

# Tenofovir Improves the Outcome in Patients with Spontaneous Reactivation of Hepatitis B Presenting as Acute-On-Chronic Liver Failure

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Spontaneous reactivation of chronic hepatitis B (CHB) is an important cause of acute-on-chronic liver failure (ACLF). Antiviral drugs may help reduce the high morbidity and mortality in such patients, especially in places where liver transplant is not available. The aim was to evaluate the efficacy of tenofovir and to determine the predictors of mortality in patients with spontaneous reactivation of CHB with ACLF. Consecutive patients of ACLF due to spontaneous reactivation of CHB were randomized to receive either tenofovir or placebo. The primary endpoint was survival at 3 months. Of the 90 patients with ACLF of different etiologies, 27 (26%) were due to reactivation of CHB and were enrolled. The median baseline hepatitis B virus (HBV) DNA level was  $9 \times 10^5$  IU/mL. Fourteen patients received tenofovir and 13 placebo. At 3 months the probability of survival was higher in the tenofovir than the placebo group (8/14 [57%] versus 2/13 [15%], respectively;  $P = 0.03$ ). The cause of death in the 15 patients was progressive liver failure leading to multiorgan failure. Liver transplantation could not be offered due to its nonavailability. In the surviving patients, there was a significant improvement in the Child-Turcotte Pugh (CTP) and model for end-stage liver disease (MELD) scores and significant decline in the HBV DNA levels in the tenofovir group, whereas these parameters did not change significantly in the placebo group. More than 2 log reduction in HBV DNA levels at 2 weeks was found to be an independent predictor of survival. **Conclusion:** Tenofovir significantly reduces HBV-DNA levels, improves CTP and MELD scores, and reduces mortality in patients with severe spontaneous reactivation of CHB presenting as ACLF. Reduction in HBV-DNA levels at 2 weeks should be a desirable goal and is a good predictor of survival. (HEPATOLOGY 2011;000:000-000.)

Chronic hepatitis B virus (HBV) infection is a well-established cause of liver-related morbidity

*Abbreviations:* ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; CHB, chronic hepatitis B; CTP, Child-Turcotte Pugh; GI, gastrointestinal; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HVP, hepatic venous pressure gradient; MELD, model for end-stage liver disease; TDF, tenofovir disoproxil fumarate; TJLB, transjugular liver biopsy.

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and mortality and it is the commonest cause of liver cirrhosis and hepatocellular carcinoma in Southeast Asia.<sup>1</sup>

Reactivation of hepatitis B is a well-characterized syndrome marked by the abrupt reappearance or rise of HBV DNA in the serum of a patient with previously inactive or resolved HBV infection. Reactivation is often spontaneous, but can also be triggered by cancer chemotherapy, immune suppression, or alteration in immune function. Spontaneous acute exacerbation of chronic hepatitis B (CHB) infection is seen with a cumulative probability of 15%-37% after 4 years of follow-up.<sup>2</sup> A significant number of patients of spontaneous acute exacerbation of CHB may present with very high alanine aminotransferase (ALT) levels, jaundice, and liver failure.<sup>3</sup> This condition has been defined as acute-on-chronic liver failure (ACLF) according to a recent Asia-Pacific consensus recommendation.<sup>4</sup> Although the symptoms of severe acute

exacerbation of CHB can be very similar to those of acute hepatitis B, they are quite distinct from acute liver failure, in which the individual has no underlying liver disease, as commonly seen in the West.<sup>5</sup> Some patients presenting with severe acute exacerbation of CHB may not know that they have asymptomatic chronic HBV infection. In other words, the severe acute exacerbation of liver disease may be the first presenting feature of their CHB.<sup>6</sup> We have shown previously that a high HBV DNA level ( $>10^5$  copies/mL) is useful to identify severe acute exacerbation of CHB from acute hepatitis B.<sup>7</sup>

The short-term prognosis of patients with spontaneous severe acute exacerbation of CHB leading to ACLF-like presentation is extremely poor, with a mortality rate ranging from 30%-70%.<sup>8-10</sup> Liver transplantation has been the only definitive therapy available to salvage this group of patients; however, this is not readily available nor feasible in many parts of the world where HBV is highly endemic. Another therapeutic option is antiviral therapy for HBV. In previous studies, the efficacy of lamivudine (LAM) was not found to be superior to historical controls.<sup>8-10</sup> However, a study from Taiwan showed a survival benefit in a subgroup of patients who were on LAM and had baseline bilirubin below 342 mmol/L (20 mg/dL).<sup>11</sup>

Tenofovir disoproxil fumarate (TDF) is a potent, rapidly acting, oral acyclic nucleotide analog, reverse transcriptase inhibitor that has been shown to be highly effective in suppressing HBV replication.<sup>12</sup> TDF has shown excellent activity against HBV in both LAM-naïve and LAM-resistant patients.<sup>13,14</sup> Its efficacy, however, has not been evaluated in patients with severe reactivation of HBV who present as ACLF.

We undertook a randomized trial to assess the efficacy of TDF in reduction of HBV DNA levels and associated improvement in disease severity, biochemical recovery, and likely improvement in survival in patients with ACLF due to HBV reactivation.

## Patients and Methods

**Patients.** This study was conducted between 2007 and 2009 in patients fulfilling the criteria of ACLF.<sup>4</sup> The inclusion criteria were: Reactivation of CHB characterized by a rise in ALT level  $>5$  times upper limit of normal along with HBV DNA level  $>10^5$  copies/mL ( $\approx 1.8 \times 10^4$  IU/mL) presenting as ACLF, defined as the presence of acute hepatic insult, jaundice (bilirubin  $\geq 5$  mg/dL), and coagulopathy (international normalized ratio  $>1.5$ ), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previ-

ously diagnosed or undiagnosed chronic liver disease. The exclusion criteria were: superinfection with other viruses (hepatitis E, A, D, or C), other causes of chronic liver failure, coexistent hepatocellular carcinoma (HCC), portal vein thrombosis, coexistent renal impairment, pregnancy, coinfection with human immunodeficiency virus (HIV), or patients who had received a previous course of any antiviral, immunomodulator, or cytotoxic/immunosuppressive therapy for chronic hepatitis or other illness within at least the preceding 12 months.

A written informed consent for inclusion in the trial was obtained from all included patients. The potential benefits and risks of the use of TDF were explained and the nonavailability of the liver transplant facilities was also provided to the patients. The study conformed to the Helsinki Declaration of 1975 and was duly approved by the departmental scientific committee.

**Baseline Assessment of Patients.** Prospectively collected data included patient demographics, clinical, all laboratory variables including virological tests, genotyping by direct sequencing, abdominal ultrasound, and upper gastrointestinal (GI) endoscopy. Transjugular liver biopsy (TJLB) and hepatic venous pressure gradient (HVPG) were done in patients when it was not evident whether the underlying liver disease was chronic based on clinical, biochemical, radiological investigations, and upper GI endoscopy. Severity of the liver disease was assessed by Child-Turcotte Pugh score (CTP) and model for endstage liver disease (MELD) score.

**Diagnosis of HBV:** Serological tests for hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), immunoglobulin M (IgM) anti-HBc, total anti-HBc, and anti-HBe were done by commercially available enzyme-linked immunoassays. HBV DNA estimation was done with the real-time polymerase chain reaction (PCR) method (lower limit of detection 50 IU/mL, Roche Taqman assay).

**Study Design.** Patients were randomized to receive placebo or TDF, 300 mg/day, and were followed for at least 3 months or death. Randomization was done with a random number table. The investigators as well as the patients were blinded to the randomization.

**General Management of Patients.** Every patient received standard medical treatment including intravenous antibiotics, barrier nursing, high calorie diet (35-40 cal/kg/day), lactulose, bowel wash, and intensive care monitoring. Patients also received albumin, terlipressin, and proton pump inhibitors if required. Enteral or parenteral nutrition was provided to those

**Table 1. Demographic, Clinical, and Laboratory Variables of Included Patients at Admission**

Parameters	Tenofovir (n=14)	Placebo (n=13)	P-value
Age (yr)	47.5 (16-62)	45 (16-67)	NS
Males	10 (71%)	10 (77%)	NS
WBC ( $\times 10^3/\text{mm}^3$ )	12 (4-28)	12 (4.5-32)	NS
Platelet ( $\times 10^3/\text{mm}^3$ )	178 (68-380)	130 (72-260)	NS
Sodium (meq/dL)	133 (125-143)	130 (114-141)	NS
Creatinine (mg/dL)	0.8 (0.4-1.4)	0.9 (0.6-1.4)	NS
Bilirubin (mg/dL)	24.5 (11.3-41)	18.2 (8.0-40.0)	NS
INR	1.85 (1.55-4.9)	1.93 (1.50-4.9)	NS
Albumin (gm/dL)	2.9 (2.1-3.7)	2.8 (2.0-3.9)	NS
ALT (IU/L)	226 (188-1185)	206 (186-2000)	NS
Encephalopathy	1(7%)	1 (7%)	NS
Ascites	13 (93%)	12 (92%)	NS
e antigen positivity	8 (54%)	7 (46%)	NS
HBV DNA (IU/ml)	$7.5 \times 10^5$ ( $1.7 \times 10^4$ - $3.1 \times 10^7$ )	$1.7 \times 10^6$ ( $2.0 \times 10^4$ - $1.7 \times 10^9$ )	NS
Genotype D: A	11 (79%) : 3 (21%)	12 (92%) : 1 (8%)	NS
Grade of Varix	1.5 (0-3)	1 (0-3)	NS
HVPG (mm Hg)(n=14, 8:6)	15 (9.5-20.5)	18(15.5-21)	NS
Liver biopsy (n=14)	(n=8)	(n=6)	
HAI	5.5 (4-9)	8 (6-15)	NS
Fibrosis (Modified Ishak)	3 (2-6)	4 (2-6)	NS
CTP score	11 (9-13)	11 (9-13)	NS
MELD score	27 (19-36)	25 (18-40)	NS

All values are expressed as median (range) or number (%).

Abbreviations: WBC, white blood cells; INR, international normalized ratio; ALT, alanine aminotransferase; UGIE, upper gastrointestinal endoscopy; HVPG, hepatic venous pressure gradient; HAI, histology activity index; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease.

patients where caloric requirement was not fulfilled by mouth.

**Follow-Up.** Clinical assessment and routine investigations were done every day during the first 15 days and then every 15 days till 90 days. HBV DNA levels were repeated at days 15 and 90. Upper GI endoscopy, ultrasound abdomen, and viral serology were repeated at day 90. Side effects were closely monitored during the whole study period.

**Endpoints.** The primary endpoint of the study was survival at 3 months and secondary endpoints were improvement in CTP and MELD scores and reduction in HBV DNA levels. The cause of death was determined as variceal bleeding, liver failure, renal failure, respiratory failure, shock, or multiorgan failure. Multiorgan failure was defined when there was failure of more than two organs.

**Statistical Analysis.** Precise data for the calculation of the sample size for such a study were not available. However, based on data from previous studies which suggested a mortality rate in the placebo-treated group as 72%<sup>10</sup> and mortality rate in the LAM-treated group as 21%,<sup>9</sup> we calculated the sample size. TDF being much more potent than LAM, the expected mortality rate with TDF was taken as 15%. Using Fisher's exact test, taking alpha of 0.05 (one-sided) and power of 80%, the resulting sample size was 12 in each group.

Descriptive statistics are expressed as median (range) unless otherwise stated. Comparison of continuous variables was done by Mann-Whitney *U* test. For categorical variables the chi-square or Fisher's exact test were used. Variables found significantly predicting mortality on univariate analysis were entered into multivariate analysis by binary logistic regression analysis. Actuarial probability of survival was calculated by Kaplan-Meier graph and was compared by log-rank test. Analysis was done according to intention-to-treat. All statistical tests were 2-tailed, and a significance level (*P*) of 0.05 was used. The statistical tests were performed using SPSS for Windows v. 15 (Chicago, IL).

## Results

**Patients.** From October 2007 through January 2009, 90 patients presenting as ACLF due to different etiological causes were screened. After baseline investigations, 27 patients with spontaneous reactivation of CHB presenting as ACLF were enrolled and randomized; 14 (52%) were randomized to TDF and 13 (48%) to the placebo group. All the patients were followed for at least 3 months or until death. The median duration of hospital stay was 14 (range 7-26) days.

**Baseline Characteristics.** Baseline characteristics in both the patient groups were similar (Table 1). The median age was 45 (16-67) years and 74% were men.

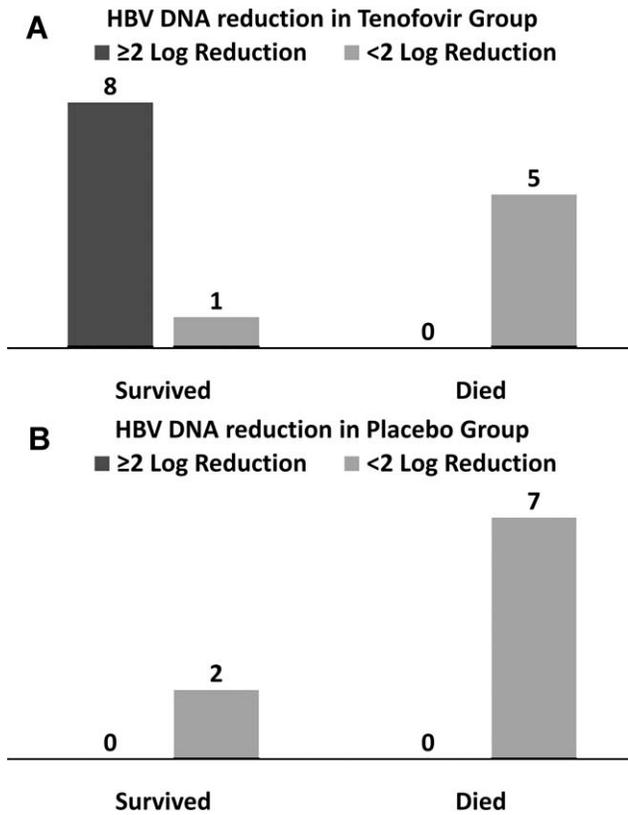


Fig. 1. 2-log reduction in HBV DNA level at 2 weeks predicts survival (A: TDF group; B: placebo group).

Of 27 patients, 10 (37%) survived, eight in the TDF and two in the placebo group ( $P < 0.01$ ).

At admission, serological profile showed HBsAg positivity in all 27 (100%); 15 (56%) were HBeAg-positive. Twenty (74%) patients were serum IgM anti-HBc-positive. Twenty-three patients were genotype D, whereas four patients were genotype A. The median HBV DNA level was  $7.5 \times 10^5$  IU/mL in the TDF, and  $1.7 \times 10^6$  IU/mL in the placebo group ( $P > 0.05$ ). Hepatic encephalopathy was present in only two patients at the time of presentation.

Trans-jugular liver biopsy (TJLB) and hepatic venous pressure gradient (HVPG) was done in 14 patients (TDF group 8 of 14 and placebo group 6 of 13). The median histological activity index and stage of fibrosis were comparable between both the patient groups as assessed by modified Ishak scoring system. HVPG values were also similar in both patient groups (Table 1).

**Reduction in HBV DNA.** TDF significantly reduced HBV DNA levels from baseline 6.64 log to 4.07 ( $P < 0.001$ ) at day 15 and to 3.04 at day 90 ( $P < 0.01$ ). In the placebo group, out of the 10 surviving patients at day 15 HBV DNA values could be obtained in nine. None of these nine patients had  $>2$

log reduction. In the TDF group, at day 15,  $>2$  log reduction in the HBV DNA level was seen in nine patients; out of them eight (90%) survived, whereas  $<2$  log reduction was seen in five patients and all of them died within 3 months (Fig. 1). Undetectable HBV DNA was achieved in three of eight (37%) patients at 12 weeks in the TDF-treated group, whereas none in the placebo group.

After 3 months of follow up, one of eight (12.5%) patients lost the HBsAg in the TDF-treated patients, whereas none in the placebo group. Similarly, three of five (60%) patients lost the HBe antigen status in the TDF group, whereas none in the placebo group.

**Probability of Survival.** Of the 27 patients, 17 (63%) died during the study period (6 [43%] in the TDF and 11 [85%] in the placebo group,  $P < 0.03$ ). The actuarial probability of survival at the end of follow-up of 3 months; 57% in the TDF group and 17% in the placebo group, and this was significant ( $P < 0.01$ ) (Fig. 2).

In the study, 17 (63%) patients died; most (12 [82%]) deaths occurred because of development of multiorgan failure. Multiorgan failure resulted due to progressive liver failure, leading to renal failure (12/17 [70%]) and hepatic encephalopathy (15/17 [88%]). Most of these patients required mechanical ventilation as their respiratory parameters deteriorated. None of them could be weaned off the ventilator due to multiorgan failure and the patients succumbed to the disease.

**Outcomes with Respect of Severity Scores.** Figure 3 shows median (interquartile range) of CTP and MELD scores in both groups of patients. There was a significant difference between the TDF-treated and placebo-treated patients at days 30 and 45 ( $P = 0.01$ ).

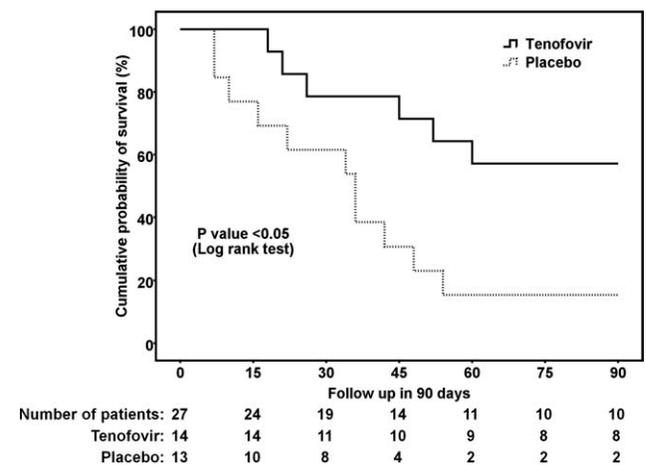


Fig. 2. Cumulative survival in the two groups of ACLF patients, treated with TDF or placebo.

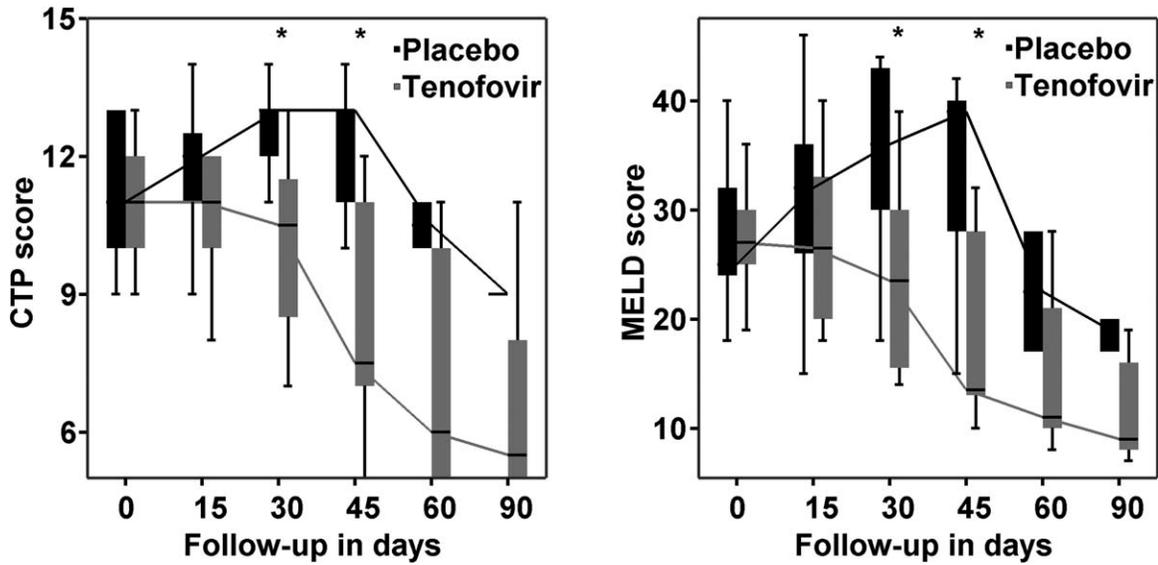


Fig. 3. Median (interquartile range) CTP and MELD scores in both groups of patients. Comparisons were done by Mann-Whitney *U* test.

Similarly, the CTP and MELD scores were also reduced significantly from baseline in the TDF group at days 45 and 90 ( $P < 0.05$ ) (Fig. 4).

**Predictors of Mortality.** Various baseline clinical and laboratory variables were analyzed as possible predictors of mortality. On univariate analysis, the presence of low platelets, less than 2 log HBV DNA reduction in 2 weeks, large esophageal varices, high HVPG, and treatment with TDF were found to be significantly associated with mortality (Table 2). When these significant variables (except those with missing values) were entered into multivariate analysis by binary logistic regression analysis, only more than 2 log HBV DNA reduction in 2 weeks was found to be an independent baseline predictor of survival.

None of the patients could be offered liver transplantation due to the nonavailability of the facilities of liver transplantation services at our institute at that time.

**Safety.** None of the patients developed significant renal failure that could be attributed to TDF, and all the patients tolerated therapy without dose modification or the need for early discontinuation.

**Discussion**

This novel prospective randomized controlled trial compared the use of a potent antiviral drug, TDF, with placebo for the treatment of acute-on-chronic liver failure due to severe reactivation of HBV. The results clearly indicate significant benefits of rapid

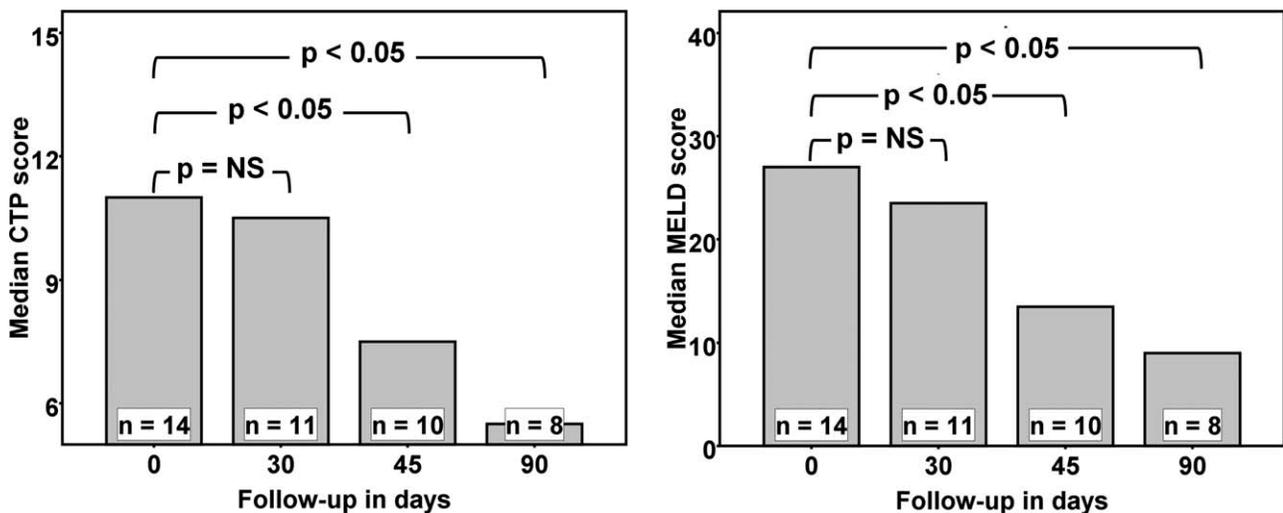


Fig. 4. Median CTP and MELD scores in the TDF group. Wilcoxon signed rank test was used for comparisons.

**Table 2. Univariate Analysis of Baseline Predictors of Mortality**

Variable	Alive (n=10)	Died (n=17)	P- value
M:F	4:1	2.4:1	0.6
Age (yr)	44 (16-67)	45 (18-62)	0.8
WBC (x10 <sup>3</sup> /mm <sup>3</sup> )	10.3 (4-14.3)	13.4 (4.5-32)	0.2
Platelet (x10 <sup>3</sup> / mm <sup>3</sup> )	217 (106-380)	110 (68-230)	0.001
Sodium (meq/dL)	133.5 (128-141)	130 (114-143)	0.1
Bilirubin (mg/dL)	17.5 (9-34)	24 (8-41)	0.3
Albumin (gm/dL)	3.1 (2.0-3.9)	2.8 (2.0-3.8)	0.4
INR	1.83 (1.50-2.97)	1.93 (1.56-4.9)	0.57
Creatinine (mg/dL)	0.80 (0.4-1.4)	0.90 (0.6-1.4)	0.18
HBV DNA (IU/mL)	7.5X10 <sup>5</sup> (2.0X10 <sup>4</sup> -3.1X10 <sup>7</sup> )	1.7X 10 <sup>6</sup> (1.7X10 <sup>4</sup> -1.7X10 <sup>9</sup> )	0.9
>2 Log DNA reduction at 2 wks	8/10 (80%)	1/13 (8%)	0.001
HBeAg status	6 (60%)	9 (53%)	0.5
Genotype D:A	8 (80%) vs. 2 (20%)	15 (88%) vs. 2 (12%)	0.6
UGIE (grade of varix)	1 (0-2)	2 (0-3)	0.05
HVPG (mm Hg) (n=14, 8:6)	13.2 (9.5-20.0)	19 (15.0-21.0)	0.03
HAI (N=14, 8:6)	7 (4-9)	7.5 (4-15)	0.4
Fibrosis (n=14, 8:6)	2.5 (2-4)	4 (2-6)	0.2
Treatment with tenofovir	8 (80%)	6 (35%)	0.03
Encephalopathy	1 (10%)	1 (5%)	0.5

All values are expressed as median (range) or number (%).

Abbreviations: WBC, white blood cells; INR, international normalized ratio; ALT, alanine aminotransferase; UGIE, upper gastrointestinal endoscopy; HVPG, hepatic venous pressure gradient; HAI, histology activity index.

reduction of HBV DNA levels and concomitant improved patient survival. It is important to note that most patients had severe jaundice, with a median bilirubin of 23.2 (8-41) mg/dL. The results are quite pertinent as none of the patients was a previously diagnosed case of HBV and had presented for the first time to us with reactivation.

Previous studies have suggested that LAM treatment was not effective in improving hepatic function and conferring survival advantage among severe reactivation of HBV with jaundice as compared to placebo.<sup>8-11</sup> This was one of the reasons that we did not use LAM to compare its efficacy against TDF. It could be argued that in patients with ACLF due to reactivation of HBV, an antiviral should have been added. However, because of the poor results with LAM as reported by others as well as in our own previous study,<sup>15</sup> we wanted to first assess the efficacy of a potent antiviral like TDF against placebo and study the natural history of the untreated patients.

However, in our study TDF therapy in ACLF patients significantly reduced the serum HBV DNA levels ( $P < 0.01$ ), improved the CTP and MELD score ( $P$  value 0.01), and thereby reduced mortality ( $P$  value 0.03).

The high mortality rate of these patients despite LAM treatment could be related to the delayed commencement (median time 7-30 days) of the weak antiviral properties of LAM and consequent viral suppression during the initial 4-8 weeks of high viral replication. The pathogenesis of severe acute exacerbation

is believed to be associated with vigorous immune response, which results in severe hepatic necroinflammation and finally hepatic decompensation. Suppressing the HBV DNA replication with TDF, which is more potent and has a more rapid onset of action than most other antiviral agents, was found to be quite effective in the ACLF patients. It is quite likely that TDF therapy inhibited the ongoing necroinflammation and might even have permitted hepatic regeneration. Our data convincingly shows that a rapid reduction in HBV DNA was associated with improvement in indicators of injury and even survival.

After a 3-month follow-up, one of eight (12.5%) patients lost the surface antigen in the TDF-treated group, whereas none in the placebo group. Similarly, three of five (60%) patients lost the HBeAg in the TDF, whereas none in placebo group. Both these serological responses were much higher as compared to previous studies.<sup>16</sup> This may be explained by the vigorous immune response of the body to clear the virus that was supplemented by the antiviral actions of TDF. The other advantage of TDF is the low frequency of viral mutations on prolonged use.<sup>17</sup> The drug, therefore, could be recommended for prolonged use.

Univariate analysis showed low platelets, more than 2 log HBV DNA reduction within 2 weeks, large esophageal varices, high HVPG, and treatment with TDF as significantly associated with mortality. In a previous study<sup>9</sup> low platelet count and high serum bilirubin were found to be independent predictors of mortality.

However, on multivariate analysis, only 2 log HBV DNA reduction within 2 weeks was found to be independent baseline predictor of mortality. This underscores the utility of rapid and potent viral suppression. This information also has great clinical relevance in determining the need and selection of patients for urgent liver transplantation. Because the chances of survival are significantly reduced in patients if their HBV DNA is not decreased at 2 weeks, high priority should be given to an early liver transplantation.

There were a few limitations in our study. Due to the lack of availability of the liver transplantation facility in our institute at that time, a decision for early enrollment for the life-saving treatment option could not be offered to the patients. This could have also helped us in identifying the predictive parameters for disease progression and mortality better. Second, a larger sample size could also have helped in better identifying the predictors of mortality, especially in defining them with respect to disease course and respective organ failure. Large prospective studies would be worthwhile in addressing these issues.

In conclusion, antiviral treatment with TDF significantly reduces HBV DNA levels and improves the CTP and MELD scores and thereby improves survival in patients with ACLF. TDF reduced within 2 weeks two or more log HBV DNA in two-thirds of the patients and such a rapid reduction independently predicted 3-month survival. TDF was well tolerated during whole study period. It would be worthwhile to investigate whether a combination of more than one antiviral agent can achieve more than 2 log reduction within 1-2 weeks in all patients and this could result in improved survival in this group of seriously ill patients.

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