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Meta-analysis: oral anti-viral agents in adults with decompensated hepatitis B virus cirrhosis

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SUMMARY

Background
The optimal oral anti-viral agent to use in patients with decompensated HBV cirrhosis remains unclear.

Aim
We performed a meta-analysis of the oral nucleos(t)ide analogues in patients with decompensated HBV cirrhosis.

Methods
One year efficacy and safety outcomes in 22 studies published in English between 1995 and 2010 were analysed.

Results
Substantial heterogeneity was noted in the inclusion/exclusion criteria, controls, and sensitivity of the HBV DNA assay used. Pooled 1-year data showed benefit favouring lamivudine (LAM) vs. untreated controls for Child-Turcotte-Pugh (CTP) score improvement by ≥ 2 (OR: 117 (15 921), $P \leq 0.0001$) and transplant-free survival (OR: 3.2 (1.2, 9), $P = 0.022$). Adefovir (ADV) led to undetectable HBV DNA at 1-year in 41% compared to 83% with LAM and 80% with entecavir (ETV). Overall, 1-year transplant-free survival rates varied from 78% with LAM to 95% and 94% with Tenofovir (TDF) and Telbivudine (TBV), respectively. The 1-year incidence of drug resistant HBV was 0% with ADV, ETV and TDF and 11% with LAM although TBV was associated with a 29% incidence at 2 years. Drug-related adverse events were infrequently reported.

Conclusions
All the oral anti-viral agents were associated with improved virological, biochemical and clinical parameters at 1-year. However, the efficacy of lamivudine and telbivudine is limited by drug resistance, and adefovir is limited by its potency and slower onset of action. Additional studies of tenofovir and entecavir are needed to determine the optimal agent(s) for treatment naïve patients and in those with drug-resistant decompensated HBV cirrhosis.

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INTRODUCTION

An estimated 15–40% of untreated patients with chronic hepatitis B virus (HBV) infection may develop cirrhosis, liver failure and/or hepatocellular carcinoma (HCC).[1, 2] The goal of anti-viral therapy in these patients is to prevent the development of cirrhosis and its associated complications in an effort to improve patient survival and quality of life.[3] However, patients with decompensated HBV cirrhosis at initial presentation have a poor short-term prognosis with an estimated 5-year survival of only 14%.[4] Although liver transplantation (LT) is an effective treatment option for decompensated HBV cirrhosis, the ongoing shortage of donor organs and limited availability of this resource worldwide precludes the majority of HBV patients in endemic areas from undergoing transplantation.[5] Therefore, the development of anti-viral agents that can safely and effectively suppress HBV replication and lead to improvement or stabilisation in liver function represents an important unmet medical need.

Natural history studies have demonstrated that sustained, active HBV replication with high serum HBV DNA levels is associated with a poorer prognosis compared to HBV patients with low or undetectable HBV DNA.[5, 6] In addition, a randomised controlled trial (RCT) in Asian HBV patients with advanced but compensated fibrosis and high HBV DNA levels demonstrated that lamivudine (LAM)-treated patients were less likely to experience liver related morbidity and mortality compared to untreated controls.[7, 8] Seven drugs are currently approved for the management of chronic HBV infection: standard interferon or IFN (Early 1990's), LAM (1997), adefovir or ADV (2002), entecavir or ETV (2005), peginterferon-α2a or PEGIFN (2005), telbivudine or TBV (2006) and Tenofovir or TDF (2008).[6] Interferons enhance host immunity against HBV-infected hepatocytes but have a number of dose-dependent side effects including neuropsychiatric toxicity and myelotoxicity which preclude their safe use in patients with advanced HBV.[6] For example, interferon was not only poorly tolerated in patients with decompensated HBV cirrhosis but also associated with disease flares and worsening liver disease status.[9] In contrast, oral anti-viral agents have a generally favourable side effect profile and are well tolerated in patients with compensated as well as decompensated HBV.[7] In addition, these agents can directly and rapidly inhibit HBV replication and lead to improvement in hepatic necroinflammation, serum alanine aminotransfersase (ALT) levels and global liver function even in patients with advanced disease.[7] However, many of the studies in patients with decompensated HBV have been small pilot protocols with variable inclusion criteria and without an active contemporary control arm. In addition, many of these studies were not designed to establish the safety and efficacy of these drugs in this challenging patient population but rather to provide early access to the medications. The aim of this systematic review is to evaluate the efficacy and safety of the five available oral anti-viral agents in patients with decompensated HBV cirrhosis including the nucleoside analogues (lamivudine, entecavir and telbivudine) and nucleotide analogues (adefovir and tenofovir). Based upon the pooled 1-year safety and efficacy data, we sought to identify the preferred agent(s) for use in patients with decompensated HBV cirrhosis.

MATERIALS AND METHODS

Study selection

Search strategy. Electronic databases (Medline, Cochrane reviews, and EMBASE, ISI Web of science) from 1995 through 2010 were searched for publications including abstracts in English language. The initial search terms were hepatitis B, cirrhosis and treatment. The search was later expanded using the MeSH terms lamivudine, adefovir, entecavir, tenofovir and telbivudine. Boolean logic was used to combine the words. In addition, manual search was made for cross references from manuscripts.

Criteria for study selection. Both authors reviewed the literature for study selection including references from the included studies. All the studies that were included were carefully reviewed by both authors to insure that the studies met the pre defined selection criteria of (i) Patient population – adult patients with decompensated HBV cirrhosis (treatment naïve as well as treatment experienced) defined as CTP score of 7 or more; (ii) Treatment regimen– oral nucleos(t)ide analogues either alone or in combination; (iii) Study design – any design including retrospective or open-label prospective studies with or without a control group. Efficacy and safety data of individual drugs in comparative studies were analysed separately. Studies with a total sample size of <20 were excluded as were studies of patients with a previous or newly diagnosed HCC, children and liver transplant recipients.

Assessment of study quality. A quality score for each study was determined using several binomial parameters

(Table S1).[10, 11] Parameters were chosen based on their relevance to the analysis of observational studies. Each parameter was given a numerical score of 0 or 1 with an overall quality score ranging from 0 to 10. Studies with a quality score of <5 were rated as poor while those ≥5 were rated as high quality studies.

Outcome measures

Efficacy and safety outcomes at 1 year after starting treatment were evaluated. Efficacy measures were categorised as: (i) Virological – proportion of patients with undetectable HBV DNA, HBeAg loss and HBeAg seroconversion (i.e. HBeAg loss and anti-HBe positivity); (ii) Biochemical – proportion of patients with normalisation of elevated baseline serum alanine aminotransferase (ALT) levels and; (iii) Clinical – proportion of patients with improvement of CTP score by ≥2 points, LT-free survival defined as proportion of patients surviving without LT, overall survival defined as proportion of patients surviving with or without LT, proportion of patients developing HCC, and proportion of patients being removed from the LT waiting list due to clinical improvement. Safety for each drug was evaluated with the following outcomes at 1 year (i) proportion of patients with drug-related serious adverse events; (ii) proportion of patients with renal insufficiency defined as an increase in serum creatinine by 0.5 mg/dL from baseline; and (iii) proportion of patients with confirmed drug resistant HBV determined using direct sequencing or line probe assay.

Data collection and analysis

Data were extracted for (i) Study characteristics (author and year of publication, country of origin, study design, sample size, study quality); (ii) Patient demographics (age, gender, ethnicity, per cent HBeAg positive); (iii) Inclusion and exclusion criteria; (iv) Treatment details (anti-viral agent used, dose of drug, duration of treatment, lower limit of detection (llod) for HBV DNA assay used and duration of follow-up); and (v) Study outcomes at 1 year after starting the treatment. Data were extracted from each study by AKS and confirmed for accuracy by RJF who independently read through each study. If the outcomes data were not clear from the manuscript, the corresponding authors were contacted for further information. Individual data for each outcome were entered into the Comprehensive meta-analysis software (Biostat, Engelwood, NJ, USA). Pooled effects with 95% confidence interval (CI) are reported for the uncontrolled data while odds ratios (OR) with 95% CI are reported for studies with a control group of untreated patients.Heterogeneity of the pooled data was reported using the Chi-squared or Q statistic using a random effects model. Publication bias was assessed looking at the funnel plots and analysed using the Egger's test. Results were considered significant for *P*-value of <0.05.

RESULTS

Characteristics of the included studies

A total of 22 studies of nucleos(t)ide analogues fulfilled the criteria for this systematic review (Figure 1 and Table 1). Of the 14 studies evaluating LAM (two abstracts), eight were open-label studies, four compared LAM to untreated or historical controls, and two compared LAM to either ETV or TBV.[12–25] Five studies evaluated ADV(one abstract), of which two were open-label and three had a comparator group (LAM + ADV in two and ETV alone in one).[26–30] Five studies evaluated ETV

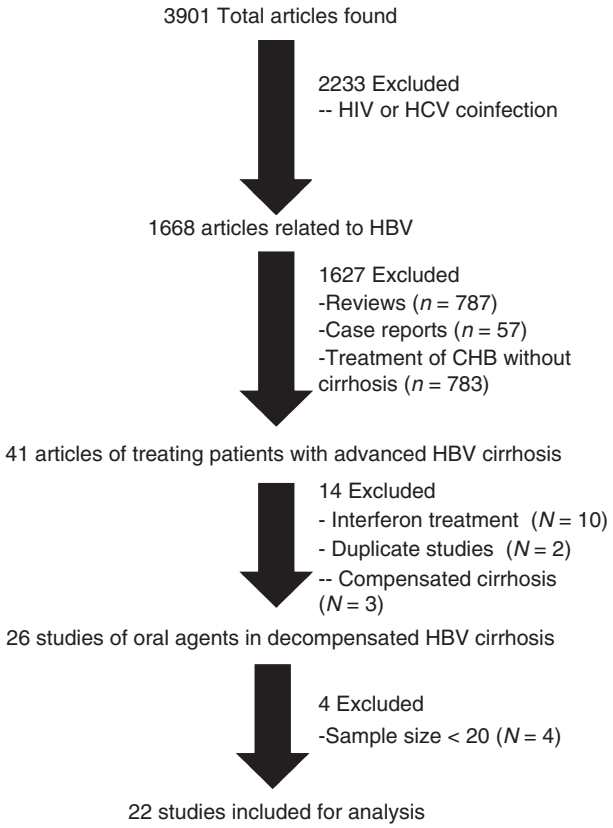

Figure 1 | Attrition diagram for study selection. Of the 3901 studies initially identified from our electronic search, 22 met the inclusion criteria and were included in this systematic review.

Table 1 | Baseline characteristics of patients receiving oral anti-viral agents for decompensated HBV cirrhosis

Year Ref.	Country	No. of subjects†	No. and type of controls	Availability of LT*	Key inclusion criteria	CTP score at entry	Key exclusion criteria	Llod of HBVDNA assay (copies/mL)	% HBeAg+	Duration treatment (months)
Studies using lamivudine										
2000[12]	Canada	35	NA	Y	HBV DNA+	≥8	HIV coinfection	1.4×10^5	57	36
2001[13]**	US	23	23 historical controls	Y	HBV DNA+	≥10	Alcohol abuse, anti-viral within 12 months	0.7×10^6	74	NA
2001[14]	US	30‡	30 historical controls	Y	Awaiting LT	NA	HCV or HIV coinfection, HCC	0.7×10^5	60	29 (1–38)
2002[15]	US	162	147 untreated on LT list	Y	Awaiting LT	NA	FHF	0.7×10^5	52	40
2002[16]	Italy	25	NA	Y	HBVDNA+ HBeAg− waiting LT	≥7	HCV or HIV coinfections, HCC, other anti-viral	250–500	NA	12
2003[17]	US	75	NA	Y	HBVDNA+ Age ≥13 years	≥7	FHF, HIV coinfection	0.7×10^6	62	13 (1–33)
2004[18]	UK	30	30 untreated controls	Y	HBVDNA+, HBeAg−, ALT >1.5 N ULN	≥7	HCV or HIV coinfection, HCC, renal insufficiency	400	0	24
2005[19]	Greece	20	NA	Y	HBVDNA+, HBeAg− awaiting LT	≥7	Alcohol abuse, HCV or HIV coinfection, HCC	200	NA	60
2005[20]	Taiwan	30	NA	Y	HBVDNA+ or ALT > 1.5 × ULN	≥7	Alcohol abuse, HCV or HIV coinfection, HCC, prior anti-viral treatment	0.5×10^6	30	10 (1–32)
2007[21]	US	160	NA	Y	Awaiting LT	Mean MELD 15†	FHF, prior LT	200	35	48
2007[22]	US	122	NA	Y	Awaiting LT	Median MELD 12†	FHF, other non viral diseases, prior LT	200	40	41

Table 1 | (Continued)

Year Ref.	Country	No. of subjects†	No. and type of controls	Availability of LT*	Key inclusion criteria	CTP score at entry	Key exclusion criteria	Llod of HBVDNA assay (copies/mL)	% HBeAg+	Duration treatment (months)
2008[23]	Japan	43§	NA	Y	HBV DNA > 5 log10, Age >20 years, liver biopsy, ALT > 2 × ULN	NA	FHF, Alcohol abuse, HCC, HCV or HIV coinfection	30	58	NA
2009[24]††	Taiwan	24	24 ETV	N	NA	≥7	NA	300	NA	48
2010[25]††	Asia-Pacific	116	116 TBV	N	CTP >7	>7	NA	300	40	24
Summary		894		86% LT available					42%	32 months
Studies using adefovir										
2005[26]	Korea	18	28 (ADV + LAM)	N	HBV DNA+, HBeAg+, ALT >1.3 × ULN, LAM resistance, Age ≥18 years	≥7	HBeAg−, HCV or HIV coinfection, anti-viral within 12 months, HCC	100	100	12
2006[27]	Taiwan	18	10 (ADV + LAM)	N	LAM resistant HBV cirrhosis	NA	NA	1.4×10^5	50	12
2007[28]	US	226	NA	Y	LAM resistance awaiting LT	≥5¶	NA	1000	100	48
2009[29]	France	68	NA	Y	LAM resistance and ≥3 fibrosis on biopsy	NA	HIV coinfection	2000	57	12
2009[30]††	Worldwide	91 (34% LAM-R)	100 ETV	N	HBV DNA >5 log, age >16 years, ALT ≤15 × ULN	≥7	HCC, creatinine >2.5 mg/dL	300	55	24
Summary		421		40% LT available					72%	22 months
Studies using entecavir										
2009[24] **,††	Taiwan	24	24 LAM	N	NA	≥7	NA	300	NA	48
2009[30] ††	Worldwide	100	91 ADV	N	HBV DNA >5 log, age >16 years, ALT ≤15 × ULN	≥7	HCC, creatinine >2.5 mg/dL	300	54	24

Table 1 | (Continued)

Year Ref.	Country	No. of subjects†	No. and type of controls	Availability of LT*	Key inclusion criteria	CTP score at entry	Key exclusion criteria	Llod of HBVDNA assay (copies/mL)	% HBeAg+	Duration treatment (months)
2011[31]	Worldwide	22 (33% LAM-R)	45 TDF and 45 TVD	Y	HBVDNA > 1000 cpm, ALT < 10 × ULN, CrCl ≥50 mL/min, Age ≥18 years	7–12	HCV, HIV, HDV coinfection, HCC, prior anti-viral treatmen, ≥3 grade HE	400	32	12
2009[32] ††	MC Italy	42	20 (ADV + LAM)	N	LAM resistance awaiting LT	NA	NA	NA	NA	12
2009[33] **	Korea	70	NA	Y	HBVDNA+ HBeAg+	≥7	HCC, ALT >10 × ULN, prior anti-viral treatment, HCV or HIV coinfection	300	49	NA
Summary		258		40% LT available					45%	24 months
Study using tenofovir										
2011[31]	Worldwide	45	22 ETV and 45 TVD	Y	HBV DNA > 1000 cpm, ALT < 10 × ULN, CrCl ≥50 mL/min, Age ≥18 years	7–12	HCV, HIV, HDV coinfection, HCC, prior anti-viral treatment, ≥ grade 3 HE	400	31	48
Study using telbivudine										
2010[25] ††	Asia-Pacific	116	116 LAM	N	CTP >7	≥7	NA	300	45	24

A, abstract; ADV, adefovir; C, control; CTP, child Turcott Pugh; ETV, entecavir; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IFN, interferon; LAM, lamivudine; LAM-R, lamivudine resistance; LOD, lower limit of detection; LT, orthotopic liver transplantation; MC, multicenter; NA, not available; TDF, tenofovir; TVD, truvada (Emtricitabine plus tenofovir).

* Determined from the methods section of the respective articles and if not mentioned then presumed to be not available.

† CTP score not reported.[35]

‡ Of 77 enrolled, 30 patients did not undergo LT and were analysed.

§ Subset data on 43 patients with decompensated cirrhosis out of a total of 153 HBV patients.

¶ 40% patients had CTP stage A or compensated cirrhosis.

** Dose of LAM 150 mg/day and ETV 0.5 mg/day; otherwise the doses of drugs were as follows: LAM 100 mg/day, ADV 10 mg/day, ETV 1.0 mg/day, TDF 300 mg/day and TBV 600 mg/day.

†† Abstract publications.

(three abstracts), of which only one study was open-label and the remaining four had a comparator group (LAM + ADV, LAM, ADV, TDF in one study each).[24, 30–33] Tenofovir and TBV were evaluated in one randomised controlled study each and compared to ETV and LAM, respectively.[25, 31] Of note, one RCT comparing LAM to placebo and another comparing LAM to ADV were excluded from this review since these studies included compensated patients with CTP scores of ≤ 6.[7, 34]

Baseline characteristics of the patients enrolled in the studies demonstrated a highly variable sample size that ranged from 20 to 269 treated patients (Table 1). A total of 15 (68%) studies were conducted in North America or Europe whereas 7 (32%) included patients only from Asia. Two of the seven Asian studies did not have access to LT. There was great variability among the studies regarding inclusion criteria (e.g. mean CTP score at entry, percent HBeAg positive), exclusion criteria (co-infection with HCV and/or HIV, HCC, acute liver failure), and the llod of the HBV DNA assay used (Table 1). Furthermore, the selection of controls was variable among the controlled studies. Nonetheless, the majority of the studies[15] were of good quality with a total quality score of ≥ 5 (see Table S1).

Efficacy analysis

Virological response. Analysis of the pooled 1-year open-label data showed beneficial effects for LAM, ADV and ETV regarding the proportion of patients with undetectable HBV DNA, HBeAg loss and HBeAg seroconversion (Table 2). Lamivudine and ETV were associated with similar rates of undetectable HBV DNA at 1 year of 83% and 80%, respectively. However, ADV was less potent with only 41% of the ADV-treated patients having undetectable HBV DNA at 1 year and the 95% CI for the pooled ADV studies did not overlap with those of the pooled LAM nor ETV studies (Table 2). However, the rates of HBeAg loss and HBeAg seroconversion were similar with these three agents (Table 2). Compared to untreated control patients, LAM was also significantly better in achieving undetectable HBV DNA at 1 year of follow-up (Table 3 and Figure 2). However, rates of HBeAg loss with LAM were not significantly higher compared to untreated controls (Table 3).

In one prospective RCT, ETV achieved higher rates of undetectable HBV DNA at 1 year compared to LAM (100% vs. 73%; $P = 0.02$) using a highly sensitive HBV DNA assay.[24] Entecavir was also superior in achieving undetectable HBV DNA at 1 year compared to ADV in another prospective RCT (57% vs. 20%, $P = 0.0001$).[30] Although ETV ($n = 22$) and TDF ($n = 45$) were similar in achieving undetectable HBV DNA at 1 year (73% vs. 71%; $P = 0.89$) in one RCT, TDF led to more frequent HBeAg seroconversion compared to ETV (21% vs. 0%, $P = 0.023$) but the number of HBeAg + treated patients was very limited.[31] The frequency of undetectable HBV DNA at 1 year was similar with TBV compared to LAM (40% vs. 36%, $P = 0.12$).[25]

Clinical response. The use of LAM, ADV and ETV was also associated with a decrease in CTP scores of ≥ 2 points and normalisation of serum ALT (Table 2). Transplant-free survival varied between 78% and 87% at 1 year with the various agents (Table 2). Other beneficial effects with the oral nucleo(t)side agents included removal from the LT waiting list in 6% of patients receiving ADV, 21% receiving LAM and 11% treated with ETV.[31] Development of HCC at 1 year was reported in 3%, 7% and 6% of patients receiving LAM, ADV and ETV, respectively, (Table 2). Comparison of the pooled data of all five drugs together showed no significant differences from the pooling of the individual agents with overlapping 95% CI (Table 2).

Similar beneficial effects were seen with LAM treatment in the controlled studies (Table 3). The odds of a decrease in CTP by ≥ 2 points was 117 times higher with LAM as compared to untreated patients (Table 3) ($P < 0.0001$). These beneficial effects translated into improved transplant-free survival at 1 year for patients treated with LAM as compared to untreated patients (Figure 3). However, LAM was not effective in reducing the incidence of HCC at 1 year compared to untreated controls (Table 3).[18]

A single study of 195 patients comparing LAM ($n = 97$) and TBV ($n = 98$) showed similar efficacy for mean CTP improvement (0.6 ± 0.3 vs. 0.4 ± 0.3, $P = 0.22$) and serum ALT normalisation (50% vs. 58%, $P = 0.22$) at 2 years whereas data were similar for 1-year survival (88% vs. 94%, $P = 0.11$).[25] In another study, ETV ($n = 100$) and ADV ($n = 91$) were similar in regard to the proportion of patients with stable or decreased CTP scores (61% vs. 67%, $P = 0.08$). However, ETV was superior to ADV for serum ALT normalisation at 1 year (63% vs. 46%, $P = 0.045$).[30] Finally, in an ongoing study of 112 patients entered into a RCT of three agents, ETV ($n = 22$) and TDF ($n = 45$) were similar in their rate of serum ALT normalisation (55% vs. 57%; $P = 0.80$) and transplant-free survival at 1-year (91% vs. 91%; $P = 0.98$).[31]

Table 2 | Pooled effect from the open-label studies on 1-year efficacy and safety outcomes

	Decrease CTP ≥ 2 (%)	Normal ALT (%)	HBVDNA undetectable (%)	HBeAg loss (%)	HBeAg seroconversion (%)	Off LT list (%)	LT (%)	LT free survival (%)	Overall survival (%)	HCC (%)	Drug-related SAE (%)	Renal insufficiency (%)	Drug resistance (%)
Studies using lamivudine													
No. of studies	7	3	10	7	5	5	9	13	13	9	8	8	11
Pooled effect (95% CI)	62 (44–77)	65 (44–82)	83 (75–89)	31 (22–40)	20 (10–38)	21 (7–48)	14 (6–32)	78 (70–84)	87 (82–91)	3 (2–4)	0*	0*	11 (8–14)
Studies using adefovir													
No. of studies	1	5	5	5	5	2	3	4	5	2	2	2	4
Pooled effect (95% CI)	72	61 (47–74)	41 (22–64)	28 (17–41)	16 (10–25)	6 (2–65)	12 (5–25)	87 (66–96)	89 (81–95)	7 (4–14)	4 (2–7)	9 (5–17)	0
Studies using entecavir													
No. of studies	2	3	5	3	2	1	2	2	3	2	2	2	2
Pooled effect (95% CI)	49 (36–60)	66 (53–77)	80 (60–91)	21 (4–64)	11 (3–31)	11	4 (1–10)	87 (78–92)	86 (77–92)	5 (2–10)	6 (3–12)	10 (6–17)	0
Combining all studies (including TBV and TDF)													
No. of studies	12	13	22	16	14	8	15	21	23	13	14	13	19
Pooled effect (95% CI)	57 (45–68)	62 (55–68)	73 (62–81)	30 (22–39)	17 (12–24)	14 (11–48)	11 (6–20)	82 (77–87)	88 (85–91)	4 (3–6)	4 (2–15)	7 (3–21)	8 (5–13)

CTP, child Turcotte-Pugh; LT, liver transplantation; HCC, hepatocellular carcinoma; NA, not available; SAE, serious adverse effects.

* As none of the patients receiving LAM developed drug-related SAE or renal insufficiency, pooled analysis on these outcomes could not be performed.

Table 3 | Pooled effect of four lamivudine studies with an untreated control group in decompensated HBV cirrhosis

	Lamivudine			No treatment		Effect size		Heterogeneity		
	Studies (N)	Sample size	Events	Sample size	Events	OR (95% CI)	*P*	Q statistics	*P*	Egger's P
↓ CTP ≥2 pts	2	53	27	53	0	117 (915–921)	<0.0001	0.22	0.64	NA
Normal ALT	2	51	38	60	0	173 (22–1376)	<0.0001	0.04	0.84	NA
Undetectable DNA	4	149	115	193	29	117 (2–6574)	0.02	32	<0.0001	0.007
HBeAg loss	3	82	25	156	10	14 (0.3–563)	0.16	14.9	0.001	0.20
HBeAg seroconversion	1	16	1	23	0	4.6 (0.2–12)	0.36	NA	NA	NA
Off OLT list	2	185	14	170	7	2 (1–5)	0.22	0.55	0.46	NA
LT	2	185	97	170	101	0.38 (0.1–3)	0.34	8.29	0.004	NA
HCC	1	30	2	30	2	1 (0.1–8)	0.17	0.60	0.44	NA
OLT free survival	4	245	155	216	87	5 (1.5–15)	0.022	8.59	0.035	0.31
Overall survival	4	245	214	216	87	14 (2–119)	0.017	35	<0.0001	0.82
Drug resistance	4	223	28	205	0	16 (4–72)	<0.0001	0.71	0.87	0.02

CTP, child Turcotte Pugh; HCC, hepatocellular carcinoma; LT, liver transplantation; OR, odds ratio.

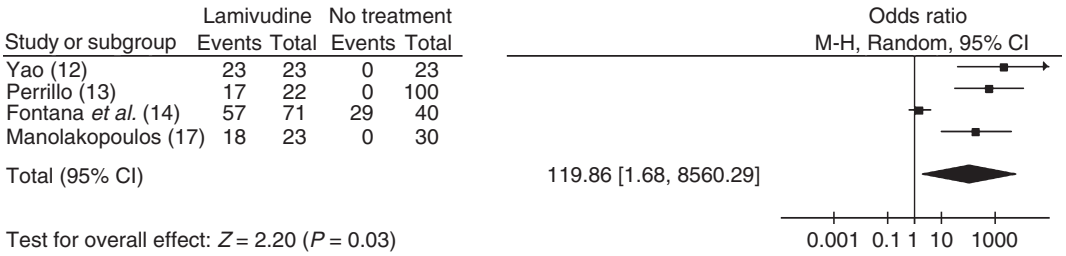

Figure 2 | Pooled data from four controlled studies of lamivudine in achieving undetectable HBV DNA at 1 year in decompensated HBV cirrhosis patients. At 1 year, 83% of the 139 lamivudine treated patients were negative for HBV DNA as compared to 15% of the 193 untreated controls with an odds ratio of 120 (95% CI: 1.7–8560, $P = 0.03$).

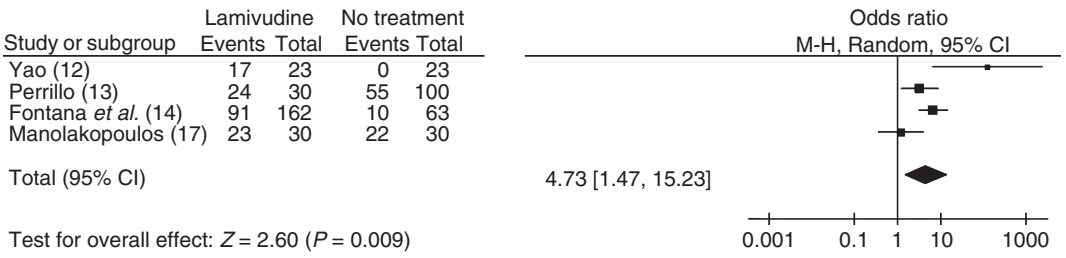

Figure 3 | Pooled data from 4 controlled studies of lamivudine on 1-year transplantation free survival in decompensated HBV cirrhosis patients. At 1 year, 63% of the 249 lamivudine treated patients were alive without transplantation compared to only 40% of the 216 untreated controls with an odds ratio of 4.7 (95% CI: 1.5–15, $P = 0.009$).

Sensitivity analysis of the pooled studies

In Table 2, most of the viral and clinical efficacy effects were similar for LAM, ADV and ETV with the exception of HBV DNA undetectability which was significantly lower with ADV. As a result, all of these data were then pooled together with the TFV and TBV data to determine the overall pooled safety and efficacy of the five agents combined. To determine the importance of other factors that differed amongst the studies, we conducted a sensitivity analysis based upon the geographical location of the studies, the availability of LT and the study quality score. Geographical location could influence study results

since HBV genotypes, routes of HBV transmission and the natural history of chronic HBV differ in eastern vs. western countries. Similarly, subjects managed at a liver transplant centre may have a better 1-year survival compared to those without access to LT. Lastly, the impact of treatment efficacy may be better discerned in studies with a high vs. low quality score. Per supplementary Table S2, the geographical location of the studies did not impact any of the pooled efficacy parameters measured. However, patients treated at liver transplant centres had a lower transplant-free survival presumably due to their ability to undergo transplantation and these patients also had a significantly higher rates of HBeAg seroconversion. Furthermore, the patients enrolled in higher quality studies (i.e. quality score ≥ 6) that were more often prospective, controlled trials demonstrated a significantly lower overall survival rate compared to the patients enrolled in the lower quality studies which may be due to prospective tracking of patient outcomes. Lastly, the llod of the HBV DNA assay used in the LAM treatment studies did not lead to any significant differences in any of the efficacy outcomes reported (Table S3).

Safety analysis

Adverse events and renal insufficiency. None of the studies of lamivudine reported any serious adverse events (SAE) associated with this agent. Adefovir was associated with an SAE in 4% of treated patients with a low serum phosphate reported in 4 of 226 (2%) patients in one study.[28] Entecavir was associated with an SAE in 6% of treated patients in a pooled analysis of two studies.[31] In addition, a comparison of ADV and ETV in one prospective study and of TDF and ETV in another prospective study showed similar rates of SAE's (4% vs. 0%, $P = 0.89$) and (7% vs. 9%, $P = 0.72$), respectively.[30, 31]

Renal insufficiency defined as an increase of serum creatinine by ≥ 0.5 mg/dL over baseline occurred in 9% (5–17%) of patients treated with ADV and 10% (6–17%) of patients treated with ETV (Table 2). In contrast, none of the studies using LAM reported any instances of renal insufficiency. In the prospective RCT of TBV and LAM, there was a greater improvement in the calculated estimated glomerular filtration rate (GFR) from baseline amongst patients treated with TBV as compared to LAM (3.3 ± 3.3 mL vs. -4.3 ± 3.1 mL, $P = 0.02$).[25] In another study, the incidence of renal insufficiency at 1-year was similar with ETV and TDF (5% vs. 9%, $P = 0.53$).[31]

Drug resistance. The pooled rate of drug resistant HBV at 1-year with LAM of 11% (8–14%) was significantly higher than that seen with ADV (0%) and ETV (0%) (Table 2) However, two patients with pre-existing LAM-resistant HBV developed an additional point mutation that prompted a switch to TDF with continued suppression of HBV replication in one ETV study.[31] Finally, a trend towards a higher rate of drug resistance was seen with LAM compared to TBV after 2 years of treatment (39% vs. 29%; $P = 0.12$).[25]

DISCUSSION

A recent systematic review of anti-viral therapy in treatment naïve chronic HBV patients demonstrated that ETV and TDF are the preferred first line oral anti-viral agents due to their potency and low rate of inducing drug-resistant mutations during prolonged therapy. However, that systematic review only included RCTs of the available agents in patients with compensated chronic HBV.[36] Therefore, the aim of the current systematic review was to assess the efficacy and safety of the various oral anti-viral agents in patients with decompensated HBV cirrhosis. The size and design of these studies was quite heterogeneous (Table 4). Overall, the largest amount of data involved lamivudine monotherapy in decompensated HBV cirrhosis presumably due to the fact that this agent has been available for over 15 years in many countries. However, many of the early lamivudine studies did not have a contemporary control group and used fairly insensitive HBV DNA assays with a llod of 10^5 copies/mL (i.e. 43% of LAM studies) which may lead to an overestimate of its anti-viral efficacy and underestimate the rate of drug-resistant HBV. Nonetheless, significant objective improvements in liver disease severity were consistently noted with LAM compared to untreated controls. For example, LAM use in 245 patients was associated with an approximately threefold higher rate of 1-year transplant-free survival compared to 230 untreated controls ($P = 0.022$) (Table 3). However, resistance to lamivudine which occurred in 11% of these patients at 1 year has emerged as a major limitation particularly in patients with advanced disease who do not tolerate biochemical flares with emergence of drug-resistant HBV.[5] In addition, the RCT of LAM vs. placebo in compensated HBV cirrhosis patients demonstrated a higher rate of clinical outcomes in those who developed drug resistance during follow-up compared to those without resistance (11% vs. 5% at 32 months, $P = 0.031$) and a higher mortality rate in those with decompensation and drug-resistant HBV during post-treatment follow-up vs. the placebo-treated patients (35% vs 10% $P = 0.043$).[7, 8]

Table 4 | One year outcomes of patients with decompensated HBV cirrhosis treated for >6 months with oral anti-viral agents

Year (ref)	Country	December CTP ≥2 pts (%)	Normal ALT (%)	HBVDNA undetectable* (%)	HBeAg loss (%)	HBeAg sero-conversion (%)	Off LT list (%)	HCC (%)	LT (%)	LT free survival (%)	Overall survival (%)	Drug resistance (%)	Drug related-SAE (%)	Renal insuff
Studies using lamivudine														
2000[12]	Canada	22/23 (96)	NA	23/23 (100)	6/13 (46)	6/13 (46)	2/3 (67)	1/35 (3)	7/35 (20)	23/35 (66)	27/35 (77)	2/23 (9)	NA	NA
2001[13]	US	14/23 (61)‡	NA	23/23 (100)	4/16 (25)	1/16 (7)	8/23 (35)	NA	6/23 (26)	17/23 (74) †	23/23 (100)	2/20 (10)	None	None
2001[14]	US	NA	19/27 (71)	17/22 (77)	4/6 (67)	NA	NA	NA	Not applicable§	24/30 (80)	24/30 (80)	3/18 (17) ¶	None	None
2002[15]	US	NA	NA	57/71 (80)	17/60 (28)	NA	12/162 (7)**	NA	91/162 (56)††	53/162 (33)	144/162 (89)	18/162 (11)	None	None
2002[16]	Italy	12/25 (48)	NA	23/25 (92)	Not applicable	Not applicable	9/25 (36)	NA	11/25 (44)	13/25 (52)	24/25 (96)	1/14 (7)	None	None
2003[17]	US	23/75 (31)	25/52 (48)	30/41 (73)	12/36 (33)	7/36 (20)	Not applicable‡‡	0/75 (0)	1/75 (1)	63/75 (84)	64/75 (85)	8/75 (11)	None	None
2004[18]	UK	23/30 (77)	19/24 (79)	18/23 (78)	Not applicable	Not applicable	0/30 (0)	2/30 (7)	0/30 (0)	23/30 (77)	23/30 (77)	5/23 (22)	NA	NA
2005[19]	Greece	11/20 (55)	NA	19/20 (95)	Not applicable	Not applicable	NA	0/20 (0)	3/20 (15)	16/20 (80)	19/20 (95)	0/20 (0)	None	None
2005[20]	Taiwan§§	15/22 (68)	NA	24/24 (100)	3/9 (30)	3/9 (30)	Not applicable	1/30 (3.3)	Not applicable	21/30 (70)	21/30 (70)	2/24 (8)	NA	NA
2006[21]	US	NA	NA	NA	NA	NA	NA	5/160 (3)	11/160 (7)	149/149 (100)	160/160 (100)	NA	NA	NA
2007[22]	US	NA	NA	NA	NA	NA	NA	NA	8/122 (7)	100/122 (82)	108/122 (89)	6/122 (5)	NA	NA
2008[23]	Japan	NA	NA	NA	7/43 (16)	4/43 (10)	NA	1/43 (2.3)	NA	42/43 (98)	42/43 (98)	7/43 (16)	None	None
2009[24]	Taiwan	NA	NA	17/24 (73)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2010[25]	Asia-Pacific	NA	48/97‡‡ (50)	35/97‡‡ (36)	NA	NA	NA	13%‡‡	NA	102/116 (88)	102/116 (88)	38/97 (39) ‡‡	None	1/18 (6)
Studies using adefovir														
2005[26]	Korea*	13/18 (72)	14/18 (78)	15/18 (83)	4/18 (22)	3/18 (17)	NA	NA	0/46 (0)	18/18 (100)	18/18 (100)	0/18 (0)	None	1/18 (6)
2006[27]	Taiwan	NA	9/18 (50)	2/18 (11)	3/9 (33)	3/9 (33)	Not applicable	0/18 (0)	Not applicable	18/18 (100)	18/18 (100)	0/18 (0)	None	NA
2007[28]	US	NA	49/64 (77)	45/76 (59)	15/31 (48)	7/31 (23)	21/100 (21)	NA	43/226 (19)	151/226 (67)	194/226 (86)	0/226 (0)	8 (4) Low P: 4 (2)	6 (11)
2009[29]	France	NA	32/58 (55)	28/68 (41)¶¶	9/39 (23)	4/39 (10)	0/68 (0)	1/68 (1.5)	6/68 (9)	60/68 (97)	66/68 (97)	0/68 (0)	None	None
2009[30] §§§	Worldwide	60/89 (67)****	33/71 (46)	18/89 (20)	9/51 (18)	5/51 (10)	Not applicable	7/89 (8)	Not applicable	Not applicable	73/89 (80)	NA	4/89 (5)	11/89 (13)
Studies using entecavir														
2009[24]	Taiwan	NA	NA	24/24 (100)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Table 4 | (Continued)

Year (ref)	Country	December CTP ≥2 pts (%)	Normal ALT (%)	HBVDNA undetectable* (%)	HBeAg loss (%)	HBeAg sero-conversion (%)	Off LT list (%)	HCC (%)	LT (%)	LT free survival (%)	Overall survival (%)	Drug resistance (%)	Drug related-SAE (%)	Renal insuff
2009[30] §§§	Worldwide	61/100 (61) ****	49/78 (63)	57/100 (57)	6/54 (11)	3/54 (6)	Not applicable	6/100 (6)	Not applicable	Not applicable	82/100 (82)	NA	5/100 (5) LA in 1 patient	11/100 (11)
2011[31] †††	Worldwide	5/12 (42)	12/22 (55)	16/22 (73)	0/7 (0)	0/7 (0)	2/22 (11)	NA	0/22 (0)	20/22 (91)	20/22 (91)	0/3 (0)	0/22 (0)	1/22 (5)
2009[32]	Italy	NA	NA	25/35 (71)	NA	NA	NA	NA	NA	NA	NA	2/35 (6)¶¶¶	NA	NA
2009[33]	Korea	27/55 (49)	42/55 (76)	65/70 (93)***	19/35 (54)	8/35 (23)	NA	1/49 (2)	3/70 (4)	60/70 (86)	63/70 (90)	0/55 (0)	NA	NA
Study using tenofovir														
2011[31] ‡‡‡	Worldwide	7/27 (26)	26/45 (57)	31/44 (71)	3/14 (21)	3/14 (21)	NA	NA	2/45 (4)	41/45 (91)	43/45 (96)	0/8 (0)	2/45 (4)	4/45 (9)
Study using telbivudine														
2010[25]	Asia-Pacific	NA	57/98 (58)	39/98 (40)	NA	NA	NA	12%‡‡	NA	109/116 (94)	109/116 (94)	28/98 (29) ‡‡	1/116 (1); LA: 0	Increase in GFR 3.3 ± 3.3 mL from baseline.

A, abstract; CTP, child Turcotte Pugh; ETV, entecavir; HCC, hepatocellular carcinoma; LA, Lactic acidosis; LAM, lamivudine; LT, liver transplantation; NA, not available; RI, renal insufficiency (serum creratinine increase by 0.5 mg/dL from baseline); SAE, serious adverse effects; TF, tolerability failure.

* HBVDNA assays of varying sensitivity used across different studies $ Mean ALT reported 105 ± 80–41 ± 22 at 6 months.

† Time to death or LT longer with LAM compared to controls ($P < 0.001$).

‡ ≥3 CTP pts improvement.

§ Only those who did not undergo LT were analysed.

¶ Data obtained by corresponding the primary author.

** All removals were due to non liver-related causes.

†† Time pre LT longer in treated group ($P < 0.001$).

‡‡ Data at 2 years.

§§ 22 patients treated for >6 months.

¶¶ HBVDNA suppression better with HBeAg –ve disease (62% vs. 26%; $P < 0.01$).

*** HBVDNA suppression better in HBeAg –ve disease (96% vs. 81%; $P < 0.05$).

††† At 8 weeks of starting the study drug, patients not achieving predefined decrease in HBVDNA titre were considered as failures and were started on open-label truvada. Patients who discontinued study drug due to serious adverse effects related to study drug and could not start the medication again were considered and defined as tolerability failures (TF).

‡‡‡ Two patients each receiving entecavir and tenofovir died within first 6 months of starting the study medication.

§§§ Two patients initially randomised to adefovir actually received entecavir for the entire study period.

¶¶¶ Additional M-250 V resistance noted at 1 year with existing baseline LAM-resistance.

**** Data for stable or a decrease in the CTP score.

The majority of patients treated with adefovir had pre-existing LAM resistant HBV and many were treated with LAM and adefovir combination therapy (Table 1). Pooled data on the efficacy of ADV were comparable to LAM for serum ALT normalisation, improvement of CTP score and transplant-free survival. However, ADV was less potent with a slower onset of action compared to LAM with only 41% of patients having undetectable HBV DNA at 1 year compared to 83% with LAM (Table 2). Although, drug-resistant HBV was not reported in the 303 ADV-treated patients in this pooled analysis, the cumulative rate of ADV resistance is 29% at 5 years among compensated chronic HBV patients receiving ADV monotherapy.[37] These observations combined with the known dose-dependent nephrotoxicity of ADV make it a less attractive option for prolonged use in patients with decompensated HBV cirrhosis who frequently have unstable renal function.

The pooled data of ETV monotherapy in 243 patients with decompensated HBV cirrhosis showed anti-viral efficacy and suppression of HBV DNA to undetectable levels that was similar to that observed with LAM (80% vs. 83%) (Table 2). Of note, the incidence of undetectable HBV DNA was significantly higher with ETV compared to LAM in one RCT of 48 patients using a highly sensitive assay with a llod of 300 cp/mL (100% vs. 73%, $P = 0.02$).[24] Furthermore, none of the ETV-treated patients demonstrated evidence of entecavir resistant HBV at 1 year despite the presence of lamivudine resistant HBV in some of these patients. However, it should be noted that prolonged use of ETV at a dose of 1 mg per day in compensated HBV patients with lamivudine-resistant HBV is associated with a cumulative rate of entecavir-resistant HBV in up to 50% of patients treated for 5 years.[38]

Data on the use of TDF and TBV in decompensated HBV cirrhosis are restricted to one study for each drug. Tenofovir was as effective and potent as ETV with a similar side effect profile and no evidence of drug-resistant HBV at 1 year in a RCT of 112 total patients. In addition, 21% of the TDF treated patients were able to achieve HBeAg seroconversion and 4% lost HBsAg. Telbivudine was as effective as LAM with a similar side effect profile but TBV was also associated with a 29% rate of drug resistance at 2 years.[25] In addition, recent studies have demonstrated an increasing frequency of serum CPK elevations with prolonged telbivudine use.[39] Therefore, it would appear that TBV may be a second line agent for patients with decompensated HBV cirrhosis due to safety concerns.

Going forwards, a larger number of patients with drug-resistant HBV will likely be encountered in clinical practice who may present with decompensation in the midst of a biochemical flare. For example, 44 of the 122 (36%) liver transplant candidates enrolled in the HBV OLT study that received anti-viral therapy developed drug resistance during follow-up.[22] In a study of 53 patients with LAM-resistant HBV, TDF was superior to ADV in suppressing HBV DNA to undetectable levels at 1 year (100% vs. 44%; $P = 0.001$).[40] In addition, TDF was also shown to suppress as many as 80% of compensated patients with documented resistance to ADV and or LAM to undetectable levels.[41] Therefore, TDF may be of particular value in patients with drug-resistant HBV that present with decompensated cirrhosis. However, there are some concerns regarding the long-term safety of tenofovir in patients with malnutrition and low vitamin D levels.[42] Therefore, additional prospective studies with careful assessment of renal function and metabolic bone disease are needed with TDF treatment in decompensated HBV patients.

Drug safety is an important consideration when treating any disease and particularly so in patients with decompensated cirrhosis who have impaired drug metabolism, protein binding, and renal function. In our systematic review, LAM had the fewest number of SAE's reported which may, in part, relate to the retrospective nature of many of the LAM studies. Renal insufficiency with associated renal tubular dysfunction was reported in 6% of ADV-treated patients on the LT waiting list, 3% of treated patients with compensated cirrhosis and 21% of LT recipients.[28, 37, 43, 44] In our pooled analysis, the incidence of renal insufficiency with ADV was 9% which is likely an underestimate due to the lack of consistent monitoring in these studies.[28, 30]

Renal insufficiency was also reported in 10% of patients treated with ETV in our systematic review (Table 2). This is in contrast, to the experience with prolonged ETV therapy in compensated HBV cirrhosis wherein no cases of renal insufficiency were noted.[6, 45] The high rates of renal insufficiency observed in two of these studies is likely due to inclusion of patients with low baseline GFR.[30, 31] Tenofovir was also associated with renal insufficiency in 4 (9%) of the 45 patients treated in one study and the need for dose reductions in three additional patients.[31] In contrast, none of the patients treated with TBV developed renal insufficiency and in fact the mean GFR actually increased by 3.3 mL/min at 1 year.[25]

Another concern with the prolonged use of nucleos(t)ide analogues is the potential for mitochondrial toxicity

which may present with myopathy, neuropathy, rhabdomyolysis and lactic acidosis.[44–46] In the current analysis, lactic acidosis and mitochondrial toxicity were reported in only one of the 100 ETV-treated patients and it subsided despite continuing ETV.[30] Serious adverse effects with ETV also occurred in only 6% of treated patients consistent with the favourable safety profile of ETV in patients with compensated HBV cirrhosis.[47] However, an awareness of this adverse event and how it might present is critical when using these agents in patients with advanced chronic HBV.[48]

Several limitations regarding our systematic review require comment. Firstly, the inclusion criteria and study design varied greatly amongst the studies examined. However, all the study patients had decompensated liver disease and we were able to assess virological, biochemical and clinical parameters in the majority of studies (Table 1). Nonetheless, the heterogeneity in patient populations leads to a lower level of confidence in the accuracy of the pooled estimates. Secondly, the more recent studies of TDF, ETV and TBV all tended to use more sensitive assays for HBV DNA compared to the early LAM and ADV studies which limits our ability to directly compare the extent of viral suppression. Nonetheless, the overall rate of HBeAg seroconversion and ALT normalisation was fairly similar across the agents. In addition, there was only a single study of TDF and TBV which limits our ability to make recommendations regarding these agents. However, the use of randomised, controlled study designs with prospective assessment of clinical, virological and safety parameters with the newer agents provides higher quality data as reflected in the data quality scores (Table S1). Lastly, we were unable to complete a cost-effectiveness analysis comparing the available drugs due to the lack of quality of life data and associated costs of clinical care in most studies.

In summary, our systematic review indicates that all of the available oral agents can lead to improved virological, biochemical and clinical parameters amongst patients with decompensated HBV cirrhosis at 1 year of follow-up (Table 4). Furthermore, use of these agents in decompensated HBV patients is generally safe and well tolerated at 1 year but the increasing incidence of nephrotoxicity with prolonged ADV therapy and its slower onset of action make it a less attractive option for this patient population. In addition, the increasing rates of drug-resistant HBV with prolonged use of LAM, ADV and TBV monotherapy make these three agents less attractive for decompensated HBV patients. Therefore, although ETV and TDF had similar 1-year efficacy to LAM and TBV in our study, the lower rate of drug resistance associated with these drugs during prolonged use would make them more attractive as initial agents for decompensated HBV patients who require life-long treatment.[6] Our systematic review also highlights the need for additional prospective studies on the long-term safety and efficacy of TDF and ETV in a large cohort of previously untreated decompensated patients that are prospectively monitored for compliance, anti-viral drug resistance and safety parameters. In addition, further studies of the risks and benefits of these two agents in patients with drug-resistant HBV are needed to assist clinicians in the management of this expanding pool of patients.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Quality scores of the studies included in this systematic review.

Table S2. Sensitivity analysis of the pooled data from open-label studies.

Table S3. Sensitivity analysis of lamivudine open-label studies based on lower limit of detection (LLOD) of HBVDNA assay used.

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