# Clinical Events After Cessation of Lamivudine Therapy in Patients Recovered From Hepatitis B Flare With Hepatic Decompensation

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**BACKGROUND & AIMS:** **Before guidelines were issued, many patients with hepatitis B flare and hepatic decompensation had discontinued lamivudine therapy instead of indefinite therapy. We investigated their outcomes.**

**METHODS:** **We performed a retrospective cohort study of 263 consecutive patients with chronic hepatitis B (94 with cirrhosis) who recovered from a flare of hepatitis with hepatic decompensation and were followed after cessation of lamivudine therapy. Clinical events that occurred during the follow-up period were assessed by chart review and analysis of results from retrospective assays.**

**RESULTS:** **The mean duration of lamivudine therapy was 12.1 ± 8.6 months; data were collected from patients for 89.1 ± 38.7 months after therapy ended. In the first year off therapy, 29.9% of patients had clinical relapse, 16.2% had hepatitis flares, and 8.2% had hepatic decompensation. There was no significant difference in the incidence of hepatic decompensation between patients with and without cirrhosis. Hepatocellular carcinoma developed in 14 patients 20–109 months after cessation of therapy, with 5-year cumulative incidence of 5.2% in patients with cirrhosis. Three patients with cirrhosis died of hepatic decompensation 38–76 months after cessation of therapy (5-year cumulative mortality, 2.9%). Multivariate analyses showed that men were more likely than women to have recurrence of hepatic decompensation (hazard ratio [HR], 4.339; $P = .014$). Liver cirrhosis (HR, 2.766; $P = .041$) and age (HR, 1.054; $P = .023$) increased risk for hepatocellular carcinoma.**

**CONCLUSIONS:** **Cessation of lamivudine therapy after recovery from hepatitis B flare with decompensation was safe for most patients. However, 8.2% develop decompensation within 1 year and can be rescued by timely retreatment. With close monitoring, the stopping strategy could be a feasible alternative to indefinite therapy, especially in low resource settings.**

*Keywords:* Antiviral Therapy; Cirrhosis; Liver Cancer; Nucleos(t)ide Analog.

Chronic hepatitis B virus (HBV) infection has potential adverse outcomes including hepatic decompensation (HD), cirrhosis, and hepatocellular carcinoma (HCC).[1] Hepatitis flare with HD in chronic hepatitis B (CHB) patients is a serious complication with high mortality,[2] so that requires immediate nucleos(t)ide analog (Nuc) therapy[3–6]; most experts recommend indefinite or even lifelong therapy.[4,6] Of note, indefinite or lifelong Nuc therapy has problems of concern, including cost, lack of long-term safety data beyond 5–10 years, negligible rate of hepatitis B surface antigen (HBsAg) loss,[7] and emergence of drug resistance.[8] Furthermore, the 1-year Nuc persistent rate was only 73.4% in new patients,[9] and the medication possession rate ≥80% was only 53.7% in patients treated with entecavir (ETV) or tenofovir (TDF).[10] This may bring CHB patients to unpredictable hazards. Weighted against all these potential problems, Asian Pacific guidelines have recommended that cessation of Nuc therapy can be considered in hepatitis B e antigen (HBeAg) negative patients if undetectable HBV DNA has been documented on 3 occasions at least 6 months apart.[5] By using this stopping rule, we have shown that ETV therapy can be safely discontinued in HBeAg-negative CHB patients, even with compensated cirrhosis, under proper off-therapy

***Abbreviations used in this paper:*** **ADV, adefovir; AFP, alpha fetoprotein; ALT, alanine aminotransferase; anti-HBe, hepatitis B e antibody; cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; δPT, prolongation of prothrombin time; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HD, hepatic decompensation; HDV, hepatitis delta virus; HR, hazard ratio; LAM, lamivudine; Nuc, nucleos(t)ide analogue; TDF, tenofovir; ULN, upper limit of normal; US, ultrasonography.**


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monitoring.[11] Whether this stopping strategy is applicable to patients with HD remains to be studied.

Before the Asian Pacific stopping rule was issued, lamivudine (LAM) was widely used and was discontinued in most of our patients after recovery from HD because of the concerns about drug resistance and cost/reimbursement issues. These patients were followed up off-therapy. Their medical records were available for reviewing what happened after cessation of LAM therapy. Considering that the dogma of indefinite/lifelong Nuc therapy in patients with HD was based on expert opinion rather than solid scientific evidence, we conducted a retrospective cohort study to examine the off-LAM events with survival analyses in CHB patients recovered from hepatitis flare with HD.

## Patients

Excluding patients with other causes of liver disease such as hepatitis C virus (HCV) or hepatitis delta virus (HDV) infection, alcohol, autoimmune, and malignancy and those with pregnancy or breastfeeding, severe pancreatitis, prior liver transplantation, or need for mechanical ventilation, 318 consecutive CHB patients ($\geq$18 years old) who had hepatitis flare with HD were treated with 100 mg LAM daily in our unit. Forty-one of them died, mostly within 6 months after starting LAM therapy, and 14 underwent liver transplantation. The remaining 263 patients recovered during LAM therapy and were followed up after cessation of therapy (Figure 1). HD was defined as a severe clinical syndrome with hepatic function impairment as indicated by jaundice and a prolonged prothrombin time ($\delta$PT) and/or occurrence of ascites/encephalopathy in patients with or without cirrhosis, as described elsewhere since 1980s.[12,13]

LAM treatment was discontinued in all patients with clinical recovery (normalization of prothrombin time and bilirubin level) and at a time point at the discretion of their physician, usually within reimbursement allowance (18 months before November 1, 2009, 36 months thereafter). Then the patients were followed up every 1–6 months, more frequently within the first 3 months and when alanine aminotransferase (ALT) became abnormal. Follow-up studies included clinical assessment, liver biochemical tests, and serum HBV DNA when appropriate. Alpha fetoprotein (AFP) and abdominal ultrasonography (US) were performed every 3–6 months for HCC surveillance. The primary events of concern were life-threatening safety issues including HD and mortality. The secondary events of concern included clinical relapse, hepatitis flare, or HCC. Retreatment was instituted when indicated.

Clinical relapse was defined as virologic relapse (serum HBV DNA $>$2000 IU/mL) plus ALT elevation greater than 2 times upper limit of normal (ULN).[5] Hepatitis flare was defined as abrupt rise of serum ALT to level greater than 5$\times$ ULN.[14] Cirrhosis was diagnosed by histologic findings or repeated US findings consistent with cirrhosis, supplemented with clinical features such as varices and thrombocytopenia, as described elsewhere.[15] HCC was diagnosed by histology/cytology or US findings plus high AFP level or imaging findings of enhanced arterial contrast uptake followed by washout in the portal venous phase and equilibrium phase (dynamic computed tomography or magnetic resonance imaging), as described in generally accepted guidelines.[16] HCC that developed within 1 year after cessation of therapy was considered as preexisting and therefore was excluded as an off-therapy event.[17]

## Methods

Liver biochemical tests were performed by using routine automated techniques. Serum HBsAg, HBeAg/anti-HBe, and anti-HDV were assayed by using radioimmunoassay kits (Abbott Diagnostics, North Chicago, IL). Anti-HCV was assayed by using a commercial enzyme immunoassay (Abbott Diagnostics). HBV genotype was determined retrospectively by using polymerase chain reaction–restriction fragment length polymorphism of the surface gene of HBV. Serum HBV DNA level was measured by using the hybrid Capture II assay (Digene Corp, Gaithersburg, MD; lower limit of detection, $1.4 \times 10^5$ copies/mL) before April 2007. Because Digene assay reported HBV DNA level in copies/mL, we divided the levels by a factor of 5 to become IU/mL in the analyses of this study. Ultrasensitive polymerase chain reaction assay (Cobas Amplicor HBV Monitor, lower limit of detection, 300 copies/mL; or the Roche COBAS TaqMan HBV Test, lower limit of detection, 69 copies/mL, or 12 IU/mL; Roche Diagnostics, Pleasanton, CA) was used for stored serum samples. Gender, age, HBV DNA level, HBeAg status, HBV genotype, presence of cirrhosis, ALT, bilirubin, $\delta$PT, albumin, creatinine, as well as treatment duration were used for comparisons where appropriate.

### *Statistics*

The follow-up period was calculated from cessation of LAM therapy until the last visit of the patient or when an event occurred. The follow-up period was censored when treatment was resumed in the secondary analyses. Events in patients with and without cirrhosis were compared. All statistical analysis was performed by using Statistics Package for Social Science software (version 18.0; SPSS Inc, Chicago, IL). To compare between groups, continuous variables were analyzed by using Student $t$ test or Mann–Whitney $U$ test, whereas categorical variables were analyzed by using $\chi^2$ test or Fisher exact test when appropriate. Kaplan–Meier and univariate Cox regression were used to assess the relationship of various variables to the events. Variables found to be significant were included in multivariate Cox regression models. Statistical significance was defined at the 5% level on the basis of two-tailed test of the null hypothesis.

The study was approved by the hospital institutional review board.