

Tenofovir disoproxil for the treatment of chronic hepatitis B

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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1 Recommendations

This guidance does not apply to people with chronic hepatitis B who also have hepatitis C, hepatitis D or HIV.

- 1.1 Tenofovir disoproxil, within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.

2 The technology

- 2.1 Tenofovir disoproxil (Viread, Gilead) is a nucleotide analogue. It works by blocking the enzyme reverse transcriptase, which is responsible for hepatitis B virus (HBV) replication. Tenofovir disoproxil has a marketing authorisation in the UK for the treatment of chronic hepatitis B in adults with compensated liver disease, with evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.
- 2.2 Adverse events associated with the use of nucleotide analogues include lactic acidosis and progression of hepatomegaly. Additional adverse events reported for tenofovir disoproxil include headache, fatigue and gastrointestinal disorders. For full details of side effects and contraindications, see the summary of product characteristics.
- 2.3 The acquisition cost of tenofovir disoproxil (excluding VAT; BNF edition 56) is £255.00 for a 30-tablet pack. Costs may vary in different settings because of negotiated procurement discounts. Tenofovir disoproxil is licensed for use in adults over 18 years. The dosage is a once-daily tablet of 245 mg. The optimal treatment duration is currently unknown. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

- 3.1 The Appraisal Committee considered evidence submitted by the manufacturer of tenofovir disoproxil and a review of this submission by the Evidence Review Group (ERG).
- 3.2 The manufacturer approached the decision problem by comparing tenofovir disoproxil monotherapy with lamivudine, adefovir dipivoxil and entecavir in adults with compensated liver disease and active chronic hepatitis B (that is, evidence of viral replication and active liver inflammation). The manufacturer did not compare tenofovir disoproxil with any of the interferons. The primary outcome measures outlined in the decision problem were virological response (hepatitis B virus [HBV] DNA), histological improvement (inflammation and fibrosis), biochemical response (for example, ALT levels), and hepatitis B surface antigen (HBsAg) and hepatitis B 'e' antigen (HBeAg) seroconversion rate.
- 3.3 The manufacturer's submission presented evidence on the clinical effectiveness of tenofovir disoproxil from two randomised controlled trials (RCTs) that compared tenofovir disoproxil with adefovir dipivoxil. The protocol for both studies specified that the populations would be people who had not previously received nucleotide analogue therapy, although prior experience of the nucleoside analogues lamivudine or emtricitabine was allowed in the study of people with HBeAg-negative chronic hepatitis B. One trial compared tenofovir disoproxil with adefovir dipivoxil in people with HBeAg-positive hepatitis B (176 participants received tenofovir disoproxil and 90 adefovir dipivoxil); the other made the same comparison in people with HBeAg-negative disease (250 participants received tenofovir disoproxil and 125 adefovir dipivoxil).
- 3.4 The results of the two RCTs showed that at 48 weeks tenofovir disoproxil gave a greater proportion of complete responses (that is, histological response and HBV DNA below 400 copies per ml) than adefovir dipivoxil in people with HBeAg-positive and HBeAg-negative disease. The difference was statistically significant ($p < 0.001$, in both trials). A similar proportion of people with HBeAg-positive disease had seroconversion or HBeAg loss with tenofovir disoproxil and adefovir dipivoxil, but significantly more people treated with tenofovir disoproxil had hepatitis B surface antigen (HBsAg) loss at 48 weeks (3.2% versus 0.0%,

p=0.018). No people with HBeAg-negative disease in either treatment group had experienced HBsAg loss or seroconverted to anti-HBs at 48 weeks.

- 3.5 Both RCTs reported a smaller proportion of people with HBV mutation-conserved site changes (suggestive of a potential for future resistance) with tenofovir disoproxil than with adefovir dipivoxil at 48 weeks. There were no cases of substitution in the HBV polymerase/reverse transcriptase associated with resistance to tenofovir disoproxil in either study. There were no cases of viral resistance.
- 3.6 The incidence of severe, life-threatening or disabling adverse events was similar between treatment groups, with no deaths reported in either study. However, more participants had at least one treatment-related adverse event in the tenofovir disoproxil treatment group in one study (30.7% versus 16.7%, p=0.018); the manufacturer attributed this to a higher incidence of 'mild nausea'. The incidence of arthralgia was higher for the group receiving tenofovir disoproxil in the other study (6.0% versus 0.0%, p=0.003).
- 3.7 The manufacturer pointed out that there were no trials that included all treatment options in any of the patient populations and therefore a series of mixed-treatment comparison meta-analyses were carried out to assess the relative efficacy of adefovir dipivoxil, entecavir, lamivudine, tenofovir disoproxil and placebo in nucleoside-naïve and lamivudine-refractory patients. For HBeAg-positive disease, the included outcomes were the probability of achieving HBV DNA suppression (less than 300 copies per ml), and the probability of HBeAg seroconversion over 1 year of treatment. All analyses were conducted using random-effects models unless the between-studies standard deviation was close to zero. For HBeAg-positive nucleoside- and nucleotide-naïve participants, the mixed-treatment comparison showed that tenofovir disoproxil had a statistically significantly higher predicted probability of HBV DNA suppression than all comparators. There was no statistically significant difference between the antiviral drugs for the probability of seroconversion.
- 3.8 For HBeAg-negative disease, the manufacturer explained that no meaningful analysis could be undertaken because of the small number of trials identified. The manufacturer undertook an additional analysis combining trials investigating patients with HbeAg-positive disease and those with HbeAg-negative disease. In

this additional analysis, the proportion of participants who were HBeAg positive was considered as a covariate. The results for HBeAg-negative participants were similar to those seen in the HBeAg-positive subgroup in terms of the probability of achieving HBV DNA suppression (less than 300 copies per ml). The manufacturer pooled data from the RCTs and the observational studies identified while undertaking the systematic review in order to obtain and compare estimates of resistance for available treatments for HBeAg-positive treatment-naive and lamivudine-refractory patients. The results suggested a low risk of viral resistance with tenofovir disoproxil in both treatment-naive and lamivudine-refractory patients and there were no cases of resistance with up to 2 years of use.

- 3.9 The manufacturer submitted a cost-effectiveness analysis using a Markov model that could be applied either to a cohort of people with HBeAg-positive or HBeAg-negative disease at the start of treatment. The model had 11 main states defined as: active chronic hepatitis B (HBV DNA less than or equal to 300 copies per ml), viral suppression (HBV DNA less than 300 copies per ml), HBeAg seroconverted (not applicable to HBeAg-negative disease), HBsAg seroconverted, compensated cirrhosis with detectable HBV DNA, compensated cirrhosis with undetectable HBV DNA, decompensated cirrhosis, hepatocellular carcinoma, liver transplantation (year in which transplantation occurs), post liver transplantation and death. These were based on health states used in previous economic evaluations. The model was designed to compare tenofovir disoproxil, adefovir dipivoxil, lamivudine and entecavir. It incorporated sequences of first-, second- and third-line treatments and people were assumed to move on to the next treatment regimen if they developed resistance to their current treatment. For people with HBeAg-positive disease and those with HBeAg-negative disease the model has a lifetime horizon, a cycle length of 1 year, and patients are assumed to continue to receive an antiviral regimen until they die, undergo HBeAg seroconversion, undergo HBsAg seroconversion, or develop resistance, at which stage they would switch to an alternative regimen.
- 3.10 In the base-case manufacturer's economic analysis, after treatment sequences that were dominated or extendedly dominated were excluded, the incremental cost-effectiveness ratios (ICERs) of interest in HBeAg-positive chronic hepatitis B were as follows:
- lamivudine as first-line treatment followed by tenofovir disoproxil had an ICER

of £6,014 per quality-adjusted life year (QALY) relative to lamivudine followed by best supportive care

- tenofovir disoproxil as first-line treatment followed by lamivudine had an ICER of £9,940 per QALY relative to lamivudine followed by tenofovir disoproxil
- tenofovir disoproxil as first-line treatment followed by the combination of tenofovir disoproxil and lamivudine had an ICER of £13,619 per QALY relative to tenofovir disoproxil followed by lamivudine
- tenofovir disoproxil as first-line treatment followed by the combination of tenofovir and lamivudine followed by entecavir had an ICER of £36,583 per QALY relative to tenofovir disoproxil followed by tenofovir disoproxil plus lamivudine.

3.11 In the base-case manufacturer's economic analysis, after treatment sequences that were dominated or extendedly dominated were excluded, ICERs of interest in HBeAg-negative chronic hepatitis B were as follows:

- tenofovir disoproxil as first-line treatment followed by lamivudine had an ICER of £9,811 per QALY relative to best supportive care
- tenofovir disoproxil as first-line treatment followed by the combination of tenofovir and lamivudine had an ICER of £13,854 per QALY relative to tenofovir disoproxil followed by lamivudine alone
- tenofovir disoproxil as first-line treatment followed by the combination of tenofovir and lamivudine followed by entecavir had an ICER of £20,781 per QALY relative to tenofovir disoproxil followed by tenofovir disoproxil plus lamivudine.

3.12 The manufacturer also presented results for an analysis in a cohort in which lamivudine resistance had developed:

- tenofovir disoproxil alone as treatment for lamivudine-refractory HBeAg-positive disease had an ICER of £7,707 per QALY relative to best supportive care
- tenofovir disoproxil alone as treatment for lamivudine-refractory HBeAg-negative disease had an ICER of £11,078 per QALY relative to best supportive

care.

- 3.13 The ERG viewed the mixed-treatment comparison methodology to be generally sound, but pointed out that it was weakened by the small number of studies (as low as 1 in some networks), a lack of quality assessment of included studies, no discussion of potential clinical heterogeneity and limited discussion of statistical heterogeneity. Therefore the ERG concluded that the results should be treated with caution.
- 3.14 The ERG viewed the pooled analysis of resistance in the manufacturer's submission as appropriate, but pointed out that data for long-term resistance (more than 2 years) are currently unavailable.
- 3.15 The ERG pointed out that there were a number of analytical errors in the manufacturer's electronic model and therefore re-ran the model with discount factors for future health effects applied to all of the model cycles, amendments to transition matrices and a once-only application of a reduction of excess mortality for patients with compensated cirrhosis achieving viral suppression. The results for people with HBeAg-positive disease gave an ICER for first-line tenofovir disoproxil followed by lamivudine relative to lamivudine followed by tenofovir disoproxil of £17,590. The ICER for tenofovir disoproxil followed by lamivudine plus tenofovir disoproxil relative to first-line tenofovir disoproxil followed by lamivudine was £27,479. The results for people with HBeAg-negative disease gave an ICER for first-line tenofovir disoproxil followed by lamivudine relative to lamivudine followed by tenofovir disoproxil of £17,640. The ICER for tenofovir disoproxil followed by lamivudine plus tenofovir disoproxil relative to first-line tenofovir disoproxil followed by lamivudine was £28,324.
- 3.16 Full details of all the evidence are in the [manufacturer's submission and the ERG report](#).

4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of tenofovir disoproxil, having considered evidence on the nature of the condition and the value placed on the benefits of tenofovir disoproxil by people with chronic hepatitis B, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.
- 4.2 The Committee was advised by the clinical experts of the importance of having a variety of treatments available in order to combat the problem of viral resistance. The Committee heard from the patient experts that tenofovir disoproxil was well tolerated with few adverse effects. The patient experts also explained that treatments which are associated with a low risk of viral resistance would increase peace of mind and hence quality of life. The Committee was also mindful of the long-term risk of progression to cirrhosis or hepatocellular carcinoma associated with chronic hepatitis B infection, and the impact of this in terms of costs, mortality and health-related quality of life.
- 4.3 The Committee considered the treatment options available for patients with chronic hepatitis B in the UK. The Committee discussed the relevance of previous NICE guidance on chronic hepatitis B and where in the treatment pathway tenofovir disoproxil should be considered. The Committee understood that tenofovir disoproxil could be considered an alternative to other antiviral drugs as primary first-line therapy if an interferon is considered inappropriate (because of a contraindication or intolerance) or as second-line therapy when either a course of an interferon has not brought about seroconversion, or resistance has developed to another antiviral drug.
- 4.4 The Committee discussed the clinical effectiveness of tenofovir disoproxil in treating chronic hepatitis B and considered all of the available evidence. It acknowledged that in the RCTs tenofovir disoproxil was more effective than adefovir dipivoxil in terms of surrogate endpoints. The Committee then considered the indirect mixed-treatment comparison undertaken by the manufacturer to compare tenofovir disoproxil with entecavir, lamivudine and adefovir dipivoxil in people with HBeAg-positive and HBeAg-negative disease.

The Committee noted discrepancies between the results from the mixed-treatment comparison and those from the individual RCTs. The Committee also took into account the ERG's remarks on the quality of the analysis of the mixed-treatment comparison. However, the Committee agreed that the identified weaknesses in the analysis were not sufficiently serious to prevent it making a decision on the use of tenofovir disoproxil in chronic hepatitis B in the light of the evidence available from the individual RCTs.

- 4.5 The Committee discussed the limitations and the degree of uncertainty in the economic models presented. The Committee noted that both the manufacturer's and ERG's estimates of the ICERs for tenofovir disoproxil as first-line monotherapy in both HBeAg-positive and -negative disease were below £20,000 per additional QALY gained. The Committee also noted that the results of the probabilistic sensitivity analysis showed a 60% and 58% probability that first-line therapy with tenofovir disoproxil is the most cost-effective antiviral strategy for treatment of HBeAg-positive and HBeAg-negative disease at a willingness to pay threshold of £20,000 per QALY. The Committee noted that the effectiveness estimates used in the economic model were taken from the mixed-treatment comparison and that concern had been expressed about this comparison. However, the Committee was satisfied that the effectiveness of tenofovir disoproxil was at least comparable to that of other currently recommended options, notably entecavir, and that the acquisition cost of tenofovir disoproxil was lower. Therefore the Committee concluded that tenofovir disoproxil is a cost-effective option for the treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B.
- 4.6 The Committee understood the high-degree of mutability of the hepatitis B virus and noted that tenofovir disoproxil appeared to have a low potential for inducing viral resistance. The Committee also noted that the estimates of resistance rates for tenofovir disoproxil and other antiviral drugs used in the cost-effectiveness analysis were based on a pooled analysis of resistance data undertaken by the manufacturer. Taking into account the ERG's comments and the clinical expert views on the biological plausibility of the findings, the Committee agreed that tenofovir disoproxil had a similar or more favourable resistance profile at 1 year compared with other available treatments for chronic hepatitis B. However, the Committee agreed that given the data available it could not be assumed that this low rate of resistance would be maintained in the long term.

4.7 The Committee discussed the possibility that tenofovir disoproxil might be used as combination therapy with another antiviral agent as a strategy to reduce resistance. They heard from the clinical experts that this strategy would be based on experience gained in treating HIV, and that there was little evidence to support such a strategy in chronic hepatitis B at present. Furthermore, the experts noted that current European guidelines recommended entecavir or tenofovir disoproxil monotherapy as first-line therapy. The Committee heard that there was a lack of data from RCTs to allow an evaluation of the effectiveness of tenofovir disoproxil in combination with other agents as first-line or subsequent therapy. The Committee also heard that data on long-term resistance would be needed to guide decisions on whether combination therapy should be given, and these data are presently unavailable. However, the Committee noted comments from the consultees that there may be circumstances in which combination therapy might be appropriate (for example, tenofovir disoproxil could be added to another drug as rescue therapy when resistance to the first drug has developed). Although acknowledging that evidence on the long-term clinical effectiveness and cost-effectiveness of combination therapy was lacking, the Committee agreed that using tenofovir disoproxil in combination regimens might be acceptable when evidence supporting its clinical effectiveness becomes available. The Committee concluded that the available evidence only supported the use of tenofovir disoproxil as monotherapy, but it accepted that there may be exceptional circumstances in which tenofovir disoproxil might be used in combination with other antiviral agents. Therefore in recommending tenofovir disoproxil as an option for the treatment of chronic hepatitis B, the Committee did not specify that the treatment should be restricted absolutely to use as monotherapy, but noted that this was the approach that was supported by the evidence.

5 Implementation

- 5.1 Section 7 of the [National Institute for Health and Care Excellence \(Constitution and Functions\)](#) and the [Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has chronic hepatitis B and the healthcare professional responsible for their care thinks that tenofovir disoproxil is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for further research

- 6.1 A phase III trial of entecavir plus tenofovir disoproxil combination therapy versus entecavir monotherapy in treatment-naive people with chronic hepatitis B is currently recruiting participants.
- 6.2 Research on the long-term risk of resistance with tenofovir disoproxil monotherapy and tenofovir disoproxil in combination with other antiviral agents is needed because few RCTs are currently available.

7 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committee is one of NICE's standing advisory committees. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each Appraisal Committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor David Barnett

Professor of Clinical Pharmacology, University of Leicester

Dr David W Black

Director of Public Health, Derbyshire County Primary Care Trust

Mr Mark Campbell

Director of Standards, Bury Primary Care Trust

Professor Mike Campbell

Professor of Medical Statistics, University of Sheffield

Mr David Chandler

Lay member

Mr Peter Clarke

Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Merseyside

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance R & D Unit

Dr Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Dyfrig Hughes

Reader in Pharmacoeconomics, Centre for Economics and Policy in Health, Bangor University

Dr Catherine Jackson

Professor of Primary Care Medicine, University of St Andrews

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Professor Peter Jones

Pro Vice Chancellor for Research and Enterprise, Keele University

Mr Henry Marsh

Consultant Neurosurgeon, St George's Hospital, London

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Richard Alexander Nakielny

Consultant Radiologist, Royal Hallamshire Hospital, Sheffield

Mrs Ruth Oliver-Williams

Head of Nursing/Quality Improvement Lead Surgical Services, Royal Derby Hospital, Derby

Dr Katherine Payne

Health Economics Research Fellow, University of Manchester

Dr Danielle Preedy

Lay member

Dr Philip Rutledge

Consultant in Medicines Management, NHS Lothian

Mr Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Dr Surinder Sethi

Consultant in Public Health Medicine, North West Specialised Services Commissioning Team

Professor Andrew Stevens (Chair)

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Dr Matt Stevenson

Technical Director, School of Health and Related Research, University of Sheffield

NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Helen Tucker

Technical Lead

Janet Robertson

Technical Adviser

Laura Malone

Project Manager

8 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessments Centre:

- Jones J, Colquitt J, Shepherd J, et al, Tenofovir disoproxil fumarate for the treatment of chronic hepatitis B, January 2009.

The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Manufacturers or sponsors, were also invited to make written submissions. Professional or specialist and patient or carer groups and commentator organisations had the opportunity to give their expert views. Manufacturers, or sponsors, professional or specialist and patient or carer groups and commentator organisations also have the opportunity to appeal against the final appraisal determination.

Manufacturer or sponsor

- Gilead Sciences (tenofovir disoproxil fumarate)

Professional or specialist and patient or carer groups:

- Association of Clinical Microbiologists
- Association of Medical Microbiologists
- Association of Nurses in Substance Abuse
- British Association for Sexual Health and HIV
- British Association for the Study of the Liver
- British Infection Society
- British Transplantation Society
- Chinese National Healthy Living Centre

- Health Protection Agency
- Hepatitis B Foundation UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- South Asian Health Foundation

Other consultees

- Department of Health
- Liverpool Primary Care Trust
- Welsh Assembly Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- Bristol Myers Squibb (entecavir)
- Department of Health, Social Services and Public Safety for Northern Ireland
- GlaxoSmithKline (lamivudine)
- MRC Clinical Trials Unit
- National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA Programme)
- NHS Quality Improvement Scotland
- Roche Products (interferon alfa 2a and peginterferon alfa 2a)
- Southampton Health Technology Assessment Centre, University of Southampton

The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer or sponsor consultees and commentators. They gave their expert personal view on tenofovir disoproxil by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to

comment on the ACD.

- Professor Geoffrey Dusheiko, nominated by Royal College of Physicians – clinical specialist
- Dr Mark Nelson, nominated by Royal College of Physicians – clinical specialist
- Mr Anil Patel, nominated by the Hepatitis B Foundation UK – patient expert
- Ms Stella Pendleton, nominated by the Hepatitis B Foundation UK – patient expert

Update information

February 2014: Implementation section updated to clarify that tenofovir disoproxil is recommended as an option for treating chronic hepatitis B.

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