dysfunction remains a concern with TDF [9–11]. Prior studies in human immunodeficiency virus (HIV)-infected patients have indicated that TDF is associated with a small but significant decline in renal function [12]. By contrast, HBV cohort studies have demonstrated comparable effects on renal function from TDF and ETV [13, 14]. However,

the majority of studies evaluated patients with preserved renal function and excluded liver transplant recipients.

In the setting of LT, one must always consider the possibility of renal dysfunction because of the concomitant use of calcineurin inhibitors [15, 16]. Furthermore, many liver transplant patients exhibit renal dysfunction at the time of transplant under the recent model for end-stage liver disease (MELD) score-based allocation system [17]. However, the renal effects of TDF and ETV in liver transplant recipients have not been well studied [18, 19]. In the present study, we evaluated the renal safety of TDF and ETV after LT using nationwide registry data.

Methods

Study design and participants

The Korean Organ Transplantation Registry (KOTRY) is a national, multicenter, observational cohort study containing prospectively collected data from solid organ transplant patients. The KOTRY liver transplant database includes demographic information and clinical data, including information regarding immunosuppressive regimens and HBV prophylaxis. Detailed descriptions of collected data have been previously described [20].

For this retrospective study, we retrieved de-identified patient data from the KOTRY liver transplant database and screened all adults who underwent LT for HBV-related complications from April 2014 to December 2017. Patients who received TDF or ETV were included in this study. These exclusion criteria were applied: (1) coinfection with hepatitis C, (2) use of other antiviral agents, (3) delayed use of TDF or ETV (initiated > 1 month after transplantation), (4) baseline (1 month post-LT) estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m², and (5) missing data (Fig. 1).

This cohort study was based on data from the KOTRY liver transplant database. The KOTRY study protocol satisfied the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of Severance Hospital and at each participating institution. The requirement for written informed consent was waived because of the retrospective nature of this study.

Hepatitis B virus prophylaxis

All patients were treated with TDF or ETV to prevent HBV recurrence. The antiviral agent dosage was adjusted for the patient's renal function during the study period (TDF: 300 mg oral dose every 48 hours for an eGFR of 30–49 mL/min/1.73 m² and 300 mg every 72 hours for an eGFR of 10–29 mL/min/1.73 m²; ETV: 0.5 mg oral dose every 48 hours for an eGFR of 30–49 mL/min/1.73 m² and 0.5 mg every 72 hours for an eGFR of 10–29 mL/min/1.73 m²). Because reimbursement criteria for ETV and TDF were identical, the antiviral agents were selected at the physician's discretion.

Most patients received HBIG in combination with an antiviral agent, in accordance with institutional protocols. Briefly, HBIG was administered at 10,000–20,000 IU during the anhepatic phase, 10,000–20,000 IU daily for the first 7 days after surgery (20,000 IU for HBV e antigen positive or HBV DNA positive recipients), and then 10,000 IU weekly for the next 3 weeks. Thereafter, 10,000 IU of HBIG was infused once per month to maintain antibodies to HBV surface antigen > 500 IU/L.

Immunosuppressive regimens

Most patients received basiliximab for induction therapy (20 mg on days 0 and 4 post-LT). In the majority of patients, the maintenance regimen was tacrolimus and glucocorticoid, with or without mycophenolate mofetil (MMF).

Study endpoints and definitions

The primary study endpoint was renal dysfunction, and the secondary endpoint was patient survival. Renal dysfunction was defined as an eGFR decline of at least 20% from baseline that persisted until the end of follow-up (at the end of the study period, when the data were analysed). Transient dysfunction with recovery of renal function during the study period was not counted as an event. Baseline eGFR was defined as the eGFR at 1 month after LT. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [21]. Patient survival was evaluated from the date of transplantation to the date of death or December 31, 2019 (end of the follow-up period).

Statistical analysis

Results were expressed as frequency (percentage), mean and standard deviation, or median and interquartile range (IQR), depending on the type of data. The Chi-square test was used to compare categorical variables. Continuous variables were compared using Student's t-test, for parametric data, or the Wilcoxon rank-sum test, for nonparametric data. Cox proportional hazard regression analysis was used to evaluate the associations between use of TDF and time to renal dysfunction. Patient survival was analysed using the Kaplan-Meier method and compared using the log-rank test. All statistical analyses were performed using SAS version 9.4 (SAS, Inc., Cary, NC, USA) and SPSS version 25.0 (SPSS Inc., Chicago, IL, USA), and *P* values < 0.05 were considered statistically significant.

Results

Patients characteristics

During the study period, 1444 patients who underwent LT for HBV were screened. Of these, 640 were excluded because of hepatitis C virus coinfection, use of other antiviral agents, delayed use of antiviral agents (initiated > 1 month after transplantation), baseline eGFR < 30 mL/min/1.73 m², or missing data. In total, 804 recipients who received TDF or ETV for antiviral prophylaxis after LT were included in the final analysis.

Recipient and donor characteristics are presented in Table 1. No significant differences were observed between groups for age, sex, body mass index (BMI), proportion of living donors, or proportions of patients with hypertension or diabetes mellitus. The proportion of patients with hepatocellular carcinoma at LT was higher in the TDF group (309; 69.8%) than in the ETV group (275; 76.2%; $p = 0.042$). The Model for end-stage liver disease sodium (MELD Na) score was significantly higher in the TDF group than in the ETV group. Pre-transplant INR and serum creatinine were significantly higher in the TDF group than in the ETV group, whereas pre-transplant eGFR and baseline (1 month post-LT) eGFR were not significantly different between groups. In 24 patients, renal function was significantly impaired (eGFR < 30 mL/min/1.73 m²) prior to LT and recovered 1 month after transplantation (baseline mean eGFR: 69.5 ± 2.74 mL/min/1.73 m²). All patients continued to receive either TDF or ETV throughout the study period, and 797 patients (99.1%) received HBIG in combination with these antiviral agents. Median follow-up duration after LT was 29 months (IQR 19 to 42).

Immunosuppression

Immunosuppression data are presented in Table 2. In the entire cohort, 732 (91.0%) patients received basiliximab as the induction immunosuppressive agent. For maintenance immunosuppressive regimens, 73.5% of recipients received tacrolimus, glucocorticoid, and MMF; 20.0% received tacrolimus and glucocorticoid; and 3.4% received tacrolimus and MMF. Mean tacrolimus trough levels were not significantly different between the TDF and ETV groups throughout the study period.

Renal outcomes

During the median follow-up period of 29 months, 363 (45.1%) patients experienced a significant decline in eGFR, with a decrease of at least 20% below baseline. In 128, renal function recovered before the end of follow-up (i.e., transient dysfunction), whereas 235 (29.2%) patients had persistent renal dysfunction. The cumulative probability of renal dysfunction was significantly higher in the TDF group than in the ETV group (Fig. 2). The median time from LT to occurrence of renal dysfunction was 12 months (IQR 6 to 24). The median eGFR decline from baseline to last visit was -10.1% (IQR -22.5 to -0.7) for the entire cohort, -11.3% (IQR -24.2 to -0.6) for the TDF group, and -8.5% (IQR -19.2 to -0.8) for the ETV group. Mean eGFR at the last visit was 79.2 ± 22.0 mL/min/1.73 m² in the TDF group and 81.4 ± 21.0 mL/min/1.73 m² in the ETV group ($p = 0.153$).

On univariable analysis, use of TDF was significantly associated with an increased risk of renal dysfunction. After adjusting for age, diabetes, BMI, immunosuppression, and baseline renal function, use of TDF was independently associated with an increased risk of renal dysfunction (hazard ratio [HR] = 1.47, 95% confidence interval [CI] 1.12-1.92; $p = 0.005$). Older age (HR 1.45, 95% CI 1.07-1.96, $p = 0.016$), worse baseline renal function (HR 0.98, 95% CI 0.97-0.99, $p < 0.001$), and low BMI (HR 1.70, 95% CI 1.30-2.24, $p = 0.002$) were also independent risk factors for renal dysfunction (Table 3).

Patient survival

As shown in Fig. 3, renal dysfunction was associated with a significant reduction in overall patient survival ($p < 0.001$). Overall survival rates of patients with and without renal dysfunction were 88.9% and 96.8%, respectively, at 36 months post-LT. Multivariable analysis confirmed the independent association between renal dysfunction and increased risk of death (HR = 1.444, 95% CI 1.105–1.887; $p = 0.007$).

Overall patient survival was comparable in the TDF and ETV groups. At 36 months after LT, the overall survival rate was 95.3% in the TDF group and 93.4% in the ETV group ($p = 0.349$).

Discussion

ETV and TDF are the two first-line NAs for preventing HBV recurrence after LT. However, limited data exist regarding the renal safety of TDF and ETV in liver transplant recipients, who are more susceptible to nephrotoxicity [7, 8, 18]. In the present study, we evaluated the renal effects of TDF and ETV in 804 liver transplant patients. Multivariable analysis showed that the risk of renal dysfunction was significantly higher in the TDF group than in the ETV group, and development of renal dysfunction after LT was independently associated with increased mortality. To our knowledge, this is the first nationwide cohort study evaluating the renal safety of TDF and ETV in liver transplant patients.

TDF, a prodrug of tenofovir diphosphate, is widely prescribed for the treatment of HIV and HBV infections. Although TDF is generally well tolerated, there are increasing concerns about its nephrotoxicity [9–11]. The mechanism of TDF nephrotoxicity involves mitochondrial toxicity in renal proximal tubule cells [22]. There have been conflicting results regarding the effects of TDF on renal function. In HIV patients, the authors of a meta-analysis concluded that patients treated with TDF experienced a small but significant loss of renal function during treatment, compared with controls [12]. However, findings in HIV patients should be extrapolated to other populations with caution because of HIV-associated nephropathy and concomitant use of antiretroviral agents [23].

In HBV patients, several randomized clinical trials have shown that TDF has no significant effects on renal function [24, 25]. In contrast, some real-world observational studies reported that TDF significantly increases the risk of renal dysfunction, compared with ETV [26, 27]. Possible reasons for these discrepancies include the use of different definitions for renal dysfunction and differences in inclusion/exclusion criteria. As a reflection of these conflicting results, recent international guidelines for selecting antiviral agents differ in their recommendations related to renal safety issues. The European Association for the Study of the Liver guidelines recommended selecting ETV or tenofovir alafenamide fumarate (TAF) over TDF for patients with an old age (> 60 years), eGFR < 60 mL/min per 1.73 m², or albuminuria, as well as for patients receiving hemodialysis [7]. By contrast, the American Association for the Study of Liver Disease guidelines suggest no preference for TDF or ETV regarding renal safety issues [8]. Of note, there is a distinct paucity of data regarding the renal safety of TDF and ETV in liver transplant recipients, who are particularly susceptible to nephrotoxicity because of concomitant use of calcineurin inhibitors. Considering that liver transplant patients with HBV require lifelong use of antiviral agents in

combination with calcineurin inhibitors, there is an urgent need for comprehensive research regarding the renal safety of these agents in this patient population [18, 19].

Our results suggest that TDF significantly increases the risk of renal dysfunction after LT. Previous studies revealed that older age, diabetes mellitus, low BMI, worse baseline renal function, and use of nephrotoxic agents are associated with TDF-induced nephrotoxicity [22, 28]. In agreement with these findings, we also found that older age, low BMI, and worse baseline renal function were significantly associated with renal dysfunction in liver transplant recipients. Therefore, TDF should be used with caution in these patients.

Renal dysfunction is a common and serious complication after LT [15, 16]. Despite advances in perioperative management and reduction of calcineurin inhibitor exposure, the risk of renal dysfunction following LT has substantially increased in the MELD era [17]. Our data confirmed that the development of renal dysfunction after LT is significantly associated with increased mortality. Since post-LT renal dysfunction has a significant impact on patient survival, it is important to carefully evaluate the risk for renal dysfunction.

Despite its higher risk of renal dysfunction, TDF cannot be totally replaced by ETV [27]. Prior exposure to other NAs increases ETV resistance, whereas TDF is effective for treating HBV strains resistant to ETV, lamivudine, telbivudine, or even multiple drugs [7, 8, 29]. Although TAF has shown better renal safety than TDF, limited data exist regarding its use in liver transplant recipients [30]. Thus, TDF continues to have an important role in the treatment of liver transplant patients, and more attention should be given to patients at risk for renal dysfunction.

The present study has several limitations. First, as with any registry study, selection bias and confounders are the major limitations of this study. Although reimbursement criteria for ETV and TDF are identical in South Korea, patients at higher risk for renal dysfunction might be more likely to receive ETV rather than TDF. In addition, it is difficult to determine the specific effects of TDF on renal dysfunction in liver transplant patients receiving calcineurin inhibitors. To minimize potential confounding factors as much as possible, we adjusted for tacrolimus serum trough levels, as well as other well-known risk factors for renal dysfunction. Second, this study included a large number of living donor transplant recipients with a low MELD Na score. Thus, our results may not be generalizable to deceased donor transplant patients with a high MELD Na score. Third, we were unable to obtain data about tubular dysfunction, such as urinary β_2 microglobulin and fractional excretion of phosphate. However, these tests are not commonly used in real-world practice.

Despite these limitations, the study design involving use of data from a nationwide registry has enabled us to analyse a large patient cohort. This study includes real-world clinical data in liver transplant patients receiving first-line antiviral agents with calcineurin inhibitors. Previous scientific evidence is limited regarding the renal safety of TDF in this patient population, which has resulted in inconsistencies between recent international guidelines. Thus, our data provide valuable insights into the renal safety of TDF in liver transplant recipients.

In conclusion, use of TDF in liver transplant recipients was associated with a higher risk of renal dysfunction, when compared with ETV. TDF should be used with caution in this patient population, especially in individuals with other risk factors for renal dysfunction.

Abbreviations

BMI, Body mass index

CI, Confidence interval

eGFR, Estimated glomerular filtration rate

ETV, Entecavir

HBIG, Hepatitis B immune globulin

HBV, Hepatitis B virus

HIV, Human immunodeficiency virus

HR, Hazard ratio

IQR, Interquartile range

KOTRY, Korean Organ Transplantation Registry

LT, Liver transplantation

MELD, Model for end-stage liver disease

MELD Na, Model for end-stage liver disease sodium

MMF, Mycophenolate mofetil

NAs, Nucleos(t)ide analogues

TAF, Tenofovir alafenamide fumarate

TDF, Tenofovir disoproxil fumarate

Declarations

Author contributions

J. Lee, J.G. Lee, and M.S. Kim involved in study concept and design. J. Lee and M.S. Kim drafted the manuscript. All authors interpreted the data and critically revised the manuscript for important intellectual

content. All authors approved the final manuscript.

Availability of data and material: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of interest: None to declare

Ethics approval: The study protocol was approved by the institutional review boards of Severance Hospital (2019-2303-001).

Consent to participate: The requirement for written informed consent was waived because of the retrospective nature of this study.

Consent for publication: All authors approved the manuscript for publication.

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Tables

Table 1. Recipient and donor characteristics

	ETV (n=361)	TDF (n=443)	<i>p</i> value
Age (years)	54.6 ± 7.6	53.7 ± 7.4	0.087
Male, n (%)	285 (78.9)	367 (82.8)	0.160
Body mass index (kg/m ²)	24.2 ± 3.3	24.0 ± 3.5	0.199
Hypertension, n (%)	69 (19.1)	65 (14.1)	0.093
Diabetes mellitus, n (%)	88 (24.4)	94 (21.2)	0.287
Hepatocellular carcinoma, n (%)	275 (76.2)	309 (69.8)	0.042
Laboratory MELD Na score	10.5 (8.0, 16.9)	11.5 (8.3, 20.1)	0.038
INR	1.3 (1.1, 1.6)	1.3 (1.1, 1.8)	0.027
Bilirubin (mg/dL)	1.5 (0.8, 3.2)	1.6 (0.7, 4.9)	0.295
Creatinine (mg/dL)	0.8 (0.7, 0.9)	0.8 (0.7, 1.0)	0.028
Sodium (mmol/L)	140.0 (136.0, 142.0)	139.0 (135.0, 141.0)	0.036
eGFR at transplant (mL/min/1.73 m ²)	99.9 (88.8, 107.6)	98.8 (83.5, 108.2)	0.375
Baseline creatinine (mg/dL)	0.8 (0.7, 1.0)	0.9 (0.7, 1.0)	0.093
Baseline eGFR (mL/min/1.73 m ²)	97.0 (80.6, 105.4)	98.9 (75.9, 105.3)	0.300
Living donor, n (%)	285 (78.9)	355 (80.1)	0.678
Donor age (years)	35.3 ± 13.9	34.8 ± 14.3	0.602
Male donor, n (%)	216 (59.8)	282 (63.7)	0.267
Use of HBIG, n (%)	358 (99.2)	439 (99.1)	>0.999
Discontinuation of HBIG, n (%)	13/358 (3.6)	12/439 (2.7)	0.470

*Values expressed as mean ± standard deviation or median (interquartile range) or number (%).

**Baseline creatinine and eGFR refer to values measured at 1 month after transplantation.

eGFR estimated glomerular filtration rate, *ETV* entecavir, *HBIG* hepatitis B immune globulin, *HCC* hepatocellular carcinoma, *INR* international normalized ratio, *MELD Na* Model for End-stage Liver Disease sodium, *TDF* tenofovir disoproxil fumarate

Table 2. Immunosuppressive treatment

	ETV (n=361)	TDF (n=443)	p value
Induction, n (%)			0.282
None	28 (7.8%)	44 (9.9%)	
Basiliximab	333 (92.2%)	399 (90.1%)	
Maintenance regimen, n (%)			0.463
TAC + glucocorticoid + MMF	271 (75.1%)	320 (72.2%)	
TAC + glucocorticoid	64 (17.7%)	97 (21.9%)	
TAC + MMF	14 (3.9%)	13 (2.9%)	
Others	12 (3.3%)	13 (2.9%)	
Mean tacrolimus trough level (ng/dL)			
During the first year after LT	6.3 ± 2.1	6.6 ± 2.1	0.051
2 years after LT	5.0 ± 2.8	5.0 ± 2.3	0.912
3 years after LT	4.6 ± 2.2	4.8 ± 2.8	0.439

*Values are expressed as mean ± standard deviation or number (%).

ETV entecavir, *LT* liver transplantation, *MMF* mycophenolate mofetil, *TAC* tacrolimus, *TDF* tenofovir disoproxil fumarate

Table 3. Risk factors for renal dysfunction

Variable	Univariable		Multivariable	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Female	1.19 (0.87, 1.62)	0.272		
Elderly (age ≥ 60 years)	1.48 (1.11, 1.97)	0.007	1.45 (1.07, 1.96)	0.016
Low body mass index (< 21.9 kg/m ²)	1.81 (1.38, 2.37)	<0.001	1.70 (1.30, 2.24)	0.002
Hypertension	0.85 (0.59, 1.21)	0.363		
Mean tacrolimus trough level within 1 year	0.98 (0.92, 1.04)	0.541		
Baseline eGFR, mL/min/1.73 m ²	0.98 (0.96, 0.99)	<0.001	0.98 (0.97, 0.99)	<0.001
Pretransplant diabetes mellitus	1.55 (1.10, 2.18)	0.066	1.23 (0.92, 1.64)	0.168
Use of TDF	1.47 (1.13, 1.92)	0.004	1.47 (1.12, 1.92)	0.005
MELD Na score ≥ 25	1.61 (1.20, 2.17)	0.002	1.30 (0.89, 1.91)	0.171
Combined hepatocellular carcinoma	0.83 (0.63, 1.09)	0.176	0.91 (0.66, 1.24)	0.536

CI confidence interval, *eGFR* estimated glomerular filtration rate, *HR* hazard ratio, *MELD Na* Model for End-stage Liver Disease sodium, *TDF* tenofovir disoproxil fumarate

Figures

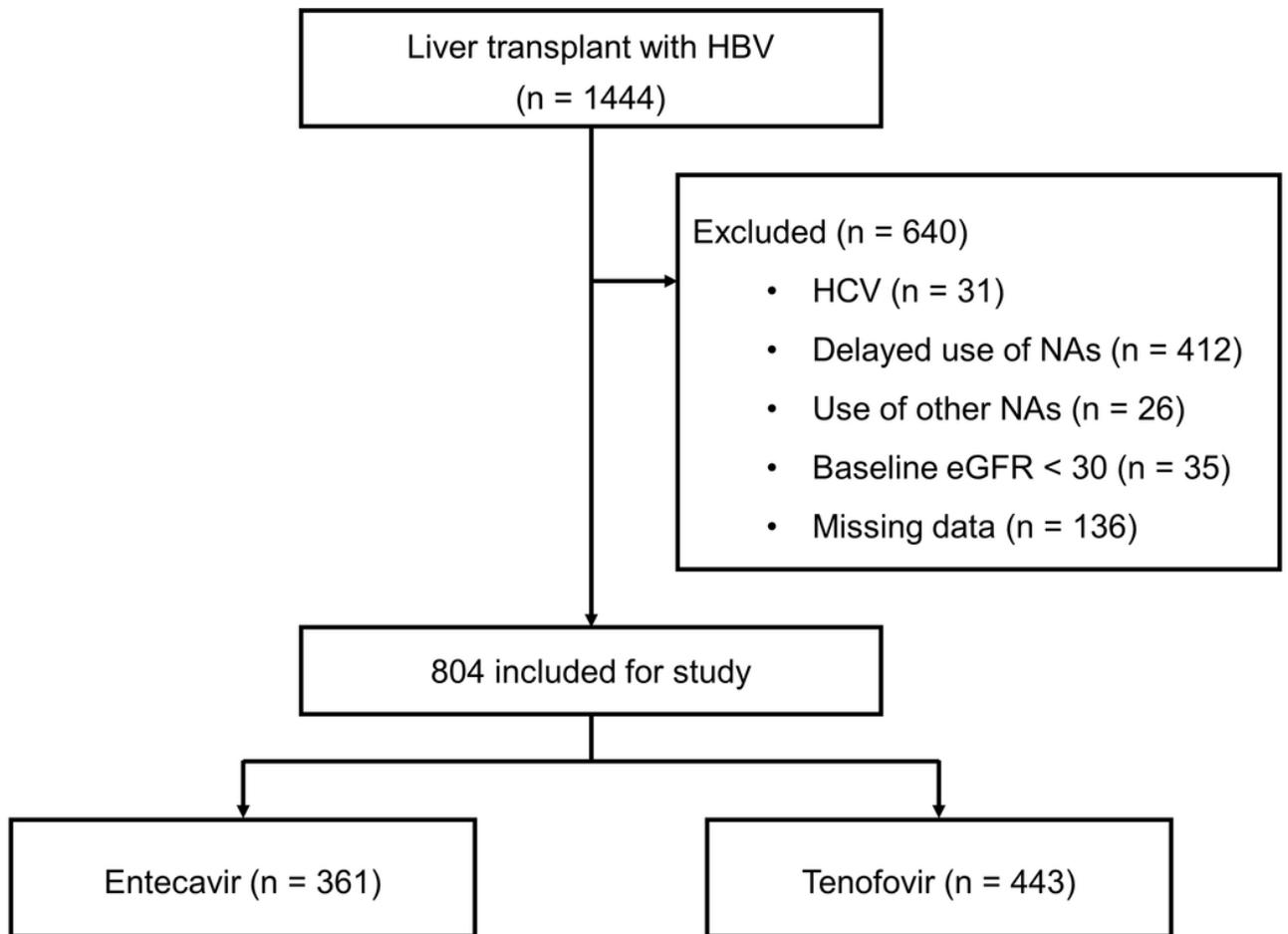
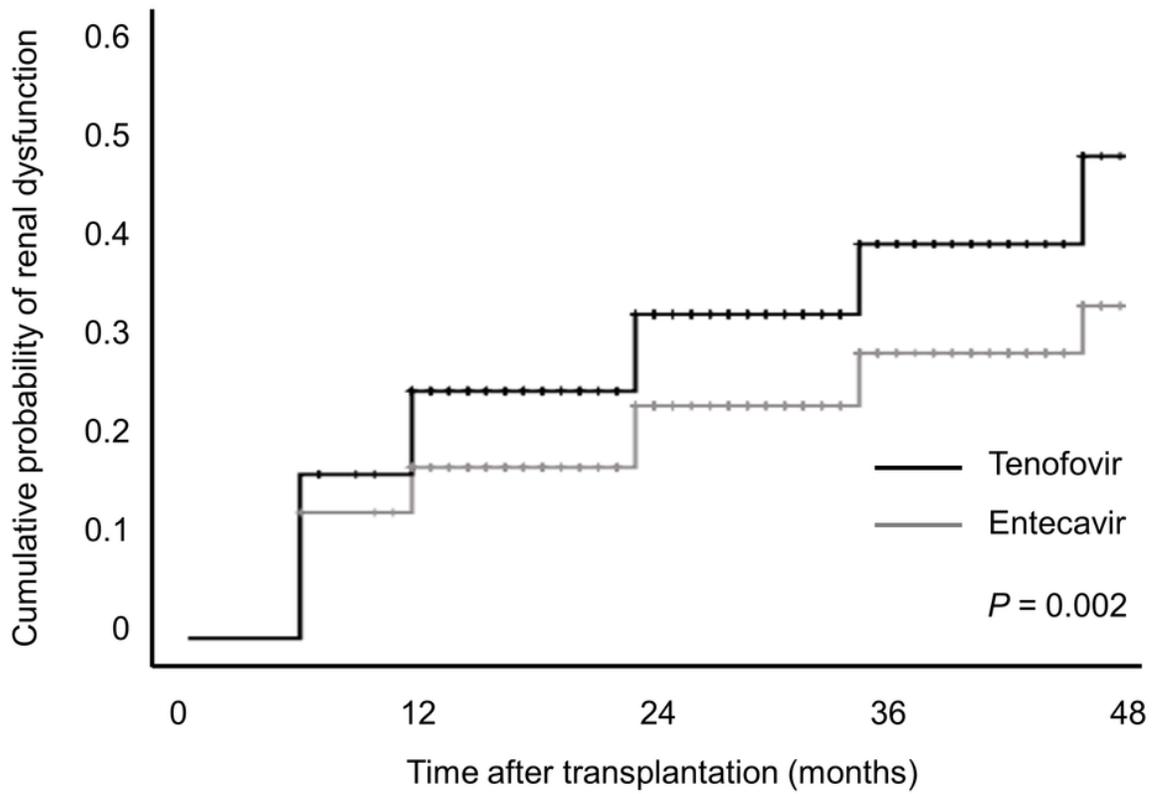


Figure 1

Study flow. eGFR estimated glomerular filtration rate, HBV hepatitis B virus, HCV hepatitis C virus, NAs Nucleos(t)ide analogues

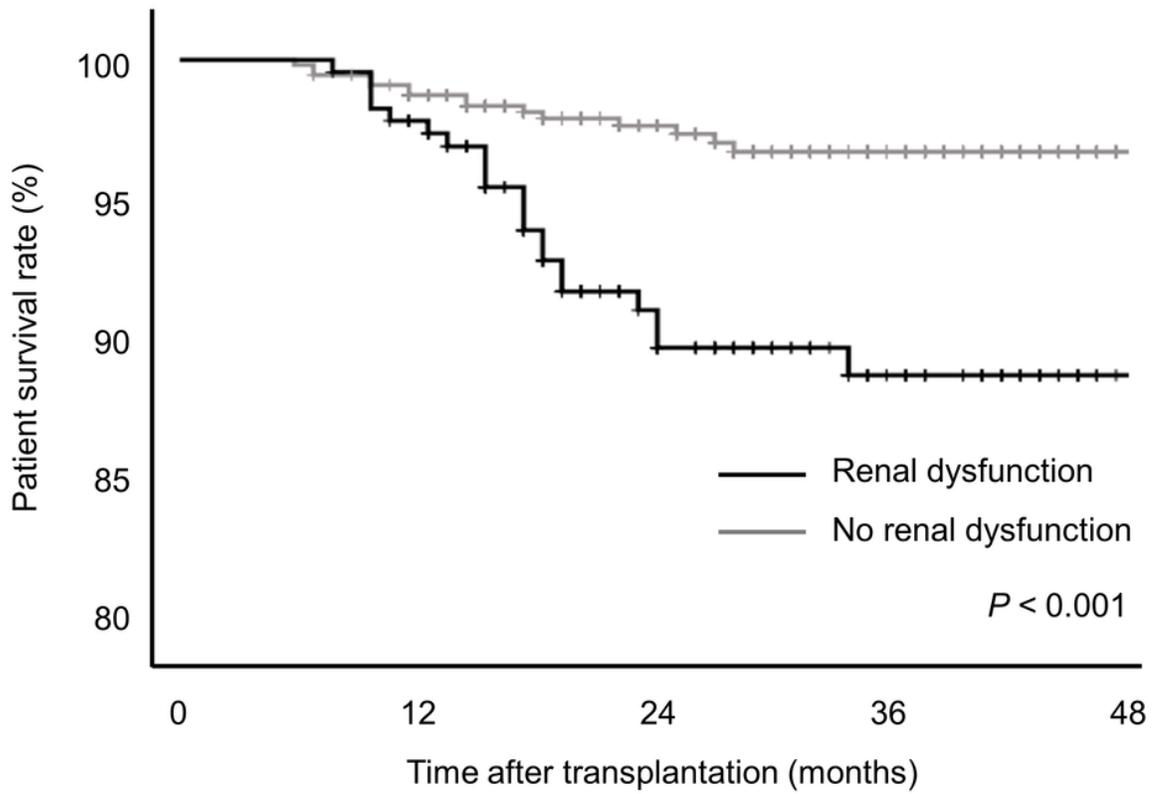


Patients at risk

Tenofovir	443	366	228	117	35
Entecavir	361	313	204	118	46

Figure 2

Cumulative probability of renal dysfunction according to antiviral agents.



Patients at risk					
	0	12	24	36	48
Renal dysfunction	235	228	140	84	25
No renal dysfunction	569	561	366	207	73

Figure 3

Patient survival with and without renal dysfunction.