

# Prevention of Recurrent Hepatitis B Post–Liver Transplantation

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## Key Points

1. Factors associated with a lower rate of recurrent hepatitis B post–liver transplantation (LT) are negative hepatitis B e antigen and/or serum hepatitis B virus DNA pre-LT, hepatitis D virus superinfection, and fulminant hepatitis B.
2. Long-term intravenous hepatitis B immune globulin (HBIG) monotherapy can reduce the overall rate of recurrent hepatitis B to 20% to 35%.
3. Long-term lamivudine monotherapy is associated with a risk for drug resistance and overall 3-year rate of recurrent hepatitis B of 40% to 50%.
4. Combination prophylaxis with HBIG and lamivudine can reduce the overall rate of recurrent hepatitis B to 0% to 10%.
5. The dose and duration of HBIG therapy needed when used in combination with lamivudine may be lower, but the optimal regimen remains to be determined.
6. Lamivudine resistance before LT is associated with an increased risk for recurrent hepatitis B post-LT.
7. A cost-effective prophylactic regimen to prevent recurrent hepatitis B should be tailored according to risk. (*Liver Transpl* 2002;8:S67-S73.)

Results of liver transplantation (LT) for hepatitis B in the early 1980s were poor, with recurrence rates greater than 80% and 2-year mortality rates of 50%. During the past 15 years, significant advances have been made in the management of patients who require LT for hepatitis B. Using combination prophylaxis with hepatitis B immune globulin (HBIG) and lamivudine, the rate of recurrent hepatitis B can be reduced to less than 10%. However, lifelong combination prophylaxis, especially with a high-dose intravenous (IV) infusion of HBIG, is very expensive and inconvenient. In addition, the increasing use of lamivudine in patients awaiting LT will lead to an increased proportion of patients with lamivudine resistance before LT. Thus, challenges for the future are to establish more cost-effective prophylaxis for recurrent hepatitis B post-LT, optimize the use of lamivudine pre-LT, and develop effective prophylactic therapy for patients who develop lamivudine resistance before LT.

## HBIG Monotherapy

The administration of HBIG to prevent recurrent hepatitis B post-LT was pioneered in Europe. Initial studies showed that short-term HBIG therapy delayed, but did

not prevent, recurrent hepatitis B. Subsequent studies showed that long-term HBIG therapy significantly decreased the rate of recurrent hepatitis B and improved patient survival. The European Concerted Action on Viral Hepatitis Study reported that IV infusions of HBIG for longer than 6 months reduced the overall rate of recurrent hepatitis B post-LT to 35%.<sup>1</sup> Multivariate analysis showed that independent predictors of a lower rate of recurrent hepatitis B were hepatitis D virus (HDV) superinfection, fulminant hepatic failure, and negative hepatitis B e antigen (HBeAg) and hepatitis B virus (HBV) DNA pre-LT (Table 1). Fulminant hepatitis B frequently is accompanied by rapid clearance of HBV, whereas HDV superinfection has been shown to suppress HBV replication. Thus, the most important factor associated with a lower rate of recurrent hepatitis B is a low virus load pre-LT. Pharmacokinetic studies showed that the half-life of hepatitis B surface antibody (anti-HBs) after HBIG infusion is shorter in patients who were HBeAg positive pre-LT.<sup>2</sup> Therefore, fixed-dose HBIG regimens may be insufficient to maintain protective anti-HBs levels in patients with a high virus load pre-LT.

The HBIG dose regimen used in most European centers aims to maintain trough anti-HBs titers at greater than 100 IU/L. Most US centers use a fixed-dose regimen, with an IV infusion of 10,000 IU of HBIG during the anhepatic phase, followed by 10,000 IU/d for 7 days, then 10,000 IU/mo (Table 2). This regimen results in a wide range of anti-HBs titers among patients, as well as within patient, but most patients maintain trough anti-HBs titers greater than 500 IU/L, and many have trough anti-HBs titers greater than 1,000 IU/L.<sup>3</sup> The high-dose regimens used in US centers have been reported to reduce the rate of recurrent hepatitis B to less than 20%<sup>3,4</sup>; however, these

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**Table 1.** Factors Associated With Decreased Risk for Recurrent Hepatitis B Post-LT

<p>Low virus load pre-LT HBeAg negative Undetectable serum HBV DNA HDV superinfection Fulminant hepatitis B</p>
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regimens are very expensive (first year charges > US \$100,000; subsequent yearly charges > US \$50,000). In addition, hepatitis B still recurs at a rate of 20% to 30% among patients who are HBeAg and/or HBV DNA positive pre-LT.<sup>4</sup>

Recurrent hepatitis B during the first 6 months post-LT usually is related to inadequate HBIG doses in patients with a high viral load pre-LT, whereas late recurrence is caused mainly by the selection of immune escape mutants.<sup>5,6</sup> The most common mutation involves a glycine to arginine substitution at codon 145 (G145R) of the HBV S protein. This mutation results in reduced binding to anti-HBs and may escape neutralization by HBIG. Cessation of HBIG therapy is accompanied by reversion to wild-type sequence, supporting the role of HBIG in the selection of these mutations.<sup>6</sup>

Potential side effects of HBIG include immune-mediated reactions and anaphylaxis, mercury toxicity, and transmission of blood-borne infections. These side effects are extremely rare with current formulations of HBIG, which have gone through viral inactivation steps and have lower protein content and no thimerosal preservative.

## Lamivudine Monotherapy

### Prevention of Recurrent Hepatitis B Post-LT

Lamivudine, an orally administered nucleoside analogue, is a potent inhibitor of HBV DNA synthesis. Several studies showed that lamivudine monotherapy

**Table 2.** Efficacy of HBIG Monotherapy in Preventing Recurrent Hepatitis B Post-LT

	European Studies	US Studies
Target trough anti-HBs titer (IU/L)	>100	>500
Recurrence rate 3 yr post-LT (%)	35	20

**Table 3.** Efficacy of Lamivudine Monotherapy in Preventing Recurrent Hepatitis B Post-LT

	UK <sup>8</sup>	N America <sup>9</sup>	Hong Kong <sup>10</sup>
No. of patients	12	37	26
Recurrence rate post-LT (%)			
1-Yr	10	32	23
3-Yr	50	41	Not available

can prevent recurrent hepatitis B post-LT, but drug resistance develops with long duration of therapy (Table 3). The initial trial in England reported that only 1 of 10 patients who survived the early post-LT period developed recurrent hepatitis B.<sup>7</sup> A subsequent report from the same group found that 5 of 10 patients administered lamivudine monotherapy developed recurrent hepatitis B because of the selection of drug-resistant mutants after a median post-LT follow-up of 966 days.<sup>8</sup> Two of these 5 patients died of recurrent hepatitis B.

In the North American multicenter study, overall 1- and 3-year post-LT recurrence rates were 32% and 41%, respectively.<sup>9</sup> One- and 3-year post-LT recurrence rates were 40% (9 of 20 patients) and 60% (9 of 15 patients) among patients who were HBV DNA positive before the initiation of lamivudine therapy (native replicators) and 18% (3 of 17 patients) and 0% (0 of 7 patients) among patients who were HBV DNA negative before the initiation of lamivudine therapy (native nonreplicators). Of the three native nonreplicators who were hepatitis B surface antigen (HBsAg) positive at 1 year post-LT, 1 patient was lost to follow-up, 1 patient remained HBsAg positive during the second year, and 1 patient became HBsAg negative during the second year. Thus, the actuarial recurrence rate at 3 years post-LT among native nonreplicators was approximately 10% to 20%.

These data confirmed the strong association between recurrent hepatitis B post-LT and HBV replicative status pre-LT, in particular, replicative status before lamivudine therapy. Although lamivudine is significantly more economical (charges of ~ US \$1,800/yr), current data suggest that lamivudine monotherapy is not sufficient for the prevention of recurrent hepatitis B among native replicators. The North American multicenter trial found a significantly lower, but not zero, recurrence rate among patients with undetectable serum HBV DNA before lamivudine therapy; however, baseline serum HBV DNA level was tested by means of a relatively insensitive assay (detection limit, ~10<sup>7</sup> cop-

ies/mL). Whether lamivudine monotherapy is sufficient for the prevention of recurrent hepatitis B among native nonreplicators with lower baseline serum HBV DNA levels is not known.

Contrary to studies in Europe and North America, a report from Hong Kong noted that only 1 of 26 patients (58%, HBeAg positive; 35%, HBV DNA detected by branched DNA assay at initial evaluation) administered lamivudine monotherapy developed recurrent hepatitis B, defined as the reappearance of HBV DNA in serum.<sup>10</sup> Five additional patients remained HBsAg positive, but maintained normal aminotransferase levels and mild nonspecific changes on liver biopsy. Thus, overall, 6 patients (23%) had recurrent or persistent HBV infection post-LT during a median follow-up of 16 months. This study highlights the need to standardize the definition of recurrent hepatitis B post-LT.

### Prevention of the Need for LT

Lamivudine has been used not only to reduce virus load at the time of LT, but also to improve or stabilize liver disease in the hope of delaying or obviating the need for LT. In one study, 23 of 35 patients (66%) with decompensated HBV-related cirrhosis who were administered lamivudine for more than 6 months had improvement in liver function, defined as a greater than two-point decrease in Child-Turcotte-Pugh (CTP) score.<sup>11</sup> However, 7 patients underwent LT, and 5 patients died during the first 6 months. Of initial responders, 2 patients later died (1 patient, hepatocellular carcinoma; 1 patient, spontaneous bacterial peritonitis) and 3 patients subsequently developed lamivudine resistance. Another study reported that 14 of 23 lamivudine-treated patients (61%) with severely decompensated HBV-related cirrhosis (CTP score  $\geq 10$ ) had improvement in CTP scores by greater than three points.<sup>12</sup> Compared with historic controls, treated patients were less likely to require LT (35% *v* 74%;  $P = .04$ ). A third study of 309 North American patients with HBV-related cirrhosis awaiting LT found that lamivudine treatment was not associated with overall improvement in LT-free survival, but a subset of patients had a decrease in liver disease severity.<sup>13</sup>

These studies showed that lamivudine therapy can stabilize or improve liver function and may improve LT-free survival. However, clinical improvement takes 3 to 6 months. Thus, lamivudine may not be able to slow disease progression or reduce the need for LT in patients who present very late. The slow clinical effect argues for early initiation of lamivudine therapy; how-

ever, the risk for resistance increases with duration of treatment. Based on the limited data available, it seems that liver disease remains stable in most patients despite the emergence of lamivudine-resistant mutants. However, duration of follow-up is short, and rapidly worsening liver failure has been reported. In addition, selection of lamivudine-resistant mutants pre-LT may increase the risk for recurrent hepatitis B post-LT. Thus, the optimal timing to initiate lamivudine therapy in patients with hepatitis B awaiting LT remains unclear.

### Combination of HBIG and Lamivudine

HBIG and lamivudine have different mechanisms of action and resistance profiles. Thus, combination therapy with HBIG and lamivudine may be more effective than monotherapy with either agent. Several studies have shown that combination therapy with HBIG and lamivudine can reduce rates of recurrent hepatitis B to 0% to 10%<sup>14-18</sup> (Table 4). The largest study involved 59 patients.<sup>14</sup> Lamivudine therapy was initiated before LT in 9 of 20 patients who had detectable HBeAg and/or HBV DNA by molecular hybridization at initial evaluation and in 15 of the remaining 39 patients. HBIG was administered IV in doses of 10,000 IU during the anhepatic phase and then daily for 7 days, followed by 10,000 IU every month. All patients remained HBsAg negative after a median follow-up of 15 months (range, 1 to 60 months). These data suggest that combination therapy with lamivudine and high-dose IV HBIG may completely prevent recurrent hepatitis B post-LT; however, this regimen is very inexpensive.

Other centers have reported similarly impressive results using lower HBIG doses.<sup>15-18</sup> Of note, Angus et al<sup>15</sup> reported a recurrence rate of only 3% among 32 patients in Australia and New Zealand followed up for a mean of 18 months (range, 5 to 45 months). In this study, HBIG was administered as intramuscular (IM) injections in doses of 400 IU (17 patients) or 800 IU (20 patients) daily for the first week and monthly thereafter. Excellent results were achieved with less than 10% of HBIG doses used in most US centers, although 50% of patients were HBeAg and/or HBV DNA positive before lamivudine treatment, 97% did not have HDV superinfection, and none had fulminant hepatitis. HBIG doses in other studies varied from 10,000 to 80,000 IU during the first month and 1,500 to 5,000 IU during subsequent months.<sup>16-18</sup> Recurrence rates less than 10% were reported. These data confirm that combination prophylaxis with lamivudine and HBIG

**Table 4.** Efficacy of Combination Prophylaxis With Lamivudine and HBIG in Preventing Recurrent Hepatitis B Post-LT

Reference	Year	No. of Patients	HBeAg/HBV DNA* Pre-Lam* (%)	HDV/FH (%)	HBIG Dose ( $\times 1,000$ IU)		Lam Pre-LT (%)	Recurrent Hepatitis B (%)	Follow-Up (mo)
					Mo 1	Subsequent Mo			
Yao et al <sup>18</sup>	1999	10	90	0/0	13-83 IV	1.5 IM	100	10	16
Yoshida et al <sup>17</sup>	1999	6	67	NA/0	43 IM	4.3-6.8 IM	100	0	18
Angus et al <sup>15</sup>	2000	32	50	3/0	1.6-3.2 IM	0.4-0.8 IM	100	3	18
Han et al <sup>14</sup>	2000	58	34	19/2	80 IV	10 IV	41	0	15
Marzano et al <sup>16</sup>	2001	26	46	0/0	46.5 IV	5 IV	100	4	30
Rosenau et al <sup>19</sup>	2001	19	52	29/0	45 IV	2.3 IV	90	11†	20
Seehofer et al <sup>20</sup>	2001	17	100	NA/0	29 IV	1.5-2 IV	100‡	18§	25

Abbreviations: Lam, lamivudine therapy; NA, not available; FH, fulminant hepatitis.

\*HBV DNA by non-polymerase chain reaction-based assay or  $10^6$  copies/mL or greater.

†Both patients with recurrence had lamivudine resistance before LT.

‡Famciclovir therapy failed in 6 of 17 patients before lamivudine treatment.

§All three patients with recurrence had lamivudine resistance before LT.

can achieve better results at lower costs than prophylaxis with HBIG only. However, the heterogeneity of patient populations and HBIG dose schedules, small number of patients on most studies, and short duration of follow-up preclude definitive recommendations on the HBIG dose required to achieve optimal results. Greater recurrence rates, 11% and 18%, were reported in two recent studies.<sup>19,20</sup> In both studies, high doses (29,000 to 45,000 IU) of HBIG were administered during the peri-LT period, and thereafter, HBIG was administered to maintain trough anti-HBs titers at greater than 100 IU/L. The five patients who developed recurrent hepatitis B had evidence of lamivudine resistance before LT. These findings indicate that combination prophylaxis using low maintenance doses of HBIG may not be sufficient to prevent recurrent hepatitis B in patients with lamivudine resistance.

### Sequential Prophylaxis With HBIG Followed by Lamivudine

In attempts to reduce long-term costs, several investigators have examined the feasibility of switching patients from lifelong HBIG therapy to lamivudine therapy. In one study, 24 patients who were HBeAg and/or HBV DNA negative before LT and had been administered HBIG for at least 6 months were randomized to the administration of HBIG or lamivudine for 1 year.<sup>21</sup> Three patients developed recurrent hepatitis B (1 of 12 patients on HBIG therapy and 2 of 12 patients on lamivudine therapy). All 3 patients entered the study within 1 year of LT. The early recurrence (2 and 12 weeks after discontinuation of HBIG therapy) in the lamivudine group may be related to the presence of

subclinical reinfection at entry onto the study; 2 patients had detectable serum HBV DNA by liquid hybridization assay, and 4 patients had detectable serum HBV DNA by polymerase chain reaction.

In another study, 30 patients who were HBeAg negative before LT were considered for lamivudine substitution after 24 months of HBIG therapy.<sup>22</sup> None of the 16 patients who participated in the study developed recurrent hepatitis B after a median follow-up of 13 months (range, 5 to 28 months).

These studies suggest that although lamivudine monotherapy is insufficient as initial prophylaxis against recurrent hepatitis B after LT, it may be adequate as maintenance prophylaxis in some patients. Further studies are needed to define this subset of patients and the optimal timing to discontinue HBIG therapy.

### HBV Vaccination

The success of passive prophylaxis using HBIG suggests that active prophylaxis may be equally effective and more economical. However, patients who require LT for hepatitis B tend to be older (>40 years), are immunosuppressed, and may not be able to mount an adequate response to HBV vaccines. A study from Spain reported that 14 of 17 patients (82%) developed anti-HBs titers greater than 10 IU/L after one to two courses of double-dose recombinant HBV vaccines.<sup>23</sup> None of the vaccine responders developed recurrent hepatitis B during a median follow-up of 14 months (range, 3 to 50 months), although HBIG therapy was stopped, lamivudine therapy was not initiated, and only 4 patients had anti-HBs titers greater than 100 IU/L. However, these

**Table 5.** Outcome of Patients With Lamivudine Resistance Before LT

Reference	Year	No. of Patients	Post-LT Prophylaxis		Follow-Up/Time to Reinfection (mo)	No. With HBV Recurrence
			HBIG (IU)	Lamivudine		
Saab et al <sup>25</sup>	2000	1	IV 70,000, then 10,000/mo	Yes	32	0
Yao et al <sup>18</sup>	1999	1	IV 80,000, then IM 1,100 every 3 wk	Yes	10	0
Fontana et al <sup>13</sup>	2002	6			11	1
		1	—	Yes		0
		4	Indefinite	Yes		0
		1	IV × 3 mo only	Yes	9	1
Rosenau et al <sup>19</sup>	2001	2	IV 40,000, then IV 2,000 as needed	Yes	0.5, 2.5	2
Seehofer et al <sup>20</sup>	2001	3	IV 30,000, then IV 1,500-2,000	Yes	Not available	3

encouraging results were not confirmed in a subsequent study. In this study, only 3 of 17 Italian patients (18%) developed anti-HBs titers greater than 10 IU/L after three courses of reinforced HBV vaccination (double dose or intradermal administration).<sup>24</sup> Vaccination was commenced 4.5 months after discontinuing HBIG therapy, and lamivudine was maintained throughout the study. Both studies enrolled patients who were HBeAg and serum HBV DNA negative pre-LT and had been administered HBIG for greater than 18 months post-LT. The exact reason for the discrepant results is not clear. Further data are needed before active prophylaxis can be recommended to substitute for HBIG. Studies of more immunogenic vaccines that incorporate pre-S antigens and/or more potent adjuvants are warranted.

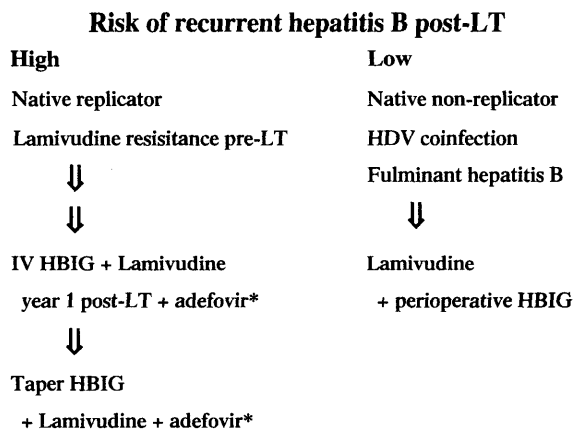
### Prevention of Recurrent Hepatitis B in Patients With Lamivudine Resistance Before LT

Increasing use of lamivudine in patients with chronic hepatitis B, in particular, in patients awaiting LT, will lead to a growing number of patients with lamivudine resistance before LT. To date, there are very few data on the efficacy of current prophylactic therapies in patients with lamivudine-resistant mutants. A recent case report found that indefinite administration of high-dose IV HBIG, together with lamivudine, was effective in preventing recurrent hepatitis B in a patient who had been followed up to 32 months post-LT<sup>25</sup> (Table 5). Other investigators also suggested that recurrence is not invariable, although the number of patients studied was small and duration of post-LT follow-up was short.<sup>18,26</sup> Two studies reported more discouraging results, with the 5 patients who had lamivudine resistance pre-LT developing recurrent hepatitis B soon after LT despite

the use of combination prophylaxis.<sup>19,20</sup> Further studies are needed to determine the rate of recurrent hepatitis B in patients with lamivudine resistance pre-LT and the optimal prophylactic regimen for these patients. It is possible that these patients may need to be maintained on lifelong high-dose HBIG therapy. Alternately, these patients may benefit from newer antiviral agents that are effective in suppressing the replication of lamivudine-resistant HBV.

### Role of Adefovir Dipivoxil and Entecavir

Adefovir dipivoxil and entecavir have been shown to have in vitro, as well as in vivo, efficacy in suppressing the replication of lamivudine-resistant HBV. Both compounds are investigational drugs. Adefovir dipivoxil was evaluated in a compassionate-use protocol in 40 patients with lamivudine-resistant HBV awaiting LT and 127 patients with recurrent hepatitis B post-LT secondary to lamivudine-resistant HBV.<sup>27,28</sup> Adefovir resulted in a mean reduction in serum HBV DNA levels by two to three log<sub>10</sub>, with accompanying improvement in liver biochemistry results. None of the patients awaiting LT developed significant worsening in renal function; however, 14% of post-LT patients had an increase in serum creatinine level greater than 0.5 mg/dL. Although the use of other nephrotoxic medications, such as cyclosporine and tacrolimus, may have contributed to the impairment in renal function in post-LT patients, further data on long-term safety are needed before adefovir can be used as primary prophylaxis against recurrent hepatitis B. Currently, the role of adefovir is mainly that of salvage therapy in patients with lamivudine resistance pre-LT. The efficacy of adefovir in this setting and dose and duration of HBIG required remain to be determined. Experience with entecavir in transplant recipients is more limited. Pre-



**Figure 1. Proposed strategy for prophylaxis against recurrent hepatitis B post-LT based on risk for recurrence. \*, for patients with lamivudine resistance pre-LT.**

liminary data suggest that entecavir is well tolerated and effective in reducing serum HBV DNA levels in patients with lamivudine resistance<sup>28</sup>; however, further data are needed to establish its safety and efficacy as primary prophylaxis or salvage therapy.

### Cost-Effective Prophylaxis of Recurrent Hepatitis B Post-LT

Significant advances have been made in the prevention of recurrent hepatitis B post-LT in the past 15 years. Recurrent hepatitis B can be reduced to 0% to 10% by using combination prophylaxis with indefinite high-dose HBIG and lamivudine therapy. However, this regimen is extremely expensive and inconvenient to patients. Thus, a more cost-effective prophylactic regimen must be developed. Many investigators have explored combination prophylaxis using lower dose IM administration or shorter duration of HBIG therapy, but most studies have been limited by a small number of patients, short duration of follow-up, and heterogeneity of patients studied. Future endeavors should focus on tailoring the prophylactic regimen based on risk for HBV recurrence (Fig. 1). These regimens likely will be more cost-effective than currently used one-size-fits-all approaches and will permit gradual tapering of prophylactic therapy over time.

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