ORIGINAL RESEARCH

Entecavir monotherapy versus de novo combination of lamivudine and adefovir for compensated hepatitis B virus-related cirrhosis: a real-world prospective multicenter cohort study

Xiaoning Wu,[1–3,]* Jialing Zhou,[1–3,]* Wen Xie,[4] Huiguo Ding,[5] Xiaojuan Ou,[1–3] Guofeng Chen,[6] Anlin Ma,[7] Xiaoyuan Xu,[8] Hui Ma,[9] Youqing Xu,[10] Xiaoqing Liu,[11] Tongtong Meng,[1–3] Lin Wang,[1–3] Yameng Sun,[1–3] Bingqiong Wang,[1–3] Yuanyuan Kong,[1–3] Hong Ma,[1–3] Hong You,[1–3] Jidong Jia[1–3]

[1]Liver Research Centre, Beijing Friendship Hospital, Capital Medical University, Beijing, China; [2]Beijing Key Laboratory of Translational Medicine in Liver Cirrhosis, Beijing, China; [3]National Clinical Research Center of Digestive Diseases, Beijing, China; [4]Liver Fibrosis Centre, Beijing Ditan Hospital, Capital Medical University, Beijing, China; [5]Department of Digestive Diseases, Beijing Youan Hospital, Capital Medical University, Beijing, China; [6]Liver Fibrosis Centre, Beijing 302 Hospital, Beijing, China; [7]Department of Infectious Diseases, China-Japan Friendship Hospital, Beijing, China; [8]Department of Infectious Diseases, Peking University First Hospital, Beijing, China; [9]Liver Research Centre, Peking University People's Hospital, Beijing, China; [10]Department of Digestive Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; [11]Department of Infectious Diseases, Peking Union Medical College Hospital, Beijing, China

*These authors contributed equally to this work

Correspondence: Jidong Jia; Hong You
Beijing Friendship Hospital, Capital Medical University, 95 Yong'an Road, Xicheng, Beijing 100050, China
Email jia_jd@ccmu.edu.cn; youhong30@sina.com

Background: De novo combination of lamivudine (Lam) and adefovir (Adv) was not rarely used in clinical practice. However, head-to-head comparisons of entecavir (Etv) monotherapy with this combination in hepatitis B virus (HBV)-related compensated cirrhosis patients are unavailable. This study aimed to compare the efficacy and safety of Etv monotherapy with combination therapy in patients with HBV-related compensated liver cirrhosis.

Methods: Treatment-naïve patients with HBV-related compensated liver cirrhosis were recruited to receive either Etv monotherapy or a de novo combination of Lam and Adv. Data were collected at baseline and every 6 months thereafter.

Results: A total of 578 patients (485 in Etv group, 93 in combination group) were included. Baseline characteristics were comparable between the two groups. At the end of 1, 2, and 3 years, HBV DNA was undetectable in 82.7%, 96.2%, and 94.3% of patients in the Etv group and 88.9%, 81.7%, and 84.6% in the combination group, respectively (all P>0.05). The cumulative virological breakthrough rate at 1, 2, and 3 years was 2.7%, 6.7%, and 9.8% in the Etv group and 2.9%, 13.3%, and 32.2% in the combination group, respectively (P=0.003). After propensity-score adjustment for age, sex, and baseline HBeAg, ALT, and total bilirubin, virological breakthrough was higher in the de novo combination of Lam and Adv (HR 2.83, 95% CI 1.37–5.86; P<0.01). The cumulative rate of liver-related events, including decompensation and hepatocellular carcinoma, at 1, 2, and 3 years was 2.9%, 4.2%, and 6.1% in the Etv group and 2.2%, 2.2%, and 6.7% in combination group, respectively (P=0.83). Biochemical response and serological response were similar between the groups.

Conclusion: Etv treatment had less virological breakthrough and potentially higher HBV-DNA suppression than de novo combination of Lam and Adv during 3 years in treatment-naïve HBV-related compensated liver cirrhosis.

Keywords: entecavir, de novo combination, lamivudine, adefovir, compensated HBV-related cirrhosis, real-world, virological breakthrough

Introduction

In 2015, 257 million people worldwide were living with chronic hepatitis B virus (HBV) infection, with an estimated 68% of them residing in the African and the Western Pacific regions.[1] Untreated chronic HBV infection can progress to life-threatening complications, such as decompensated liver cirrhosis and hepatocellular carcinoma (HCC).

Timely and effective antiviral therapy for high-risk patients, such as those with cirrhosis, is an important measure to reduce HBV-related morbidity and mortality.

Patients with compensated HBV-related liver cirrhosis are at high risk of developing liver-related events (LREs) such as ascites, variceal bleeding, encephalopathy, and HCC,[2–4] especially those with active viral replication. Therefore, antiviral therapy should be initiated immediately after cirrhosis is diagnosed if the patient has active HBV replication.

Antiviral therapy with potent and low-resistance nucleos(t)ide analogues (NAs), such as entecavir (Etv) or tenofovir disoproxil fumarate (TDF), has been recommended by major international guidelines.[5] However, in China Etv was much more expensive than lamivudine (Lam) or adefovir (Adv) dipivoxil until a couple of years ago. Furthermore, TDF was not approved for HBV until 2014 and eight to ten times as expensive for HBV than for HIV until 2017, with Lam and Adv being the only reimbursable HBV medication in many provinces of China.[6] As a result, unpreferred antiviral drugs, such as Lam and Adv, have been widely used in China. Studies have shown that rescue therapy with an Adv add-on to Lam is more effective than or at least as equally effective as switching to Etv in patients with Lam resistance in noncirrhotic and cirrhotic chronic hepatitis B (CHB).[6–9] However, the efficacy and safety of Etv monotherapy versus a de novo combination of Lam and Adv in patients with HBV-related compensated cirrhosis has not been verified. Therefore, we initiated this large-cohort study in 2012 with the aim of comparing the efficacy and safety of de novo combination therapy with Lam and Adv vs Etv monotherapy in patients with HBV-related compensated cirrhosis.

Methods
Study design and population
This was a real-world, prospective, multicenter cohort study conducted across nine centers in Beijing, China from June 2012 to June 2017. The study was conducted in accordance with the ethical principles enshrined in the Declaration of Helsinki and complied with good clinical practice guidelines and applicable local regulatory requirements. The protocol, patient-information sheets, and consent forms were approved by the Medical Ethics Committee of Beijing Friendship Hospital, Capital Medical University (BJFH-EC/2013–067). The trial is registered at ClinicalTrials.gov as NCT01720238.

As reported previously,[10] treatment-naïve patients aged 18–70 years who presented with HBV-related compensated cirrhosis were eligible for recruitment if they had an HBV-DNA level >2×10³ IU/mL (for HBeAg-positive patients) or >2×10² IU/mL (for HBeAg-negative patients). Cirrhosis was defined clinically as at least two of the following four criteria being met: 1) imaging (ultrasonography, contrast-enhanced computed tomography [CT], or magnetic resonance imaging [MRI]) findings of surface irregularity and texture echogenicity or nodularity; 2) platelet (Plt) count <100×10⁹/L with no other interpretation; 3) serum albumin (Alb) <35.0 g/L or international normalized ratio >1.3 (prothrombin time prolonged >3 seconds); and 4) liver-stiffness measurement (LSM) >12.4 kPa (in patients with ALT levels <5× upper limit of normal).

Patients were excluded if they had any of the following: 1) history of decompensated cirrhosis, including ascites, hepatic encephalopathy, variceal bleeding, or other complications of decompensated cirrhosis or HCC; 2) allergy to Etv, Lam, or Adv or their components, or patients considered not suitable for medications used in this study; 3) coinfection with HCV or HIV, with alcoholic, autoimmune, genetic, drug-induced, and severe nonalcoholic fatty-liver disease, or any other chronic liver diseases; 4) baseline serum AFP level >100 ng/mL and suspected malignant lesion on imaging, or AFP level >100 ng/mL for 3 consecutive months; 5) serum creatinine >1.5× upper limit of normal; 6) presence of other uncured malignant tumors; 7) severe diseases of the heart, lung, kidney, brain, blood system, or other organs; 8) severe neurological or psychological disease (epilepsy, depression, mania, or schizophrenia); and 9) patients not suitable for the study for any other reason.

Treatment allocation
Treatment-naïve patients with HBV-related compensated cirrhosis were treated with Etv (0.5 mg/day) monotherapy or a de novo combination of Lam (100 mg/day) and Adv (10 mg/day; taking both medications from the very beginning of antiviral therapy) at their own discretion after detailed explanation of the pros and cons of the two choices.

Follow-up and clinical evaluation
Patients were evaluated at baseline and every 6 months for 3 years. Clinical symptoms, physical examination findings, adverse events, and concurrent medications were recorded at each visit. Complete blood count, HBV DNA, liver-function tests, creatinine, AFP, prothrombin time, LSM, and liver ultrasonography were performed at baseline and every 6 months. HBsAg and HBeAg levels were measured once a year. HBV DNA was measured with a Cobas TaqMan HBV test (Roche Molecular Systems, Branchburg, NJ, USA) with a detectable level of 20 IU/mL. The AST:Plt ratio index (APRI) was calculated as an indicator of liver fibrosis as previously reported.[11] LSM was performed with a FibroScan 502 (Echosens, Paris, France) following the manufacturer's

instructions. LSM was considered reliable only if at least ten successful measurements were obtained with a success rate ≥60% and an IQR:median ratio ≤0.30.

CT or MRI was performed in patients with high suspicion of HCC. Virological response, biochemical response, serological response, and adverse events were assessed every 6 months. "HBV undetectable" was defined as <200 IU/mL. "Primary nonresponse" was defined as less than a 2 $\log_{10}$ decrease in serum HBV DNA after 6 months of therapy. "Suboptimal response" was defined as a decrease in HBV DNA of more than 2 $\log_{10}$ IU/mL but still detectable after six months of therapy. "Virological breakthrough" was defined as increase in HBV DNA from nadir by more than 1 $\log_{10}$ IU/mL on therapy or increase to >200 IU/mL from ≤200 IU/mL. Also, we defined "stepwise response" as a gradual decrease in but still detectable HBV DNA after at least 12 months of therapy in compliant patients. Both primary nonresponders and virological breakthrough patients were recommended to switch to TDF 300 mg per day as rescue therapy.

The cumulative probability of LREs (development of decompensated cirrhosis and HCC) was evaluated for 3 years. Decompensated cirrhosis was defined as presence of ascites, hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, or hepatorenal syndrome. HCC was confirmed by at least two radiological studies, such as contrast-enhanced CT, MRI, or angiography. Serious adverse events were reported to the Medical Ethics Committee within 24 hours of notification to the investigator.

Statistical analyses

Since decisions on the medication were based on the discretion of the patients and their doctors, a propensity score (PS) may be applied if the final sample size were unbalanced between two groups. Continuous variables are expressed as mean ± SD or median (range), as appropriate. Qualitative and quantitative between-group differences with respect to categorical variables were analyzed using χ^2 tests. The cumulative incidence of hepatic decompensation and HCC was calculated and plotted with Kaplan–Meier's method and between-group differences assessed with log-rank tests. $P<0.05$ was considered statistically significant. Data analyses were performed with SPSS version 20.0.

Results
Demographic data and baseline characteristics

A total of 578 treatment-naïve patients with compensated cirrhosis were enrolled in this study. Of these, 485 (84%) were treated with Etv and 93 with a de novo combination of Lam and Adv (Figure 1). The two groups were comparable with respect to baseline demographic characteristics, HBV-DNA level, HBeAg positivity, biochemical tests, AFP, LSM, Child–Turcotte–Pugh score, and model for end-stage liver-disease score (Table 1).

Virological response

A dramatic decrease in HBV-DNA level was observed after 6 months of treatment ($P<0.05$, repeated measurement). HBV DNA–undetectable rates at years 1, 2, and 3 were 82.7% (286 of 346), 96.2% (252 of 262), and 94.3% (132 of 140) for Etv monotherapy, and 88.9% (64 of 72), 81.7% (49 of 60), and 84.6% (22 of 26) for the Lam and Adv combination, respectively ($P>0.05$ for all). Cumulative virological response analysis showed similar HBV DNA–undetectable rates in the two groups ($P=0.96$, Figure 2). None of the following variables were independent predictors of HBV DNA–undetectable status after treatment: age, sex, baseline HBeAg status, HBV-DNA level, Child–Turcotte–Pugh score, and treatment allocation (data not shown).

A total of 41 patients (7.1%) exhibited virological breakthrough: 27 patients (5.6%) on Etv monotherapy and 14 (15.1%) on the Lam and Adv combination. Virological breakthrough rates at years 1, 2, and 3 were 2.7% (nine of 333), 1.5% (four of 265), and 1.5% (two of 137) in Etv monotherapy and 2.9% (two of 69), 6.6% (four of 61), and 12.0% (three of 25) in Lam and Adv combination, respectively. Cumulative virological breakthrough-rate analysis showed less virological breakthrough for Etv monotherapy than de novo Lam and Adv combination ($P=0.003$, Figure 3).

We also used multivariate conventional Cox regression. After adjustment for age, sex, baseline HBeAg, ALT, and total bilirubin (TBil), the de novo combination of Lam and Adv was the independent risk factor in virological breakthrough (HR 2.80, 95% CI 1.37–5.79; $P<0.01$). As there was skewed distribution of sample size between the two groups, we also calculated a PS using age, sex, HBeAg, ALT, and TBil at baseline using a logistic regression model. Then we used multivariate conventional Cox regression, and HRs were adjusted for the PS. Consistent results were found on the PS-adjusted Cox regression model, and treatment was still an independent influential factor in HBV-DNA breakthrough (HR 2.83, 95% CI 1.37–5.86; Table 2).

Among those with virological breakthrough, 19 (70.4%) patients on Etv monotherapy and eleven (78.6%) on the Lam and Adv combination spontaneously reverted to HBV DNA–undetectable status at the subsequent 6-monthly visit
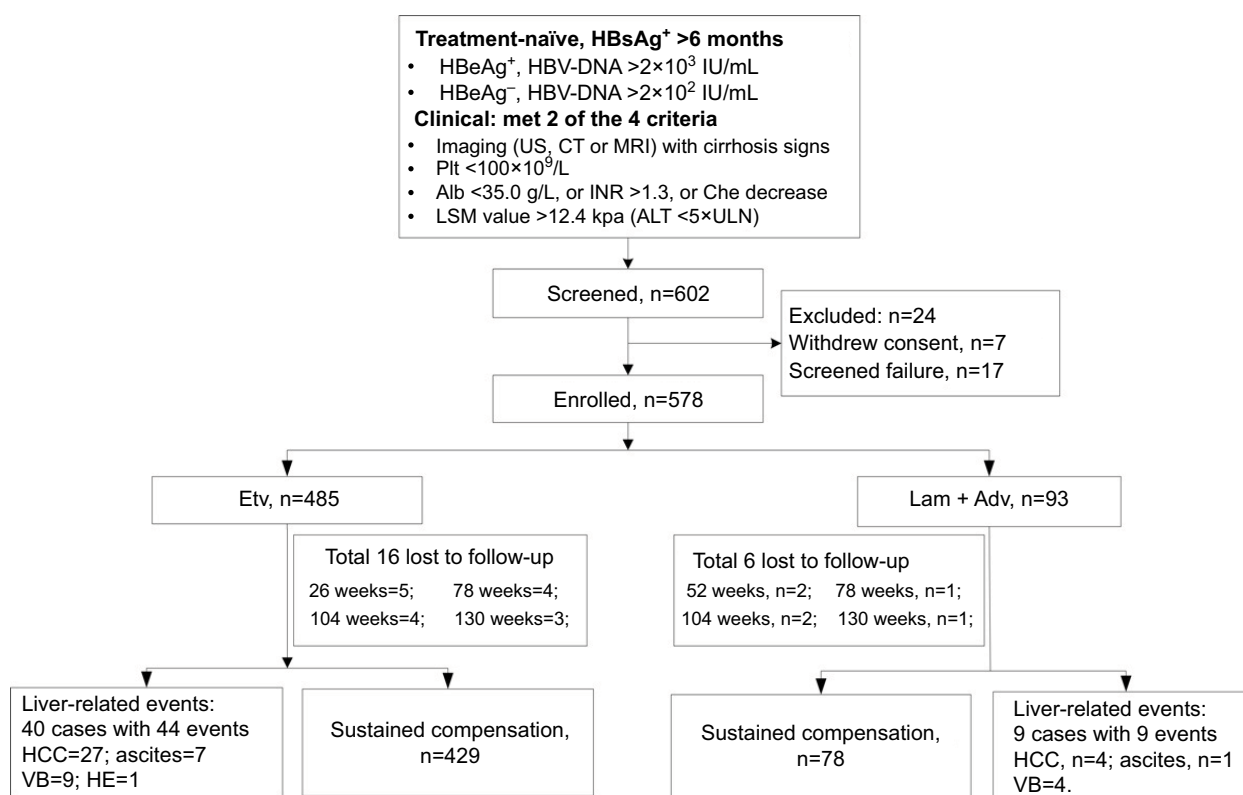
Figure 1 Flowchart of patient enrollment and follow-up.
Notes: All patients enrolled were allocated into Etv monotherapy or de novo combination of Lam plus Adv treatment, according to the patients' final decision after fully neutral introduction of the doctor. Three cases were concurrent of ascites and VB, one case was concurrent of ascites and HCC in Etv group.
Abbreviations: HBV, hepatitis B virus; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; Plt, platelet; Alb, albumin; INR, international normalized ratio; LSM, liver-stiffness measurement; Che, cholinesterase; Etv, entecavir; Lam, lamivudine; Adv, adefovir; HCC, hepatocellular carcinoma; VB, variceal bleeding; HE, hepatoencephalopathy.

Table 1 Demographics and baseline characteristics of 578 patients with HBV-related compensated cirrhosis

	Etv (n=485)	Lam + Adv (n=93)	*P*-value
Age, years	47.3±11.1	47.8±10.6	0.71
Male, n (%)	352 (72.6%)	69 (74.2%)	0.85
HBeAg-positive, n (%)	256 (52.8%)	51 (54.8%)	0.81
HBV DNA, log IU/mL	4.11 (2.6–6.0)	4.24 (2.4–6.1)	0.66
Platelets, ×10⁹/L,	98 (72–141)	93 (64–140)	0.36
ALT, U/L	53.0 (31.8–97.5)	48.0 (33.0–80.0)	0.53
AST, U/L	47.3 (31.9–79.2)	49.3 (34.0–49.3)	0.89
Albumin, g/L	40.3 (35.0–44.2)	40.7 (35.7–45.2)	0.53
Bilirubin, µmol/L	18.7 (14.2–27.8)	18.9 (14.7–27.4)	0.97
Cholinesterase, kU/L	5.08 (3.02–6.82)	4.30 (1.56–6.90)	0.43
INR	1.11 (1.03–1.21)	1.09 (1.01–1.18)	0.43
Creatinine, µmol/L	71.4 (61.2–80.6)	69.6 (64.5–81.5)	0.60
AFP, ng/mL	8.2 (3.9–29.4)	7.1 (3.4–21.5)	0.28
LSM, kPa	18.5 (13.9–27.0)	17.3 (12.0–27.5)	0.33
CTP score A, n (%)	401 (82.7%)	79 (84.9%)	0.59

Abbreviations: HBV, hepatitis B virus; Etv, entecavir; Lam, lamivudine; Adv, adefovir; INR, international normalized ratio; LSM, liver-stiffness measurement; CTP, Child–Turcotte–Pugh.

without any change in treatment regimen. Rescue therapy was initiated in three patients (11.1%) on Etv monotherapy and two patients (14.3%) on the Lam and Adv combination. All patients who received rescue therapy achieved HBV DNA–undetectable status. Five patients (51.9%) in the Etv monotherapy group and one (7.1%) in the Lam + Adv group discontinued follow-up, due to withdrawal of informed consent.
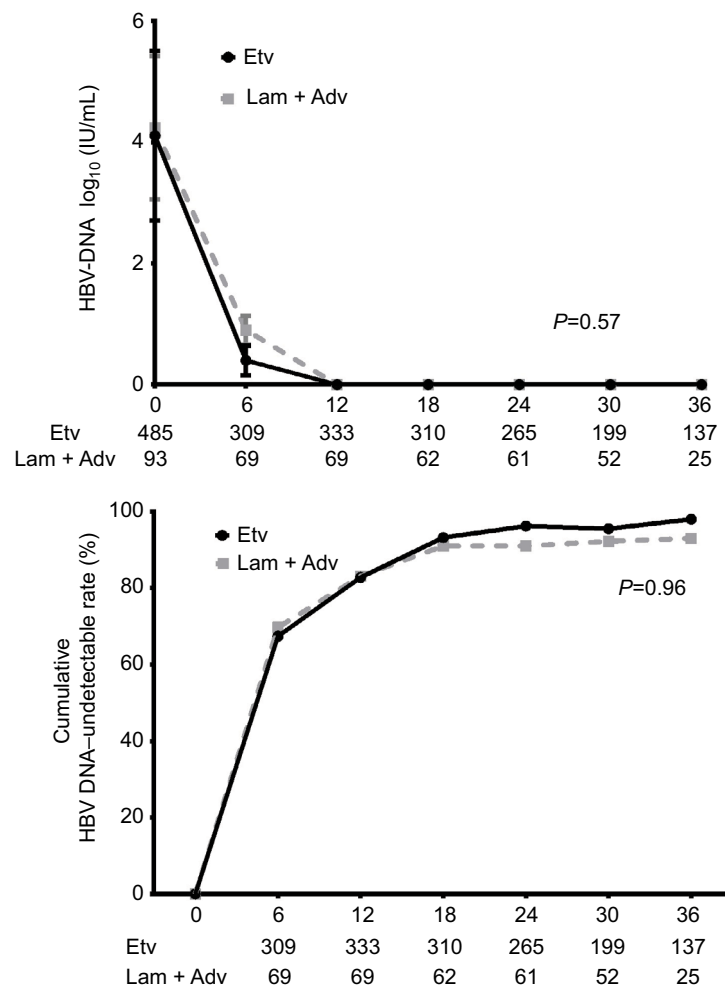
Figure 2 Virological response in cirrhotic patients treated with Etv monotherapy or de novo combination of Lam plus Adv.
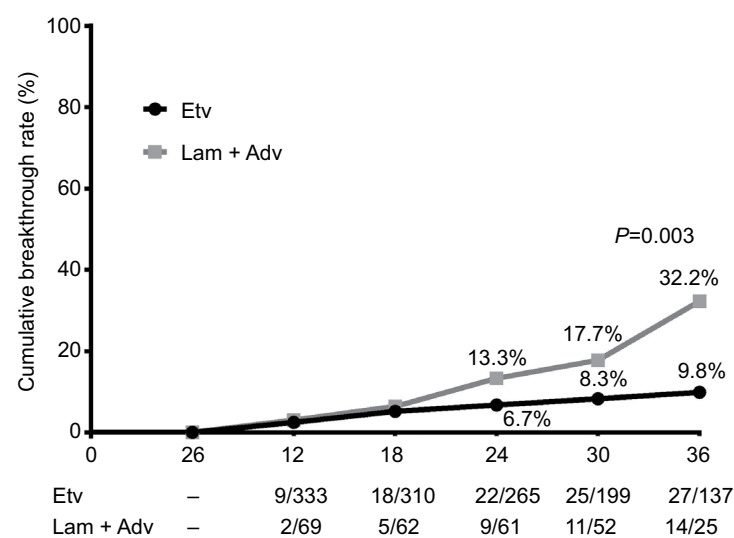**Abbreviations:** Etv, entecavir; Lam, lamivudine; Adv, adefovir.

Figure 3 Cumulative virological breakthrough rate.
Abbreviations: Etv, entecavir; Lam, lamivudine; Adv, adefovir.

Table 2 Factors in virological breakthrough between the two groups

	Cox regression model				Adjustment	Cox regression model (PS)	
	Unadjusted HR (univariate)	**P-value**	**Adjusted HR (multivariate)**	**P-value**		**Adjusted HR**	**P-value**
Age, years	0.998 (0.971–1.026)	0.90	0.998 (0.966–1.032)	0.92	PS	115.558 (0–740170000)	0.55
Sex	0.941 (0.480–1.845)	0.86	0.828 (0.380-1.804)	0.64			
HBeAg, +/–	1.968 (0.968–3.998)	0.06	2.026 (0.951–4.315)	0.07			
ALT, U/L	0.999 (0.998–1.001)	0.53	1.000 (0.998–1.001)	0.73			
TBil, μmol/L	0.995 (0.982–1.008)	0.44	0.997 (0.983–1.010)	0.62			
Combined treatment	2.799 (1.468–5.337)	<0.01	2.797 (1.351–5.793)	0.01		2.832 (1.368–5.864)	0.01

Note: PS = $0.000027 \times age + 0.0838 \times sex + 0.1032 \times HBeAg_{baseline} - 0.00072 \times ALT_{baseline} - 0.00382 \times TBil_{baseline} - 1.6572$.
Abbreviations: TBil, total bilirubin; PS, propensity score.

Since not all patients achieved HBV DNA–undetectable status, we reviewed HBV-DNA levels in HBV DNA–positive patients after treatment. Three patterns were observed during the first 6 months of therapy: poor treatment compliance (<80% of prescribed doses taken) was observed in two patients (0.4%) in the Etv group and two (2.2%) in the Lam and Adv combination group; 2) primary nonresponders were recognized in four patients (0.8%) in the Etv group (P=0.76); and 3) suboptimal responses were found in 27 patients (5.6%) on Etv monotherapy and nine (9.7%) on the Lam and Adv combination (P=0.31).

After six months of therapy, seven patients (1.4%) in the Etv-monotherapy group were found to be stepwise responders, which is a phenomenon newly identified in this study, ie, gradual decrease in but still detectable HBV DNA after at least 12 months of therapy in compliant patients. During follow-up, three of the seven stepwise responders finally achieved HBV DNA–undetectable status.

Serological response

At years 1, 2, and 3, HBeAg loss occurred in 16.8% (20 of 119), 20.7% (18 of 87), and 33.3% (19 of 57) of patients on Etv monotherapy, and in 15.8% (three of 19), 21.4% (three of 14), and 27.3% (three of eleven) of patients on Lam and Adv combination, respectively. HBeAg-seroconversion rates at years 1, 2, and 3 were 12.6% (15 of 19), 11.5% (ten of 87), and 12.3% (seven of 57) in Etv monotherapy, and 15.8% (three of 19), 21.4% (three of 14), and 18.2% (two of eleven) in the Lam and Adv combination, respectively. Three patients in the Etv group achieved HBsAg loss, whereas there was none in the Lam and Adv combination group.

Biochemical response

Before treatment, 58.8% (340 of 578) patients had elevated ALT levels. After 6 months of antiviral therapy, ALT levels had decreased dramatically (P=0.04, repeated measurement), with no significant differences between the two groups (P=0.75, Figure 4). ALT-normalization rates at years 1, 2, and 3 were 95.6% (240 of 251), 93.5% (261 of 279), and 91.6% (263 of 278) in Etv monotherapy, and 91.5% (43 of 47), 90.2% (46 of 51), and 88.6% (47 of 53), in de novo Lam and Adv combination, respectively.

Total bilirubin (TBil) levels did not change significantly after antiviral therapy (P<0.05, repeated measurement), with no differences between the two groups (P=0.53). A significant increase in Alb level and Plt count was observed 6 months after treatment (P<0.05, repeated measurement); however, there were no significant differences between the two groups (P=0.11 and P=0.39, respectively; Figure 4).

Liver-stiffness measurement and APRI

A significant decrease in LSM and APRI was observed in both groups after 6 months of treatment (P<0.05, repeated measurement), with no significant difference between the two groups (P=0.12 and P=0.94, respectively; Figure 5).

Cumulative incidence of LREs

Overall, 49 patients (8.5%) developed LREs: 40 (8.3%) occurred on Etv monotherapy and nine (9.7%) on the Lam and Adv combination. The cumulative incidence of LREs at 1, 2, and 3 years was 2.9%, 4.2%, and 6.1% in Etv monotherapy and 2.2%, 2.2%, and 6.7% in the Lam and Adv combination, with no significant difference among the groups at any time point (P>0.05, Figure 6A). Conventional multivariate Cox regression showed no significant differences in the cumulative rate of LREs between the two groups (HR 0.94, 95% CI 0.42–2.11) either. Further, after adjustment for age, sex, baseline HBeAg, ALT, TBil, and HBV DNA by PS, there were no significant differences in cumulative
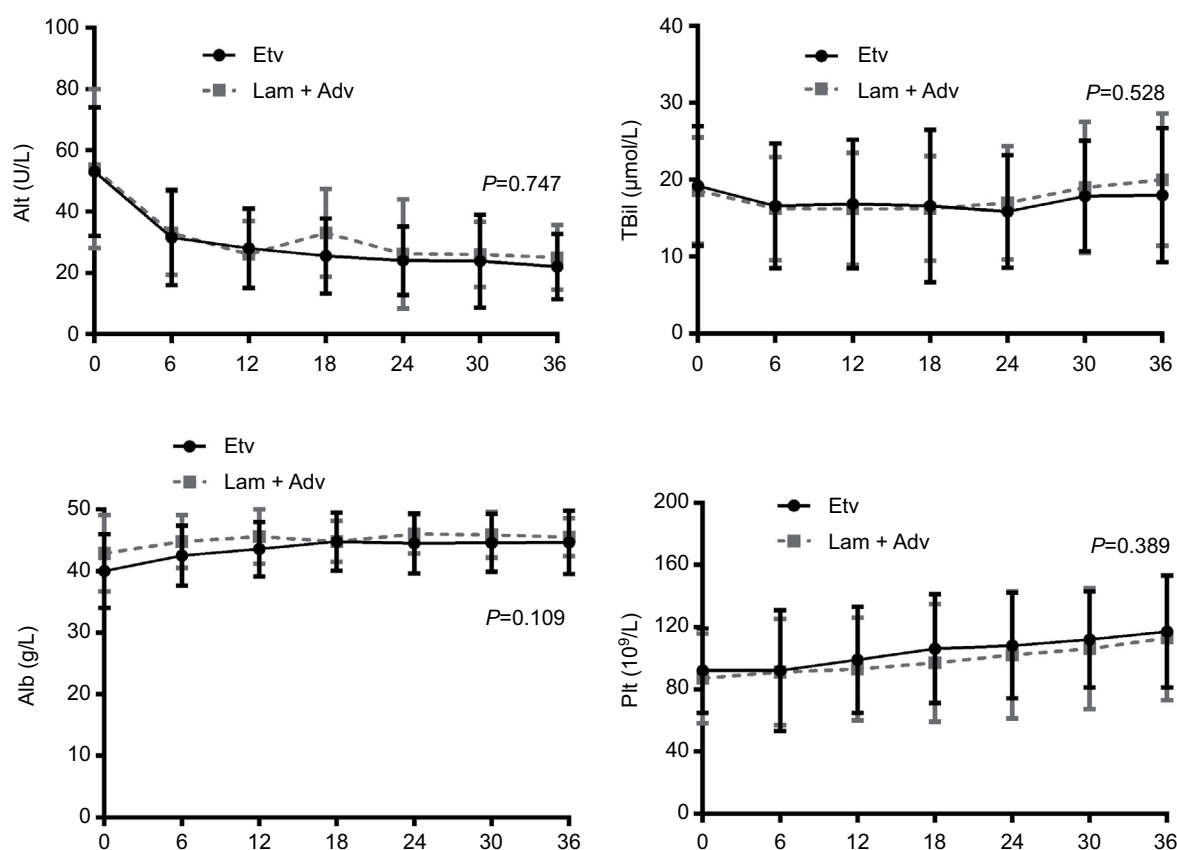
Figure 4 Biochemical response in cirrhotic patients treated with Etv monotherapy or de novo combination of Lam plus Adv.
Abbreviations: Etv, entecavir; Lam, lamivudine; Adv, adefovir; TBil, total bilirubin; Alb, albumin; Plt, platelet.

rate of LREs between the two groups (HR 0.94, 95% CI 0.42–2.16; Table S1).

The cumulative incidence of hepatic decompensation after 1, 2, and 3 years' antiviral treatment was 1.0%, 1.5%, and 2.4% in Etv monotherapy and 2.2%, 2.2%, and 4.5% in the Lam and Adv combination, respectively, with no significant difference between the two groups (P>0.05, Figure 6C). Subgroup analysis of hepatic decompensation disaggregated by presence of variceal bleeding and ascites showed no significant differences between the two groups (P>0.05, Figure 1) either. A total of 31 patients developed HCC: 27 (5.5%) on Etv monotherapy and four (4.3%) on the Lam and Adv combination. The cumulative incidence of HCC after 1, 2, and 3 years of treatment was 1.9%, 2.9%, and 4.4% in Etv monotherapy, and 0, 0, and 2.3% in Lam and Adv combination (P>0.05, Figure 6B), respectively.

Safety analysis

In general, both Etv monotherapy and Lam + Adv were well tolerated. Seven patients on Etv monotherapy developed non-liver-related serious adverse events (one each of lung cancer, colon cancer, endometrial cancer, chronic glomerulonephritis, autoimmune pancreatitis, diabetes mellitus, and duodenal ulcer), whereas there was none in the Lam and Adv combination group. None of the seven patients showed evidence of association of adverse events with CHB or Etv, and all continued Etv therapy. There was no significant change in serum-creatinine levels in three years of antiviral treatment in either group.

Discussion

In this large-scale, prospective, multicenter, real-world study, most patients achieved HBV-DNA suppression in both groups. Etv monotherapy showed a lower virological breakthrough rate than the de novo combination of Lam and Adv, whereas there were no significant differences between the groups in terms of serological or biochemical response or cumulative incidence of LREs during the 3 years of antiviral therapy.

Both Etv monotherapy and the combination of Lam plus Adv were found to be effective in terms of HBV-DNA suppression in patients with compensated cirrhosis during 3 years of treatment. In context of availability, pricing, and reimbursement policy, several studies have reported the
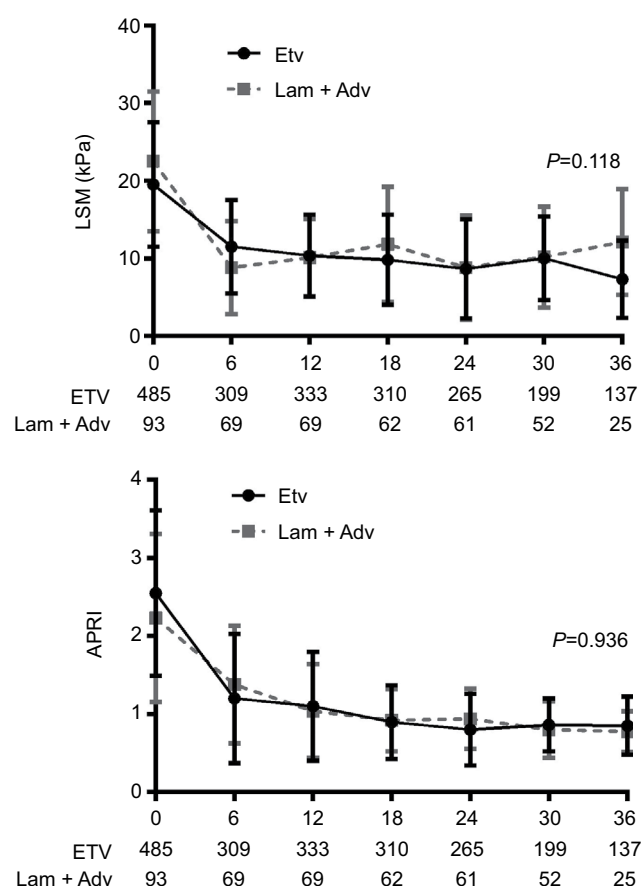
Figure 5 LSM and APRI in cirrhotic patients treated with Etv monotherapy or de novo combination of Lam plus Adv.
Abbreviations: LSM, liver-stiffness measurement; APRI, AST:platelet ratio index; Etv, entecavir; Lam, lamivudine; Adv, adefovir.

clinical efficacy of Lam plus Adv compared with Etv monotherapy in developing countries. In an Indian observational study, Etv monotherapy was found to be more effective than Lam + Adv in reducing HBV-DNA levels after 24 weeks of treatment.[12] Another study showed that in treatment-naïve patients with HBeAg-negative CHB, both Lam + Adv and Etv monotherapy were effective after 48 weeks' treatment.[13] Meta-analysis suggested that for treatment-naïve patients with CHB, Lam + Adv was better than Etv monotherapy in terms of biochemical response and HBeAg-seroconversion rate up to 96 weeks.[14] However, only five studies were included in this meta-analysis, and most of these were single-center studies with few CHB patients.

Virological breakthrough is an important indicator that requires close monitoring during long-term antiviral therapy, especially with use of low-genetic-barrier drugs, such as Lam and Adv. In this 3-year head-to-head study on patients with HBV-related compensated cirrhosis, the cumulative virological breakthrough rate of Etv monotherapy (9.8%) was lower

than that of Lam + Adv (32.2%). In previous studies, after 48 weeks' therapy with Etv alone or Lam + Adv in CHB patients, virological breakthrough rates were between 0 and 4.3% in HBeAg-positive patients,[15,16] while no virological breakthrough was observed in HBeAg-negative patients.[14] Similarly, in a real-world longitudinal observational study in China, Lam-based treatment was associated with higher probability of virological breakthrough (21.4%) compared to Etv (1.6%) after 52 weeks of therapy.[17]

Treatment adherence is an important issue in the long-term management of CHB, because it has been reported that nonadherence was one of the factors independently associated with virological breakthrough.[18,19] Actually, most of the patients in our cohort had good adherence, with only two patients (0.4%) in the Etv group and two patients (2.2%) in the combination group observed to have poor adherence (<80% of prescribed doses taken) and virological breakthrough. After excluding these four patients, we found a higher risk of virological breakthrough in adherent patients with Lam + Adv than with Etv monotherapy.

Though relatively stringent cirrhosis-diagnosis criteria were used in our study, similar to those described in previous studies,[15] there were no significant differences in cumulative rate of LREs, including hepatic decompensation and HCC. It has been reported that compared with no treatment or historical controls, both Etv[20] and Lam[21] significantly reduced the incidence of LREs in patients with compensated cirrhosis. With similar incidence of LREs in our Etv group, we may deduce that the prognosis of compensated cirrhosis was greatly improved after effective antiviral therapy in our study.

Radiology and LSM are widely accepted methods for cirrhosis diagnosis. Their use in combination with routine blood tests has been shown to improve the accuracy of cirrhosis detection.[22,23] We used a combination of at least two of radiology, transient elastography, thrombocytopenia, and decrease in albumin or coagulopathy, which seems to be more convenient and reasonably reliable for clinical use. Though histology is the gold standard for diagnosis of cirrhosis, its application is limited in cirrhotic patients, because of thrombocytopenia and/or coagulopathy.[24]

As a real-world observational study, several limitations need to be discussed. First, the rationale of this study needs to be considered in the context of the unique scenario of HBV-drug availability, pricing, and reimbursement policy in China. Second, unbalanced treatment allocation is caused by the changing landscape of HBV therapy in China. However, the two groups had comparable baseline characteristics and results remained unchanged after planned PS analysis. Third,
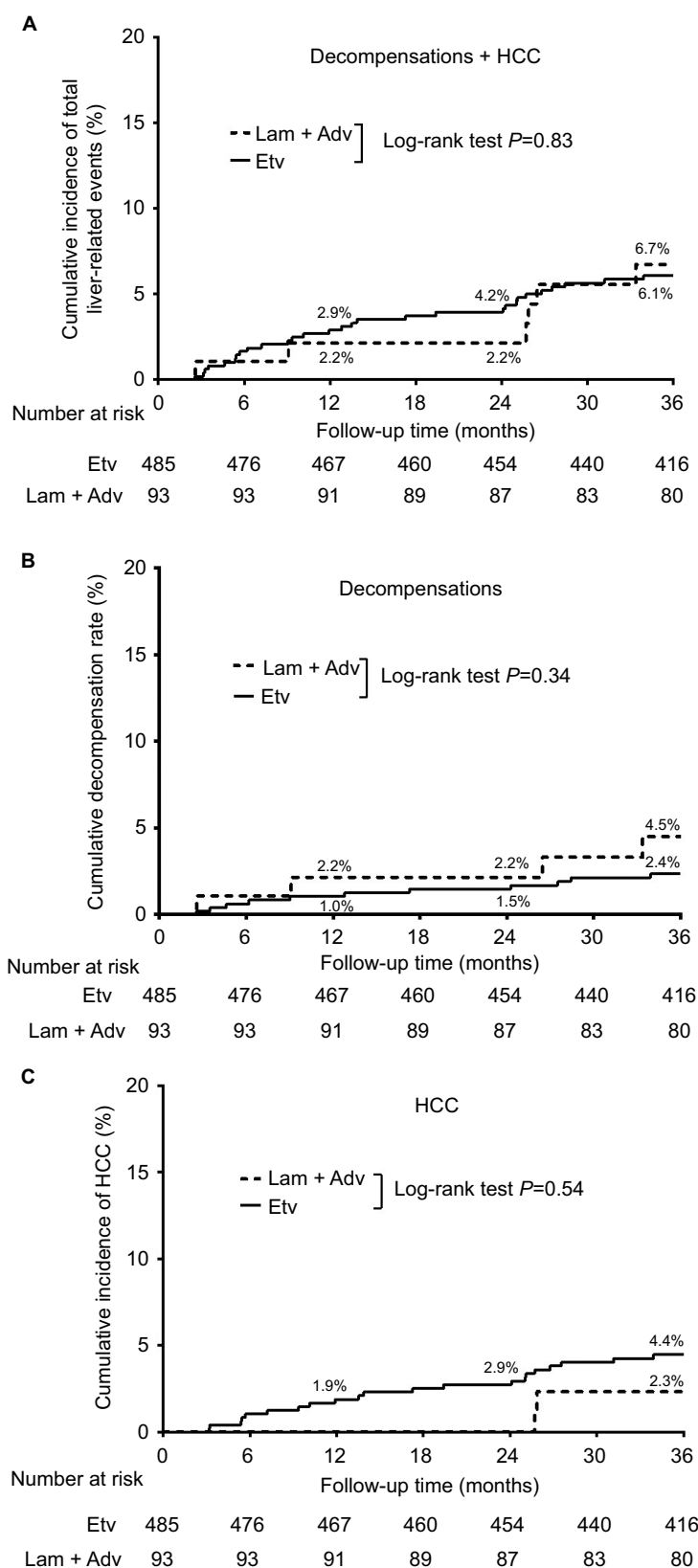
A

B

C

Figure 6 Kaplan–Meier estimates of cumulative incidence of liver-related events.
Notes: Decompensation and HCC (**A**), cumulative incidence of decompensation (**B**), and cumulative incidence of HCC (**C**) during treatment.
Abbreviations: HCC, hepatocellular carcinoma; Etv, entecavir; Lam, lamivudine; Adv, adefovir.

follow-up was relatively short. We will continue to follow up the cohort of patients to confirm the long-term clinical outcomes of different treatment groups. Finally, though 287 (49.7%) patients were from 18 (56.3%) other provinces in China, all nine centers were in Beijing, and this result should not be over generalized to other regions or settings.

Conclusion

In this prospective, multicenter, real-world, cohort study, Etv monotherapy achieved more stable HBV-DNA suppression than Lam + Adv in patients with compensated HBV-related cirrhosis. Biochemical and serological responses and cumulative incidence of LREs were comparable during the 3 years of treatment. Long-term follow-up of these patients is required to elucidate the longer-term efficacy and safety of these two treatment choices.

Ethics approval and consent to participate

The protocol, patient-information sheets, and consent forms were approved by the Medical Ethics Committee of Beijing Friendship Hospital, Capital Medical University, and each center (approval code BJFH-EC/2013-067). The authors confirm that all participants provided written informed consent.

Data sharing

The data sets generated and/or analyzed during the current study are not publicly available, due to patient-privacy protection, but will be available from the corresponding author on reasonable request by email within 3 months of agreement of the research group and approval of the ethics committee. The study protocol is available on ClinicalTrials.gov (NCT01720238).

Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

References

1. World Health Organization. Global Hepatitis Report. 2017. Available from: https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/April 2017. Accessed March 26, 2019.
2. McMahon BJ. The natural history of chronic hepatitis B virus infection. *Semin Liver Dis*. 2004;24(Suppl 1):17–21.
3. Lai CL, Ratziu V, Yuen M-F, Poynard T. Viral hepatitis B. *Lancet*. 2003;362(9401):2089–2094.
4. Fattovich G. Natural history and prognosis of hepatitis B. *Semin Liver Dis*. 2003;23(1):47–58.
5. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol*. 2012;57:167–185.
6. Lim SG, Amarapurkar DN, Chan HL, et al. Reimbursement policies in the Asia-Pacific for chronic hepatitis B. *Hepatol Int*. 2015;9(1):43–51.
7. Sheng YJ, Liu JY, Tong SW, et al. Lamivudine plus adefovir combination therapy versus entecavir monotherapy for lamivudine-resistant chronic hepatitis B: a systematic review and meta-analysis. *Virol J*. 2011;8(1):393.
8. Lin Z, Lu X, Liu C. Clinical effects comparison of lamivudine combined with adefovir dipivoxil or entecavir alone on HBV-related hepatocirrhosis in 3 years. *Pharmacy Today*. 2015;1:168–174.
9. Woo HY, Choi JY, Yoon SK, et al. Rescue therapy with adefovir in decompensated liver cirrhosis patients with lamivudine-resistant hepatitis B virus. *Clin Mol Hepatol*. 2014;20(2):168–176.
10. Wu S, Kong Y, Piao H, et al. On-treatment changes of liver stiffness at week 26 could predict 2-year clinical outcomes in HBV-related compensated cirrhosis. *Liver Int*. 2018;38(6):1045–1054.
11. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*. 2003;38(2):518–526.
12. Jayakumar R, Joshi Y, Singh S. Laboratory evaluation of three regimens of treatment of chronic hepatitis B: tenofovir, entecavir and combination of lamivudine and adefovir. *J Lab Physicians*. 2012;4:10–16.
13. Wang LC, Chen EQ, Cao J, et al. De novo combination of lamivudine and adefovir versus entecavir monotherapy for the treatment of naïve HBeAg-negative chronic hepatitis B patients. *Hepatol Int*. 2011;5(2):671–676.
14. Liu F, Wang X, Wei F, et al. Efficacy and resistance in de novo combination lamivudine and adefovir dipivoxil therapy versus entecavir monotherapy for the treatment-naive patients with chronic hepatitis B: a meta-analysis. *Virol J*. 2014;11(1):59.
15. Cai S, Yu T, Jiang Y, et al. Comparison of entecavir monotherapy and de novo lamivudine and adefovir combination therapy in HBeAg-positive chronic hepatitis B with high viral load: 48-week result. *Clin Exp Med*. 2016;16(3):429–436.
16. Du QW, Ding JG, Sun QF, et al. Combination lamivudine and adefovir versus entecavir for the treatment of naive chronic hepatitis B patients: a pilot study. *Med Sci Monit*. 2013;19:751–756.
17. Jia J, Tang H, Ning Q, et al. Real-world evidence for nucleoside/nucleotide analogues in a 5-year multicentre study of antiviral-naive chronic hepatitis B patients in China: 52-week results. *Antivir Ther*. 2017;23(3):201–209.
18. Sheppard-Law S, Zablotska-Manos I, Kermeen M, et al. Factors associated with HBV virological breakthrough. *Antivir Ther*. 2016;22(1):53–60.
19. Liu Y, Miller MD, Kitrinos KM. Tenofovir alafenamide demonstrates broad cross-genotype activity against wild-type HBV clinical isolates and maintains susceptibility to drug-resistant HBV isolates in vitro. *Antiviral Res*. 2017;139:25–31.

20. Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. *Hepatology*. 2010;52(3):886–893.
21. Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med*. 2004;351(15): 1521–1531.
22. Liang XE, Dai L, Yang SL, et al. Combining routine markers improves the accuracy of transient elastography for hepatitis B cirrhosis detection. *Dig Liver Dis*. 2016;48(5):512–518.
23. Lee HS, Kim JK, Cheong JY, et al. Prediction of compensated liver cirrhosis by ultrasonography and routine blood tests in patients with chronic viral hepatitis. *Korean J Hepatol*. 2010;16(4):369–375.
24. Papatheodoridis GV, Manolakopoulos S. EASL clinical practice guidelines on the management of chronic hepatitis B: the need for liver biopsy. *J Hepatol*. 2009;51(1):226–227.

Supplementary materials

Table S1 Factors in liver-related events in the two groups

	Cox regression model				Adjustment	Cox regression model (PS)	
	Unadjusted HR (univariate)	**P-value**	**Adjusted HR (multivariate)**	**P-value**		**Adjusted HR**	**P-value**
Age, years	1.022 (0.996–1.049)	0.09	1.021 (0.992–1.050)	0.16	PS	1,886.192 (0.012–287710000)	0.22
Sex	2.022 (0.948–4.314)	0.07	2.214 (1.011–4.848)	0.05			
HBeAg, +/–	0.768 (0.428–1.381)	0.38	0.763 (0.416–1.401)	0.38			
ALT, U/L	1.000 (0.999–1.001)	0.77	1.000 (0.999–1.001)	0.97			
TBil, μmol/L	0.994 (0.982–1.006)	0.33	0.989 (0.973–1.006)	0.20			
HBV DNA, log	1.009 0.893 1.140	0.89	1.013 (0.892–1.150)	0.85			
Combined treatment	1.081 (0.524–2.231)	0.83	0.939 (0.417–2.114)	0.88		0.952 (0.423–2.146)	0.91

Note: PS = $-0.00026 \times$ age $+ 0.1059 \times$ sex $+ 0.1272 \times$ HBeAg$_{baseline}$ $-0.00067 \times$ ALT$_{baseline}$ $- 0.00391 \times$ TBil$_{baseline}$ $+ 0.0381 \times$ HBV DNA$_{baseline}$ $- 1.8413$.
Abbreviations: TBil, total bilirubin; HBV, hepatitis B virus; PS, propensity score.
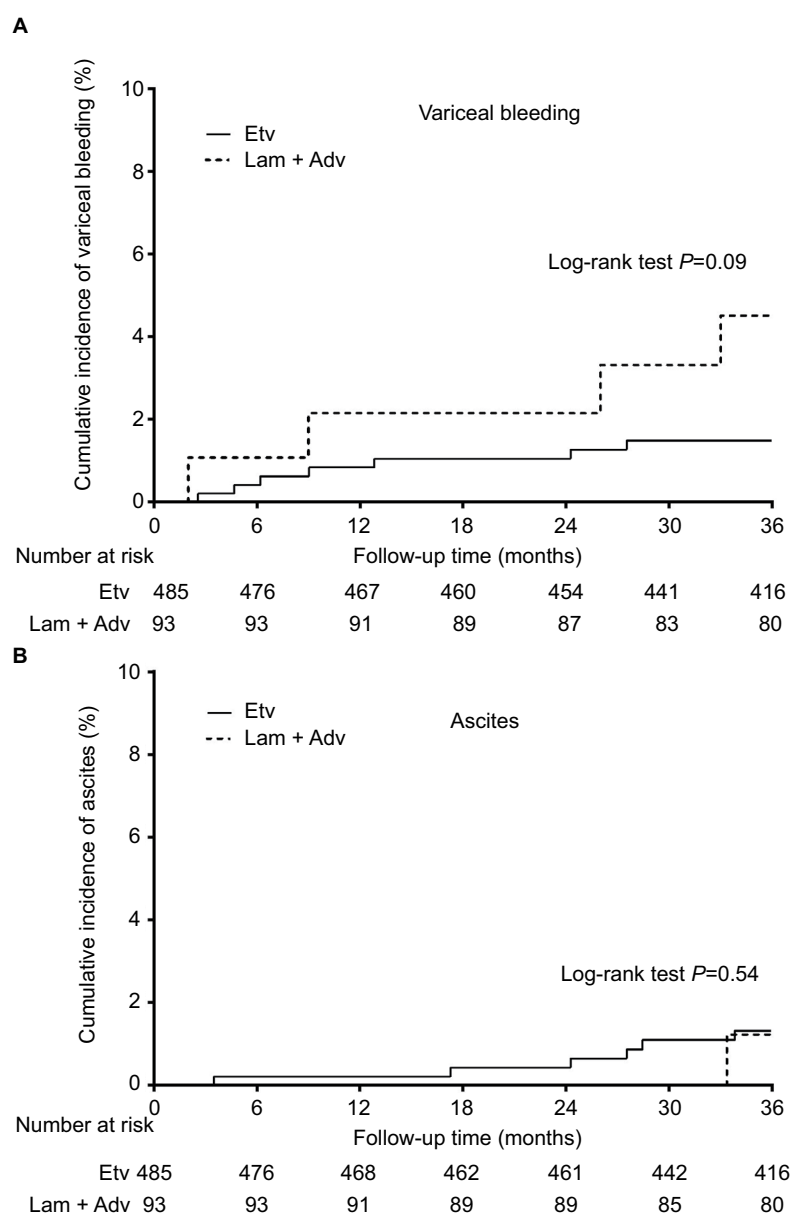

Figure S1 Kaplan–Meier estimates of cumulative incidence of variceal bleeding and ascites.
Abbreviations: Etv, entecavir; Lam, lamivudine; Adv, adefovir.