Cost-effectiveness of antiviral treatment of chronic hepatitis B in Belgium. Part 1: Literature review and results of a national study

KCE reports 127C

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
Belgian Health Care Knowledge Centre
2010

The Belgian Health Care Knowledge Centre

Introduction: The Belgian Health Care Knowledge Centre (KCE) is an organization of public interest, created on the 24th of December 2002 under the supervision of the Minister of Public Health and Social Affairs.
KCE is in charge of conducting studies that support the political decision making on health care and health insurance.

Administrative Council

Actual Members: Pierre Gillet (President), Dirk Cuypers (Vice-president), Jo De Cock (Vice-president), Frank Van Massenhove (Vice-president), Yolande Avondtroodt, Jean-Pierre Baeyens, Ri de Ridder, Olivier De Stexhe, Johan Pauwels, Daniel Devos, Jean-Noël Godin, Floris Goyens, Jef Maes, Pascal Mertens, Marc Moens, Marco Schetgen, Patrick Verertbruggen, Michel Foulon, Myriam Hubinon, Michael Callens, Bernard Lange, Jean-Claude Praet.

Substitute Members: Rita Cuypers, Christiaan De Coster, Benoît Collin, Lambert Stamatakis, Karel Vermeyen, Katrien Kesteloot, Bart Ooghe, Frederic Lernoux, Anne Vanderstappen, Paul Palsterman, Geert Messiaen, Anne Remacle, Roland Lemeye, Annick Poncé, Pierre Smiets, Jan Bertels, Catherine Lucet, Ludo Meyers, Olivier Thonon, François Perl.

Government commissioner: Yves Roger

Management

Chief Executive Officer: Raf Mertens

Assistant Chief Executive Officer: Jean-Pierre Closon

Information

Federaal Kenniscentrum voor de gezondheidszorg - Centre fédéral d'expertise des soins de santé –
Belgian Health Care Knowlegde Centre.
Centre Administratif Botanique, Doorbuilding (10th floor)
Boulevard du Jardin Botanique 55
B-1000 Brussels
Belgium
Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85
Email : info@kce.fgov.be
Web : http://www.kce.fgov.be

Cost-effectiveness of Antiviral Treatment of Chronic Hepatitis B in Belgium. Part 1: Literature Review and Results of a National Study

KCE reports 127C

YVES HORSMANS, NANCY THIRY, MAÏTÉ LE POLAIN, MICHAEL ADLER,
ISABELLE COLLE, JEAN DELWAIDE, PETER MICHIELSEN,
HANS ORLENT, PIERRE VAN DAMME, FRANK HULSTAERT

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
Belgian Health Care Knowledge Centre
2010

KCE reports 127C

Title : Cost-effectiveness of antiviral treatment of chronic hepatitis B in Belgium. Part 1: Literature review and results of a national study.

Authors : Yves Horsmans (University Hospital Saint-Luc, Brussels), Nancy Thiry (KCE), Maïté le Polain (KCE), Michael Adler (University Hospital ULB Erasme, Brussels), Isabelle Colle (Ghent University Hospital), Jean Delwaide (University Hospital of Liège), Peter Michielsen (University Hospital Antwerp), Hans Orlent (AZ St Jan AV, Brugge), Pierre Van Damme (University of Antwerp), Frank Hulstaert (KCE)

External experts : Philippe Beutels (University of Antwerp), Thierry Christiaens (University of Ghent), Chantal de Galocsy (HIS Bracops Hospital, Brussels), André Elewaut (University Hospital Ghent), Patrick Goubau (University Hospital Saint-Luc, Brussels), Catharina Mathei (University of Leuven), Frederik Nevens (University Hospital of Leuven), Marc Vandecasteele (University Hospital of Leuven and RIZIV/INAMI).

Acknowledgements : The authors wish to thank Stephan Devriese (KCE) for accessing the permanent population sample, Stefaan Van De Sande (KCE) for assistance in the preparation of the requests to the privacy commission and the team from VeedaCR nv/sa and in particular Eva Vannieuwenhuyse, Marie-Paule Derde and Leonard Kaufman for the organization of the patient survey. We also wish to acknowledge the many investigators who actively participated to the survey: Collins Assene, Stefan Bourgeois, Stephane de Maeght, Eric Goffin, Joannes Holvoet, Pierre Lammens, Luc Lasser, Hendrik Reynaert, Geert Robaeys, Dirk Sprengers and all co-investigators.

External validators : Anna Lok (University of Michigan, USA), Steven Simoens (University of Leuven), Stefan Zeuzem (University of Frankfurt, Germany).

Conflict of interest : Prof Horsmans declares to have received research funds from Roche, Schering and GSK, consultancy fee's from GSK, Roche, Schering, Gilead, Bayer, Novartis and BMS, and to have participated as investigator in trials of GSK, Roche, Schering, Gilead, Novartis and BMS. Prof Colle declares that her department received research funds from Roche and Schering Plough. She further received consultancy fees from BMS, speaker fees from BMS and Schering Plough, and travel allowances from Roche, Schering Plough, BMS and Gilead. Prof Lok declares that she received research funds from Schering, Roche, GSK, Gilead and Bristol-Myers Squibb; and honoraria for attending advice committees at Roche, Gilead, BMS and Bayer. Prof Zeuzem declares to have received speaker fee's from BMS, Gilead, Novartis, Roche and Schering Plough.

Disclaimer: The external experts were consulted about a (preliminary) version of the scientific report. Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.

Layout: Ine Verhulst

Brussels, 7th April 2010

Study nr 2008-11

Domain: Health Technology Assessment (HTA)

MeSH: Hepatitis B virus; Hepatitis B, Chronic; Antiviral Agents; Interferon-alpha; Cost-Benefit Analysis

NLM classification: WC 536

Language: English

Format: Adobe® PDF™ (A4)

Legal depot: D/2010/10.273/24

How to refer to this document?

Horsmans Y, Thiry N, le Polain M, Adler M, Colle I, Delwaide J, Michielsen P, Orlent H, Van Damme P, Hulstaert F. Cost-effectiveness of antiviral treatment of chronic hepatitis B in Belgium. Part 1: Literature review and results of a national study. Health Technology Assessment (HTA). Brussels: Belgian Health Care Knowledge Centre (KCE). 2010. KCE Reports 127C. D/2010/10.2738/24.

Executive summary

RESEARCH SUBJECT AND METHODS

In this project we study the natural history and epidemiology of chronic infections with the hepatitis B virus (HBV), and the efficacy, effectiveness and cost-effectiveness of the currently approved antiviral treatments for this infection.

Parts of the project were outsourced by KCE to a group of Belgian hepatologists. This concerned the sections on epidemiology, natural history, and the efficacy and effectiveness of antiviral treatment. These parts were mainly based on existing literature reviews and treatment guidelines. The systematic literature review and critical appraisal of the cost-effectiveness evaluations of chronic hepatitis B (CHB) treatments was performed by KCE.

In addition, individual clinical patients' information and quality of life (QoL) data were collected in collaboration with the Belgian hepatologists and a contract research organisation. These data were subsequently linked to individual healthcare consumption data. This prospective study allowed to better characterise the patients seeking specialised healthcare in Belgium for their chronic HBV infection or complications thereof.

The analysis of the healthcare consumption data by disease phase and the construction of a Markov model will be covered in a second report on this topic. The budget impact for the National Institute for Health and Disability Insurance (NIHDI) of introducing new treatments will also be considered.

NATURAL HISTORY AND EPIDEMIOLOGY

The hepatitis B virus is a small circular DNA virus. Chronic infections (HBsAg+) with this virus affect about 5% of the world population and 0.7% of the Belgian population. Compared with a prevalence of 0.1-2% in Western Europe and the US, the prevalence is 2-8% in the Mediterranean countries and Eastern Europe, and 8-20% in high endemic regions such as South Asia and sub-Saharan Africa. Vaccination can prevent infection but not cure it. In low endemic countries, such as Belgium, infection is usually acquired via injecting drug use, sexual contact or body piercing. In most of these cases the immune system will suppress the virus and only 5 to 10% of the infections will become chronic. An increasing proportion of the population chronically infected in Western Europe consists of immigrants from endemic regions. Most of these subjects have been infected from their infected mother during birth, and infections at that young age have a high probability of becoming chronic. During many years or decades the virus does not cause any significant symptoms and the infection is often discovered by chance during a blood examination in these patients. The presence of HBV can be detected based on its DNA (HBV DNA) or its antigens, e.g. hepatitis B surface antigen (HBsAg) and e antigen (HBeAg). The human immune response to the virus is reflected by detectable antibody levels to these antigens.

After years or decades of 'immune tolerance' the immune system starts to attack the virus and more severe inflammation and damage may occur in the liver (hepatitis), most often reflected by increased levels of liver enzymes (e.g. alanine aminotransferase, ALT). Sometimes the virus can be suppressed during this 'immune reactive phase' and the patient becomes an 'inactive carrier'. Infections in patients who develop anti-HBs antibodies and who are no longer HBsAg+ are considered 'resolved'. However, many patients spontaneously develop a mutated virus that prevents HBeAg expression, resulting in 'HBeAg negative chronic hepatitis'. The characteristics of the major phases of the HBV infection are given below. Not all patients go through every phase (Table A).

The chronic hepatitis leads to scar formation in the liver (fibrosis), sometimes resulting in life threatening liver cirrhosis. This process is accelerated e.g. by alcohol (ab)use. The annual transition rate to cirrhosis is higher in HBeAg- chronic hepatitis and in low endemic areas and varies from 1.6% to 9.7%. In addition, patients with CHB have an increased risk of developing hepatocellular carcinoma (HCC). For patients with a final stage of cirrhosis or limited forms of HCC a liver transplantation can be life saving.

Table A. The distinct phases of infections with the hepatitis B virus

Phases	Immune tolerance	Immune active CHB		Inactive carrier	Reactivation	Resolved
		HBeAg+ (wild type) Immune reactive	HBeAg- (precore mutant) CHB			
HBsAg	+	+	+	+	+	-
HBeAg	+	+	-	-	+ or -	-
Anti-HBe	-	-	+	+	+ or -	+
ALT	Normal	Elevated	Fluctuating	Normal	Elevated or normal	Normal
HBV DNA	> 2 Mio IU/mL	Typically > 20 000 IU/mL	> 2 000 IU/mL	< 2 000 IU/mL	> 2 000 IU/mL	< 2 000 IU/mL in most
Histologic progression	Minimal	Yes	Yes	Minimal	Yes	No
Consider treatment ?	No	Yes	Yes	No	Yes	No

TREATMENT

Guidelines for treatment of CHB have been updated over the last few years with the market introduction of a number of antiviral agents. The reimbursement criteria in Belgium have remained very restrictive for a long time, and were in part in contradiction with the updated guidelines. Only very recently, reimbursement criteria were adapted and now are somewhat more in line with international guidelines. They also became less restrictive, now also allowing treatment in CHB patients without liver fibrosis.

A complete elimination of HBV is not possible. The RCTs used to support marketing approval of antiviral drugs in CHB showed histologic (various scores used for inflammation and fibrosis), virologic (HBV DNA), biochemical (ALT), and serologic (HBe seroconversion in HBeAg+ CHB) improvement over placebo after one year of treatment. The long-term goal of the treatment is to prevent the development of cirrhosis and HCC. It is recommended not to treat patients who are in the 'immune tolerance' phase and 'inactive carriers' (Table A).

In order to be reimbursed, all antiviral drugs require a prescription by a medical specialist in internal medicine and approval by the sickness fund.

Interferon-alpha was introduced in 1991 and was replaced in 2007 by pegylated interferon-alfa2a (Peg-IFN, Pegasys®). It requires medical monitoring for side-effects, including depression. Depression is however seen less frequently compared with Peg-IFN treatment in chronic hepatitis C patients. It is administered subcutaneously weekly for one year and will result in HBeAg loss in about a third of HBeAg+ CHB patients and in HBsAg loss in 3% of HBeAg+ and 4% of HBeAg- CHB patients.

Antiviral nucleos(t)ide analogues (NAs) are available as pills, are generally well tolerated and may need to be taken lifelong. The first NA, i.e. lamivudine (Zeffix®), obtained reimbursement in 2001 as a first line treatment. It was followed by adefovir dipivoxil (Hepsera®), but only for second line treatment. Only very recently tenofovir (Viread®) and entecavir (Baraclude®) obtained reimbursement for first line treatment.

The NA class of drugs has the potential for mitochondrial damage, leading to myopathy and neuropathy. For telbivudine, not marketed in Belgium, elevations of creatinine kinase and occasional cases of myopathy have been reported. In combination with Peg-IFN alpha severe neuropathy has been seen. Another NA was recently withdrawn for mitochondrial toxicity. Adefovir and tenofovir may cause nephrotoxicity and renal tubular damage.

After 4 years of lamivudine treatment HBV will have developed mutations causing resistance to lamivudine in over half of the patients. HBV develops much less frequently resistance to the more recently introduced NAs. Therefore, these agents are more likely to lower HBV DNA for more than 5 years in most patients. In studies with duration up to 5 years, they have also shown to improve liver inflammation and fibrosis scores. In about half of the HBeAg+ CHB patients HBeAg seroconversion can be induced, but this effect is frequently reverted after treatment discontinuation. The major reason for giving an antiviral treatment is that long-term lowering of HBV DNA levels will translate in fewer cases of liver cirrhosis and HCC. These assumptions are however still uncertain as there are no high-quality long-term research studies to support them. Such long-term studies have not been a requirement for obtaining marketing approval nor for obtaining reimbursement.

However, a single RCT of lamivudine in 651 Asian patients with chronic hepatitis B (58% were HBeAg+) and cirrhosis or advanced fibrosis showed about a 50% decreased rate of hepatic decompensation. The reduction in the rate of HCC approached statistical significance. No other RCTs with NAs have confirmed these important findings.

THE PATIENT SURVEY

Prospective clinical and QoL data were collected in patients visiting their liver specialist in Belgium during the first half of 2009 for chronic HBV infection or a non-acute complication thereof. Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) co-infections were excluded. Patients completed the EQ-5D QoL questionnaire. The investigators completed a clinical case-report form including the disease phase/stage, laboratory values and antiviral treatment for 2009 and, if available, for 2006. These data were linked to the 2006 costs for the NIHDI (National Institute for Health and Disability Insurance, INAMI/RIZIV), respecting the privacy legislation.

A total of 18 study centres/investigators participated, including all 6 liver transplant centres. Written informed consent to participate was obtained in 544 patients. According to the investigators most immigrant patients without residence permit refused to participate to the study. In larger cities, these patients reportedly accounted for about 20% of all consulting patients.

The EQ-5D form was completed by 527 patients. Patients were on average 46 years old, two thirds of them were male. About half of all patients in the study had a country of origin outside Europe. We extrapolated the results of the survey, the data from the transplant centres and the number of patients receiving Zeffix in Belgium, and estimate that in 2009 about 3300 patients consulted a medical specialist for chronic HBV infection without HCV or HIV co-infection (Table B). The patient subgroup distribution is in agreement with another large Belgian survey conducted in 2008. As about 2% of the Belgian population received an HBeAg test prescription in the 2002-2008 period (data extracted from the permanent population sample), the HBsAg+ prevalence may be higher than 0.7%, a rate based on 1993 data. These subjects are expected to consist mainly of inactive carriers, never visiting a liver specialist or only occasionally.

Table B. Mean utility score and estimated number of patients visiting a liver specialist for chronic HBV infection in Belgium in 2009

Hepatitis B infection phase or complication	Mean utility score*	Estimated number for Belgium	% of patients
Immune tolerance phase	0.81 (n=22)	119	3.6
Inactive carrier phase	0.83 (n=153)	1266	38.6
Immune reactive phase (HBeAg+)	0.82 (n=78)	462	14.1
HBeAg- chronic hepatitis B	0.82 (n=127)	735	22.4
Resolved phase (HBsAg-)	0.74 (n=6)	53	1.6
Compensated cirrhosis	0.78 (n=69)	383	11.7
Decompensated cirrhosis	0.70 (n=2)	10	0.3
Hepatocellular carcinoma	0.67 (n=10)	49	1.5
Liver transplant	0.82 (n=60)	200	6.1
Total		3277	100

* Utility scores range between 0 (= worst health state) and 1 (= perfect health).

Utility scores were based on the EQ-5D data. Mean utility scores for patients in the phases of immune tolerance, inactive carrier, immune reactive and HBeAg- CHB were very similar, in the 0.81 to 0.83 range (Table B). Also patients having received a liver transplant had on average a utility score of 0.82. Average utility scores were slightly lower in compensated cirrhosis (n=69: 0.78), in decompensated cirrhosis (n=2: 0.66 and 0.75) and in HCC (n=10: 0.67). The mean utility score was only 0.74 in 6 HBsAg-patients without cirrhosis. The average utility score was 0.80 in the subgroup analysis of 102 patients without cirrhosis responding to NA antiviral treatment with a DNA level under 2000 IU/mL. No major differences were seen between the overall results and those for patients of European origin. After adjustment for disease stage, age is a significant predictor of these utility scores.

LITERATURE REVIEW ON COST-EFFECTIVENESS

We identified and reviewed 9 articles on the cost-effectiveness of antiviral treatment for CHB which were not covered in the systematic reviews because they were published recently (2007-2009). Without exception, these 9 publications were sponsored by the companies marketing the antiviral agent under study and all positively concluded on the cost-effectiveness of the studied antiviral agent.

Long-term effectiveness data (cirrhosis, HCC, transplantation, overall mortality) should ideally be used for credible cost-effectiveness evaluations. In the absence of robust long-term clinical effectiveness data, the models used in all selected studies are based on rather arbitrary assumptions, mostly favouring a treatment effect, for translating the short-term results in terms of HBeAg seroconversion or HBV DNA levels into long-term prevention of cirrhosis and HCC. Only a single model uses liver histology data from clinical trials showing a 85.7% reduction (from 14% to 2%) of the annual transition rate to cirrhosis after one year of lamivudine. However, the authors did not include the very wide 95% confidence interval which even slightly overlapped with the 0% reduction cut-off. Slight variations of this rate in the sensitivity analysis already had a major effect on the incremental cost-effectiveness ratio.

Most models assume a normal life expectancy after HBeAg seroconversion or low HBV DNA. Some models include the possibility of HBeAg seroreversion but assume the same rate as after spontaneous HBeAg seroconversion. Some models extrapolate the transition rates to cirrhosis observed after spontaneous HBeAg seroconversion (0.1% to 1.3%) to treatment-induced HBeAg seroconversion or even to HBV DNA treatment response in HBeAg- patients.

Most Bristol-Myers Squibb (BMS) sponsored models are based on transition rates by DNA level as seen in REVEAL-HBV, a BMS co-sponsored epidemiological study in 3653 untreated HBsAg+ subjects in Taiwan, most with normal ALT and HBeAg- (no exclusion of inactive carriers). Extrapolation to use these non-treated cohort data to predict long-term response after treatment for HBeAg+ and HBeAg- CHB, as done in the models, takes a leap of faith.

Finally, all studies where utilities are mentioned assume a QoL improvement after treatment-induced HBeAg seroconversion or when a low level of HBV DNA is obtained, without any measurements in patients to support this. Our measures of QoL do not suggest any improvement in QoL with the lowering of HBV DNA. Some models supporting NAs include a disutility for patients treated with Peg-IFN, again without measurements in patients.

SUMMARY OF THE FINDINGS

While vaccination protects a growing proportion of the population in Belgium against HBV infection, chronic hepatitis B is relatively more frequently diagnosed among immigrants from Eastern Europe and endemic countries in Asia and Africa, including immigrants without residence permit. We estimate that 3300 patients were seen by a liver specialist in 2009, including 1700 patients with active chronic hepatitis B, 400 patients with liver cirrhosis, 50 with HCC and 200 with a liver transplant. In contrast to Peg-IFN which has a rather limited efficacy and lamivudine which induces resistant strains, the more recently introduced NA antiviral drugs have been shown in trials to suppress HBV DNA, now for up to 5 years. Reduction of cirrhosis and HCC rates, yet to be demonstrated, is expected to require lifelong NA treatment in most patients. Long term safety of NAs still remains to be demonstrated. Cost-effectiveness publications often model optimistic assumptions on long-term effectiveness without inclusion of an appropriate range of uncertainty. The authors also assume a significant improvement of quality of life after a surrogate marker (HBeAg, HBV DNA) response, an assumption which is in contrast with our assessment of QoL in real patients with a low HBV DNA under NA treatment.

RECOMMENDATIONS

- Many publications of cost-effectiveness of antiviral treatment of chronic hepatitis B lack credibility. All assumptions included in the model should be checked in case the use of such model is considered for decision making.
- In particular the assumption of an improvement in quality of life after a short-term antiviral treatment response (HBV DNA, HBeAg) should not be included in such models.
- Assumptions on long-term effectiveness and safety should include an appropriate range of uncertainty as long as no long-term treatment data are available. The reimbursement criteria should be re-evaluated when such long-term data become available.
- Recently, reimbursement criteria were adapted and are now somewhat more in line with international guidelines. They also became less restrictive, now also allowing treatment in CHB patients without liver fibrosis. The change in reimbursement criteria should however not be interpreted as a proof of long term efficacy and safety of these agents. Potential benefits and risks should be weighed carefully when starting a lifelong treatment.
- Chronic hepatitis B care in Belgium for patients without residence permit is covered by the OCMW/CPAS budget of each community, and is not covered by the NIHDI criteria for reimbursement nor the NIHDI budget. Monitoring of these costs, at least for prescription medicines, may be feasible and should be considered.
- Scientific journals should use more strict criteria for the publication of cost-effectiveness models, including the need to base utility scores on real patient assessments and the use of the real range of uncertainty in the models.

RESEARCH AGENDA

- The large number of subjects tested for HBeAg suggests that the prevalence of HBsAg+ in Belgium is higher than the published estimate of 0.7%, indicating the need for a new prevalence survey.
- Evaluation of a screening programme for HBV infection (and vaccination if still possible) in children born to mothers from an HBV-endemic country, or born to HBsAg+ mothers, or living in a household with anyone positive for HBsAg.
- The documentation of the long term side-effects and efficacy (incidence of cirrhosis and HCC) in patients on antiviral therapy for CHB.

Scientific summary

Table of contents

ABBREVIATIONS

AASLD	American Association for the Study of Liver Disease
ADV	Adefovir
AFP	Alpha-fetoprotein
ALT	Alanine aminotransferase
Anti-HBc	Antibodies to the hepatitis B virus core antigen
Anti-HBe	Antibodies to the hepatitis B virus e antigen
Anti-HBs	Antibodies to the hepatitis B virus surface antigen
BASL	Belgian Association for the Study of Liver
BCLC	Barcelona Clinic Liver Cancer
CC	Compensated cirrhosis
cccDNA	Covalently closed circular DeoxyriboNucleic Acid
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-effectiveness analysis
CHB	Chronic hepatitis B
CI	Confidence interval
CL	Confidence limit
CLIP	Cancer of Liver Italian Program
CMD	Centres for Molecular Diagnosis
CPAS	Centre Public d'Action Sociale (CPAS/OCMW)
CRD	Centre for Review and Dissemination
CRF	Case-report form
CUA	Cost-utility analysis
DC	Decompensated cirrhosis
EASL	European Association for the Study of the Liver
EOT	End of treatment
ETV	Entecavir
EQ-5D	EuroQol-5Dimensions
GP	General practitioner
HBeAg	Hepatitis B Virus e Antigen
HBeAg-	Hepatitis B Virus e Antigen negative
HBeAg+	Hepatitis B Virus e Antigen positive
HBsAg	Hepatitis B virus surface Antigen
HBV	Hepatitis B virus
HBV DNA	Hepatitis B virus deoxyribonucleic acid
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IEC	Independent ethics committee
IFN-alpha	Interferon-alpha
IMA	Intermutualistic agency
INAHTA	International Network of Agencies for Health Technology Assessment
IU	International unit
IU/mL	International unit per millilitre
JIS	Japan Integrated Stage
KCE	Belgian Healthcare Knowledge Centre
kD	Kilodalton
LAM	Lamivudine
LT	Liver transplant

LYG	Life-year gained
MELD	Model for End-stage Liver Disease
NA	Nucleos(t)ide analogue
NIHDI	National Institute for Health and Disability Insurance (INAMI/RIZIV)
OCMW	Openbare Centrum voor Maatschappelijk Welzijn (OCMW/CPAS)
PCR	Polymerase chain reaction
Peg	Polyethylene glycol
Peg-IFN	Pegylated interferon
po	Per os, orally
PPS	Permanent population sample
QALY	Quality-adjusted life year gained
QoL	Quality of life
rcDNA	Relaxed circular deoxyribonucleic acid
RCT	Randomized controlled trial
SC	Subcutaneous
SG	Standard gamble
TLB	Telbivudine
TNF	Tenofovir
TSH	Thyroid stimulating hormone
TTO	Time trade-off

1 AIMS AND METHODS

1.1 AIMS

In this project the Belgian Healthcare Knowledge Centre (KCE) collaborated with a group of liver specialists in Belgium to answer the following research questions.

1. What is the natural history and epidemiology of chronic infections with the hepatitis B virus (HBV), in Belgium and abroad?
2. What are the efficacy and the effectiveness of the currently approved antiviral treatments?
3. What is the lifetime cost-effectiveness of the antiviral treatment of chronic hepatitis B (CHB) in Belgium and what is the budget impact?

1.2 METHODS

Parts of the project were outsourced by KCE to a group of experts, headed by Prof. Yves Horsmans, Cliniques Universitaires Saint-Luc, Brussels. This concerned the synthesis of the literature on epidemiology, natural history and current treatment options. These parts were mainly based on existing literature reviews and treatment guidelines; they were not aimed to be formal systematic literature reviews, nor to provide up to date practice guidelines.

In addition, in collaboration with the Belgian hepatologists and a contract research organisation, individual clinical patients' information and quality of life (QoL) data were collected. These data were afterwards linked to individual healthcare consumption data, respecting the privacy legislation. This prospective study was aimed to better characterise the patients seeking specialised healthcare in Belgium for their chronic HBV infection or complications thereof.

Finally, a systematic literature review and critical appraisal of the economic evaluations of CHB treatments was performed, in preparation of the construction of a cost-effectiveness and budget impact model.

1.3 OVERVIEW OF THE REPORT, PART 1 AND PART 2

Here we present the first part of the report consisting of a review of the literature on epidemiology and natural history, including transition rates, followed by a chapter on the treatment of chronic HBV infections.

Second, we present the clinical and QoL results of the prospective data collection in Belgium.

Third, a systematic literature review and critical appraisal of the economic evaluations of CHB treatments is presented.

The second part of the report will be published later and present a Markov model based on the data presented here and the healthcare consumption data by patient subgroup as obtained in the context of the prospective study. Also the budget impact for the National Institute for Health and Disability Insurance (NIHDI) of introducing new treatments will be considered. Practical details (structure, population, treatment options…) regarding those models will be described in the second forthcoming report.

2 NATURAL HISTORY AND EPIDEMIOLOGY

2.1 HEPATITIS B: TRANSITION AND NATURAL EVOLUTION

2.1.1 Introduction

Chronic infection with HBV is a disease of global importance with a 5% worldwide prevalence, varying between 0.1-2% in Western Europe, Australia and the US, 2-8% in the Mediterranean countries and Eastern Europe, and 8-20% in South Asia and sub-Saharan Africa.[1, 2] The prevalence of HBsAg has been used to categorize endemicity as high (≥ 8%), intermediate (2-8%), low (< 2%) and very low (< 0.5%).[3, 4]

Over 70% of chronically infected patients are Asians. Chronic hepatitis B (CHB) can lead to end-stage liver disease and hepatocellular carcinoma (HCC) and is responsible for an estimated 500 000 deaths worldwide per year.[5] Asian studies show that CHB-related liver disease contributes to approximately 20 deaths per 100 000 each year.[6] A follow-up of 3233 Chinese CHB patients for a median of 29 (range 6-291) months showed a calculated cumulative risk of development of complications of 8% and 12% respectively after 10 and 15 years follow-up. As these were patients visiting a liver clinic the results cannot be generalised to the entire population with chronic HBV infection. A total of 170 patients (5.3%) developed at least one complication: ascites (n=96), spontaneous bacterial peritonitis (n=30), oesophageal varices (n=59), encephalopathy (n=40) and HCC (n=95).[7]

Data on morbidity and mortality of CHB in the West are scarce. Realdi et al.[8] reported on 366 patients with compensated hepatitis B related cirrhosis, predominantly of Caucasian origin, followed for a mean period of 72 months. About one third was HBeAg+. Cumulative probability of survival was 84% and 68% at 5 and 10 years, respectively. Main causes of death were liver failure and HCC. In France, the estimated number of deaths attributable to hepatitis B was 2.2 per 100 000 inhabitants; at death 93% had cirrhosis and 35% HCC.[9]

In the Netherlands, a recent modelling study shows that, within a 20-year period, 26% of the patients with active CHB and high viremia will die because of liver-related causes. In the absence of cirrhosis at entry, 29% will develop cirrhosis. Of those with cirrhosis at entry, 74% will die within the 20-year period. If this active CHB cohort is fully detected and treated, mortality related to liver disease could in this model be reduced by 80% if a low-resistance profile drug is chosen from the start.[10] The effect is due to both the reduction in complications of cirrhosis and the prevention of the development of cirrhosis. In this model it is assumed that disease progression is 100% blocked in HBeAg+ patients who show seroconversion and in HBeAg- patients who have an on-treatment HBV DNA level under the assay detection limit. These optimistic assumptions on long term treatment effect are however not fully supported by clinical data.

Also in Belgium CHB is an important public health problem.[11] In addition to the consequences of CHB on morbidity and mortality due to liver disease, the social and economic costs of the health burden of CHB is high due to reduced QoL, loss of economic productivity and high treatment costs including liver transplantation.

2.1.2 Natural history of infections with the HBV

The risk of development of chronicity of hepatitis B depends on the age at infection and the type of transmission.[12] It is 90% when the infection is acquired perinatally, 20-30% when acquired horizontally during childhood, or 5-10 % when acquired in adolescence or adult age through risk behaviour.

The majority of Asian persons with hepatitis B acquire the disease perinatally from an infected mother. In sub-Saharan Africa, in Eastern Europe and the Mediterranean areas, the transmission is acquired horizontally within 2 years after birth by means of close contact with infected relatives. In Western countries, patients are usually infected in adolescence or adulthood by means of sexual contact or sharing intravenous needles.

There are 5 distinct major phases (Table 1) resulting from the interaction between the virus, hepatocytes and host immune response: immune tolerance, immune active, inactive carrier phase, reactivation phase and resolved phase, although all patients do not go through every phase.[13]

2.1.2.1 The immune tolerance phase

The immune tolerance phase is characterized by HBeAg+, very high viral load (HBV DNA >2 000 000 IU/mL), persistently normal ALT, age < 40 years, near normal liver histology. This phase is typically observed after perinatally acquired infection. Patients in the immune-tolerant phase have mild disease. In those who remain in the immune-tolerant phase, disease progression is minimal, but an increased risk to develop HCC should not be neglected. The monitoring that may be needed remains a point of discussion. However, immune-tolerant patients who progress to the immune clearance phase (or immune active phase) often face disease progression[14] with fibrosis/cirrhosis being possible after 30 years of age. Treatment is not considered except above 30-40 years of age in case of liver fibrosis.

2.1.2.2 The immune active phase

The immune active phase is subdivided in 2 distinct profiles:

HBeAg+ (wild type virus) CHB (immune reactive phase) with high DNA (>20 000 IU/mL), elevated ALT, histologic activity and or fibrosis. When this phase is prolonged the risk of progression of liver disease increases. Medical treatment must be considered and prolonged up to HBeAg conversion. Spontaneous HBeAg seroconversion can occur, resulting in suppression of viral replication and clinical improvement, leading to the 'inactive carrier state'. Evolution to the precore/core promoter HBeAg- immune active phase is also possible. HBeAg- hepatitis is caused by strains with mutations in the core promoter or precore regions that prevent HBe antigen expression.

HBeAg-, anti-HBe positive (precore or core promoter mutant variants) CHB with HBV DNA typically >2000 IU/mL, fluctuating ALT (with possible long periods of normal values) and progressive liver disease. Persistent HBV replication despite HBeAg seroconversion or HBV reactivation following a period of remission after HBeAg seroconversion leads to HBeAg- chronic hepatitis. During this phase, there is failure of HBeAg secretion but with remaining risk for progressive liver disease. HBeAg- chronic hepatitis is associated with a lower rate of spontaneous remission and a poorer long term prognosis than HBeAg+ chronic hepatitis, even if circulating HBV DNA is lower, because these less antigenic variants are able to better avoid immune control than the wild-type variants. Medical treatment must be considered often lifelong or until HBsAg seroconversion. It is the predominant form of CHB seen in many Western areas in the world including Belgium,[11, 15] but also in Chinese immigrants.[16]

2.1.2.3 The inactive carrier phase

This stage is characterized by HBeAg-, anti-HBe positive; extremely low HBV DNA (<2000 IU/mL); persistent normal ALT; normal or minimal activity/fibrosis at liver biopsy. Treatment is not considered.

2.1.2.4 The reactivation phase

The reactivation phase is characterized by reappearance of HBV DNA with or without ALT elevation, from the inactive carrier state towards the immune active phase (HBeAg + or -). This can occur either spontaneously or during immunosuppression (chemotherapy, corticosteroids, biological therapy in inflammatory bowel disease or rheumatoid arthritis, HIV).

Table 1 : The 5 major phases of infections with the HBV

Phases	Immune tolerance	Immune active CHB		Inactive carrier	Reactivation	Resolved
		HBeAg+ (wild type) Immune reactive	HBeAg- (precore mutant) CHB			
HBsAg	+	+	+	+	+	-
HBeAg	+	+	-	-	+ or -	-
Anti-HBe	-	-	+	+	+ or -	+
ALT	Normal	Elevated	Fluctuating	Normal	Elevated or normal	Normal
HBV DNA	> 2 Mio IU/mL	Typically > 20 000 IU/mL	> 2 000 IU/mL	< 2 000 IU/mL	> 2 000 IU/mL	< 2 000 IU/mL in most
Histologic progression	Minimal	Yes	Yes	Minimal	Yes	No
Consider treatment?	No*	Yes	Yes	No	Yes	No

*except in case of fibrosis (see above)

2.1.2.5 The resolved phase

Persons who become HBsAg- usually develop anti-HBs. They have anti-HBc positivity. A small proportion has detectable HBV DNA in the blood or in the liver ('occult hepatitis B'), which can reactivate by immunosuppression.

Other factors involved in disease progression include host factors (age > 40, male gender, immune status and liver inflammation translated by ALT elevation, HBV/HIV and HBV/HCV coinfections), viral factors (high serum DNA, prolonged time of the immune active/clearance phase, genotype C) and environmental factors (diabetes, obesity, and alcohol consumption).[17, 18]

The aim of this study was to summarize literature data on transition rates between the different clinical conditions described in CHB patients as well as rates of disease progression and incidence of complications of chronic infection.

2.1.3 Methods

A literature study was performed based on the recent review by Fattovich et al.[19] and other longitudinal studies of untreated patients with long follow-up.[2, 20-23] The natural history of CHB is different between high endemic (Asia, sub-Saharan Africa) and low endemic areas (Western Europe, US, Australia).

The differences originate mainly by the predominant age and way of transmission. Due to immigration fluxes, it is estimated that 47-70% of the chronic cases in the US were born outside the country.[5] In Belgium, 49% of patients in the Belgian Association for the Study of Liver (BASL) registry were of non-Caucasian origin.[11] Transition rates from one clinical condition to another, incidence of cirrhosis, HCC, hepatic decompensation and liver-related mortality are given according to the geographic area (high or low endemicity) where the patient is born. The incidence rate estimates are computed per 100 person years. Cofactors involved in disease progression were not evaluated in this study.

The following clinical conditions are considered:

- Immune tolerance phase
- Inactive carrier phase
- Chronic hepatitis (HBeAg+ or HBeAg-) without cirrhosis
- Compensated cirrhosis

- Decompensated cirrhosis, characterized by ascites, and/or variceal bleeding, jaundice, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatic encephalopathy.
- HCC
- Death

The following definitions are used:

- HBeAg seroconversion: loss of HBeAg with development of anti-HBe on at least two consecutive follow-ups
- HBeAg seroreversion: loss of anti-HBe and regaining of HBeAg on at least two consecutive follow-ups in patients who had HBeAg seroconversion.
- Acute hepatitis B exacerbation (note that this definition not generally accepted): increase in ALT to more than 1.5 times the upper limit of normal after excluding other common causes of ALT elevation, including other viral hepatitis, drug induced hepatitis, alcoholic hepatitis and dysmetabolic steatohepatitis.

2.1.4 Results

2.1.4.1 Immune tolerance phase

The rate of spontaneous HBeAg seroconversion is low in high endemic areas where children are infected in the perinatal period: 0.75% per year.[24] By the age of 10-15 years around 90% of children remain HBeAg+.[25]

The immune tolerant phase is generally absent or very short in adolescents and adults infected in low endemic areas.

2.1.4.2 Immune active phase: HBeAg-positive chronic hepatitis B

HBeAg seroconversion

In high endemic areas, HBeAg seroconversion occurs at the mean age of 30-35 years with most cases (90%) occurring before age of 40.[26] Cumulative HBeAg conversion rates at years 1, 2, 3, 4 and 5 in 1215 patients were reported as 18, 31, 41.3, 47.6 and 53.5% respectively.[1] Among 1274 patients positive for HBeAg on presentation, 512 (40.2%) had HBeAg seroconversion at subsequent follow-up.[7] In general, HBeAg seroconversion should ideally be adjusted for age, ALT and HBV genotype, e.g. the higher the ALT level on presentation, the higher the chance of HBeAg seroconversion during subsequent follow-up. HBeAg seroconversion is usually followed by clinical remission but only in a subset of patients this results in a lifelong inactive state with an excellent outcome.[27]

In low endemic countries, the HBeAg seroconversion rate was estimated at 18% per year, with 95.1% HBeAg seroconversion after 10 years.[19]

Risk of cirrhosis

In high endemic areas, patients with HBeAg+ CHB have a cirrhosis incidence of 1.6% per year, the corresponding 5 year cumulative incidence of cirrhosis being 8%.[26-31]

In low endemic countries, the risk is estimated at 3.8% per year.[32, 33]

Risk of HCC

In high endemic areas this risk is estimated at 0.6% per year[7, 26, 28, 30, 34-38]

In low endemic areas this risk is estimated at 0.3% per year.[33, 39-43]

Liver-related mortality

Liver-related mortality is estimated <0.1% based on eastern and western data (thus applicable to high and low endemic countries).[34, 40]

2.1.4.3 *Inactive carrier state*

HBsAg loss

Spontaneous HBsAg loss may occur at a rate of 1-2% per year in low endemic areas[44] and even lower (0.05-0.8%) in high endemic areas.[45] This usually confers an excellent long-term outcome if there is no pre-existing cirrhosis.

Reactivation

After HBeAg seroconversion, 1-4% have HBeAg reversion, whereas a greater proportion of patients develop HBeAg- CHB because of reactivation of HBV precore or core promoter mutants.[27, 46] The incidence of HBeAg- CHB from inactive carriers ranges from 1-3% per year in high endemic areas[27] to 1-5% per year in low endemic areas.[19, 47]

Risk of cirrhosis

The risk of cirrhosis development is very low, < 0.1% per year in high endemic[27] and 0.01% per year in low endemic areas.[48]

Risk of HCC

The risk of HCC is estimated at 0.2% per year in high endemic,[27] and 0.02% per year in patients in low endemic areas.[48, 49]

Liver-related death

The liver-related death rate is only estimated in western studies (low endemic countries), being 0.03% per year.[48, 49]

2.1.4.4 *Immune active phase: HBeAg-negative chronic hepatitis B*

Risk of cirrhosis

The risk of cirrhosis development is estimated at 2.8% per year in high endemic[27] and 9.7% per year in low endemic areas.[19, 50]

The risk of HCC

The risk of HCC is not specified for HBeAg- CHB.

2.1.4.5 *Cirrhosis*

Risk of decompensated cirrhosis

The risk of decompensated cirrhosis is estimated at 3-4% per year in high[34, 51, 52] and low endemic areas.[53]

Risk of HCC

The risk of HCC development is estimated at 3.7% per year in high endemic,[30, 43, 51, 52, 54-59] and 2.2% per year in low endemic areas.[42, 43, 53, 60-63]

Liver-related mortality

Liver-related mortality is estimated at 2.9% per year in high endemic[34, 51, 59, 64] and 3.3% per year in low endemic areas.[53, 62]

2.1.4.6 *Decompensated cirrhosis*

Once hepatic decompensation occurs mortality rate increases remarkably, around 15% per year ranging from 70-85% at 5 year follow-up both in low and high endemic areas.[44, 53, 65]

2.1.4.7 Hepatocellular carcinoma

In most neoplasms, the prognosis is defined by tumour stage at the time of diagnosis. In patients with HCC, this is more complex as cirrhosis underlies HCC in most patients and prognosis depends on the evolutionary stage in which the neoplasm is diagnosed, the degree of liver function impairment of the underlying cirrhosis, and the treatment received.[66] Overall median survival of HCC patients depends on tumor stage and liver function.

Several multidimensional systems have been proposed to grade patients according to life expectancy. Of these systems, the Barcelona Clinic Liver Cancer (BCLC) proposal has been validated and links staging with treatment indication.[67] Patients are stratified into different stages according to tumour stage, liver function and presence of symptoms. Stage A comprises tumours diagnosed at an early stage when curative treatment (resection, transplantation, and ablation) is feasible. They have a preserved liver function (Child-Pugh A or B) and present with solitary tumours (< 5 cm) or up to 3 nodules, each < 3 cm in size. Survival at 5 years may range between 50-75%. Patients with large or multifocal disease that are asymptomatic belong to an intermediate stage (Stage B), they are candidate for transarterial chemoembolization and will achieve a 3-year survival around 50%. Patients who report cancer-related symptoms, or present with vascular invasion or extrahepatic spread correspond to Stage C. With the exception of sorafenib (Nexavar), offering a median survival benefit of 12 to 13 weeks, there is no standard treatment for them and their survival at 3 years is less than 10%. Patients with severe impairment of liver function (Child-Pugh C) or major physical deterioration correspond to stage D, and have a median survival less than 6 months. A recent Belgian study on 131 HCC's reported a 60% survival after a mean follow-up of 180 days. Tumours within the Milan criteria[68] had a 5 times better survival.[69]

In an extensive review, Tandon et al.[70] showed that when the 22 studies in whom 100% of the patients had cirrhosis were analysed, the most common predictors of death were the CLIP score (Cancer of Liver Italian Program, which includes Child-Pugh score, tumoral extension, alpha-fetoprotein (AFP) and portal vein invasion), tumour size, the Child–Pugh class, tumour number, AFP and portal vein thrombosis.

In high endemic areas, again most studies are coming from the Asia-Pacific regions where chronic HBV infection accounts for 75-80% of the HCC cases.[71] In these studies we observed differences in survival rates among all categories by the CLIP and the JIS (Japan Integrated Stage) systems, which appear superior than the BCLC as a system for the prediction of the prognosis of patients with HCC.[72, 73] This may be partly because the BCLC system had been originally established for the selection of treatment options and not for the prediction of prognosis. Japanese studies recently compared the stratification ability, prognosis, and likelihood ratio between JIS and CLIP systems for more than 4500 patients with HCC and reported the superiority of JIS system as a prognostic staging system for HCC.[74, 75]

The overall median survival among the 2010 Taiwanese HCC patients was 18.2 months, and the 1, 2, 3, 5 and 10-year survival rates were 57.3%, 43.6%, 35.8%, 23.9% and 13.5%, respectively.[73] The applicability of staging systems for patients with HCC depends on the type of population, the aetiology of the disease and the treatment methods which all vary between the low endemic and the high endemic areas.

2.2 HBV IN BELGIUM AND SURROUNDING COUNTRIES

2.2.1 Introduction and search strategy

In this present text we give an overview of the epidemiology of HBV infection in Belgium and its surrounding countries (France, The Netherlands and Germany).

The search of papers was performed by using Medline(PUBMED) from 2005 until December 2008 with as key words: ('hepatitis B' or 'hepatitis B virus') and 'epidemiology' and ('Europe' or 'Belgium' or 'France' or 'Germany' or 'The Netherlands'). A similar search in Embase was conducted on March, 3 2009 with the following terms: 'hepatitis b' AND 'epidemiology' AND [2005-2009]/py.

Important Belgian papers from earlier periods were also included, together with reports from the Scientific Institute for Public Health, Brussels, and the 'Vlaams Agentschap Zorg en Gezondheid'.

2.2.2 Epidemiology for Belgium, France, Germany and The Netherlands

2.2.2.1 Belgium

In 1993, Beutels et al.,[76] based on a sero-epidemiological study (residual samples), described a prevalence of anti-HBs+, anti-HBc+ of 5.1%; a prevalence of anti-HBs-, anti-HBc+ (situation just before anti-HBs+ status) of 0.6% and of anti-HBs+, anti-HBc- (vaccination status) of 3.5%. The HBsAg carrier rate was 0.7% for Belgians and 1.2% for non-Belgians in Flanders.

In the study of Nardone et al.,[77] a comparison of HBV sero-epidemiology in 10 European countries is performed by using standardized serology between 1996 and 2003. The sera were obtained by residual sera, collected during routine lab testing (6/10 countries) and by population-based random sampling (4/10).

In Belgium 0.7% of the population between 1 and 39 years was carrier of HBV (HBsAg+) and 1.3% had been in contact with HBV (anti-HBc +).[77] For The Netherlands 0.1% is HBV carrier and 1.7% was in contact with HBV.[77] For Germany, only anti-HBc numbers were available, with 6% of the population having been in contact with HBV.[77] Seroprevalence data for a number of European countries are summarized in Table 2.

Table 2: Age specific seroprevalence of anti-HBc positive and HBsAg positive samples in 10 European countries between 1996 and 2003. Adapted from Nardone et al.[77]

Countries	TOTAL		1 -15 years		16 – 39 years		≥ 40 years	
	% Anti HBc +	% HBs Ag +	% Anti HBc +	% HBs Ag +	% Anti HBc +	% HBs Ag +	% Anti HBc +	% HBs Ag +
Belgium	1.3	0.7	1.1	0.7	1.9	0.6	-	-
Germany	6	-	-	-	2.9	-	8.2	
The Netherlands	1.7	0.1	0.3	0.0	1.4	0.2	2.6	0.2
Luxemburg	2.9	-	0.9	-	4.3	-	4.1	-
Ireland	1.7	0.1	1	0.0	1.7	0.1	2.8	0.2
Italy	5.6	0.6	1.9	0.1	4.3	0.9	18.8	1.5
Czech Republic	2.5	0.3	0.2	0.3	1.9	0.2	8.3	0.8
Slovakia	10.5	0.6	7.1	0.1	10.6	0.9	18.6	1.5
Romania	20.5	5.6	9.4	5.1	23.6	7.6	38.0	5.1
Finland	2.7	0.2	1.7	0.2	2.8	0.3	4.3	0.2

In accordance with the study of Nardone et al.,[77] a population-based cross-sectional study in Flanders using oral fluid (saliva tests) showed a prevalence for HBsAg of 0.66% in 2003.[78] These 2 studies (Nardone et al.[77] and Quoilin et al.[78]) confirmed the results of Beutels et al.[76] showing that the prevalence of HBsAg carrier rate remains stable in Belgium (around 0.7%). In the study of Quoilin et al.[78] performed in 2003, the prevalence is probably underestimated as people with a lower socioeconomic status, people who know their immune status or subpopulations at higher risk such as drug users, persons in prison or in institutions were probably missed. Also non-Belgians were underrepresented in that study. On the other hand, the study of Beutels et al.[76] in 1993 probably overestimates the prevalence as the study was done in 11 hospitals (non-gastroenterology units) located in urban areas.

In a registration overview 2007 of "Infection Combat Flanders" under supervision of the Federal Agency of Health, Ministry of Flemish Community, the number of cases with acute HBV infection are presented.[79] These infections were reported in accordance with the law of 1995, in which each doctor is obliged to report some specific infectious diseases to "Toezicht Volksgezondheid van de Vlaamse Gemeenschap". Based on this reporting, in Flanders the incidence of acute HBV is 1.77 per 100.000 inhabitants.[79] In Table 3 the evolution of the incidence of acute HBV in Flanders is given.[79] Some degree of underreporting is likely but this has not been quantified.

Table 3: Incidence of acute HBV cases in Flanders from 2003 to 2007 (Ruud Mak[79])

	2007	2006	2005	2004	2003
Number of inhabitants	6,11 million	5,93 million	5,93 million	5,93 million	5,93 million
HBV (incidence per 100.000 inhabitants)	108 (1.77)	341 (5.7)	410 (6.9)	479 (8)	568 (9.6)

HBV genotyping from blood donors and sera from 3 university hospitals between 1991 and 2002 was done by Micalessi et al.[80] in 128 Belgian patients. The prevalence of genotype A was 53%; genotype D 37%; mixed A + D genotype 8% for a group of blood donors. This was comparable for patients from the gastroenterology units. So genotypes A and D are predominant in Belgium.

Between January 2003 and December 2003, Belgian gastroenterologists were asked on a voluntary base to report all new cases of HCC.[69] 131 patients were reported and in 17% HBV was the underlying disease.

In conclusion, Belgium and Flanders (most studies were performed in Flanders) comply with the criteria for a low endemic region with a prevalence for HBsAg of 0.7% (carrier) and with as main genotypes A and D.

2.2.2.2 France

In 2004, the Institut National de Veille Sanitaire estimated the prevalence of HBsAg carriers in France at 0.68% with for males 1.19% and for females 0.16%.[81] These results were confirmed by Zarski et al.[82] They found a prevalence of 0.68% for HBsAg carriers and 8.18% were anti-HBc positive.

An epidemiological surveillance in France between 2001 and 2003 revealed a prevalence of HBsAg positivity of 0.12% in new blood donors. The prevalence is significantly higher in men than in women.[83] The risk of HBV infection by a blood transfusion was 1/640 000 transfusions.[83] By applying a new model, the HBV residual risk ranged from 1.06 per million blood donations (2000-2002) to 0.49 per million donations (2004-2006).[84]

A recent prospective study between 2001 and 2002 was done in 58 non-university hospitals in France with a population area of 15.6 million people by Cadranel et al.[85] Nearly 1166 HBsAg+ patients were detected: 29% were inactive carriers (younger, more females, more born in sub-saharian Africa than active carriers) and 71% were active carriers with: 3% acute hepatitis B infection; 69% chronic HBV without cirrhosis; 18% compensated cirrhosis; 4% decompensated cirrhosis; 3% had HCC; 0.03% received a liver transplantation and 2% were classified in a different group.

Within the group of patients with chronic hepatitis, 35% were HBeAg+ and 65% were HBeAg-. These results are in line with the results of Zarski et al.,[15] who found in 2003 (study during 2 months in 26 University hospitals in 865 HBsAg patients) that 28% were HBeAg+ and 72% were HBeAg-. These recent results reveal a time dependent change in the proportion of HBeAg + and – patients. A possible contribution of the evolution to more sensitive viral load assays can however not be excluded. A previous study of Zarski et al.[86] in 1994 showed that 78% were HBeAg+ and only 22% were HBeAg-. The risk factors for cirrhosis are age > 40 years, platelets < 150 000/mm³, viral co-infection and HBeAg negativity.[85] The fibrosis stages with metavir score F2-F3-F4 were found in 75% of HBeAg- patients and in 59% of HBeAg+ patients. The co-infection rate was 4% for anti-HCV antibodies; 4% for anti-HIV antibodies and 3% anti-delta antibodies in active carriers.[85] Anti-delta antibodies are antibodies to hepatitis D virus, a satellite virus infection. If present, it is always seen together with HBV infection.

In both studies, patients who were HBeAg- had a longer duration of the infection, lower ALT levels and lower HBV DNA levels and more fibrosis than HBeAg+ patients.[82, 85]

In the Seine Saint Denis district of Paris, 109 consecutive patients with biopsy proven HBV chronic hepatitis were examined for genetic variability. The prevalence of genotype A was 26.6%; genotype B 12.8%; genotype C 18.3%; genotype D 18.3% and genotype E 14.7%. Genotype B or C were found in 97% of Asian patients and genotype E was only found in sub-Saharan African and Caribbean patients.[87] The prevalence of HBV genotypes in South Western France between 1999-2004 (Bordeaux) was somewhat different: for genotype A the proportion was 51%; genotype B 6.7%; genotype C 5.7%; genotype D 26.3%; genotype E 7.7%; genotype F 0.5% and genotype G 2.1%.[88]

The estimated annual number of deaths associated with HBV infection is 2.5 per 100 000 inhabitants in France. In this group 93% had cirrhosis and 35% had a HCC. Alcohol consumption and HIV infection were important cofactors.[9]

For France, we can conclude that the prevalence for HBsAg carriers is 0.68%, not very different from Belgium; in new blood donors (a highly selected population) HBsAg prevalence is 0.12%. In the group of HBsAg carriers, around 29% are inactive carriers and 71% active carriers (3% acute HBV, 69% chronic HBV without cirrhosis; 18% compensated cirrhosis; 4% decompensated cirrhosis; 3% had HCC; 0.03% received a liver transplantation). Within the group of active HBV carriers there may be an evolution towards more HBeAg- patients (65%) and less HBeAg+ (35%) patients. All genotypes are distributed in France depending on the regions and on the pattern of immigrants. The region of Bordeaux has a distribution of genotypes which is similar to the situation in Belgium, with A (51% in France and 53% in Belgium) and D (26% in France and 37% in Belgium) as most frequent genotypes.

2.2.2.3 Germany

Marschall et al.[89] studied the prevalence of HBsAg in adult foreign citizens and resettlers in Germany compared with the prevalence among the adult German native population during 2003. The prevalence of HBsAg positivity in the total German population is 0.75 %; the German population without emigrants: 0.49%; the German foreigners born outside Germany 2.14 % and the German foreigners born in Germany 1%.

Jilg et al.[90] investigated 5305 individuals considered to be representative for the adult German population. The prevalence of anti-HBc was 8.71% and HBsAg was 0.62% with a maximum of HBsAg carriers of 1.12% in the age group of 41-50y old. The prevalence of anti-HBc is in accordance with the results of Nardone et al.[77] who reported a 6% prevalence.

In 1998, Thierfelder et al.[91] studied serological markers in sera from a representative German population. The overall prevalence of HBV exposure (anti-HBc+) was 7% and prevalence of HBsAg carriers was 0.6%. Immunity after exposure to HBV with positive anti-HBs was found in 80% of anti-HBc+ persons.

Between 2001 and 2005, 1064 patients were screened in the orthopaedic surgery unit of Leipzig for HBsAg positivity: 0.41% were HBV carriers.[92] The seroprevalence of HBsAg in 5518 women in the reproductive age was 1.59% in Heidelberg.[93] Most of the infected women originated from high HBV prevalence countries.

The prevalence rate of HBsAg positivity in Germany was 0.16 per 100 blood donations in 2003 as well as in 2004. The incidence of new cases of HBsAg+ in blood donors was low and the risk of being infected after blood transfusion was 1/100 000 donations (= 0.001%) in 2003 and 0.0006% in 2004.[94] The study of Hourfar et al.[95] between 1997 and 2005 showed that the residual risk per unit transfused is 1 in 360 000 for HBV.

In the study of Niederau et al.,[96] most of the HBV infected patients were HBeAg- (66.4%), while 33.6% were HBeAg+. This is comparable with the studies in France.[15, 85] Genotype A accounts for 32% of the chronic HBV infections in Germany.[97]

We can conclude for Germany that the prevalence of HBsAg carriers varies between 0.41% to 1.59% with a mean around 0.6-0.7% in the general population, quite similar to that of Belgium and France. In blood donors, a selected population, the prevalence of HBsAg is 0.16 per 100 blood donations. The variability depends on the percentage of immigrants that were included in the studies. The prevalence of anti-HBc varies between 6% and 8.7%. As in France, 66% of all HBV carriers are HBeAg-.

2.2.2.4 The Netherlands

In 2004, a seroprevalence study was done in the general adult urban population of Amsterdam. Anti-HBc was present in 9.9% and 0.4% were carriers of HBsAg.[98] Anti-HBc prevalence was highest in first-generation immigrants from Surinam, Morocco and Turkey and in men who have sex with men. The seroprevalence in second-generation immigrants was comparable to Western persons.[98] A recent study by Veldhuijzen et al.,[99] performed in a multi-ethnic area of Rotterdam, showed a prevalence of anti-HBc, a marker for previous or current infection, of 20%. This illustrates the high burden of hepatitis B in areas with large immigrant populations. In the study of Nardone et al.,[77] the prevalence of anti-HBc was 1.7% and HBsAg was 0.1%. In this study the high-risk group of immigrants was probably underrepresented.

To overcome this under-representation of some risk groups, Marschall et al.[100] calculated an adjusted HBsAg prevalence estimate for the total Dutch population. The HBsAg prevalence in the Dutch population was estimated between 0.32% and 0.51% and when including mentally handicapped persons and injecting drug users, the prevalence rates ranged between 0.36% and 0.55%.[100]

In the area of Rotterdam, the HBV genotypes of 464 consecutive HBV carriers between 2002 and 2005 were analysed.[101] In the Dutch born group the prevalence for genotype A was 35%; genotype B was 15%; genotype C was 11%; genotype D was 37% and genotype G was 2%. In this group, sexual transmission was the most frequent cause of infection. In the foreign born group, the prevalence for genotype A was 20%; genotype B was 15%; genotype C was 11%; genotype D was 40% and genotype E was 15%. In this last group, perinatal transmission was the main cause of HBV infection. Phylogenetic analysis of sera of acute HBV infections in the Netherlands in 2004 identified genotype A in 64%; genotype B in 3%; genotype C in 3%; genotype D in 21%; genotype E in 5% and genotype F in 5% of all acute cases.[102] Sexual transmission, especially by men having sex with men, was also the most important transmission route of HBV.[102]

To conclude, in The Netherlands the prevalence for anti-HBc varies between 20% (in ethnic groups) and 1.7% (in the Dutch population) and for HBsAg carriers between 0.1% and 0.55%. Genotype A is the most prevalent genotype in HBV carriers.

2.2.2.5 *Europe*

An European surveillance program of hepatitis B was performed by Eurohep.net between 2002 and 2005.[103] The prevalence of HBsAg carriers in Belgium and Germany ranges between 0.5% and 1.5%; for The Netherlands it is below 0.5%. Genotypes A and D are the most common ones, but genotype A is prevailing in Belgium and The Netherlands. The prevalence rates by genotype vary both between and within countries, depending on the populations, the ethnic background and geographical origins. In intravenous drug users the prevalence of HBsAg ranges from 0% to 20% and of anti-HBc from 20% to 85%.

The incidence rates of HBV per 100 000 inhabitants are given in Table 4.[103] The differences between years and countries should be interpreted with caution as frequency of reporting as well as reporting systems can differ.

Table 4: The incidence of reported hepatitis B cases per 100 000 inhabitants between 1995 and 2005 (adapted from Rantala et al.[103])

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Belgium	0.7	3.2	3	1.3	1.2	2.5	5.2	6.9	7	-	5.3
France	-	-	-	-	-	-	-	-	-	-	0.2
Germany	7.5	7.4	7.4	6.3	5.6	5.5	2.9	1.7	1.6	1.5	1.4
The Nether-lands	1.5	1.5	1.6	1.8	4.3	9.7	10.2	11.5	11.7	11.6	1.7

2.2.3 General Conclusion

The prevalence of HBsAg carriers in Belgium and surrounding countries varies between 0.6% and 1.4% (mostly around 0.7%). The prevalence is higher in immigrants from high endemic regions.

The prevalence of anti-HBc varies between 1.4% and 9.9% in Belgium and surrounding countries.

The French study of Cadranel et al.[85] shows that about 66% of the patients with CHB are HBeAg- with a higher risk for more fibrosis, lower ALT and HBV DNA levels.

Genotype A and D are most prevalent in Belgium and neighbouring countries.

3 TREATMENT

3.1 INDICATIONS FOR TREATMENT

As a number of new antiviral drugs have been marketed over the last years, the field of treatment of CHB is evolving quickly. The data of this report are mainly derived from the guidelines published in December 2007 by the BASL.[104] These 2007 guidelines are to some extent outdated but have been included as, bearing in mind the local reimbursement situation, they are of help to understand the treatment used in Belgium until recently as detailed in the next chapter. A separate font (small italics) has been used to reflect this. These 2007 guidelines have been adapted taking into account data concerning tenofovir[105] and telbivudine,[106] the Guidelines of the European Association for the Study of the Liver (EASL)[107] and the 2008 update of the treatment algorithm.[108] More recent publications have been included based on the author's opinion. For tenofovir and entecavir 3 and 5 year data, respectively, have become available recently. They are in line with earlier report and not covered in detail here. No systematic search was conducted, and this report should not be considered as a source of validated practice guidelines.

3.1.1 Treatment goals

Clearance of HBV is rarely, if ever, achievable. Therefore, the aim of the therapies is the prevention of disease progression and complications (development of cirrhosis, end-stage liver disease and HCC). However, these clinical endpoints take years or decades to occur and are therefore impractical targets for clinical trials. As a result, surrogate markers, believed to correlate with clinical outcome (loss of HBeAg, suppression of viral replication, improvement of liver biopsy), were used to evaluate therapy. None of these surrogate markers is ideal on its own.[109] Current evidence has been reported as insufficient to assess antiviral treatment effect on clinical outcomes. Current evidence is also not sufficient to determine whether the inconsistent improvements seen in selected intermediate measures are reliable surrogates.[110]

Nevertheless, currently, the most used surrogate marker is suppression of viral replication. It is assumed that significant suppression of HBV DNA replication results in lessening of the liver disease progression to cirrhosis and its complications including HCC. This surrogate endpoint is at the basis of all the treatment guidelines, despite its clinical validation is still insufficient and further research is needed.

In patients who are HBeAg+, the treatment goal is HBeAg seroconversion (anti-HBe occurrence) with sustained suppression of HBV DNA, and hopefully HBsAg seroconversion.

In patients who are HBeAg-, the therapeutic goal is sustained suppressed HBV DNA and HBsAg seroconversion (anti-HBs occurrence).

3.1.2 Definition of response

There exist several types of response:

3.1.2.1 Interferon alpha therapy

Primary non-response: less than 1 $\log_{10}$ IU/mL decrease in HBV DNA level from baseline at 3 months of therapy; this endpoint was changed to a 2 log decrease after 6 months.[111]

Virologic response: HBV DNA of less than 2000 IU/mL at 24 weeks of therapy.

Serological response: HBe seroconversion in patients with HBeAg+ CHB.

3.1.2.2 Nucleos(t)ide analogues (NAs) therapy:

Primary non-response: less than 1 log_{10} IU/mL decrease in HBV DNA level from baseline at 3 months of therapy.

Virologic response: undetectable HBV DNA within 48 weeks of therapy.

Partial virologic response (this endpoint was not retained in the American Association for the Study of Liver Disease (AASLD) September 2009 consensus[111]): decrease of HBV DNA of more than 1 log_{10} IU/mL but detectable HBV DNA. A partial virologic response should be assessed to modify therapy at 24 weeks of treatment for moderately potent drugs or drugs with a low genetic barrier to resistance (lamivudine and telbivudine) and at 48 weeks of treatment for highly potent drugs, drugs with a higher genetic barrier to resistance or drugs with a late emergence of resistance (entecavir, adefovir and tenofovir).

Virologic breakthrough: increase in HBV DNA level of more than 1 log_{10} IU/mL compared to nadir (lowest value) HBV DNA level on therapy in 2 subsequent blood samples 1 month apart in patients who have responded and have been compliant with the antiviral medication.[45, 112]

HBV resistance to NAs: selection of HBV variants with amino acid substitution that confer reduced susceptibility to the administered NA. Resistance may result in primary treatment failure or virologic breakthrough on therapy.

Histologic response: a variety of histologic outcomes were used in the literature including improvement in fibrosis or necroinflammatory scores, or both.[110]

3.1.3 Treatment options

Currently, the following therapies are licensed in Europe:

- NAs: lamivudine (Zeffix®), adefovir dipivoxil (Hepsera®), entecavir (Baraclude®), telbivudine (Sebivo®), tenofovir (Viread®)
- Interferon-based therapy: interferon alpha2a (Roferon A®), interferon alpha2b (Intron A®), pegylated interferon-alpha2a (Pegasys®) (Peg-IFN-alpha2a).

NAs are chain terminators that block the HBV polymerase and hence viral replication. They belong to three classes: L-nucleosides (lamivudine, telbivudine), deoxyguanosine analogues (entecavir) and acyclic nucleoside phosphonates (adefovir, tenofovir). They often need to be administered for prolonged periods and often indefinitely. Interferon-based therapy enhances the immune clearance of certain viruses including HBV and is given for a fixed time period.

We discuss below the suggested treatment options for different patient populations.

3.1.4 Interferon and pegylated interferon

Peg-IFN-alpha2a (40kD) (Pegasys®) is a recombinant interferon-alpha2a (IFN-alpha2a) covalently bound to a 40kD branched polyethylene glycol (Peg) molecule. Pegylation increases systemic exposure by decreasing clearance of the molecule, resulting in a prolonged drug effect. Peg-IFN has both immunomodulatory effects and inhibits viral replication and / or viral functions.[113] In this review we will only discuss the use of Peg-IFN-alpha2a as it is often preferred over IFN-alpha2 for reasons of ease of use: 1 subcutaneous (SC) administration per week with Peg-IFN-alpha2a versus three times per week or daily SC injections with IFN-alpha2a or IFN-alpha2b.[114]

Peg-IFN-alpha2b (12kD)(PegIntron®) is a recombinant interferon-alpha2b (IFN-alpha2b) covalently bound to a 12kD branched Peg molecule. However, currently only Peg-IFN-alpha2a is licensed and reimbursed for treatment of hepatitis B.

3.1.4.1 Pegylated interferon in HBeAg-positive chronic hepatitis B

In a phase III study, patients were randomised in 3 arms: Peg-IFN-alpha2a + placebo or Peg-IFN-alpha2a + lamivudine 100mg/d orally (po) or lamivudine 100mg/d po alone.[115] Despite the more important drop in HBV DNA at the end of treatment in the combined Peg-IFN-alpha2a + lamivudine arm (-7.2 log) compared to Peg-IFN-alpha2a alone (-4.5 log) or lamivudine alone (-5.8 log), this did not result in more HBeAg or HBsAg seroconversions. HBeAg seroconversion 6 months after the end of treatment occurred in 32%, 27% and 19% in respectively Peg-IFN-alpha2a alone, Peg-IFN-alpha2a + lamivudine and lamivudine monotherapy ($p < 0.001$ for Peg-IFN-alpha2a alone versus lamivudine; $p < 0.02$ for Peg-IFN-alpha2a + lamivudine versus lamivudine).[115] HBsAg seroconversion was observed in 3%, 3% and 0% respectively.[115] Similar results were reported with Peg-IFN-alpha2b.[116, 117] Histologic response rates were similar in the 3 groups: 38%, 41% and 34% respectively.[115]

Currently, Peg-IFN-alpha2a appears to be superior to NAs, especially due to the highest rates of HBeAg and HBsAg loss after 1 year treatment and the absence of resistance. Thus Peg-IFN-alpha2a monotherapy can be proposed as a first-line therapy in HBeAg+ patients.[13, 45, 118]

Combination with lamivudine does not lead to better viral response.[13, 45, 115] Combination therapy Peg-IFN-alpha2a with adefovir can have favourable effects on covalently closed circular DNA (cccDNA) in the liver. However results are too scarce to give guidelines.

Note that the main reason for the rebound of HBV DNA to its pretreatment level after antiviral treatment withdrawal is that these agents have a profound effect on relaxed circular DNA (rcDNA) and almost no effect on cccDNA, which provides the template for the transcription of all viral genes. After hepatocytes are infected with HBV, cccDNA is formed through DNA repair of the rcDNA inside the nuclei of hepatocytes.

3.1.4.2 Pegylated interferon in HBeAg-negative chronic hepatitis

In a phase III study, patients were randomised in 3 arms: Peg-IFN-alpha2a + placebo or Peg-IFN-alpha2a + lamivudine 100mg/d po or lamivudine 100mg/d po alone.[119] Despite the more important drop in HBV DNA at the end of treatment in the combined Peg-IFN-alpha2a + lamivudine arm (-5 log) compared to Peg-IFN-alpha2a alone (-4.1 log) or lamivudine alone (-4.2 log), this did not result in more sustained viral response or HBsAg seroconversions. HBV DNA below 400 copies/mL 6 months after the end of treatment occurred in 19%, 20% and 7% in respectively Peg-IFN-alpha2a alone, Peg-IFN-alpha2a + lamivudine and lamivudine monotherapy ($p < 0.001$ for both comparisons with lamivudine monotherapy). HBsAg seroconversion was observed in 4%, 3% and 0% respectively. Histologic response rates were similar in the 3 groups: 48%, 38% and 40% respectively.[119]

Three years post treatment with Peg-IFN-alpha2a during 48 weeks leads to a sustained normalisation of ALT in 31% and HBV DNA levels below 10 000 copies/mL and below 400 copies/mL in 28% and 18% of the patients with HBeAg- CHB. The number of patients losing HBsAg increased over time to 8% at 3 years post-treatment.[119]

Thus Peg-IFN-alpha2a can be used as first-line therapy for chronic HBeAg- patients.[13, 45, 115]

We should notice that in these trials of Marcellin et al.[119] and Lau et al.,[115] withdrawal of lamivudine was associated with transient exacerbation of the disease and led in some cases to mortality.[13, 120]

3.1.4.3 Dosage and administration of Peg-IFN-alpha2a

The recommended dosage of Peg-IFN-alpha2a is 180µg administered once weekly by SC injection for 48 weeks. Dose reduction down to 135 µg/week SC in patients with end stage renal disease undergoing haemodialysis is recommended.[113]

3.1.4.4 Predictors of Response to Peg-IFN-alpha2a

Predictors of response to Peg-IFN-alpha2a treatment in HBeAg+ patients[117, 121-123] are:

- high baseline ALT levels (> twice normal value (>2N), or even better > 5N)
- low baseline viral HBV DNA load (< 7 log copies/mL = 2 10^6 IU/mL)
- high disease activity on liver biopsy
- HBV genotypes A and B

There are no consistent predictors of response for HBeAg- patients.

3.1.4.5 On-treatment monitoring

During treatment with Peg-IFN-alpha2a blood count and liver panel should be monitored every 4 weeks. Tests for HBV DNA, HBeAg, anti-HBe, HBsAg, anti-HBs and Thyroid Stimulating Hormone (TSH) should be performed every 12 weeks.

In HBeAg+ patients, HBeAg and anti-HBe should be checked at weeks 24 and 48 and 24 weeks post-treatment. HBe seroconversion together with ALT normalisation and HBV DNA below 2000 IU/mL (10 000 copies/mL) is the desired outcome. Undetectable HBV DNA during the follow-up is the optimal outcome since it is associated with a high chance of HBsAg loss. Patients who develop HBe seroconversion require long follow-up because of the possibility of HBe seroreversion or HBeAg- CHB. In case of primary non-response (i.e. failure to achieve a 1 $\log_{10}$ reduction from baseline at 12 weeks), interferon treatment should be stopped and replaced by a NA. This statement is however not evidence-based.

In HBeAg- patients, a virologic response with HBV DNA below 2000 IU/mL (10 000 copies/mL) is generally associated with remission of the liver disease. Undetectable HBV DNA is the ideal desired off-treatment sustained response with a high probability of HBsAg loss in the longer term.

3.1.4.6 Tolerability and side effects

Peg-IFN-alpha2a is reasonably well tolerated in HBeAg+ and - patients and this tolerability is not modified by lamivudine co-administration.[114, 115, 119] The most common side effects are flu-like symptoms (myalgia, fever, chills, headache and malaise), fatigue, anorexia, weight loss, emotional lability, hypo-and hyperthyroidism and hair loss. Severe myelodepression is uncommon (neutropenia < 1000/µL; thrombocytopenia < 50 000/µL) except in patients who have diminished cell counts before starting the treatment. Depression occurs but with a lower frequency compared to patients with chronic hepatitis C (hepatitis B 5% versus 22% in hepatitis C patients).[124] Discontinuation of Peg-IFN-alpha2a because of side effects was necessary in ≤ 7%.[114, 115, 119] Flares of ALT levels occur in about 30 to 40% during treatment. They represent a change in immunological response to HBV and are a predictor for favourable response.[125] However, these flares can cause liver failure and decompensation, especially in patients with cirrhosis.[45]

3.1.4.7 Pregnancy

Because of antiproliferative effects, Peg-IFN-alpha2a is contraindicated during pregnancy and treatment should be stopped if the patient becomes pregnant.[13]

3.1.5 Nucleos(t)ide analogues in HBeAg-positive patients

In Table 5, a summary of the efficacy of the different drugs is given for HBeAg+ patients. Perhaps with the exception of lamivudine, long term safety data of a continued administration of the oral NAs is lacking. Members of this class have the potential for mitochondrial damage, leading to myopathy and neuropathy.[126] Such adverse events recently caused the discontinuation of the clinical development of clevudine.[126] Adefovir and tenofovir may cause nephrotoxicity and renal tubular damage. Tenofovir has been reported to decrease bone mineral density.

3.1.5.1 Lamivudine (Zeffix)

Lamivudine (3-thiacytidine) was the first L-nucleoside analogue licensed for use in CHB and has been considered the standard of therapy for this disease.

This drug has few and only minor side effects and the daily oral dose is 100 mg.

Response to lamivudine

Loss of HBeAg was 32% vs. 11%, with HBeAg seroconversion observed in 16% to 18% after 1 year of treatment, compared with 4% to 6% of controls.[127, 128] HBeAg seroconversion rates increased with the duration of treatment to 50% after 5 years of continued treatment.[129-132] Pretreatment serum ALT was the strongest predictor of response among HBeAg+ patients. HBeAg seroconversion occurred in 2%, 9%, 21%, and 47% of patients with ALT levels within normal, 1-2 times normal, 2-5 times normal, and >5 times normal range, respectively; the corresponding seroconversion rates for patients in the placebo group were 0%, 5%, 11%, and 14%, respectively.[133, 134] HBV DNA was < 10^5 copies/mL after 1 year of treatment in 44% compared to 16% in placebo-treated patients. HBsAg loss was very rare (<1% after 1 year). ALT normalization occurred in 41-72% of treated patients compared to 7-24% of controls. Finally, histology improved in 49% to 56% of treated patients and in 23% to 25% of controls.

Lamivudine treatment for up to 6 years had an excellent safety profile in patients with HBeAg+ compensated liver disease.[132]

Durability of response to lamivudine

50 to 77% of patients with HBeAg seroconversion had durable response. Several factors have been found to be associated with increased durability of lamivudine-induced HBeAg seroconversion, including longer duration of consolidation treatment.[127, 135]

For how long should lamivudine be continued?

The end point of treatment in HBeAg+ patients is HBeAg seroconversion. Treatment can be discontinued in patients who have confirmed HBeAg seroconversion on 2 occasions and who received at least 6 months of consolidation therapy after the appearance of anti-HBe. In other patients, treatment should be continued if no resistance occurs.[45, 114]

Resistance and long-term outcome of lamivudine-treated patients

Because of the development of resistant strains, virologic and biochemical response decreased with time.[132] After 4 years of treatment 70% of the patients will have developed a resistant strain, as shown in Table 5 and 6. This is mainly due to the development of Tyrosine-methionine-aspartate-aspartate (YMDD) mutant hepatitis B strains. In patients in whom viral suppression could be maintained, necroinflammation and fibrosis were reduced and regression of cirrhosis was observed.[136] Moreover, hepatic decompensation, liver-related mortality and development of HCC were lower in patients with sustained viral suppression.[41]

3.1.5.2 Adefovir dipivoxil (Hepsera®)

Adefovir dipivoxil was the second oral antiviral drug to be licensed for use in CHB. Adefovir dipivoxil is the pro-drug of adefovir, a nucleotide analogue. The 10 mg oral daily dose is well tolerated, even after 5 years of therapy.[137] Higher daily doses (≥ 30mg) were associated with increased risk of renal damage and dose adjustment is recommended in patients with pre-treatment renal impairment.[138]

Response to adefovir

Patients treated for 48 weeks with adefovir 10 mg per day had a 12% chance of HBeAg seroconversion as compared to 6% for the placebo group. Serum HBV DNA levels decreased by a mean of 3.5 $\log_{10}$ copies/mL (0.6 for placebo) with undetectable levels (< 400 copies/mL) of serum HBV DNA in 21% vs. 0%. Normalization of ALT levels was observed in 16% and 48% of patients who received placebo or adefovir 10 mg per day, respectively.

Finally, histologic response was observed in 53% of patients who received adefovir 10 mg per day vs. 25% of those receiving placebo.[139] HBe seroconversion increased after prolonged treatment to 33% and 46% after 96 and 144 weeks of treatment, respectively.[118]

Decompensated cirrhosis

Adefovir has not been evaluated as a primary treatment for patients with decompensated cirrhosis.[45]

For how long should adefovir be continued?

As for lamivudine-treated patients, treatment with adefovir may be discontinued after confirmed HBeAg seroconversion and an additional 6 months of consolidation treatment. HBeAg seroconversion was maintained in approximately 92% of patients. Treatment may be continued in patients who have not achieved HBeAg seroconversion but in whom HBV DNA levels remain suppressed.[45]

Long-term outcome of adefovir-treated patients

Long-term treatment was associated with a decrease in necroinflammation and fibrosis score in the vast majority of patients.[137]

Adefovir resistance

Resistance during adefovir treatment is lower as compared to lamivudine. In lamivudine-naïve patients, no adefovir-resistant mutations were reported after 1 year of treatment.[139, 140] However, resistance emerged after prolonged treatment: 3%, 11% and 18% after respectively 2, 3 and 4 years of treatment.[141] In patients with lamivudine-resistant HBV, adefovir resistance was approximately 20% after 1 year of adefovir monotherapy.[142, 143] In contrast, in lamivudine-resistant HBV patients treated with the combination of lamivudine and adefovir, there was no evidence of resistance to adefovir after 3 years.[143]

3.1.5.3 Entecavir (Baraclude®)

Entecavir is a deoxyguanosine (nucleoside) analogue with potent activity against HBV. The recommended oral daily dose is 0.5 mg for non-lamivudine-resistant patients and the profile is safe in general. The dosage is to be adapted in case of elevated creatinine levels. In patients with decompensated cirrhosis lactic acidosis has been reported.

Response

After 48 weeks of treatment, the rates of histologic, virologic and biochemical improvement were significantly higher with entecavir than with lamivudine, with a similar safety profile. Histologic improvement was observed in 72% in the entecavir group compared to 62% in the lamivudine group. The mean reduction in serum HBV DNA was greater with entecavir than with lamivudine (-6.9 vs. -5.4 $\log_{10}$ copies/mL). Undetectable serum HBV DNA levels (PCR assay) occurred in 67% vs. 36% and normalization of ALT levels was seen in 68% vs. 60%. HBeAg seroconversion was not significantly different in the two groups (21% vs. 18%).[144] After 2 years of treatment, HBeAg seroconversion was significantly higher in entecavir-treated patients.[118]

Durability of response

Among HBeAg+ patients who underwent HBeAg seroconversion during the first year and who stopped treatment at week 48, approximately 70% of patients remained HBeAg-.[45]

Entecavir resistance

Virologic breakthrough was extremely rare in nucleos(t)ide-naive patients (<1% of patients after 1 and 2 years of entecavir treatment, respectively).[144, 145] Moreover, entecavir resistance was only observed in patients who harbored a lamivudine-resistant strain at entry. In patients previously treated with lamivudine who became refractory to lamivudine, resistance to entecavir was detected in 7% and in 16% of patients after 1 and 2 years of treatment.[145, 146] The cumulative probability of a virologic breakthrough due to entecavir resistance through 4 years was 0.8% in naïve and 39.5% in lamivudine refractory patients.[147]

Predictors of response

HBeAg seroconversion rates were lower in patients with normal ALT (12%) as compared to patients with mildly elevated ALT (23%) and patients with ALT > 5 times normal value (39%).[45]

Telbivudine (Sebivo®)

Telbivudine is a NA with potent antiviral activity against HBV. The oral daily dose is 600 mg. Doses should be decreased in patients with renal failure.[45] The safety profile of telbivudine is comparable to lamivudine. Elevations of creatinine kinase and occasional cases of myopathy have been reported. In combination with Peg-IFN-alpha severe neuropathy has been seen.

Telbivudine response

Patients treated for 1 year with telbivudine had a significantly greater mean reduction in HBV DNA levels (-6.01 vs -4.57 $\log_{10}$ copies/mL), clearance of detectable HBV DNA (61% vs. 32%) (Quantiplex branched DNA assay <3 Meq/mL) and normalization of ALT levels (86% vs. 63%) compared with lamivudine monotherapy.[148] Also, after 2 years of treatment, the results were favourable for telbivudine. However, there was no difference in the rate of HBeAg loss at the end of 1 and 2 years of treatment: 26% vs. 23%, and 34% vs. 29% of patients who received telbivudine and lamivudine, respectively.[106, 149, 150]

Telbivudine resistance

As lamivudine, telbivudine is associated with a substantial rate of drug resistance which increases after the first year of treatment. Genotypic resistance after 1 and 2 years of treatment was observed in 4.4% and 21.6% of HBeAg+ patients, with viral breakthrough of 4.5% after 1 year.[149, 150 106, 148]

Tenofovir (Viread®)

In a randomized, double-blind trial comparing tenofovir 300 mg daily and adefovir 10 mg daily, 76% of patients treated with tenofovir had undetectable HBV DNA (<400 copies/mL) after 48 weeks of therapy. Cumulative HBeAg seroconversion was observed in 21% and HBsAg loss in 3.2%.[105]

3.1.5.4 Combination therapy

Combination therapy has the theoretical advantage of higher efficacy and reduced occurrence of resistance. The major disadvantage is increased costs. At present there are no solid data indicating that combination therapy is superior to monotherapy in inducing sustained viral response.[45] Furthermore, although resistance to lamivudine is reduced, it is not completely prevented. Currently, no data indicate that combination therapy reduces the risk of resistance to drugs with a low resistance rate. Therefore, at this time combination therapy is not advocated as first-line treatment in naïve HBeAg+ patients.

3.1.6 Nucleos(t)ide analogues in HBeAg-negative patients

In HBeAg- patients, normalization of transaminases (biochemical response) and sustained HBV DNA suppression (virologic response) and HBs seroconversion (in rare cases) are the only practical measures of response to therapy.[118]

In Table 6, a summary of the efficacy of the different drugs for HBeAg- patients is given.

3.1.6.1 Lamivudine (Zeffix®)

Biochemical and virologic responses, even detected by sensitive PCR assays, ranged from 60 to 90% patients after 1 year of therapy,[151-156] with histologic improvement in the same proportion. Unfortunately, biochemical and virologic relapses were observed in the majority of patients (around 90%) after stopping a 1 year course of therapy.[152]

The association of lamivudine with Peg-IFN did not improve post-therapy response rate.[119] The same negative results were found for combination therapy with interferon alpha2b with lamivudine.[157]

Around 30% of patients have a sustained biochemical and virologic response after long term therapy up to 5 years.[41, 156, 158, 159] However, it seems that the majority of these patients relapses after discontinuation of lamivudine.[151, 160] The optimal duration of therapy and the outcome after discontinuation of lamivudine in patients with such prolonged remission is currently unknown.[160, 161]

Extending the duration of treatment was characterized by a progressive decrease of lamivudine efficacy and increasing rate of virologic breakthroughs due to the appearance of YMDD mutant hepatitis B strains.[151, 153, 154, 158]

Resistance to lamivudine, characterized by a rise in HBV DNA, increased from 19-27% after 1 year of therapy[151, 158, 162] to 66% after 4 years.[158] High pretreatment HBV DNA level was a strong predictive factor of drug resistant mutation.[158] The emergence of lamivudine-resistant mutants can be associated with clinically significant hepatitis and worsening of liver histology,[155, 156] mainly in cirrhotic patients.[41, 158] To date there are no controlled data comparing the efficacy of starting with lamivudine plus salvage therapy upon lamivudine resistance against initial therapy with agents with a better resistance profile than lamivudine.[161]

Because of the need for long treatment durations and high resistance profile, lamivudine is not an optimal first-line treatment in HBeAg- patients.[45]

The efficacy of lamivudine did not differ in naïve or previously interferon-treated patients.[41] Lamivudine retreatment in patients who developed YMDD mutants after a previous course of lamivudine is ineffective because of the rapid re-emergence of YMDD mutants.[163]

3.1.6.2 Adefovir dipivoxil (Hepsera®)

Efficacy

After 1 year of therapy, the efficacy of adefovir was significantly higher than placebo: normalisation of transaminases in 72% of patients treated with adefovir (versus 29% in the placebo group), undetectable serum HBV DNA by PCR assay in 51% (versus 0%) and improvement of liver histology in 64% (versus 33%).[164] However, the response is usually lost after discontinuation of such short therapy.

After 2 and 3 years of therapy, a decrease in serum HBV DNA of respectively 3.47 $\log_{10}$ and 3.63 $\log_{10}$ copies/mL was observed in patients treated with adefovir and HBV DNA levels were less than 1000 copies/mL in respectively 71% and 79 %. Resistance mutations developed in 5.9 % of patients after 3 years.[165]

After 5 years of therapy, HBV DNA was less than 1000 copies/mL in 67% of patients, and transaminases were normal in 69%. Improvement of liver histology was observed with a decrease of inflammation and fibrosis in respectively 83% and 73% of patients. The cumulative probability of mutations was 29%; the cumulative probability of mutations with virologic resistance was 20%.[137]

Significant improvement of liver fibrosis, even with reversion of histologically proven cirrhosis, was observed after a 5 year period of therapy and was associated with HBsAg loss in 5% of patients.[165]

The main advantage of adefovir compared with lamivudine is the infrequent development of viral resistance (around 20% versus 66% after 4 years of therapy). Serum HBV DNA levels at 1 year seem to be a good predictive factor of development of resistance under long-term therapy with adefovir.[166] The development of adefovir resistance is uncommon in the first 2 years of therapy but can be associated with biochemical and virologic rebound and hepatic decompensation.[167] As mentioned previously, in lamivudine-resistant HBV patients treated with the combination of lamivudine and adefovir, there was no evidence of resistance to adefovir after 3 years.[143]

3.1.6.3 Entecavir (Baraclude®)

Efficacy

After 2 years of therapy, it has been demonstrated that entecavir was more effective than lamivudine.[168] Normalisation of transaminases was observed in 78% of patients treated with entecavir versus 71% of patients treated with lamivudine; the decrease of serum DNA levels and improvement of liver histology were also significantly higher in patients treated with entecavir (respectively 90% versus 72% and 70% versus 61%). The safety profile was similar for the two drugs and no entecavir resistance was observed.[168]

Resistance

Resistance to entecavir has been described mainly in patients with lamivudine resistance.[145, 147] Around 9% of lamivudine-resistant patients treated with entecavir developed resistance to entecavir after 2 year of therapy.

3.1.6.4 Telbivudine (Sebivo®)

Efficacy

A phase III study showed, after 1 year of therapy, a significantly higher percentage of patients with undetectable HBV DNA (≤ 20 000 IU/mL) in patients treated with telbivudine compared to patients treated with lamivudine (88% versus 71%). Normalization of transaminases was similar in the two groups of patients (74% versus 79%).[148] After 2 years, patients treated with telbivudine had a significantly higher level of transaminases normalisation (75% versus 67%) and undetectable HBV DNA (≤ 20 000 IU/mL) (79% versus 53%) in comparison to patients treated with lamivudine.[106]

Resistance

Telbivudine is associated with a lower rate of drug resistance than lamivudine. However, the resistance rate is substantial and increased exponentially after the first year of therapy. After 1 and 2 years of therapy, resistance was observed respectively in 2.7% and 8.6% in telbivudine treated patients compared to 9.8% and 21.9% in lamivudine-treated patients.[106, 148]

3.1.6.5 Tenofovir (Viread)

In a randomized, double-blind trial comparing tenofovir 300 mg daily and adefovir 10 mg daily, 93% of patients treated with tenofovir had undetectable HBV DNA (<400 copies/mL), after 48 weeks of therapy. No patient had HBsAg loss.[105]

3.1.7 Nucleos(t)ide analogues in patients with cirrhosis or advanced fibrosis

In a multicenter, prospective, randomized, double-blind, placebo-controlled trial of lamivudine in 651 Asian patients with chronic hepatitis B (58% were HBeAg+) and cirrhosis (61%) or advanced fibrosis it was shown that lamivudine decreased progression of the disease, thereby reducing clinically important complications. In particular, treatment with lamivudine approximately halved the rate of hepatic decompensation during 32 months of continuous treatment. The reduction in the rate of HCC approached statistical significance.[52] No other RCTs with NAs have however confirmed these important findings.

Table 5 : Treatment results in HBeAg-positive patients

In HBeAg+	Peg IFN	PegIFN + Lam	Lamivudine (48-52 wks)	Adefovir (48 wks)	Entecavir (48 wks)	Telbivudine (104 wks)	Tenofovir (48 wks)
HBV DNA < 400 IU/mL at :							
- EOT	25%	69%	44%	21%	67%	56%	76%
- 6m after stop	14%	14%	5%	8%	-	-	-
HBeAg loss :							
- EOT	30%	27%	22%	24%	22%	35%	22%
- 6m after stop	34%	28%	21%	-	-	-	-
HBeAg seroconversion at :							
- EOT	27%	24%	16-20%	12%	21%	30%	21%
- 6m after stop	32%	27%	*(75%*)*	*(90%*)*	*(70%*)*	-	-
-2y of	-	-	-	33%	-	34%	-
treatment	-	-	-	46%	-	-	-
-3y of	-	-	50%	-	-	-	-
treatment	-	-	-	-	-	-	-
-4y of treatment							
-5y of treatment							
HBsAg loss :							
- 1y	3%	-	< 1%	-	2%	< 1%	3,2%
- 2y	-	-	-	-	-	-	-
- 3y	-	-	-	0%	-	-	-
- 4y	-	-	*(20%**)*	-	-	-	-
HBsAg seroconversion	3%	3%	0%	0%	0%	0%	-
ALT normalization :							
- EOT	39%	46%	40-75%	48%	68%	77%	68%
- 6m after stop	41%	39%	28%	-	-	-	-
Histologic improvement 12m	38%	41%	49-56%	53%	72%	65%	74%
Resistance at :							
- 1y	0%	4%	27%	0%	0,2%	5%	-
- 2y	0%	-	42%	2%	0,5%	25%	0%
- 3y	0%	-	53%	11%	1,2%	-	-
- 4y	0%	-	70%	18%	1,2%	-	-
- 5y	0%	-	-	-	1,2%	-	-
Treatment duration	48w	48w	Unclear	Unclear	Unclear	Unclear	Unclear
Dosage	180µg/wk SC	-	100 mg/d	10 mg/d	0.5 mg/d	600 mg/d	300 mg/d

Note that these results were not obtained in head to head comparisons. EOT: end of treatment; SC: subcutaneous; po: per os; ALT: alanine aminostransferase; Lam: lamivudine; PegIFN: pegylated interferon; w: week. Data of the table are derived from the BASL guidelines[104] and from the US 2008 update.[108] Data for tenofovir are derived from Marcellin et al.[105] Data for telbivudine are derived from Liaw et al.[106]

*of those who had seroconversion.

**of those who had HBe seroconversion

Table 6 : Treatment results in HBeAg-negative patients.

In HBeAg-	Peg IFN	PegIFN + Lam	Lamivudine (52 wks)	Adefovir (48 wks)	Entecavir (48 wks)	Telbivudine (104 wks)	Tenofovir (48 wks)
HBV DNA < 400 IU/mL at :							
- EOT	63%	87%	73%	51%	90%	82%	93%
- 6m after stop	19%	20%	7%	71-79%	-	-	-
- 2y	-	-	-	67%	-	-	-
- 5y	-	-	-	-	-	-	-
HBsAg loss:							
- 6m after stop	4%	3%	0%	-	<1%	<1%	0%
- 5y	-	-	-	-	-	-	-
HBsAg seroconversion at :							
- 6m after stop	3%	2%	0%	-	-	-	-
ALT normalization :							
- EOT	38%	49%	73%	72%	78%	74%	77%
- 6m after stop	59%	60%	44%	-	-	-	-
- 2y	-	-	-	69%	-	-	-
- 5y	-	-	-	-	-	-	-
Histologic improvement :							
- 12m	48%	38%	40%	64%	70%	67%	72%
- 5 y	-	-	-	83-73%	-	-	-
Resistance at :							
- 1y	0%	1%	14%	0%	0,2%	2,2%	-
- 2y	0%	-	-	3%	0,5%	11%	0%
- 3y	0%	-	-	11%	1,2%	-	-
- 4y	0%	-	70%	18%	1,2%	-	-
- 5y	0%	-	-	29%	1,2%	-	-
Durable undetectable DNA < 400 IU/mL :							
- 1y	15%	12%	-	-	-	-	-
- 2y	16%	11%	-	-	-	-	-
- 3y	18%	13%	-	-	-	-	-
Treatment duration	48w	48w	Unclear	Unclear	Unclear	Unclear	Unclear
Dosage	180µg/w SC	-	100mg/d	10mg/d	0.5 mg/d	600 mg/d	300 mg/d

Note that these results were not obtained in head to head comparisons. EOT: end of treatment; SC: subcutaneous; po: per os; ALT: alanine aminostransferase; Lam: lamivudine; PegIFN: pegylated interferon; w: week.

Data are derived from the BASL guidelines[104] and from the US 2008 update.[108] Data for tenofovir are derived from Marcellin et al.[105]

3.2 RECOMMENDATIONS FOR THE TREATMENT

3.2.1 The BASL 2007 recommendations

The BASL recommendations have been based on the US recommendations published in 2007. As management guidelines have changed after 2007, some of these recommendations are no longer up to date, including the lack of recommendations to use tenofovir, the assessment of primary non-response and the recommended switch from lamivudine to entecavir. Therefore the 2007 BASL guidelines are presented in a smaller and italic font.

3.2.1.1 Recommendations for the treatment of HBeAg-positive CHB.[45]

Patients with ALT > twice normal value or moderate/severe hepatitis on biopsy and HBV DNA >20 000 IU/mL should be considered for treatment.

Treatment should be delayed for 3 to 6 months in persons with compensated liver disease to determine if spontaneous HBeAg seroconversion occurs.

Special groups:

- *Patients with icteric ALT flares should be promptly treated.*
- *Patients with persistently normal or minimally elevated ALT (< twice normal value) should generally not be started on treatment.*

In patients with fluctuating or minimally elevated ALT levels, liver biopsy may be considered, especially in those above 35-40 years of age. Treatment may be initiated if there is moderate or severe necroinflammation or significant fibrosis on liver biopsy.

3.2.1.2 Recommendations for the treatment of HBeAg-negative CHB.[45, 118]

Because HBeAg- patients tend to have lower levels of serum HBV DNA than HBeAg+ patients but still may have active disease, it is recommended to treat patients who have HBV DNA levels of > 2000 IU/mL and elevated transaminases.

Special groups:

- *In patients with HBV DNA levels of > 2000 IU/mL and normal transaminases, a liver biopsy has to be considered and the same therapeutic recommendations are proposed in case of histologic active disease.*
- *In the absence of liver biopsy, follow-up of transaminases is recommended and therapy is proposed only in patients with elevated transaminases.*
- *Patients with HBV DNA levels ≤ 2000 IU/mL and normal transaminases are considered as inactive HBsAg carriers and no therapy is recommended.*

Recommendations in patients with cirrhosis:

- *Patients with compensated cirrhosis should be considered for treatment if HBV DNA is > 2000 IU/mL regardless of ALT levels.[45, 118]*
- *In decompensated cirrhosis, independent of the viral load, antiviral treatment should be promptly initiated with NA producing rapid viral suppression and low risk of resistance. Evaluation for liver transplantation should be considered.[45, 118]*

3.2.2 The EASL 2009 recommendations

The EASL 2009 recommendations[107] are roughly similar. In the EASL recommendations, however, the indications for the treatment are considered as being similar for both HBeAg+ and HBeAg- patients. One consequence is that the cut-off of DNA level to initiate a treatment is > 2000 IU/mL, whatever the status HBeAg+ or -. The cut-off of transaminases is also adapted to the cut-off of HBeAg- patients (elevated transaminases), whatever the status HBeAg+ or -.

As in the BASL guidelines, the decision to treat is based mainly on the combination of three criteria: serum HBV DNA levels, transaminases, histologic grade and stage. Patients should be considered for treatment when DNA levels are above 2000 IU/mL (10000 copies/mL) and/or the serum ALT levels are above the upper limit of normal, and when liver biopsy shows at least grade A2 or stage F2 by METAVIR scoring (moderate to severe active necroinflammation and/or fibrosis).

The EASL recommendations for special groups are similar to those proposed by the BASL:

- Immunotolerant patient do not require therapy.
- Patients with mild hepatitis B (ALT less than 2 times upper limit of normal and METAVIR score less than A2F2) may not require therapy.
- Patients with compensated cirrhosis and detectable DNA may be considered for treatment even if ALT are normal and/or HBV DNA levels are < 2000 IU/mL .
- Patients with decompensated cirrhosis require urgent antiviral therapy and should be considered for liver transplantation.

3.2.3 Treatment strategies

3.2.3.1 Advantages and disadvantages of the available drugs

The main theoretical advantages of interferon alpha (conventional or pegylated) are the absence of resistance and the potential for immune-mediated containment of HBV infection with an opportunity to obtain a sustained virologic response off-treatment and a chance of HBsAg loss in patients who achieve and maintain undetectable HBV DNA. Frequent side effects and SC injection are the main disadvantages of interferon alpha treatment. Interferon alpha is contraindicated in patients with decompensated HBV-related cirrhosis or autoimmune disease and in those with uncontrolled severe depression or psychosis.

Entecavir and tenofovir are potent HBV inhibitors and they have a high barrier to resistance.[105, 169] Thus they can be confidently used as first-line monotherapies. The role of monotherapy with entecavir or tenofovir could be modified if higher rates of resistance become apparent with longer treatment duration.

Adefovir is more expensive than tenofovir, is less efficacious and engenders higher rates of resistance. Telbivudine is a potent inhibitor of HBV but, due to a low genetic barrier to resistance, a high incidence of resistance has been observed in patients with high baseline levels of replication and in those with detectable HBV DNA after 24 weeks of therapy.[148] Lamivudine is an inexpensive agent, but engenders very high rates of resistance with monotherapy.

3.2.3.2 How to treat? BASL 2007 consensus

HBeAg-positive

Treatment may be initiated with any of the approved antiviral medications, but Peg-IFN-alpha2a and the NAs with the highest efficacy in suppressing HBV DNA and the lowest resistance rate (highest genetic barrier) are preferred as first-line option. Peg-IFN-alpha2a should be considered as first-line in patients with high transaminases, low HBV DNA and active disease. Lamivudine is not considered a reasonable first-line treatment option because of the high risk of resistance with long-term therapy and proven inferiority to Peg-IFN-alpha2a and entecavir in randomized clinical trials.

HBeAg-negative

Peg-IFN-alpha2a and the NAs with the highest efficacy in suppressing HBV DNA and the lowest resistance rate (highest genetic barrier) are preferred as first line options. Currently, NA treatment in HBeAg- patients should be viewed as indefinite and even lifelong. Lamivudine is not considered a reasonable first-line treatment option because of the high risk of resistance with long-term therapy and proven inferiority to Peg-IFN-alpha2a and entecavir in randomized clinical trials.

Recommendations for compensated cirrhosis

Given the risk of interferon-induced flares, NAs should be preferred. In view of the need for long term therapy and because of the rapid emergence of resistant mutants with lamivudine, first-line treatment with adefovir or entecavir should be started. Note that list of preferred NA has changed after 2007 and adefovir is no longer recommended in this setting.

Recommendations for decompensated cirrhosis

IFN-alpha and Peg-IFN-alpha should not be used in patients with decompensated cirrhosis.

In 2007, the combination of lamivudine and adefovir was recommended for achieving a rapid effect and reducing the emergence of resistance. Entecavir is a promising treatment in this setting but clinical data were lacking in 2007. Note that recently lactic acidosis has been reported when entecavir was used in this setting.

3.2.3.3 How to treat? EASL 2009 recommendations

The recommendations are globally similar. In the EASL recommendations, more precise recommendations are given to define patients who could have a treatment of finite duration.

Two different treatment strategies are applicable in both HBeAg+ and HBeAg- CHB patients: treatment of finite duration with Peg-IFN-alpha or NAs and long-term treatment with NAs.

Treatment of finite duration with Peg-IFN-alpha or NAs

This strategy is intended to achieve a sustained virologic response off-treatment.

1. Finite-duration treatment with Peg-IFN-alpha: a 48-week course of Peg-IFN-alpha is mainly recommended for HBeAg+ patients with the best chance of HBe seroconversion. It can also be used for HBeAg- patients who have the best chance of a sustained response off-treatment. In both groups, these are patients with high baseline ALT (>3 times ULN) and HBV DNA less than 2×10^6 IU/mL (approximately 10^7 copies/mL) or 6.3 l log10 IU/mL at baseline.
2. Finite-duration treatment with NAs is achievable for HBeAg+ patients who develop HBe seroconversion on treatment. However, duration is unpredictable prior to therapy as it depends on when HBe seroconversion occurs. HBe seroconversion is more frequent in patients with high baseline ALT (>3 times ULN) and HBV DNA less than 2 × 106 IU/mL (approximately 107 copies/mL) or 6.3 log10 IU/mL at baseline. An attempt at finite treatment should use the most potent agents with the highest barrier to resistance (entecavir or tenofovir) to rapidly reduce levels of viremia to undetectable levels and avoid rebounds due to HBV resistance. Telbivudine might be used in patients with good predictors of response (HBV DNA <2 × 106 IU/mL, i.e. approximately 107 copies/mL, or 6.3 log10 IU/mL at baseline) with verification of HBV DNA suppression below detection in real-time PCR assay at 24 weeks. Once HBe seroconversion occurs on NA, treatment should be prolonged for an additional 6 to (preferentially) 12 months; a durable response (persistence of anti-HBe antibodies off-treatment) can be expected in 80% of these patients.

Long-term treatment with nucleos(t)ide analogues

This strategy is necessary for patients who cannot achieve a sustained virologic response off-treatment and require extended therapy, i.e. for HBeAg+ patients who do not develop HBe seroconversion and in HBeAg- patients. This strategy is also recommended in patients with cirrhosis irrespective of HBeAg status or HBe seroconversion on treatment.

The most potent drugs with the optimal resistance profile, i.e. tenofovir or entecavir, should be used as first-line monotherapies. It is optimal to maintain HBV DNA suppression to undetectable HBV DNA in real-time PCR, whatever the drug used. The long-term effects, safety and tolerability of entecavir and tenofovir (i.e. after five to ten years) are still unknown.

There are as yet no data to indicate an advantage of de novo combination treatment with NAs in naive patients receiving either entecavir or tenofovir. Therapeutic trials are in progress.

Recommendations for compensated cirrhosis

Interferon-alpha increases the risk of sepsis and decompensation in patients with advanced cirrhosis. However, interferon can be used for the treatment of well compensated cirrhosis.[170] The use of potent NAs with very low risk of resistance, i.e. tenofovir or entecavir, is particularly relevant in this group of patients. Close monitoring of HBV DNA levels is important and resistance must be prevented by adding a second drug without cross-resistance if HBV DNA is not undetectable at week 48 of therapy. If lamivudine has to be prescribed (because of local policy), it should be used in combination with adefovir or preferably tenofovir.

Recommendations for decompensated cirrhosis

End-stage liver disease should be treated as a matter of urgency. Treatment is indicated even if HBV DNA level is low in order to prevent recurrent reactivation. Potent NAs with good resistance profiles (entecavir or tenofovir) should be used. However, there are little data for the safety of these agents in decompensated cirrhosis. It should be noted that lactic acidosis has been reported in entecavir treated patients with decompensated cirrhosis.

Patients may show slow clinical improvement over a period of 3–6 months. However some patients with advanced hepatic disease with a high Child–Pugh or Model for End-stage Liver Disease (MELD) score may have progressed beyond the point of no return, and may not benefit, thus requiring transplantation if possible.[171] In that situation, treatment with NAs will decrease the risk of HBV recurrence in the graft.

3.2.4 Management of antiviral resistance to current NA therapy

3.2.4.1 Introduction

A major concern with long-term NA treatment is the selection of antiviral-resistant mutations, marked by appearance of circulating HBV with reduced sensitivity to the antiviral agent.[172-175] Data on the occurrence and management of resistance to NA is a continuous evolving field with new data being presented and published regularly parallel to the availability of accumulating follow-up data in NA treated patients. This text summarizes recommendations made over the recent years in both national and international guidelines as in expert consensus texts on the management of NA resistance.[13, 45, 107, 111, 112, 176-178]

Among the approved NA therapies for hepatitis B, lamivudine is associated with the highest and entecavir and tenofovir with the lowest rates of drug resistance in NA-naïve patients. The rate at which resistant mutants are selected is related to pre-treatment serum HBV DNA level, rapidity of viral suppression, duration of treatment and prior exposure to NA therapies.[179] The table below summarizes the definition of terms commonly used in describing antiviral resistance.[111] Primary non response to NA therapy is defined as the inability of the NA treatment to reduce serum HBV DNA substantially in the early months of treatment. There has been variation in the numeric definition of non response over the last 2 years in the above mentioned guidelines and expert recommendations, ranging from the absence of a >1 $\log_{10}$ IU/mL decline after 3 months to the absence of a > 2 $\log_{10}$ IU/mL after the first 6 months of NA administration.[111] Primary non response however is rare in compliant patients for most NA. It is predominantly seen with adefovir treatment. This definition will therefore become less important when entecavir and tenofovir replace adefovir in first line treatment. Primary non response with NA therapy other than adefovir most often indicates poor compliance.

Table 7 : Definition of terms relating to antiviral resistance to nucleoside analogue treatment[111]

- **Virologic breakthrough**: increase in serum HBV DNA by > 1 log_{10} (10-fold) above nadir after achieving virologic response, during continued treatment
- **Viral rebound:** increase in serum HBV DNA to > 20000 IU/ml or above pretreatment level after achieving virologic response, during continued treatment
- **Biochemical breakthrough**: increase in ALT above upper limit of normal after achieving normalization, during continued treatment
- **Genotypic resistance**: detection of mutations that have been shown in *in vitro* studies to confer resistance to the NA that is being administered
- **Phenotypic resistance**: in vitro confirmation that the mutation detected decreases susceptibility (as demonstrated by increase in inhibitory concentrations) to the NA administered

3.2.4.2 Definitions of resistance

Resistance is typically categorized as genotypic, viral and clinical. Genotypic resistance is based upon detection of HBV mutations that are associated with *in vitro* and *in vivo* resistance to antiviral agents. During treatment with NAs, mutations in the polymerase gene of HBV can often be detected before there is a rise in HBV DNA or ALT levels.[180, 181] The difficulty with this definition is that it requires molecular testing which is expensive and may not be warranted clinically if there are no other signs of antiviral resistance.

Viral resistance or virologic breakthrough indicates that HBV DNA levels have increased, the usual criteria being ≥ 1 log_{10} IU/mL increase from a previous nadir on ≥ 2 occasions 1 month apart, in a patient who is compliant and still on treatment.

Clinical resistance or biochemical breakthrough is defined by a rise in serum ALT levels. For patients in whom serum ALT levels fall into the normal range during therapy, clinical resistance can be defined as a rise to above twice the upper limit of the normal range in conjunction with a rise in HBV DNA levels and/or genotypic resistance. These criteria become difficult to apply in the situation in which ALT levels never fall into the normal range, or were normal before therapy, or fluctuate spontaneously.

Virologic breakthrough is usually followed by biochemical breakthrough. Emergence of antiviral-resistant mutations can lead to negation of the initial response, and in some cases hepatitis flares and hepatic decompensation.[167, 175, 179, 182-185] Antiviral-resistant mutations can be detected months and sometimes years before biochemical breakthrough. Thus, early detection and intervention can prevent hepatitis flares and hepatic decompensation, and this is particularly important in patients who are immunocompromised and those with underlying cirrhosis. Waiting for clinical breakthrough should absolutely be abandoned.

Judicious use of NA in patients with CHB is the most effective prophylaxis against the development of antiviral-resistant HBV. Thus, patients with minimal disease and those who are unlikely to achieve sustained response should not be treated with NA, particularly if they are young (<30 years). When possible, the most potent NA with the lowest rate of genotypic resistance should be administered and compliance reinforced.

Up to 30% of virologic breakthrough observed in clinical trials is related to medication non-compliance. Compliance should thus be ascertained before testing for genotypic resistance.

Location and terminology of antiviral resistant mutations

The pattern of development of HBV resistant mutants varies by chemical class of NAs, which can be categorized as:

- L-nucleosides, such as lamivudine and telbivudine
- Acyclic phosphonates such as adefovir and tenofovir.
- Cyclopente(a)nes such as entecavir.

Nomenclature in discussing HBV resistance uses an abbreviation for the gene region in lower case (rt for reverse transcriptase, c for HBcAg, s for HBsAg) followed by the wild-type amino acid symbol, its position in the gene region and finally the mutant or variant amino acid symbol.[112] Detection of resistant mutations usually requires sequencing of the polymerase gene, but various assays including reverse hybridization and restriction fragment length polymorphism have been developed that detect the more common mutations.[186] Eight codons in HBV polymerase are associated with NA resistance: 169, 180, 181, 184, 202, 204, 236 and 250. There are 4 major pathways involved in HBV NA drug resistance. (1) the rtM204V/L pathway for L-nucleosides; (2) the rt N236T pathway for the acyclic phosphonates; (3) the rtA181T/V pathway which is shared between the L-nucleosides and alkyl phosphonates and (4) the cylopentane entecavir pathway (rtL180M+rtM204V+I169T+T184S/G/C+S202C/G/I+M250I/V).[187] Potential consequences of these antiviral-resistant mutations are cross-resistance with other NA limiting future treatment options and the possibility of multi-drug resistance with sequential monotherapy.

Whereas published clinical data are available to guide patient management for lamivudine resistant patients, recommendations for the management of the resistance to the newer NAs and of multi-drug resistant mutations are largely derived from in vitro data or case reports.

3.2.4.3 Lamivudine resistance

Lamivudine has a high rate of antiviral resistance (low genetic barrier), averaging 15% to 20% per year.[174] For these reasons, long-term results of lamivudine therapy are poor.

The most common mutation involves substitution of methionine in the YMDD motif of the HBV DNA polymerase for valine or isoleucine rtM204V/I, changing it to YVDD or YIDD.[188, 189] The rtM204V/I mutation is usually accompanied by a compensatory mutation upstream of the YMDD motif at rtL180M and/or rtV173L. The rtM204V/I mutations are considered primary resistant mutations that lower the susceptibility of HBV to lamivudine, while the rtL180M and rtV173L mutations are considered secondary or compensatory, allowing for the resistant mutant to replicate at a higher rate. Resistance has been mapped to a rtA181T/V mutation in a minority of patients during prolonged lamivudine therapy.[190] Generally, development of the lamivudine resistant HBV makes other L-nucleosides ineffective.

Genotypic resistance can be detected in 14% to 32% after 1 year of lamivudine treatment[127, 128, 191] and increases with the duration of treatment to 60% to 70% after 5 years of treatment.[129, 132] Factors associated with an increased rate of lamivudine resistance include long duration of treatment, high pretreatment serum HBV DNA level and a high level of residual virus after initiation of treatment.[132, 183] One study reported that the rate of lamivudine resistance was significantly higher in patients whose serum HBV DNA level exceeded 200 IU/mL (1000 copies/mL) after 6 months of treatment compared to those with lower HBV DNA levels (63% vs. 13%).[183]

The clinical course of patients with lamivudine-resistant mutants is variable. In vitro studies showed that rtM204V/I mutation decreases replication fitness of HBV but compensatory mutations selected during continued treatment can restore replication fitness.[192, 193] Virologic breakthrough is usually followed by biochemical breakthrough and in some patients may be associated with acute exacerbations of liver disease and rarely hepatic decompensation and death.[175, 179, 185] Exacerbations of hepatitis associated with the emergence of lamivudine-resistance have also been reported to be associated with HBeAg seroconversion, possibly via immune mediated mechanisms.[185] Hepatitis flares may also occur after withdrawal of treatment due to rapid outgrowth of wild type virus, but two studies in Asia found that the occurrence of hepatitis flares and hepatic decompensation were similar among patients with lamivudine breakthrough who stopped or continued lamivudine treatment.[194, 195]

In patients who have breakthrough infection, testing for lamivudine-resistant mutants should be performed when possible. The vast majority of patients with confirmed lamivudine-resistance should receive rescue therapy with antiviral agents that are effective against lamivudine-resistant HBV mutants. Entecavir has reduced efficacy against rtM204V/I mutants and should not be used in this case.[196]

Adefovir and tenofovir have a potent activity against lamivudine-resistant strains *in vitro* and *in vivo*[193, 197] except in the rare case of rtA181V/T mutation.[198] A minority of patients may consider stopping treatment, particularly if they had normal ALT, or if the biopsy showed mild inflammation and no or minimal fibrosis prior to initiation of treatment.[194, 195]

Adefovir for lamivudine-resistant hepatitis B

DECOMPENSATED CIRRHOSIS AND LIVER TRANSPLANT RECIPIENTS

In a compassionate use study involving 128 patients with decompensated cirrhosis and 196 patients with recurrent hepatitis B after liver transplantation, addition of adefovir was associated with a 3-4 $\log_{10}$ reduction in serum HBV DNA levels, which was sustained throughout the course of treatment.[199] Among the patients who completed 48 weeks of treatment, 81% of the pre- and 34% of the post-transplant patients had undetectable HBV DNA by PCR assay, and 76% and 49% respectively had normalization of ALT. The Child-Turcotte-Pugh score improved in more than 90% of the pre-transplant patients, and 1-year survival was 84% for the pre- and 93% for the post-transplant patients. Follow-up data on 226 pre-transplant patients showed that viral suppression was maintained in 65% of patients after 96 weeks of treatment with accompanying improvement in Child-Turcotte-Pugh scores as well as MELD scores.[200]

COMPENSATED LIVER DISEASE

While a pilot study in patients with compensated CHB and lamivudine resistance found no differences in HBV DNA suppression and ALT normalization in persons treated with the combination of lamivudine and adefovir compared to those receiving adefovir alone,[201] patients who discontinued lamivudine were more likely to develop ALT flares during the first 12 weeks of adefovir monotherapy. In addition, recent data showed that switching to adefovir in patients with lamivudine-resistant HBV was associated with a higher risk of adefovir-resistance compared to adding-on adefovir.[143, 202, 203] Thus, increasing evidence supports that adding adefovir is better than switching to adefovir monotherapy for patients with lamivudine-resistant HBV. For most patients with lamivudine-resistant mutants, particularly those with decompensated cirrhosis or recurrent hepatitis B post-transplant, long-term treatment will be required. Increasing data indicate that lamivudine should be continued indefinitely after the addition of adefovir to reduce the risk of adefovir resistance.

Tenofovir for lamivudine-resistant hepatitis B

Tenofovir disoproxil fumarate is an acyclic adenine nucleotide with potent activity against both HBV and HIV in vitro and in vivo. Tenofovir appears to be more potent than adefovir and is effective against lamivudine-resistant strains of HBV DNA.[204] Small comparative studies have been conducted in cohorts of patients with HBeAg+ CHB and lamivudine-resistance without HIV co-infection. In a study with greater than 48 weeks of follow-up, all 35 patients (100%) treated with 300 mg of tenofovir daily were HBV DNA negative compared to only 44% (7 of 15 patients) treated with 10 mg of adefovir daily.[205] Tenofovir could also rescue patients with lamivudine resistance who had an inadequate response to adefovir.[206] Side effects and renal toxicity were comparable. These results suggest that tenofovir may be the agent of choice for lamivudine-resistant HBV and may ultimately replace adefovir in treatment of hepatitis B.

Entecavir for lamivudine-resistant hepatitis B

In a dose-finding phase II trial, entecavir was shown to be effective in suppressing lamivudine-resistant HBV but a higher dose of 1 mg was required.[207] In a subsequent study, 286 HBeAg+ patients with persistent viremia while on lamivudine were randomized to receive entecavir 1 mg or lamivudine 100 mg daily. At week 48, entecavir resulted in significantly higher rates of histologic (55% vs. 28%), virologic (21% vs. 1%) and biochemical (75% vs. 23%) responses compared to lamivudine.[146] Seventy-seven entecavir-treated patients who remained HBeAg+ and had serum HBV DNA < 0.7 Meq/mL (< 150 000 IU/mL) at week 52 continued treatment up to week 96. Between week 48 and end of dosing, the proportion of patients with undetectable serum HBV DNA increased from 21% to 40% and ALT normalization from 65% to 81%. HBeAg seroconversion was achieved by 10% of patients. Entecavir resistance emerged in 6 (7.8%) patients in year 2.[208] These data indicate that while continued treatment resulted in virus suppression in a higher percent of patients, it is currently recommended not to use entecavir in case of lamivudine-refractory HBV.

Peginterferon for lamivudine-resistant hepatitis B

Although previous exposure to lamivudine did not seem to affect the overall rates of HBeAg seroconversion of Peg-IFN-alpha2a in HBeAg+ patients in one study,[115] Peg-IFN-alpha2b therapy showed only marginal efficacy in patients harbouring lamivudine-induced YMDD lamivudine resistance.[209] Analysis of the patient subgroup harbouring an YMDD-mutation should be included in all future studies of Peg-IFN-alpha in CHB to find out if Peg-IFN-alpha therapy is beneficial in this situation.

3.2.4.4 Telbivudine resistance

Telbivudine (L-deoxythymidine) selects for mutations in the YMDD motif. To date, only rtM204I mutants have been observed.[150] Although telbivudine is associated with a slightly lower rate of drug resistance than lamivudine, the resistance rate is substantial and increases exponentially after the first year of treatment. Therefore, telbivudine monotherapy has a limited role in the treatment of hepatitis B. In the phase III clinical trial, genotypic resistance after 1 and 2 years of treatment was observed in 4.4% and 21.6% of HBeAg+ and in 2.7% and 8.6% of HBeAg- patients who received telbivudine compared to 9.1% and 35% of HBeAg+ and 9.8% and 21.9% of HBeAg- patients who received lamivudine.[106, 148] The lower resistance rate in the lamivudine group compared to previously reported clinical trials on lamivudine[132] may be related to the fact that only patients with virologic breakthrough were tested and a less sensitive method (direct sequencing) was used for detection of resistant mutations. There is limited evidence from a small series that switching to or adding adefovir is a viable salvage option in telbivudine-treated patients exhibiting virologic breakthrough.[210]

3.2.4.5 Adefovir resistance

Resistance occurs at a slower rate during adefovir treatment compared to lamivudine and no adefovir-resistant mutations were found after 1 year of treatment in the patients who participated in the Phase III trials.[140] However, novel mutations conferring resistance to adefovir have been described since.[211, 212] Aggregate data from 5 studies including 3 studies using the combination of lamivudine and adefovir in patients with lamivudine resistant HBV estimated the cumulative rate of adefovir resistance to be 15% by 192 weeks.[166] The phase III trial in HBeAg- patients found that the cumulative probabilities of genotypic resistance to adefovir at 1, 2, 3, 4 and 5 years were 0, 3%, 11%, 18% and 29%, respectively.[165] Cumulative rate of genotypic resistance to adefovir in the phase III trial in HBeAg+ patients was estimated to be 20% after 5 years of treatment.[213]

Recent studies using more sensitive methods have reported detection of adefovir-resistant mutations after 1 year of treatment and rates of genotypic resistance exceeding 20% after 2 years of treatment.[142, 203] In these studies, adefovir resistance was predominantly found in patients with prior lamivudine resistance switched to adefovir monotherapy.

The most common resistant mutations associated with adefovir therapy have been rtA181V/T and rtN236T.[211, 212] In vitro studies showed that adefovir-resistant mutations decrease susceptibility 3-15 -fold only.[211, 212] Nevertheless, clinical studies found that viral rebound, hepatitis flares and even hepatic decompensation can occur.[167] Risk factors for adefovir resistance that have been identified include suboptimal viral suppression and sequential monotherapy.[142, 203] Sequential treatment with lamivudine followed by adefovir had also been reported to select for dual-resistant HBV mutants.[167] In vitro and clinical studies showed that rtN236T adefovir-resistant HBV mutants are susceptible to lamivudine and entecavir.[212] One case series reported that two patients with adefovir-resistant HBV responded to entecavir with a decrease in serum HBV DNA to undetectable levels.[203]

The rtA181V/T mutation has reduced susceptibility to both lamivudine and entecavir in vitro, but remains sensitive to tenofovir.[166] Indeed re-emergence of lamivudine-resistant mutations has been reported soon after reintroduction of lamivudine in patients with prior lamivudine resistance and who developed adefovir resistance after being switched to adefovir monotherapy.[167] There is one published case series where switching from adefovir to tenofovir resulted in a decrease in serum HBV DNA levels.[206] However, serum HBV DNA remained detectable and adefovir-resistant mutations persist after switching to tenofovir monotherapy in a second case series indicating that these two drugs are cross-resistant.[214] By contrast, rescue therapy with combination of lamivudine or emtricitabine and tenofovir resulted in suppression of serum HBV DNA to undetectable levels.[214, 215]

Adefovir and primary non-response. Some studies have reported that 20%-50% of patients receiving the 10 mg dose of adefovir have primary non-response.[216] Whether this suboptimal response to adefovir results from a host pharmacological effect or from patient compliance issues rather than from a reduced susceptibility of HBV to adefovir is still debated.[216, 217] Higher doses of adefovir have greater potency against HBV, but are associated with an unacceptably high rate of renal toxicity. Alternative treatments should be considered for patients who exhibit a primary non-response to adefovir. Updated data on the use of tenofovir in case of adefovir resistance have become available recently but are not included.

3.2.4.6 Tenofovir resistance

Tenofovir disoproxil fumarate has a potent activity against both HBV and HIV *in vitro* and *in vivo*.[218] Tenofovir is licensed for use in HIV infection and has been evaluated extensively in patients with HIV/HBV co-infection.[219-221] It was approved for the treatment of CHB in 2008. One study of two patients with HBV and HIV co-infection reported that alanine to threonine substitution at position 194 (rtA194T) is associated with resistance to tenofovir.[222] The association between rtA194T and resistance to tenofovir was not confirmed in another study.[223] A recent study found that the rtA194T mutation is associated with decreased replication fitness in *in vitro* studies but replication can be restored in the presence of precore G1896A stop codon mutation suggesting that rtA194T mutation may be more likely to be selected in HBeAg- patients. In vitro data suggest that telbivudine or entecavir are effective alternative treatment options for patients with the rtA194T mutation.[224]

In the two phase III clinical trials in hepatitis B monoinfected patients, 7 patients were observed to have virologic breakthrough during 96 weeks of treatment but tenofovir-resistant HBV mutations were not detected in any of these patients.[225] Data on resistance to tenofovir monotherapy beyond 72 weeks cannot be determined from the two pivotal trials since patients who had persistent detection of serum HBV DNA at week 72 received additional treatment with emtricitabine in both trials.

3.2.4.7 Entecavir resistance

In preliminary studies and in randomized controlled trials, entecavir showed excellent potency, high rates of suppression of HBV DNA levels and improvements in biochemical and histologic features of disease.[144, 168] Virologic breakthrough was rare in nucleoside-naïve patients, and was observed in only 3% of patients by week 96 of entecavir treatment in the two phase III clinical trials.[226] Resistant mutations to lamivudine and entecavir were detected in only two (≤ 1%) patients while resistant mutations to lamivudine only were found in three patients.[145] However, virologic breakthrough was detected in 7% of patients after 48 weeks, in 16% after 96 weeks and 38% after 3 years of treatment in the phase III trial of lamivudine-refractory patients.[145, 147, 227] Resistance to entecavir appears to occur through a two-hit mechanism with initial selection of M204V/I mutation followed by amino acid substitutions at rtI169, rtT184, rtS202 or rtM250.[196] In vitro studies showed that the mutations at positions 169, 184, 202 or 250 on their own have minimal effect on susceptibility to entecavir, but susceptibility to entecavir is decreased 10-250-fold when one of these mutations is present with lamivudine resistant mutations, and ≥ 500-fold when two or more entecavir-resistant mutations are present with lamivudine-resistant mutations. In vitro studies showed that entecavir-resistant mutations are susceptible to adefovir or tenofovir, but there are very few clinical data on the efficacy of adefovir or tenofovir in patients with entecavir-resistant HBV.

3.2.4.8 BASL 2007 recommendations for treating patients with HBV resistant mutants

The BASL 2007 guidelines[104] recommend avoiding unnecessary treatment with NAs. Initiate first-line treatment with a potent antiviral drug that has low rate of drug resistance. Check for primary NA non response (after 6 months of treatment) and subsequently for NA viral resistance/breakthrough with 3 monthly PCR. Always check for patient's compliance in case of primary non-response or viral resistance/breakthrough before changing to an alternative treatment regime.

In lamivudine-resistant patients adefovir add-on therapy should be preferred to adefovir sequential monotherapy. Alternatively, therapy can be switched to sequential entecavir monotherapy in case of contraindications to adefovir.

First line adefovir resistant patients generally respond to add-on lamivudine therapy or switch to entecavir or telbivudine or tenofovir. Second-line adefovir use with resistance: discuss switch to entecavir or tenofovir.

Current data suggest that tenofovir is superior to adefovir in treatment of both naïve and lamivudine- or adefovir-resistant patients. Once this drug is licensed for CHB monoinfection (as is the case now), tenofovir might replace adefovir.

3.2.4.9 EASL 2009 recommendations for treating patients with HBV resistant mutants

The EASL 2009 guidelines[107] recommend in case of lamivudine resistance: add tenofovir (add adefovir if tenofovir not yet available).

Adefovir resistance: it is recommended to switch to tenofovir if available and add a second drug without cross-resistance. If an N236T substitution is present, add lamivudine, entecavir or telbivudine or switch to tenofovir plus emtricitabine (in one tablet). If an A181T/V substitution is present, add entecavir (the safety of the tenofovir–entecavir combination is unknown) or switch to tenofovir plus emtricitabine.

Telbivudine resistance: add tenofovir (add adefovir if tenofovir not yet available). The long-term safety of these combinations is unknown.

Entecavir resistance: add tenofovir (the safety of this combination is unknown).

Tenofovir resistance: resistance to tenofovir has not been described so far.

4 SITUATION IN BELGIUM

As mentioned in the epidemiology section above, the prevalence of HBsAg carriers in Belgium and surrounding countries varies between 0.6% and 1.4% (mostly around 0.7%). The prevalence is higher in immigrants from high endemic regions. Here we first present the history of reimbursement of antiviral drugs for CHB in Belgium. Second, the prospective data collection and its results are presented and used together with other data sources to estimate the number of patients visiting a gastro-enterologist for a chronic HBV infection.

4.1 HISTORY OF REIMBURSEMENT OF ANTIVIRAL DRUGS

A prescription by a specialist in internal medicine is required to obtain reimbursement of antiviral drugs for CHB in Belgium. Regarding the history of drug reimbursement in Belgium by NIHDI in the context of antiviral treatment of CHB two interferons alpha were the first drugs being reimbursed in Belgium in 1991. Much later in 2007, one pegylated interferon (Peg-IFN-alpha2a) was also reimbursed for hepatitis B patients with a viral load between 2000 and 2 Mio IU/mL, an increase in transaminase level above 2 times the upper limit of normal and presence of inflammation and/or fibrosis on liver histology. The duration for reimbursement is limited to one period of 48 weeks.

The first oral drug (lamivudine) had access to reimbursement in 2001 for patients with HBV with positive HBV DNA level, elevated transaminase level and signs of inflammation and/or fibrosis on liver histology. The duration of reimbursement has been firstly fixed to 3 years in 2001 and secondly extended to 5 years in 2004.

In 2004, a second oral drug using a different mechanism of action has gained access to reimbursement (adefovir). The reimbursement was limited to a second line therapy, i.e. limited to patients in whom a resistance to lamivudine treatment (increase in transaminase) had been demonstrated.

The reimbursement was limited to 3 years. In 2007, the criteria for adefovir reimbursement have been adapted as follows: reimbursement for the combination lamivudine and adefovir has been introduced for patients who are HBeAg- and have a viral load above 20 000 IU/mL. The reimbursement was limited to 5 years duration. Also, in 2007, entecavir 1 mg daily was accepted for reimbursement but with well-defined criteria: second line therapy for patients in whom a resistance to lamivudine has been observed and for a limited period of time (3 years).

In 2008, the criteria for lamivudine reimbursement have been modified: HBV DNA level should be higher than 20 000 IU/mL and serum transaminase level higher than 2 times the upper limit of normal. Only for HBV-liver transplanted patients, reimbursement duration was no more limited.

In 2009, different modifications have been introduced in the reimbursement system:

- Entecavir 0.5 mg daily was reimbursed for HBV naive patients (i.e. patients never treated previously by an oral anti-HBV drug).
- Tenofovir gained access to reimbursement as second line treatment (in case of lamivudine or entecavir resistance) and third line treatment (in case of adefovir or entecavir resistance).

For these 2 drugs, criteria for reimbursement were also limited to an increase in transaminase level higher than 2 times the upper limit of normal and to a viral load above 20 000 IU/mL.

In February 2010, numerous modifications were introduced.

- For interferons and oral drugs, transaminase level should only be higher than the upper limit of normal.
- For all oral drugs, the lower limit for HBV viral load has been decreased to 2000 IU/mL.

- For lamivudine, entecavir and tenofovir, limitations regarding treatment duration have been suppressed in absence of HBe or HBs seroconversion.
- For tenofovir, reimbursement has also been approved for naive patients.

For nucleos(t)id analogs the reimbursement criteria are current as follows :

First line (i.e. naive to previous nucleos(t)ide analog treatment) for CHB patients (definition: AgHBs + more than 6 months, abnormal ALT level and HBV-DNA level above 2,000 IU/ml and absence of decompensated cirrhosis and transplantation):

- entecavir 0.5 mg daily or tenofovir 245 mg daily.

Same criteria but also in case of decompensated cirrhosis or transplantation:

- lamivudine 100 mg daily (note this option is no longer included in international guidelines)

Second line in case of resistance to lamivudine:

- adefovir 10 mg daily (combined to lamivudine 100 mg daily only for HBeAg- patients)
- or entecavir 1 mg daily (note this is in contradiction with current guidelines)
- or tenofovir 245 mg daily

Second line in case of resistance to entecavir 0.5 mg daily:

- tenofovir 245 mg daily

Third line in case of resistance to entecavir 1 mg daily or adefovir:

- tenofovir 245 mg daily.

In conclusion, reimbursement criteria for NAs were adapted and are now somewhat more in line with international guidelines. They also became less restrictive, now also allowing treatment in CHB patients without liver fibrosis. Note that the use in first line of lamivudine is no longer recommended in international guidelines and that use of entecavir in case of resistance to lamivudine is to be avoided as it has reduced efficacy against rtM204V/I mutants.

4.2 THE PROSPECTIVE STUDY

4.2.1 Rationale

A major aim of the project was to develop a Markov state-transition model for cost-effectiveness evaluation of possible treatments for chronic infections with HBV, as well as a budget impact for NIHDI.

As only very few data on the subject have been published, a multi-centre prospective study was conducted in collaboration with the Belgian hepatologists to collect individual clinical information both for the 2006 and 2009 situation and 2009 QoI data for representative disease stages. VeedaCR nv/sa, Brussels, a contract research organisation, was the trusted third party for the collection and coding of individual patient data, and their transfer to the Intermutualistic Agency (IMA) for linkage to individual healthcare (NIHDI) consumption data of 2006. The procedures were approved by the "Sectorial Committee Social Security and Health" of the Belgian Privacy Commission. The study would also allow estimating the overall number of patients by disease stage visiting a medical specialist in Belgium, both patients with and without Belgian social security number (INSZ/NISS).

In the absence of utility data specific for CHB patient subgroups, most cost-effectiveness evaluations have used utility data obtained from patients with chronic hepatitis C. It is well known that utility values obtained for chronic hepatitis C cannot be used for CHB patients, and that QoL responses may vary across continents and cultures. In this study the EQ5D QoL questionnaire has been selected as it is a very simple generic instrument for which a value set from the Belgian population exists.

This is in accordance with the Belgian Guidelines for Pharmacoeconomic Evaluations that recommend that QoL weights for cost-utility analyses should best be based on Belgian empirical data and be obtained with a generic QoL instrument for which public preference values exist.[228]

The use of a generic instrument further allows for a comparison with other patients groups. State transition data for the current situation were obtained from the literature by the external partner and validated by KCE.

Before being used in a model, linked expenses data will need to be cleaned by an expert physician in order to select only the disease-related (i.e. chronic HBV infection) expenses as expenses due to the disease under study.

4.2.2 Objectives

The objectives of this data collection study were:

- To estimate the number of patients visiting a specialist for chronic HBV infection
- To document the distribution of the different disease stages in this population
- To document the QoL per disease stage
- To document the expenses for the health insurance per disease stage, after linkage with sickness fund (IMA) cost data.

4.2.3 Ethics and privacy protection

4.2.3.1 Independent Ethics Committee and informed consent

This study consisted of a non-interventional collection of clinical, laboratory and QoL data. The study presented no physical risks or harms to the participating subjects. The protocol was reviewed and approved by a central Independent Ethics Committee (IEC) of the Cliniques Universitaires Saint-Luc, Brussels, and in the hospital setting also the local IEC, prior to implementation of the study.

Written informed consent was obtained prior to the inclusion of each subject in the study, with the exception of deceased patients seen in 2006 with liver transplant for CHB or with HCC.

4.2.3.2 Sectorial Committee of the Belgian Privacy Commission

Subject confidentiality was maintained at all times, within the legal constraints. As the clinical, laboratory and QoL data forms collected contained a patient identifier, the data forms were managed by a trusted third party, using a procedure approved by the "Sectorial Committee Social Security and Health" of the Belgian Privacy Commission. Two requests to the "Sectorial Committee" were prepared by KCE for this study and were approved.

Request no. 1.

Identification of potential investigators based on their prescription of Zeffix in 2006: 50 physicians were selected who had prescribed lamivudine (Zeffix) for at least three different patients or 247 patients overall. This is considered a representative sample as it represents about half of the 474 patients for whom Zeffix had been prescribed in 2006 and reimbursed under the compulsory health insurance in Belgium. Remark that per patient only a single antiviral agent against HBV was reimbursed. In case of combination of Zeffix with another antiviral (adefovir), reimbursement was requested only for the more expensive other antiviral agent. The total volume of use of Zeffix is thus larger than presented above.

Request no. 2.

Linkage of identifiable clinical stage and sickness fund (IMA) financial data (NIHDI expenses). All parties agreed to respect the requirements as specified by the "Sectorial Committee".

The full date of birth was collected to help identify any patients entered twice in the study (also those for whom no INSZ/NISS is available). For later data processing, only the year of birth was kept in the database.

4.2.4 Study design and schedule

4.2.4.1 Investigator selection

Coordinates of 50 physicians managing patients with chronic HBV infection were identified using the Pharmanet prescription database, selecting for prescription of Zeffix which is only used for CHB. The full coordinates were obtained from the NIHDI physicians' database. This selection included all liver transplant centres.

4.2.4.2 Subject selection criteria

All inactive carriers of HBV, patients in the immune tolerance phase or patients with CHB seeing their specialist for a ROUTINELY PLANNED visit during the study period, planned from January 2009 to the end of June 2009, were to be included independent of treatment status (or no treatment) or the presence (or absence) of a regular health insurance. A single patient should only be included ONCE (the first planned visit during the study period). Patients should NOT be included if the visit is UNPLANNED (emergency situation might impact QoL). Patients for whom no 2006 clinical information was available could also be included. Known HIV infection or HCV infection were exclusion criteria. Patients were informed of the study using a patient information sheet, and were to give their written informed consent before completing the EuroQol 5-dimensions (EQ-5D) questionnaire. Only patients aged 18 years and older could be included in the study.

Compared with other included patients, those who were already in a more advanced disease stage in 2006 (HCC) were less likely to be still alive and get included in this study. In order to minimize the potential for bias, medical records of patients who visited in 2006 with a HCC in a context of CHB (mono-infection) and not during current study period (because of death), could be used to complete the 2006 part of the clinical case report form (CRF) (without current visit and thus also without QoL information). These additional subject data would allow for a more accurate and less biased calculation of yearly expenses for the NIHDI for this patient group.

Similarly, for transplant patients who visited in 2006 but not in the study period (because of death) the clinical CRF could be completed for the 2006 part.

4.2.4.3 Clinical, laboratory and quality of life data

The clinical disease stage information was obtained using a one page CRF (clinical CRF, see below) for recording both the 2006 situation (if available) and the current (2009) situation for each patient visiting for chronic infection with HBV during the survey period. As the frequency of visits per year was also recorded and the presence of regular health insurance, a corrected distribution of patients per disease stage and presence of health insurance could be calculated. At the same visit the patient was requested to complete a QoL questionnaire (EQ-5D CRF, see English version in appendix) in Dutch, French, English or German. A panel of hepatologists reviewed clinical phase/complication and reported laboratory results and antiviral treatment for inconsistencies. Data queries to resolve these issues were sent to the investigators two to three months after the recruitment period

The clinical CRF

KCE HTA 2008-11 Hep B - Centre no (see protocol) ☐☐ **Patient no (start with 01)** ☐☐

Please include all patients routinely visiting for chronic HBV infection (plus 2006 HCC and transplant dossiers)

Pat. Birth ☐☐ ☐☐ ☐☐☐☐ (D D M M Y Y Y Y) **INSZ** ☐☐☐☐☐☐ - ☐☐☐

Male ☐ Female ☐ No INSZ but other insurance ☐ No INSZ, no other insurance ☐

Belgian ☐ EU ☐ non-EU ☐ Country of origin ☐☐☐☐☐☐☐☐☐☐

2006 data available?	yes ☐	no ☐			**current visit?**	yes ☐	no ☐		
Visits per year for hep. B			**in 2006** ☐☐		**current year (incl planned)** ☐☐				
(Enter last result of the year)	**HBeAg**	pos ☐	neg ☐	unk ☐		pos ☐	neg ☐	unk ☐	
	HBeAb	pos ☐	neg ☐	unk ☐		pos ☐	neg ☐	unk ☐	
	HBsAg	pos ☐	neg ☐	unk ☐		pos ☐	neg ☐	unk ☐	
	HBsAb	pos ☐	neg ☐	unk ☐		pos ☐	neg ☐	unk ☐	
DNA > 10 000 copies/mL (or 2000 IU/mL)		yes ☐	no ☐	unk ☐		yes ☐	no ☐	unk ☐	
DNA > 100 000 copies/mL (or 20 000 IU/mL)		yes ☐	no ☐	unk ☐		yes ☐	no ☐	unk ☐	

Stage/phase (cross all applicable)

immune tolerance	ongoing ☐	new diagnosis ☐	ongoing ☐	new diagnosis ☐
inactive carrier	ongoing ☐	new diagnosis ☐	ongoing ☐	new diagnosis ☐
chronic hepatitis B	ongoing ☐	new diagnosis ☐	ongoing ☐	new diagnosis ☐
compensated cirrhosis	ongoing ☐	new diagnosis ☐	ongoing ☐	new diagnosis ☐
decompensated cirrhosis	ongoing ☐	new diagnosis ☐	ongoing ☐	new diagnosis ☐
HCC	ongoing ☐	new diagnosis ☐	ongoing ☐	new diagnosis ☐
liver transplant	ongoing ☐	new ☐	ongoing ☐	new ☐

Antiviral medication (started, ongoing or discontinued that year)	
	none ☐
	interferon alfa ☐
	PEG interferon alfa ☐
	lamivudin ☐
	adefovir ☐
	entecavir ☐
	tenofovir ☐
	Other: ☐☐☐☐☐☐☐☐☐☐

Antiviral medication (started, ongoing or discontinued that year)	
	none ☐
	interferon alfa ☐
	PEG interferon alfa ☐
	lamivudin ☐
	adefovir ☐
	entecavir ☐
	tenofovir ☐
	Other: ☐☐☐☐☐☐☐☐☐☐

Most recent result **HBV genotype** ☐☐ year tested ☐☐☐☐☐☐ unk ☐

Liver biopsy Metavir fibrosis score (F0-F4) ☐☐ year tested ☐☐☐☐☐☐ unk ☐

and/or Fibroscan score (0-99) ☐☐ year tested ☐☐☐☐☐☐ unk ☐

I confirm the patient has signed the informed consent sheet and has completed the QoL questionnaire

completed ☐☐ ☐☐ (D D M M) 2008 **MD (stamp+signature)** ☐☐☐☐☐☐☐☐☐☐ (Last name First name)

4.3 RESULTS OF THE STUDY

4.3.1 Patient characteristics

Data from 554 patients were entered in 18 centres in Belgium, mainly during a routine visit to their gastro-enterologist. The following investigators participated to the study: Michael Adler, Collins Assene, Stefan Bourgeois, Isabelle Colle, Chantal de Galocsy, Jean Delwaide, Stephane de Maeght, Eric Goffin, Joannes Holvoet, Yves Horsmans, Pierre Lammens, Luc Lasser, Peter Michielsen, Frederik Nevens, Hans Orlent, Hendrik Reynaert, Geert Robaeys, Dirk Sprengers.

Three patients were found to be non-eligible and their data were excluded from the analyses. For 7 patients who were seen with HCC or a liver transplant in 2006 but who were no longer alive during the study period, the 2006 data were collected. A total of 544 patients had a 2009 visit and were eligible. Of these patients 527 completed the EQ-5D QoL questionnaire. Missing QoL data were mainly restricted to a single centre and these results were not included on the QoL analysis. One should note that the coding by centre was known only to the trusted third party and could not be used for any further analyses by centre. As subsequent patients were invited to participate, the differences in recruitment per centre are mainly a reflection of the patient population seen at the centre. Investigators however confirmed that patients without residence permit were unlikely to give their consent for participation to the study. Based on the 180 (130 monotherapy) patients receiving Zeffix in 2009 included in the 18 centres, and based on an overall number 247 patients who received reimbursement of Zeffix in 2006 (prescribed by the 50 physicians who were invited to participate), we conclude that the larger centres participated and that we probably enrolled the majority of the patient population at most of the participating centres.

Table 8 : Number of patients by centre number.

Centre number	Number of patients
1	22
2	56
4	14
5	56
6	24
7	36
8	16
9	14
10	4
11	9
12	4
13	58
14	163
15	21
16	3
17	36
19	8
20	10
TOTAL	554

Note that recruitment was not started in centres no. 3 and 18.

Table 9 : Patient age by gender and region of origin.

Region of origin:	Male		Female		Total	
	N (% of total)	Mean age (years)	N (% of total)	Mean age (years)	N (% of total)	Mean age (years)
Europe	192 (35.3%)	52	84 (15.4%)	53	276 (50.9%)	52
Turkey	37 (6.8%)	46	11 (2.0%)	37	48 (8.6%)	44
Africa	76 (14.0%)	40	46 (8.5%)	34	122 (22.4%)	38
Asia	64 (11.8%)	43	34 (6.3%)	40	98 (18.0%)	42
Total	369 (67.8%)	47	175 (32.2%)	44	544 (100%)	46

About two thirds of the patients are male. About half of the patients have a European country of origin. The mean age of the patients with an European country of origin is 52 years, while patients with a country of origin in Africa or Asia are on average more than 10 years younger (Table 9). A total of 194 patients were seen in 2009 and not in 2006 (at least not at the same centre) and 60% of these 'new' patients have a country of origin outside of Europe (Table 10).

Table 10 : Patients without 2006 data, seen in 2009; patient age by region of origin.

Region of origin:	N (% of total)	Mean age (years)
Europe	77 (39.7%)	48
Turkey	19 (9.8%)	43
Africa	61 (31.4%)	36
Asia	37 (19.1%)	41
Total	194 (100%)	42

Patients were grouped according to the phase of the disease as proposed by EASL,[107] ("immune tolerant", "inactive carrier", "immune reactive", "HBeAg- CHB", "HBsAg-") as well as based on the absence or presence of liver cirrhosis, decompensated cirrhosis, HCC or a liver transplant (Table 11, Table 12, Table 13). The results reflect the opinion of the investigators after resolution of the data queries. In addition, patients with metavir fibrosis F4 as most recent result were listed as compensated cirrhosis, also when cirrhosis had not explicitly been indicated by the investigator. The group of HBsAg- patients included three patients reported by the investigator as cured and another three HBsAg- patients with DNA levels under 2000 IU/mL in absence of cirrhosis and liver transplantation. Patients who were reported as inactive (but HBsAg+) as a result of treatment started for CHB were grouped with immune reactive or HBeAg- CHB as appropriate. Tables 14 to 17 present the results by 2009 disease phase/complication for HBV DNA, antiviral medication and 2006 phase/complication.

Table 11 : Number of patients by phase of disease and disease complications or liver transplantation.

	Immune tolerant	Inactive carrier	Immune reactive HBeAg+	CHB HBeAg-	HBsAg-	Total
No cirrhosis	22	157	83	130	6	398
Compensated cirrhosis	0	3	14	54	2	73
Decompensated cirrhosis	0	0	1	1	0	2
HCC*	0	0	1	9	0	10
Transplanted	NA	NA	NA	NA	NA	61
Total	22	166	99	194	8	544

*For two of these patients also liver transplant was recorded for 2009; NA=not applicable

Table 12 : Number of patients by phase of disease and disease complications or liver transplantation (first visit 2009 / all patients).

	Immune tolerant	Inactive carrier	Immune reactive HBeAg+	HBeAg- CHB	HBsAg-	Total
No cirrhosis	14/22	91/157	25/83	31/130	0/6	161/398
Compensated cirrhosis	0/0	0/3	6/14	14/54	0/2	20/73
Decompensated cirrhosis	0/0	0/0	0/1	0/1	0/0	0/2
HCC	0/0	0/0	0/1	3/9	0/0	3/10
Transplanted	NA	NA	NA	NA	NA	10/61
Total	14/22	91/166	31/99	48/194	0/8	194/544

About half (n=91) of the patients visiting the centre for the first time (n=194) are in the inactive carrier phase.

Table 13 : Patient age by disease phase/complications in 2009 and region of origin, and absence of 2006 visit (2009 new)

	Africa		Asia		Europe		Turkey		Total		2009 new	
	N	Mean age	N	Mean age	N	Mean age	N	Mean age	N	Mean age	N	Mean age
Immune tolerance	13	38y	6	32y	3	34y	.	.	22	36y	14	32y
Inactive carrier	59	35y	22	41y	63	46y	13	42y	157	41y	91	40y
Immune reactive	9	32y	22	35y	41	50y	11	40y	83	43y	25	43y
HBeAg neg CHB	21	39y	22	43y	73	50y	14	41y	130	46y	31	43y
HBsAg neg	1	34y	1	61y	4	57y	.	.	6	54y	.	.
Comp. Cirrhosis	13	42y	15	51y	40	58y	5	51y	73	54y	20	50y
Decomp. Cirrhosis	1	58y	1	33y	.	.	.	.	2	46y	.	.
HCC	.	.	2	37y	8	67y	.	.	10	61y	3	47y
Liver transplant	5	55y	7	51y	44	61y	5	60y	61	59y	10	54y
Total	122	38y	98	42y	276	52y	48	44y	544	46y	194	42y

Table 14 : Last available 2009 DNA level by patient group.

	No 2009 results	< 2000IU/mL	2000-20000IU/mL	> 20000IU/mL	Total N
Immune tolerance	2	0	9	11	22
Inactive carrier	14	115	23	5	157
Immune reactive	2	30	13	38	83
HBeAg neg CHB	6	88	14	22	130
HBsAg neg	0	6	0	0	6
Comp. Cirrhosis	0	48	8	17	73
Decomp. Cirrhosis	0	2	0	0	2
HCC	1	6	0	3	10
Liver transplant	2	51	2	6	61
Total	27	346	69	102	544

Note that data queries were produced based on laboratory values not matching the clinical phase. The results presented here reflect the final clinical phase after query resolution.

Table 15 : Patient age and antiviral medication use in 2009 by patient group.

2009 therapy	No antiviral		PEG-IFN		Lamivudine		Lamiv.+Adef.		Adefovir		Entecavir		Tenofovir	
	N	Mean age	N	Mean age	N	Mean age	N	Mean age	N	Mean age	N	Mean age	N	Mean age
Immune tolerance	22	36y	.	.	.	.	.	.	.	.	.	.	.	.
Inactive carrier	157	41y	.	.	.	.	.	.	.	.	.	.	.	.
Immune reactive	10	48y	14	36y	24	42y	12	46y	7	43y	11	44y	5	46y
HBeAg- CHB	33	42y	4	27y	51	46y	18	51y	10	45y	12	55y	2	43y
HBsAg-	3	56y	.	.	1	42y	.	.	2	56y	.	.	.	.
Comp. Cirrhosis	14	55y	3	52y	31	52y	14	55y	5	62y	4	45y	2	54y
Decomp. Cirrhosis	.	.	.	.	1	33y	1	58y	.	.	.	.	.	.
HCC	2	64y	.	.	5	55y	1	88y	2	59.00	.	.	.	.
Liver transplant	33	61y	.	.	17	59y	4	62y	2	53y	3	56y	2	44y
Total	274	44y	21	37y	130	49y	50	53y	28	50y	30	50y	11	47y

Table 16 : Disease phase or complication, situation in 2006 compared with 2009.

2009 situation --> 2006 situation	***immune toler.***	***inactive carrier***	***immune react.***	***HBeAg-CHB***	***HBsAg-***	***comp. cirrh.***	***dec. cirrh.***	***HCC***	***liver transpl.***	***death***	**Total**
immune toler.	**5**	1	3	0	0	0	0	0	0	0	**9**
inactive carrier	3	**64**	2	3	1	0	0	0	0	0	**73**
immune react.	0	1	**52**	10	2	0	0	0	0	0	**65**
HBeAg- CHB	0	0	1	**86**	3	3	0	2	0	0	**95**
HBsAg-	0	0	0	0	**0**	0	0	0	0	0	**0**
comp. cirrh.	0	0	0	0	0	**48**	1	2	2	0	**53**
dec. cirrh.	0	0	0	0	0	2	**1**	0	2	0	**5**
HCC	0	0	0	0	0	0	0	**3**	2	6	**11**
liver tranpl.	0	0	0	0	0	0	0	0	**45**	1	**46**
Total	**8**	**66**	**58**	**99**	**6**	**53**	**2**	**7**	**51**	**7**	**357**

Table 17 : Disease phase or complication, situation in 2006 compared with 2009 (cirrhosis patients subgrouped by HBeAg status).

2009 situation --> 2006 situation	*immune toler.*	*inactive carrier*	*immune react.*	*HBeAg-CHB*	*HBsAg-*	*comp. cirrh. e+*	*comp. cirrh. e-*	*comp. cirrh.*	*dec. cirrh.*	*HCC*	*liver transpl.*	*death*	Total
immune toler.	5	1	3	0	0	0	0	0	0	0	0	0	9
inactive carrier	3	64	2	3	1	0	0	0	0	0	0	0	73
immune react.	0	1	52	10	2	0	0	0	0	0	0	0	65
HBeAg- CHB	0	0	1	86	3	0	3	0	0	2	0	0	95
HBsAg-	0	0	0	0	0	0	0	0	0	0	0	0	0
comp. cirrh. e+	0	0	0	0	0	6	3	0	0	0	0	0	9
comp. cirrh. e-	0	0	0	0	0	2	32	0	1	2	2	0	39
comp. cirrh.	0	0	0	0	0	0	0	5	0	0	0	0	5
dec. cirrh.	0	0	0	0	0	0	2	0	1	0	2	0	5
HCC	0	0	0	0	0	0	0	0	0	3	2	6	11
liver tranpl.	0	0	0	0	0	0	0	0	0	0	45	1	46
Total	8	66	58	99	6	8	40	5	2	7	51	7	357

4.3.2 Estimation of the number of patients by disease stage, visiting a medical specialist for chronic HBV infection in Belgium.

As the recorded number of patient visits per year differed by disease stage, so did the probability of patients to get included into the survey. As the effective patient recruitment period for the study was on average 4 months, patients for whom the physician reported a number of visits per year of at least 3 received a weight of 1, whereas other patients received a weight of 3 divided by the number of visits per year (patients with 2 visits per year thus received a weight of 1.5). We did not adjust for patients with a visit frequency lower than once per year as we did not obtain this information. For each disease stage an average weight was then computed and used to correct the under representation in the study of disease stages with a lower visit frequency. The number of patients on lamuvidine (Zeffix) monotherapy per disease stage was also adjusted using the same weight explained above.

This adjusted number of patients on lamivudine monotherapy and the estimated number of patients in Belgium receiving lamivudine monotherapy in 2008 (n=714) were used to estimate the number of patients visiting with CHB in Belgium by disease stage.

Table 18 : Estimation of number of patients on Zeffix monotherapy.

	Patients 2007	Patients 2008
NIHDI reimbursed Zeffix monotherapy (source Farmanet)	429	457
NIHDI reimbursed Zeffix and Hepsera (source Farmanet)	63	82
NIHDI reimbursed Zeffix total (source Farmanet)	492	539
Proportion of Zeffix sales in Belgium (IMS Health) not reimbursed by NIHDI (data kindly provided by NIHDI)	52%	36%
Adjusted number of patients on Zeffix monotherapy based on sales	894	714

Please note that an undocumented number of patients receiving Zeffix under a compassionate use program are not included in the numbers above.

The Farmanet number of patients receiving Zeffix reimbursement in 2008 was 539 (Table 18). This number includes 82 patients (15%) who got reimbursement for both Zeffix and Hepsera (adefovir) during that year. Our survey data show for 2009 that among the 180 patients on Zeffix, 50 patients (28%) received both Zeffix and Hepsera. The IMS Health sales data for Belgium (kindly provided by NIHDI) show that in 2008 about 36% of the Zeffix sales were not reimbursed by NIHDI. This rather large proportion is the sum of out of pocket payments by the patient because use is out of reimbursement criteria, financing of medication by the CPAS/OCMW for those patients without regular social security, and reimbursement by non NIHDI sources as for employees of international institutions, e.g. European Commission. The number of treatments for CHB in prisons is small and not included. These costs are covered by a NIHDI lump sum to the department of justice (personal communication, Dr P. Laukens, Brugge).

As NIHDI reimbursement for the combination treatment is now possible but still restrictive, some patients still pay the Zeffix treatment out of pocket. Only 1.5% of the patients (2 out of 130) in the survey on lamivudine monotherapy had no social security number (INSZ) and are thus not included in Farmanet. Investigators however confirmed that patients without residence permit were unlikely to give their consent for participation to the study, and this group may account for 20% of the patients seen in centres in larger cities. Many of these patients were thus not included in the survey.

Given the underrepresentation of immigrant patients without residence permit in the study as well as the overrepresentation of university hospitals in the survey we may have underestimated the number of patients with a less advanced disease stage and overestimated the number of liver transplants. In order to more correctly document the number of liver transplants for hepatitis B in Belgium an additional survey form was mailed to the six centres performing liver transplants. The number of liver transplants was documented for the last 15 or 20 years as well as the main reason for transplantation in the context of hepatitis B (HCC or cirrhosis or fulminant hepatitis) (Table 19). Also the number of hepatitis B patients under follow-up in 2009 with a liver transplant was recorded.

Table 19 : Reasons for liver transplants for hepatitis B in Belgium.

Centre / period covered	Overall number of transplants for hepatitis B	Transplants for HCC (hepatitis B)	Transplants for cirrhosis (hepatitis B)	Transplants for acute or fulminant hepatitis B
A / 1989-2008	62	14	38	10
B / 1995-2008	56	16	31	9
C / 1991-2008	81	13	61	7
D / 1995-2008	7	2	5	0
E / 1983- 2009	40	6	25	9
F / 1995-2009	59	20	33	6
Total	305 (100%)	71 (23%)	193 (63%)	41 (13%)

Based on the detailed numbers obtained per year from four centres accounting for 57% of the hepatitis B related liver transplants, the annual number of liver transplants for hepatitis B related liver transplants during the period 1996-2008 remained more or less stable at about 12 transplants per year (range 9 to 17). The most recent numbers were for 17 in 2005, 12 in 2006, 16 in 2007, 9 in 2008 and 8 in 2009 (up to mid November 2009). Extrapolated to all Belgian centres this would correspond to about 22 hepatitis B related liver transplants per year during the period 1996-2008, of which about 19 to 20 are related to CHB: 14 to 15 transplants per year for cirrhosis and 5 for HCC.

The proportion of these liver transplant patients under follow-up in 2009 in the centres was 72%, or 190 of the 264 liver transplants in the period 1995-2009 for hepatitis B related cirrhosis or HCC. One should also note that in the nineties a limited number of liver transplants took place in Belgium especially in Italian patients, who are no longer under follow-up in Belgian centres.

Based on the transplant centres survey, we used an estimate of 200 liver transplant patients in follow-up (Table 20), which was indeed lower than the number we would have estimated based on extrapolations of the study data.

Table 20 : Estimated number of patients by phase/complication and region of origin, visiting a liver specialist in Belgium for chronic HBV infection or its complications, situation early 2009. Co-infections with HIV or HCV are not included.

	Africa	Asia	Europe	Turkey	Total N	%
Immune tolerance	70	32	16	0	119	3,6%
Inactive carrier	476	177	508	105	1266	38,6%
Immune reactive	50	123	228	61	462	14,1%
HBeAg neg CHB	119	124	412	79	735	22,4%
HBsAg neg	9	9	36	0	53	1,6%
Comp. Cirrhosis	68	79	210	26	383	11,7%
Decomp. Cirrhosis	5	5	0	0	10	0,3%
HCC	0	10	39	0	49	1,5%
Liver transplant	16	23	145	16	200	6,1%
Total N	813	582	1595	287	3277	100,0%

Note that co-infections with HIV or HCV are excluded. Inactive carriers may not be visiting their specialist every year, so the total number of inactive carriers visiting a specialist occasionally is probably much higher.

Our results are in agreement with the results of the BASL registry of HBsAg chronic carriers, as documented by 26 Belgian centres (hepatologists) between 1st March 2008 and 28th February 2009 (or just preceding the KCE survey, many centres participated to both surveys). The survey assessed the epidemiologic characteristics of HBsAg+ patients presenting at the consultation. A total of 1421 patients (mean age 42 years, 67% male) from 26 centres were included. 71% were prevalent cases. 52% were Caucasians and 25% were black Africans. Ten (10) patients (0.7%) were immunotolerants, 622 (44%) were inactive carriers, 249 (17.5%) had chronic active HBeAg+ hepatitis and 413 (29%) had chronic active HBeAg- hepatitis. One-hundred and twenty-seven (127) patients (9%) could not be classified. Ninety-two (92) patients (12%) were co-infected: 26 with HDV, 28 with HCV, 32 with HIV, 2 with HDV-HCV and 4 with HCV-HIV. Liver biopsy was performed in 641 patients. Fibrosis distribution was F0=16%, F1=24%, F2=24%, F3=19% F4=17%. This recent study shows us that 44% of the patients are inactive carriers, that about one third has HBeAg- chronic hepatitis and that F3-4 is reported in 35% of the patients when a liver biopsy is performed.[11]

Other data sources we used to verify our estimate of the number of patients under medical specialist care for chronic infection with HBV are the reports of the Centres of Molecular Diagnosis (CMDs) and the Permanent Population Sample (PPS) database. One should note that HIV/HCV co-infections were not excluded from these sources.

Based on the CMD activity report for the period February 1, 2002 to January 31, 2003 a total of 2799 patients had a quantitative test for HBV.[229] Taking into account the ongoing immigration, the number of patients under follow-up in 2009 is expected to be higher than 2799 and could be in agreement with our estimates. It may be of relevance to note that any tests performed for patients without a regular health insurance are also included in the CMD statistics. The financing of the CMDs was independent of the patient's compulsory health insurance and is explained in KCE report no.20 on molecular diagnostics.[229]

The PPS database or "permanente steekproef / échantillon permanent" is a unique database. In Belgium, registered inhabitants in principle have a compulsory health insurance provided by one of the seven national sickness funds and funded by social security contributions withhold on wages and earned incomes. For all sickness funds health care reimbursement data of their members are joined into a large database at the IMA. From this population a sample of 1/40 was selected among subjects aged 65 or younger (random selection stratified for age and sex) and a sample of 1/20 among subjects of 66 years and older (random selection stratified for age and sex). This sample contains about 300 000 individuals and was started in 2002. The database was updated every year since. For all the individuals in the sample demographic and socio-economic information is updated, in addition to the detailed information on health care expenditure. We checked the PPS for the number of patients in Belgium who had one or more HBsAg or HBeAg tests in the 2002-2008 period and extrapolated the numbers to the national level.

Compared with about 2 million inhabitants tested for HBsAg in the 2002-2008 period, about 200 000 subjects were tested for HBeAg and about 30 000 persons had multiple HBeAg tests. Even after taking into account that inappropriate test prescriptions are a reality, these data suggest the total pool of patients in medical follow-up for a chronic infection with HBV could be significantly higher than the number of patients under regular follow-up by a gastro-enterologist. The majority of the HBeAg tests in the period 2002-2008 were requested by general practitioners (GP), suggesting many patients with chronic HBV infection, most probably inactive carriers, are followed at the GP level and may visit a liver specialist only occasionally. Considering an estimated prevalence of HBsAg positivity in 75 000 subjects in Belgium (0.7%), the data indicate either that at least two thirds of the HBeAg tests are requested in subjects not chronically infected or that the prevalence of HBsAg positivity is higher than 0.7%.

4.3.3 Conclusion for situation in Belgium

While vaccination protects a growing proportion of the population in Belgium against HBV infection, chronic hepatitis B is relatively more frequently diagnosed among immigrants from Eastern Europe and endemic countries in Asia and Africa, including immigrants without residence permit. We estimate that 3300 patients were seen by a liver specialist in 2009, including 1700 patients with active chronic hepatitis B, 400 patients with liver cirrhosis, 50 with HCC and 200 with a liver transplant. The large number of subjects tested for HBeAg (about 2% of the population in the 2002-2008 period) suggests that the prevalence of HBsAg+ in Belgium is higher than the published estimate of 0.7%.

4.3.4 Quality of life results

The utility scores were calculated based on the EQ-5D scores of 527 patients and processed based on social preference data collected in Flanders.[228] Age but not gender was a significant predictor of these utility scores. The number of patients studied is small for patients in the immune tolerance or resolved (HBsAg negative) phase, and for complications such as decompensated cirrhosis and HCC, limiting the use of our finding for these patient groups. In addition, we only made a single measure of quality of life per patient and we excluded acute medical situations. In addition, we did not study QoL in children.

Table 21 : Quality of life measures by disease phase or complication in 2009 for patients with a European country of origin.

2009 situation	N	Variable	Median	Mean	Lower 95%	Upper 95%	Minimum	Maximum
(European origin)					CL for Mean	CL for Mean		
Immune tolerance	3	Age	22.00	33.67	-18.70	86.03	21.00	58.00
		Utility	1.00	0.92	0.55	1.28	0.75	1.00
		VAS	83.00	87.67	60.87	114.46	80.00	100.00
Inactive carrier	62	Age	47.00	45.76	42.37	49.15	20.00	86.00
		Utility	1.00	0.83	0.77	0.90	0.03	1.00
		VAS	80.00	77.13	72.48	81.78	30.00	100.00
Immune reactive	38	Age	47.00	50.26	45.60	54.93	22.00	75.00
		Utility	0.76	0.78	0.69	0.86	-0.00	1.00
		VAS	72.00	69.82	64.53	75.10	40.00	100.00
HBeAg neg CHB	71	Age	49.00	49.61	46.57	52.64	20.00	80.00
		Utility	0.77	0.80	0.74	0.86	0.19	1.00
		VAS	80.00	73.06	68.71	77.40	21.00	100.00
HBsAg neg	4	Age	54.00	56.50	33.35	79.65	42.00	76.00
		Utility	0.69	0.67	0.07	1.28	0.30	1.00
		VAS	68.50	68.50	45.46	91.54	52.00	85.00
Comp. cirrhosis	39	Age	59.00	58.31	54.67	61.95	33.00	83.00
		Utility	0.76	0.79	0.72	0.86	0.03	1.00
		VAS	70.00	68.85	64.15	73.54	35.00	100.00
HCC	8	Age	67.50	66.50	52.03	80.97	40.00	89.00
		Utility	0.70	0.59	0.33	0.85	0.03	1.00
		VAS	47.50	44.75	27.92	61.58	16.00	80.00
Liver transplant	44	Age	64.50	60.86	57.13	64.59	34.00	81.00
		Utility	1.00	0.82	0.75	0.89	0.19	1.00
		VAS	80.00	74.43	69.93	78.94	34.00	95.00

VAS = Visual analogue scale result for QoL

The mean utility scores calculated for immune tolerance, inactive carrier, immune reactive and HBeAg- CHB patients are in the 0.81 to 0.83 range (Table 22). The six patients in the HBsAg- phase scored surprisingly low for QoL. HCC and decompensated cirrhosis were associated with low utility scores. Liver transplant patients (for all but one patient this was an ongoing condition at the 2009 visit) on average had very similar utility scores as uncomplicated hepatitis. Because of the low numbers and the similarity in the QoL scores, HCC patients were grouped with the two patients for whom both HCC and liver transplant were recorded as ongoing clinical situation. A comparison of our findings with the literature will be included in the second report on this topic.

Table 22 : Quality of life measures by disease phase or complication in 2009 for all patients.

2009 situation	N Obs	Variable	Median	Mean	Lower 95%	Upper 95%	Minimum	Maximum
(All regions)					CL for Mean	CL for Mean		
Immune tolerance	22	Age	36.50	36.09	31.45	40.73	21.00	58.00
		Utility	0.75	0.81	0.72	0.90	0.23	1.00
		VAS	80.00	78.32	72.00	84.64	40.00	100.00
Inactive carrier	153	Age	39.00	40.58	38.56	42.59	18.00	86.00
		Utility	1.00	0.83	0.80	0.87	-0.08	1.00
		VAS	80.00	77.24	74.36	80.12	20.00	100.00
Immune reactive	78	Age	40.00	43.10	39.98	46.22	21.00	75.00
		Utility	1.00	0.82	0.77	0.87	-0.00	1.00
		VAS	79.00	74.29	70.37	78.21	24.00	100.00
HBeAg neg CHB	127	Age	46.00	45.70	43.43	47.98	20.00	80.00
		Utility	1.00	0.82	0.78	0.86	0.19	1.00
		VAS	80.00	75.27	72.13	78.41	5.00	100.00
HBsAg neg	6	Age	54.00	53.50	37.88	69.12	34.00	76.00
		Utility	0.89	0.74	0.40	1.08	0.30	1.00
		VAS	68.50	66.67	49.63	83.70	45.00	85.00
Comp. cirrhosis	69	Age	55.00	53.36	50.13	56.60	25.00	85.00
		Utility	0.76	0.78	0.73	0.84	0.03	1.00
		VAS	70.00	69.94	66.17	73.71	25.00	100.00
Decomp. Cirrhosis	2	Age	45.50	45.50	-113.33	204.33	33.00	58.00
		Utility	0.70	0.70	0.17	1.24	0.66	0.75
		VAS	55.00	55.00	-8.53	118.53	50.00	60.00
HCC	10	Age	62.00	60.60	46.51	74.69	36.00	89.00
		Utility	0.74	0.67	0.44	0.90	0.03	1.00
		VAS	52.50	54.80	35.03	74.57	16.00	95.00
Liver transplant	60	Age	60.50	59.10	56.00	62.20	34.00	81.00
		Utility	1.00	0.82	0.75	0.88	0.02	1.00
		VAS	80.00	75.07	71.11	79.02	34.00	100.00

VAS = Visual analogue scale result for QoL

We also examined QoL by current or past treatment and response to antiviral treatment for patients in the immune reactive, HBeAg- CHB and HBsAg- groups (n=211) (Table 23).

Table 23 : Mean utility scores and QoL VAS score by current or past antiviral treatment.

Antiviral treatment	N	Variable	Median	Mean	Lower 95% CL for Mean	Upper 95% CL for Mean	Minimum	Maximum
Interferon alpha	17	Age	32.00	33.12	28.89	37.35	22.00	54.00
in 2009		Utility	0.76	0.80	0.73	0.86	0.63	1.00
		VAS	79.00	74.35	67.11	81.60	40.00	95.00
Lamivudin only	79	Age	44.00	45.42	42.42	48.42	20.00	75.00
in 2009		Utility	1.00	0.81	0.76	0.87	-0.00	1.00
		VAS	80.00	77.22	73.59	80.84	28.00	100.00
Other antiviral	72	Age	47.50	47.49	44.82	50.15	21.00	71.00
or combination		Utility	0.89	0.80	0.75	0.86	0.20	1.00
in 2009		VAS	72.00	70.92	66.95	74.89	30.00	100.00
No antiviral 2009	9	Age	38.00	42.56	30.12	54.99	24.00	76.00
Antiviral 2006		Utility	1.00	0.97	0.91	1.03	0.76	1.00
		VAS	90.00	86.11	75.12	97.11	52.00	100.00
No antiviral 2009	34	Age	41.50	45.12	39.51	50.73	21.00	80.00
No antiviral 2006		Utility	0.88	0.84	0.77	0.91	0.10	1.00
		VAS	80.00	73.76	65.82	81.71	5.00	100.00

VAS = Visual analogue scale result for QoL

The 9 patients who discontinued antiviral treatment after 2006 have on average a high QoL utility score. Patients without antiviral treatment in 2006 and 2009 score slightly higher for QoL compared with patients under treatment. Underneath (Table 24), the same groups were analysed according to the last 2009 DNA value available as a surrogate for treatment response. Utility scores do not seem to vary consistently with DNA levels.

Table 24 : Mean utility scores by last DNA level and current or past antiviral treatment.

	No DNA data		<2000IU/mL		2000-20000IU/mL		>20000IU/mL	
	N	Mean	N	Mean	N	Mean	N	Mean
Interferon alpha	.	.	5	0.74	1	0.63	11	0.84
Lamivudin only	4	0.85	53	0.81	5	0.95	17	0.76
Other antiviral or combination	3	0.60	49	0.79	12	0.79	8	0.97
2006 antiviral, but not in 2009	.	.	5	0.95	2	1.00	2	1.00
No 2006 nor 2009 antiviral	.	.	9	0.91	7	0.96	18	0.75

4.3.5 Conclusion for quality of life assessment

Utility scores were based on EQ-5D data of 527 patients in a non-acute condition. Mean utility scores for patients in the phases of immune tolerance, inactive carrier, immune reactive and HBeAg- CHB were very similar, in the 0.81 to 0.83 range. The average utility score was 0.80 in the subgroup analysis of 102 patients without cirrhosis responding to NA antiviral treatment with a DNA level under 2000 IU/mL, suggesting no change in utility score upon treatment response in CHB. Average utility scores were slightly lower in compensated cirrhosis (n=69: 0.78), in decompensated cirrhosis (n=2: 0.66 and 0.75) and in HCC (n=10: 0.67). Patient numbers in latter groups were low however. Patients who had received a liver transplant had on average a utility score of 0.82.

No major differences were seen between the overall results and those for patients of European origin. After adjustment for disease stage, age is a significant predictor of these utility scores.

5 REVIEW OF THE COST-EFFECTIVENESS LITERATURE

5.1 METHODS

5.1.1 Literature search strategy

The search for the economic literature about options to treat CHB patients was performed by consulting electronic databases up to mid September 2009. The HTA(CRD) database, the CDSR Technology Assessment database and the websites of Health Technology Assessment (HTA) institutes listed on the INAHTA (International Network of Agencies for Health Technology Assessment) website were consulted to retrieve HTA reports on this topic. The NHS EED(CRD), Medline(OVID), EMBASE, Econlit(OVID) and CDSR Economic Evaluation databases were searched to retrieve full economic evaluations and reviews of full economic evaluations of CHB treatments. The same databases and websites were searched for QoL measures. No restrictions on the time period and language were imposed. See appendix 2 for an overview of the search strategies and results.

5.1.2 Selection criteria

All retrieved references were assessed against pre-defined selection criteria (in terms of population, intervention, comparator and design - Table 25) in a two-step procedure: initial assessment of the title, abstract and keywords; followed by full-text assessment of the selected references. When no abstract was available and the citation was unclear or ambiguous, the citation was assessed on the basis of keywords and full-text assessments. Reference lists of the selected studies were checked for additional relevant citations. The selected full economic evaluations (i.e. studies comparing at least two alternative treatments in terms of costs and outcomes - appendix 3) were critically assessed and summarized in data extraction sheets (appendix 4).

This whole literature search and selection procedure was replicated by a second reviewer to assess the quality of this process and control the literature selection.

Table 25 : Economic evaluation selection criteria

	Inclusion criteria	Exclusion criteria
Population	Adult CHB patients	Inactive HBV carriers, immune-tolerant HBV, liver transplants
Intervention	Interferon-based & NA therapy	HBV vaccine, HBV screening and other treatments
Comparator	Standard therapy	Non-active treatment
Design	Full economic evaluation (primary or secondary studies)	Non full economic evaluation (see appendix 3)

The population under study was HBsAg+ patients with HBeAg + or - CHB and elevated HBV DNA (See patients-groups definition in section 2.1.2). Inactive HBV carriers and immune-tolerant patients (mostly seen in Asians) were not considered. Likewise, studies focusing on liver transplant patients were excluded. The treatment options were lamivudine (Zeffix®), adefovir dipivoxil (Hepsera®), entecavir (Baraclude®), telbivudine (Sebivo®) and tenofovir (Viread®) for the NAs; interferon alpha2a (Roferon A®), interferon alpha2b (Intron A®) and pegylated interferon-alpha2a (Pegasys®) for the interferon-based therapy. All drugs could be used alone or in combination.

QoL studies were selected only if they pertained specifically to (chronic) hepatitis B patients.

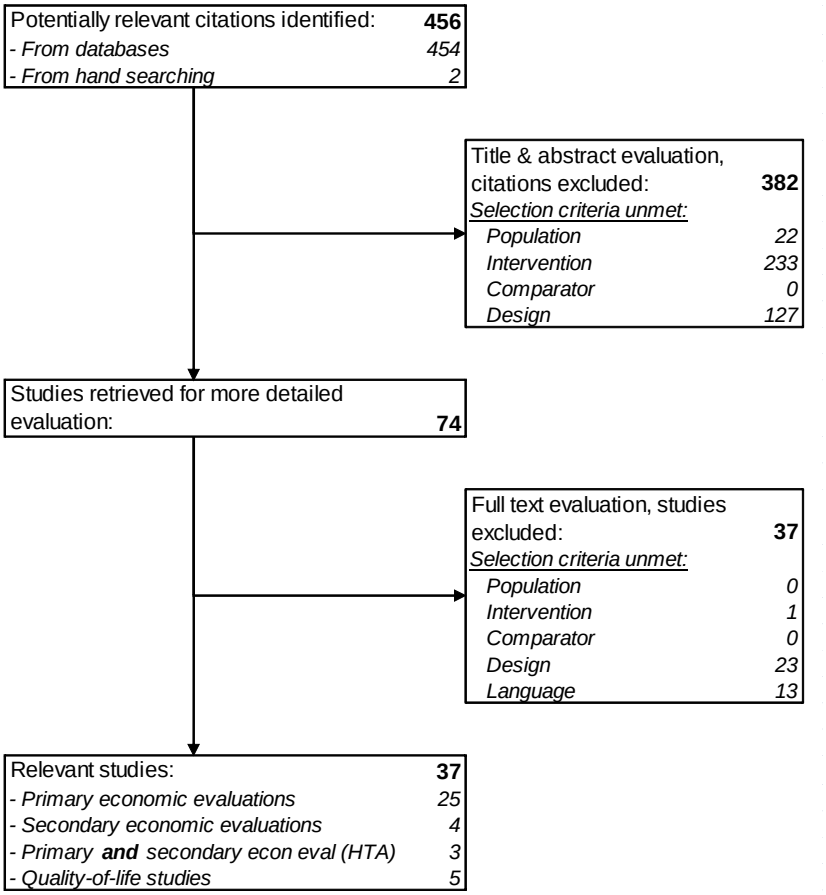
5.1.3 Selection process

The searches on the databases and local HTA websites returned 629 citations. After exclusion of 173 duplicates, 456 unique citations were left. Of those 456 references, 382 did not meet our inclusion criteria based on title and abstract evaluation. Of the 74 citations retained for full-text assessment, 37 were excluded leaving 37 relevant articles. Further exploration of those articles' references did not bring additional citations. There were no discordances on the articles selected by the first and the second reviewer. The 37 selected articles pertained to the following categories:

- 25 primary economic evaluations[230-254]
- 4 reviews of economic evaluations[255-258]
- 3 HTA reports including a primary economic evaluation and a review of previously published economic evaluations.259-261 Of those three references, Jones et al.[259] is the most recent HTA (2009) and an update of the economic evaluations and the literature reviews of the two older references.[260, 261]
- 5 QoI studies[262-266]

The flow chart of the selection process is presented in Figure 1.

Figure 1 : Flow chart of the literature selection process



The economic evaluations included in the 7 literature reviews identified (4 secondary economic evaluations and 3 HTA reports) are listed in Table 26. The present study aims at extending those literature reviews and only assesses the economic evaluations not already included in the reviews. Therefore, of the 25 primary economic evaluations identified by our literature search, only the following 9 studies pertaining to the most recent pharmacological treatments of CHB are critically reviewed: Lacey et al.,[240] Arnold et al.,[231] Costa et al.,[232] Lacey et al.,[233] Orlewska et al.,[234] Spackman et al.,[235] Veenstra et al.,[236] Veenstra et al.[237] and Buti et al.[230]

Table 26 : Articles reviewed by the secondary economic evaluations of antiviral treatments of CHB (x = full economic evaluation included)

Authors of secondary economic evaluations		Jones et al., 2009 [259]	You et al., 2008[258]	Takeda et al., 2007 [261]	Sun et al., 2007[257]	Rajendra et al., 2007 [256]	Shepherds et al., 2006 [260]	Han et al., 2006 [255]
Literature time-coverage		**2005 – Sept 2007**	**1998 - Apr 2008**	**1995 - Jan 2006**	**1980 - Dec 2006**	**Not stated**	**1995 - Apr 2005**	**Not stated**
Number of articles reviewed		**5**	**4**	**2**	**6**	**8**	**7**	**6**
Entecavir	Yuan et al., 2008[238]		X					
	Yuan et al., 2008[239]		X					
	Veenstra et al., 2007[242]		X					
	Kanwal et al., 2006[245]		X					
Peg-IFN-alpha	Veenstra et al., 2007[243]	X						
	Sullivan et al., 2007[241]	X			X	X		
Peg-IFN-alpha Adefovir	Shepherds et al., 2006 [260]					X		
Adefovir	Buti et al., 2006[244]	X		X	X			
	Kanwal et al., 2006[245]	X						
	Kanwal et al., 2005[246]	X		X	X	X	X	X
Lamivudine Interferon-alpha	Orlewska et al., 2002[249]				X	X	X	
	Crowley et al., 2002[248]				X	X	X	X
	Brooks et al., 2001[251]				X		X	X
	Crowley et al., 2000[252]						X	X
	Dusheiko et al., 1995[253]					X	X	X
	Wong et al., 1995[254]					X	X	X
	Louis-Jacques et al., 1997[267]					X		

5.2 OVERVIEW OF THE ECONOMIC EVALUATIONS - TRANSVERSAL

Table 27 gives an overview of the characteristics of the 9 economic evaluations. The studies were performed in countries with a low (the USA,[235, 236] Australia[231]), intermediate (Poland,[234] Brazil,[232] Spain[230]) or high (Taiwan,[237] Singapore[240]) CHB prevalence. All studies were Markov model-based economic evaluations.

Table 27 : General characteristics of the economic evaluations

Author	Publicat° year	Country	Analysis		Time horizon	Discount rate[a]	Costing perspective: cost items included
			CEA	CUA			
Buti et al.[230]	2009	Spain	X	X	Lifetime	3%	Direct medical costs
Veenstra et al.[237]	2008	Taiwan	X	X	Lifetime	3%	Direct medical costs
Spackman et al.[235]	2008	USA	-	X	Lifetime	3%	Direct medical costs
Veenstra et al.[236]	2008	USA	-	X	Lifetime	3%	Direct medical costs
Arnold et al.[231]	2008	Australia	X	X	20 years	5%	Direct medical costs
Orlewska et al.[234]	2008	Poland	X	X	10 years	5%	Direct medical costs
Costa et al.[232]	2008	Brazil	X	X	10 years	3%	Direct medical costs
Lacey et al.[240]	2007	Singapore	X	X	40 years	5%	Direct medical costs
Lacey et al.[233]	2008	Taiwan	X	X	40 years	3%	Direct medical costs

CEA: cost-effectiveness analysis; CUA: cost-utility analysis.
a. Discount rate for both costs and outcomes, except in Costa et al.[232] where this is not specified.

5.2.1 Analytical technique

The majority of the studies reported their results both in terms of cost-utility ratios (with outcomes expressed as quality-adjusted life years gained – QALY) and cost-effectiveness ratios (with outcomes expressed a life-years gained – LYG).[230-234, 237, 240] Two studies were cost-utility analyses only.[235, 236]

5.2.2 Perspective

All studies adopted a Health Care Payers perspective in their base-case, with direct medical (intervention and treatment) costs.

Although CHB affects people in the workforce age, indirect productivity costs were never considered.

5.2.3 Time horizon and discount rate

The time horizon of the economic evaluations spanned from 10 years to a lifetime. Given the chronic nature of hepatitis B and the relatively slow progression of the disease, short time horizons may not be long enough to capture significant clinical endpoints (cirrhosis, HCC). By contrast, long-term data are usually scarce and populating lifelong model can be a difficult endeavour that may decrease the validity of the models.

All studies discounted their costs and outcomes with the same discount rate, being 3% or 5%. In Costa et al.[232] it is not clear whether the 3% discount rate was applied to both costs and outcomes or to costs only.

5.2.4 Population

The population targeted was CHB patients, with either HBeAg+,[235] HBeAg-,[236, 237] or both HBeAg + and - patients.[230-234, 240]

CHB patients modelled had the same characteristics as the patients in the RCTs used to populate the models. Patients had persistent HBsAg; they were serum HBV DNA positive, non-cirrhotic and had elevated ALT levels. In addition, patients were treatment-naïve (i.e. they had no previous NA or interferon treatment).

In the economic evaluations, HBeAg- CHB patients were slightly older than HBeAg+ patients, i.e. about 40 years versus 30 years. This is in contrast with the results of the Belgian CHB-patients database where the average age at treatment initiation was 40 years, whatever the HBeAg status (see previous section).

5.2.5 Interventions

The treatments were adefovir dipivoxil (Hepsera®), entecavir (Baraclude®), telbivudine (Sebivo®) and tenofovir (Viread®) for the NAs; and pegylated interferon-alpha2a (Pegasys®) for the interferon-based therapy.

The interventions evaluated in the economic evaluations together with the treatment duration and stopping rule are summarized in Table 28.

Table 28 : Interventions evaluated in the economic evaluations

Author	HBeAg status	Interventions	Treatment duration
Buti et al., 2009[230]	HBeAg + HBeAg -	No treatment LAM, then ADV + LAM[a] ADV, then ADV + LAM[a] ETV, then ADV + LAM[a] TLB, then ADV + LAM[a] TNF, then ADV + LAM[a] Alternative for rescue: TNF+ETV	HBeAg+ : treatment stops 6 months after HBeAg seroconversion HBeAg- : lifelong treatment
Veenstra et al., 2008[237]	HBeAg -	Peg-IFN LAM	48 weeks
Spackman et al., 2008[235]	HBeAg +	No treatment LAM (+ ADV)[b] ETV (+ ADV)[b] TLB (+ ADV)[b] ADV (+ ETV)[b] Peg-IFN, then ETV [c]	Up to 4 years. Use of HBeAg seroconversion stopping rule not explicitly stated
Veenstra et al., 2008[236]	HBeAg -	LAM (+ ADV)[b] ETV (+ ADV)[b] ADV (+ ETV)[b]	For each intervention: 5 years treatment duration; 10 years treatment duration; Lifelong treatment; "5-years-on 1-year-off" [d]
Arnold et al., 2008[231]	HBeAg + HBeAg -	LAM, then ETV[b], then ADV[b] ETV, then ADV[b], then LAM[b]	HBeAg+ : Up to 10 years. Treatment stops 12 months after HBeAg seroconversion. HBeAg- : 10 years treatment duration
Orlewska et al., 2008[234]	HBeAg +	ETV LAM	HBeAg+ : 2 years treatment duration HBeAg- : 2 years treatment duration
	HBeAg -	ADV[b] ETV[b]	10 years in LAM-refractory patients

Author	HBeAg status	Interventions	Treatment duration
Costa et al., 2008[232]	HBeAg + HBeAg -	ETV LAM, then ADV[b]	HBeAg+ : 1 year , viral load assumed unchanged thereafter HBeAg- : 1 year , viral load assumed unchanged thereafter
Lacey et al., 2007[240]	HBeAg + HBeAg -	LAM[e] ADV[e] Peg-IFN[e]	1 year treatment duration
		IFN	4-6 months treatment duration
		ADV, then LAM[b] LAM, then ADV[b]	HBeAg+ : Up to 5 years. Treatment stops at HBeAg seroconversion HBeAg- : Up to 5 years. Treatment stops at HBsAg seroconversion
Lacey et al., 2008[233]	HBeAg + HBeAg -	LAM[e] ADV[e] Peg-IFN[e]	1 year treatment duration
		IFN	4-6 months treatment duration
		ADV, then LAM or ADV + LAM in F3/4[b] LAM, then ADV or LAM + ADV in F3/4[b]	HBeAg+ : Up to 2 or 5 years. Treatment stops at HBeAg seroconversion HBeAg- : Up to 2 or 5 years. Treatment stops at non-detectable HBV DNA

Peg-IFN: Pegylated interferon; LAM: Lamivudine; ADV: Adefovir; ETV: Entecavir; TLB: Telbivudine; TNF: Tenofovir

a. Rescue therapy for drug resistants or non-responders (i.e. HBV DNA detectable after 48 weeks of treatment)

b. Rescue therapy for drug resistants

c. Therapy with ETV if no HBeAg seroconversion after 2 years of treatment with Peg-IFN.

d. "5-years-on 1-year-off" strategy consists in treating patients for 5 years, stopping treatment in responders for 1 year and re-initiating lifetime therapy for patients who relapse.

e. For those strategies, treatment duration was limited to 1 year, whatever the HBeAg status.

Even though most studies were recently performed, the latest therapeutic disease management was not always used. Most interventions assessed in the 9 most economic evaluations are already outdated now, especially regarding treatment duration. This justifies why we did not find it appropriate to include a summary of the results of older reviews of the literature in this chapter.

5.2.6 Outcomes

Estimates of QoL values (utilities) used in the studies are presented in Table 29, together with the population from which utilities were derived and the source references.

Most studies obtained their utility weights from Levy et al.[264] In this study, standard gamble (SG) utilities were elicited using an interviewer-administered survey from populations in six countries, with a total of 534 HBV-infected patients and 600 uninfected respondents. Note that Levy et al.[264] did not assess the utility of the health state "responders to antiviral treatment". Utilities from the subset of respondents which was the most appropriate for each economic evaluation's setting was selected (infected versus uninfected respondents, mixed versus country-specific populations, see Table 29). In Veenstra et al.,[237] mean health utilities were mostly obtained by interviewing 12 Taiwanese clinicians using the time trade-off (TTO) technique.[250] By lack of data, QoL weight for liver transplant were obtained from hepatitis C patients.

Note that there were discrepancies between the utilities reported in Veenstra et al.'s article[237] and the utilities reported in their stated source article.[250] Lacey et al.[240] and Lacey et al.[233] took QoL values from the study of Crowley et al.,[252] who administered a questionnaire to a group of 4 Australian clinicians to estimate the HBV health-state values.

Health-state utilities were not differentiated between HBeAg+ or HBeAg- CHB patients.

The impact of treatment adverse effect was quantified in Spackman et al.[235] with an assumed disutility of 0.05 QALY during Peg-IFN treatment (clinicians' opinion). Lacey et al.[240] and Lacey et al.[233] assume drug-treatment disutilities of 0.23 QALY with IFN and 0.11 QALY with Peg-IFN (clinicians' opinion). Such utility adjustment for adverse events is in contrast with the assumption in most publications of a gain in QALY in patients responding to an ongoing treatment (e.g. drop in HBV DNA).

Gains in Qol attributed to successfully treated patient were never based on evaluations of real patients and were not always clearly detailed.[230, 232, 234] In Arnold et al.,[231] patients directly exit the model once they are successfully treated. In Veenstra et al.,[237] respondents (i.e. HBV DNA suppression and ALT normalisation) were assumed to return to perfect health, i.e. 1(0.98 – 1.00). In Veenstra et al.[236] and in Spackman et al.[235] the health states "HBeAg seroconversion (HBeAg- and HBsAg+)" and "HBsAg loss" were both associated with a 0.99 (0.94 – 1.00) Qol. Such weights were obtained from the consensus opinion of an expert panel of general practitioners.[254] Lacey et al.[240] and Lacey et al.[233] used 0.783 for "HBeAg seroconversion" and "HBV response (HBV DNA suppression)", also derived from clinicians opinion.[252] In all studies reporting the utility scores, the Qol of patients showing a response to treatment was estimated to be higher than that of CHB.

Table 29 : Health-state utilities used in the economic evaluations

Author (Country)	Treatment responder	CHB	CC	DC	HCC	LT (year 1)	Post LT	Respondent population	Method	References
Buti et al.[230] (Spain)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Spanish population	Not reported	Herdman et al., 2006[268]
Veenstra et al.[237] (Taiwan)	1.00 (0.98 – 1.00)	0.95 (0.90–0.95)	0.90 (0.80–0.92)	0.54 (0.50–0.65)	0.50 (0.30–0.50)	0.50[a] (0.50–0.60)	0.70[a] (0.60–0.80)	Clinicians HCV patients (LT & Post LT)	TTO	Pwu et al., 2002;[250] Wong et al., 1995;[254] Bennett et al., 1997[269]
Spackman et al.[235] (USA)	0.99 (0.94 – 1.00)	0.81 (0.76–0.86)	0.82 (0.77–0.87)	0.36 (0.31–0.41)	0.41 (0.36–0.46)	0.66 (0.61–0.71)	0.76 (0.71–0.81)	US general population	SG	Levy et al., 2008,[264] Wong et al., 1995;[254]
Veenstra et al.[236] (USA)	0.99 (0.94 – 1.00)	0.81 (0.76–0.86)	0.82 (0.77–0.87)	0.36 (0.31–0.41)	0.41 (0.36–0.46)	0.66 (0.61–0.71)	0.76 (0.71–0.81)	US general population	SG	Levy et al., 2008[264]
Arnold et al.[231] (Australia)	Patient exits the model	0.77	0.80	0.35	0.41	-	-	Mixed general population	SG	Levy et al., 2008[264]
Orlewska et al.[234] (Poland)	Not reported	0.82	0.83	0.36	0.46	-	-	British general population	SG	Levy et al., 2008[264]
Costa et al.[232] (Brazil)	Not reported	0.68	0.69	0.35	0.38	-	-	Mixed HBV patients	SG	Levy et al., 2008[264]
Lacey et al.[240] (Singapore)	0.78	0.69	0.56	0.15	0.12	-	-	Clinicians	Opinion based	Crowley et al., 2000[252]
Lacey et al.[233] (Taiwan)	0.78	0.69	0.56	0.15	0.12	-	-	Clinicians	Opinion based	Crowley et al., 2000[252]

CHB: chronic hepatitis B; CC: compensated cirrhosis; DC: decompensated cirrhosis; HCC: hepatocellular carcinoma; LT: liver transplant; SG: standard gamble; TTO: time trade-off. a. Utilities derived from HCV patients, source Bennett et al.[269] b. Source references cited for all health states, except for the "successful treatment" state that is based on assumption.

5.2.7 Effectiveness / modelling

5.2.7.1 Clusters of models

Economic evaluations could be grouped according to the structure of their model since they relied on previously developed models which they adapted to reflect their needs. Similarities in the models' structure and assumptions could also be found in studies sponsored by the same companies (Table 30).

Table 30 : clusters of models' structure

Authors	Source of funding	Authors' affiliations	Source of model
Buti et al., 2009[230]	Gilead	Consultancy, hospital and Gilead	Original model
Veenstra et al., 2008[237]	Hoffmann-La Roche	Hoffmann-La Roche and universities	Original model
Spackman et al., 2008[235]	Bristol-Myers Squibb	Universities	Veenstra et al., 2007[242]
Veenstra et al., 2008[236]	Bristol-Myers Squibb	Universities	Veenstra et al., 2007[242]
Arnold et al., 2008[231]	Bristol-Myers Squibb	Bristol-Myers Squibb	Yuan et al., 2008[238] Yuan et al., 2008[239]
Orlewska et al., 2008[234]	Bristol-Myers Squibb	Bristol-Myers Squibb and universities	Same structure as Arnold et al., 2008[231]
Costa et al., 2008[232]	Not stated	Bristol-Myers Squibb and universities	Same structure as other BMS models
Lacey et al., 2007[240]	Not stated. GSK copyright	Consultancy and hospital	Crowley et al., 2000[252]
Lacey et al., 2008[233]	Not stated. GSK mentioned	Consultancy and hospital	Lacey et al., 2007[240]

5.2.7.2 Efficacy and disease progression

The treatment effects modelled in the economic evaluations are presented in Table 31, with the long-term impact on disease progression and the source references.

Table 31 : Drug treatment effect and disease progression

Authors Publication year	Treatment effect modelled		Impact on disease progression		
	Surrogate endpoint	Source	Outcome	Value (95% CI)	Source
Buti et al., 2009[230]	HBV DNA response (<300-400 copies / mL) vs. no response (HBeAg- and HBeAg+) Note: HBV DNA cut-off in Idris et al.[270] is 100 000 copies/mL	Marcellin et al.[105] Chang et al.[144] Lai et al.[148] Lai et al.[168] Peters et al.[201]	Mortality rate	Not clear. Assume the mortality of the general population after e-seroconversion (HBeAg+) or DNA < 100 000 copies/mL (HBeAg-)	Idris et al.[270]
Veenstra et al., 2008[237]	HBV DNA (<20 000 copies / ml) and ALT normalisation vs. no combined response (HBeAg-)	Marcellin et al.[119]	Annual transition rate from CHB to CC	9% (6-12) vs. 1.3% (1-2)	Liaw et al.[28]
Spackman et al., 2008[235]	HBeAg seroconversion vs. no seroconversion (HBeAg+)	Marcellin et al.[139] Iloeje et al.[271] Chang et al.[144] Lau et al.[115] Lai et al.[148]	Annual transition rate from CHB to CC	4.4% (2.2-8.8) vs. 0.1% (0.1-0.2)	Liaw et al.[28] Hsu et al.[27]
			Annual transition rate from CHB to HCC	0.8% (0.4-1.6) vs. 0.3% (0.15-0.6)	Liaw et al.[272] Hsu et al.[27]
Veenstra et al., 2008[236]	HBV DNA response (<400 copies / ml) vs. no response (HBeAg-)	Lai et al.[168] Hadziyannis et al.[164] Hadziyannis et al.[165]	Annual transition rate from CHB to CC	2.9% (1.5-5.8) vs. 0.1% (0.1-0.2)	Hsu et al.[27] Iloeje et al.[271]
			Annual transition rate from CHB to HCC	0.8% (0.4-1.2) vs. 0.3% (0.15-0.6)	Hsu et al.[27] Chen et al.[55]
Arnold et al., 2008[231]	HBV DNA control (HBeAg- and HBeAg+)	Chang et al.[144] Lai et al.[168]	Risk of developing CC, DC and HCC according to HBV DNA status	< 300 copies/mL; 300-10^4 ; 10^4-10^5 ; 10^5-10^6 ; > 10^6	REVEAL-CHB. Chen et al.[55] Iloeje et al.[271]
Orlewska et al., 2008[234]	HBV DNA control (HBeAg- and HBeAg+)	Chang et al.[144] Lai et al.[168] Peters et al.[201]	Risk of developing CC, DC and HCC according to HBV DNA status	< 300 copies/mL; 300-10^4 ; 10^4-10^5 ; 10^5-10^6 ; > 10^6	REVEAL-CHB. Chen et al.[55] Iloeje et al.[271]
Costa et al., 2008[232]	HBV DNA control (HBeAg- and HBeAg+)	Chang et al.[144] Lai et al.[168]	Risk of developing CC, DC and HCC according to HBV DNA status	< 300 copies/mL; 300-10^4 ; 10^4-10^5 ; 10^5-10^6 ; > 10^6	REVEAL-CHB. Chen et al.[55] Iloeje et al.[271]

Authors Publication year	Treatment effect modelled		Impact on disease progression		
	Surrogate endpoint	Source	Outcome	Value (95% CI)	Source
Lacey et al., 2007[240]	HBeAg seroconversion vs. no seroconversion (HBeAg+) HBV DNA response (<300-400 copies / mL) vs. no response (HBeAg-)	Lau et al.[115] Marcellin et al.[273] Perrillo et al.[134] Marcellin et al.[119] Hadziyannis et al.[164]	Annual transition rate from CHB to CC	HBeAg+: 2.6% vs. 0.37% HBeAg- : 9% vs. 1.29%	Liaw et al.[52] Crowley et al.[248]
			Annual transition rate from CC to HCC	HBeAg + & - : 4.3% vs. 3.5%	
Lacey et al., 2008[233]	HBeAg seroconversion vs. no seroconversion (HBeAg+) HBV DNA response (<300-400 copies / mL) vs. no response (HBeAg-)	Chien et al.[133]	Annual transition rate from CHB to CC	HBeAg+: 2.4% vs. 0.34% HBeAg- : 9% vs. 1.29%	Liaw et al.[51] Crowley et al.[248]
			Annual transition rate from CC to HCC	HBeAg + & - : 2.80% vs. 2.31%	

CI: confidence interval; CHB: chronic hepatitis B; CC: compensated cirrhosis; DC: decompensated cirrhosis; HCC: hepatocellular carcinoma

In Lacey et al.,[240] Lacey et al.[233] and Spackman et al.,[235] the treatment response was HBeAg seroconversion for HBeAg+ CHB patients. Treatment response in other studies and patients was based on HBV DNA suppression or control. Those surrogate endpoints are used because most models assume that disease progression to more severe health states varies with the viremia level and reaching low levels of HBV DNA with drug treatment would slow down disease progression. However, while HBV DNA level has been shown to be correlated with disease progression in untreated HBeAg- patients (REVEAL-HBV study[55, 271]) this correlation may not be true to the same extent for HBeAg+ patients or for a treated population. Another criticism about using the surrogate endpoints HBV DNA level and HBeAg seroconversion is that although they are more frequently achieved, they are less stable over time compared with a "cured" health state reflected by HBsAg seroconversion, which is still difficult to achieve with current interventions.

Cut-off levels for HBV DNA suppression were not uniform across studies, varying from 300 copies/mL[230, 233, 240] up to 20 000[237] or 100 000 copies/mL.[230] HBV DNA levels were assessed with various DNA amplification techniques. The sensitivity of assays for detecting serum or plasma HBV DNA has improved over time and the first quantitative test for HBV DNA was approved by FDA in 2008, at that time even without demonstration of absence of interference with entecavir.[274]

All studies suffer from a lack of long-term treatment efficacy (and safety) data and a lack of high quality studies showing treatment-induced decreases in DC, HCC and mortality. Efficacy rates of CHB treatments were all obtained from studies with a relatively short time span (5 years at maximum).

Because long-term data are lacking, extrapolations and assumptions for rates of disease progression and duration of treatment efficacy had to be done. For example, in HBeAg+ CHB patients, disease progression after treatment-induced e-seroconversion is assumed to be the same as after spontaneous e-seroconversion, or even absence of further disease was assumed.

Only some models include the possibility of e-seroreversion.[233, 235, 240]

Assumptions and extrapolations decrease the internal validity of the studies. High quality studies of long-term use of antiviral treatment for CHB are needed to obtain "real" data on (single or combined) treatment efficacy, drug-resistance and disease progression.

5.2.8 Costs

Cost inputs used by the economic evaluations were not reviewed in the present chapter. The main reason is that costs data and results are not easily extrapolable across countries and none of the studies reviewed here pertained to Belgium. Another reason was our will to focus on detailing the clinical assumptions made by the authors, since those were found to be crucial for the validity of the models and the robustness of the results.

5.2.9 Results

A synthesis of the results of the economic evaluations is presented in Table 32.

Table 32 : Results of studies - Incremental cost-effectiveness ratios (ICER) and benefits of the various treatment options

Author (currency, costing year)	Intervention	Average discounted QALYs (95% CI)	Incremental discounted QALYs (95%CI)	Incremental cost-effectiveness ratio
HBeAg-positive				
Buti et al., 2009[230]	No treatment[a]	13.69	-	-
(€, 2008)	LAM, then ADV + LAM[a]	14.67	0.98	TNF dominant
	ADV, then ADV + LAM[a]	14.68	0.01	TNF dominant
	TLB, then ADV + LAM[a]	14.96	0.28	TNF dominant
	ETV, then ADV + LAM[a]	15.21	0.25	TNF dominant
	TNF, then ADV + LAM[a]	15.43	0.22	2 426
Spackman et al., 2008[235]	No treatment[a]	17.88 (16.48–19.28)	-	-
(US$, 2008)	ADV (+ ETV)[a]	18.25 (17.03–19.51)	0.37	Dominated
	LAM (+ ADV)[a]	18.38 (17.14–19.59)	0.13	Dominated
	TLB (+ ADV)[a]	18.55 (17.39–19.71)	0.17	Dominated
	Peg-IFN, then ETV[a]	18.64 (17.56–19.83)	0.09	Dominated
	ETV (+ ADV)[a]	18.70 (17.50–19.86)	0.06	27 184
Arnold et al., 2008[231]	LAM, then ETV, then ADV	Not reported	-	-
(AU$, 2006)	ETV, then ADV, then LAM		0.22	5 952
Orlewska et al., 2008[234] (PLN, 2006)	LAM – 2 y	Not reported	-	-
	ETV – 2 y		0.28-0.30	ETV dominant
Costa et al., 2008[232] (BR, 2005-6)	LAM, then ADV – 1 y	Not reported	-	-
	ETV – 1 y		0.397	ETV dominant
Lacey et al., 2007[240] (SGP$, 2003-5)	IFN – 1 y[b]	Not reported	-0.21	Dominated
	Peg-IFN – 1y[b]		0.25	67 540
	ADV – 1y[b]		-0.02	Dominated
	ADV, then LAM – 5 y[b]		0.49	17 403
	LAM, then ADV – 5 y[b]		0.54	11 604
Lacey et al., 2008[233] (NT$, 2003-5)	IFN – 1 y	Not reported	-0.16	Dominated
	Peg-IFN – 1 y[b]		0.41	413 145
	ADV – 1 y[b]		-0.01	Dominated
	ADV, then LAM – 2 y[b]		0.21	408 363
	LAM, then ADV – 2 y		0.26	116 041
	ADV, then LAM – 5 y[b]		0.70	276 235
	LAM, then ADV – 5 y		0.72	154 733
HBeAg-negative				
Buti et al., 2009[230]	No treatment[a]	12.48	-	-
(€, 2008)	ADV, then ADV + LAM[a]	14.21	1.73	TNF dominant
	LAM, then ADV + LAM[a]	14.3	0.09	3 949
	TLB, then ADV + LAM[a]	15.47	1.17	TNF dominant
	ETV, then ADV + LAM[a]	16.11	0.64	TNF dominant
	TNF, then ADV + LAM[a]	16.28	0.17	5 212
Veenstra et al., 2008[237] (US$, 2004)	LAM – 48 weeks	10.12	-	10 900
	Peg-IFN – 48 weeks	10.57	0.45	(7 100–17 700)
Veenstra et al., 2008[236] (US$, 2006)	ADV (+ ENT) – 5 y[a]	15.85	-	Dominated
	LAM (+ ADV) – 5 y[a]	16.07	0.22	-
	ADV (+ ENT) – 10 y[a]	16.69	0.62	Dominated
	ETV (+ ADV) – 5 y[a]	16.71	0.02	16 272
	LAM (+ ADV) –10 y[a]	16.99	0.28	Dominated
	ETV (+ ADV) – 10 y	17.59	0.60	Dominated
	ADV (+ ENT) – 5on-1off[ac]	18.00	0.41	Dominated
	ADV (+ ENT) – Life[a]	18.42	0.42	Dominated

Author (currency, costing year)	Intervention	Average discounted QALYs (95% CI)	Incremental discounted QALYs (95%CI)	Incremental cost-effectiveness ratio
	LAM (+ ADV) – 5on-1off[ac]	18.49	0.07	Dominated
	LAM (+ ADV) – Life[a]	18.83	0.34	Dominated
	ETV (+ ADV) – 5on-1off[ac]	19.21	0.38	24 080
	ETV (+ ADV) – Life[a]	19.46	0.25	148 199
Arnold et al., 2008[231] (AU$, 2006)	LAM, then ETV, then ADV	Not reported	-	-
	ETV, then ADV, then LAM		0.22	8 003
Orlewska et al., 2008[234] (PLN, 2006)	LAM – 2 y	Not reported	-	-
	ETV – 2 y		0.13-0.15	ETV dominant
Costa et al., 2008[232] (BR, 2005-6)	LAM, then ADV – 1 y	Not reported	-	-
	ETV – 1 y		0.30	ETV dominant
Lacey et al., 2007[240] (SGP$, 2003-5)	Peg-IFN – 1 y[b]	Not reported	-0.08	Dominated
	ADV – 1y[b]		-0.09	Dominated
	LAM, then ADV – 5 y[b]		1.17	7 528
	ADV, then LAM – 5 y[b]		1.25	8 960
Lacey et al., 2008[233] (NT$, 2003-5)	Peg-IFN – 1 y[b]	Not reported	-0.08	Dominated
	ADV – 1 y[b]		-0.12	Dominated
	ADV, then LAM or ADV + LAM in F3/4b – 2 y[b]		0.35	272 481
	LAM, then ADV or LAM + ADV in F3/4 – 2 y[b]		0.40	95 556
	ADV, then LAM or ADV + LAM in F3/4b – 5 y[b]		1.56	168 427
	LAM, then ADV or LAM + ADV in F3/4 – 5 y[b]		1.50	103 855
LAM-refractory patients				
Orlewska et al., 2008[234] (PLN, 2006)	ADV – 10 y	Not reported	-	-
	ETV – 10 y		0.26-0.29	ETV dominant

Peg-IFN: Pegylated interferon; LAM: Lamivudine; ADV: Adefovir; ETV: Entecavir; TLB: Telbivudine; TNF: Tenofovir; y: year
AU: Australian; BR: Brazilian Reais; NT: New Taiwanese; SGP: Singapore; PLN: Polish zloty
a. Incremental analysis. Each option is compared with the next most effective option
b. Each treatment scenario is compared with 1 year of LAM treatment (LAM – 1 y)
c. 5on-1off : the 5-years-on-1-year-off strategy consists in treating patients for 5 years, stopping treatment in responders for 1 year and re-initiating lifetime therapy for patients who relapse

Based on the results of a single study, TNF was dominant (i.e. less costly and more effective) or cost-effective compared with other treatments in HBeAg + and - CHB patients.[230]

In HBeAg- CHB patients, Peg-IFN administered for 48 weeks was cost-effective compared with LAM.[237] In comparison with LAM and/or ADV, treatment with ETV was cost-effective or even dominant in Veenstra et al.,[236] Arnold et al.,[231] Orlewska et al.[234] and Costa et al.[232]

In HBeAg+ CHB patients, treatment initiation with ETV was the most cost-effective option compared with other treatments (LAM, ADV or TLB).[231, 232, 234, 235]

Lacey et al.[240] and Lacey et al.[233] found that compared with 1-year treatment with LAM, sequential antiviral therapies for up to 5 years were the most clinically attractive and cost-effective options in both HBeAg + and - CHB patients.

At first sight, the results obtained by the economic evaluations of CHB treatments appear rather consistent and positive towards the most recent drugs. All studies further state that those favourable results are fairly robust to changes in their model's assumptions. In most models, however, only limited one way or scenario sensitivity analyses were performed.

However, given the numerous concerns exposed in the methodological sections above, the validity of such results can be questioned. In order to clarify this, the following chapter describes each economic evaluation individually, stressing their internal inconsistencies, which may not directly be apparent when describing them transversally.

5.3 OVERVIEW OF THE ECONOMIC EVALUATIONS - INDIVIDUAL

The report by **Lacey et al.,**[240] copyright GlaxoSmithKline, concludes that compared with 1-year treatment with LAM, sequential antiviral therapies for up to 5 years (i.e. LAM+ADV) are highly cost-effective by international standards.

- The cohort includes HBeAg+ patients of 30 years old and HBeAg- patients of 40 years old in Singapore, modelled for 40 years, with a male to female ratio of 1.
- The annual transition rates are 1% from response (i.e. HBeAg seroconversion or low HBV DNA) to CC. From CHB to CC they are 2.6% (HBeAg+) and 9% (HBeAg-). Also a 85.7% decrease in annual rate of progression from CHB to CC is mentioned in absence of resistance, i.e. 0.37% in HBeAg+ and 1.29% in HBeAg-. The authors state that the ICER in this study heavily depends on the 85.7% rate of reduction of progression from CHB to CC under LAM, which was based on an exploratory integrated analysis of various LAM studies showing at year 1 a progression rate of 14% under placebo vs. 2% under LAM, but statistically not significant (LAM vs. placebo 95%CI: -0.14 to 26.86).[252] This improvement was then extrapolated for 5 years of treatment.
- The annual spontaneous HBeAg-seroconversion rate is 10.2%. Under LAM, it increases to 30.7%, under Peg-IFN to 26.6% and under ADV to 15.2%.
- The annual HBV DNA response rate is 0% without treatment. Under LAM it becomes 89.5%, under PEG-IFN 63.3% and under ADV 51.2%.
- Seroreversion at a rate of 10.2% annually for LAM was included (26.6% for Peg-IFN and 8% for ADV), and a yearly loss of HBV DNA response in 90.3% after discontinuation of LAM or ADV, and in 69.6% after response to Peg-IFN.
- There was no development of resistance during treatment IFN or Peg-IFN. Annual resistance rates during treatment with ADV and LAM were 6.40% and 25.7% respectively.
- The model assumes a normal (general population) life expectancy after seroconversion or low HBV DNA.
- The utility associated with the health state "Response" (seroconversion or low HBV DNA) is 0.783 vs. 0.692 for CHB. A disutility of 0.11 is used while patients are being treated using Peg-IFN. The utility of CC is 0.561.

Lacey et al.,[233] contracted by GlaxoSmithKline, conclude that in Taiwan, treatment with LAM and ADV sequential therapies for up to 5 years results in survival benefits and is highly cost-effective. The previous model of Lacey et al.[240] is also used in this report, with some values specific for Taiwan.

The report by **Veenstra et al.,**[237] financially supported by Roche, concludes that in HBeAg- CHB patients, 48 weeks Peg-IFN compared with 48 weeks LAM appears to offer life expectancy and QoI improvements at an acceptable cost-effectiveness ratio.

- The cohort includes HBeAg- Taiwanese patients aged 40 years onwards and modelled for the rest of their life.

- The treatment is discontinued after 1 year of LAM, which is not in agreement with the treatment guidelines. The combined response (i.e. ALT normalization and DNA < 20 000 copies/mL) at 18 months (i.e. 6 months after treatment discontinuation) is 36% for Peg-IFN and 23% for LAM. The combined response at 24 months however is assumed to be 27% for Peg-IFN and 20% for LAM, a rather arbitrary choice but critical for the outcome of this evaluation.
- A 6% annual spontaneous relapse rate from combined response to CHB is modelled.
- The transition rate used from combined response in HBeAg- CHB patients to CC is 1.3% per year vs. 9% without treatment. The 1.3% transition rate was however based on a reported transition rate to CC after spontaneous seroconversion in HBeAg+ patients.[28]
- The combined response health state was given a mean utility value of 1 vs. 0.95 for CHB and 0.90 for CC. These values were obtained by interviews with 12 Taiwanese hepatologists and 53 patients using the TTO technique.

Veenstra et al.,[236] in a study fully funded by BMS, suggest that in HBeAg- CHB patients a "5 on – 1 off" treatment strategy with ETV improves health outcomes and is cost-effective compared to alternative strategies.

- The cohort includes HBeAg- patients aged 44 years in the US, modelled for their lifetime.
- A natural progression rate of 2.9% is assumed from CHB to CC and 0.8% to HCC. The authors use a very low 0.1% progression rate to CC and a 0.3% progression rate to HCC after DNA < 400 copies/mL in HBeAg- patients; referring to the study of Hsu et al.[27] Hsu et al.[27] however reported this 0.1% progression rate for HBeAg+ patients showing a spontaneous HBeAg seroconversion and furthermore this proportion was based on very low numbers.
- A treatment durability of 30% after 5 years of treatment was estimated based on a small follow-up study after 5 years of ADV treatment.
- A health state utility of 0.99 after treatment response was assumed.

Spackman et al.,[235] in a study sponsored by BMS, concludes that initiation of treatments for HBeAg+ CHB with a favourable combination of seroconversion, viral suppression and resistance profile appear to offer the greatest clinical and economical value.

- The cohort includes HBeAg+ patients of 35 years old in the US, modelled for a lifetime.
- The authors assume the same course of disease progression after treatment-induced HBeAg seroconversion as after spontaneous seroconversion.
- The authors use relative risks of cirrhosis compared with a baseline risk of 4.4% for patients who did not achieve seroconversion: 0.13% for ETV, 0.51% for LAM, 0.77% for ADV, 0.57% to 0.95% for Peg-IFN, and 0.17% for TLB, based on the lowering of DNA levels and referring to the REVEAL study.
- A HBeAg seroreversion rate of 20% was modelled.
- A health state utility of 0.99 after treatment response was assumed.

Arnold et al.[231] for Australia, **Orlewska et al.**[234] for Poland and **Costa et al.**[232] for Brazil conclude in support of ETV in BMS sponsored studies.

- These cost-effectiveness studies use disease progression rates from CHB to CC, DC or HCC by viral load category as assessed at baseline in the REVEAL study and use these rates both for HBeAg+ and HBeAg- CHB. REVEAL is a BMS US co-sponsored epidemiological study in untreated Taiwanese patients. The REVEAL study is further discussed below.

The report by **Buti et al.,**[230] supported in part by a research grant from Gilead, concludes that TNF is cost-effective or even cost-saving.

- The cohort includes both HBeAg + and - patients in Spain, modelled from age 40 onwards for a period of 20 years.
- Treatment is stopped after HBeAg seroconversion in HBeAg+ patients and continued in HBeAg- patients.
- The possibility of HBe seroreversion is not included in the model.
- The study mentions that probabilities of disease progression were based on serum HBV DNA, but no further details are given. The reference model by Idris et al.[270] assumes a 100% stop of disease progression and normal mortality rate after HBeAg seroconversion or low DNA for HBeAg- patients.
- The assumptions on the response rates used after year 1 are not clear. Only year 1 response rates are given. The discussion mentions extrapolation of data of treatment given for 2-5 years and the need for more "real data" to better validate the model.
- The utilities used are not listed and the reference given is an abstract. It is possible these utilities were included in the publication by Levy et al.[264]

We should note that the methodological flaws as described above are not restricted to company-sponsored studies. For example, the recent publication by **Veldhuijzen et al.,**[275] a non-industry-sponsored study that evaluates the cost-effectiveness of early detection and treatment of chronic infections with HBV in a Dutch setting. This study was excluded because it evaluates a HBV screening programme (Intervention criteria not fulfilled - Table 25). It is only detailed here to illustrate our purpose.

- The cohort includes both HBeAg + and - patients in The Netherlands, modelled for the rest of their life.
- The authors assume there is no progression of disease after HBeAg seroconversion or decrease in HBV DNA below the assay detection limit.
- Also here a utility of 1.00 was used for the base-case estimate of "treatment response", or 0.32 utility points higher than the utility of the CHB health-state, based on assumptions only.

5.4 GENERAL DISCUSSION AND CONCLUSIONS

Although the results of the economic evaluations on CHB treatments appear rather consistent and favourable, all studies suffer from major flaws casting doubts on the validity of their conclusions. The limitations of the studies pertained to the following:

- Lack of long-term hard endpoint data and use of much less robust surrogate endpoints
- Use of rather optimistic assumptions regarding disease progression after treatment response (i.e. HBeAg seroconversion or low HBV DNA).
- Extrapolation of disease progression rates observed after spontaneous HBeAg seroconversion to the rates applied after treatment-induced seroconversion or even to HBV DNA response in HBeAg- patients.
- Extrapolation of the progression based on HBV DNA baseline results of the REVEAL study in untreated HBeAg- patients (most with normal ALT) to treated HBeAg + and - patients (most with elevated ALT).
- No consideration of the wide uncertainty in the estimates.
- Discrepancies across the studies in the natural disease transition rates.
- Non-validated quality-of-life scores for the "treatment response" health state.

Each point is briefly summarized below.

Long term effectiveness data (cirrhosis, HCC) are a requirement for credible cost-effectiveness evaluations. In the absence of credible long-term treatment efficacy data,[110] health-economic models are built on extrapolations of imperfect short term (maximum follow-up of 5 years) surrogates such as HBeAg seroconversion and the HBV DNA level in serum. HBeAg seroconversion is indeed more frequently achieved but is a less durable marker of response compared with HBsAg seroconversion. Treatment-induced HBsAg seroconversion could be a better surrogate predicting long term response. However, even after successful suppression of HBV DNA levels, the frequency of HBsAg seroconversion is still low and the sustainability of such response after discontinuation of treatment is not well documented. Only the study of Lacey et al.[240] modelled the decrease in annual rate of progression from CHB to CC on real treatment efficacy data (at 1 year).

Some models assume a normal life expectancy after HBeAg seroconversion or low HBV DNA.[240] Some models even assume the absence of further disease and a normal life expectancy in 100% of the patients who show treatment-induced HBeAg seroconversion.[230, 275] Recent data contradict previous reports and suggest 74% of patients serorevert within three years after treatment-induced HBeAg seroconversion.[276] Some models include the possibility of HBeAg seroreversion and assume the same rate as after spontaneous HBeAg seroconversion, which varies by model from 10.2%[240] to 20%[235] per year. The spontaneous seroconversion rate was also assumed to be 10.2% by Lacey et al.[240]

Some models extrapolate the transition rates to cirrhosis observed after spontaneous HBeAg seroconversion. The rates used vary from 0.1%[235, 236] based on very low numbers reported in 2002 by Hsu et al.[27] to 1.3%[237] based on the 1988 publication by Liaw et al.,[28] who also reported a 2.4% transition rate for HBeAg+ patients. These rates are then extrapolated to treatment-induced HBeAg seroconversion[235] or even to HBV DNA treatment response in HBeAg- patients.[236, 237]

Most BMS sponsored models are based on transition rates seen in the REVEAL study.[55, 271] REVEAL is a BMS US co-sponsored epidemiological study in untreated patients in Taiwan. Cirrhosis was detected using ultrasound every 6-12 months and no biopsy data were analysed. 3653 HBsAg+ subjects were enrolled free of HCC and seronegative for HCV (no other criteria, e.g. no exclusion of inactive carriers). Most patients were HBeAg- at enrolment (n=3037), of whom 2923 had normal ALT. Overall 365 cases (261 with two ultrasounds) of cirrhosis were identified over 40 038 person-years, or an average transition rate of 0.65% to 0.9%. REVEAL's results illustrate that inactive carriers or HBeAg- patients with low HBV DNA have a low transition rate to cirrhosis (0.34%) compared with CHB HBeAg- patients with a high HBV DNA level (2 to 2.5%). The 565 HBeAg+ patients had a transition rate of 4.4%[235] but no data were shown to support an association of cirrhosis development with DNA level. The data shown rather suggest an absence of association of DNA level with HCC development in this 'smaller' group.[55] Extrapolation of these data to the natural history of HBeAg+ patients may thus not be appropriate. Extrapolation to use these non-treated cohort data to predict long term response after treatment for HBeAg+ and HBeAg- CHB takes a leap of faith. Yet, all BMS sponsored models assume that natural transition rates by HBV DNA level in untreated HBeAg- patients and inactive carriers in the REVEAL study[55, 271] are the same as for treatment-induced lowering of HBV DNA levels in HBeAg+ patients with elevated ALT.[231, 232, 234, 235]

A last point concerning the use of HBV DNA testing as a surrogate endpoint concerns the need for validation of this measurement, as various assays have been used in trials. The study of Lacey et al.[240] models an 85.7% decrease in annual rate of progression from CHB to CC in absence of resistance. The strong point is that this rate was based on real data: an exploratory integrated analysis of various LAM studies showing at year 1 a progression rate of 14% under placebo vs. 2% under LAM. However it was statistically not significant (LAM vs. placebo 95%CI: -0.14 to 26.86).[252] This point estimate was then extrapolated for 5 years of treatment. In the sensitivity analysis the point estimate was however varied with only 20%, much less than the very wide 95% CI. Despite this artificially reduced variation introduced in the sensitivity analysis the authors found that the ICER in this study heavily depended on this rate of reduction of progression.

All studies report they performed sensitivity analyses on uncertain parameters. While this is true, only a limited one-way sensitivity analysis was performed in most studies without using CIs around the point estimates. Three studies performed a comprehensive probabilistic sensitivity analysis.[230, 235, 236]

The natural transition rates included in the models vary considerably between studies. For example, the natural transition rates from CHB to CC modelled for HBeAg+ patients vary from 2.6%[240] to 4.4%.[235] In HBeAg- patients, the rate varies from under 2%[231, 232, 234] or 2.9%[236] based on REVEAL,[55, 271] up to 9%.[237, 240]

All studies assume a QoI improvement after treatment-induced HBeAg seroconversion or after low level of HBV DNA without any measurements confirming this. The utility values used for CC, CHB and treatment-induced response are 0.56, 0.69 and 0.78 in the model by Lacey et al.;[240] 0.90, 0.95 and 1.00 in the model by Veenstra et al.;[237] 0.82, 0.81, and 0.99 in the models using the study by Levy et al.[235, 236, 264] It seems important to mention that to our knowledge no measurements of health utility in treatment responders have been reported to date, also not in the study of Levy et al.[264] Also the use of a disutility for Peg-IFN by Lacey et al.[240] and Spackman et al.[235] was not based on measurements in CHB patients.

In view of those limitations, more robust studies should be performed to assess the cost-effectiveness of recent CHB treatments.

6 APPENDIXES

APPENDIX 1: EQ-5D HEALTH QUESTIONNAIRE – ENGLISH VERSION (© EUROQOL GROUP)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

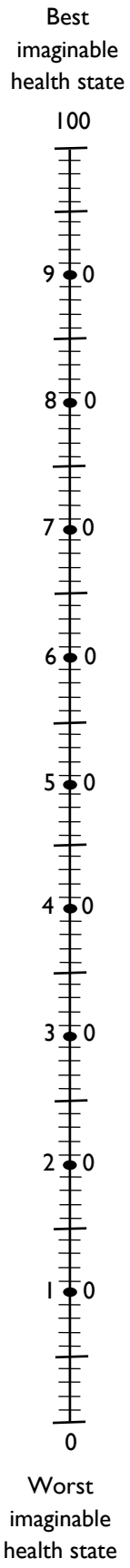
Anxiety/Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



APPENDIX 2: SEARCH FOR COST-EFFECTIVENESS STUDIES

SEARCH STRATEGY

In September 2009, the websites of HTA institutes (Table 33) and following databases were searched: Medline(OVID), Embase, Centre for Reviews and Dissemination (CRD) databases: NHS Economic Evaluation Database (NHS EED) and HTA database, Cochrane Database of Systematic Reviews (CDSR) (Technology Assessments and Economic Evaluations), and Econlit(OVID). The following tables (Table 34 to Table 40) provide an overview of the search strategy and results for each database.

Table 33 : List of INAHTA member websites searched for HTA reports

Agency		Country
AETMIS	Agence d´Évaluation des Technologies et des Modes d´Intervention en Santé	Canada
AETS	Agencia de Evaluación de Tecnologias Sanitarias	Spain
AETSA	Andalusian Agency for Health Technology Assessment	Spain
AHRQ	Agency for Healthcare Research and Quality	USA
AHTA	Adelaide Health Technology Assessment	Australia
AHTAPol	Agency for Health Technology Assessment in Poland	Poland
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures	Australia
AVALIA-T	Galician Agency for Health Technology Assessment	Spain
CADTH	Canadian Agency for Drugs and Technologies in Health	Canada
CAHTA	Catalan Agency for Health Technology Assessment and Research	Spain
CEDIT	Comité d'Évaluation et de Diffusion des Innovations Technologiques	France
CENETEC	Centro Nacional de Excelencia Tecnológica en Salud Reforma	Mexico
CMT	Centre for Medical Technology Assessment	Sweden
CRD	Centre for Reviews and Dissemination	UK
CVZ	College voor Zorgverzekeringen	Netherlands
DACEHTA	Danish Centre for Evaluation and Health Technology Assessment	Denmark
DAHTA @DIMDI	German Agency for HTA at the German Institute for Medical Documentation and Information	Germany
DECIT-CGATS	Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia	Brazil
DSI	Danish Institute for Health Services Research	Denmark
FinOHTA	Finnish Office for Health Care Technology Assessment	Finland
GR	Gezondheidsraad	Netherlands
HAS	Haute Autorité de Santé	France
HunHTA	Unit of Health Economics and Health Technology Assessment	Hungary
IAHS	Institute of Applied Health Sciences	UK
ICTAHC	Israel Centre for Technology Assessment in Health Care	Israel
IECS	Institute for Clinical Effectiveness and Health Policy	Argentina
IHE	Institute of Health Economics	Canada
IMSS	Mexican Institute of Social Security	Mexico
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	Germany
KCE	Belgian Federal Health Care Knowledge Centre	Belgium
LBI of HTA	Ludwig Boltzmann Institut für Health Technology Assessment	Austria
MAS	Medical Advisory Secretariat	Canada
MSAC	Medicare Services Advisory Committee	Australia

Agency		Country
MTU-SFOPH	Medical Technology Unit - Swiss Federal Office of Public Health	Switzerland
NCCHTA	National Coordinating Centre for Health Technology Assessment	UK
NHS QIS	Quality Improvement Scotland	UK
NHSC	National Horizon Scanning Centre	UK
NOKC	Norwegian Knowledge Centre for Health Services	Norway
NZHTA	New Zealand Health Technology Assessment	New Zealand
OSTEBA	Basque Office for Health Technology Assessment	Spain
SBU	Swedish Council on Technology Assessment in Health Care	Sweden
UETS	Unidad de evaluacíon Technologias Santarias	Spain
VATAP	VA Technology Assessment Program	USA
VSMTVA	Health Statistics and Medical Technologies State Agency	Latvia
ZonMw	The Medical and Health Research Council of The Netherlands	Netherlands

Table 34 : Search strategy and results for CRD-HTA

Date	16/09/09		
Database	CRD - HTA		
Date covered	No restrictions		
Search strategy	**#**	**Strategy**	**Results**
	1	MeSH Hepatitis B, Chronic EXPLODE 1 2 3 4	**10**

Table 35 : Search strategy and results for CDSR-TA

Date	16/09/09		
Database	CDSR – Technology Assessment database		
Date covered	No restrictions		
Search strategy	**#**	**Strategy**	**Results**
	1	MeSH descriptor Hepatitis B explode all trees	**24**

Table 36 : Search strategy and results for CRD-NHS EED

Date	16/09/09		
Database	CRD – NHS EED		
Date covered	No restrictions		
Search strategy	**#**	**Strategy**	**Results**
	1	MeSH Hepatitis B, Chronic EXPLODE 1 2 3 4	**49**

Table 37 : Search strategy and results for CDSR EE

Date	16/09/09		
Database	CDSR – Economic Evaluations database		
Date covered	No restrictions		
Search strategy	**#**	**Strategy**	**Results**
	1	MeSH descriptor Hepatitis B explode all trees	**151**

Table 38 : Search strategy and results for Econlit (OVID)

Date	17/09/09		
Database	Econlit (OVID)		
Date covered	1969 to August 2009		
Search strategy	**#**	**Strategy**	**Results**
	1	hepatitis b chronic.mp. [mp=heading words, abstract, title, country as subject]	0
	2	hepatitis b.mp. [mp=heading words, abstract, title, country as subject]	23
	3	1 or 2	**23**

Table 39 : Search strategy and results for Medline (OVID)

Date	16/09/09		
Database	Medline (OVID) - Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)		
Date covered	1950 to Present		
Search strategy	**#**	**Searches**	**Results**
	1	economics/	25671
	2	exp "Costs and Cost Analysis"/	146238
	3	"Value of Life"/ec [Economics]	197
	4	Economics, Dental/	1793
	5	exp Economics, Hospital/	16204
	6	Economics, Medical/	7092
	7	Economics, Nursing/	3794
	8	Economics, Pharmaceutical/	2083
	9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	188716
	10	(econom$ or cost$ or pric$ or pharmacoeconomic$).tw.	357276
	11	(expenditure$ not energy).tw.	13478
	12	(value adj1 money).tw.	14
	13	budget$.tw.	13930
	14	10 or 11 or 12 or 13	371636
	15	9 or 14	462571
	16	letter.pt.	684097
	17	editorial.pt.	256374
	18	historical article.pt.	276681
	19	16 or 17 or 18	1205560
	20	15 not 19	439036
	21	Animals/	4484451
	22	human/	10991211
	23	21 not (21 and 22)	3350262
	24	20 not 23	409980
	25	quality of life.mp. or "Quality of Life"/	119892
	26	25 not 19	115117
	27	26 not 23	114592
	28	27 or 24	508791
	29	Hepatitis B, Chronic/	5856
	30	28 and 29	**204**
Note	MeSH HEADING: HEPATITIS B, CHRONIC SCOPE: INFLAMMATION of the LIVER in humans caused by HEPATITIS B VIRUS lasting six months or more. It is primarily transmitted by parenteral exposure, such as transfusion of contaminated blood or blood products, but can also be transmitted via sexual or intimate personal contact. YEAR of ENTRY: 98 PREVIOUS INDEXING: Chronic Disease (1973-1997); Hepatitis B (1973-1997); Hepatitis, Chronic (1983-1997) Used For: hepatitis b, chronic & chronic hepatitis b		

Table 40 : Search strategy and results for Embase

Date	16/09/09		
Database	Embase		
Date covered	No restrictions		
Search strategy	**#**	**Searches**	**Results**
	#1	cost minimization analysis'/exp/mj	152
	#2	health economics'/exp/mj	150.851
	#3	health care cost'/exp/mj	36.480
	#4	economic aspect'/exp/mj	276.266
	#5	cost control'/exp/mj	5.160
	#6	cost of illness'/exp/mj	2.129
	#7	cost effectiveness analysis'/exp/mj	7.104
	#8	cost benefit analysis'/exp/mj	6.087
	#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	276.266
	#10	quality of life'/exp/mj	28.737
	#11	#10 OR #9	303.894
	#12	hepatitis b'/exp/mj	31.096
	#13	#12 AND #11	184
	#14	editorial:it OR letter:it	994.293
	#15	#13 NOT #14	**166**

RESULTS OF THE SEARCH STRATEGIES

A total of 629 papers were identified from the databases consulted: 204 with Medline(OVID), 166 with Embase, 59 with the CRD NHS EED and HTA databases, 175 from the Cochrane Database of Systematic Reviews (Technology Assessments and Economic Evaluations), and 23 from Econlit(OVID) (Table 41). The manual consultation of the HTA agencies websites and of e-TOCs further returned two additional citations. After removing 173 duplicates, 455 citations were left.

Table 41 : search for HTA and cost-effectiveness studies: summary

Database	**References identified**
Medline (OVID)	204
EMBASE	166
CRD - HTA	10
CRD - NHS EED	49
CDSR - Technology Assessments database	24
CDSR - Economic Evaluations database	151
Econlit (OVID)	23
Hand search	2
Total references identified	629
Duplicates	173
Total	**456**

APPENDIX 3: CLASSIFICATION OF ECONOMIC STUDIES

Figure 2 : Classification of economic studies

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="3">Are both costs (inputs) and consequences (outputs) of the alternatives examined?</td></tr>
<tr><td colspan="2">No</td><td rowspan="2">Yes</td></tr>
<tr><td colspan="2"></td><td>Examines consequences only</td><td>Examines costs only</td></tr>
<tr><td rowspan="4">Is there a comparison of at least two alternatives?</td><td rowspan="2">No</td><td colspan="2">Partial evaluation</td><td>Partial evaluation</td></tr>
<tr><td>Outcome description</td><td>Cost description</td><td>Cost-outcome description</td></tr>
<tr><td rowspan="2">Yes</td><td colspan="2">Partial evaluation</td><td>Full economic evaluation</td></tr>
<tr><td>Efficacy or effectiveness evaluation</td><td>Cost comparison</td><td>Cost-minimisation analysis (CMA)
Cost-effectiveness analysis (CEA)
Cost-utility analysis (CUA)
Cost-benefit analysis (CBA)</td></tr>
</table>

Adapted from Drummond et al.[277]

APPENDIX 4 : DATA EXTRACTION SHEETS

Author

Lacey LF, Gane E. The cost-effectiveness of long-term antiviral therapy in the management of HBeAg-positive and HBeAg-negative chronic hepatitis B in Singapore. J Viral Hepat. 2007;14(11):751-66[240]

Country

Singapore

Study type

CEA - CUA

Model

Two Markov state-transition models (one for HBeAg+ and one for HBeAg-).
Adapted from Crowley et al., 2000 previously published model.

Perspective

Healthcare payer

Time window

40 years

Interventions

1) No treatment;
2) Short-duration therapy (4-6 months) with IFN-alpha, 5-10 MU three times a week;
3) One-year treatment with Peg-IFN-alpha, 180mg once weekly;
4) One-year treatment LAM;
5) One-year treatment ADV;
6) Five-year treatment with ADV (+LAM as salvage therapy);
7) Five-year treatment with LAM (+ADV as salvage therapy).

Population

HBeAg+ CHB patients and HBeAg- CHB patients.

Assumptions

CHARACTERISTICS OF BASELINE COHORT
Average age: 30-year-old for the HBeAg+ and 40-year-old for the HBeAg-.
Male to female ratio: 1.
Race (if appropriate): Asian (Singaporean).

DISEASE PROGRESSION RATES
Derived from literature: Lin X et al., 2005.

	CC	DC	HCC	Death
CHB	2.60% (HBeAg+) 9.00 % (HBeAg-)		0.66%	0.60%
CC		4.20%	4.30%	5.40%
DC			7.10%	16.30%
HCC				43.00%

(CHB: chronic hepatitis B; CC: compensated cirrhosis; DC: decompensated cirrhosis; HCC: hepatocellular carcinoma)

TREATMENT EFFECTS
Effects of treatment in reducing the rates of disease progression.
Derived from literature: Crowley et al., 2002 and Liaw et al., 2004.
Probabilities for first-line treatments only (LAM, IFN, Peg-IFN or ADV) in the absence of resistance.
Treatment effect is similar for all interventions (LAM, IFN, Peg-IFN or ADV).
No effects for LAM or ADV in presence of resistance.

	CC	DC	HCC
CHB	85.7% (HBeAg-ve)		
CC		22.6%	17.6%

SEROCONVERSION RATES (HBeAg+ patients only)
HBeAg-seroconversion is used as treatment-stopping criterion.
If patient achieves seroconversion, the rate of progression from response to CC is limited to 1%.
Probabilities derived from literature: Perrillo et al., 2002; Lau et al., 2005 and Marcellin et al., 2002.

Intervention	Estimate
No treatment	10.20%
LAM	30.70%
IFN	22.50%
Peg-IFN	26.60%
ADV	15.20%

RESPONSE RATES (HBeAg- patients only)
HBV response when suppression of HBV viral load occurred to <300-400 copies/mL.
If patient achieves HBV response, the rate of progression from response to CC is limited to 1%.
Probabilities derived from literature: Marcellin et al., 2002 and Hadziyannis et al., 2003.

Intervention	Estimate
No treatment	0.00%
LAM	89.50%
Peg-IFN	63.30%
ADV	51.20%

RELAPSE RATES
In percentage of patients who relapse back to CHB state (=seroreversion).
Derived from literature:
- HBeAg+ patients: Dienstag et al., 2003; Crowley et al., 2002; Lau et al., 2005 and Chang et al., 2004.
- HBeAg- patients: Marcellin et al., 2002 and Hadziyannis et al., 2003.

In HBeAg+ patients	
Intervention	**Estimate**
No treatment	10.20%
LAM	10.20%
IFN	10.20%
Peg-IFN	26.60%
ADV	08.00%
In HBeAg- patients	
No treatment	90.30%
LAM	90.30%
Peg-IFN	69.60%
ADV	90.30%

ANTIVIRAL RESISTANCE RATES
Derived from literature: Lai et al., 2003 and Locarini et al., 2005.

In HBeAg+ patients	
Intervention	**Estimate**
No treatment	0.00%
LAM	25.70%
IFN	0.00%
Peg-IFN	0.00%
ADV	6.40%

Data source for costs
Costs in Singaporean Dollars (SGD).
DRUGS: Annual drug acquisition costs (wholesale), year 2005 values.
HEALTH-STATES: Li et al., 2004, year 2003 values.

Cost items included
Drug costs.
Direct medical costs associated with health states.

Data source for outcomes
Utility estimates from Crowley et al., 2000 or adapted from it. Crowley's derived weights from a panel of clinicians.

Discounting
Costs: 5%
Outcomes: 5%

Costs
DRUGS

Treatment	**Annual costs (SGD)**
LAM	2,774.00
ADV	3,606.20
IFN	7,329.75
Peg-IFN	20,740.00

HEALTH-STATES
Values shown in a figure, but not reported.

Outcomes
QALY WEIGHTS

Health State	**Estimate**
Seroconversion	0.783
CHB	
- untreated	0.692
- LAM	0.692
- ADV	0.692
- IFN	0.467
- Peg-IFN	0.5795
CC	0.561
DC	0.150
HCC	0.118
Resistant CHB	
- untreated	0.692
- LAM	0.692
- ADV	0.692
- IFN	0.467
- Peg-IFN	0.5795
Resistant CC	0.561
Resistant DC	0.150
Resistant HCC	0.118

Cost-effectiveness
COSTS RESULTS
Total incremental cost in comparison with LAM (1 year) – lifetime discounted:

Intervention	**Costs (SGD)**
HBeAg+	
IFN	4,570.91
Peg-IFN (1 year)	16,968.32
ADV (1 year)	735.09

	LAM (5 years)	5,783.60	
	ADV (5 years)	8,989.51	
	LAM + ADV as rescue therapy (5 years)	6,207.56	
	ADV + LAM as rescue therapy (5 years)	8,597.43	
	HBeAg-		
	Peg-IFN (1 year)	17,856.93	
	ADV (1 year)	934.59	
	LAM (5 years)	8,878.72	
	ADV (5 years)	11,542.99	
	LAM + ADV as rescue therapy (5 years)	8,822.34	
	ADV + LAM as rescue therapy (5 years)	11,183.36	

OUTCOMES RESULTS

Total incremental outcome in comparison with LAM (1 year) – lifetime discounted :

Intervention	LYs	QALYs
HBeAg+		
IFN	-0.050	-0.209
Peg-IFN (1 year)	0.242	0.251
ADV (1 year)	-0.048	-0.020
LAM (5 years)	0.320	0.313
ADV (5 years)	0.414	0.422
LAM + ADV as rescue therapy (5 years)	0.548	0.535
ADV + LAM as rescue therapy (5 years)	0.481	0.494
HBeAg-		
Peg-IFN (1 year)	0.017	-0.082
ADV (1 year)	-0.109	-0.097
LAM (5 years)	0.508	0.509
ADV (5 years)	1.106	1.097
LAM + ADV as rescue therapy (5 years)	1.213	1.172
ADV + LAM as rescue therapy (5 years)	1.262	1.248

ICERs (in comparison with LAM (1 year) – lifetime discounted)

Intervention	Costs/ LYG	Costs/ QALY
HBeAg+		
IFN	Dominated	Dominated
Peg-IFN (1 year)	70,161.69	67,540.78
ADV (1 year)	Dominated	Dominated
LAM (5 years)	18,073.04	18,507.18
ADV (5 years)	21,689.93	21,313.88
LAM + ADV as rescue therapy (5 years)	11,319.95	11,604.85
ADV + LAM as rescue therapy (5 years)	17,864.69	17,403.02
HBeAg-		
Peg-IFN (1 year)	1,065,894.63	Dominated
ADV (1 year)	Dominated	Dominated
LAM (5 years)	17,461.19	17,453.01
ADV (5 years)	10,439.73	10,524.11
LAM + ADV as rescue therapy (5 years)	7,271.76	7,528.61
ADV + LAM as rescue therapy (5 years)	8,861.37	8,960.64

Sensitivity analysis	ONE-WAY SENSITIVITY ANALYSES Analyses carried on individual model inputs (not specified) over a range of values obtained from the literature (not reported) Results are most sensitive to variation in the discount factor, the rates of disease progression, the treatment effects, health state utilities and health care costs.
	MULTIVARIATE SENSITIVITY ANALYSES Not reported: "analyses were carried out in which several model inputs were varied simultaneously".
	PROBABILISTIC SENSITIVITY ANALYSES Not performed.
Conclusions	"Treatment with LAM or ADV for up to 5 years using the alternative agent as rescue medication was found highly cost-effective, in comparison with no treatment or one-year treatment with LAM ".
Conflict of interests	Not stated but GSK copyright. Authors are from consultancy and hospitals

Author	**Arnold E, Yuan Y, Iloeje U, Cook G. Cost-effectiveness analysis of entecavir versus lamivudine in the first-line treatment of australian patients with chronic hepatitis B. Applied Health Economics and Health Policy. 2008;6(4):231-46.[231]**
Country	Australia
Study type	CEA - CUA
Model	Two Markov state-transition models (one for HBeAg+ and one for HBeAg-).
Perspective	Health care payer
Time window	20 years
Interventions	1) ETV - 0.5mg/day. With first and second salvage treatments: ADV 10mg/day and LAM 100mg/day.

2) LAM - 100mg/day.With first and second salvage treatments: ETV 1 mg/day and ADV 10mg/day.

Treatment duration:
HBeAg+: Up to 10 years. Treatment stops 12 months after HBeAg seroconversion.
HBeAg-: 10 years treatment duration.

Population

HBeAg+ and HBeAg- CHB patients

Assumptions

DISEASE PROGRESSION
Disease progression based on the viral load levels (HBV DNA copies/mL). Estimates derived from the REVEAL-CHB study literature: Chen et al., 2006 and Iloeje et al., 2006.
Adjusted relative risk of developing CC, DC and HCC by HBV DNA level:

HBV DNA copies/mL	**Estimates (range)**		
	CC	DC	HCC
<300	1.0% (1.0-1.0)	1.0% (1.0-1.0)	1.0% (1.0-1.0)
300-10^4	1.4% (0.9-2.2)	2.7% (0.5-13.4)	1.1% (0.5-2.3)
10^4-10^5	2.5% (1.6-3.8)	-	2.3% (1.1-4.9)
10^5-10^6	5.6% (3.7-8.5)	5.9% (1.1-32.7)	6.6% (3.3-13.1)
>10^6	6.5% (4.1-10.2)	19.3% (4.4-84.8)	6.1% (2.9-12.7)

TREATMENT EFFECTS
Effects of the two different treatments on the viral load levels (HBV DNA copies/mL).
Estimates from literature : Chang et al., 2006 and Lai et al., 2006.
Proportion of patients in each category of viral load at week 48 of treatment:

	First-line setting				*Salvage setting*
	HBeAg+ patients		*HBeAg- patients*		
HBV DNA copies/mL	ETV	LAM	ETV	LAM	ADV+LAM+ETV
<300	69.1%	39.8%	93.3%	75.6%	20.3%
300-10^4	24.7%	18.2%	4.1%	12.5%	20.3%
10^4-10^5	4.4%	11.7%	1.6%	5.1%	19.6%
10^5-10^6	0.6%	9.3%	0.3%	2.0%	24.8%
≥10^6	1.2%	21.0%	0.6%	4.8%	15.0%

SEROCONVERSION RATES (HBeAg+ patients only)
Derived from literature: Gish et al., 2007.

First-line setting					
	Year 1	Year 2	Year 3	Year 4	Year 5+
ETV or LAM	11.5%	17%	8%	8%	7.5%

Derived from literature: Sherman et al., 2006 and Peters et al., 2004.

Salvage setting					
	Year 1	Year 2	Year 3	Year 4	Year 5+
ETV or LAM or ADV	9.5%	7.5%	7.5%	7.5%	7.5%

ANTIVIRAL RESISTANCE RATES
Derived from literature: Colonno et al., 2006; Colonno et al., 2007; Tenney et al., 2004 and Conjeevaram et al., 2003. Adapted with an expert panels.

In the first-line setting						
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6+
ETV	0.15%	0%	0.67%	0%	0%	0%
LAM	14%	24%	11%	17%	3%	5%

Derived from literature: Colonno et al., 2007, Osiowy et al., 2005 and Lee et al., 2005. Adapted with an expert panels.

In the salvage setting						
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6+
ADV	18%	15%	5%	5%	5%	5%
LAM/ETV	1.1%	9.6%	16.4%	12.4%	5%	5%

Data source for costs

Costs in Australian dollars (AUD), year 2006 values.
Drug costs from Australian Government's Schedule of Pharmaceutical Benefits.
Direct medical costs associated with health states from literature (Butler et al., 2004)

Cost items included

Drug costs.
Direct medical costs associated with health states.

Data source for outcomes

Age specific life expectancy for the Australian population (Australian Bureau of Statistics).
Utility estimates from a published study by Levy et al., 2008 which used a SG method in mixed general population.

Discounting

Cost: 5%
Outcome: 5%

Costs

DRUGS

Treatment	**Annual costs (AUD)**
In the first-line setting	
ETV - 0.5mg/day	4,995.90
LAM – 100mg /day	2,091.04
In the salvage setting	
ADV - 100mg/day	8,125.00
ETV – 1 mg/day	8,125.00

	LAM - 100mg/day: 2,091.04 HEALTH-STATES Health-state / Annual costs (AUD) CC: 1,692 DC: 14,521 HCC: 14,268
Outcomes	QALY WEIGHTS Health State / Estimate CHB: 0.77 CC: 0.80 DC: 0.35 HCC: 0.41
Cost-effectiveness	COSTS RESULTS Total costs – 20 years discounted: Treatment / Costs (AUD) *HBeAg+ patients* ETV - 0.5mg/day: 32,029,260 LAM – 100mg /day: 30,709,295 *HBeAg- patients* ETV - 0.5mg/day: 46,258,008 LAM – 100mg /day: 44,488,745
	OUTCOMES RESULTS Not reported.
	ICERs – ETV vs. LAM: In the HBeAg- CHB patient population: ICER: AUD 5952/ QALY gained; ICER: AUD 5046/ LYG. In the HBeAg+ CHB patient population: ICER: AUD 5952/ QALY gained; ICER: AUD 5046/ LYG. Under the assumption of a ratio of HBeAg+ patients to HBeAg- patients equal to 60:40: ICER: AUD 6772/ QALY; ICER: AUD 5853/ LYG
Sensitivity analysis	UNIVARIATE SENSITIVITY ANALYSES Varied parameters: model duration, treatment duration, ADV salvage treatment, virologic response failure rate, ETV resistance rate, ETV and LAM seroconversion rate, health state utilities and discount rate. ICER ranges from AUD 0-12200/QALY gained for HBeAg+ CHB patients ICER ranges from AUD 0-18990/QALY gained for HBeAg- CHB patients Most influential parameters: model duration; treatment duration; virologic response failure rate; ETV resistance rate
	PROBABILISTIC SENSITIVITY ANALYSES Not performed.
Conclusions	"Initiating therapy with ETV in CHB patients would be cost effective and therefore economically attractive the Australian health care payers".
Conflict of interests	The study is funded by Bristol-Myers Squibb. All authors are employees of Bristol-Myers Squibb. Ms Arnold, Dr Iloeje and Dr Cook own stock in Bristol-Myers Squibb.

Author	**Costa AMN, L'italien G, Nita ME, Araujo ESA. Cost-effectiveness of entecavir versus lamivudine for the suppression of viral replication in chronic hepatitis B patients in Brazil. Braz J Infect Dis. 2008;12(5):368-73.**
Country	Brazil
Study type	CEA - CUA
Model	Two Markov state-transition models (one for HBeAg+ and one for HBeAg-).
Perspective	Health care payer
Time window	10 years
Interventions	1) One-year treatment ETV; 2) One-year treatment LAM (+ADV as rescue therapy for LAM-resistants).
Population	HBeAg+ and HBeAg- CHB patients
Assumptions	DISEASE PROGRESSION Disease progression based on the viral load levels (HBV DNA copies/mL). Estimates derived from the REVEAL-CHB study published in the literature: Chen et al., 2006 and Iloeje et al., 2006. Distribution (%) of cases according to HBV DNA level:

	Distribution (%) of cases according to HBV DNA level		
HBV DNA copies/mL	CC	DC	HCC
<300	3.9%	0.7%	1.3%
300-10^4	4.9%	0.5%	1.3%
10^4-10^5	8.7%	0.3%	3.4%
10^5-10^6	19.5%	1.4%	10.6%
>10^6	25.6%	3.0%	12.6%

TREATMENT EFFECTS

Effects of the two different treatments on the viral load levels (HBV DNA copies/mL).
Estimates derived from literature: Chang et al., 2006 and Lai et al., 2006).
Proportion of patients in each category of viral load at week 48 of treatment:

HBV DNA copies/mL	*HBeAg+*		*HBeAg-*	
	ETV	LAM	ETV	LAM
<300	69.1%	39.8%	93.3%	75.6%
300-10^4	24.7%	18.2%	4.1%	12.5%
10^4-10^5	4.4%	11.7%	1.6%	5.1%
10^5-10^6	0.6%	9.3%	0.3%	2.0%
>10^6	1.2%	21.0%	0.6%	4.8%

ANTIVIRAL RESISTANCE RATES

Used in the long-term treatment analysis only.
Cumulated LAM viral resistance rates.

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6+
LAM	14%	38%	49%	66%	69%	69%

Data source for costs

Costs in Brazilian Reais (BRL), 2005-2006.
Drugs costs: *Sistema Único de Saúde* (SUS) – Brazilian public health system. Year 2006 value
Direct medical costs from a local study: Castelo et al., 2007. Year 2005 values.

Cost items included

Drugs costs.
Direct medical costs associated with health states.

Data source for outcomes

Life Expectancy estimated from 2003 data of the *Instituto Brasileiro de Geografia e Estatística.*
Utility Estimates from a published study by Levy et al., 2007 which used a SG method in a mixed population of CHB patients.

Discounting

3%
(Not specified if both for outcomes and costs)

Costs

DRUGS

Treatment	**daily costs (BRL) per patient**
ETV	12.13
LAM	0.69

HEALTH-STATES

Health-states	**Annual costs (BRL)**
CC	3,597.90
DC	22,022.61
HCC	4,764.95

Outcomes

QALY WEIGHTS

Health State	**Estimate**
CHB	0.66
CC	0.69
DC	0.35
HCC	0.38

Cost-effectiveness

COSTS RESULTS
Total costs – 10 yrs discounted:

	Drugs	**Medical**	**TOTAL (BRL)**
		HBeAg+	
ETV	2,178,574	2,179,846	4,358,420
LAM	119,740	5,402,020	5,521,760
		HBeAg-	
ETV	2,170,946	1,522,534	3,693,480
LAM	124,060	4,049,592	4,173,652

OUTCOMES RESULTS
Total outcomes – 10 yrs discounted:

	% with undetectable viral load	**Patients with undetectable viral load**	**Lost life-years**	**Lost quality life-years**
		HBeAg+		
ETV	69.1	346	-224	-201
LAM	39.8	199	-667	-598
		HBeAg-		
ETV	93.3	467	-142	-127
LAM	75.6	378	-479	-429

ICERs – ETV vs. LAM
In the HBeAg+ CHB patients:
ICER: BRL 7,938 /patient with undetectable viral load;
ICER: BRL 2,626/LYG;
ICER: BRL 2,930/QALY gained.
In the HBeAg- CHB patients:
ICER: BRL 5,420 /patient with undetectable viral load;
ICER: BRL 1,424/LYG;

	ICER: BRL 1,590/QALY gained.
Sensitivity analysis	Sensitivity analysis performed on direct medical costs by health states (10% variation) and on treatment duration (10 years versus one-year in the base-case analysis).
	PROBABILISTIC SENSITIVITY ANALYSES Not performed.
Conclusions	"ETV, in comparison with LAM, was considered a cost-saving drug, promoting lower ICERs for three endpoints assessed." "ETV treatment is cost effective, in addition to having superior efficacy."
Conflict of interests	Costa A.M., 'Italien G., Nita M. E. are employees of Bristol-Myers Squibb Company.

Author	**Lacey L, Chien R-N, Chuang W-L, Pwu R-F. Economic evaluation of chronic hepatitis B treatments in Taiwan. J Gastroenterol Hepatol. 2008;23(4):571-9.[233]**
Country	Taiwan
Study type	CUA
Model	Two Markov state-transition models (one for HBeAg+ and one for HBeAg-). Adapted from Lacey and Gane, 2007.
Perspective	National Health Insurance
Time window	40 years
Interventions / strategies	1) No treatment; 2) Short-duration (4-6 months) therapy with IFN-alpha; 3) One-year treatment with Peg-IFN-alpha; 4) One-year treatment with LAM ; 5) One-year treatment with ADV; 6) Two-year treatment with ADV (+LAM as salvage therapy) or LAM (+ADV as salvage therapy); 7) Five-year treatment with ADV (+LAM as salvage therapy) or LAM (+ADV as salvage therapy).
Population	HBeAg-positive CHB patients and HBeAg-negative CHB patients
Assumptions	CHARACTERISTICS OF BASELINE COHORT Average age: 30-year-old for the HBeAg+ and 40-year-old for the HBeAg-. Male to female ratio: 1 Race: Asian.
	DISEASE PROGRESSION RATES Values from Lacey and Gane, 2007 (see above). Additional Taiwan-specific data derived from literature: Liaw X et al., 1988; Liaw et al., 1989.

	CC	DC	HCC
CHB	2.4% (HBeAg+ only)		
CC		2.3%	2.8%

(CHB: chronic hepatitis B; CC: compensated cirrhosis; DC: decompensated cirrhosis; HCC: hepatocellular carcinoma)

	TREATMENT EFFECT Values from Lacey and Gane, 2007 (see above)
	SEROCONVERSION RATES (HBeAg+ patients only) Values from Lacey and Gane, 2007 (see above). Additional Taiwan-specific data derived from literature: Chien et al., 1999

Intervention	Estimate
No treatment	7.1%
LAM	38.1%

	RESPONSE RATES Values from Lacey and Gane, 2007 (see above).
	RELAPSE RATES Values from Lacey and Gane, 2007 (see above).
	ANTIVIRAL RESISTANCE Values from Lacey and Gane, 2007 (see above). Additional Taiwan-specific data derived from literature: Chang et al, 2004.

HBeAg+	
Intervention	**Estimate**
LAM	17%

Data source for costs	Costs in New Taiwan Dollars (TWD), year 2003, 2004 and 2005 values DRUGS: Acquisition costs for treatment alternatives, year 2005 values. HEALTH-STATES: For CHB and CC: derived from Pwu et al., 2002, year 2003 values. For DC and HCC: derived from Hsieh et al., 2004, year 2004 values
Cost items included	Drug costs. Direct medical costs associated with health states.
Data source for outcomes	From literature: Lacey and Gane, 2007.
Discounting	Costs: 3% Outcomes: 3%

Costs

DRUGS

Treatment	Annual costs (TWD)
LAM	33,488
ADV	68,068
IFN	218,400
Peg-IFN	86,400

HEALTH-STATES

Costs values shown in a figure, but not reported.

Outcomes

QALY WEIGHTS

Similar to those used in Lacey and Gane, 2007 (see above).

Cost-effectiveness

COSTS RESULTS

Incremental total costs in comparison with LAM (1 year) – lifetime (discounted):

Treatment	Costs (TWD)
HBeAg+	
IFN	52,827.15
Peg-IFN (1 year)	170,774.64
ADV (1 year)	31,776.78
LAM (2 years)	22,953.61
ADV (2 years)	85,030.85
LAM + ADV as rescue therapy (2 years)	30,770.91
ADV + LAM as rescue therapy (2 years)	85,030.85
LAM (5 years)	75,156.44
ADV (5 years)	202,784.78
LAM + ADV as rescue therapy (5 years)	111,980.09
ADV + LAM as rescue therapy (5 years)	192,555.75
HBeAg-	
Peg-IFN (1 year)	183,564.72
ADV (1 year)	34,194.26
LAM (2 years)	30,107.81
ADV (2 years)	96,465.23
LAM + ADV as rescue therapy (2 years)	38,052.79
ADV + LAM as rescue therapy (2 years)	96,465.23
LAM (5 years)	116,655.70
ADV (5 years)	269,480.92
LAM + ADV as rescue therapy (5 years)	152,280.04
ADV + LAM as rescue therapy (5 years)	262,764.89

OUTCOMES RESULTS

Incremental total outcomes in comparison with LAM (1 year) – lifetime (discounted):

Treatment	LYG	QALY
HBeAg+		
IFN	-0.066	-0.164
Peg-IFN (1 year)	0.363	0.413
ADV (1 year)	-0.054	-0.006
LAM (2 years)	0.216	0.201
ADV (2 years)	0.182	0.208
LAM + ADV as rescue therapy (2 years)	0.286	0.265
ADV + LAM as rescue therapy (2 years)	0.182	0.208
LAM (5 years)	0.451	0.418
ADV (5 years)	0.611	0.599
LAM + ADV as rescue therapy (5 years)	0.782	0.724
ADV + LAM as rescue therapy (5 years)	0.707	0.697
HBeAg-		
Peg-IFN (1 year)	0.025	-0.075
ADV (1 year)	-0.138	-0.116
LAM (2 years)	0.277	0.255
ADV (2 years)	0.390	0.353
LAM + ADV as rescue therapy (2 years)	0.445	0.398
ADV + LAM as rescue therapy (2 years)	0.390	0.353
LAM (5 years)	0.672	0.625
ADV (5 years)	1.484	1.368
LAM + ADV as rescue therapy (5 years)	1.629	1.466
ADV + LAM as rescue therapy (5 years)	1.697	1.560

ICERs (in comparison with LAM (1 year) – lifetime discounted)

Treatment	ICER	ICUR
HBeAg+		
IFN	Dominated	Dominated
Peg-IFN (1 year)	469,140.37	413,145.80
ADV (1 year)	Dominated	Dominated
LAM (2 years)	106,137.53	114,287.13
ADV (2 years)	466,947.57	408,363.30
LAM + ADV as rescue therapy (2 years)	107,454.15	116,041.32

	ADV + LAM as rescue therapy (2 years)	466,957.57	408,363.30
	LAM (5 years)	166,678.16	179,760.75
	ADV (5 years)	332,017.59	338,510.02
	LAM + ADV as rescue therapy (5 years)	143,235.90	154,733.19
	ADV + LAM as rescue therapy (5 years)	272,248.79	276,235.42
	HBeAg-		
	Peg-IFN (1 year)	7389,104.83	Dominated
	ADV (1 year)	Dominated	Dominated
	LAM (2 years)	108,553.63	117,934.05
	ADV (2 years)	247,237.86	273,481.57
	LAM + ADV as rescue therapy (2 years)	85,588.88	95,556.61
	ADV + LAM as rescue therapy (2 years)	247,237.86	273,481.57
	LAM (5 years)	173,683.46	95,556.61
	ADV (5 years)	181,623.34	273,481.57
	LAM + ADV as rescue therapy (5 years)	93,472.79	186,783.36
	ADV + LAM as rescue therapy (5 years)	154,828.95	197,024.23

Sensitivity analysis	ONE-WAY SENSITIVITY ANALYSES Analyses carried on individual model inputs (not specified) over certain ranges of values obtained from the literature (not reported).
	MULTIVARIATE SENSITIVITY ANALYSES Not specified.
	PROBABILISTIC SENSITIVITY ANALYSES Not performed.
Conclusions	"Antiviral treatment of CHB with LAM or ADV for up to 5 years using the alternative antiviral agent as rescue medication (or as combination therapy) upon emergence of antiviral drug resistance is predicted to substantially improve patient survival, in both HBeAg+ and to a larger extent in HBeAg- CHB in Taiwan".
Conflict of interests	The first author Laurence Lacey was contracted by GSK Taiwan to carry out an economic evaluation of CHB treatments in Taiwan using the models.

Author	**Orlewska E, Zammit D, Yuan Y, Kutikova L, Berak H, Halota W, et al. The cost-effectiveness analysis of entecavir in the treatment of chronic hepatitis B (CHB) patients in Poland. Experimental and Clinical Hepatology. 2008;4(3-4):20-8.[234]**
Country	Poland
Study type	CEA - CUA
Model	Two Markov state-transition models (one for HBeAg+ and HBeAg- patients and one for LAM-refractory patients).
Perspective	Healthcare payer
Time window	10 years
Interventions	1) ETV – 0.5mg/day for 2 years vs. LAM – 100 mg/day for 2 years and ADV in patients LAM-resistant for 10 years; 2) For LAM-refractory patients: ETV – 1mg/day for 10 years vs. ADV – 10 mg/day for 10 years.
Population	Nucleoside-naïve patients (HBeAg+ CHB patients and HBeAg-) and LAM-refractory patients.
Assumptions	CHARACTERISTICS OF BASELINE COHORTS No information given on average age, sex distribution or any other characteristics of the two cohorts

DISEASE PROGRESSION
Disease progression based on the viral load levels (HBV DNA copies/mL). Estimates derived from the REVEAL-HBV study published in the literature: Chen et al., 2006 and Iloeje et al., 2006.

TREATMENT EFFECTS
Effects of the two different treatments on the viral load levels (HBV DNA copies/mL) after 48 weeks of treatment.
Estimated from previously published literature or adapted from it: Chang et al., 2006; Lai et al., 2006; Sherman et al., 2004 and Peters et al., 2004.
Proportion of patients with different viral load at week 48 of treatment:

	HBeAg+ patients		*HBeAg- patients*		*LAM-refractory patient*	
copies/mL	ETV	LAM	ETV	LAM	ETV	ADV
<300	69.1%	39.8%	93.3%	75.6%	20.3%	9.6%
300-10^4	24.7%	18.2%	4.1%	12.5%	20.3%	17.6%
10^4-10^5	4.4%	11.7%	1.6%	5.1%	19.6%	16.9%
10^5-10^6	0.6%	9.3%	0.3%	2.0%	24.8%	20.7%
≥10^6	1.2%	21.0%	0.6%	4.8%	15.0%	35.2%

ANTIVIRAL RESISTANCE RATES
Estimates from the published literature: Guan et al., 2001.
Estimates similar in HBeAg+ and HBeAg- patients.
Cumulative drug viral resistance rates:

	Year 1	Year 2	Year 3	Year 4	Year 5+
LAM	14%	38%	49%	66%	69%
ETV	No resistance assumed				
ADV	No resistance assumed				

RELAPSE RATES
Probability of rebounding to higher levels of HBV DNA post treatment discontinuation: 50% for all

comparators and all patient populations (assumption).

Data source for costs

Costs in Polish Zloty (PLN), year value 2006.
DRUGS: Drug gross wholesale prices.
HEALTH-STATES: From Polish literature (Orlewska et al., 2000).

Cost items included

Drug costs.
Direct medical costs associated with health states.

Data source for outcomes

Utility estimates from a published study by Levy et al., 2008 which used a SG method in British uninfected respondents.

Discounting

Costs: 5%
Outcomes: 5%

Costs

DRUGS

Treatment	Monthly costs (PLN)
LAM – 100mg	334.50
ADV – 10 mg	2288.00
ETV - 0.5mg	2288.00
ETV – 1 mg	2288.00

HEALTH-STATES

Health State	Costs in PLN (range)
CC	2028 (1014 – 3042)
DC	40,381 (20,190 - 60,572)
HCC	41,760 (20,880 - 62,640)

Outcomes

QALY WEIGHTS

Health State	Estimate
CHB	0.82
CC	0.83
DC	0.36
HCC	0.46

Cost-effectiveness

COSTS RESULTS
Total costs – 10 yrs discounted:

Treatment	Costs (PLN)
HBeAg+	
ETV (for men)	647,348
ETV (for women)	655,899
LAM (for men)	1,017,600
LAM (for women)	1,029,600
HBeAg-	
ETV (for men)	1,442,456
ETV (for women)	1,463,452
LAM (for men)	1,627,522
LAM (for women)	1,651,016
LAM-refractory patients	
ETV (for men)	920,100
ETV (for women)	932,740
ADV (for men)	1,344,483
ADV (for women)	1,361,747

OUTCOMES RESULTS
Total outcomes – 10 yrs discounted:

Treatment	LY lost	QALY lost
HBeAg+		
ETV (for men)	-51	-47
ETV (for women)	-55	-50
LAM (for men)	-81	-75
LAM (for women)	-87	-80
HBeAg-		
ETV (for men)	-110	-103
ETV (for women)	-120	-112
LAM (for men)	-124	-116
LAM (for women)	-136	-127
LAM-refractory patients		
ETV (for men)	-59	-55
ETV (for women)	-64	-61
ADV (for men)	-86	-83
ADV (for women)	-94	-90

ICERs – ETV vs. LAM:

Treatment	Costs/ LYG	Costs/ QALY
HBeAg+		
ETV (for men)	Dominant	Dominant
ETV (for women)	Dominant	Dominant
HBeAg-		
ETV (for men)	Dominant	Dominant

	ETV (for women)	Dominant	Dominant
	LAM-refractory patients		
	ETV (for men)	Dominant	Dominant
	ETV (for women)	Dominant	Dominant

Sensitivity analysis	Types of sensitivity analyses not specified. Parameters varied in the analyses: health state utilities for CC, DC and HCC, age at therapy initiation, treatment duration, discount rate and estimated treatment cost per health state. Ranges over which parameters are varied only reported for the costs. The Authors conclude that the results are robust given that the results were insensitive to all variations in the key parameters. No probabilistic sensitivity analysis
Conclusions	"ETV is a dominant treatment option across all patient populations under study".
Conflict of interests	"The study has been founded by unrestricted grand from Bristol-Myers Squibb International Corporation Pharmaceutical Research Institute, Brussels, Belgium"

Author	**Spackman DE, Veenstra DL. A cost-effectiveness analysis of currently approved treatments for HBeAg-positive chronic hepatitis B. PharmacoEconomics. 2008;26(11):937-49.[235]**
Country	United States
Study type	CUA
Model	Markov state-transition model
Perspective	Healthcare payer
Time window	Lifetime
Interventions	Up to 4 years: 1) ADV with ETV as salvage therapy; 2) ETV with ADV added in the salvage therapy; 3) LAM with ADV added in the salvage therapy; 4) TLB with ADV added in the salvage therapy; 5) Peg-IFN with ETV as second-line treatment for those not seroconverting after 2 years.
Population	HBeAg+ CHB patients.
Assumptions	CHARACTERISTICS OF BASELINE COHORT Average age: 35 year-old.

SEROCONVERSION RATES

Patients who achieve HBeAg seroconversion because of treatment have the same course of disease as patients who spontaneously seroconvert.

Partial responders continue to receive therapy up to year 4;

Estimates from published clinical trials: Marcellin et al., 2003; Chang et al., 2006; Lau et al., 2005 ; Perillo et al., 2004.

	Estimates (range)			
Intervention	**Year 1**	**Year 2**	**Year 3**	**Year 4**
ADV	12% (10-14)	13% (10-16)		
ETV	21% (19-23)	13% (10-16)		
LAM	18% (15-21)	13% (10-16)		
Peg-IFN	25% (23-27)	14% (12-16)	13% (8-18)	
TLB	19% (17-21)	13% (10-16)		
Salvage therapy				

DURABILITY OF SEROCONVERSION

The authors assume the use of a six-month consolidation therapy (i.e. continuation of treatment beyond the point at which seroconversion is achieved) to assume 80% of durable seroconversion.

Probabilities from published literature: Marcellin et al., 2003; Chang et al., 2006 ; Lai et al., 2007 and Lau et al., 2005.

	Estimates (range)			
Intervention	**Year 1**	**Year 2**	**Year 3**	**Year 4**
ADV	80% (76.7-82-3)			
ETV	80% (76.7-82-3)			
LAM	80% (76.7-82-3)			
Peg-IFN	82% (79-85)		80% (76.7-82-3)	
TLB	80% (76.7-82-3)			
Salvage therapy	70% (67-73)			

TREATMENT EFFECTS (on the relative risk or cirrhosis)

The relative risk of cirrhosis is compared with baseline of 4.4% (2.2-8.8) for patients who have not achieved seroconversion, resulting from suppression of HBV DNA.

Patient who did not seroconvert but achieved complete viral suppression have a reduced risk or cirrhosis, but in the first year of treatment only.

Probabilities derived from published literature: Marcellin et al., 2006; Iloeje et al.,2006 ; Chang et al., 2006; Lau et al., 2005; Lai et al., 2007.

	Estimates (range)			
Intervention	**Year 1**	**Year 2**	**Year 3**	**Year 4**
ADV	0.77% (0.67-0.87)			
ETV	0.13% (0.07-0.23)			
LAM	0.51% (0.41-0.61)			

	Peg-IFN	0.95% (0.85-1.00)	0.57% (0.13-1.00)	
	TLB	0.17% (0.07-0.27)		

RESISTANCE RATES
Patients who develop virologic breakthrough due to resistance have ADV or ETV added to their treatment. Probabilities derived from published literature: Qi et al., 2004 ; Tenney et al., 2008 ; Lai et al., 2007; Han et al., 2007 ; and Lau et al., 2005.

	Estimates (range)			
Intervention	**Year 1**	**Year 2**	**Year 3**	**Year 4**
ADV	0% (0-1)	2% (0-3)		
ETV	0.5% (0-1)			
LAM	11% (9-13)	27% (25-29)		
Peg-IFN	0%		0.5% (0-1)	
TLB	5% (3-7)	17.5% (15.5-19.5)		

RELAPSE RATES
Patients who relapse once treatment was discontinued have the same disease progression rates as the untreated patients (assumption).

Data source for costs
Costs in United States dollars (USD), year 2008 values.
DRUGS: AnalySource – 03/03/08.
HEALTH-STATES: From published literature (Lee et al., 2004 ; Crowley et al., 2002; Kanwal et al.,2005 ; Salomon et al., 2003).

Cost items included
Drug costs.
Direct medical costs associated with health states.

Data source for outcomes
Utility Estimates from published literature by Levy et al., 2008 and Wong et al., 1995. Weights obtained with a SG method from US uninfected respondents.

Discounting
Cost: 3%
Outcome: 3%

Costs
DRUGS

Intervention	**Annual costs in USD (range)**
ADV	7,832
ETV	8,297
LAM	3,445
Peg-IFN	20,222
TLB	6,848

HEALTH-STATES

Health State	**Annual costs in USD (range)**
CHB	1,019 (823-1,372)
HBeAg seroconversion	430 (323-538)
HBsAg loss	59 (44-74)
flare	15,341 (11,506-19,176)
resistance	1,019 (764-1,274)
CC	1,148 (861-1,435)
NRC	1,019 (764-1,274)
DC	15,341 (11,506-19,176)
HCC	10,085 (7,564-12,606)
LT	124,750 (86,873-144,789)
Post-LT	18,110 (12,611-21,019)

Outcomes
QALY WEIGHTS

Health State	**Estimate (range)**
CHB	0.81 (0.76-0.86)
HBeAg seroconversion	0.99 (0.94-1.00)
HBsAg loss	0.99 (0.94-1.00)
flare	0.77 (0.72-0.82)
resistance	0.81 (0.76-0.86)
CC	0.82 (0.77-0.87)
NRC	0.81 (0.76-0.86)
DC	0.36 (0.31-0.41)
HCC	0.41 (0.36-0.46)
LT	0.66 (0.61-0.71)
Post-LT	0.76 (0.71-0.81)

Cost-effectiveness
COSTS RESULTS
Total costs – lifetime discounted:

Intervention	**Annual costs in USD (range)**
No treatment	28,017 (21,950-36,584)
ADV	51,914 (46,805-53,595)
ETV	46,176 (41,086-53,595)
LAM	53,618 (48,714-60,486)
Peg-IFN	53,482 (48,749-60,388)
TLB	50,264 (45,343-57,301)

OUTCOMES RESULTS
Total outcomes – lifetime discounted:

Intervention	**QALYs (range)**

	No treatment	17.88 (16.48-19.28)
	ADV	18.25 (17.03-19.51)
	ETV	18.38 (17.14-19.59)
	LAM	18.55 (17.39-19.71)
	Peg-IFN	18.64 (17.56-19.83)
	TLB	18.70 (17.50-19.86)

ICERs
Each option is compared with the next most effective alternative: ADV < LAM; TLB < Peg-IFN; Peg-IFN < ETV; LAM extendedly < ETV.
ICER of ETV compared with No treatment: USD 27,184/QALY.

Sensitivity analysis

One-WAY SENSITIVITY ANALYSES
Varied parameters: Seroconversion rates, seroconversion durability, relative risks of cirrhosis, resistance rates, drugs costs, health state costs, health state utilities, disease progression probabilities.
Results sensitive to: seroconversion rates for patients treated with ETV in years 2-4; the year 3-4 seroconversion rates for patients initially treated with Peg-IFN but subsequently treated with ETV; Relative risk of cirrhosis associated with ETV treatment after having been treated with Peg-IFN.

SCENARIO ANALYSES
Viral suppression decreases the risk of cirrhosis for all years of treatment (rather than just the first year) → ICER: USD 16,711/QALY.
Seroconversion rate varied from 7 to 13% → ICER varied from USD 18,222 to USD 41,153.

PROBABILISTIC SENSITIVITY ANALYSES (using second order Monte Carlo simulation)
CE ratio< USD 27,000/QALY → No treatment.
> USD 27,000 → ETV followed by Peg-IFN have the highest probability of being optimal.
At USD 50,0000/QALY → ETV has the greatest health benefit in 57% of the simulations.

Conclusions

"Initiation of treatment for HBeAg+ CHB with ETV or Peg-IFN provides improved long-term clinical outcomes compared with ADV, LAM or TLB. ETV appears to offer to greatest value for money as a result of moderate seroconversion rates, high viral suppression and low resistance".

Conflict of interests

The study was supported by an unrestricted grant from Bristol-Myers Squibb to the University of Washington. The authors are full control of study design, data analysis and interpretation, and preparation of the manuscript.

Author

Veenstra DL, Sullivan SD, Lai M-Y, Lee C-M, Tsai C-M, Patel KK. HBeAg-negative chronic hepatitis B: cost-effectiveness of peginterferon alpha-2a compared to lamivudine in Taiwan. Value Health. 2008;11(2):131-8.[237]

Country

Taiwan

Study type

CEA - CUA

Model

Markov state-transition model

Perspective

Taiwan Bureau of National Health Insurance

Time window

Lifetime

Interventions

1) 48 weeks treatment with Peg-IFN – 180microg/day;
2) 48 weeks treatment with LAM – 100mg/day.

Population

HBeAg-ve CHB patients

Assumptions

CHARACTERISTICS OF BASELINE COHORT
Average age: 40 year-old
Race: Asian (Taiwanese)

DISEASE PROGRESSION RATES
Probabilities derived from literature: Lin et al., 2001; Liaw et al., 1986; Liaw et al., 1988; Kao et al., 2003; Lau et al., 1997; Chen et al., 2003; Rizzetto et al., 2002; Crowley et al., 2000 ; Wong et al., 1995; Pwu et al., 2002; Kanwal et al., 2005.

	SR	CC	DC	HCC	LT	Post-LT	Death
CR	6% (3-10)	1.3% (1-2)					
CHB	1.6% (1-3)	9% (6-12)		0.83% (0.5-2)			
CC			5% (2.3-5.6)	7.1% (2.8-7.1)			5.1% (3.4-5.1)
DC				2.5% (2-8)	1.4% (0.05-3.1)		39%(23.5-40)
HCC					0.08% (0.02-0.08)		37.2%(37-56)
LT						85% (79-90)	15%(10-21)
Post-LT							1.5% (1.0-5.7)

(SR: spontaneous response; CR: combined response; CHB: chronic hepatitis B; CC: compensated cirrhosis; DC: decompensated cirrhosis; HCC: hepatocellular carcinoma; LT: liver transplant)

RESPONSE RATES
Response rates is defined as the combination of HBV DNA suppression to < 20 000copies/mL and ALT normalization:

Treatment	Estimate
Peg-IFN - By the end of treatment (week 48)	36%

	- By the end of follow-up (week 72): 36% LAM - By the end of treatment (week 48): 69% - By the end of follow-up (week 72): 23%
Data source for costs	Costs in New Taiwan Dollars (TWD), year value not mentioned (seem to be 2004) DRUGS: from Taiwan Bureau of National Health Insurance (Fee schedule for Medical Service and Reference list for Drugs) HEALTH-STATES: From the Taiwan Bureau of National Health Insurance (Fee schedule for Medical Service and Reference list for Drugs), from Chang Gung Memorial Hospital website and from published literature (Wang et al., 2004)
Cost items included	Drug costs. Direct medical costs associated with health states.
Data source for outcomes	Utilities estimates from published literature (Pwu et al., 2002, Bennett et al., 1997 and Wong et al., 1995). Weights were obtained from a panel of physicians (CHB, CC, DC and HCC) or from weights derived for CHC patients (LT and Post-LT).
Discounting	Cost: 3% Outcome: 3%
Costs	DRUGS Not reported.
	HEALTH-STATES

Health State	Costs in TWD (range)
CHB	11,806 (8,855-14,758)
CC	20,821 (15,616-26,026)
DC	44,431 (33,323-55,539)
HCC	96,510 (72,383-130,638)
LT	1,720,632 (1,290,474-2,150,790)
Post-LT	508,901 (381,676-636,126)

Outcomes	QALY WEIGHTS

Health State	Estimate (range)
Seroconversion	1 (0.98-1)
CHB	0.95 (0.90-0.95)
CC	0.90 (0.80-0.92)
DC	0.54 (0.50-0.65)
HCC	0.50 (0.30-0.50)
LT	0.50 (0.50-0.60)
Post-LT	0.70 (0.60-0.80)

Cost-effectiveness	COSTS RESULTS Total and incremental costs – lifetime discounted:

Treatment	Costs (TWD)
Peg-IFN	389,375
LAM	232,992
Incremental cost	156,992

OUTCOMES RESULTS
Total and incremental outcomes – lifetime discounted:

Treatment	LYG	QALY
Peg-IFN	11.45	10.57
LAM	11.07	10.12
Incremental outcome	0.38	0.45

ICERs Peg-IFN vs. LAM:
413,770 TWD/LY
346,868 TWD/QALY (equivalent to 10,900 USD/QALY)

Sensitivity analysis	ONE-WAY SENSITIVITY ANALYSES All parameters varied Results most sensitive to: relapse rate for Peg-IFN-alpha-2a treatment, spontaneous relapse rate, probability of developing CC from CHB and the relapse rate for LAM
	PROBABILISTIC SENSITIVITY ANALYSES The 95% central range from the probabilistic sensitivity analysis for the discounted ICUR is 228,000-556,00 NTD
Conclusions	"Peg-IFN-alpha-2a therapy versus LAM treatment for HBeAg-ve CHB in Taiwan provides incremental benefits in life expectancy and quality of life at an increased total cost that is within the range of commonly reimbursement medical interventions".
Remarks	Drug resistance rates were not included in the model
Conflict of interests	"Source of financial support: Hoffman-La Roche"

Author	**Veenstra DL, Spackman DE, Bisceglie A, Kowdley KV, Gish RG. Evaluating anti-viral drug selection and treatment duration in HBeAg-negative chronic hepatitis B: A cost-effectiveness analysis. Alimentary Pharmacology & Therapeutics. 2008;27(12):1240-52.[236]**
Country	United States
Study type	CUA

Model: Markov state-transition model. Adapted from Veenstra et al., 2007.

Perspective: Health care payer

Time window: Lifetime

Interventions:
1) Five-year ETV treatment
versus five-year LAM treatment or five-year ADV treatment;
2) Ten-year ETV treatment
versus ten-year LAM treatment or ten-year ADV treatment;
3) Lifetime ETV treatment
versus lifetime LAM treatment or lifetime ADV treatment
4) Five-year on - 1 off ETV treatment
versus five-year on - 1 off LAM treatment or five-year on - 1 off ADV treatment

Population: HBeAg- CHB patients

Assumptions:

CHARACTERISTICS OF BASELINE COHORT
Average age: 44-year old

DISEASE PROGRESSION RATES
Probabilities derived from literature: Iloeje et al., 2006; Chen et al. 2006; Hsu et al., 2002 ; Kim et al., 2005 ; Fattovich et al., 2002 ; Kim et al., 2004; Fattovich et al., 1997 and Bolondi et al., 2001.

	CHB	CC	DC	HCC	LT	Death
CHB		2.9% (1.5-5.8)		0.80% (0.4-1.2)		
CR	70.0% (70.0-90.0)					
CC			3.1% (1.6-6.2)	2.2% (1.1-4.4)		5.1%(3.4-5.1)
NRC		2.9% (1.5-5.8)	0.8% (0.4-1.6)	2.2% (1.1-4.4)		
DC				2.2% (1.1-4.4)	2.6 % (1.3-5.2)	22.0%(11.0-44.0)
HCC						23.3%(11.6-44.6)
LT						13.0%(6.5-26.0)
Post-LT						2.5%(1.3-5)

(CHB: Chronic hepatitis B**;** R: response; CC: compensated cirrhosis; NRC: non-replicating cirrhosis, DC: decompensated cirrhosis; HCC: hepatocellular carcinoma; LT: Liver transplant)

RESPONSE RATES
Response rates are defined by HBV DNA negativity by PCR assay.
Probabilities derived from literature: Lai et al., 2006; Hadziyannis et al., 2003; Hadziyannis et al., 2005 and Hadziyannis et al., 2006.
Treatment-related responses (From CHB):

Treatment	Estimate (range)
ETV - year 1	91.0% (86.0-96.0)
ETV - years 2-5	42.0% (37.0-47.0)
LAM - year 1	73.0% (68.0-78.0)
LAM - years 2-5	29.0% (24.0-34.0)
ADV -year 1	51.0% (46.0-710)
ADV - years 2-5	15.0% (10.0-20.0)

DRUG RESISTANCE RATES
Probabilities derived from literature: Lai et al., 2006; Hadziyannis et al., 2003; Hadziyannis et al., 2005; Hadziyannis et al., 2006; Colonno et al., 2006; Colonno et al., 2006 ; Di Marco et al., 2004 and Lok et al., 2003.
Treatment-related resistance (from CHB) :

Treatment	Estimate
ETV - year 1	0.0% (0.0-1.0)
ETV - years 2-5	1.0% (0.0 – 2.0)
LAM - year 1	6.0% (3.0-12.0)
LAM - years 2-5	25.0% (20.0-30.0)
ADV - year 1	0.0% (0.0-1.0)
ADV - years 2-5	5.0% (2.5-7.5)

Patients who developed virologic breakthrough because of resistance received ADV or ETV added to their treatment (the probability for drug resistants to achieve response is assumed 60.0% (50.0-70.0)).

RELAPSE RATES
Probabilities derived from literature: Lai et al., 2006; Hsu et al., 2002 ; Hadziyannis et al., 2006 ; Hadziyannis et al., 2006 and Kim et al., 2005.
Relapse rate assumed at 70% (70.0-90.0) in the year after treatment cessation (assumption).

	CHB (off treatment)	HBsAg loss	NRC	HCC
Response	70.0% (70.0-90.0)	1.0% (0.5-2.0)	0.1% (0.1-0.2)	0.3% (0.15-0.6)

Data source for costs: Costs in United States Dollars (USD), year 2006 value for health states-related costs and 2007 for drugs costs.
DRUGS: From AnalySource, wholesale acquisition costs, April 2007.
HEALTH-STATES: From the published literature (Lee et al., 2004; Kanwal et al., 2005; Crowley et al., 2002; Salomon et al., 2003)

Cost items included

Drug costs.
Direct medical costs associated with health states.

Data source for outcomes

Utilities estimates from published literature (Wong et al., 1995; Levy et al., 2008). Estimates from the US general population using SG utility.

Discounting

Cost: 3%
Outcome: 3%

Costs

DRUGS

Treatment	Annual costs in USD (range)
ETV	7,490 (7,116-7,865)
LAM	2,778 (2,639-2,917)
ADV	6,975 (6,626-7,324)

HEALTH-STATES

Health State	Annual costs in USD (range)
CHB	1,019 (764-1,274)
HBeAg seroconversion	430 (323-538)
HBsAg loss	59 (44-74)
flare	15,341 (11,506-19,176)
resistance	1,019 (764-1,274)
CC	1,148 (861-1,435)
NRC	1,019 (764-1,274)
DC	15,341 (11,506-19,176)
HCC	10,085 (7,564-12,606)
LT	115,831 (86,873-144,789)
Post-LT	16,815 (12,611-21,019)

Outcomes

QALY WEIGHTS

Health State	Estimate (range)
CHB	0.81 (0.76-0.86)
HBeAg seroconversion	0.99 (0.94-1.00)
HBsAg loss	0.99 (0.94-1.00)
flare	0.77 (0.72-0.82)
resistance	0.81 (0.76-0.86)
CC	0.82 (0.77-0.87)
NRC	0.81 (0.76-0.86)
DC	0.36 (0.31-0.41)
HCC	0.41 (0.36-0.46)
LT	0.66 (0.61-0.71)
Post-LT	0.76 (0.71-0.81)

Cost-effectiveness

COSTS RESULTS
Total costs – lifetime discounted:

Treatment	Costs (USD)
LAM – 5 years	47,346
ETV – 5 years	57,758
ADV – 5 years	60,058
LAM – 10 years	72,673
ETV – 10 years	81,891
ETV – 5 on -1 off	81,891
ADV – 10 years	86,936
LAM – 5 on -1 off	117,186
ADV – 5 on -1 off	140,615
LAM – lifetime	152,127
ETV – lifetime	155,351
ADV – lifetime	181,702

OUTCOMES RESULTS
Total outcomes – lifetime discounted:

Treatment	QALY
ADV – 5 years	15.85
LAM – 5 years	16.07
ADV – 10 years	16.69
ETV – 5 years	16.71
LAM – 10 years	16.99
ETV – 10 years	17.59
ADV – 5 on -1 off	18.00
ADV – lifetime	18.42
LAM – 5 on -1 off	18.49
LAM – lifetime	18.83
ETV – 5 on -1 off	19.21
ETV – lifetime	19.46

	ICERs Each option is compared with the next most effective alternative: **Treatment** / **ICER** ADV – 5 years: Dominated LAM – 5 years: - ADV – 10 years: Dominated ETV – 5 years: 16,272 LAM – 10 years: Dominated ETV – 10 years: Dominated ADV – 5 on -1 off: Dominated ADV – lifetime: Dominated LAM – 5 on -1 off: Dominated LAM – lifetime: Dominated ETV – 5 on -1 off: 24,080 ETV – lifetime: 148,199
Sensitivity analysis	ONE-WAY SENSITIVITY ANALYSES All parameters were varied. Results most sensitive to: resistance rates, baseline cirrhosis risk, ETV drug cost, response to salvage treatment, and the quality of life upon achieving treatment response.
	PROBABILISTIC SENSITIVITY ANALYSES (with second-order Monte Carlo simulation) The ETV 5 on – 1 off strategy has the greatest expected net health benefit from a threshold ratio of USD 1,000 up to USD 150,000 per QALY.
Conclusions	"Longer-term anti-viral therapy in HBeAg- CHB is cost-effective compared to shorter-term therapy, ETV is cost-effective in comparison to ADV or LAM; and a strategy of stopping therapy after several years of treatment to identify durable responders may be an optimal treatment strategy".
Remarks	Drug resistance rates were not included in the model
Conflict of interests	"The study was funded in full by an unrestricted grand to the University of Washington from Bristol-Myers Squibb".

Author	**Buti M, Brosa M, Casado MA, Rueda M, Esteban R. Modeling the cost-effectiveness of different oral antiviral therapies in patients with chronic hepatitis B. J Hepatol.2009;51(4):640-6.** [230]
Country	Spain
Study type	CEA - CUA
Model	Two Markov state-transition models (one for HBeAg+ and one for HBeAg-).
Perspective	National Health System
Time window	Lifetime
Interventions	*First-line strategies*: 1) No treatment 2) LAM – 100mg/day 3) ADV – 10mg/day 4) ETV – 0.5mg/day 5) TLB – 600mg/day 6) TNF – 300mg/day Treatment durations: HBeAg+: treatment stops 6 months after HBeAg seroconversion. HBeAg- : lifelong treatment *Second-line strategies* (for non-responders or for patients with HBV drug resistance): 7) Salvage therapy 1: Combination of ADV+LAM 8) Salvage therapy 2: Combination of TNF+ETV
Population	HBeAg- and HBeAg+ CHB patients
Assumptions	CHARACTERISTIS OF THE BASELINE COHORT Average age: 40-year old.
	RESPONSE RATES Response rates is defined by HBV DNA <300-400 copies/mL at year 1. Probabilities were obtained from published literature: Liaw et al., 1986; Chen et al., 2006; Perrillo et al.,2006; Mommeja-Marin et al., 2003; Lok et al., 2005; Lok et al., 2007 and Lipscomb et al., 1996.

Treatment	**Estimate**
HBeAg+	
TNF	74%
LAM	39%
ADF	21%
ETV	67%
TLB	60%
Salvage therapy 1 (ADV+LAM)	35%
Salvage therapy 2 (TNF+ETV)	60-85%
HBeAg-	
TNF	91%
LAM	72%
ADF	51%
ETV	90%

	TLB: 88% Salvage therapy 1 (ADV+LAM): 61% Salvage therapy 2 (TNF+ETV): 70-95%
	RESISTANCE RATES Similar in HBeAg+ and HBeAg- CHB patients

Intervention	Estimate: year1 – year>5
TNF	0.0%-1.2%
LAM	24.0%-70.0%
ADF	0.0%-29.0%
ETV	0.2%-1.2%
TLB	4.0%-22.0%
Salvage therapy 1 (ADV+LAM)	0.0%-0.0%
Salvage therapy 2 (TNF+ETV)	0.0%-0.0%

Data source for costs	Costs in Euros (EUR), year 2008 values DRUGS: From the Medicine database of the General Council of Pharmacists Official College. HEALTH-STATES: From the published literature (Idris et al., 2008)
Cost items included	Drug costs. Direct medical costs associated with health states.
Data source for outcomes	Utilities estimates from non-published literature = abstract (Herdman et al., 2006). Weights obtained in the Spanish population but method not mentioned.
Discounting	Cost: 3% Outcome: 3%
Costs	DRUGS

Treatment	Annual costs (EUR)
TNF	3474.80
LAM	678.90
ADF	4894.65
ETV	4745.00
TLB	4745.00
Salvage therapy 1 (ADV+LAM)	5573.65
Salvage therapy 2 (TNF+ETV)	8219.80

HEALTH-STATES

Health State	Costs in year 1 (EUR)	Costs in years > 1 (EUR)
CHB	1271.15	1157.89
CC	1512.29	1254.50
DC	3016.83	1512.29
HCC	6476.24	6771.20
LT	133039.40	41602.36
Death	6764.38	-

Outcomes	QALY WEIGHTS Not reported.
Cost-effectiveness	COSTS RESULTS Total costs – lifetime discounted:

HBeAg+		*HBeAg-*	
Treatment	**Costs (EUR)**	**Treatment**	**Costs (EUR)**
No treatment	83,406	No treatment	90,866
Base case			
LAM	87,134	LAM	95,547
TNF	87,615	ADV	103,916
ETV	90,273	TNF	105,889
TLB	90,721	TLB	111,097
ADV	91,199	ETV	114,968
Salvage 1			
TNF	95,806	LAM	97,525
LAM	96,132	ADV	105,917
ETV	98,699	TNF	107,285
TLB	99,413	TLB	112,738
ADV	100,180	ETV	116,479
Salvage 2			
TNF	112,585	LAM	120,874
LAM	114,717	TNF	123,446
ETV	116,005	ADV	129,558
TLB	117,313	TLB	131,919
ADV	118,725	ETV	133,246

OUTCOMES RESULTS
Total outcomes – lifetime discounted:

HBeAg+			*HBeAg-*		
Treatment	**LY**	**QALY**	**Treatment**	**LY**	**QALY**
No treatment	16.70	13.69	No treatment	15.69	12.48
Base case					

	LAM	17.65	14.67	ADV	17.36	14.21
	ADV	17.67	14.68	LAM	17.44	14.30
	TLB	17.94	14.96	TLB	18.53	15.47
	ETV	18.18	15.21	ETV	19.13	16.11
	TNF	18.39	15.43	TNF	19.28	16.28
	Salvage 1					
	LAM	17.94	14.96	ADV	17.60	14.46
	ADV	17.96	14.98	LAM	17.67	14.54
	TLB	18.21	15.24	TLB	18.72	15.66
	TNF	18.64	15.69	ETV	19.29	16.28
	ETV	19.34	16.42	TNF	19.44	16.45
	Salvage 2					
	LAM	18.92	15.99	ADV	20.05	17.16
	ADV	18.94	16.00	LAM	20.09	17.78
	ETV	19.34	16.42	TLB	20.60	17.20
	TLB	19.15	16.23	ETV	20.88	18.10
	TNF	19.50	16.60	TNF	20.95	18.17

ICERs

Incremental cost per incremental LY saved and incremental QALY saved in reference with the most efficacious treatment (TNF). *(Note that Buti didn't consider cases of extended dominance when computing ICERs)*

HBeAg+			*HBeAg-*		
Treatment	**ICER**	**ICUR**	**Treatment**	**ICER**	**ICUR**
Base Case					
TNF	-	-	TNF	-	-
LAM	654	632	LAM	5,621	5,212
ADV	Dominated	Dominated	ADV	1,028	954
ETV	Dominated	Dominated	ETV	Dominated	Dominated
TLB	Dominated	Dominated	TLB	Dominated	Dominated
No treatment	2,494	2,426	No treatment	4,179	3,949
Salvage 1					
TNF	-	-	TNF	-	-
LAM	Dominated	Dominated	LAM	5,534	5,112
ADV	Dominated	Dominated	ADV	744	688
ETV	Dominated	Dominated	ETV	Dominated	Dominated
TLB	Dominated	Dominated	TLB	Dominated	Dominated
No treatment	6,385	6,204	No treatment	4,383	4,136
Salvage 2					
TNF	-	-	TNF	-	-
LAM	Dominated	Dominated	LAM	3,007	2,647
ADV	Dominated	Dominated	ADV	Dominated	Dominated
ETV	Dominated	Dominated	ETV	Dominated	Dominated
TLB	Dominated	Dominated	TLB	Dominated	Dominated
No treatment	10,432	10,052	No treatment	6,198	5,718

Sensitivity analysis	PROBABILISTIC SENSITIVITY ANALYSES (with second-order Monte Carlo simulation) The PSA showed that TNF is a cost effective option in comparison over ADV, ETV and TLB in 100% of the cases, and LAM and no treatment in 56% and 14% respectively (HBeAg+ patients). The PSA showed that TNF is a cost effective option in comparison over ADV, ETV and TLB in 100% of the cases, and LAM and no treatment in 56% and 14% respectively (HBeAg- patients).
Conclusions	"TNF is a cost-effective strategy for the first-line treatment of patients with CHB compared with oral antiviral therapies".
Conflict of interests	One of the authors is an employee at Gilead Sciences Inc.

7 REFERENCES

1. Yuen M-F, Sablon E, Hui C-K, Li T-M, Yuan H-J, Wong DK-H, et al. Prognostic factors in severe exacerbation of chronic hepatitis B. Clin Infect Dis. 2003;36(8):979-84.
2. Liaw Y, Chun C. Hepatitis B virus infection. Lancet. 2009;373:582-92 (c).
3. Mahoney FJ, Kane M. Hepatitis B vaccine. In: Plotkin SA, Orenstein WA, editors. Vaccines: W.B. Saunders & Co; 2004. p. 707-43.
4. Van Damme P, Vorsters A. Hepatitis B control in Europe by universal vaccination programmes: the situation in 2001. J Med Virol. 2002;67(3):433-9.
5. Sorrell MF, Belongia EA, Costa J, Gareen IF, Grem JL, Inadomi JM, et al. National Institutes of Health Consensus Development Conference Statement: management of hepatitis B. Ann Intern Med. 2009;150(2):104-10.
6. Liaw YF, Leung N, Guan R, Lau GK, Merican I, McCaughan G, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2005 update. Liver Int. 2005;25(3):472-89.
7. Yuen M, Yuan H, Wong D. Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications. Gut. 2005;54:1610-14.
8. Realdi G, Fattovich G, Hadziyannis S. Survival and prognostic factors in 366 patients with compensated cirrhosis type B: a multicenter study. J Hepatol. 1994;21:656-66.
9. Marcellin P, Pequinot F, Delarocque-Astagneau E. Mortality related to chronic hepatitis B and chronic hepatitis C in France: evidence for the role of HIV coinfection and alcohol consumption. J Hepatol. 2008;48:200-7.
10. Toy M, Veldhuijzen I, de Man R. Potential impact of long-term nucleoside therapy on the mortality and morbidity of active chronic hepatitis B. Hepatology. 2009;May 6.
11. Deltenre P, Laleman W, Van Gossum M, Vos B, Colle I, Adler M, et al. Hepatitis B virus infection in Belgium: preliminary results of the Belgian Association of the Study of the Liver (BASL) registry of HBsAg chronic carriers. . AASLD Meeting 30 Oct – 3 Nov 2009 Boston. Hepatology 2009; 50: suppl Abstract 493 (poster presentation). 2009.
12. Alter M. Epidemiology of hepatitis B in Europe and worldwide. J Hepatol. 2003;39:64-9.
13. Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. Hepatology. 2007;45(4):1056-75.
14. Hui C-K, Leung N, Yuen S-T, Zhang H-Y, Leung K-W, Lu L, et al. Natural history and disease progression in Chinese chronic hepatitis B patients in immune-tolerant phase. Hepatology. 2007;46(2):395-401.
15. Zarski JP, Marcellin P, Leroy V, Trepo C, Samuel D, Ganne-Carrie N, et al. Characteristics of patients with chronic hepatitis B in France: predominant frequency of HBe antigen negative cases. J Hepatol. 2006;45(3):355-60.
16. Cotler S, Dhamija M, Siqueira F. Hepatitis B seroprevalence and disease characteristics in an urban Chinatown community. Clin Gastroenterol Hepatol. 2009;7:776-80.
17. Yim HJ, Hussain M, Liu Y, Wong SN, Fung SK, Lok AS. Evolution of multi-drug resistant hepatitis B virus during sequential therapy. Hepatology. 2006;44(3):703-12.
18. Marx G, Martin S, Chicoine J, Alvarez F. Long-term follow-up of chronic hepatitis B virus infection in children of differen ethnic origins. J Infect Dis. 2002;186:295-301.
19. Fattovich G, Olivari N, Pasino M. Long-term outcome of chronic hepatitis B in Caucasian patients: mortality after 25 years. Gut. 2008;57:84-90.
20. Elgouhari H, Abu-Rjab Tamimi T, Carey W. Hepatitis B virus infection: understanding its epidemiology, course, and diagnosis. Cleve Clin J Med. 2008;75:881-9.
21. Liaw Y. Antiviral therapy of chronic hepatitis B: opportunities and challenges in Asia. J Hepatol. 2009;51:403-10 (a).
22. Liaw Y. Natural history of chronic hepatitis B virus infection and long-term outcome under treatment. Liver Int. 2009;29(suppl 1):100-7 (b).
23. Kim S, Han K, Nam C. Natural history of hepatitis B virus-related cirrhotic patients hospitalized to control ascites. J Gastroenterol Hepatol. 2008;23:1722-7.

24. Lok A, Lai C, Wu P, Leung E, Lam T. Spontaneous hepatitis B e antigen to antibody seroconversion and reversion in Chinese patients with chronic hepatitis B virus infection. Gastroenterology. 1987;92:1839-43.
25. Chu C, Liaw Y. Chronic hepatitis B virus infection acquired in childhood: special emphasis on prognostic and therapeutic implications of delayed HBeAg seroconversion. J Viral Hepat. 2007;14:147-52.
26. Chu C, Hung S, Lin J. Natural history of hepatitis B e antigen to antibody seroconversion in patients with normal aminotransferase levels. Am J Med. 2004;116:829-34.
27. Hsu Y, Chien R, Yeh C. Long-term outcome after spontaneous HBeAg serconversion in patients with chronic hepatitis B. Hepatology. 2002;35:1522-27.
28. Liaw YF, Tai DI, Chu CM, Chen TJ. The development of cirrhosis in patients with chronic type B hepatitis: a prospective study. Hepatology. 1988;8(3):493-6.
29. Huo T, Wu J, Hwang S. Factors predictive of liver cirrhosis in patients with chronic hepatitis B: a multivariate analysis in a longitudinal study. Eur J Gastroenterol Hepatol. 2000;12:687-93.
30. Lin S, Yu M, Lee C. Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma. J Hepatol. 2007;46:45-52.
31. Jang J, Lee Y, Kim M. A 13-year longitudinal study of the impact of double mutations in the core promoter region of hepatitis B virus on HBeAg serovconversion and disease progression in patients with genotype C active hepatitios. J Viral Hepat. 2007;14:169-75.
32. Moreno-Otero R, Garcia-Monzon C, Gercia-Sanchez A. Development of cirrhosis after chronic type B hepatitis: a clinicopathologic and follow-up study of 46 HBeAg-positive asymptomatic patients. Am J Gastroenterol. 1991;86:560-64.
33. Mazzella G, Saracco G, Festi D. Long-term results with interferon therapy in chronic type B hepatitis: a prospective randomized trial. Am J Gastroenterol. 1999;94:2246-50.
34. Xu B, Hu D, Rosenberg D. Chronic hepatitis B: a long-term retrospective cohort study of disease progression in Shangai, China. J Gastroenterol Hepatol. 2003;18:1345-52.
35. Chan H, Hui A, Wong M. Genotype C hepatitis B virus infection is associated with an increased risk of hepatocellular carcinoma. Gut. 2004;53:1494-8.
36. Park B, Park Y, Ahn S. Long-term outcome of chronic hepatitis B based on histological grade and stage. J Gastroenterol Hepatol. 2007;22:383-8.
37. Takano S, Yokosuka O, Imazeki F. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. Hepatology. 1995;21:650-5.
38. Ikeda K, Saitoh S, Suzuki Y. Disease progression and hepatocellular carcinogenesis in patients with chronic viral hepatitis: a prospective observation in 2215 patients. J Hepatol. 1998;28:930-8.
39. Brunetto M, Oliveri F, Coco B. Outcome of anti-HBe positive chronic hepatitis B in alpha-interferon treated and untreated patients: a long term cohort study. J Hepatol. 2002;36:263-70.
40. Fattovich G, Brollo L, Giustina G, al. e. Natural history and prognostic factors of chronic hepatitis type B. Gut. 1991;32:294-8.
41. Di Marco V, Marzano A, Lampertico P, Andreone P, Santantonio T, Almasio PL, et al. Clinical outcome of HBeAg-negative chronic hepatitis B in relation to virological response to lamivudine. Hepatology. 2004;40(4):883-91.
42. Papatheodoridis G, Manesis E, Hadziyannis S. The long-term outcome of interferon-alpha treated and untreated patients with HBeAg negative chronic hepatitis B. J Hepatol. 2001;34:306-13.
43. Tong M, Blatt L, Kao J. Precore/basal core promoter mutants and hepatitis B viral DNA levels as predictors for liver deaths and hepatocellular carcinoma. WorldJ Gastroenterol. 2006;12:6620-6.
44. Fattovich G. Natural history and prognosis of hepatitis B. Semin Liver Dis. 2003;23:47-68.
45. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology. 2007;45(2):507-39.
46. Yuen M-F, Sablon E, Yuan H-J, Hui C-K, Wong DK-H, Doutreloigne J, et al. Relationship between the development of precore and core promoter mutations and hepatitis B e antigen seroconversion in patients with chronic hepatitis B virus. J Infect Dis. 2002;186(9):1335-8.

47. Krogsgaard K, Aldershvile J, Kryger P. Reactivation of viral replication in anti-HBe positive chronic HBsAg carriers. Liver. 1990;10:54-8.
48. Manno M, Camma C, Schepis F. Natural history of chronic HBV carriers in Northern Italy; morbidity and mortality after 30 years. Gastroenterology. 2004;127:756-63.
49. de Franchis R, Meucci G, Vecchi M. The natural history of asymptomatic hepatitis B surface antigen carriers. Ann Intern Mad. 1993;118:191-4.
50. Brunetto M, Oliveri F, Rocca G. Natural course and response to interferon of chronic hepatitits B accompanied by antibody to hepatitis B e antigen. Hepatology. 1989;10:198-202.
51. Liaw Y, Lin D, Chen T. Natural course after the development of cirrhosis in patients with chronic type B hepatitis Liver. 1989;9:235-41.
52. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N.Engl.J Med. 2004;351(15):1521-31.
53. Fattovich G, Pantalena M, Zagni I, al. e. Effect of hepatitis B and C virus infections on the natural history of compensated cirrhosis: a cohort study of 297 patients. Am J Gastroenterol 2002;97:2886-95.
54. Beasley R. Hepatitis B virus. The major etiology of hepatocellular carcinoma. . Cancer. 1988;61:1942-56.
55. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA. 2006;295(1):65-73.
56. Oon C. Long-term survival following treatment of hepatocellular carcinoma in Singapore: evaluation of Wellferon in the prophylaxis of high-risk pre-cancerous conditions. Cancer Chemother Pharmacol. 1992;31:S137-42.
57. Kato Y, Nakata K, Omagari K. Ris of hepatocellular carcinoma in patients with cirrhosis in Japan. Cancer. 1994;74:2234-8.
58. Ikeda K, Saitoh S, Suzuki Y. Interferon decreases hepatocellular carcinogenenis in patients with cirrhosis caused by the hepatitis B virus. Cancer. 1998;82:827-35.
59. Kobayashi M, Ikeda K, Hosaka T. Natural history of compensated cirrhosis in the Child-Pugh class A compared betwee 490 patients with hepatitis C and 167 with B virus infections J Med Virol. 2006;78:459-65.
60. Di Marco V, Lo Iancono O, Camma C. The long-term course of chronic hepatits B. Hepatology. 1999;30(257-64).
61. Mazzella G, Accogli E, Sottili S. Alpha interferon treatment may prevent heptocellular carcinoma in HCV-related liver cirrhosis. J Hepatol. 1996;24:141-7.
62. Benvegnu L, Chemello L, Noventa F. Retrospective analysis of the effect of interferon therapy on the clinical outcome of patients with viral hepatitis. Cancer. 1998;83:901-9.
63. Chiaramonte M, Stroffolini T, Vian A, Stazi MA, Floreani A, Lorenzoni U, et al. Rate of incidence of hepatocellular carcinoma in patients with compensated viral cirrhosis. Cancer. 1999;85(10):2132-7.
64. Chen Y-C, Chu C-M, Yeh C-T, Liaw Y-F. Natural course following the onset of cirrhosis in patients with chronic hepatitis B: a long-term follow-up study. Hepatol Int. 2007;1(1):267-73.
65. Hui A, Chan H, Leung N. Survival and prognostic indicators in patients with hepatitis B virus-related cirrhosis after onset of hepatic decompensation. J Clin Gastroenterol. 2002;34:569-72.
66. Llovet J, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet. 2003;362:1907-17.
67. Llovet J, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19:329-38.
68. Mazzaferro V, Regalia E, Doci R. Liver transplantation for the treatment of small hepatocellular carcinoma in patients with cirrhosis N Enl J Med. 1996;334:693-9.
69. Van Vlierberghe H, Colle I, Henrion J, Michielsen P, Delwaide J, Reynaert H, et al. The HepCar registry: Report on a one-year registration program of hepatocellular carcinoma (HCC) in Belgium. What is daily practice in HCC? Acta Gastro-Enterologica Belgica. 2005;68(4):403-11.
70. Tandon P, Garcia-Tsao G. Prognostic indicators in hepatocellular carcinoma: a systematic review of 72 studies. liver Int. 2009;29:502-10.

71. Yuen M, Hou J, Chutaputti A. Hepatocellular carcinoma in the Asia pacific region: Asia Pacific Working Party on Prevention of Hepatocellular Carcinoma. J Gastroenterol Hepatol. 2009;24:346-53.
72. Toyoda H, Kumada T, Kiriyama S, Sone Y, Tanikawa M, Hisanaga Y, et al. Comparison of the usefulness of three staging systems for hepatocellular carcinoma (CLIP, BCLC and JIS) in Japan. Am J Gastroenterol. 2005;100:1764-71.
73. Chen C, Hu F, Huang G. Applicability of staging systems for patiens with hepatocellular carcinoma is dependent on treatment method-analysis of 2010 Taiwanese patients. Eur J Cancer. 2009;4:1630-9.
74. Kudo M, Chung H, Haji S. Validation of a new prognostic staging system for hepatocellular carcinoma: the JIS score compared with the CLIP score. Hepatology. 2004;40:1369-405.
75. Chung H, Kudo M, Takahashi S. Comparison of three current staging systems for hepatocellular carcinoma: Japan integrated staging score, new Barcelona Clinic Liver Cancer staging classification,and Tokyo socre. J Gastroenterol Hepatol. 2008;23:445-52.
76. Beutels M, Van Damme P, Aelvoet W, Desmyter J, Dondeyne F, Goilav C, et al. Prevalence of hepatitis A, B and C in the Flemish population. Eur J Epidemiol. 1997;13(3):275-80.
77. Nardone A, Anastassopoulou CG, Theeten H, Kriz B, Davidkin I, Thierfelder W, et al. A comparison of hepatitis B seroepidemiology in ten European countries. Epidemiol Infect. 2008:1-9.
78. Quoilin S, Hutse V, Vandenberghe H, Claeys F, Verhaegen E, De Cock L, et al. A population-based prevalence study of hepatitis A, B and C virus using oral fluid in Flanders, Belgium. European Journal of Epidemiology. 2007;22(3):195-202.
79. Mak Ruud. Epi NewsOost-Vlaanderen en Vlaanderen. Registratie overzicht 2007. http://www.iph.fgov.be/epidemio/labo. 2008.
80. Micalessi MI, De CL, Vranckx R. Hepatitis B virus (HBV) genotyping in Belgian patients with chronic HBV infection. Clin Microbiol Infect. 2005;11(6):499-501.
81. INVS. Estimation des taux de prevalence des anticorps anti-VHC et des marqueurs de l'hépatite B chez les assurés sociaux du régime général de France métropolaine, 2003-2004. Analyse descriptive , InVS, Janvier 2005. http://www.invs.sante.fr/publication/2005 .). 2005.
82. Zarski JP. Epidemiology of chronic hepatitis B. Presse Medicale. 2006;35(2 II):304-7.
83. Pillonel J, Le Marrec N, Girault A, David D, Laperche S. Epidemiological surveillance of blood donors and residual risk of blood-borne infections in France, 2001 to 2003. Transfusion Clinique et Biologique. 2005;12(3):239-46.
84. Laperche S, Maniez M, Barlet V, El Ghouzzi MH, Le VF, Levayer T, et al. A revised method for estimating hepatitis B virus transfusion residual risk based on antibody to hepatitis B core antigen incident cases. Transfusion. 2008;48(11):2308-14.
85. Cadranel JF, Lahmek P, Causse X, Bellaiche G, Bettan L, Fontanges T, et al. Results of a nationwide survey. Alimentary Pharmacology and Therapeutics. 2007;26(4):565-76.
86. Zarski JP, Marcellin P, Cohard M, Lutz JM, Bouche C, Rais A. Comparison of anti-HBe-positive and HBe-antigen-positive chronic hepatitis B in France. French Multicentre Group. J Hepatol. 1994;20(5):636-40.
87. Ganne-Carrie N, Williams V, Kaddouri H, Trinchet JC, Dziri-Mendil S, Alloui C, et al. Significance of hepatitis B virus genotypes A to E in a cohort of patients with chronic hepatitis B in the Seine Saint Denis District of Paris (France). J Med Virol. 2006;78(3):335-40.
88. Trimoulet P, Boutonnet M, Winnock M, Faure M, Loko MA, De Ledinghen V, et al. Hepatitis B virus genotypes: A retrospective survey in Southwestern France, 1999-2004. Gastroenterologie Clinique et Biologique. 2007;31(12):1088-94.
89. Marschall T, Kramer A, Prufer-Kramer L, Mikolajczyk R, Kretzschmar M. Does migration from high and intermediate endemic regions increase the prevalence of hepatitis B infection in Germany? Dtsch Med Wochenschr. 2005;130(48):2753-8.
90. Jilg W, Hottentrager B, Weinberger K, Schlottmann K, Frick E, Holstege A, et al. Prevalence of markers of hepatitis B in the adult German population. J Med Virol. 2001;63(2):96-102.
91. Thierfelder W, Hellenbrand W, Meisel H, Schreier E, Dortschy R. Prevalence of markers for hepatitis A, B and C in the German population. Results of the German National Health Interview and Examination Survey 1998. Eur J Epidemiol. 2001;17(5):429-35.

92. Lobstein S, Kaiser T, Liebert U, Wojan M, Leichtle A, Mossner J, et al. Prevalence, aetiology and associated co-morbidities of elevated aminotransferases in a German cohort of orthopaedic surgery patients. Zeitschrift fur Gastroenterologie. 2008;46(5):415-20.

93. Knorr B, Maul H, Schnitzler P. Prevalence of hepatitis B virus infection among women at reproductive age at a German university hospital. Journal of Clinical Virology. 2008;42(4):422-4.

94. Offergeld R, Ritter S, Faensen D, Hamouda O. Infection epidemiological data among blood donors in Germany 2003-2004. Report of the Robert Koch Institute in accordance with Article 22 of the Transfusion Act. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2005;48(11):1273-87.

95. Hourfar MK, Jork C, Schottstedt V, Weber-Schehl M, Brixner V, Busch MP, et al. Experience of German Red Cross blood donor services with nucleic acid testing: results of screening more than 30 million blood donations for human immunodeficiency virus-1, hepatitis C virus, and hepatitis B virus. Transfusion. 2008;48(8):1558-66.

96. Niederau C. Epidemiology of hepatitis B in Germany. Med Klin (Munich). 2007;102(5):351-7.

97. Deterding K, Constantinescu I, Nedelcu FD, Gervain J, Nemecek V, Srtunecky O, et al. Prevalence of HBV genotypes in Central and Eastern Europe. Journal of medical virology. 2008;80(10):1707-11.

98. Baaten GGG, Sonder GJB, Dukers NHTM, Coutinho RA, Van Den Hoek JAR. Population-based study on the seroprevalence of hepatitis A, B, and C virus infection in Amsterdam, 2004. Journal of medical virology. 2007;79(12):1802-10.

99. Veldhuijzen IK, van Driel HF, Vos D, de Zwart O, van Doornum GJJ, de Man RA, et al. Viral hepatitis in a multi-ethnic neighborhood in the Netherlands: results of a community-based study in a low prevalence country. International Journal of Infectious Diseases. 2009;13(1):e9-e13.

100. Marschall T, Kretzschmar M, Mangen MJJ, Schalm S. High impact of migration on the prevalence of chronic hepatitis B in the Netherlands. European Journal of Gastroenterology and Hepatology. 2008;20(12):1214-25.

101. Toy M, Veldhuijzen IK, Mostert MC, de Man RA, Richardus JH. Transmission routes of hepatitis B virus infection in chronic hepatitis B patients in the Netherlands. Journal of medical virology. 2008;80(3):399-404.

102. Van Houdt R, Bruisten SM, Koedijk FDH, Dukers NHTM, Op De Coul ELM, Mostert MC, et al. Molecular epidemiology of acute hepatitis B in the Netherlands in 2004: Nationwide survey. Journal of medical virology. 2007;79(7):895-901.

103. Rantala M, van de Laar MJ. a review. Euro surveillance : bulletin europeen sur les maladies transmissibles = European communicable disease bulletin. 2008;13(21).

104. Colle I, Adler M, Brenard R, Henrion J, Langlet P, Michielsen P, et al. Management and treatment of chronic hepatitis B virus: Belgian Association for the Study of the Liver (BASL) 2007 guidelines. Acta Gastroenterol Belg. 2007;70(4):389-420.

105. Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med. 2008;359(23):2442-55.

106. Liaw Y-F, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, et al. 2-Year GLOBE trial results: telbivudine Is superior to lamivudine in patients with chronic hepatitis B. Gastroenterology. 2009;136(2):486-95.

107. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of chronic hepatitis B. Journal of Hepatology. 2009;50(2):227-42.

108. Keeffe EB, Dieterich DT, Han S-HB, Jacobson IM, Martin P, Schiff ER, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. Clin Gastroenterol Hepatol. 2008;6(12):1315-41; quiz 286.

109. Feld JJ, Wong DKH, Heathcote EJ. Endpoints of therapy in chronic hepatitis B. Hepatology. 2009;49(5 Suppl):S96-S102.

110. Shamliyan TA, MacDonald R, Shaukat A, Taylor BC, Yuan J-M, Johnson JR, et al. Antiviral therapy for adults with chronic hepatitis B: a systematic review for a National Institutes of Health Consensus Development Conference. Ann Intern Med. 2009;150(2):111-24.

111. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009;50(3):661-2.

112. Lok AS, Zoulim F, Locarnini S, Bartholomeusz A, Ghany MG, Pawlotsky JM, et al. Antiviral drug-resistant HBV: Standardization of nomenclature and assays and recommendations for management. Hepatology. 2007;46(1):254-65.

113. Robins GW, Scott LJ, Keating GM. Peginterferon-alpha-2a (40kD): a review of its use in the management of patients with chronic hepatitis B. Drugs. 2005;65(6):809-25.

114. Cooksley WG, Piratvisuth T, Lee SD, Mahachai V, Chao YC, Tanwandee T, et al. Peginterferon alpha-2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. J.Viral Hepat. 2003;10(4):298-305.

115. Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N.Engl.J.Med. 2005;352(26):2682-95.

116. Chan HL, Leung NW, Hui AY, Wong VW, Liew CT, Chim AM, et al. A randomized, controlled trial of combination therapy for chronic hepatitis B: comparing pegylated interferon-alpha2b and lamivudine with lamivudine alone. Ann.Intern.Med. 2005;142(4):240-50.

117. Janssen HL, van ZM, Senturk H, Zeuzem S, Akarca US, Cakaloglu Y, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. Lancet. 2005;365(9454):123-9.

118. Keeffe EB, Dieterich DT, Han SH, Jacobson IM, Martin P, Schiff ER, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update. Clin.Gastroenterol.Hepatol. 2006;4(8):936-62.

119. Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N.Engl.J.Med. 2004;351(12):1206-17.

120. Orlent H. Treatment of HBeAg-positive hepatitis B with peginterferon and lamivudine. N.Engl.J Med. 2005;353(15):1630-1.

121. Hoofnagle JH, Seeff LB. Peginterferon and ribavirin for chronic hepatitis C. N.Engl.J Med. 2006;355(23):2444-51.

122. Flink HJ, van ZM, Hansen BE, de Man RA, Schalm SW, Janssen HL. Treatment with Peg-interferon alpha-2b for HBeAg-positive chronic hepatitis B: HBsAg loss is associated with HBV genotype. Am.J.Gastroenterol. 2006;101(2):297-303.

123. Wai CT, Chu CJ, Hussain M, Lok AS. HBV genotype B is associated with better response to interferon therapy in HBeAg(+) chronic hepatitis than genotype C. Hepatology. 2002;36(6):1425-30.

124. Kleinman A. Culture and depression. N.Engl.J.Med. 2004;351(10):951-3.

125. Perrillo RP. Acute flares in chronic hepatitis B: the natural and unnatural history of an immunologically mediated liver disease. Gastroenterology. 2001;120(4):1009-22.

126. Fleischer RD, Lok ASF. Myopathy and neuropathy associated with nucleos(t)ide analog therapy for hepatitis B. J Hepatol. 2009;51(4):787-91.

127. Dienstag JL, Cianciara J, Karayalcin S, Kowdley KV, Willems B, Plisek S, et al. Durability of serologic response after lamivudine treatment of chronic hepatitis B. Hepatology. 2003;37(4):748-55.

128. Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, et al. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. N.Engl.J Med. 1998;339(2):61-8.

129. Chang TT, Lai CL, Chien RN, Guan R, Lim SG, Lee CM, et al. Four years of lamivudine treatment in Chinese patients with chronic hepatitis B. J Gastroenterol.Hepatol. 2004;19(11):1276-82.

130. Leung NW, Lai CL, Chang TT, Guan R, Lee CM, Ng KY, et al. Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: results after 3 years of therapy. Hepatology. 2001;33(6):1527-32.

131. Liaw YF, Leung NW, Chang TT, Guan R, Tai DI, Ng KY, et al. Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. Gastroenterology. 2000;119(1):172-80.

132. Lok AS, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology. 2003;125(6):1714-22.

133. Chien RN, Liaw YF, Atkins M. Pretherapy alanine transaminase level as a determinant for hepatitis B e antigen seroconversion during lamivudine therapy in patients with chronic hepatitis B. Asian Hepatitis Lamivudine Trial Group. Hepatology. 1999;30(3):770-4.

134. Perrillo RP, Lai CL, Liaw YF, Dienstag JL, Schiff ER, Schalm SW, et al. Predictors of HBeAg loss after lamivudine treatment for chronic hepatitis B. Hepatology. 2002;36(1):186-94.

135. Lee KM, Cho SW, Kim SW, Kim HJ, Hahm KB, Kim JH. Effect of virological response on post-treatment durability of lamivudine-induced HBeAg seroconversion. J Viral Hepat. 2002;9(3):208-12.

136. Dienstag JL, Goldin RD, Heathcote EJ, Hann HW, Woessner M, Stephenson SL, et al. Histological outcome during long-term lamivudine therapy. Gastroenterology. 2003;124(1):105-17.

137. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. Gastroenterology. 2006;131(6):1743-51.

138. Knight W, Hayashi S, Benhamou Y. Dosing guidelines for adefovir dipivoxil in the treatment of HBV infected patients with renal or hepatic impairment. J Hepatol. 2002;36(suppl 1).

139. Marcellin P, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N.Engl.J Med. 2003;348(9):808-16.

140. Westland CE, Yang H, Delaney WE, Gibbs CS, Miller MD, Wulfsohn M, et al. Week 48 resistance surveillance in two phase 3 clinical studies of adefovir dipivoxil for chronic hepatitis B. Hepatology. 2003;38(1):96-103.

141. Marcellin P, Asselah T. Resistance to adefovir: a new challenge in the treatment of chronic hepatitis B. J Hepatol. 2005;43(6):920-3.

142. Lee YS, Suh DJ, Lim YS, Jung SW, Kim KM, Lee HC, et al. Increased risk of adefovir resistance in patients with lamivudine-resistant chronic hepatitis B after 48 weeks of adefovir dipivoxil monotherapy. Hepatology. 2006;43(6):1385-91.

143. Rapti I, Dimou E, Mitsoula P, Hadziyannis SJ. Adding-on versus switching-to adefovir therapy in lamivudine-resistant HBeAg-negative chronic hepatitis B. Hepatology. 2007;45(2):307-13.

144. Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med. 2006;354(10):1001-10.

145. Colonno RJ, Rose R, Baldick CJ, Levine S, Pokornowski K, Yu CF, et al. Entecavir resistance is rare in nucleoside naive patients with hepatitis B. Hepatology. 2006;44(6):1656-65.

146. Sherman M, Martin P, Lee W, Yurdaydin C, Sollano J, Vaughan R, et al. Entecavir results in continued virologic and biochemical improvement and HBeAg seroconversion through 96 weeks of treatment in lamivudine-refractory, HBeAg (+) chronic hepatitis B patients (ETV 026). Gastroenterology. 2006;130(suppl 2).

147. Colonno R, Rose R, Pokornowski K, Baldick CJ, Eggers B, Yu D, et al. Four year assessment of entecavir resistance in nucleoside-naive and lamivudine refractory patients. J Hepatol. 2007;46(suppl 1):S294.

148. Lai C-L, Gane E, Liaw Y-F, Hsu C-W, Thongsawat S, Wang Y, et al. Telbivudine versus lamivudine in patients with chronic hepatitis B. N Engl J Med. 2007;357(25):2576-88.

149. Lai CL, Leung N, Teo EK, Tong M, Wong F, Hann HW, et al. Phase Ib extended-treatment trial of telbivudine versus lamivudine versus combination treatment in hepatitis B patients: two year results. Gastroenterology. 2005;128.

150. Lai CL, Leung N, Teo EK, Tong M, Wong F, Hann HW, et al. A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. Gastroenterology. 2005;129(2):528-36.

151. Tassopoulos NC, Volpes R, Pastore G, Heathcote J, Buti M, Goldin RD, et al. Efficacy of lamivudine in patients with hepatitis B e antigen-negative/hepatitis B virus DNA-positive (precore mutant) chronic hepatitis B.Lamivudine Precore Mutant Study Group. Hepatology. 1999;29(3):889-96.

152. Santantonio T, Mazzola M, Iacovazzi T, Miglietta A, Guastadisegni A, Pastore G. Long-term follow-up of patients with anti-HBe/HBV DNA-positive chronic hepatitis B treated for 12 months with lamivudine. J Hepatol. 2000;32(2):300-6.

153. Lok AS, Hussain M, Cursano C, Margotti M, Gramenzi A, Grazi GL, et al. Evolution of hepatitis B virus polymerase gene mutations in hepatitis B e antigen-negative patients receiving lamivudine therapy. Hepatology. 2000;32(5):1145-53.

154. Hadziyannis SJ, Papatheodoridis GV, Dimou E, Laras A, Papaioannou C. Efficacy of long-term lamivudine monotherapy in patients with hepatitis B e antigen-negative chronic hepatitis B. Hepatology. 2000;32(4 Pt 1):847-51.

155. Rizzetto M, Volpes R, Smedile A. Response of pre-core mutant chronic hepatitis B infection to lamivudine. J Med.Virol. 2000;61(3):398-402.

156. Papatheodoridis GV, Dimou E, Laras A, Papadimitropoulos V, Hadziyannis SJ. Course of virologic breakthroughs under long-term lamivudine in HBeAg-negative precore mutant HBV liver disease. Hepatology. 2002;36(1):219-26.

157. Akyuz F, Kaymakoglu S, Demir K, Aksoy N, Karaca C, Danalioglu A, et al. Lamivudine monotherapy and lamivudine plus interferon alpha combination therapy in HBeAg negative chronic hepatitis B not responding to previous interferon alpha monotherapy. Acta Gastroenterol.Belg. 2007;70(1):20-4.

158. Papatheodoridis GV, Dimou E, Dimakopoulos K, Manolakopoulos S, Rapti I, Kitis G, et al. Outcome of hepatitis B e antigen-negative chronic hepatitis B on long-term nucleos(t)ide analog therapy starting with lamivudine. Hepatology. 2005;42(1):121-9.

159. Hadziyannis SJ, Papatheodoridis GV, Vassilopoulos D. Treatment of HBeAg-negative chronic hepatitis B. Semin.Liver Dis. 2003;23(1):81-8.

160. Hadziyannis SJ, Papatheodoridis GV. Hepatitis B e antigen-negative chronic hepatitis B: natural history and treatment. Semin.Liver Dis. 2006;26(2):130-41.

161. Gaia S, Marzano A, Smedile A, Barbon V, Abate ML, Olivero A, et al. Four years of treatment with lamivudine: clinical and virological evaluations in HBe antigen-negative chronic hepatitis B. Aliment.Pharmacol.Ther. 2004;20(3):281-7.

162. Buti M, Cotrina M, Jardi R, de Castro EC, Rodriguez-Frias F, Sanchez-Avila F, et al. Two years of lamivudine therapy in anti-HBe-positive patients with chronic hepatitis B. J Viral Hepat. 2001;8(4):270-5.

163. Lau DT, Khokhar MF, Doo E, Ghany MG, Herion D, Park Y, et al. Long-term therapy of chronic hepatitis B with lamivudine. Hepatology. 2000;32(4 Pt 1):828-34.

164. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. N.Engl.J Med. 2003;348(9):800-7.

165. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. N.Engl.J Med. 2005;352(26):2673-81.

166. Locarnini S, Qi X, Arterburn S, et al. Incidence and predictors of emergence of adefovir resistance HBV during four years of adefovir dipivoxil therapy for patients with chronic hepatitis B. J Hepatol. 2005;42(suppl 2).

167. Fung SK, Andreone P, Han SH, Rajender Reddy K, Regev A, Keeffe EB, et al. Adefovir-resistant hepatitis B can be associated with viral rebound and hepatic decompensation. J Hepatol. 2005;43(6):937-43.

168. Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N.Engl.J Med. 2006;354(10):1011-20.

169. Chang TT, Lai CL. Hepatitis B virus with primary resistance to adefovir. N.Engl.J Med. 2006;355(3):322-3.

170. Buster EHCJ, Hansen BE, Buti M, Delwaide J, Niederau C, Michielsen PP, et al. Peginterferon alpha-2b is safe and effective in HBeAg-positive chronic hepatitis B patients with advanced fibrosis. Hepatology. 2007;46(2):388-94.

171. Fontana RJ, Hann HW, Perrillo RP, Vierling JM, Wright T, Rakela J, et al. Determinants of early mortality in patients with decompensated chronic hepatitis B treated with antiviral therapy. Gastroenterology. 2002;123(3):719-27.

172. Doo E, Liang TJ. Molecular anatomy and pathophysiologic implications of drug resistance in hepatitis B virus infection. Gastroenterology. 2001;120(4):1000-8.

173. Ling R, Mutimer D, Ahmed M, Boxall EH, Elias E, Dusheiko GM, et al. Selection of mutations in the hepatitis B virus polymerase during therapy of transplant recipients with lamivudine. Hepatology. 1996;24(3):711-3.

174. Locarnini S. Molecular virology and the development of resistant mutants: implications for therapy. Semin.Liver Dis. 2005;25 Suppl 1:9-19.

175. Tipples GA, Ma MM, Fischer KP, Bain VG, Kneteman NM, Tyrrell DL. Mutation in HBV RNA-dependent DNA polymerase confers resistance to lamivudine in vivo. Hepatology. 1996;24(3):714-7.

176. Lok AS, McMahon BJ. Corrections to AASLD guidelines on chronic hepatitis B. Hepatology. 2007.

177. Pawlotsky JM, Dusheiko G, Hatzakis A, Lau D, Lau G, Liang TJ, et al. Virologic monitoring of hepatitis B virus therapy in clinical trials and practice: recommendations for a standardized approach. Gastroenterology. 2008;134(2):405-15.

178. Ghany MG, Doo EC. Antiviral resistance and hepatitis B therapy. Hepatology. 2009;49(5 Suppl):S174-84.

179. Bartholomeusz A, Locarnini SA. Antiviral drug resistance: clinical consequences and molecular aspects. Semin.Liver Dis. 2006;26(2):162-70.

180. Liaw YF. Impact of YMDD mutations during lamivudine therapy in patients with chronic hepatitis B. Antivir.Chem.Chemother. 2001;12 Suppl 1:67-71.

181. Liu CJ, Chen PJ, Lai MY, Kao JH, Chen DS. Hepatitis B virus variants in patients receiving lamivudine treatment with breakthrough hepatitis evaluated by serial viral loads and full-length viral sequences. Hepatology. 2001;34(3):583-9.

182. Nafa S, Ahmed S, Tavan D, Pichoud C, Berby F, Stuyver L, et al. Early detection of viral resistance by determination of hepatitis B virus polymerase mutations in patients treated by lamivudine for chronic hepatitis B. Hepatology. 2000;32(5):1078-88.

183. Yuen MF, Sablon E, Hui CK, Yuan HJ, Decraemer H, Lai CL. Factors associated with hepatitis B virus DNA breakthrough in patients receiving prolonged lamivudine therapy. Hepatology. 2001;34(4 Pt 1):785-91.

184. Lai CL, Dienstag J, Schiff E, Leung NW, Atkins M, Hunt C, et al. Prevalence and clinical correlates of YMDD variants during lamivudine therapy for patients with chronic hepatitis B. Clin Infect Dis. 2003;36(6):687-96.

185. Liaw YF, Chien RN, Yeh CT, Tsai SL, Chu CM. Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy. Hepatology. 1999;30(2):567-72.

186. Stuyver L, C. VG, S. DG, G. VR, Zoulim F, Leroux-Roels G, et al. Line probe assay for monitoring drug resistance in hepatitis B virus-infected patients during antiviral therapy. J Clin.Microbiol. 2000;38(2):702-7.

187. Yuen LK, Ayres A, Littlejohn M, Colledge D, Edgely A, Maskill WJ, et al. SeqHepB: a sequence analysis program and relational database system for chronic hepatitis B. Antiviral Res. 2007;75(1):64-74.

188. Allen MI, Deslauriers M, Andrews CW, Tipples GA, Walters KA, Tyrrell DL, et al. Identification and characterization of mutations in hepatitis B virus resistant to lamivudine. Lamivudine Clinical Investigation Group. Hepatology. 1998;27(6):1670-7.

189. Stuyver LJ, Locarnini SA, Lok A, Richman DD, Carman WF, Dienstag JL, et al. Nomenclature for antiviral-resistant human hepatitis B virus mutations in the polymerase region. Hepatology. 2001;33(3):751-7.

190. Yeh CT, Chien RN, Chu CM, Liaw YF. Clearance of the original hepatitis B virus YMDD-motif mutants with emergence of distinct lamivudine-resistant mutants during prolonged lamivudine therapy. Hepatology. 2000;31(6):1318-26.

191. Schalm SW, Heathcote J, Cianciara J, Farrell G, Sherman M, Willems B, et al. Lamivudine and alpha interferon combination treatment of patients with chronic hepatitis B infection: a randomised trial. Gut. 2000;46(4):562-8.

192. Melegari M, Scaglioni PP, Wands JR. Hepatitis B virus mutants associated with 3TC and famciclovir administration are replication defective. Hepatology. 1998;27(2):628-33.

193. Ono-Nita SK, Kato N, Shiratori Y, Lan KH, Yoshida H, Carrilho FJ, et al. Susceptibility of lamivudine-resistant hepatitis B virus to other reverse transcriptase inhibitors. J Clin.Invest. 1999;103(12):1635-40.

194. Liaw YF, Chien RN, Yeh CT. No benefit to continue lamivudine therapy after emergence of YMDD mutations. Antivir.Ther. 2004;9(2):257-62.

195. Wong VW, Chan HL, Wong ML, Tam JS, Leung NW. Clinical course after stopping lamivudine in chronic hepatitis B patients with lamivudine-resistant mutants. Aliment.Pharmacol.Ther. 2004;19(3):323-9.

196. Tenney DJ, Levine SM, Rose RE, Walsh AW, Weinheimer SP, Discotto L, et al. Clinical emergence of entecavir-resistant hepatitis B virus requires additional substitutions in virus already resistant to Lamivudine. Antimicrob.Agents Chemother. 2004;48(9):3498-507.

197. Zoulim F. In vitro models for studying hepatitis B virus drug resistance. Semin.Liver Dis. 2006;26(2):171-80.

198. Villet S, Pichoud C, Billioud G, Barraud L, Durantel S, Trepo C, et al. Impact of hepatitis B virus rtA181V/T mutants on hepatitis B treatment failure. J Hepatol. 2008;48(5):747-55.

199. Schiff ER, Lai CL, Hadziyannis S, Neuhaus P, Terrault N, Colombo M, et al. and post-liver transplantation patients. Hepatology. 2003;38(6):1419-27.

200. Schiff E, Lai CL, Hadziyannis S, Neuhaus P, Terrault N, Colombo M, et al. Adefovir dipivoxil for wait-listed and post-liver transplantation patients with lamivudine-resistant hepatitis B: final long-term results. Liver Transpl. 2007;13(3):349-60.

201. Peters MG, Hann HH, Martin P, Heathcote EJ, Buggisch P, Rubin R, et al. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. Gastroenterology. 2004;126(1):91-101.

202. Lampertico P, Vigano M, Manenti E, Iavarone M, Sablon E, Colombo M. Low resistance to adefovir combined with lamivudine: a 3-year study of 145 lamivudine-resistant hepatitis B patients. Gastroenterology. 2007;133(5):1445-51.

203. Fung SK, Chae HB, Fontana RJ, Conjeevaram H, Marrero J, Oberhelman K, et al. Virologic response and resistance to adefovir in patients with chronic hepatitis B. J Hepatol. 2006;44(2):283-90.

204. Kuo A, Dienstag JL, Chung RT. Tenofovir disoproxil fumarate for the treatment of lamivudine-resistant hepatitis B. Clin Gastroenterol Hepatol. 2004;2(3):266-72.

205. van Bommel F, Wunsche T, Mauss S, Reinke P, Bergk A, Schurmann D, et al. Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection. Hepatology. 2004;40(6):1421-5.

206. van Bommel F, Zollner B, Sarrazin C, Spengler U, Huppe D, Moller B, et al. Tenofovir for patients with lamivudine-resistant hepatitis B virus (HBV) infection and high HBV DNA level during adefovir therapy. Hepatology. 2006;44(2):318-25.

207. Chang TT, Gish RG, Hadziyannis SJ, Cianciara J, Rizzetto M, Schiff ER, et al. A dose-ranging study of the efficacy and tolerability of entecavir in Lamivudine-refractory chronic hepatitis B patients. Gastroenterology. 2005;129(4):1198-209.

208. Sherman M, Yurdaydin C, Simsek H, Silva M, Liaw YF, Rustgi VK, et al. Entecavir therapy for lamivudine-refractory chronic hepatitis B: improved virologic, biochemical, and serology outcomes through 96 weeks. Hepatology. 2008;48(1):99-108.

209. Leemans WF, Flink HJ, Janssen HL, Niesters HG, Schalm SW, de Man RA. The effect of pegylated interferon-alpha on the treatment of lamivudine resistant chronic HBeAg positive hepatitis B virus infection. J Hepatol. 2006;44(3):507-11.

210. Gane E, Lai CL, Min A, et al. GLOBE study: add or switch to adefovir a viable salvage option for telbivudine-treated patients exhibiting virologic breakthrough. J Hepatol. 2007;2007(46 suppl 1).

211. Angus P, Vaughan R, Xiong S, Yang H, Delaney W, Gibbs C, et al. Resistance to adefovir dipivoxil therapy associated with the selection of a novel mutation in the HBV polymerase. Gastroenterology. 2003;125(2):292-7.

212. Villeneuve JP, Durantel D, Durantel S, Westland C, Xiong S, Brosgart CL, et al. Selection of a hepatitis B virus strain resistant to adefovir in a liver transplantation patient. J Hepatol. 2003;39(6):1085-9.

213. Marcellin P, Chang TT, Lim SG, Sievert W, Tong M, Arterburn S, et al. Long-term efficacy and safety of adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. Hepatology. 2008;48(3):750-8.

214. Tan J, Degertekin B, Wong SN, Husain M, Oberhelman K, Lok AS. Tenofovir monotherapy is effective in hepatitis B patients with antiviral treatment failure to adefovir in the absence of adefovir-resistant mutations. J Hepatol. 2008;48(3):391-8.

215. Choe WH, Kwon SY, Kim BK, Ko SY, Yeon JE, Byun KS, et al. Tenofovir plus lamivudine as rescue therapy for adefovir-resistant chronic hepatitis B in hepatitis B e antigen-positive patients with liver cirrhosis. Liver Int. 2008;28(6):814-20.

216. Carrouee-Durantel S, Durantel D, Werle-Lapostolle B, Pichoud C, Naesens L, Neyts J, et al. Suboptimal response to adefovir dipivoxil therapy for chronic hepatitis B in nucleoside-naive patients is not due to pre-existing drug-resistant mutants. Antivir Ther. 2008;13(3):381-8.

217. Schildgen O, Sirma H, Funk A, Olotu C, Wend UC, Hartmann H, et al. Variant of hepatitis B virus with primary resistance to adefovir. N.Engl.J Med. 2006;354(17):1807-12.

218. Gallant JE, Deresinski S. Tenofovir disoproxil fumarate. Clin.Infect.Dis. 2003;37(7):944-50.

219. Benhamou Y, Poynard T. Treatment of chronic hepatitis B virus infection in patients co-infected with human immunodeficiency virus. J Hepatol. 2003;39 Suppl 1:S194-S9.

220. Peters MG, Andersen J, Lynch P, Liu T, Alston-Smith B, Brosgart CL, et al. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. Hepatology. 2006;44(5):1110-6.

221. Ristig MB, Crippin J, Aberg JA, Powderly WG, Lisker-Melman M, Kessels L, et al. Tenofovir disoproxil fumarate therapy for chronic hepatitis B in human immunodeficiency virus/hepatitis B virus-coinfected individuals for whom interferon-alpha and lamivudine therapy have failed. J Infect.Dis. 2002;186(12):1844-7.

222. Sheldon J, Camino N, Rodes B, Bartholomeusz A, Kuiper M, Tacke F, et al. Selection of hepatitis B virus polymerase mutations in HIV-coinfected patients treated with tenofovir. Antivir.Ther. 2005;10(6):727-34.

223. Delaney WEt, Ray AS, Yang H, Qi X, Xiong S, Zhu Y, et al. Intracellular metabolism and in vitro activity of tenofovir against hepatitis B virus. Antimicrob Agents Chemother. 2006;50(7):2471-7.

224. Amini-Bavil-Olyaee S, Herbers U, Sheldon J, Luedde T, Trautwein C, Tacke F. The rtA194T polymerase mutation impacts viral replication and susceptibility to tenofovir in hepatitis B e antigen-positive and hepatitis B e antigen-negative hepatitis B virus strains. Hepatology. 2009;49(4):1158-65.

225. Snow-Lampart A, Chappell BJ, Curtis M, al. e. Week 96 resistance surveillance for HBeAg positive and negative subjects with chronic HBV infection randomized to receive tenofovir DF 300 mg qd. Hepatology. 2008;48(Suppl):745A.

226. Gish RG, Lok AS, Chang TT, de Man RA, Gadano A, Sollano J, et al. Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. Gastroenterology. 2007;133(5):1437-44.

227. Sherman M, Yurdaydin C, Sollano J, Silva M, Liaw YF, Cianciara J, et al. Entecavir for treatment of lamivudine-refractory, HBeAg-positive chronic hepatitis B. Gastroenterology. 2006;130(7):2039-49.

228. Cleemput I. A social preference valuations set for EQ-5D health states in Flanders, Belgium. Eur J Health Econ. 2009.

229. Hulstaert F, Huybrechts M, Van Den Bruel A, Cleemput I, Bonneux L, Vernelen K, et al. HTA Moleculaire Diagnostiek in België. KCE reports 20 A. (D2005/10.273/23). Brussels: Federaal Kenniscentrum voor de Gezondheidszorg (KCE); 2005.

230. Buti M, Brosa M, Casado MA, Rueda M, Esteban R. Modeling the cost-effectiveness of different oral antiviral therapies in patients with chronic hepatitis B. J Hepatol. 2009;51(4):640-6.

231. Arnold E, Yuan Y, Iloeje U, Cook G. Cost-effectiveness analysis of entecavir versus lamivudine in the first-line treatment of australian patients with chronic hepatitis B. Applied Health Economics and Health Policy. 2008;6(4):231-46.

232. Costa AMN, L 'italien G, Nita ME, Araujo ESA. Cost-effectiveness of entecavir versus lamivudine for the suppression of viral replication in chronic hepatitis B patients in Brazil. Braz J Infect Dis. 2008;12(5):368-73.

233. Lacey L, Chien R-N, Chuang W-L, Pwu R-F. Economic evaluation of chronic hepatitis B treatments in Taiwan. J Gastroenterol Hepatol. 2008;23(4):571-9.

234. Orlewska E, Zammit D, Yuan Y, Kutikova L, Berak H, Halota W, et al. The cost-effectiveness analysis of entecavir in the treatment of chronic hepatitis B (CHB) patients in Poland. Experimental and Clinical Hepatology. 2008;4(3-4):20-8.

235. Spackman DE, Veenstra DL. A cost-effectiveness analysis of currently approved treatments for HBeAg-positive chronic hepatitis B. PharmacoEconomics. 2008;26(11):937-49.

236. Veenstra DL, Spackman DE, Bisceglie A, Kowdley KV, Gish RG. Evaluating anti-viral drug selection and treatment duration in HBeAg-negative chronic hepatitis B: A cost-effectiveness analysis. Alimentary Pharmacology & Therapeutics. 2008;27(12):1240-52.

237. Veenstra DL, Sullivan SD, Lai M-Y, Lee C-M, Tsai C-M, Patel KK. HBeAg-negative chronic hepatitis B: cost-effectiveness of peginterferon alfa-2a compared to lamivudine in Taiwan. Value Health. 2008;11(2):131-8.

238. Yuan Y, Iloeje U, Li H, Hay J, Yao GB. Economic implications of entecavir treatment in suppressing viral replication in chronic hepatitis B (CHB) patients in China from a perspective of the Chinese Social Security program. Value Health. 2008;11(Supplement 1):S11-S22.

239. Yuan Y, Iloeje UH, Hay J, Saab S. Evaluation of the cost-effectiveness of entecavir versus lamivudine in hepatitis BeAg-positive chronic hepatitis B patients.[see comment]. J Managed Care Pharm. 2008;14(1):21-33.

240. Lacey LF, Gane E. The cost-effectiveness of long-term antiviral therapy in the management of HBeAg-positive and HBeAg-negative chronic hepatitis B in Singapore. J Viral Hepat. 2007;14(11):751-66.

241. Sullivan SD, Veenstra DL, Chen P-J, Chang T-T, Chuang W-L, Tsai C, et al. Cost-effectiveness of peginterferon alpha-2a compared to lamivudine treatment in patients with hepatitis B e antigen positive chronic hepatitis B in Taiwan.[see comment]. J Gastroenterol Hepatol. 2007;22(9):1494-9.

242. Veenstra DL, Sullivan SD, Clarke L, Iloeje UH, Tafesse E, Di Bisceglie A, et al. Cost effectiveness of entecavir versus lamivudine with adefovir salvage in HBeAg-positive chronic hepatitis B. PharmacoEconomics. 2007;25(11):963-77.

243. Veenstra DL, Sullivan SD, Dusheiko GM, Jacobs M, Aledort JE, Lewis G, et al. Cost-effectiveness of peginterferon alpha-2a compared with lamivudine treatment in patients with HBe-antigen-positive chronic hepatitis B in the United Kingdom. Eur J Gastroenterol Hepatol. 2007;19(8):631-8.

244. Buti M, Casado MA, Calleja JL, Salmeron J, Aguilar J, Rueda M, et al. Cost-effectiveness analysis of lamivudine and adefovir dipivoxil in the treatment of patients with HBeAg-negative chronic hepatitis B. Alimentary Pharmacology & Therapeutics. 2006;23(3):409-19.

245. Kanwal F, Farid M, Martin P, Chen G, Gralnek IM, Dulai GS, et al. Treatment alternatives for hepatitis B cirrhosis: a cost-effectiveness analysis. Am.J Gastroenterol. 2006;101(9):2076-89.

246. Kanwal F, Gralnek IM, Martin P, Dulai GS, Farid M, Spiegel BM. Treatment alternatives for chronic hepatitis B viral infection: a cost-effectiveness analysis (Structured abstract). Annals of Internal Medicine. 2005;142:821-31.

247. Aggarwal R, Ghoshal UC, Naik SR. Treatment of chronic hepatitis B with interferon-alpha: cost-effectiveness in developing countries.[see comment]. Natl Med J India. 2002;15(6):320-7.

248. Crowley S, Tognarini D, Desmond P, Lees M, Saal G. Introduction of lamivudine for the treatment of chronic hepatitis B: Expected clinical and economic outcomes based on 4-year clinical trial data. J Gastroenterol Hepatol. 2002;17(2):153-64.

249. Orlewska E. The cost-effectiveness of alternative therapeutic strategies for the management of chronic hepatitis B in Poland. Value Health. 2002;5(5):405-21.

250. Pwu R-F, Chan KA. Cost-effectiveness analysis of interferon-alpha therapy in the treatment of chronic hepatitis B in Taiwan. J Formos Med Assoc. 2002;101(9):632-41.

251. Brooks EA, Lacey LF, Payne SL, Miller DW. Economic evaluation of lamivudine compared with interferon-(alpha) in the treatment of chronic hepatitis B in the United States. Am J Managed Care. 2001;7(7):677-82.

252. Crowley SJ, Tognarini D, Desmond PV, Lees M. Cost-effectiveness analysis of lamivudine for the treatment of chronic hepatitis B. PharmacoEconomics. 2000;17(5):409-27.

253. Dusheiko GM, Roberts JA. Treatment of chronic type B and C hepatitis with interferon alfa: an economic appraisal (Structured abstract). Hepatology. 1995;22(6):1863-73.

254. Wong JB, Koff RS, Tine F, Pauker SG. Cost-effectiveness of interferon-alpha-2b treatment for hepatitis B e antigen-positive chronic hepatitis B (Structured abstract). Annals of Internal Medicine. 1995;122(9):664-75.

255. Han S-HB. Natural course, therapeutic options and economic evaluation of therapies for chronic hepatitis B. Drugs. 2006;66(14):1831-51.

256. Rajendra A, Wong JB. Economics of chronic hepatitis B and hepatitis C. J Hepatol. 2007;47(4):608-17.

257. Sun X, Qin W-X, Li Y-P, Jiang X-H. Comparative cost-effectiveness of antiviral therapies in patients with chronic hepatitis B: a systematic review of economic evidence. J Gastroenterol Hepatol. 2007;22(9):1369-77.

258. You JHS, Chan FWH. Pharmacoeconomics of entecavir treatment for chronic hepatitis B. Expert Opinion on Pharmacotherapy. 2008;9(15):2673-81.

259. Jones J, Shepherd J, Baxter L, Gospodarevskaya E, Hartwell D, Harris P. Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation. Health Technology Assessment. 2009;13(35):1-212.

260. Shepherd J, Jones J, Takeda A, Davidson P, Price A. Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation. Health Technol.Assess. 2006;10(28):iii-xiv, 1.

261. Takeda A, Jones J, Shepherd J, Davidson P, Price A. A systematic review and economic evaluation of adefovir dipivoxil and pegylated interferon-alpha-2a for the treatment of chronic hepatitis B. J Viral Hepat. 2007;14(2):75-88.

262. Bondini S, Kallman J, Dan A, Younoszai Z, Ramsey L, Nader F, et al. Health-related quality of life in patients with chronic hepatitis B.[see comment]. Liver Int. 2007;27(8):1119-25.

263. Lam ETP, Lam CLK, Lai CL, Yuen MF, Fong DYT, So TMK. Health-related quality of life of Southern Chinese with chronic hepatitis B infection. Health and Quality of Life Outcomes. 2009;7.

264. Levy AR, Kowdley KV, Iloeje U, Tafesse E, Mukherjee J, Gish R, et al. The impact of chronic hepatitis B on quality of life: a multinational study of utilities from infected and uninfected persons. Value Health. 2008;11(3):527-38.

265. Ong SC, Mak B, Myat OA, Li SC, Lim SG. Health-related quality of life in chronic hepatitis B patients. Hepatology. 2008;47(4):1108-17.

266. Owens DK, Cardinalli AB, Nease Jr RF. Physicians' assessments of the utility of health states associated with Human Immunodeficiency Virus (HIV) and Hepatitis B Virus (HBV) Infection. Quality of Life Research. 1997;6(1):77-86.

267. Louis-Jacques O, Olson AD. Cost-benefit analysis of interferon therapy in children with chronic active hepatitis B (Structured abstract). Journal of Pediatric Gastroenterology and Nutrition. 1997;24(1):25-32.

268. Herdman M, Ossa D, Briggs A, Casanovas T, García-Samaniego J, Fusté L, et al. Measuring preferences for health states resulting from chronic hepatitis B infection in a Spanish population. In: 12th international symposium on viral hepatitis and liver disease. Paris; 2006.

269. Bennett WG, Inoue Y, Beck JR, Wong JB, Pauker SG, Davis GL. Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. Ann Intern Med. 1997;127(10):855-65.

270. Idris BI, Brosa M, Richardus JH, Esteban R, Schalm SW, Buti M. Estimating the future health burden of chronic hepatitis B and the impact of therapy in Spain. Eur J Gastroenterol Hepatol. 2008;20(4):320-6.

271. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology. 2006;130(3):678-86.

272. Liaw Y, Tai D, Chu C. Early detection of hepatocellular carcinoma in patients with chronic type B hepatitis. A prospective study Gastroenterology. 2006;90:263-7.

273. Marcellin P, Chang T, Lim S, et al. Baseline ALT predicts histologic and serologic response in patients with HBeAg+ chronic hepatitis B treated with adefovir dipivoxil (ADV). J Hepatol. 2002;36(Suppl.1):S122-3.

274. FDA. Summary of Safety and Effectiveness Data - Nucleic acid assay for detection of Hepatitis B Virus (HBV) DNA. In: http://www.accessdata.fda.gov/cdrh_docs/pdf5/P050028b.pdf; 2008. p. 21.

275. Veldhuijzen I, Toy M, Hahne S, De Wit G, Schalm S, De Man R, et al. Screening and Early Treatment of Migrants for Chronic Hepatitis B Virus Infection Is Cost-Effective. Gastroenterology. 2009.

276. Perquin M, Reijnders J, Zhang N, Hansen B, Janssen H. HBeAg seroconversion during nucleos(t)ide analogue treatment does not lead to durable remission of chronic hepatitis B. Abstract 219. In: AASLD Meeting Proceedings. Boston, MA; 2009.

277. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the economic evaluation of health care programmes. Oxford University Press, editor.; 2005.

This page is left intentionally blank.

Legal depot : D/2010/10.273/24

KCE reports

33 Effects and costs of pneumococcal conjugate vaccination of Belgian children. D/2006/10.273/54.
34 Trastuzumab in Early Stage Breast Cancer. D/2006/10.273/25.
36 Pharmacological and surgical treatment of obesity. Residential care for severely obese children in Belgium. D/2006/10.273/30.
37 Magnetic Resonance Imaging. D/2006/10.273/34.
38 Cervical Cancer Screening and Human Papillomavirus (HPV) Testing D/2006/10.273/37.
40 Functional status of the patient: a potential tool for the reimbursement of physiotherapy in Belgium? D/2006/10.273/53.
47 Medication use in rest and nursing homes in Belgium. D/2006/10.273/70.
48 Chronic low back pain. D/2006/10.273.71.
49 Antiviral agents in seasonal and pandemic influenza. Literature study and development of practice guidelines. D/2006/10.273/67.
54 Cost-effectiveness analysis of rotavirus vaccination of Belgian infants D/2007/10.273/11.
59 Laboratory tests in general practice D/2007/10.273/26.
60 Pulmonary Function Tests in Adults D/2007/10.273/29.
64 HPV Vaccination for the Prevention of Cervical Cancer in Belgium: Health Technology Assessment. D/2007/10.273/43.
65 Organisation and financing of genetic testing in Belgium. D/2007/10.273/46.
66. Health Technology Assessment: Drug-Eluting Stents in Belgium. D/2007/10.273/49.
70. Comparative study of hospital accreditation programs in Europe. D/2008/10.273/03
71. Guidance for the use of ophthalmic tests in clinical practice. D/200810.273/06.
72. Physician workforce supply in Belgium. Current situation and challenges. D/2008/10.273/09.
74 Hyperbaric Oxygen Therapy: a Rapid Assessment. D/2008/10.273/15.
76. Quality improvement in general practice in Belgium: status quo or quo vadis? D/2008/10.273/20
82. 64-Slice computed tomography imaging of coronary arteries in patients suspected for coronary artery disease. D/2008/10.273/42
83. International comparison of reimbursement principles and legal aspects of plastic surgery. D/200810.273/45
87. Consumption of physiotherapy and physical and rehabilitation medicine in Belgium. D/2008/10.273/56
90. Making general practice attractive: encouraging GP attraction and retention D/2008/10.273/66.
91 Hearing aids in Belgium: health technology assessment. D/2008/10.273/69.
92. Nosocomial Infections in Belgium, part I: national prevalence study. D/2008/10.273/72.
93. Detection of adverse events in administrative databases. D/2008/10.273/75.
95. Percutaneous heart valve implantation in congenital and degenerative valve disease. A rapid Health Technology Assessment. D/2008/10.273/81
100. Threshold values for cost-effectiveness in health care. D/2008/10.273/96
102. Nosocomial Infections in Belgium: Part II, Impact on Mortality and Costs. D/2009/10.273/03
103 Mental health care reforms: evaluation research of 'therapeutic projects' - first intermediate report. D/2009/10.273/06.
104. Robot-assisted surgery: health technology assessment. D/2009/10.273/09
108. Tiotropium in the Treatment of Chronic Obstructive Pulmonary Disease: Health Technology Assessment. D/2009/10.273/20
109. The value of EEG and evoked potentials in clinical practice. D/2009/10.273/23
111. Pharmaceutical and non-pharmaceutical interventions for Alzheimer's Disease, a rapid assessment. D/2009/10.273/29
112. Policies for Orphan Diseases and Orphan Drugs. D/2009/10.273/32.
113. The volume of surgical interventions and its impact on the outcome: feasibility study based on Belgian data
114. Endobronchial valves in the treatment of severe pulmonary emphysema. A rapid Health Technology Assessment. D/2009/10.273/39
115. Organisation of palliative care in Belgium. D/2009/10.273/42
116. Interspinous implants and pedicle screws for dynamic stabilization of lumbar spine: Rapid assessment. D/2009/10.273/46

117. Use of point-of care devices in patients with oral anticoagulation: a Health Technology Assessment. D/2009/10.273/49.
118. Advantages, disadvantages and feasibility of the introduction of 'Pay for Quality' programmes in Belgium. D/2009/10.273/52.
119. Non-specific neck pain: diagnosis and treatment. D/2009/10.273/56.
121. Feasibility study of the introduction of an all-inclusive case-based hospital financing system in Belgium. D/2010/10.273/03
122. Financing of home nursing in Belgium. D/2010/10.273/07
123. Mental health care reforms: evaluation research of 'therapeutic projects' - second intermediate report. D/2010/10.273/10
124. Organisation and financing of chronic dialysis in Belgium. D/2010/10.273/13
125. Impact of academic detailing on primary care physicians. D/2010/10.273/16
126. The reference price system and socioeconomic differences in the use of low cost drugs. D/2010/10.273/20.
127. Cost-effectiveness of antiviral treatment of chronic hepatitis B in Belgium. Part 1: Literature review and results of a national study. D/2010/10.273/24.

This list only includes those KCE reports for which a full English version is available. However, all KCE reports are available with a French or Dutch executive summary and often contain a scientific summary in English.