A Multicenter Study of Lamivudine Treatment in 33 Patients With Hepatitis B After Liver Transplantation

Robert J. Fontana,[*] Hie-Won L. Hann,[†] Teresa Wright,[‡] Gregory Everson,[§] Alfred Baker,[‖] Eugene R. Schiff,[¶] Carolyn Riely,[#] Gaya Anschuetz,[**] Melanie Riker-Hopkins,[**] and Nathaniel Brown[**] for the US Lamivudine Compassionate Use Study Group

Hepatitis B virus (HBV) infection after liver transplantation (LT) may lead to severe and rapidly progressive graft failure. Antiviral treatment may be of benefit in selected patients with recurrent hepatitis B post-LT. The aim of this prospective open-label study is to determine the safety and efficacy of lamivudine in 33 liver transplant recipients with active HBV infection. The median time from LT to study enrollment was 51 months, all patients were hepatitis B surface antigen positive, and 75% and 94% of subjects had detectable hepatitis B e antigen (HBeAg) and HBV DNA at entry, respectively. The median duration of lamivudine treatment on study was 85 weeks, during which time median HBV DNA levels became undetectable by 16 weeks and 9% of patients lost previously detectable HBeAg. Serum alanine aminotransferase (ALT) levels improved in most patients and normalized in 27% of patients with elevated values pretreatment. Serum bilirubin and albumin levels significantly improved in patients with abnormal values at entry ($P < .05$). Virological breakthrough was detected in 13 subjects after a median of 61 weeks of lamivudine treatment and was confirmed to be caused by YMDD mutants in all patients tested. None of the patients with virological breakthrough showed a complete loss of clinical response to lamivudine. Serum ALT and bilirubin levels in patients with and without virological breakthrough were not significantly different at last study follow-up. Study results show that lamivudine is safe and effective in liver transplant recipients with recurrent hepatitis B. However, the high rate of virological breakthrough with prolonged therapy indicates the need for further studies of combination antiviral therapy in this patient population. Our results and others further establish the improving long-term outcomes with LT for patients with hepatitis B through advances in prevention of reinfection, as well as the availability of safe and effective antiviral therapies to treat patients with HBV recurrence. (*Liver Transpl 2001;7:504-510.*)

Hepatitis B virus (HBV)-related liver disease accounts for approximately 200 of the 4,500 liver transplantations (LTs) performed each year in the United States.[1,2] In the absence of adequate immunoprophylaxis, graft reinfection occurs in 80% to 100% of hepatitis B surface antigen–positive ($HBsAg^+$) liver transplant recipients and is frequently associated with poor clinical outcomes.[3,4] The introduction of long-term high-dose hepatitis B immunoglobulin (HBIg) prophylaxis with or without lamivudine has led to a marked reduction in the rate of graft reinfection and improved patient and graft survival.[5-8] However, high-risk patients who are HBV DNA^+ or hepatitis B e antigen $(HBeAg)^+$ before LT remain at significant risk for developing graft reinfection and potentially severe liver disease.[3,5]

High levels of viral replication are frequently noted in liver transplant recipients with HBV infection.[3,4,9,10] Although reduction in immunosuppression has proven beneficial, antiviral treatment may still be needed in some patients.[11,12] Treatment with interferon (IFN)-α has been disappointing, with no consistent effect on HBV replication or liver histological characteristics.[13,14] In addition, such potentially serious side effects of IFN as myelotoxicity and neuropsychiatric toxicity have limited the use of IFN in liver transplant recipients.[14] Conversely, several studies have shown that lamivudine, a potent inhibitor of HBV polymerase, is a safe and potentially effective therapy with biochemical, virological, and histological improvements reported in liver transplant recipients with HBV.[15,16] Case reports also suggest that liver transplant recipients with fibrosing cholestatic hepatitis may benefit from lamivudine therapy.[17,18]

However, prolonged administration of lamivudine can lead to virological breakthrough because of the

*From the *Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI; †Department of Medicine, Jefferson Medical College, Philadelphia, PA; ‡Department of Medicine, University of California San Francisco, San Francisco, CA; §Department of Medicine, University of Colorado Health Sciences Center, Denver, CO; ‖Department of Medicine, University of Chicago Medical Center, Chicago, IL; ¶Department of Medicine, University of Miami, Miami, FL; #Department of Medicine, University of Tennessee, Memphis, TN; and **GlaxoSmithKline, Research Triangle Park, NC.*

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Address reprint requests to Robert J. Fontana, MD, Department of Internal Medicine, 3912 Taubman Center, Ann Arbor, MI 48109-0362. Telephone: 734-936-4780; FAX: 734-936-7392; E-mail: Rfontana@umich.edu

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emergence of drug-resistant strains of HBV, termed YMDD mutants.[19,20] The incidence of drug resistance increases with the duration of treatment, but appears to be greater in immunosuppressed patients with high levels of HBV replication compared with other patients administered lamivudine.[15,21] Although YMDD mutants are replication defective in vitro compared with wild-type HBV, severe liver disease has been reported in some patients with YMDD-related virological breakthrough post-LT.[15,19,22,23]

The primary aim of this study is to assess the safety and efficacy of extended lamivudine monotherapy in 33 liver transplant recipients with active HBV infection.

Patients and Methods

Patient Population

Liver transplant recipients with established HBV infection at any US clinical site were eligible for participation in this open-label prospective study conducted between January 1996 and June 1999. Key inclusion criteria included age older than 13 years, prior LT, and persistently detectable HBsAg for more than 12 weeks post-LT or HBsAg positive ($HBsAg^+$) and HBV DNA^+ for more than 4 weeks post-LT. All subjects were required to be at risk for progressive liver injury based on any of the following 3 pretreatment liver biopsy findings: active necroinflammatory changes consistent with HBV-related hepatitis, hepatitis B core antigen–positive hepatocytes on immunohistochemical staining, or evidence of fibrosing cholestatic hepatitis. Exclusion criteria were acute liver failure, pregnancy or breast-feeding, severe pancreatitis, or the need for mechanical intubation.

Study Protocol

Informed consent for study participation was obtained from eligible subjects per local institutional review board guidelines. Enrolled patients were prospectively monitored at weeks 0, 2, 4, 8, 12, and 16 and every 8 weeks thereafter until study completion. Centralized laboratory monitoring (Covance Laboratories, Indianapolis, IN) included complete blood counts and serum electrolyte and amylase levels, as well as serum aspartate aminotransferase, alanine aminotransferase (ALT), bilirubin, and albumin levels. Hepatitis B serological tests, including HBsAg, antibody to HBsAg (anti-HBs), HBeAg, and antibody to HBeAg (anti-HBe), were measured every 8 weeks using commercially available enzyme-linked immunosorbent assays. Serum HBV DNA levels were measured every 16 weeks using the Chiron branched-chain amplification (bDNA) assay (Chiron Corp, Emeryville, CA) with a lower limit of detection of 0.7 mEq/mL (7×10^5 genome equivalents per milliliter).

Open-label lamivudine (Epivir-HBV; GlaxoSmithKline, Research Triangle Park, NC) was orally self-administered by the patients as a single 100-mg tablet daily. Because lamivudine is renally cleared, patients with an estimated creatinine clearance less than 50 mL/min derived from the Cockroft-Gault equation were administered a reduced dose of lamivudine oral suspension.[24] Patient compliance was assessed by reviewing drug diaries and unused vials at each study visit. Safety assessment included recording all patient deaths, adverse events, and clinically significant laboratory test result abnormalities at each study visit regardless of attributability to study drug. Lamivudine therapy was discontinued at the discretion of the local investigator if patients were not believed to be deriving benefit.

Study End Points

All subjects were prospectively followed up until death, discontinuation of lamivudine therapy, or last available follow-up. The primary efficacy end point was virological response, defined as a loss of previously detectable serum HBV DNA using the bDNA assay. Secondary end points included HBeAg loss and seroconversion to anti-HBe, HBsAg loss and seroconversion to anti-HBs, serum ALT level normalization, assessment of improvement in serum albumin and bilirubin levels in all patients and those with low albumin and elevated bilirubin levels pretreatment, and safety assessments. Breakthrough infection was defined as the reappearance of detectable serum HBV DNA using the bDNA assay for 2 consecutive visits, including the last visit, in a patient who was HBV DNA^+ at baseline with viral levels suppressed to undetectable during treatment or those who had detectable HBV DNA at the last visit. When breakthrough infection was suspected, the clinical investigator was encouraged to send the patient's sera to the central virology laboratory for additional studies, including YMDD genotyping by polymerase chain reaction (PCR)-based methods, as previously reported.[25]

Data Analysis

Data were entered into a centralized database using SAS software (SAS Institute, Cary, NC). Efficacy and safety data were analyzed according to a predefined data analysis plan. Exploratory analyses were performed to assess the impact of virological breakthrough on efficacy and safety outcomes. Quantitative data are described using summary measures of central tendencies; *P* for within-subject changes at last study visit (compared with baseline) were derived using a paired *t*-test or sign test for normally distributed and non–normally distributed variables, respectively. Discrete measurements are based on contingency tables, and Chi-squared test was used to obtain *P*. All *P* are intended to be descriptive in nature because the sample size was not based on power considerations. *P* less than .05 is considered statistically significant.

Results

Patient Population and Disposition

Thirty-three $HBsAg^+$ liver transplant recipients at 14 US clinical sites were enrolled. The median time from

LT to study entry was 51 months (range, 6 to 123 months; Table 1). At the time of study enrollment, none of the 33 patients was administered HBIg for post-LT immunoprophylaxis. Serum markers of HBV replication before treatment included detectable HBsAg in all patients, detectable HBeAg in 75% of patients (24 of 32 patients), and detectable HBV DNA by bDNA testing in 94% of patients (29 of 31 patients) tested. Eighty-four percent of patients (26 of 31 patients) had elevated pretreatment serum ALT levels, whereas 39% (12 of 31 patients) had elevated serum bilirubin levels and 29% (9 of 31 patients) had low serum albumin levels at entry. Six patients were coinfected with hepatitis C virus, and 1 patient was coinfected with hepatitis D virus. Immunosuppressive medications were not altered as a result of participation in this study and included corticosteroids (79%), cyclosporine (73%), tacrolimus (18%), and azathioprine (21%). Three subjects were administered open-label famciclovir (Famvir; SmithKline Beecham, Pittsburgh, PA) for HBV infection at entry, which was continued throughout the duration of the study in 1 patient.

During the course of the study, lamivudine treatment was prematurely discontinued in 7 patients, 1 patient died of an unrelated cause, and 25 patients were treated until study termination (Fig. 1). Lamivudine treatment was prematurely discontinued because of investigator preference to switch to a commercially available formulation of lamivudine (3 patients), patient relocation (1 patient), sleep disturbance (1 patient), increased liver enzyme levels (1 patient), and lack of improvement in liver enzyme levels (1 patient).

Table 1. Pretreatment Clinical Features of 33 Liver Transplant Recipients With Active HBV Infection

Demographics	
Median age (yr)	47 (22-71)
Male	22 (67)
Ethnic background	
White	25 (76)
Asian	3 (9)
Other	5 (15)
Disease parameters	
Median time from LT (mo)	51 (65-123)
$HBeAg^+$	24 (75)
$HBV\ DNA^+$*	29/31 (94)
Median HBV DNA (mEq/mL)	2,816 (0.35-106,700)
Median serum ALT (IU/L)	80 (17-276)
Median serum bilirubin (mg/dL)	1.0 (0.3-4.5)
Median serum albumin (g/dL)	3.6 (2.0-4.4)

NOTE. Values expressed as number (range) or number (percent).
*Two additional patients were $HBV\ DNA^+$ pretreatment using PCR-based assays performed locally.

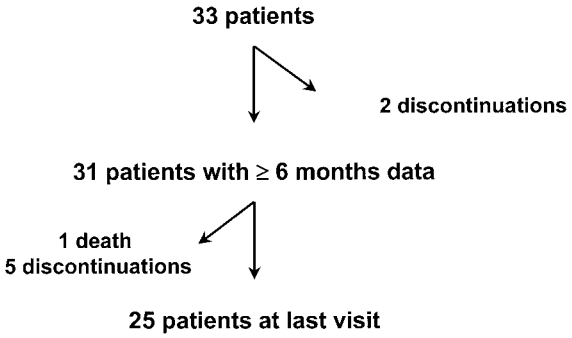

Figure 1. Patient disposition during the study. The 2 early discontinuations were because of investigator preference (1 patient) and increased liver enzyme levels (1 patient), whereas the 5 late discontinuations were because of investigator preference (3 patients), patient relocation (1 patient), and sleep disturbance (1 patient).

Virological Efficacy Response

The median duration of lamivudine treatment in the 33 patients was 85 weeks (range, 16 to 142 weeks). Median serum HBV DNA levels at entry (2,816 mEq/mL; range, 0.35 to 106,700 mEq/mL) became undetectable within 16 weeks of starting therapy and were significantly lower at last follow-up compared with entry (2 mEq/mL; range, 0.35 to 4,675 mEq/mL; $P = .0279$; Fig. 2). The proportion of patients who became HBV DNA negative was 72% at 6 months, 50% at 12 months, and 36% at last visit. Seven of the 18 patients who were $HBV\ DNA^+$ at the last study visit were confirmed to have YMDD variants, whereas the other 11 patients did not undergo testing for YMDD variants. During the study, 9% of patients (3 of 23 patients) lost previously detectable HBeAg at the last visit, and 1 of these patients developed anti-HBe. There was no loss

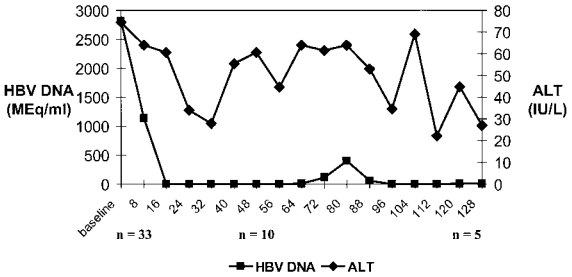

Figure 2. Median serum HBV DNA and ALT levels during lamivudine treatment of 33 liver transplant recipients with active HBV infection.

Table 2. Pretreatment and Last-Visit Laboratory Values of Liver Transplant Recipients With and Without Virological Breakthrough

	No Breakthrough (n = 16)	With Breakthrough (n = 13)	*P**
Median time from LT (mo)	51 (6-123)	69 (12-109)	
Lamivudine (wk)	59.3 (16-133)	119 (41-142)	.0047
HBV DNA (mEq/mL)	5,339/0†	2,226/78.5	.0054
Serum ALT (IU/L)	82/39	77/53	.519
Serum bilirubin (mg/dL)	1.0/0.9	1.1/1.0	.855
Serum albumin (g/dL)	3.6/3.9	3.6/3.6	.0411

NOTE. Values expressed as median entry/last value or number (range).
* Comparison of laboratory values of patients at the last visit with and without virologic breakthrough performed using Wilcoxon's rank-sum test.
† Undetectable by Chiron bDNA assay.

of previously detectable HBsAg or development of anti-HBs in any of the treated subjects.

Clinical Efficacy Response

The median serum ALT level at the last visit was 51 IU/L, with a range of 18 to 339 IU/L, which was significantly lower than pretreatment levels ($P = .0093$, paired *t*-test). Serum ALT levels normalized in 27% of patients (7 of 26 patients) with previously elevated levels, and the last serum ALT level was lower than the pretreatment value in 78% of treated patients (Fig. 2). Median serum albumin and bilirubin levels remained stable in the entire cohort during the study. However, in the 12 patients with an elevated pretreatment bilirubin level (>1.4 mg/dL) and the 9 patients with a low serum albumin level (<3.5 g/dL), a statistically significant improvement was observed at last follow-up compared with pretreatment ($P = .0273$ and $P = .0263$, respectively, sign test; Fig. 3). Complications of liver disease reported during the course of treatment included 1 patient with a variceal bleed (patient no. 6; Table 3), 1 patient with an episode of hepatic encephalopathy, and 1 patient with hepatic encephalopathy and ascites (patient no. 12, Table 3) that resolved over time. None of these episodes of decompensation were believed to be caused by the administration of lamivudine. The single patient administered lamivudine in combination with famciclovir was treated for 103 weeks. Serum ALT levels improved from 254 IU/L pretreatment to 34 IU/L at last follow-up, whereas HBV DNA levels remained unchanged at 275.5 mEq/mL pretreatment and 938.7 mEq/mL at the last study visit.

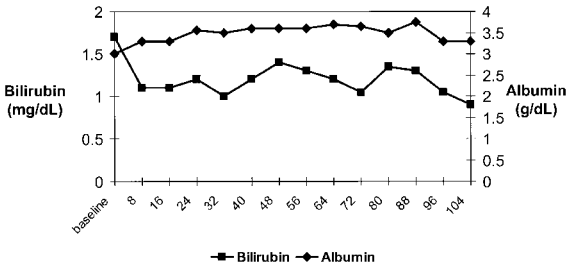

Figure 3. Median serum bilirubin and albumin levels in patients administered lamivudine with abnormal values at study entry. Twelve patients had elevated pretreatment bilirubin levels (>1.4 mg/dL) and 9 patients had low pretreatment serum albumin levels (<3.5 g/dL).

Virological Breakthrough

Virological breakthrough was detected in 13 of 29 patients (45%) with adequate available HBV DNA data during the study (Tables 2 and 3). Patients with virological breakthrough were treated for a median of 119 weeks compared with a median of 59.3 weeks in patients without virological breakthrough ($P = .0047$). The median duration of lamivudine therapy before virological breakthrough was 61 weeks (range, 26 to 118 weeks). Seven of the 13 patients (54%) with virological breakthrough were confirmed to have PCR-detectable YMDD mutants. Twelve of the 13 patients with virological breakthrough were alive at last visit; only 1 patient (patient no 1, Table 3) died of an unrelated cerebral hemorrhage.

Clinical, virological, and biochemical parameters of patients with and without virological breakthrough were similar at entry (Table 2). As expected, serum HBV DNA levels were greater at the last visit in patients with virological breakthrough compared with patients without virological breakthrough, but the median HBV DNA level remained lower than the pretreatment value

Table 3. Clinical Parameters of 13 Liver Transplant Recipients Administered Lamivudine With Virological Breakthrough

Patient No.	Time to Breakthrough/ Total (wk)	Serum ALT (IU/L)		HBV DNA (mEq/mL)		Clinical Status	YMDD Mutants*
		Pre	Last	Pre	Last		
1	42/94	45	53	6,227	902.9	Death†	B, C
2	114/130	131	90	2,816	3.1		—
3	118/134	135	67	712.5	1.4		—
4	89/142	77	18	187.1	71.8		B, C
5	113/134	56	22	976.7	1.2		—
6	63/128	172	80	3,765	63.6	Variceal bleed	B, C
7	85/127	84	58	3,175	4,675		C
8	54/119	169	82	509	134.9		—
9	50/114	40	36	6,731	1,048		B, C
10	43/103	70	31	3,680	78.5		B, C
11	61/100	69	99	2,226	353.5		B, C
12	27/68	53	49	1,301	2.6	Encephalopathy, ascites	—
13	26/40	89	47	1,381	132.8		—

* YMDD mutants determined in 7 of the 13 patients using restriction fragment length polymorphism.[25] B mutants refer to viral isolates with mutations identified in the B domain, L528M. C mutants refer to viral isolates with mutations identified in the C domain, including M552V and M552I.
† Death from unrelated cerebral hemmorhage.

in both patient subgroups. Median serum ALT and bilirubin levels at last follow-up in patients with and without virological breakthrough were not significantly different, whereas albumin levels were lower in patients with virological breakthrough.

Safety

One patient died during this study of a cerebral hemorrhage after 21 months of lamivudine therapy, which was not believed to be related to the study medication. Serious adverse events were reported in 11 patients. Of note, 7 of the 13 patients with virological breakthrough (54%) reported serious adverse events during treatment that were unrelated to liver disease or the study drug compared with 2 of the 16 patients (12%) without virological breakthrough ($P = .041$, Fischer's exact test). Grades 3 and 4 laboratory abnormalities were reported in 23 patients and were not more common in patients with virological breakthrough compared with patients without virological breakthrough.

Discussion

Several studies suggest that lamivudine may be a safe and effective treatment for liver transplant recipients with active HBV infection.[15,16] In our study, lamivudine was well tolerated and not associated with an identified pattern of drug-attributable adverse events. As a potent inhibitor of HBV polymerase, lamivudine treatment led to a rapid suppression of HBV replication in this group of immunosuppressed liver transplant recipients with high pretreatment serum HBV DNA levels (Fig. 2). Although follow-up liver biopsies were not performed in our study, serum ALT levels tended to improve over time in patients with elevated levels pretreatment. In addition, serum albumin and bilirubin levels significantly improved in patients with abnormal levels pretreatment, suggesting that lamivudine-mediated suppression of HBV replication can result in improved liver disease in patients with ongoing HBV-related graft injury (Fig. 3).

Our study represents the longest duration of lamivudine treatment in a large group of liver transplant recipients with HBV reported in the literature (Table 4). Not surprisingly, 45% of our patients developed evidence of virological breakthrough after a median of 61 weeks of lamivudine treatment. The majority of these patients were shown to have developed PCR-detectable YMDD mutants, which have been associated with lamivudine resistance in vitro and diminished clinical response to continued lamivudine therapy.[20,21] HBV genotyping results in this study are similar to those reported in another study of transplant recipients.[15] The greater incidence of virological breakthrough in our patient population may be caused in part by the longer duration of lamivudine treatment in our study. Pretreatment demographic characteristics and time

Table 4. Studies of Lamivudine Treatment for Chronic HBV Infection After LT

Study	No. of Patients	Median Time From LT (mo)	Median Duration of Lamivudine (wk)	Virologic Breakthrough (%)
Perrillo et al[15]	52	49 (2-142)	52*	27
Malkan et al[16]†	15	19 (1-84)	106 (52-156)	13
Nery et al[31]‡	8	17 (2-51)	108 (44-156)	37
Fontana et al	33	51 (6-123)	85 (16-142)	45

* All patients had recurrent hepatitis B and received 52 weeks of lamivudine therapy.
† Twenty-seven percent of patients were electively converted from HBIg to lamivudine for post-LT prophylaxis.
‡ HBIG treatment failed in all patients and 2 patients were administered concomitant famciclovir.

from LT were not predictive of virological breakthrough, but patients with virological breakthrough were administered lamivudine for a longer time than those without virological breakthrough. Nonetheless, serum HBV DNA levels at last follow-up remained lower than pretreatment levels in 12 of the 13 patients with virological breakthrough. In addition, serum ALT and bilirubin levels were similar to those of patients without virological breakthrough at the last follow-up (Table 2). During a median study follow-up of 86 weeks, none of the patients in our series have required re-LT.

Our observations are in contrast to those of Perrillo et al[15] and others who reported that a subgroup of patients with YMDD-associated virological breakthrough may develop worsening liver function and hepatic insufficiency during relatively short-term follow-up.[23,26] The reason for a lack of clinical deterioration in our patients is unclear because the biochemical severity of illness before treatment was similar.[15,26] Interestingly, the median time to develop virological breakthrough in our study was 61 weeks compared with 32 weeks in the study of Perrillo et al,[15] although pretreatment serum HBV DNA levels and degree of immunosuppression appeared similar.

In summary, the results of our study show that prolonged lamivudine treatment is well tolerated in liver transplant recipients with active HBV infection. Lamivudine treatment was associated with a significant improvement in serum albumin and bilirubin levels in a subgroup of patients with more severe biochemical abnormalities at baseline. Randomized controlled trials are needed to define which patients with hepatitis B after LT may benefit from antiviral therapy. As additional antiviral agents become available for clinical investigation, liver transplant recipients at high risk for poor clinical outcomes deserve further study through controlled trials in which all treatment arms use putatively active agents (or combinations of agents). The relatively high rate of virological breakthrough encountered with prolonged lamivudine monotherapy in our study and others indicates that studies of combination antiviral therapy are desirable for this patient group. For lamivudine-treated patients with virological breakthrough and evidence of a loss of clinical response, controlled trials of potential salvage therapies are warranted. Adefovir dipivoxil, another potent inhibitor of HBV polymerase, appears to be effective in patients with lamivudine-resistant strains of HBV.[27,28] However, further studies clarifying the potential nephrotoxicity of adefovir are needed. Other potent nucleoside analogues, such as entecavir, may also prove useful in combination with lamivudine in liver transplant recipients with HBV, but these agents will also require further study as single agents to establish their safety and efficacy.[29,30]

In conclusion, our study results further establish that long-term outcomes for patients with advanced HBV undergoing LT are improving through advances in the prevention of viral recurrence (with HBIg and lamivudine) and the availability of safe and effective antiviral therapies for patients with recurrent HBV after LT.

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