

Observational study on the response of tenofovir monotherapy versus tenofovir plus telbivudine dual therapy in patients with hepatitis B virus related acute on chronic liver failure

Abul H Manik¹, Debraj Malakar², Sheikh M Noor-E-Alam³, Mamun A Mahtab³, Dulal C Das³, Ayub A Mamun³, Sakirul Khan⁴, Mohammad Fazle Akbar⁵, Zakiur Rahman⁶, Salimur Rahman¹

¹Department of Hepatology, Dhaka Medical College Hospital, Dhaka, ²Civil Surgeon Office, Munshiganj, ³Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, ⁴Department of Anatomy and Embryology, ⁵GDepartment of Gastroenterology and Metabolism, Ehime University Graduate School of Medicine, Ehime, Japan, ⁶Department of Primary Care and Microbiology, Brahminbaria Medical College, Brahminbaria, Bangladesh

ABSTRACT

Introduction: HBV is major health problem globally due to complications, including ACLF, cirrhosis and hepa-to-cellular carcinoma. ACLF due to exacerbation of CHB is associated with 30%-70% mortality. Reduction of HBV-DNA is therefore a target of therapy in ACLF-B. **Methods:** Patients with spontaneous reactivation of HBV [(ALT >5×ULN or >2× baseline) and HBV-DNA >20,000 IU/ml] were randomized to Tenofovir mono therapy (300 mg/day) or Tenofovir plus Telbivudine (600 mg/day) dual therapy with standard care. Clinical and biochemical parameters were evaluated at baseline, 1 week, 4 weeks and at 3 months. Virological evaluation was done at baseline and at 3 months. Primary end points were reduction of HBV-DNA and resolution of ascites, as applied. Secondary end point was reduction of liver related complications, therapy related adverse effects and survival at 3 months. **Results:** 27 patients were enrolled. 15 received mono therapy with Tenofovir and 12 received dual therapy (Tenofovir plus Telbivudine). Baseline parameters in 2 groups had no significant difference. In both groups there was significant improvement of S. bilirubin, ALT, INR, CTP score and MELD score. Only MELD score showed significant improvement in patient with dual therapy at 3 months in comparison to mono therapy. 11 patients on Tenofovir mono therapy (n=15) showed undetectable HBV-DNA (91.7%) at 3 months and one patient had detectable HBV-DNA (<2,000 IU/ml). 10 patients on dual therapy (n=12) had undetectable HBV-DNA (100%). Ascites resolved in 3 patients in both groups. Patients receiving dual therapy showed significant improvement in AKI on follow up compared to those on Tenofovir mono therapy. Among 5 deaths, 3 received mono therapy with Tenofovir and 2 dual therapy. Predictors of mortality had high S. bilirubin, HBV-DNA, MELD score and CTP score. **Conclusion:** In spontaneous reactivation of HBV presenting as ACLF, combination of Telbivudine plus Tenofovir is safer with less nephrotoxicity and better outcomes.

Keywords: ACLF-B, monotherapy, telbivudine, tenofovir

Address for correspondence: Prof. Mamun Al Mahtab, Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Bangladesh. Postal Address: House # 109, Road # 4, Block # B, Banani, Dhaka-1213, Bangladesh. E-mail: shwapnil@agni.com

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Introduction

Acute on chronic liver failure (ACLF) is a disease entity that encompasses acute deterioration of liver function in patients with chronic liver disease.^[1] The term ACLF was first used in 1995 to describe a condition where two simultaneous insults to the liver, one acute on the background of a chronic liver disease, lead to rapid hepatic decompensation.^[2] The Asia-Pacific Association for the Study of the Liver (APASL) in 2009 defined ACLF as a clinical condition manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.^[2]

ACLF secondary to reactivation of chronic hepatitis B virus (ACLF-B) is a distinct condition with high mortality which can be managed with potent antiviral therapy. Lamivudine and entecavir have shown short-term survival benefits, however, drug resistance is a concern with Lamivudine. Monotherapy with tenofovir is promising for improving survivals.^[3] However, nephrotoxicity of tenofovir is a deterring factor for its uses in ACLF-B. The renoprotective effect of telbivudine has been shown and its addition to tenofovir in managing ACLF-B may, therefore, be beneficial. Combination antiviral therapy may achieve synergistic antiviral effects compared to monotherapy and achieve better hepatitis B virus deoxyribonucleic acid (HBV-DNA) suppression. Combination of a nucleoside analogue with a nucleotide analogue will also ensure that there will be no cross-resistance to HBV. Currently, however, monotherapy is recommended for ACLF-B and data of combination therapy is sparse.

Methods

ACLF patients admitted to the Department of Hepatology of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, were recruited in this study. The study protocol was approved by the Institutional Review Board (IRB) of BSMMU. They were randomized into two groups. Half of them (Group A) were selected for tenofovir and half (Group B) for telbivudine plus tenofovir. Group A patients received tenofovir 300 mg daily and group B received telbivudine 600 mg plus tenofovir 300 mg daily at least 1 hour before or 2 hours after breakfast along with standard medical care. Patients were followed up for at least 3 months. Biochemistry and hematology were monitored during the enrollment at 1st week, 2nd week, 1st month, and then, 3rd month. HBV-DNA was checked during the enrollment, and then, at 3rd month.

Qualitative data was analyzed by Chi-square test and quantitative data was analyzed by Student's t-test. Chi-square test was used to check the association between two qualitative variables. Wilcoxon rank sum test was done to compare laboratory parameters and measurements obtained during the first and last visits, thereby, assessing the effectiveness of the therapy. A statistically significant result was considered when *P* value was less than 0.05.

Results

The mean age was 41.75 ± 15.0 in tenofovir plus telbivudine group and 42.73 ± 13.67 in tenofovir group. Majority of the patients were male in both tenofovir 93.3% and telbivudine plus tenofovir 91.7% groups. Patients were distributed during enrollment according to chronic liver failure-sequential organ failure assessment (CLIF-SOFA) score. In both the groups, they had coagulation failure and liver failure. Some of them had cerebral failure, kidney failure and circulatory failure [Table 1].

During enrollment, complete blood count, liver function, INR, renal function and serum electrolytes were checked in every patient. Mean serum bilirubin was 19.30 ± 7.45 in telbivudine plus tenofovir group and 17.43 ± 8.41 in tenofovir group. Serum creatinine was 1.53 ± 0.92 in telbivudine plus tenofovir group and 0.97 ± 0.27 in tenofovir group. The mean difference was only significant ($P < 0.05$) for serum creatinine in both the groups. Other baseline investigations were not statistically significant ($P > 0.05$) [Table 2].

Anti-hepatitis B virus core antigen Immunoglobulin M (HBc IgM) was found in 55.5% study patients. Among them, 58.3% cases were in telbivudine plus tenofovir group and 53.3% in tenofovir group. Hepatitis B virus surface antigen (HBsAg) was positive in 41.7% in telbivudine plus tenofovir group and 40.0% in tenofovir group. HBV-DNA polymerase chain reaction (PCR) was done in every patient. 20000 IU/ml was the cut off HBV-DNA level to identify spontaneous reactivation of chronic hepatitis B (CHB). Telbivudine plus tenofovir group had 6 cases of $>20,000$ IU/mL HBV-DNA and 6 cases of $<20,000$ IU/mL HBV-DNA. The tenofovir group had 9 cases of $>20,000$ IU/mL HBV-DNA and 6 cases of $<20,000$ IU/mL HBV-DNA. This difference was not statistically significant between the groups [Table 3].

Both monotherapy with tenofovir and dual therapy with tenofovir plus telbivudine improved liver function tests (LFT) at the 90th day and that was statistically significant. But when compared between both groups, the improvement of LFT was not

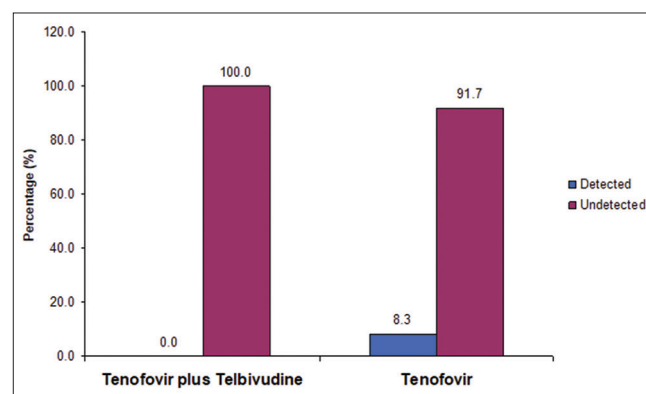


Figure 1: Reduction of HBV-DNA after therapy at 3 months in both groups

Table 1: Distribution of the study patients by organ failure between two groups

Physical examination	Tenofovir plus Telbivudine (n=12) n (%)	Tenofovir (n=15) n (%)	P
Liver failure (bilirubin >12 mg/dL)	11 (91.7%)	10 (66.7%)	0.121
Coagulation failure (INR >1.5)	12 (100.0%)	15 (100.0%)	-
Cerebral failure (hepatic encephalopathy)	3 (25.0%)	3 (23.1%)	0.813
Kidney failure (S. creatinine >1.2 mg/d)	4 (33.3%)	1 (6.7%)	0.138
Circulatory failure (DBP <70 mmHg)	1 (8.3%)	2 (13.3%)	0.681

Table 2: Comparison of baseline investigations between two groups

Baseline investigations	Tenofovir plus Telbivudine (n=12) Mean±SD	Tenofovir (n=15) Mean±SD	P
TC (cmm)	8558.3±3309.1	9125.3±4813.9	0.731 ^{ns}
Serum bilirubin (mg/dL)	19.30±7.45	17.43±8.41	0.552 ^{ns}
ALT (U/L)	214.25±152.78	357.73±222.44	0.069 ^{ns}
INR	1.98±0.34	1.90±0.36	0.576 ^{ns}
Serum albumin (gm/L)	23.94±5.01	23.76±4.12	0.918 ^{ns}
Serum creatinine (mg/dL)	1.53±0.92	0.97±0.27	0.033 ^s
Serum sodium (mmol/L)	129.08±8.49	132.40±8.38	0.319 ^{ns}
Serum potassium (mmol/L)	4.10±0.76	3.95±0.61	0.596 ^{ns}

Table 3: Distribution of the patients by HBV-DNA in two groups

HBV-DNA	Tenofovir plus Telbivudine (n=12) n (%)	Tenofovir (n=15) n (%)	P
≤20000 (IU/mL)	6 (50.0%)	6 (40.0%)	
>20000 (IU/mL)	6 (50.0%)	9 (60.0%)	
Mean±SD (Log10)	4.23±0.99	4.11±1.27	0.797
Range ()	(2.27-5.68)	(2.16-5.95)	

Table 4: Comparison of LFT between two groups after 90 days

Baseline investigations	Tenofovir plus Telbivudine (n=12) Mean±SD	Tenofovir (n=15) Mean±SD	P
Serum bilirubin (mg/dL)	3.61±2.05	2.51±1.76	0.191 ^{ns}
ALT (U/L)	45.2±21.13	59.7±17.6	0.094 ^{ns}
INR	1.33±0.19	1.31±0.15	0.817 ^{ns}
Serum albumin (gm/L)	22.85±11.11	28.36±9.16	0.217 ^{ns}
MELD score	15.17±5.24	20.70±4.37	0.015 ^s
CTP score	8.40±1.26	7.67±1.23	0.185 ^{ns}

Table 5: Tenofovir plus Telbivudine-induced improvement in S. creatinine after 90 days

S. creatinine (mg/dL)	Before treatment n (%)	After 90 days n (%)	P
Tenofovir plus Telbivudine (n=12)			
<1.5	8 (66.7%)	9 (90.0%)	
>1.5	4 (33.3%)	1 (10.0%)	
Mean±SD	1.49±0.97	1.12±0.34	0.266 ^{ns}
Tenofovir (n=15)			
<1.5	14 (93.3%)	12 (100.0%)	
>1.5	1 (6.7%)	0.0	
Mean±SD	0.91±0.17	0.81±0.13	0.143 ^{ns}

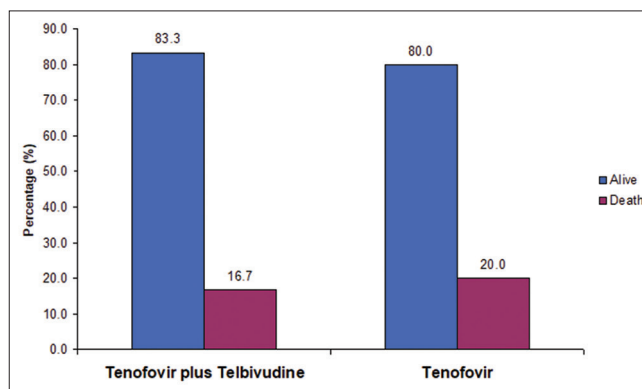


Figure 2: Outcome of patients after 90 days of antiviral therapy among the two study groups

statistically significant. Child-Pugh-Turcotte Score (CTP) scores and model for end stage liver disease (MELD) scores improved on the 90th day in both the groups. This improvement was statistically significant. However, during the comparison of CTP score between both the groups, it was not statistically significant on the 90th day. MELD score was significantly improved with tenofovir plus telbivudine therapy in comparison with tenofovir monotherapy [Table 4].

HBV-DNA reduction was observed after 3 months of antiviral therapy in both the groups. Only in one case of tenofovir group, HBV-DNA was detected on the 90th day [Figure 1].

Renal function improvement was seen on the 90th day with dual therapy. Baseline creatinine was higher in tenofovir plus telbivudine group (1.53 ± 0.92) and this improved on the 90th day after dual antiviral therapy [Table 5].

At 90 days, 22 patients were alive in total. Out of them, 83.3% of the cases were in tenofovir plus telbivudine group and 80.0% in tenofovir group. Two patients died in tenofovir plus telbivudine group and 3 patients in tenofovir group [Figure 2].

Early death (within 7 days) was experienced in four cases and another patient died after 2 months. ACLF with acute kidney injury was the predominant cause of death. One patient had multiple causes [Table 6].

Baseline high MELD and CTP scores were associated with high mortality. High-serum bilirubin and INR at baseline also predicted death. High-baseline HBV-DNA 5.18 ± 1.17 log₁₀ IU/mL was associated with high mortality [Table 7].

Table 6: Distribution of the study patients by cause of death between two groups

Cause of death	Tenofovir plus Telbivudine (n=2) n (%)	Tenofovir (n=3) n (%)
Acute kidney injury/hepatorenal syndrome	0 (0.0%)	2 (33.3%)*
Hepatic encephalopathy	0 (0.0%)	1 (33.3%)
Septicemia and circulatory failure	1 (50.0%)	1 (33.3%)
Electrolyte imbalance (hyponatremia)	1 (50.0%)	0 (0.0%)

*Multiple cause

Table 7: Comparing of variables at baseline for predicting death

Variables	Death (n=5) Mean±SD	Alive (n=22) Mean±SD	P
TC	8800.0±5643.1	8890.0±3901.2	0.966 ^{ns}
S. bilirubin	25.8±7.8	16.5±7.0	0.015
ALT	357.0±229.2	279.6±201.4	0.456 ^{ns}
S. albumin	23.4±4.3	23.9±4.6	0.812 ^{ns}
INR	2.5±0.1	1.8±0.2	<0.001*
S. creatinine	1.4±0.6	1.2±0.7	0.524 ^{ns}
HBV-DNA (Log10)	5.18±1.17	3.94±1.02	0.024*
CTP score	12.2±0.8	10.8±1.2	0.015*
MELD score	33.0±4.2	27.2±4.6	0.016*

Discussion

This study was carried out with the aim to see the survival outcome of ACLF-B at 3 months of antiviral therapy (tenofovir monotherapy or tenofovir plus telbivudine dual therapy). Tenofovir is preferred for the treatment of decompensated cirrhosis because of greater antiviral potency and a high genetic barrier to resistance.^[4] In this present study, tenofovir resulted in HBV-DNA suppression is 91.7% at 90 days. There are reports that tenofovir significantly reduced HBV-DNA level from baseline 6.64 log to 4.07 ($P < 0.05$) at day 15 and 3.04 at day 90 ($P < 0.05$).^[5] In this study, tenofovir plus telbivudine dual therapy suppressed HBV-DNA 100.0% on the 90th day. This is consistent with the findings of an Indian study.^[6]

In fact, various evolving therapies have been employed for the management of different forms of chronic liver diseases.^[7-10] Combination of drugs having additive or synergistic effect compared to monotherapy are on trial. Renoprotective effect of telbivudine has been shown in some studies. In our experience, combination of tenofovir with telbivudine lessened the risk of renal failure and improved the overall survival in ACLF-B. This finding is consistent with other experience in published literature.^[11] We analyzed various baseline clinical and laboratory variables as possible predictors of mortality. We identified serum bilirubin, HBV-DNA, MELD and CTP scores to be significantly associated with mortality. These findings are consistent with the experience of other researchers. Combination therapy was well tolerated with no safety concern. No adverse event was observed in either group.

Conclusion

It can be concluded that both groups significantly improve serum bilirubin, ALT, INR, CTP and MELD scores. Both groups

suppress HBV-DNA significantly, but there is no advantage of one over another. Combination therapy significantly improves MELD score compared to tenofovir monotherapy, but there was no survival benefit between the groups. However, both protocols were safe and effective and there is no safety-related concern. Tenofovir plus telbivudine dual therapy exhibited significant virologic and biochemical response over 3 months.

Hepatitis B poses major disease burden in the Asia-Pacific region where the management of this infection is largely carried out by the primary care physicians. In this context, this article is likely to benefit them as well.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

- Jalan R, Gines P, Olson JC, Mookerjee RP, Moreau R, Arroyo V, *et al.* Acute-on chronic liver failure. *J Hepatol* 2012;57:1336-48.
- Sarin SK, Kumar A, Almeida JA, Chawla YK, Fan ST, Garg H, *et al.* Acute-on-chronic liver failure: Consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). *Hepatol Int* 2009;3:269-82.
- Philips CA, Sarin SK. Potent antiviral therapy improves survival in acute on chronic liver failure due to hepatitis B virus reactivation. *World J Gastroenterol* 2014;20:16037-52.
- Perillo RP. Hepatitis B virus treatment: Which patients require immediate treatment. *Clin Liver Dis* 2013;2:11-4.
- Garg H, Sarin SK, Kumar M, Garg V, Sharma BC, Kumar A. Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. *Hepatology* 2011;53:774-80.
- Panda C. Telbivudine plus tenofovir in combination therapy in patients with chronic hepatitis B infection--an Indian experience. *J Assoc Physicians India* 2013;61:785-8.
- Al Mahtab M, Mohammad Fazle Akbar S, Chandra Podder D, Kumar Saha P, Jahan M, Begum L, *et al.* Relationship

between hepatitis B viral deoxyribonucleic acid load and hepatocellular carcinoma. *Euroasian J Hepatogastroenterol* 2014;4:66-7.

8. Hussain M, Al Mahtab M, Islam S, Ahmed N, Rahman S, Khan M. Therapy targeting stem cell in patients with decompensated cirrhosis of liver in a tertiary treatment care center of Bangladesh. *Euroasian J Hepatogastroenterol* 2017;7:111-2.
9. Mahtab MA, Mf Akbar S, Begum M, Islam MA , Rahim MA, Noor-E-Alam SM *et al.* Stem cell therapy for cirrhosis of liver in Bangladesh: Specific design compatible for developing country. *Euroasian J Hepatogastroenterol* 2018;8:121-5.
10. Mf Akbar S, Al-Mahtab M, I Khan S. Nature of host immunity during hepatitis B virus infection and designing immune therapy. *Euroasian J Hepatogastroenterol* 2018;8:42-6.
11. Jindal A, Kumar M, Sarin SK. A randomized comparative open label trial of tenofovir monotherapy versus tenofovir plus telbivudine dual therapy in spontaneous reactivation of hepatitis B. *J Viral Hepatitis*; 2015;22:19-35.