Evaluation économique du traitement antiviral de l'hépatite B chronique en Belgique – Tome 2

KCE reports 157B

Centre fédéral d'expertise des soins de santé
Federaal Kenniscentrum voor de Gezondheidszorg
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Evaluation économique du traitement antiviral de l'hépatite B chronique en Belgique

Tome 2

KCE reports 157B

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Disclaimer:	**Les <u>experts externes</u> ont été consultés sur une version (préliminaire) du rapport scientifique. Leurs remarques ont été discutées au cours des réunions. Ils ne sont pas co-auteurs du rapport scientifique et n'étaient pas nécessairement d'accord avec son contenu.** **Une version (finale) a ensuite été soumise aux <u>validateurs</u>. La validation du rapport résulte d'un consensus ou d'un vote majoritaire entre les validateurs. Les validateurs ne sont pas co-auteurs du rapport scientifique et ils n'étaient pas nécessairement tous les trois d'accord avec son contenu.** **Finalement, ce rapport a été approuvé à l'unanimité par le <u>Conseil d'administration.</u>**

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PRÉFACE

Durant la dernière décennie, il s'est produit une petite révolution en matière de traitement des infections virales. Après les succès spectaculaires enregistrés dans les inhibiteurs du sida, nous disposons aussi aujourd'hui de plus en plus de médicaments permettant de guérir les infections virales ou du moins d'en atténuer les conséquences les plus graves.

Il est question ici de traitements médicamenteux destinés à la suppression à long terme de la prolifération du virus de l'hépatite B, dans l'espoir de réduire le risque de deux complications tardives redoutées de l'hépatite B chronique : la cirrhose et le cancer du foie.

Nous avons essayé de réduire au minimum l'incertitude au niveau des calculs du rapport coût-efficacité, en rassemblant nous-mêmes des données de patients belges. Grâce à nos propres enquêtes et à la mise à disposition d'une cohorte clinique de l'hôpital universitaire de Leuven, nous avons pu substituer nos propres chiffres aux estimations – souvent trop optimistes- issues de publications sponsorisées la plupart du temps. Ces chiffres concernent les coûts engendrés à charge de l'assurance maladie, la qualité de vie des patients chroniques et les probabilités réelles de développer des complications.

Ce rapport s'appuie sur un rapport précédent et construit un modèle exploitant les données rassemblées pour apprécier les coûts et les bénéfices d'un traitement. Compte tenu du prix actuel de ces médicaments et de la durée importante du traitement, les coûts qui en découlent sont très élevés par rapport aux gains de santé qui ne se manifesteront qu'à terme. Les surcoûts sont à mettre en balance avec le coût d'interventions alternatives, mais nous ne disposons malheureusement pas d'une situation de référence très claire en la matière. Néanmoins, les données chiffrées rassemblées devraient permettre d'y voir plus clair dans cette décision difficile.

Nous avons pu bénéficier durant ce travail de l'aide d'hépatologues, de virologues et d'autres spécialistes belges et étrangers. Nous tenons tout particulièrement à les remercier car sans eux, nous n'aurions pas pu mener ce travail à bien.

Jean Pierre CLOSON
Directeur général adjoint

Raf MERTENS
Directeur général

Résumé

INTRODUCTION

L'hépatite B chronique (*chronic hepatitis B,* CHB) est une inflammation du foie le plus souvent asymptomatique provoquée par une infection chronique due au virus de l'hépatite B (VHB). Au départ, l'hépatite B chronique se caractérise par la présence dans le sang de l'antigène e du VHB (CHBe+). L'évolution de l'hépatite B chronique présente une grande variation. Chez de nombreux patients, la réplication virale et l'inflammation hépatique sont fortement réduites après une séroconversion de l'antigène e. Ces patients deviennent alors des 'porteurs inactifs' (*inactive carriers,* ICAR) et peuvent atteindre une séroconversion pour l'antigène de surface du VHB (HBsAg- ou stade résolu). D'autres patients peuvent évoluer vers une forme d'hépatite active à antigène e négatif (CHBe-). Tant les patients CHBe+ que les CHBe-, non cirrhotiques, se trouvent exposés au risque de développer une cirrhose du foie (compensée : CC ou décompensée : DC). Les patients avec CHB, en particulier les cirrhotiques, courent un risque de développer un carcinome hépatocellulaire (CHC), une forme de cancer hépatique. Comparé aux patients de race blanche le risque de CHC s'est révélé plus élevé chez les Asiatiques. Il est probablement également plus haut chez les Africains d'origine subsaharienne, qui représentent une proportion croissante des patients CHB en Belgique. A moins qu'une greffe du foie puisse être pratiquée, la cirrhose décompensée (DC) et le CHC sont associés à une mortalité élevée.

Pour être remboursé tout médicament antiviral contre le VHB nécessite une prescription par un spécialiste en médecine interne et une autorisation par le médecin conseil de la mutualité. Les patients doivent entre autres présenter des taux élevés d'enzymes hépatiques (ALT) et un stade de fibrose ou d'inflammation hépatique (non précisés) sur une biopsie du foie.

En Belgique environ 10% des patients traités reçoivent des injections d'interféron-alpha pégylé pendant un an. Pour beaucoup de patients cette modalité thérapeutique n'est pas considérée comme appropriée pour des raisons diverses. En revanche, les analogues de nucléos(t)ide (AN) peuvent être utilisés plus généralement comme traitement antiviral. Les AN sont disponibles sous forme orale et sont bien tolérés mais ils peuvent nécessiter une administration tout au long de la vie. Le premier AN, la lamivudine, a obtenu un remboursement en 2001 comme traitement de première ligne. Toutefois, étant donné que le VHB développe une résistance envers la lamuvidine, entraînant très probablement l'inefficacité du traitement, ce dernier n'est plus considéré approprié comme traitement de première ligne. Adefovir a succédé à la lamuvidine, mais seulement en traitement de seconde ligne.

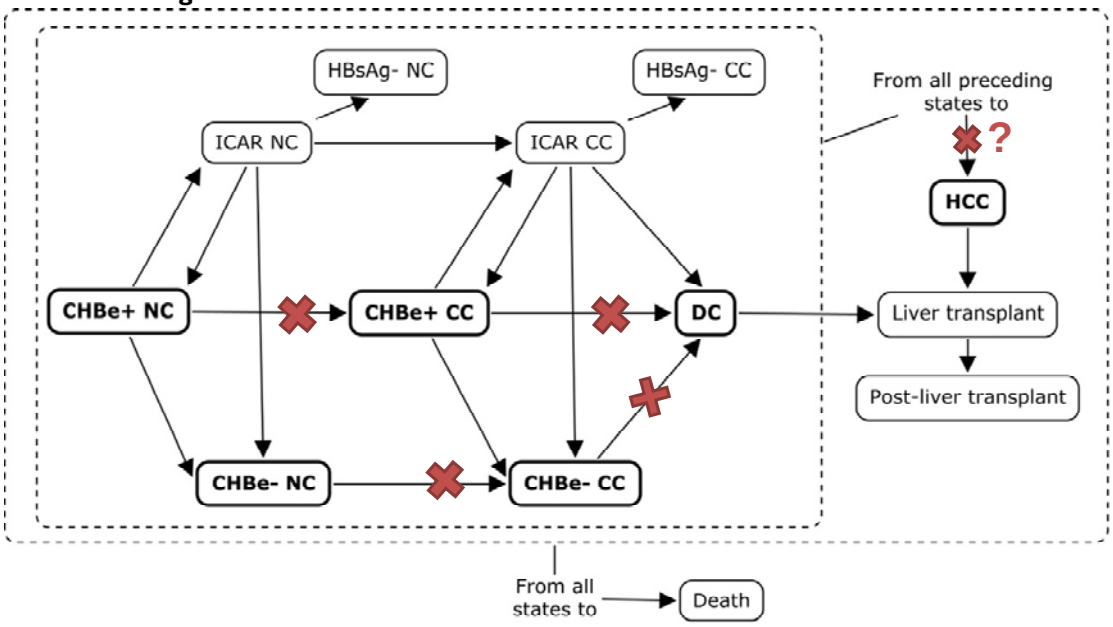
Depuis 2010 tenofovir et entecavir sont remboursés à 100% en traitement de première ligne à un coût annuel de respectivement 4 970 euros et 5 221 euros par patient. Les deux médicaments sont bien tolérés et empêchent la réplication virale avec une probabilité très faible d'entraîner une résistance au médicament, au moins chez les patients qui ne présentent pas encore de résistance à la lamuvidine. Il n'existe cependant pas d'études randomisées et contrôlées à long terme pour tenofovir ni pour entecavir démontrant un effet sur la progression de la maladie ni sur des critères d'évaluation cliniques durs.

Le présent rapport est le second des projets du KCE relatifs au traitement antiviral de l'hépatite B chronique. Dans cette seconde partie du rapport, nous étudions le rapport coût-efficacité du traitement antiviral. Nous nous basons sur la première partie dans laquelle nous avions couvert l'histoire naturelle et l'épidémiologie, les traitements antiviraux et les études de rapport coût-efficacité publiées. En outre, nous avons collecté prospectivement des informations cliniques et relatives à la qualité de vie chez 544 patients ayant consulté leur hépatologue en Belgique au cours du premier semestre 2009 pour une infection à VHB chronique ou une complication non aiguë de celle-ci. Les données cliniques enregistrées portent sur l'année 2009 et, lorsqu'elles étaient disponibles, aussi sur 2006. Les données cliniques de 2006 ont été liées aux coûts de 2006 de l'INAMI (Institut National Maladie-Invalidité). De surcroît, nous avons analysé la progression de la maladie au sein d'une vaste cohorte récente de patients de race blanche atteints de CHB et non traités, suivis à l'Hôpital universitaire de Leuven.

METHODES

STADES ET TRANSITIONS DE LA MALADIE

Figure A. Modélisation des stades et transitions de la maladie.



Abréviations:

CHBe+	hépatite B chronique, antigène e positif	CHBe-	hépatite B chronique, antigène e négatif
NC	non-cirrhotique	CC	cirrhose compensée
ICAR	porteur inactif	HBsAg-	hépatite B, antigène de surface négatif
DC	cirrhose décompensée	HCC	carcinome hépatocellulaire

Notes: En utilisant un cycle d'une durée d'un an, les patients évoluent entre les stades de la maladie. Les patients peuvent rester dans un même stade avec une certaine probabilité pendant plus d'une année, sauf au stade de la transplantation hépatique, à partir duquel ils évoluent soit vers le stade post-transplantation soit vers le décès. On part de l'hypothèse selon laquelle les patients sont **traités aux stades indiqués en gras** : CHBe+/- NC, CHBe+/- CC, DC et HCC; Dans le modèle, les transitions blocquées, en partie, de façon directe grâce au traitement antiviral sont **marquées par une croix.**

L'évaluation est basée sur un modèle Markov avec des stades de la maladie et des transitions multiples (Figure A). Les probabilités de transition pour la stratégie « aucun traitement antiviral » reposent essentiellement sur la littérature et les avis d'experts. De plus, nous avons eu accès à des données non publiées relatives à 278 patients de race blanche atteints de CHB mais non traités, avec une durée moyenne de suivi de 7,8 années à l'Hôpital universitaire de Leuven. Pour au moins deux raisons, cette base de données s'est révélée très précieuse. Premièrement, elle nous a permis d'estimer les probabilités de transition vers un état cirrhotique, spécifiques à l'âge, chez des patients CHBe+ et CHBe- non traités. Ceci a permis une découverte novatrice dans ce champ de recherche, à savoir le constat d'une augmentation considérable de la probabilité de transition vers la cirrhose hépatique après l'âge de 50 ans. Cette information a fortement amélioré la précision de nos estimations dans le modèle. Deuxièmement, nous avons observé que chez les 59 patients CHBe+, qui présentaient des taux d'enzymes hépatiques (ALT) stables en l'absence de cirrhose hépatique, aucune progression de la maladie sur une période de 10 ans n'a été observée, confirmant et renforçant les constats antérieurs.

COHORTES DE PATIENTS, STRATÉGIES THÉRAPEUTIQUES ET EFFETS

Pour nos analyses des coûts et d'efficacité, nous comparons la stratégie de traitement antiviral (avec tenofovir ou entecavir) à la stratégie de 'non-traitement antiviral'. Nous utilisons l'histoire naturelle en guise de comparateur étant donné que (1) la lamivudine n'est plus considérée comme traitement de première ligne de référence pour la CHB, (2) adefovir consiste en un traitement de seconde ligne, et (3) l'interféron-alpha pégylé n'est éligible comme traitement de première ligne que pour des patients sélectionnés.

Selon les résultats des études à court terme disponibles, l'entecavir et le tenofovir semblent présenter une efficacité équivalente pour des patients non résistant à la lamuvidine. Les patients ayant une résistance à la lamuvidine peuvent aussi manifester une résistance à l'entecavir. Vu que le tenofovir est moins coûteux que l'entecavir (et devrait probablement le rester), l'option tenofovir prédomine sur l'option entecavir. Autrement dit, le tenofovir présentera toujours un rapport coût-efficacité plus favorable que l'entecavir.

Comme point de départ, nous avons suivi des cohortes hypothétiques de patients européens, traités et non traités, âgés de 40 ans souffrant d'une hépatite B chronique à antigène e positif ou négatif, non cirrhotiques (CHBe+ NC et CHBe- NC). Par ailleurs, nous avons évalué une cohorte de patients de 50 ans atteints d'une cirrhose compensée (CC), cette cohorte étant constituée de 30% de patients CHBe+ CC et de 70% de patients CHBe- CC. Pour chacune de ces trois cohortes (toutes étant constituées à 70% de patients de sexe masculin), nous avons pris en compte des horizons temporels de 10 et de 20 ans, vu que l'expérience thérapeutique actuelle basée sur des études (non contrôlées) est limitée à environ 5 ans.

Dans les analyses de scénarios, nous avons évalué différents âges au début du traitement, nous avons augmenté la probabilité de transition vers un CHC telle qu'observée dans les cohortes asiatiques et nous avons varié les taux d'actualisation pour les coûts et les effets. Pour le scénario de base le taux d'actualisation des coûts et des effets a été fixée à 3% et 1,5% respectivement.

Notre modèle applique le traitement antiviral en accord étroit avec les recommandations internationales. Ceci implique que les patients CHBe- reçoivent leur traitement antiviral tout au long de leur vie ou jusqu'à une transplantation hépatique. En l'absence d'essai clinique contrôlé randomisé, nous nous basons pour la modélisation des effets du tenofovir et de l'entecavir sur des avis d'experts et sur des études à un seul bras avec un suivi maximal de 5 ans. Le traitement antiviral est supposé réduire fortement la progression vers la cirrhose hépatique et la décompensation: dès lors, nous appliquons une réduction de 75% des probabilités de transition. L'effet antiviral sur le CHC est beaucoup moins certain. Cette incertitude a été incluse dans le modèle.

COÛTS ET SCORES D'UTILITÉ

L'analyse utilise la perspective de l'assurance maladie-invalidité qui rembourse les soins de santé. Les coûts de la prise en charge de la maladie se fondent sur les montants réels facturés pour 2006 obtenus en utilisant l'enquête belge (Partie I du rapport). Seuls les coûts pouvant être attribués à l'hépatite B chronique par un médecin spécialiste en ce domaine ont été inclus. Nous avons constaté que les données relatives aux coûts obtenues pour les plus petits groupes (DC, CHC, année de la greffe du foie) étaient en accord avec les publications de coûts internationales. Les valeurs d'utilité sont fondées sur notre enquête EQ-5D de 2009 auprès de 500 patients dans 18 centres belges d'hépatologie (Partie 1du rapport), tandis que les valeurs pour les plus petits groupes ont été adaptées en se basant sur la littérature (Table A).

Tableau A. Nombre de patients, coûts annuels et score d'utilité par stade de la maladie

Stade la maladie	Nombre de patients ayant consulté un spécialiste en Belgique en 2009 pour une CHB°	Coûts moyens annuels par patient, liés au VHB		Score d'utilité moyen (95% intervalle de confiance)
		Pas de stratégie antivirale (euros)	Stratégie Tenofovir (euros)	
ICAR	1266	115	115	0.83 (0.82-0.87)
CHBe+/- NC	1197	591*	591+4970**	0.82 (0.78-0.86)
CHBe+/- CC	383	1115*	1115+4970**	0.78 (0.73-0.84)
DC§	10	6814*	6814+4970**	0.49 (0.46-0.51)#
CHC	49	10816*	10816+4970**	0.52 (0.49-0.54)#
Greffe hépatique	19	99998	99998	0.71 (0.69-0.74)#
Post greffe hépatique	181	7518	7518	0.82 (0.75-0.88)

°En excluant une co-infection par le VIH ou le VHC; *Coûts de prise en charge de la maladie liée au VHB après exclusion du coût des médicaments antiviraux; **Ce coût annuel du tenofovir avait été diminué dans le modèle de 17% en 2015 et de 19% en 2018. #En se basant sur la réduction absolue des scores d'utilité de la CHB, telle que rapportée par Levy et al. 2008. § Le nombre de patients avec cirrhose décompensée est clairement sous-estimé vu que les patients avec affection aigüe ont été exclus de la participation à l'enquête.

RESULTATS

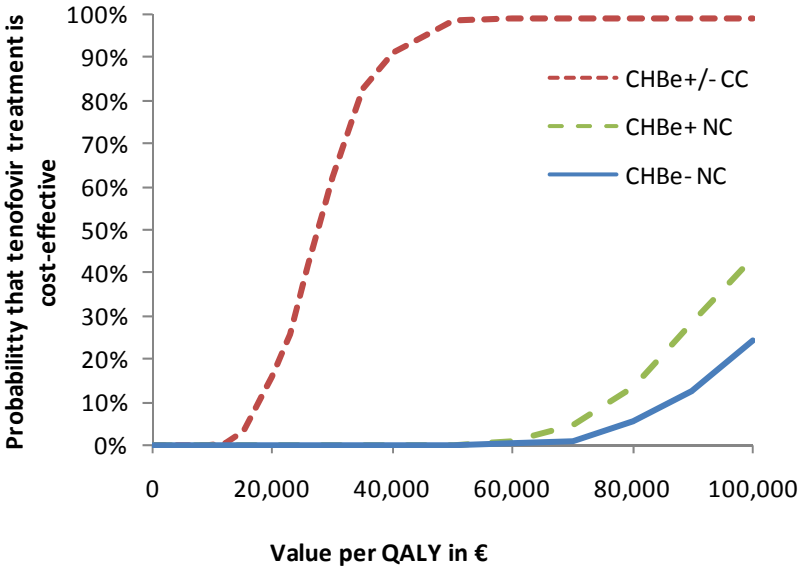
Pour le scénario de référence, les effets en termes de QALYs (quality-adjusted life year, années de vie ajustées pour la qualité) gagnées, de coûts supplémentaires et de rapports coût-efficacité différentiels (ICER) sont repris dans le tableau B. Dans le cas des patients CHBe+/- NC, les gains en QALYs sur une période de 20 ans sont faibles. Les surcoûts sont considérables, amenant à des ICER d'en moyenne plus de 100 000 euro par QALY. L'ICER est plus favorable pour les patients CHBe+/- de 50 ans et d'origine européenne, principalement en raison de gains plus élevés en QALYs sur une période de suivi de 20 ans. A un horizon d'observation de 10 ans, les ICER sont considérablement plus élevés qu'à 20 ans, en particulier pour les cohortes de patients de 40 ans CHBe+ (de 210 000 à 838 000 euro par QALY) et CHBe- (de 249 000 à 1 325 000 euro par QALY).

Tableau B. Analyse coût-utilité de base, horizon d'observation de 20 ans

Cohorte	QALY gagnés En moyenne (intervalles de confiance)	Moyenne des coûts supplémentaires en Euro (intervalles de confiance)	Moyenne des ICER en euro/QALY (intervalles de confiance)
CHBe+ NC 40 ans	0.3 (0.2 to 0.5)	33 000 (26 000 to 41 000)	110 000 (65 000 to 184 000)
CHBe- NC 40 ans	0.5 (0.3 to 0.8)	58 000 (53 000 to 62 000)	131 000 (75 000 to 240 000)
CHBe+/- CC 50 ans	1.3 (0.8 to 1.8)	32 000 (21 000 to 41 000)	29 000 (16 000 to 47 000)

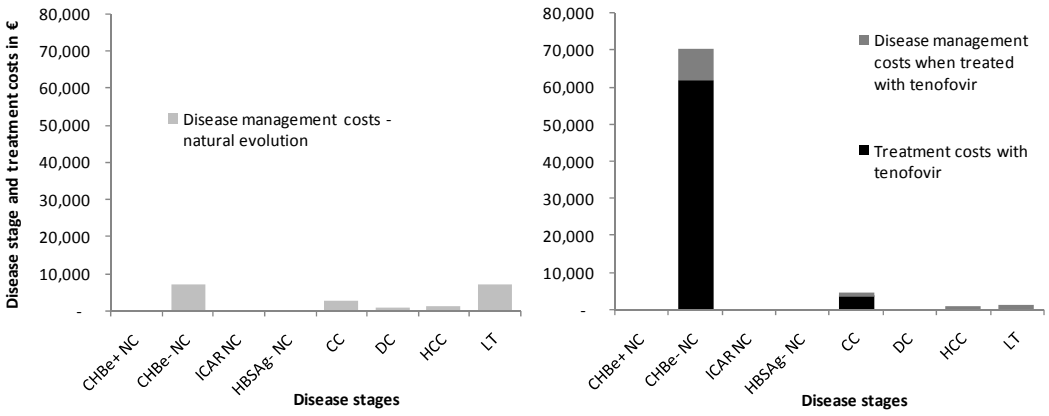
La probabilité de considérer que le traitement par tenofovir est coût-efficace va dépendre de ce que la société est prête à payer pour un QALY supplémentaire, c'est-à-dire de la valeur seuil de l'ICER. Ceci est illustré par les courbes d'acceptabilité du rapport coût-efficacité. Par exemple, dans le scénario de référence pour un patient CHB non-cirrhotique avec un suivi de 20 ans, le traitement par tenofovir ne s'avère jamais une stratégie optimale à des valeurs seuil de l'ICER allant jusqu'à 60 000 euro. Si l'on accepte un ICER de 100 000 euro par QALY la probabilité qu'un traitement par tenofovir devienne une option coût-efficace augmente à 40%. Pour les patients atteints de cirrhose, la probabilité qu'un traitement par tenofovir soit coût-efficace monte à 90% pour une valeur seuil de 40 000 euros par QALY.

Figure B. Courbes d'acceptabilité du rapport coût-efficacité pour traitement par tenofovir (versus aucun traitement antiviral) chez des patients CHBe+/- non cirrhotiques de 40 ans, pour un suivi de 20 ans.



Pour des patients non cirrhotiques, le traitement par tenofovir diminue de manière significative les coûts du traitement (et le nombre de cas) des cirrhoses hépatiques décompensées, des CHC et des transplantations hépatiques, dans le modèle sur 20 ans (Figure C). Cependant cette amélioration engendre un coût cumulé élevé pour le tenofovir qui représente la plus grande partie du coût.

Figure C. Coûts (actualisés) par patient et par stade de la maladie: comparaison des stratégie de « non traitement » et de traitement par tenofovir chez les Européens CHBe- non cirrhotiques de 40 ans, suivis sur 20 ans.



Le tableau C présente les résultats d'analyse par scénario. Les ICER diminuent avec l'avancement de l'âge du patient de 30 à 50 ans. Les ICER sont légèrement plus favorables pour les cohortes asiatiques que pour les Européennes.

Tableau C. Analyses de scenario : intervalles d'ICER pour le traitement par tenofovir de patients CHBe+ et CHBe- par âge, origine et état de cirrhose hépatique à un horizon de 20 ans (ICER exprimés en x1 000 euro/QALY)

Cohorte d'âge	Origine du patient	CHBe+ NC	CHBe- NC	CHBe+/- CC
30 ans	**Européenne**	132 - 355	143 - 461	15 - 45
	Asiatique	85 - 212	92 - 296	14 - 46
40 ans	**Européenne**	65 - 184	75 - 240	15 - 47
	Asiatique	51 - 126	58 - 157	13 - 45
50 ans	**Européenne**	28 - 97	38 - 145	16 - 47
	Asiatique	23 - 75	32 - 101	15 - 46
60 ans	**Européenne**	31 - 110	39 - 156	16 - 52
	Asiatique	28 - 83	37 - 119	15 - 50

IMPACT BUDGETAIRE

En 2009, les frais remboursés pour les médicaments antiviraux contre le VHB (en excluant les patients avec des coïnfections VIH ou VHC) se sont élevés à environ 3 millions d'euros. Si l'utilisation du tenofovir devait se généraliser chez les patients CHB tel que modélisé, le coût du remboursement du tenofovir dépasseraient les 8 millions d'euros par an, ce qui représente des dépenses additionnelles de plus de 5 millions d'euros par an (dont environ 2 millions d'euros pour le traitement des patients cirrhotiques). Cet impact budgétaire serait encore plus important si les critères de traitement étaient assouplis en faveur des patients présentant des valeurs ALT normales. Le budget global de la prise en charge des maladies liées au VHB, pourrait passer 8 à 13 millions d'euros par an.

DISCUSSION ET CONCLUSION

Le modèle que nous avons développé comporte un nombre d'avantages par rapport à ceux publiés jusqu'à présent. Primo, nous avons tenu compte de la situation belge en ce qui concerne le nombre de patients, leurs caractéristiques, leur qualité de vie et les coûts attribuables par stade clinique de la maladie. Secundo, nous avons pu avoir accès aux données non publiées d'une vaste cohorte de patients CHB non traités, de race blanche, suivis par l'Hôpital universitaire de Leuven. Cela nous a permis de construire un modèle plus précis de progression de la maladie et qui tient compte de l'âge.

Un premier constat important basé sur cette cohorte est l'absence de progression mesurable de la maladie sur une période moyenne de 10 ans chez 59 patients avec des valeurs normales pour les enzymes hépatiques. Cette observation vient en support des critères actuels de remboursement qui excluent de tels patients.

L'ICER pour un traitement permanent et coûteux visant à prévenir les complications à long terme dépend d'un certain nombre de variables clés. Les principales étant le délai survenant avant les complications qu'on veut éviter, leur fréquence et le coût annuel du traitement. Ceci explique les ICER plus favorables pour la cohorte des patients cirrhotiques que pour les non cirrhotiques : ces derniers accumulent les coûts de traitement antiviral et autre durant des périodes plus longues avant que les effets cliniques de ce traitement apparaissent.

Bien que les possibilités de transplantation du foie soient relativement élevées en Belgique, les ICER que nous avons trouvés pour les cohortes CHBe+ et CHBe- sont en général considérablement plus élevés que ceux rapportés par d'autres études (sponsorisées par les firmes pharmaceutiques). En guise d'explication, le tableau D énumère quelques déterminants majeurs.

Tableau D. Déterminants majeurs des différences d'ICER entre les modélisations du traitement antiviral de l'hépatite B chronique

	Modèles publiés (ICER plus bas)	Modèle KCE (ICER plus élevé)
Amélioration de la qualité de vie en cas de faibles taux d'ADN VHB ou de séroconversion 'e'	Oui, uniquement basé sur des suppositions	Non, basé sur des observations
Adhérence aux directives de traitement en cas de CHBe-	Non, traitement stoppé si faibles taux d'ADN VHB	Oui, traitement poursuivi
Progression naturelle vers cirrhose	Uniformément élevée pour tous âges (5% à 9%)	Dépendant le l'âge (1% à 5%)
Horizon temporel du modèle	Toute la vie	10 à 20 ans
Réduction présumée du risque de CHC sous traitement	Réduction forte, basée sur les données d'une cohorte non traitée	Réduction d'environ 50% dans des cohortes CHB, grande incertitude

Tout d'abord, de nombreux modèles partent du postulat optimiste que les scores d'utilité s'améliorent immédiatement de 0.18 lorsque la diminution de la charge virale escomptée après le traitement s'amorce. Même si le traitement coûte 5 000 euros par an, l'ICER approche ainsi facilement les 25 000 euros par QALY. En fait, nous n'avons pas mesuré de différence d'utilité chez les patients présentant des niveaux élevés ou faibles d'ADN VHB sous traitement antiviral.

Deuxièmement, nous avons trouvé chez les patients CHBe+ et CHBe- des probabilités de transition vers une cirrhose qui augmentaient avec l'âge, surtout après les 50 ans. Sans cet ajustement, on pourrait conclure qu'instaurer le traitement le plus tôt possible conduit à un rapport coût-efficacité plus favorable, tandis que notre étude indique l'inverse. En outre, des probabilités uniformément élevées de transition vers une cirrhose dans tous les groupes d'âge ne sont pas compatibles avec le taux relativement faible de patients atteints d'une cirrhose hépatique parmi les patients CHB de race blanche en Belgique.

Sur base de notre modèle les ICER s'améliorent considérablement lorsque l'horizon d'observation est prolongé. Cependant, comme l'expérience thérapeutique actuelle ne s'étend même pas à dix ans, la plus grande prudence est de mise quant à l'interprétation des projections au-delà de vingt ans.

Enfin, certains modèles partent de l'hypothèse d'effets élevés du traitement, tant pour l'évolution vers la cirrhose que vers le CHC, effets qui sont calibrés en utilisant des données de charge virale obtenues dans une cohorte de population non traitée (qui est essentiellement constituée de patients à antigène HBe négatif au Taiwan). Il reste à prouver qu'une diminution de la charge virale amenée par le traitement, entraîne une réduction à long terme de la cirrhose et de la CHC jusqu'à un niveau comparable à celui rencontré dans un état naturel de faible charge virale. La relation entre le système d'immunité, la charge virale et le stade de fibrose hépatique est plus complexe, comme cela a été rapporté dans une étude récente en Australie chez des patients CHBe+.

L'effet du traitement antiviral sur le développement du CHC est toujours peu clair et difficile à dissocier du processus de progression de la fibrose. Si l'on accepte que la présence d'une cirrhose du foie crée, en soi, un risque accru de CHC, le repoussement de l'évolution vers la cirrhose devrait également réduire le CHC. En outre, il peut y avoir un effet direct de la diminution de la charge virale sur le développement d'un CHC, ce que nous avons modélisé de manière prudente. Des données récentes du Japon semblent exclure toute réduction majeure du CHC sous traitement par entecavir. L'effet présumé du traitement sur le CHC revêt une importance essentielle pour les populations CHB asiatiques puisque ces dernières ont une incidence accrue de CHC par rapport aux cohortes de patients européennes. Le traitement des patients CHB asiatiques induit dès lors des ICER légèrement plus favorables par rapport aux cohortes de patients européennes.

Nous ne savons pas encore dans quelle mesure les données obtenues chez des asiatiques vivant en Asie peuvent être extrapolées à des patients d'Afrique sub-saharienne ayant émigré en Europe et qui représentent une fraction croissante de l'ensemble de la population CHB totale en Europe.

Enfin, le coût annuel actuel de l'entecavir administré à raison de 0.5mg par jour étant plus élevé que celui du tenofovir, les résultats ne peuvent pas être extrapolés en tant que tels à l'entecavir. De plus, chez les patients infectés par le VHB résistant à la lamivudine, on a rapporté une résistance à l'entecavir, ce qui aura également un impact sur les analyses. Bien entendu, il reste toujours des situations dans lesquelles il peut être plus adéquat de recourir à une molécule spécifique. Une analyse coûts-utilité ne doit pas être interprétée comme une recommandation pour la pratique clinique.

En conclusion, il importe de souligner qu'il n'existe aucune étude randomisée et contrôlée sur le tenofovir ni l'entecavir, qui démontre un effet sur la progression de l'affection ni sur des indicateurs cliniques durs. A cet égard, toute interprétation de résultats de modélisations à long terme, comme celle développée ici, doit se faire avec prudence. Plus particulièrement, l'effet du traitement antiviral sur le cancer hépatocellulaire reste fort incertain.

RECOMMANDATIONS[a]

- **L'ICER du traitement par tenofovir des patients à un stade plus avancé de la maladie (cirrhotiques) est plus favorable que celui du traitement des patients non cirrhotiques. De ce fait, le traitement de l'hépatite B chronique par tenofovir devrait cibler les patients avec cirrhose hépatique ou à haut risque de la développer.**
- **Le remboursement de ce traitement antiviral est recommandé chez les patients cirrhotiques souffrant d'hépatite B chronique présentant des valeurs normales pour les enzymes hépatiques (ALT).**
- **Un traitement antiviral chez les patients souffrant d'hépatite B chronique sans cirrhose et présentant des valeurs normales pour les enzymes hépatiques (ALT) ne se justifie pas tant en termes d'efficacité que de rapport coût-efficacité.**
- **Partant de l'hypothèse d'une efficacité égale chez les patients non-résistants à la lamuvidine, le tenofovir constitue en général une option thérapeutique plus coût-efficace par rapport à l'entecavir et devrait donc être utilisé de préférence.**
- **Pour le vaste groupe de patients souffrant d'une hépatite B chronique non-cirrhotique, lancer un traitement à 30 ans est clairement moins coût-efficace que de le lancer à l'âge de 50 ans.**

AGENDA DE RECHERCHE

- **Il convient d'encourager des recherches ultérieures visant à identifier les patients souffrant d'hépatite B chronique avec un risque élevé de développer une cirrhose du foie.**
- **Des recherches ultérieures sont nécessaires pour déterminer l'effet du traitement antiviral sur l'incidence du carcinome hépatocellulaire en cas d'hépatite B chronique.**

a Le KCE reste seul responsable des recommandations faites aux autorités publiques

Scientific summary

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GLOSSARY

ABBREVIATION	DEFINITION
ALT	Alanine aminotransferase
CEAC	Cost-effectiveness acceptability curves
CC	Compensated cirrhosis
CHBe- NC	Chronic hepatitis B e antigen negative without cirrhosis
CHBe+ CC	CHBe+ with compensated cirrhosis
CHBe+ NC	Chronic hepatitis B e antigen positive without cirrhosis
CHBe-CC	CHBe- with compensated cirrhosis
CI	Confidence interval
DC	Decompensated cirrhosis
eSC	e antigen seroconversion
HAI	Histology activity index
HR	Hazard ratio
HBsAg- CC	HBsAg-with compensated cirrhosis
HBsAg- NC	HBsAg- without cirrhosis
HBV	Hepatitis B virus
HCC	Hepatocellular Carcinoma
ICAR CC	Inactive carrier with compensated cirrhosis
ICAR NC	Inactive carrier (low viral replication state) without cirrhosis
ICER	Incremental cost-effectiveness ratio
LR death	Liver related death
LT	Liver transplant
LY	Life year
LYG	Life-year gained
NA	Nucleos(t)ide analogues
NC	Non cirrhotic
NIHDI	National Institute for Health and Disability Insurance, INAMI/RIZIV
Peg-IFN	Pegylated interferon
QALY	Quality-adjusted life-year
QoL	Quality of Life
RCT	Randomized controlled trials

1 BACKGROUND AND OBJECTIVES

1.1 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 causes 0.5 to 1.2 million deaths a year. [1] For Belgium, recent data are missing, but the last available estimates mention HBs antigen positivity for 0.7% of the Belgian population. [2] This is in line 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. [1] 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. [3] 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. [3] 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. 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 after e antigen seroconversion the patient may become an 'inactive carrier' (ICAR), a state with low viral replication. 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' (CHBe-). The characteristics of the major phases of the HBV infection are given below. Not all patients go through every phase (Table 1). [4] Chronic hepatitis leads to scar formation in the liver (fibrosis), sometimes resulting in compensated liver cirrhosis (CC). This process is accelerated e.g. by alcohol (ab)use. In addition, patients with CHB (and even more those with liver cirrhosis) have an increased risk of developing hepatocellular carcinoma (HCC). For patients with decompensated cirrhosis (DC) or limited forms of HCC a liver transplantation can be life saving.

Table 1. The distinct phases of infections with the hepatitis B virus.

Phases	Immune tolerance	Immune active CHB		Inactive carrier (ICAR)	Reactivation	Resolved
		HBeAg+ (wild type) Immune reactive CHBe+	HBeAg- (precore mutant) CHBe-			
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

1.2 TREATMENT

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. As the course of the chronic infection varies from very benign to life-threatening, identifying those patients at high risk of severe complications is important to guide the frequency of monitoring and to target treatment. It should be noted that a complete elimination of HBV is most probably not possible. It is recommended not to treat patients who are in the 'immune tolerance' phase and 'inactive carriers' (Table 1). In order to be reimbursed in Belgium, all HBV 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 pegylated interferon-alfa2a (Peg-IFN, Pegasys®) in 2007. Peg-IFN 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+ [9] and 4% of HBeAg- CHB patients. [10] In Belgium about 10% of the treated patients are treated for one year with injections of (pegylated) interferon-alpha but for many other patients this is not considered an appropriate treatment option for a variety of reasons.

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 (it is not considered a recommended first line treatment). Guidelines for treatment of CHB have been updated over the last few years with the market introduction of a number of antiviral agents.[5-8] Recently, the reimbursement criteria in Belgium have been adapted in accordance with the international guidelines. This means that lamivudin is no longer considered an appropriate first line treatment. Instead, in Belgium, tenofovir (Viread®, 300mg tenofovir disoproxil fumarate, equivalent to 245 mg tenofovir disoproxil, per day) and entecavir (Baraclude®, 0.5mg per day) obtained reimbursement for first line treatment of chronic hepatitis B (tenofovir was already reimbursed before for HIV treatment). Tenofovir and entecavir have a relatively high annual cost of about 5000 euro per year. The NA class of drugs has the potential for mitochondrial damage, leading to myopathy and neuropathy. [11] One NA was recently withdrawn for that reason. Adefovir and tenofovir may cause nefrotoxicity 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.[12, 13] HBV develops much less frequently resistance to tenofovir or entecavir. Therefore, these agents are more likely to lower HBV DNA for more than 5 years in most patients. However, resistance to entecavir has been detected in lamivudin-refractory patients. [14-16] In studies with a duration up to 5 years, these newer NAs 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. [17] Such long-term studies have not been a requirement for obtaining marketing approval nor for obtaining reimbursement.

1.3 OBJECTIVES AND CONTENT OF THE TWO REPORTS

This is the second report of the KCE project on health-economic aspects of antiviral treatment of chronic hepatitis B (CHB). The overall goal of the project is the study of the cost-effectiveness of the recently introduced antiviral drugs in Belgium (tenofovir and entecavir), using a model based as much as possible on Belgian data. These Belgian data allow ascertaining to a better degree the quality of our results and the possibility of drawing policy recommendations. As lamivudine is no longer considered a state-of-the-art first line treatment of CHB, as adefovir is a second line treatment, as (pegylated) interferon-alpha is an appropriate first line treatment for selected patients only, we use the natural history as comparator.

In the part 1 KCE report, we studied the natural history and epidemiology of chronic infections with the hepatitis B virus (HBV), and the literature on treatment efficacy and safety, as summarized above. We reviewed nine recent publications on the cost-effectiveness of the currently approved antiviral treatments for this infection and found they often model optimistic assumptions on long-term effectiveness without inclusion of an appropriate range of uncertainty. [18-26] 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 to our field assessment of quality of life (QoL) in real patients with a low HBV DNA under NA treatment. In our model we address several of the identified weaknesses.

QoL (EQ-5D form) data and clinical information were prospectively collected in 544 patients visiting their liver specialist in Belgium during the first half of 2009 for chronic HBV infection or a non-acute complication thereof. The investigators reported the disease state, laboratory values and antiviral treatment for 2009 and, if available, for 2006. The 2006 clinical data were linked to the 2006 costs for the NIHDI (National Institute for Health and Disability Insurance, INAMI/RIZIV). We estimated the HBV CHB related burden of disease for Belgium (Table 2).

Table 2. Estimated number of patients by stage/complication and region of origin, visiting a liver specialist in Belgium for chronic HBV infection or its complications, situation early 2009.

	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%

Notes: Based on KCE report 1. [27] Co-infections with HIV or HCV are not included. The number of patients with decompensated cirrhosis was likely underestimated as patients presenting with acute disease could not participate to the survey.

Over the last years about 19 patients per year received a life saving liver transplant in Belgium, mainly for decompensated cirrhosis or also for limited forms of HCC.

The second part of the project was conducted by KCE experts in collaboration with a number of hepatologists, in particular from Leuven University Hospital, and guided by other external experts who had been involved in part 1.

In this second part, we add to the natural history literature the preliminary results on disease progression by patient age based on a large untreated cohort of Caucasian patients followed at Leuven University Hospital. We compare and complement our measured utility scores with a review of the literature on health utilities for different CHB disease states. We analyse and report Belgian HBV-related healthcare consumption data by CHB disease state.

Table 3. Sources of input variables for Markov model.

	Disease states and transitions	**Costs by disease state**	**Utilities by disease state**
Literature review	Yes	Partly	Partly
Collection and analysis of Belgian data	Yes	Yes	Yes

All above mentioned data served as input for a Markov model to study the cost-effectiveness of two recently introduced antiviral agents (tenofovir and entecavir). The results of this model are presented in this report. We followed treated and untreated hypothetical cohorts of patients aged 40 years, with either e antigen positive or negative CHB, non cirrhotic (CHBe+ NC and CHB- NC). In addition, a cohort of 50 year old patients with compensated cirrhosis (CC) was evaluated, consisting of 30% CHBe+ CC and 70% CHBe- CC patients. For each of these three cohorts we considered time horizons of 10 and 20 years for the base-case. In sensitivity analyses we varied the age at start of the cohorts, the transition probabilities to HCC to reflect an Asian population, and the discounting rates for costs and effects.

Also the budget impact for the National Institute for Health and Disability Insurance (NIHDI) of introducing these new treatments was estimated.

2 METHODS

2.1 TARGET POPULATION

The analysis was based on the following cohorts (Table 4) reflecting the heterogeneity of the CHB patients in Belgium that have been described in the KCE report part 1.[27]

First, we distinguish between patients with versus without a European country of origin. In this document the term Caucasian is also used for patients with a European country of origin. Patients born in high endemic regions such as Asia and Central Africa are mostly infected with HBV early in life. Studies in Asia show a relatively higher incidence of HCC in CHB patients. Data from cohorts in sub-Saharan Africa are lacking so far, but it is believed the risk of HCC is also increased in these patients, who constitute a growing proportion of the CHB patients in Belgium and Europe.

Second, we also model starting antiviral treatment in patient who already developed compensated liver cirrhosis. Between 11% [28] of CHBe+ patients and up to 30% of CHBe- patients have cirrhosis at the first visit at a specialist for their CHB infection.

Third, we run the model for cohorts of patients aged 40 and 50 years at baseline, which roughly corresponds to the average ages of new non-cirrhotic and cirrhotic patients seen in Belgium, respectively [27] (CHBe- NC patients in Belgium were on average nearly three years older compared with CHBe+ NC patients). Additional results were obtained for cohorts aged 30, 50 and 60 years for the non-cirrhotic patients and 30, 40 and 60 years for cirrhotic patients.

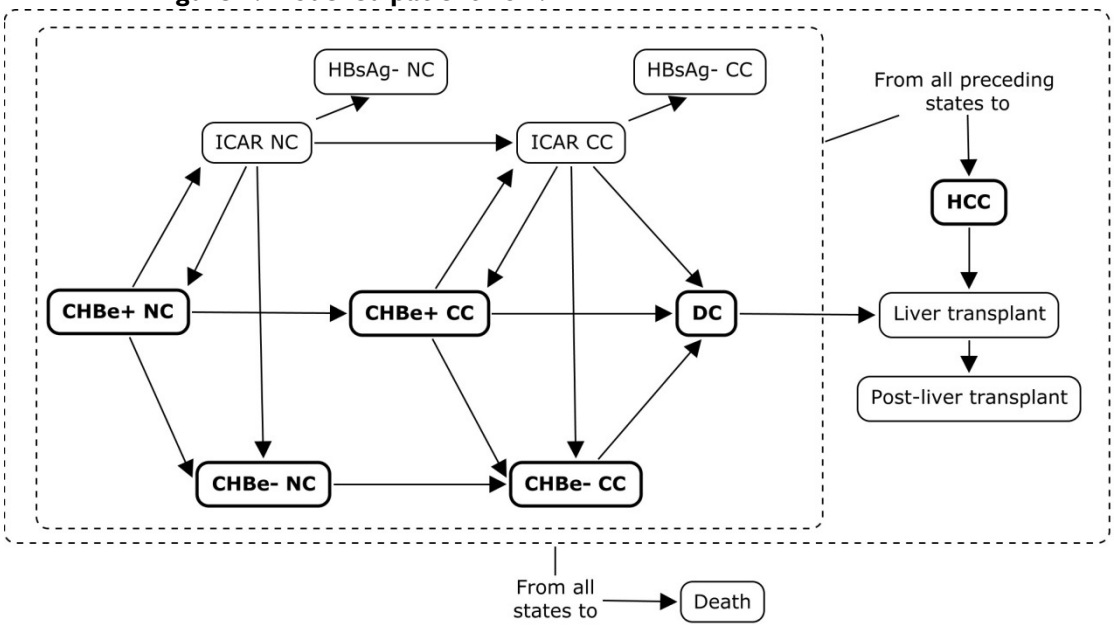
Table 4. Populations modelled.

Population at start of treatment	Mean age in years (additional cohorts studied)	Gender
European patients		
Non cirrhotic CHBe+ (CHBe+ NC)	40 (30, 50, 60)	70% men and 30% women
Non cirrhotic CHBe- (CHBe- NC)		
Mixed cohort of compensated cirrhosis (CHBe+/e- CC) patients (30% e+ and 70% e-)	50 (30, 40, 60)	
Asian population		
As above scenarios, but with transition probabilities to HCC applying to Asians		

2.2 MODEL STRUCTURE AND BASIC ASSUMPTIONS

We modelled disease progression as patient flows between 13 disease states, mainly based on the selection of states as defined in KCE report part 1. [27] Our model differs from most previously published models in the fact that we defined subgroups of patients with CHBe+, inactive carrier (ICAR) and CHBe- based on the absence (NC) or presence of compensated cirrhosis (CC), as different state transition rates have been described (see Table 5 of transition rates for references). For the states of decompensated cirrhosis (DC), HCC, liver transplant and post liver transplant, liver related death rates were applied and all-cause mortality was added; for all other states only all-cause mortality was applied. In the model we used a broad definition for DC as we did not model liver-related mortality in CC. Our DC state thus includes all non-HCC complications associated with liver related mortality, eg bleeding esophagal varices.

Figure 1. Modelled patient flow.



Notes: Using a 1-year cycle length patients move between the disease states starting from the state according to the outlined scenarios in section 2.1.Patients may remain in the same state with a certain probability for more than one year except in the liver transplant state, from where they move either to the post-liver transplant state or to death. It is assumed that patients are treated in the bold states: CHBe+/- NC, CHBe+/- CC, DC and HCC; Abbreviations: CHBe+, chronic hepatitis B e antigen positive; CHBe-, chronic hepatitis B e antigen negative; NC, non-cirrhotic; CC, compensated cirrhosis; ICAR, inactive carrier; HBsAg-, hepatitis B surface antigen negative; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma. Note that transition to ICAR is assumed to be realized when confirmed 6 months after e seroconversion, thus at a time when antiviral treatment is discontinued.

In contrast with some more recently published models, we did not define Markov states based on viral load because we do not feel confident with the data that feed such models (see also Discussion section).

Analyses

The analysis is based on a static, probabilistic Markov model with bootstrapping (visual Basic). All calculations are done in Excel, except for the estimation of transition probabilities from the non-cirrhotic to the cirrhotic states, which have been done in STATA.

Further basic structure of the model is defined by the following items:

- In our analyses of costs and effects we compare a strategy of antiviral treatment (using tenofovir or entecavir) with a "no antiviral treatment" strategy. We use the natural history as comparator because (1) lamivudine is no longer considered a state-of-the-art first line treatment of CHB, (2) adefovir is a second line treatment, and (3) (pegylated) interferon-alpha is an appropriate first line treatment for selected patients only.
- We used a 10 year and 20 year follow-up perspective as a base-case for the estimation of cost-effectiveness. This choice of these time horizons was driven by the insight that for some patient groups depending on age it may take long until the beneficial effects of treatment of avoiding disease complications materialize. Predictions beyond 20 years have however a high degree of uncertainty, both in terms of natural evolution of the cohort and especially treatment effects, as current treatment experience in trials is limited to about 5 years.
- Discounting. For the base-case, we utilized a discount rate of 3.0% for costs and 1.5% for outcomes according to the Belgian guidelines. [29]

- The analysis was performed from the perspective of health care payer, which includes payments out of the government's health care budget. Patient co-payments were calculated but not included as they constituted a very low percentage of the overall expenditures: 1% for newly transplanted patients to maximum 7% for inactive carriers, and most probably even lower when restricted to HBV related costs.
- We assumed that patients move between the states on average at the half of each yearly cycle.
- We used life-years (LY) and quality-adjusted life-years (QALYs) as model outcomes.
- The following probability distributions to the input factors of the model have been applied:
  - Transition probabilities between disease states: Beta distribution
  - Treatment effects: Beta distribution
  - Utility parameters: Beta distribution
  - Disease management costs: Gamma distribution
  - The parameters were drawn by use of the BETAINV and GAMMAINV functions in Excel.

2.3 TRANSITION PROBABILITIES

Transition probabilities were obtained from the literature review on natural history presented in part 1 of the report, completed with data from additionally identified references and a preliminary analysis of a large cohort of untreated CHB patients followed at Leuven University Hospital. This analysis is detailed in Appendix 1. The appropriateness of the Markov model for the Belgian situation and the importance of using appropriate individual transition probabilities was tested over hundreds of cycles until a steady state for each health status was achieved. With our final selection of transition rates, a distribution of disease states was obtained that was in line with the estimates for the Belgian patient population as assessed in report part 1 (assuming the 2009 situation in Caucasians of age 40 and over reflects more or less a steady state situation).

Table 5. Summary of transition probabilities.

From	To	Annual transition probability (range)#	Rationale and references
CHBe+/- NC (age < 40y)	CHBe+/- CC	1.0% (0.5 to 1.5)	Transition probabilities are based on the analysis of a large cohort of untreated Caucasian patients followed at Leuven University Hospital. Transition probability to cirrhosis varied with patient age but not with e antigen status. Others reported a transition probability 2 to 3% for clinic-based longitudinal studies, with older age, CHBe+ and high ALT as risk factors[30]. Studies included in the review by Liaw[31] report an incidence of CC in CHBe+ of 2.4% (which was higher than the overall incidence of 2.1%) to 3.5% (in CHB with persistent e+) and of 2.9% in CHBe-. Higher transition probabilities for Europe were reported by Fattovich but based on small studies: 3.7% (CHBe+, 77 patients) and 9.2% (CHBe-, 30 patients).[32] Importance of age for development of cirrhosis was also shown in a cohort in Taiwan.[33]
CHBe+/- NC (age 40 to 50y)	CHBe+/- CC	2.0% (1.0 to 3.0)	
CHBe+/- NC (age > 50 y)	CHBe+/- CC	5.0% (2.5 to 7.5)	
ICAR NC	ICAR CC	0.02% (0.01 to 0.03)	Fattovich[32] reports 0.01% and 0.07% for European and Asian patient populations. Only 1 in 184 patients developed CC after a median follow-up of 6.8 years.[31]
CHBe+ NC	ICAR NC	11% (5.5 to 16.5)	During e antigen seroconversion (eSC) about 5%[32] or 10 to 20%[30] directly transit to CHBe-; this transition is 10 times more frequent in CHBe+ CC.[34] The others transit to ICAR where about 75% will remain.[30, 32] Spontaneous eSC in CHBe+ varies from 2% to 15%,[31] 8% to 12%,[30] or 10 to 15% per year in adults with elevated ALT.[32] In the cohort of 70 CHBe+ patients,[28] only 4/8 CHBe+ CC patients showed eSC (about 4% per year) versus 57/62 CHBe+ NC patients (about 20% per year). In Taiwan eSC was 12% for CHBe+ NC and 6% for CHBe+ CC.[35]
	CHBe- NC	1.5% (0.8 to 2.3)	
CHBe+ CC	ICAR CC	2% (1.0 to 3.0)	
	CHBe- CC	4% (2.0 to 6.0)	
ICAR NC/CC	CHBe+ NC/CC	1% (0.5 to 1.5)	About 20% of the patients in ICAR experience reversions back to CHBe+ and 20% will finally transit to CHBe-. It has been reported that after 16 years 25% of all eSC patients have CHBe-.[36] The transition from CHBe- to ICAR has been reported to be very rare and was not included.
ICAR NC/CC	CHBe- NC/CC	2% (1.0 to 3.0)	
ICAR NC/CC	HBsAg- NC/CC	1.6% (0.8 to 2.4)	The annual HBsAg seroclearance rate has been reported to be 0.5% to 0.8% overall,[30] and 1.2% to 2.1%[31], 1% to 2%[32] and 2.1%[28] in ICAR patients.
CHBe+ CC	CHBe+ DC	3.5% (1.75 to 5.25)	Liver decompensation in CHBe+ CC and CHBe- CC is 4 times more frequent than in ICAR CC.[37] Liver decompensation is seen in about 14 to 15% after 5 years.[32, 36] Differences in transition probabilities in e+ versus e- CC are derived from mortality which is reportedly 6 times more frequent in CC CHBe+ and 4 times higher in CC CHBe- compared with ICAR CC.[36] The risk of death is decreased by a factor of 2.2 when eSC occurred in CHBe+ CC[38] Liver-related death rates in CC are 3.3% and 2.9% in Europe and Asia,[32] while overall mortality at 5 and 10 years in CC is 16% and 32% (annual transition probability: 3.8%).[30, 39]
ICAR CC	ICAR DC	0.75% (0.4 to 1.2)	
CHBe- CC	CHBe- DC:	3% (1.5 to 4.5)	

From	To	Annual transition probability (range)#	Rationale and references
CHBe+/- NC	HCC	0.12% (0.04 to 0.36) 0.60% (0.53 to 0.72)*	Transition rates to HCC in Europe are lower compared with Asia for all states, probably reflecting the importance of co-factors which are mainly present in Asia, such as aflatoxins.[30] The transition rates were selected as reported by Fattovich in a systematic review,[32] except for European CHB patients where we used the transition rate from the unpublished Leuven cohort. This rate is at the low end of the published transition rates for studies in Europe and the US (0.12% to 0.41% per year), not restricted to Caucasian patients.[32] Liaw[31] reports an annual incidence of HCC of 3 to 6% in Asian patients with cirrhosis.
ICAR NC		0.02% (0 to 0.05%) 0.20% (0.1 to 0.3)*	
CHBe+/- CC or DC		2.15% (1.5 to 2.8) 3.5% (3.0 to 4.0)*	
HBsAg- NC		0.01% (0 to 0.02) 0.10% (0.05 to 0.15)*	Expert opinion.
ICAR CC or HBsAg- CC		1.08% (0.5 to 1.6) 1.75% (0.9 to 2.6)*	
DC	LT-DC-y1	50% (25.0 to 75.0)	The 5 years mortality rates in DC vary from 70-85% to 86% (transition probability of 22 to 32.5%).[30, 32] In Belgium relatively many patients with DC or HCC benefit from liver transplantation. Kirchner et al.[40] reported for HCC in Southern Germany an overall transition probability to death of 35% per year.
	LR death	25% (12.5 to 37.5)	
HCC	LT-HCC-y1	15% (7.5 to 22.5)	
	LR death	35% (17.5 to 52.5)	
LT-DC-y1	LR death	9% (4.5 to 13.5)	One year mortality after liver transplantation in Leuven, Belgium, for LT-HCC-y1 is 11% versus 9% without HCC. The 10y mortality after liver transplantation for HCC is 48% versus 24% without HCC, corresponding to transition probabilities to death after y1 of 6% and 2% per year, respectively. As the overall Belgian statistics are somewhat less favourable for survival, at least after HCC,[41] and also to adjust for patient age, we add the age dependent mortality (about 1% per year at age 60y) to the LR death.
LT-HCC-y1		11% (5.5 to 16.5)	
LT-DC		2% (1 to 3)	
LT-HCC		6% (3 to 9)	

Range from 50% to 150% of point estimate value, unless the 95% confidence interval based on available study results provides a more narrow range. * Transition probabilities for Asian population. Original yearly transition rates have been converted to yearly transition probabilities for inclusion in the model using the following formula: transition probability = 1 – exp(-rate); Transition probabilities have further been transformed into the standard alpha and beta distribution moments of the beta distribution. CHBe+, chronic hepatitis B e antigen positive; CHBe-, chronic hepatitis B e antigen negative; NC, non cirrhotic; CC, compensated cirrhosis; ICAR, inactive carrier; HBsAg-, hepatitis B surface antigen negative; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; LR death, liver related death; y1, year 1.

2.4 DISEASE MANAGEMENT AND TREATMENT COSTS

Disease management costs are based on actual billing records from patients collected in 18 Belgian hepatology centres for the year 2006.[27] Since patients with CHB frequently undergo treatments related to other diseases, billing records were – in a major effort – thoroughly sorted according to their probability to be due to CHB or not (Appendix, section 6.3). The resulting disease management costs are depicted in Table 6. One drawback of this data is the low number of patients in decompensated cirrhosis, HCC and liver transplant. However, the costs are in the range of disease management costs of hepatitis B as registered in Europe (Belgium, France, Italy, Spain and UK) and Canada.[5] For comparison, these costs inflated to year 2009 Euros are estimated as follows: CHB e+/- NC: 1,306 – 3,463 €; compensated cirrhosis: 326 – 4,075 €; decompensated cirrhosis: 6,324 – 10,511 €; HCC: 4,459 – 13,041 €; liver transplant: 30,075 – 86,228 €. Thus, in the Belgian sample we have somewhat lower costs for CHB e+/- NC, we are in the range for compensated cirrhosis, decompensated cirrhosis and HCC, and we estimate higher costs for liver transplants.

Table 6. Disease management costs by disease stage (costing year 2009).

Disease state	Based on # patients	Mean cost	Standard deviation	Alpha** Parameter	Beta** parameter
Inactive carrier	71	115.22 €	29.39 €	15.4	7.5
Chronic hepatitis B e antigen +/-	141	591.06 €*	150.78 €	15.4	38.5
Compensated cirrhosis	47	1,114.90 €*	284.41 €	15.4	72.6
Decompensated cirrhosis	5	6,814.23 €*	1,738.32 €	15.4	443.5
HCC	4	10,816.24 €*	2,759.25 €	15.4	703.9
Liver transplant	5	99,997.52 €	25,509.57 €	15.4	6507.5
Post liver transplant	41	7,518.38 €	1,917.95 €	15.4	489.3

Notes: Estimates based on methodology as presented in section 6.3. Costs are inflated from year 2006 to 2009 by the using the Belgian Health Index,[42] which corresponds to a 6.7% increase . We assumed that 10% (range 5% to 15%) of all HCC patients received Nexavar (sorafenib) for an average of 18 weeks. In 2006, Nexavar was not yet reimbursed in Belgium; it is, however, reimbursed in 2010. This inflates the estimated disease management costs for patients with HCC by an average of 1610 € (Standard deviation 357.80 €). * Excluding cost of antiviral drugs, **Based on the Gamma probability distribution, the alpha parameters values are always the same, because of the previous assumption that costs vary +/-50% within the 95% confidence interval.

Based on estimates provided by the RIZIV-INAMI, the 2009 annual price of Viread (tenofovir) up to 1st July 2015 will be 4970.6 €. On the 1st July 2015 the ex-factory price of Viread will drop by 17%, and by 19% on the 1st July 2018 with reference to today's price. We have to assume in our scenarios that no generic antiviral will arrive on the market, since the impact on price developments are not quantifiable with any certainty. Otherwise, a further price decrease of Viread would have to be taken into account. Based on these price decreases, the average annual prices of tenofovir are depicted in Table 7. Similar price decreases are envisaged for Baraclude (entecavir), however starting from an annual price of 5,221 € in 2009, remaining above the annual cost of Viread in all subsequent years. No specific costs for monitoring tenofovir or entecavir therapy were included.

Table 7. Annual antiviral costs of Viread (tenofovir) in Belgium (costing year 2009).

Time period	Mean cost in €
Up to 1st July 2015	4,970.6
From 1st July 2015	4,144.1
From 1st July 2018 onwards	4,046.8

Notes: based on estimated provided by RIZIV-INAMI.

2.5 UTILITIES

Utility values to be used in the model were derived from our EQ-5D survey on the Belgian population during the first part of this study,[27] provided that the number of respondents per health state was high enough for the values to be robust. In the model, mean utilities (and 95% confidence intervals) for the health states CHB, CC, post-LT (follow-up years with liver transplant) and ICAR were thus valued at 0.82 (0.78-0.86; n=127); 0.78 (0.73-0.84; n=69), 0.82 (0.75-0.88; n=60), 0.83 (0.80-0.87; n=153). Utility values for the health state CHB was applied to both HBeAg+ and HBeAg- CHB, as no differences were seen in the survey (Table 8).

Utility values for the health states DC, HCC and LT were derived from the whole patient sample of Levy et al.[43] However, since the health preference values reported in Levy et al.[43] are much lower than ours, probably due to differences in instrument (EQ-5D vs Standard Gamble) or in subjects, we did not use the absolute values reported in this study. Instead, we computed the decrement in utility values between the states DC, HCC and LT compared with CHB in Levy et al.[43] and we subtracted this decrement from the initial CHB value (0.82) obtained in our survey.

Our EQ-5D survey did not reveal any major difference between the utilities reported from the whole patients sample (i.e. 50,9% Europe; 8,6% Turkey; 22,4% Africa; 18% Asia) and those from patients with a European origin only. By contrast Levy et al.[43] found important differences in utilities between countries with lower utilities reported from China and Hong Kong (both high endemic regions) compared to utilities reported from Canada, USA, UK and Spain. Levy et al. explains that the lower ratings of even the milder health states (CHB and CC) in China and Hong Kong may reflect a greater fear of the social consequences of infection since, for example, discrimination against Chinese carriers of CHB can result in difficulties in finding employment and access to education.

Table 8. Utilities by disease stage.

Disease states	Mean	95% CI		Source	Alpha**	Beta**
CHBe+ NC	0.82	0.78	0.86	KCE, 2010[27]	289.8	63.6
CHBe- NC	0.82	0.78	0.86	KCE, 2010[27]	289.8	63.6
Inactive Carrier	0.83	0.82	0.87	KCE, 2010[27]	719.0	147.3
Compensated cirrhosis	0.78	0.73	0.84	KCE, 2010[27]	169.2	47.7
Decompensated cirrhosis	0.49	0.46	0.51	Levy et al., 2008[43] (Adapted)	752.2	782.9
HCC	0.52	0.49	0.54	Levy et al., 2008[43] (Adapted)	797.3	735.9
Liver transplant	0.71	0.69	0.74	Levy et al., 2008[43] (Adapted)	897.8	366.7
Post liver transplant	0.82	0.75	0.88	KCE, 2010[27]	109.2	24.0
HBsAg	0.83	0.82	0.87	KCE, 2010[27]	719.0	147.3
HBsAg- CC	0.78	0.73	0.84	KCE, 2010[27]	169.2	47.7

Notes: Based on section 6.2. CHB, chronic hepatitis B; NC, non cirrhotic; HCC, hepatocellular carcinoma; HBsAg-CC, HBsAg-with compensated cirrhosis; **Based on the Beta probability distribution.

2.6 ANTIVIRAL TREATMENT

Recently, well tolerated and potent antiviral drugs with a high threshold for development of resistance, tenofovir (300mg tenofovir disoproxil fumarate, equivalent to 245 mg tenofovir disoproxil, per day) and entecavir (0.5mg per day), have been introduced in Belgium as in other countries. These antiviral drugs significantly advance the possibilities of treating patients with CHB during different stages of the disease.

In our analyses of costs and effects we compare a strategy of antiviral treatment (using tenofovir or entecavir) with a "no antiviral treatment" strategy. We use the natural history as comparator because (1) lamivudine is no longer considered a state-of-the-art first line treatment of CHB, (2) adefovir is a second line treatment, and (3) (pegylated) interferon-alpha is an appropriate first line treatment for selected patients only.

We however excluded quantifying the cost-effectiveness of entecavir, because it is dominated by tenofovir for the following reasons:

- Based on the available (short term) study results entecavir and tenofovir are assumed to be equally effective in patients who were not treated with lamivudine (the data are reviewed in detail in part 1).
- Patients, who are resistant to lamivudine and are then treated with entecavir as second-line treatment, are more likely to develop resistance than if treated with tenofovir
- With 5,221 € treatment costs per patient year, entecavir is around 250 € more expensive than tenofovir. The price difference is expected to remain after the planned price decreases mentioned in table 7.

Model follows current treatment guidelines

The aim of the therapies is preventing disease progression and complications (development of cirrhosis, end-stage liver disease and HCC). However, these hard clinical endpoints take years or decades to occur and are therefore impractical targets for clinical trials. Current evidence has been reported as insufficient to assess antiviral treatment effect on hard clinical outcomes. Note that clearance of HBV is rarely, if ever, achievable.

Most patients included in phase III pivotal trials of antiviral therapy had a liver biopsy at baseline. A 2-point reduction in the modified histology activity index (HAI) score after treatment was extensively used as a primary or secondary endpoint in these trials. In 2008, it has been reported that a 2-point increase on this same scale is associated with an increased progression to liver complications.[44] No long term histological assessments are available in RCTs of NAs. Improvements from baseline liver biopsy data after 3 years of tenofovir treatment[45] or up to 6 years of (1mg) entecavir treatment[46] have been published.

As a result, surrogate markers, believed to correlate with hard clinical outcomes (loss of HBeAg, suppression of viral replication, improvement of liver biopsy), are often used to evaluate therapies. None of these surrogate markers is ideal on its own.[47] 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 treatment guidelines, despite that 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 the model, treatment is discontinued when the patient dies, is transplanted or shows e antigen seroconversion. Treatment remains discontinued as long as the patient remains in an inactive state (ICAR NC/CC or HBsAg- NC/CC). Treatment is restarted when the patient shows re-activation from ICAR NC/CC and transitions to CHBe+ or CHBe- NC or CC state.

In patients who are HBeAg-, the therapeutic goal is sustained suppressed HBV DNA and HBsAg seroconversion (anti-HBs occurrence), but this endpoint has not been reached so far in NA studies.[45] Therefore, in the model treatment in CHBe- patients is continued lifelong or until liver transplant.

Unclear effect of antiviral treatment on the development of HCC

The effect of NA on the incidence of HBV-related HCC remains a topic of discussion as there remains a lack of hard evidence based on well controlled trials.[48] Only one randomized controlled trial of NAs reported HCC as an outcome.[49] In this trial, 651 HBsAg positive Asian patients with compensated liver disease, who were HBeAg positive and/or had serum HBV DNA >700,000 gEq/mL (roughly >140,000 IU/mL), with bridging fibrosis or cirrhosis (about a third) were randomized to receive lamivudine (n=436) or placebo (n=215). This trial was terminated after a median follow-up of 32 (range 0-42) months because a statistically significant difference in the primary endpoint (increase in Child-Turcotte-Pugh score by 2 or more points or development of 1 of the following complications: HCC, spontaneous bacterial peritonitis, renal insufficiency or variceal bleeding) was observed between the two groups. At the time the trial was terminated, 17 (3.9%) lamivudine treated patients and 16 (7.4%) placebo controls had been diagnosed with HCC, hazard ratio (HR) 0.49 (95% CI 0.25-0.99) (P = 0.047) or a 47.6% reduction from 16/215 to 17/436. When the five HCC cases in year 1 (two prevalent cases in placebo group and three in lamivudine group) were excluded, HR was 0.47 and the difference between the two groups was no longer significant (P = 0.052). Data from this trial showed that patients who experienced virological breakthrough associated with lamivudine resistance did not derive as much clinical benefit as those who had maintained viral suppression. As was also suggested by a meta-analysis of nonrandomized trials the treatment effect seemed to be stronger in patients who were HBeAg positive at baseline. In HBeAg positive patients disease progression was reduced from 20% (25/124) to 6% (15/252) whereas in HBeAg negative patients the reduction was much smaller, from 14% (13/91) to 10% (19/182). It is unclear whether this suggested difference in efficacy applies similarly to HCC and liver decompensation.

A recent systematic review of published results,[50] including the above RCT and other nonrandomized studies suggests a lower HCC incidence under nucleos(t)ide treatment of 2.8% versus 6.4%. The effect seemed to be limited to patients showing a virological response.

Incorporating treatment effects in the model

We included treatment effects of tenofovir and entecavir in a very transparent way, summarized in Table 9. For the effect on fibrosis progression we assume a reduction of 75% (65% to 85%) under treatment of the transition probabilities from CHBe+ NC or CHBe- NC to CC states and from CHBe+ CC and CHBe- CC to DC states in the model. Note that this reduction in transition rates results in a much stronger reduction of over 90% in the incidence of decompensated cirrhosis cases (see results section). This strong treatment effect is based on non-controlled relatively short term efficacy data on liver histology and expert opinion and corresponds eg to a 100% response in 75% of patients and 0% in 25% of patients (or a corresponding mix of intermediate response scenario's). We assume drug resistance and drug toxicity will not become a major issue. We assume perfect long term drug adherence in over 75% of the patients who picked up the reimbursed drugs at the pharmacy. These assumptions are more likely to remain valid for shorter time horizons. Despite the fact that we assume treatment is continued in DC and HCC states, no beneficial effects of tenofovir are modelled once the patient failed treatment (entered DC or HCC state).

As the incidence of HCC is much increased in cirrhotic states, reducing the transition to cirrhosis will also result in a decrease of HCC. In addition, a smaller direct reduction of 25% with a broad range of uncertainty (0% to 50%) on the transition from treated states to HCC was included. This reflects the uncertainty there is on the effect of antiviral treatments on HCC incidence. The combination of the indirect and direct effects results in an overall reduction of HCC of about 50% in the 40 year old CHBe+/- cohorts. In the 50 year old CC cohort, the HCC reduction is much smaller as patients remain in CC for a much longer period during which they remain at moderate risk for HCC (see results section). These effects combined are in line with the short term results seen in the single RCT (lamivudine treatment) as discussed above.[49]

Table 9. Treatment effects.

Transitions	Tenofovir				
	Mean reduction of transition probability	95% CI		Alpha*	Beta*
From CHBe+/- NC to CHBe+/- CC From CHBe+/- CC to DC	75%	65%	85%	53.3	17.8
From CHBe+/- NC to HCC From CHBe+/- CC to HCC From DC to HCC	25%	0%	50%	2.6	7.9

Notes: *Based on the Beta probability distribution.

3 RESULTS

3.1 MODEL VALIDATION: NATURAL EVOLUTION OF DISEASE WITHIN EUROPEAN COHORTS

This section aims at an intuitive (soft) evaluation of whether the model is reasonably well calibrated in terms of a comparison of life-expectancy of the modelled populations with the Belgian population. These results go beyond the 20 years horizon which we use for the cost-effectiveness analysis, and are thus more uncertain. As on average relatively few patients without cirrhosis develop complications which lead to early death, their life-expectancy could be expected (at least at lower ages) to be rather close to the Belgian average. For a mixed 40 year old cohort of 70% male and 30% female CHBe+ NC / CHBe- NC patients (representative of Belgian CHB cohorts) life-expectancy is on average 34.8 / 33.0 years, respectively. This compares to 39.5 years for the Belgian population (Table 10). The difference in life-expectancy declines with increasing age. For the cohort of 50 year old cirrhotic patients, life-expectancy is on average 20.3 years – falling thus 10 years below the Belgian average. This is due to a high incidence of life-threatening complications (DC and HCC) in this cohort.

Table 10. Life-expectancy of untreated cohorts compared to the Belgian population; in years.

Age in years		CHBe+ non-cirrhotic patients**		CHBe- non-cirrhotic patients**		CHBe+/- cirrhotic patients**		Belgian population***
30	**Mean**	43.4		41.0		27.7		49.0
	*95% range**	*42.0*	*42.0*	*38.9*	*42.8*	*30.4*	*44.5*	
40	**Mean**	**34.8**		**33.0**		24.2		39.5
	95% range	***33.7***	***33.7***	***31.2***	***34.6***	*26.5*	*35.8*	
50	**Mean**	26.5		25.4		**20.3**		30.3
	95% range	*25.4*	*25.4*	*23.9*	*26.8*	***21.8***	***27.5***	
60	**Mean**	19.5		19.1		15.8		21.8
	95% range	*19.0*	*19.0*	*18.3*	*19.8*	*16.8*	*20.0*	

Notes: Base-line scenarios highlighted in bold. Results based on Markov model as presented in section 1. * 95% range: Interval ranging from 2.5-percentile to 97.5 percentile of the distribution of simulated results. ** Undiscounted life-years in natural evolution. ***Based on data from Statbe[51] on a mixed cohort of 70% men and 30% women. CHBe+/-, chronic hepatitis B e antigen positive/ negative.

3.2 HEALTH OUTCOMES

3.2.1 Life-years gained in the three cohorts

Figure 2. Cohort evolution (undisc. LY in 40 y CHBe+ NC Europe).

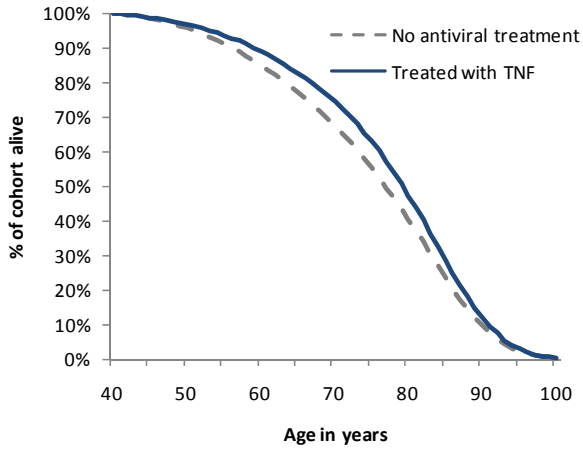


Figure 3. Cohort evolution (undisc. LY in 40 y CHBe- NC Europe).

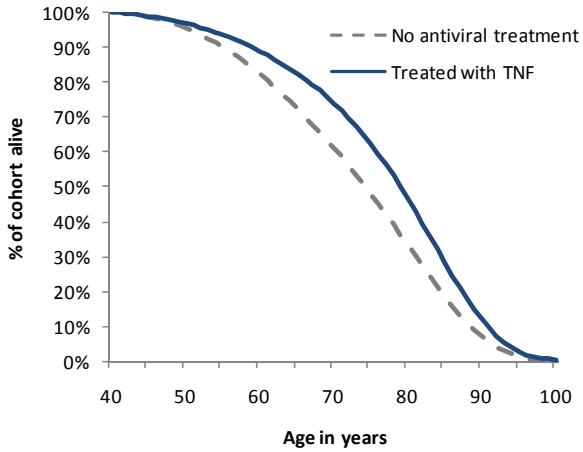
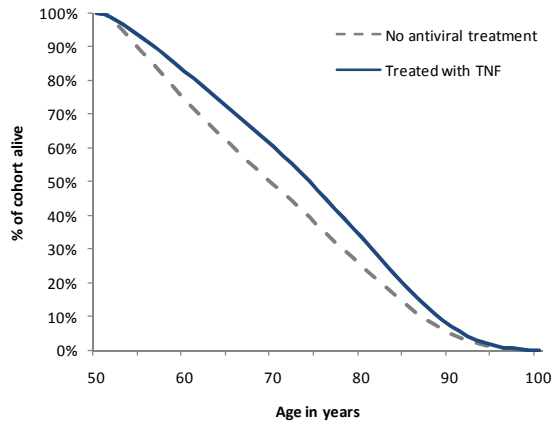


Figure 4. Cohort evolution (undisc. LY in 50 y CHBe+/- CC Europe).



3.2.2 Cumulative undiscounted life-years gained per person in DC and HCC

Figure 5. Cumul. life-years per patient in DC and HCC (40 y CHBe+ NC Europeans).

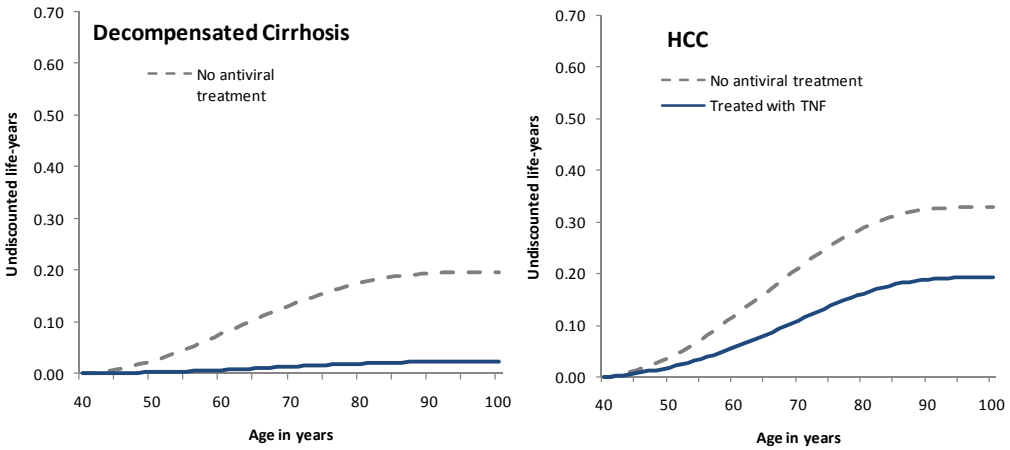


Figure 6. Cumul. life -years per patient in DC and HCC (40 y CHBe- NC Europeans).

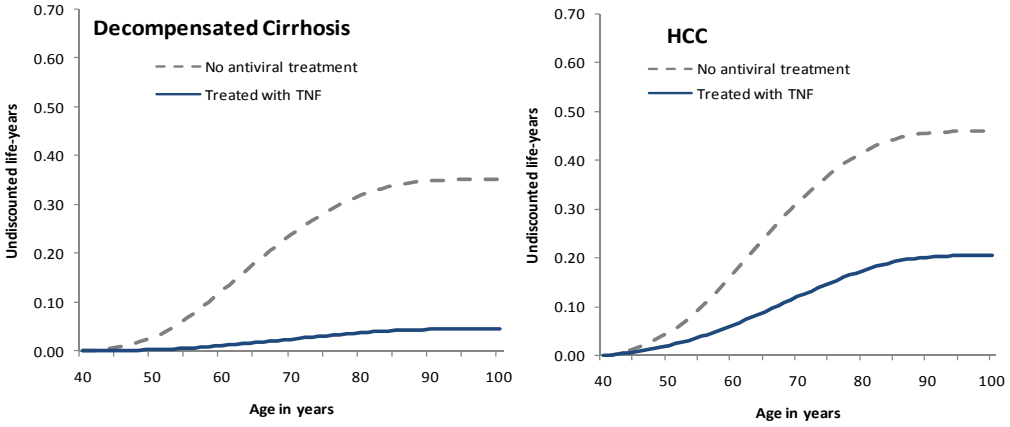
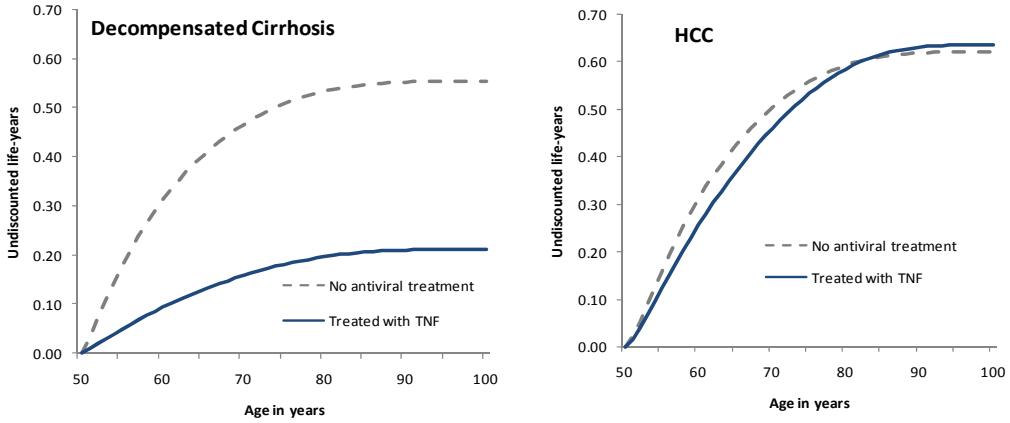


Figure 7. Cumul. life -years per patient in DC and HCC (50 y CHBe+/- CC Europeans).



As in our model tenofovir has no impact on the life-years in DC and HCC, the above figures reflect the cumulative treatment-induced decrease in number of cases of DC and HCC as a function of patient age.

3.2.3 Mean tenofovir treatment duration in CHB e+ vs e- cohorts

In contrast to CHBe+ NC patients, over 20 years of follow-up CHBe- NC patients spend most of their life-years in states treated with tenofovir (mostly in CHBe- NC) (Table 11). As such, CHBe- non-cirrhotic patients are treated with antivirals for over 90% of the 20 years of follow-up. In contrast, CHBe+ NC patients spend on average somewhat more than half of years under antiviral treatment (mostly in CHBe+ NC and CHBe- NC disease states). Also cirrhotic patients are most of the time in antiviral treatment at 20 years follow-up.

Table 11. In contrast to CHBe+ NC patients, CHBe- NC patients spend most of their life-years in disease states treated with tenofovir (20 years time horizon).

	Mean cumulative undiscounted life-years spent in states with vs. without antiviral treatment		
	With	**Without**	**Total**
40 y CHBe+ NC Europeans	9.48	7.96	17.44
40 y CHBe- NC Europeans	17.36	0.06	17.42
50 y CHBe+/- CC Europeans	12.94	1.98	14.92

Notes: Results based on Markov model as presented in section 1. 1.5% and 3.0% discount rates for outcomes and costs respectively.

3.3 BASE-CASE COST-UTILITY ANALYSES

3.3.1 Overview of the results for the three base-case cohorts

The general lines of the results are as follows. For CHBe+ NC patients (40 years old Europeans), in discounted QALYs, the treatment effect results only in 0.3 QALYs (95% CI: 0.2; 0.5) gained over a period of 20 years of treatment (Table 12). This moderate improvement in QALYs is seen despite the inclusion of a high treatment effect: a 90% reduction of life-years spent in decompensated cirrhosis and nearly a 50% reduction of life-years spent in HCC (Figure 8). For CHBe+ non-cirrhotic Europeans, antiviral treatment costs account for roughly 80% of total costs (Figure 9). At 20 years follow-up, the mean ICERs for treating patients with chronic hepatitis B with e antigen positivity are at 110,000 € per QALY gained (95% CI: 65,000; 184,000) (Table 14).

For CHBe- NC patients (40 years old Europeans), the same line of reasoning leads to slightly more unfavourable ICERs at 131,000 € per QALY gained (95% CI: 75,000; 240,000) (Table 17).

The picture is more favourable for 50 year old CHBe+/- CC Europeans, mostly due to higher gains in QALYs over 20 years of follow-up. The mean ICER is at 28,000 € per QALY gained (95% CI: 16,000; 47,000) (Table 20).

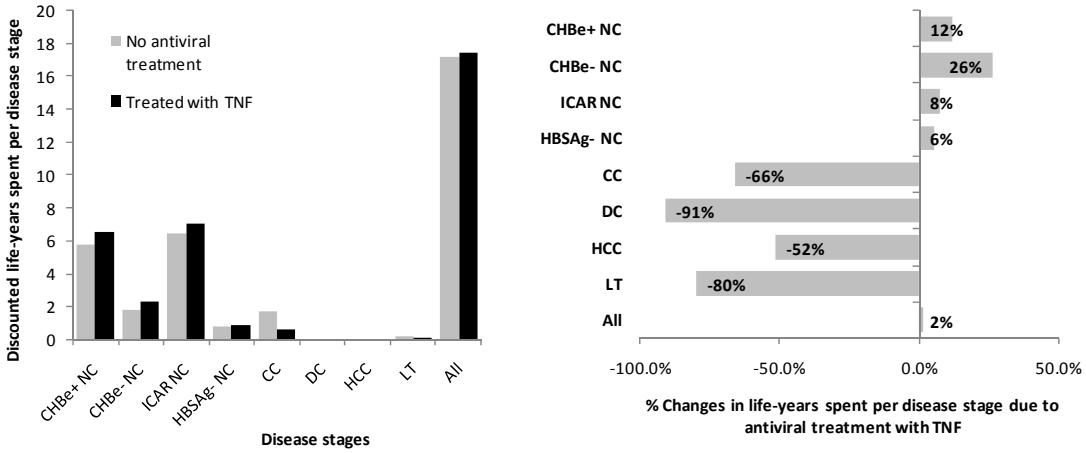
3.3.2 CHBe+ non-cirrhotic Europeans

Table 12. Up to 20 years of treatment, CHBe+ non-cirrhotic Europeans gain little in discounted QALYs when compared to no antiviral treatment.

Age in years		10 years follow-up						20 years follow-up					
		QALY no treatment		QALY : treated with tenofovir		QALYs gained		QALY no treatment		QALY : treated with tenofovir		QALYs gained	
30	Mean	8.3		8.3		0.0		14.5		14.6		0.2	
	*95% range**	*8.1*	*8.5*	*8.1*	*8.6*	*0.0*	*0.1*	*14.1*	*14.8*	*14.3*	*15.0*	*0.1*	*0.3*
40	**Mean**	**8.2**		**8.3**		**0.1**		**14.0**		**14.3**		**0.3**	
	95% range	***8.0***	***8.4***	***8.0***	***8.5***	***0.0***	***0.1***	***13.6***	***14.4***	***14.0***	***14.7***	***0.2***	***0.5***
50	Mean	8.0		8.1		0.2		13.1		13.6		0.6	
	95% range	*7.7*	*8.2*	*7.9*	*8.3*	*0.1*	*0.3*	*12.6*	*13.5*	*13.3*	*14.0*	*0.3*	*0.9*
60	Mean	7.6		7.8		0.1		11.8		12.3		0.5	
	95% range	*7.4*	*7.9*	*7.6*	*8.0*	*0.1*	*0.2*	*11.4*	*12.2*	*12.0*	*12.6*	*0.3*	*0.7*

Notes: **Base-line scenario highlighted in bold.** Results based on Markov model as presented in section 1. 1.5% and 3.0% discount rates for outcomes and costs respectively. * 95% range: Interval ranging from 2.5-percentile to 97.5 percentile of the distribution of simulated results. QALY: quality-adjusted life-year. CHBe+, chronic hepatitis B e antigen positive; Similarly small gains are observed, when life-years instead of QALYs are used as the outcome variable.

Figure 8. Low gains in discounted life-years under antiviral treatment with tenofovir over 20 years of follow-up albeit a high treatment efficacy.



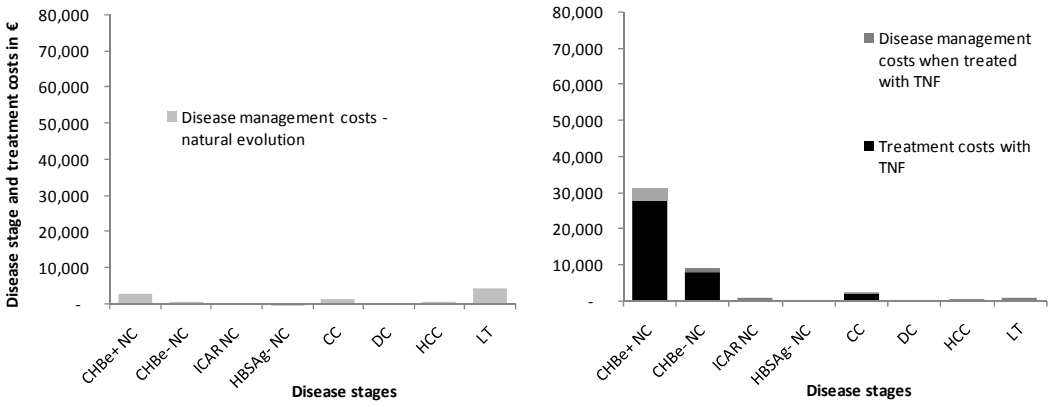
Notes: Results based on a cohort of 40 year old Europeans (70% male and 30% female) starting treatment in CHBe+ NC. TNF: tenofovir; CHBe+, chronic hepatitis B e antigen positive; CHBe-, chronic hepatitis B e antigen negative; NC; non cirrhotic; CC, compensated cirrhosis; ICAR, inactive carrier; HBsAg-, hepatitis B surface antigen negative; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant.

Table 13. Up to 20 years of treatment, CHBe+ non-cirrhotic treatment with tenofovir results in significant incremental costs when compared to no antiviral treatment.

Age in years		10 years follow-up costs in 1,000 €/patient			20 years follow-up costs in 1,000 €/patient		
		Costs no treatment*	Costs: treated with tenofovir**	Incremental costs	Costs no treatment*	Costs: treated with tenofovir**	Incremental costs
30	Mean	5	32	27	10	45	35
	95% range	4 8	26 38	22 32	7 13	36 55	27 43
40	Mean	**6**	**32**	**26**	**13**	**46**	**33**
	95% range	***4 9***	***27 39***	***21 31***	***9 17***	***37 55***	***26 41***
50	Mean	9	32	24	17	45	28
	95% range	6 12	27 38	19 29	11 24	36 55	20 37
60	Mean	8	31	23	15	42	27
	95% range	6 11	26 37	18 28	10 21	34 50	20 34

Notes: **Base-line scenario highlighted in bold.** * Disease management costs only. **Disease management costs and antiviral treatment costs; See Table 12.

Figure 9. Over 20 years of follow-up, antiviral treatment costs with tenofovir account for over 80% of total costs within non-cirrhotic CHBe+ 40 year old Europeans; Costs in €/patient.



Notes: See Figure 8.

Table 14. ICERs per QALY gained above 100,000 € and 50,000 € at 10 and 20 years of follow-up, respectively; Non-cirrhotic CHBe+ 40 year old Europeans.

Age in years		ICER: 1,000 €/QALY gained	
		At 10 years follow-up	At 20 years follow-up
30	Mean	761	212
	95% range	368 1,413	123 355
40	Mean	**411**	**110**
	95% range	***210 838***	***65 184***
50	Mean	178	54
	95% range	85 354	28 97
60	Mean	178	62
	95% range	88 366	31 110

Notes: **Base-line scenario highlighted in bold;** See Table 12.

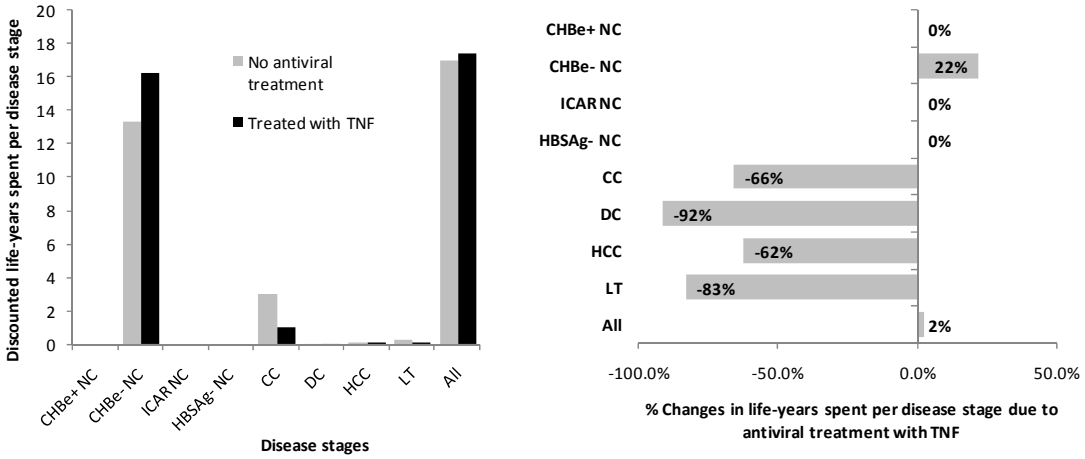
3.3.3 CHBe- non-cirrhotic Europeans

Table 15. Up to 20 years of treatment, CHBe- non-cirrhotic Europeans gain little in discounted QALYs when compared to no antiviral treatment.

Age in years		10 years follow-up			20 years follow-up		
		QALY no treatment	QALY : treated with tenofovir	QALYs gained	QALY no treatment	QALY : treated with tenofovir	QALYs gained
30	Mean	8.3	8.3	0.0	14.3	14.6	0.3
	95% range	*7.8 8.6*	*7.9 8.7*	*0.0 0.1*	*13.6 14.9*	*13.9 15.2*	*0.1 0.4*
40	**Mean**	**8.2**	**8.2**	**0.1**	**13.7**	**14.2**	**0.5**
	95% range	***7.8 8.5***	***7.9 8.6***	***0.0 0.2***	***13.1 14.3***	***13.6 14.9***	***0.3 0.8***
50	Mean	7.9	8.1	0.2	12.8	13.5	0.7
	95% range	*7.5 8.2*	*7.7 8.4*	*0.1 0.3*	*12.1 13.5*	*12.8 14.1*	*0.4 1.2*
60	Mean	7.6	7.7	0.2	11.6	12.2	0.6
	95% range	*7.2 7.9*	*7.4 8.1*	*0.1 0.3*	*11.0 12.1*	*11.6 12.7*	*0.3 1.1*

Notes: **Base-line scenario highlighted in bold.** Results based on Markov model as presented in section 1. 1.5% and 3.0% discount rates for outcomes and costs respectively. * 95% range: Interval ranging from 2.5-percentile to 97.5 percentile of the distribution of simulated results. QALY: quality-adjusted life-year; CHBe-, chronic hepatitis B e antigen negative.

Figure 10. Low gains in discounted life-years under antiviral treatment with tenofovir over 20 years of follow-up albeit a high treatment efficacy.



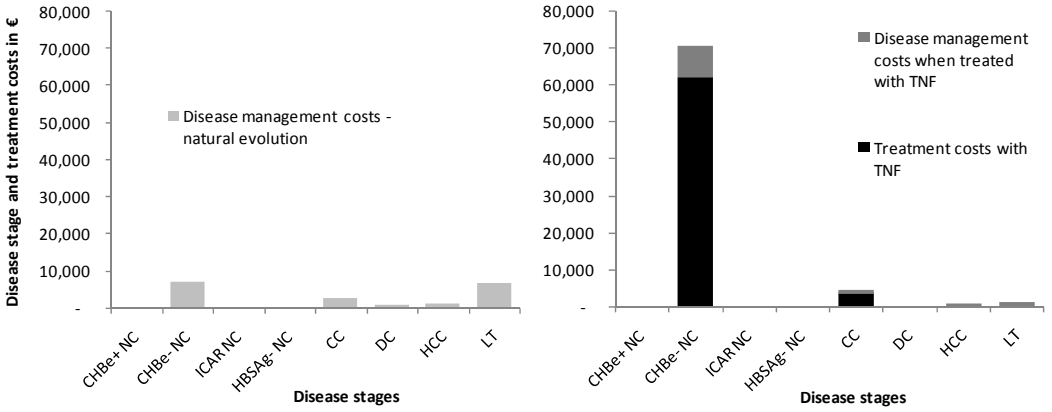
Notes: Results based on a cohort of 40 year old Europeans (70% male and 30% female) starting treatment in CHBe- NC. TNF: tenofovir; CHBe+, chronic hepatitis B e antigen positive; CHBe-, chronic hepatitis B e antigen negative; NC; non cirrhotic; CC, compensated cirrhosis; ICAR, inactive carrier; HBsAg-, hepatitis B surface antigen negative; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant.

Table 16. Up to 20 years of treatment, CHBe- non-cirrhotic treatment with tenofovir results in significant incremental costs when compared to no antiviral treatment.

Age in years		10 years follow-up costs in 1,000 €/patient			20 years follow-up costs in 1,000 €/patient		
		Costs no treatment *	Costs: treated with tenofovir**	Incremental costs	Costs no treatment*	Costs: treated with tenofovir**	Incremental costs
30	**Mean**	7	49	41	15	78	63
	95% range	*5 11*	*46 52*	*40 42*	*10 20*	*74 83*	*60 65*
40	**Mean**	**8**	**48**	**40**	**19**	**77**	**58**
	95% range	***5 11***	***46 51***	***39 41***	***13 26***	***73 82***	***53 62***
50	**Mean**	11	48	37	23	75	52
	95% range	*7 15*	*46 51*	*33 39*	*15 34*	*71 79*	*42 58*
60	**Mean**	10	46	36	20	68	48
	95% range	*7 15*	*44 49*	*32 38*	*13 30*	*65 72*	*40 53*

Notes: **Base-line scenario highlighted in bold.** * Disease management costs only. ** Disease management costs and antiviral treatment costs. See Table 12.

Figure 11. Over 20 years of follow-up, antiviral treatment costs with tenofovir account for over 80% of total costs within non-cirrhotic CHBe- 40 year old Europeans; Costs in €/patient.



Notes: See Figure 8.

Table 17. ICERs per QALY gained above 100,000 € and 50,000 € at 10 and 20 years of follow-up, respectively; Non-cirrhotic CHBe- 40 year old Europeans.

Age in years		ICER: 1,000 €/QALY gained	
		At 10 years follow-up	At 20 years follow-up
30	**Mean**	1,069	258
	95% range	*441 2,229*	*143 461*
40	**Mean**	**562**	**131**
	95% range	***249 1,325***	***75 240***
50	**Mean**	371	75
	95% range	*106 569*	*38 145*
60	**Mean**	253	84
	95% range	*109 545*	*39 156*

Notes: **Base-line scenario highlighted in bold.** See Table 12.

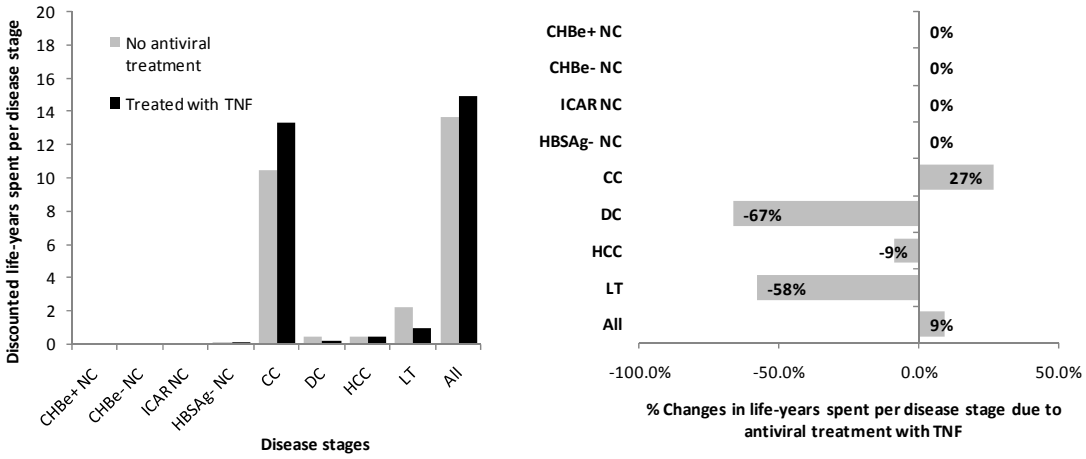
3.3.4 Patient with compensated liver cirrhosis

Table 18. Up to 20 years of treatment, CHBe+/- CC Europeans gain up to 1.3 QALYs on average when compared to no antiviral treatment.

Age in years		10 years follow-up			20 years follow-up		
		QALY no treatment	QALY : treated with tenofovir	QALYs gained	QALY no treatment	QALY : treated with tenofovir	QALYs gained
30	**Mean**	7.0	7.4	0.5	10.9	12.2	1.3
	95% range	*6.5 7.4*	*6.9 7.9*	*0.3 0.7*	*10.0 11.7*	*11.2 13.0*	*0.8 1.8*
40	**Mean**	6.9	7.4	0.5	10.9	12.2	1.3
	95% range	*6.4 7.4*	*6.8 7.8*	*0.3 0.7*	*10.0 11.7*	*11.2 13.0*	*0.8 1.8*
50	**Mean**	**6.8**	**7.2**	**0.4**	**10.9**	**12.2**	**1.3**
	95% range	***6.3 7.2***	***6.7 7.7***	***0.3 0.6***	***10.0 11.7***	***11.2 13.0***	***0.8 1.8***
60	**Mean**	6.5	7.0	0.4	10.9	12.2	1.3
	95% range	*6.1 7.0*	*6.4 7.4*	*0.3 0.6*	*10.0 11.7*	*11.2 13.0*	*0.8 1.8*

Notes: **Base-case highlighted in bold.** 1.5% and 3.0% discount rates for outcomes and costs respectively. * 95% range: Interval ranging from 2.5-percentile to 97.5 percentile of the distribution of simulated results. QALY: qality-adjusted life-year; CHBe+, chronic hepatitis B e antigen positive.

Figure 12. 9% gain in discounted life-years under antiviral treatment with tenofovir over 20 years of follow-up; 50 year old CHBe+/- CC Europeans.



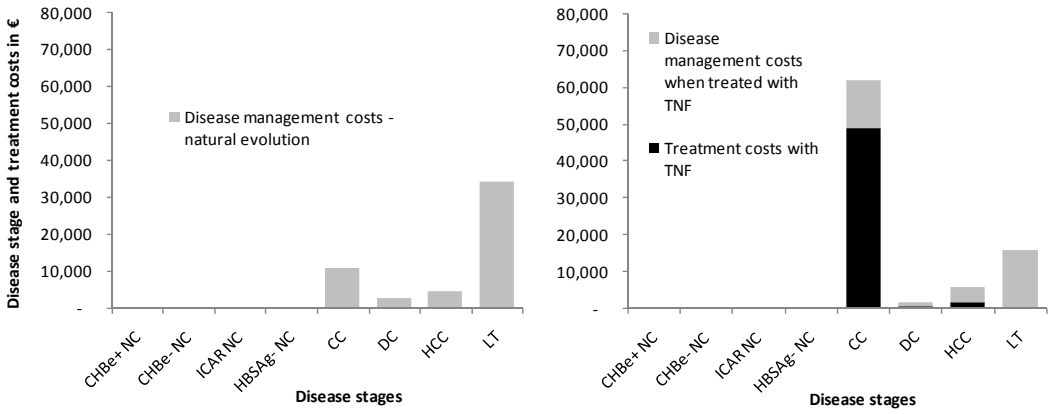
Notes: Results based on a mixed cohort of 70% CHBe+ CC and 30% CHBe- CC 50 year old Europeans (70% male and 30% female). TNF: tenofovir; CHBe+, chronic hepatitis B e antigen positive; CHBe-, chronic hepatitis B e antigen negative; NC; non cirrhotic; CC, compensated cirrhosis; ICAR, inactive carrier; HBsAg-, hepatitis B surface antigen negative; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant.

Table 19. Up to 20 years of treatment, treatment of CHBe+/- cirrhotic Europeans with tenofovir results in significant incremental costs when compared to no antiviral treatment.

Age in years		10 years follow-up costs in 1,000 €/patient			20 years follow-up costs in 1,000 €/patient		
		Costs no treatment*	Costs: treated with tenofovir**	Incremental costs	Costs no treatment*	Costs: treated with tenofovir**	Incremental costs
30	**Mean**	34	58	24	56	89	33
	95% range	*24 46*	*53 65*	*16 30*	*41 74*	*81 99*	*21 43*
40	**Mean**	34	58	24	55	88	33
	95% range	*24 46*	*53 63*	*15 30*	*40 74*	*79 98*	*20 42*
50	**Mean**	**33**	**57**	**24**	**52**	**84**	**32**
	95% range	***24 45***	***52 63***	***16 30***	***38 70***	***76 93***	***21 41***
60	**Mean**	32	55	23	48	77	29
	95% range	*23 44*	*50 60*	*15 29*	*35 65*	*70 86*	*19 38*

Notes: **Base-line scenario highlighted in bold;** *Disease management costs only; **Disease management costs and antiviral treatment costs; See Table 12.

Figure 13. Over 20 years of follow-up, antiviral treatment costs with tenofovir account for over 65% of total costs within CHBe+/- cirrhotic 50 year old Europeans; Costs in €/patient.



Notes: See Figure 8.

Table 20. ICERs per QALY gained around 57,000 € and 29,000 € at 10 and 20 years of follow-up, respectively; CHBe+/- CC Europeans.

Age in years		ICER: 1,000 €/QALY gained	
		At 10 years follow-up	At 20 years follow-up
30	**Mean**	55	28
	95% range	*30 90*	*15 45*
40	**Mean**	56	28
	95% range	*29 96*	*15 47*
50	**Mean**	**57**	**29**
	95% range	***30 96***	***16 47***
60	**Mean**	57	31
	95% range	*29 98*	*16 52*

Notes: See Table 12.

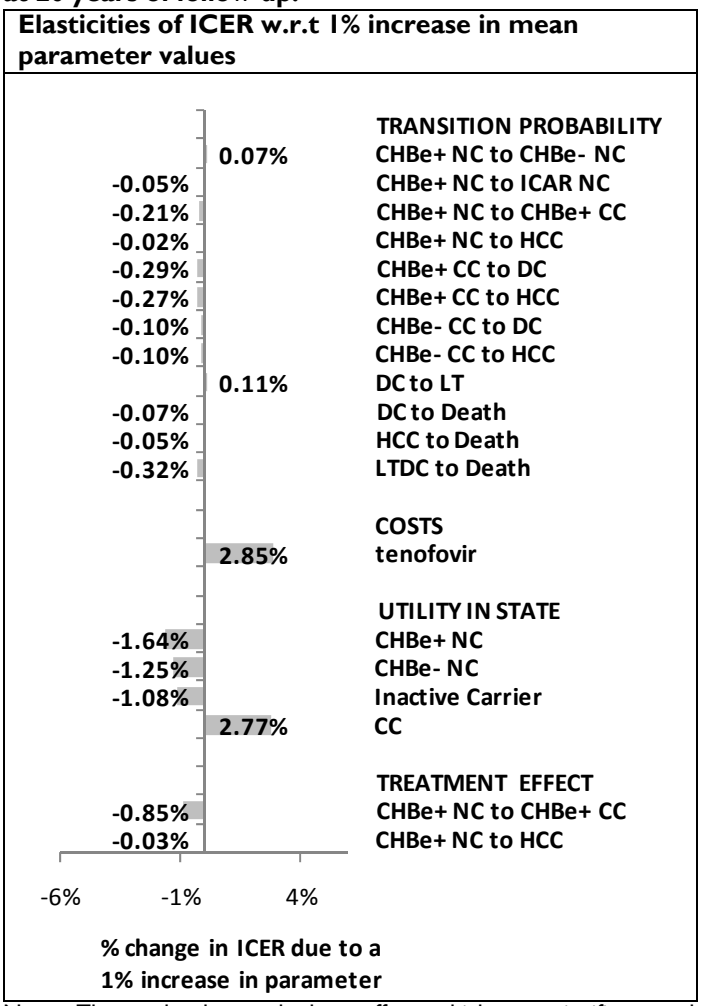
3.4 SCENARIO AND PROBABILISTIC SENSITIVITY ANALYSES

3.4.1 Probabilistic sensitivity analysis

3.4.1.1 Tornado diagrams

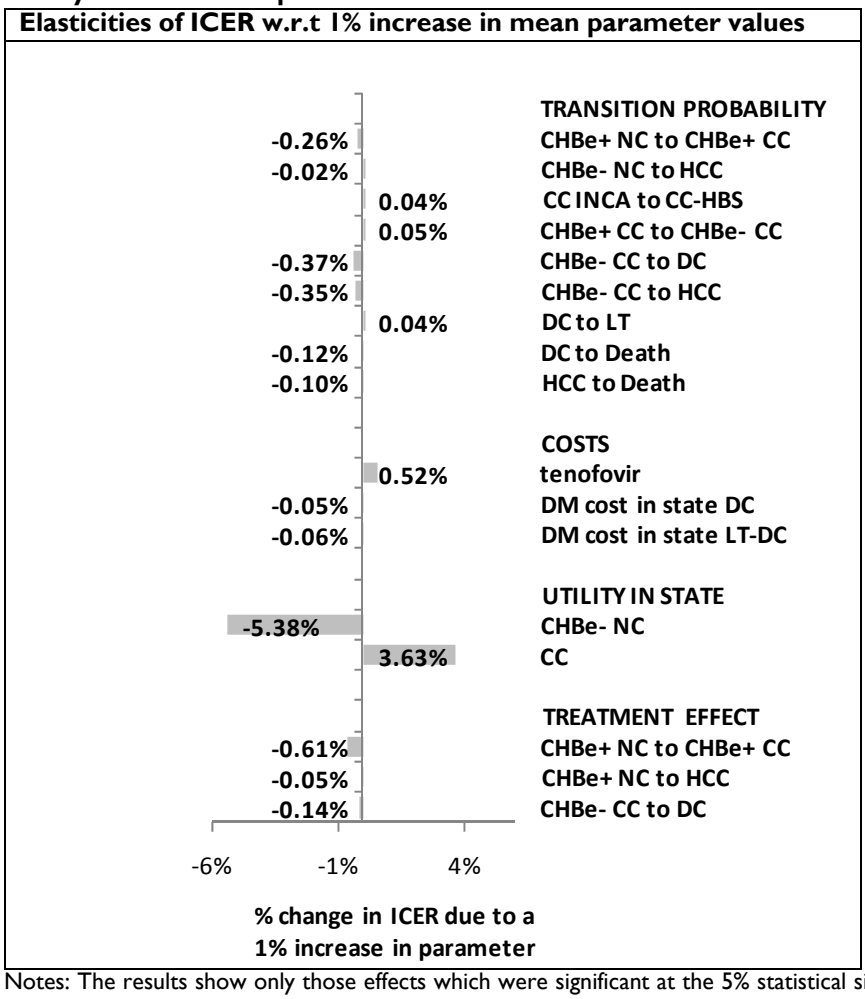
In order to assess the impact of the model input variables on the ICER, we have estimated how much the ICER changes, if the mean value of a specific input variable is increased by 1%, e.g. a 1% increase of the annual cost of tenofovir from 4,971 to 5,020 €. For both the CHBe+ NC and the CHBe- cohorts, the ICER is most sensitive to changes in the cost of tenofovir, as well as to changes in utilities, such as utility in CC (Figure 14 and 15). Now consider the sensitivity of some of the most elastic parameters. In the base case scenario for CHBe+ NC patients, in order for the ICER to decrease from 110,000 to 30,000€/QALY, the current price of tenofovir should decrease by 65% to around 1,750€. Within the CHBe- NC model, a 65% decrease in the price of tenofovir entails a drop of the ICER from 131,000 to 40,000€/QALY. Applying a relatively low utility for CC of 0.68 instead of 0.78, such as in the UK population in Levy et al. 2008, the mean ICERs decrease to 75,000€/QALY and 86,000€/QALY for the CHBe+NC and CHBe-NC cohorts, respectively. Finally, assuming a doubling of the age dependent transition probabilities from CHBe+/- NC to CHBe+/-CC, the ICER decreases to 54,000€/QALY and and 66,000€/QALY for the CHBe+NC and CHBe-NC cohorts, respectively.

Figure 14. Tornado diagram for CHBe+ NC European cohort aged 40 years at 20 years of follow-up.



Notes: The results show only those effects which were significant at the 5% statistical significance level; * Individual elasticity extrapolated to the confidence interval of each parameter. Cost of tenofovir was decreased up to 20%.

Figure 15. Tornado diagram for CHBe- NC European cohort aged 40 years at 20 years of follow-up.

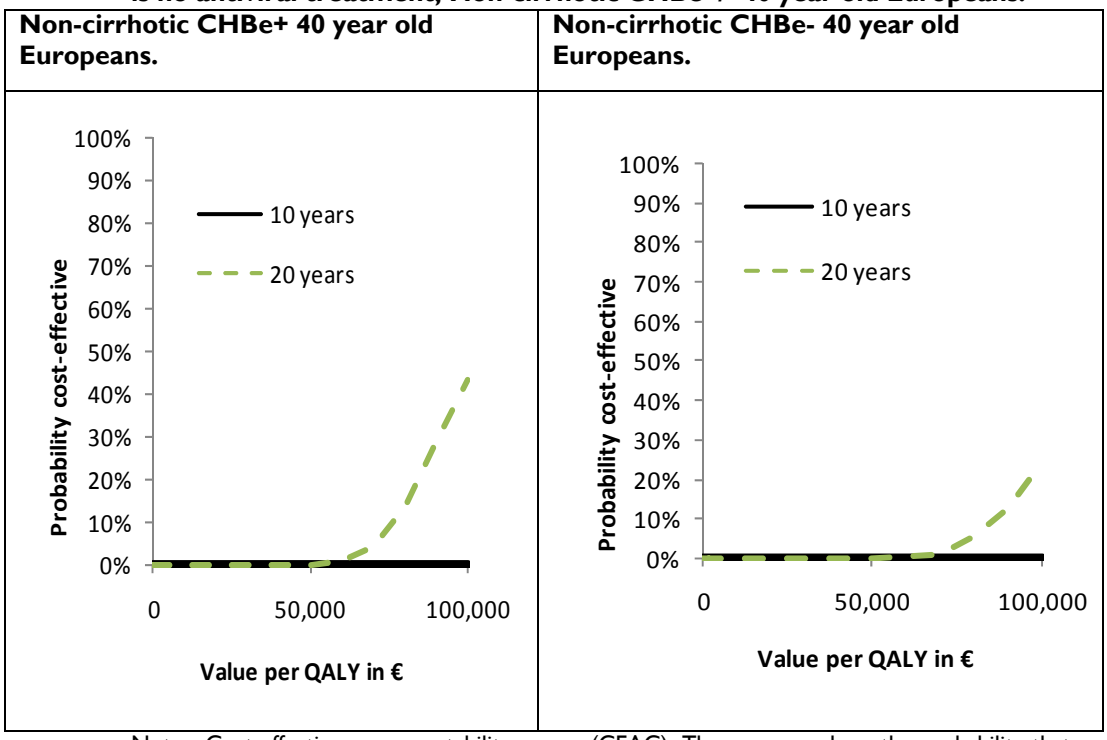


Notes: The results show only those effects which were significant at the 5% statistical significance level; * Individual elasticity extrapolated to the confidence interval of each parameter. Cost of tenofovir was decreased up to 20%.

3.4.1.2 Cost-effectiveness acceptability curves

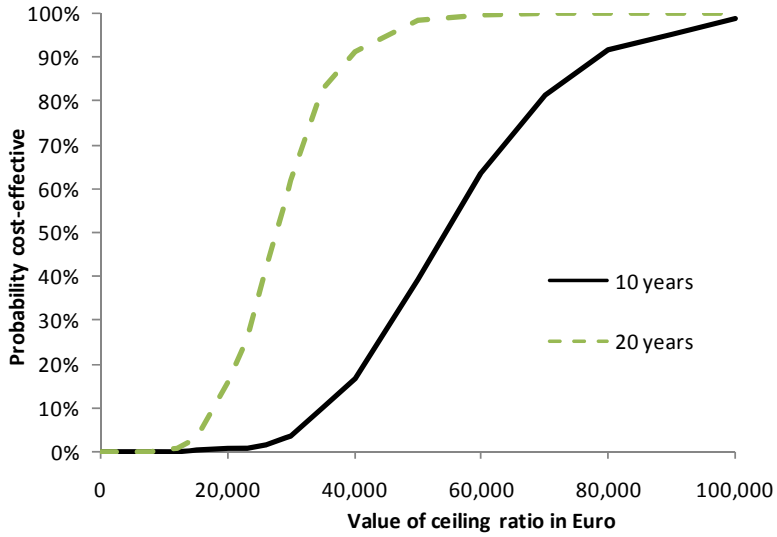
For a decision-maker it may be valuable to know, how the probability that treatment with tenofovir is cost-effective, changes with his valuation of QALYs gained. One way to illustrate this link is cost-effectiveness acceptability curves (CEAC). These curves show the probability that a specific treatment is optimal, for a range of threshold values per QALY gained.[52] For instance, at 10 years follow-up for CHBe+ non-cirrhotic Europeans, the probability that the treatment with tenofovir is cost-effective is always 0, at least up to the threshold value of 100,000 € per QALY (Figure 16). At 20 years follow-up tenofovir treatment is never an optimal strategy at threshold QALY values up to 60,000 €. The probability that tenofovir becomes a cost-effective option increases to 40% at a value of 100,000 € per QALY.

Figure 16. At 20 years follow-up, very low probability that treatment with tenofovir is cost-effective when QALY is valued below 80,000€; Comparator is no antiviral treatment; Non-cirrhotic CHBe+/- 40 year old Europeans.



Notes: Cost-effectiveness acceptability curves (CEAC). These curves show the probability that a specific treatment is optimal for a range of threshold values per QALY.[52]

Figure 17. At 20 years follow-up, 50% probability that treatment with tenofovir is cost-effective when QALY is valued around 28,000€; Comparator is no antiviral treatment; Cirrhotic CHBe+/- 50 year old Europeans.



Notes: Cost-effectiveness acceptability curves (CEAC). These curves show the probability that a specific treatment is optimal for a range of threshold values per QALY.[52]

3.4.2 ICERs in function of the time horizon

Figure 18. Steep decrease in ICERs from 10 to 20 years of follow-up, (unpredictable) uncertainty thereafter; Non-cirrhotic CHBe+/- Europeans.

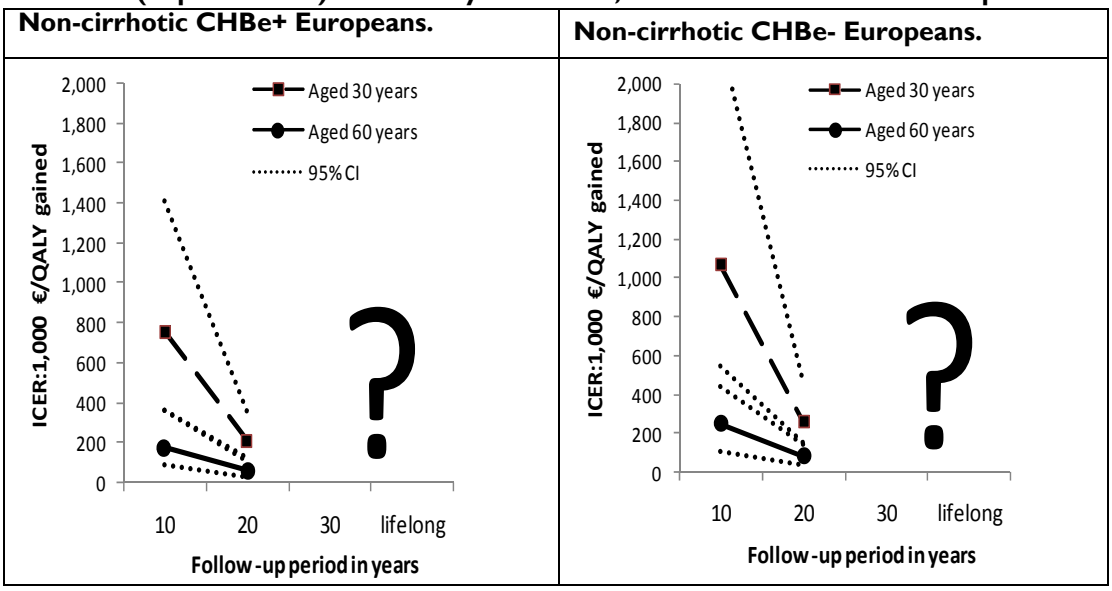
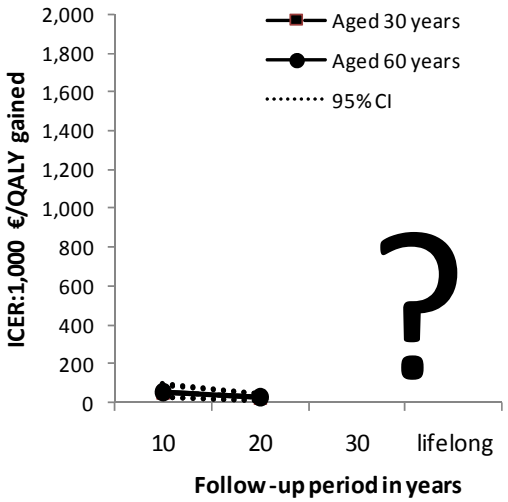


Figure 19. Steep decrease in ICERs from 10 to 20 years of follow-up, (unpredictable) uncertainty thereafter; CHBe+/- CC Europeans.



3.4.3 Asian cohorts

For the Asian cohorts, the ICERs are in general more favorable than for the European cohorts, as they have a higher probability to develop HCC under natural evolution. Accordingly, the gain of avoiding HCC under antiviral treatment with tenofovir is in general higher.

Table 21. ICERs per QALY gained around 273,000 € and 80,000 € at 10 and 20 years of follow-up, respectively; CHBe+ NC Asians.

		ICER: 1,000 €/QALY gained			
Age		**At 10 years follow-up**		**At 20 years follow-up**	
30	**Mean**	422		138	
	95% range	*240*	*758*	*85*	*212*
40	**Mean**	**273**		**80**	
	95% range	***150***	***501***	***51***	***126***
50	**Mean**	135		43	
	95% range	*70*	*242*	*23*	*75*
60	**Mean**	137		50	
	95% range	*73*	*246*	*28*	*83*

Notes: **Base-line scenario highlighted in bold.** Results based on Markov model as presented in section 1. 1.5% and 3.0% discount rates for outcomes and costs respectively. * 95% range: Interval ranging from 2.5-percentile to 97.5 percentile of the distribution of simulated results. QALY: quality-adjusted life-year; CHBe+, chronic hepatitis B e antigen positive.

Table 22. ICERs per QALY gained around 358,000 € and 96,000 € at 10 and 20 years of follow-up, respectively; CHBe- NC Asians.

		ICER: 1,000 €/QALY gained			
Age		**At 10 years follow-up**		**At 20 years follow-up**	
30	**Mean**	541		167	
	95% range	*261*	*1,211*	*92*	*296*
40	**Mean**	**358**		**96**	
	95% range	***175***	***685***	***58***	***157***
50	**Mean**	218		58	
	95% range	*167*	*219*	*32*	*101*
60	**Mean**	140		66	
	95% range	*135*	*207*	*37*	*119*

Notes: **Base-line scenario highlighted in bold.** See Table 21.

Table 23. ICERs per QALY gained around 50,000 € and 27,000 € at 10 and 20 years of follow-up, respectively; CHBe+/- CC Asians.

		ICER: 1,000 €/QALY gained			
Age		**At 10 years follow-up**		**At 20 years follow-up**	
30	**Mean**	50		27	
	95% range	*26*	*88*	*14*	*46*
40	**Mean**	51		26	
	95% range	*25*	*88*	*13*	*45*
50	**Mean**	**50**		**27**	
	95% range	***26***	***82***	***15***	***46***
60	**Mean**	52		29	
	95% range	*28*	*88*	*15*	*50*

Notes: **Base-line scenario highlighted in bold.** See Table 21.

3.4.4 Variations in the discount rates

Table 24. Variations in discount rates do not significantly impact on ICERs per QALY gained; CHBe+ NC European and Asian cohorts aged 40 years at 20 years of follow-up.

		ICER: 1,000 €/QALY gained			
Discount rates		**Europeans**		**Asians**	
Cost: 0.0%	**Mean**	105		78	
Outcome: 0.0%	*95% range*	*60*	*176*	*50*	*122*
Cost: 3.0%	**Mean**	**110**		**80**	
Outcome: 1.5%	*95% range*	***65***	***184***	***51***	***126***
Cost: 3.0%	**Mean**	133		98	
Outcome: 3.0%	*95% range*	*77*	*208*	*60*	*151*
Cost: 5.0%	**Mean**	157		114	
Outcome: 5.0%	*95% range*	*92*	*258*	*73*	*177*

Table 25. Variations in discount rates do not significantly impact on ICERs per QALY gained; CHBe- NC European and Asian cohorts aged 40 years at 20 years of follow-up.

		ICER: 1,000 €/QALY gained			
Discount rates		**Europeans**		**Asians**	
Cost: 0.0%	**Mean**	161		101	
Outcome: 0.0%	*95% range*	*115*	*163*	*60*	*161*
Cost: 3.0%	**Mean**	**131**		**96**	
Outcome: 1.5%	*95% range*	***75***	***240***	***58***	***157***
Cost: 3.0%	**Mean**	161		119	
Outcome: 3.0%	*95% range*	*124*	*161*	*70*	*191*
Cost: 5.0%	**Mean**	120		134	
Outcome: 5.0%	*95% range*	*117*	*185*	*80*	*218*

Table 26. Variations in discount rates do not significantly impact on ICERs per QALY gained; CHBe+/- CC European and Asian cohorts aged 40 years at 20 years of follow-up.

		ICER: 1,000 €/QALY gained			
Discount rates		**Europeans**		**Asians**	
Cost: 0.0%	**Mean**	29		27	
Outcome: 0.0%	*95% range*	*15*	*47*	*14*	*46*
Cost: 3.0%	**Mean**	**28**		**26**	
Outcome: 1.5%	*95% range*	***15***	***47***	***13***	***45***
Cost: 3.0%	**Mean**	34		32	
Outcome: 3.0%	*95% range*	*17*	*55*	*17*	*53*
Cost: 5.0%	**Mean**	37		36	
Outcome: 5.0%	*95% range*	*19*	*62*	*19*	*60*

3.5 BUDGET IMPACT

A comparison of the current costs of treatment of the CHB Belgian population with a situation of generalized treatment with tenofovir shows that total annual costs increase from 8.2 to 13.5 million €, i.e. an increase of around 5.3 million € (Table 25). On average and per patient, the annual costs increase from 2,642 to 4,340 €, i.e. a 64% increase in mean costs per patient. Note that patients co-infected with HIV or HCV are not included in the estimates.

Table 27. Compared to current antiviral treatment, generalized treating with tenofovir increases the annual costs by an estimated total of 5.3 million €; in €.

		HBV related DMC* incl. antiviral costs		HBV related DMC* excl. antiviral costs for CHB, CC, DC and HCC		HBV related DMC* incl. tenofovir cost in CHB, CC, DC and HCC	
Disease state	**Belgian patients**	**Mean**	**Total**	**Mean**	**Total**	**Total (tenofovir)**	**Total (tenofovir and DM costs)**
ICAR	1,266	115	145,685	115	145,685	-	145,685
CHB	1,200	2,493	2,991,028	591	708,629	5,965,200	6,673,829
CC	383	2,560	980,629	1,115	426,909	1,903,893	2,330,802
DC	10	8,406	84,055	6,814	68,143	49,710	117,853
HCC	49	11,518	564,392	10,816	529,977	243,579	773,556
LTy1	19	102,752	1,952,284	102,752	1,952,284	-	1,952,284
Ltpost	180	8,279	1,490,137	8,279	1,490,137	-	1,490,137
Total	**3,107**	**2,642**	**8,208,209**	**1,713**	**5,321,763**	**8,162,382**	**13,484,145**

Costs under treatment with tenofovir in €	
Total annual cost increase	**5,275,936**
Mean annual cost per patient	**4,340**
Annual cost increase per patient	**1,698**
% cost increase per patient	**64%**

Notes: *Disease management costs; Number of Belgian patients based on survey estimates from part I of the publication, the number of patients with decompensated cirrhosis is likely underestimated as patients with acute disease could not participate to the survey.

4 DISCUSSION AND CONCLUSIONS

Decision makers should be aware that there are no long term randomized controlled trials available for tenofovir or entecavir showing an effect on disease progression and hard clinical endpoints. Therefore results of long term models need to be interpreted with caution. Especially the effect of antiviral treatment on hepatocellular carcinoma remains highly uncertain. We opted to not model (pegylated)interferon-alpha treatment, as this treatment option is appropriate only for selected patients.

We believe our study has many advantages over previous research. First, we carefully collected and analyzed data on the Belgian situation in treatment centres for CHB, including patient numbers, characteristics, quality of life and HBV related costs by clinical disease stage. Second, we accessed an unpublished large cohort of untreated Caucasian CHB patients at Leuven University Hospital, which allowed us to more accurately model disease progression as a function of patient age.

A first important finding concerns the absence of measurable disease progression over a mean period of 10 years in 59 Caucasian CHBe+ patients with normal ALT levels during the first three years of follow-up at Leuven University Hospital (Appendix 6.1). In such patients antiviral treatment cannot be justified based on these observations.

Table 28. Estimated ICER ranges for tenofovir treatment of CHBe+ and CHBe- patients by age, origin and liver cirrhosis status (based on 20 years time horizon).

Age cohort	Patient origin	CHBe+ NC	CHBe- NC	CHBe+/- CC
30 y	European	132 - 355	143 - 461	15 - 45
	Asian	85 - 212	92 - 296	14 - 46
40 y	European	65 - 184	75 - 240	15 - 47
	Asian	51 - 126	58 - 157	13 - 45
50 y	European	28 - 97	38 - 145	16 - 47
	Asian	23 - 75	32 - 101	15 - 46
60 y	European	31 - 110	39 - 156	16 - 52
	Asian	28 - 83	37 - 119	15 - 50

In the modelled CHBe+ and CHBe- cohorts, tenofovir treatment nearly completely eliminates the occurrence of liver decompensation and roughly halves the incidence of HCC. Despite these dramatic clinical effects we find that the treatment is most probably not cost-effective over 10 or 20 years (Table 28) of follow-up, although the ICERs decrease with increasing time horizon. This contrasts with a more favourable ICER for antiviral treatment of patients with compensated liver cirrhosis (Table 26), where the clinical effects of treatment may be less dramatic but occur more in the short term. It seems to be of use to continue the research to identify CHB patients at high risk of disease progression who would benefit most from antiviral treatment. Variables that should be considered are the fibrosis stage, ALT, viral load and genotype.

The ICER of a continued and expensive treatment for the prevention of complications in the long term depends on a number of key variables. Chief are the time to complications which can be prevented, their frequency and cost as well as the annual cost of treatment. These considerations underline the importance of the selected transition probability to liver cirrhosis as an input variable for the Markov model.

The ICERs for CHBe+ and CHBe- cohorts are in general much higher than those reported in the literature thus far. We identified multiple variables in our model that may explain differences in reported ICERs.

We identified two variables in our base-case model that result in a lower ICER:

- For models with ongoing costs and benefits only in the long term the Belgian rules for discounting costs at 3% and effects at 1.5% result in more favourable ICERs when compared to discounting cost and effects equally at 3.5%, as is the case for the UK,[53] and as used in the publications we reviewed in the part 1 report.[18-26]

- The cost induced by the management of complications (DC, HCC) depends mainly on the access to and cost of liver transplantation. Both are high in Belgium when compared to transition probabilities and costs used in models for other countries.

More variables in our base-case model result in a higher ICER:

- The annual cost of tenofovir (and entecavir) is high as compared with less expensive NAs studied in some previous models.
- All studies reviewed in part 1 assume a QoI improvement after treatment-induced HBeAg seroconversion or after a low level of HBV DNA. These assumptions were not based on any assessments in real patients. The utility values used for CHB and treatment-induced response are 0.69 and 0.78 in the model by Lacey et al.;[25] 0.95 and 1.00 in the model by Veenstra et al.;[24] 0.81 and 0.99 in the models using the study by Levy et al.[18, 19, 43] Dakin et al.[53] includes a utility improvement after e seroconversion (from 0.77 to 0.85) but not based on viral suppression. In that study CHBe+ patients were not reported separately and constituted 44% of the CHB cohort.[53] 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.[43] One does not need a calculator to see that any antiviral treatment that costs 5000 euro per year will turn out to be cost-effective if such assumed improvement in utility of 0.18 is used for all patients who show a viral load decrease, independent of any long term effects. This assumption is however in contrast with the utility values we measured in patients with low and high HBV DNA levels under NA treatment.[27] Our findings restrict utility gains in our model to the reduction of disease complications.
- Point estimates of ICERs become more favourable if the time horizon is extended beyond 20 years, as done in a recent model on tenofovir.[53] Despite our efforts the documentation of the natural disease evolution of chronic hepatitis B is far from perfect to build a Markov model that covers the rest of the patient's life. Even more uncertain is the prediction of cost-effectiveness if one uses time horizons that are more than double the clinical treatment experience available today.
- Many published models use rather high transition probabilities to cirrhosis for CHBe+ and CHBe- and apply these uniformly across all age groups. The natural transition rates included in the models vary considerably between studies. For example, the natural transition rates from CHB to CC modelled for CHBe+ vary from 2.6%[25] to 4.4%[18] or 5%.[53] In CHBe-, the rate varies from under 2%[20-22] or 2.9%[19] based on REVEAL,[54, 55] up to 9%.[24, 25, 53] Uniform high transition rates result in a higher proportion (about half) of CHB patients having liver cirrhosis compared with the situation observed in clinical practice, and as documented in the part 1 report. High transition rates also result in a higher frequency of complications and lower accumulated drug costs to prevent these. The net effect is a more favourable ICER, but such models do not reflect the reality of disease progression we measured. We were fortunate to get access to a large unpublished data set of 278 untreated Caucasian CHB patients with a mean follow-up of 7.8 years. The at risk person-years in our data set contributing to the estimation of transition rate to cirrhosis in Caucasians was 2.5 times higher for active CHBe+ patients (890 versus 347 person-years) and 7.5 times higher for CHBe- patients (672 versus 90 person-years) compared with the data sets included in a systematic review on natural disease progression.[32] As a consequence of this rich data, our model is the first that includes age-specific transition probabilities for the development of liver cirrhosis in untreated CHB patients. This adjustment for patient age may seem obvious for hepatologists, but robust epidemiologic data were lacking so far. This adjustment also has additional implications: starting treatment at a more early age is no longer more cost-effective, whereas one would conclude the contrary without this adjustment, as was suggested recently in a US study recently.[56]

- As we concluded in the part 1 report, many published Markov models of CHBe- disease do not follow international clinical guidelines as they do not continue NA treatment until liver transplant or lifelong. In these models treatment is discontinued in CHBe- when a low viral load is achieved for one year.[56] Some models in CHBe+ assume no disease reactivation (or no re-treatment after reactivation) after treatment-induced e seroconversion, and assume no additional liver related mortality once e seroconversion has been observed[23, 57, 58] in CHBe+ or a low DNA value is achieved in CHBe-.
- Some models assume very high treatment effects both for progression to cirrhosis and HCC calibrated using baseline viral load data obtained in the untreated REVEAL community cohort,[54, 55] which mainly consisted of e antigen negative patients in Taiwan. It remains to be demonstrated that treatment induced lowering of viral load results in a long term HCC incidence reduction to a level that is identical to a natural state of low viral load. Extrapolating the reduction in progression to cirrhosis to the CHBe+ situation, as done in these models is even more questionable as in e positive CHB patients an inverse association between Metavir fibrosis stage and viral load was more recently reported in a hospital based study in Australia.[59]

The effect of antiviral treatment on the development of HCC in CHB is still unclear and difficult to unravel from the fibrosis progression process. If one accepts that the presence of liver cirrhosis itself creates an increased risk of HCC, avoiding progression towards cirrhosis should also reduce HCC. In addition, there may be a direct effect of lowering viral load on HCC development, which we modelled in a conservative way. In contrast with some more recently published models, we did not define Markov states based on viral load because we do not feel confident with the data that feed such models, as discussed above. A recent report from Japan showed a similar high incidence of HCC under lamivudin or entecavir treatment of about 1% per year in 194 CHB NC patients and about 8% per year in 62 CHB CC patients, followed for an average of 4.25 years.[60] These data suggest that the HCC reduction (if any) due to antiviral treatment is minimal.

The assumed effect of antiviral treatment on HCC is of high importance for the Asian CHB populations which has reportedly a higher incidence of HCC compared with European patient cohorts. Treating Asian CHB patients thus results in slightly more favourable ICERs compared with European patient cohorts. It remains unclear to what extent data obtained in Asians living in Asia can be extrapolated to sub-Saharan African patients who migrated to Europe, and who constitute a growing proportion of the overall CHB patient population in Europe.

Finally, as the current annual cost of entecavir 0.5mg daily is higher compared with tenofovir, and the price decrease for tenofovir is expected earlier, the results cannot be extrapolated to entecavir. In addition, in patients infected with lamivudin resistant HBV, development of resistance to entecavir has been reported and this will also impact on the analyses. Of course, there are also other conditions whereby it may be more appropriate to use a specific NA. A cost-utility analysis should never be interpreted as a clinical practice guideline.

5 APPENDICES

5.1 NATURAL PROGRESSION TO LIVER CIRRHOSIS IN 278 CHRONIC HEPATITIS B PATIENTS OF EUROPEAN ORIGIN, THE IMPORTANCE OF AGE AND ELEVATED ALT

5.1.1 Introduction

In absence of robust data showing the extent to which complications of chronic hepatitis B (CHB) are reduced after antiviral treatment, cost-effectiveness models comparing antiviral treatment with a "do nothing" strategy may provide a look into the future but need to be interpreted with caution. In the case of chronic infections with the hepatitis B virus (HBV) the natural evolution of the disease is not perfectly documented, despite its relatively high prevalence. This natural history is important as model input. It defines the burden of disease under the "do nothing" strategy.

Natural disease progression data based on large cohorts of chronic hepatitis B patients have been reported only for regions in Asia.[32] Higher natural annual transition rates to cirrhosis were reported for Europe but were based on very small patient numbers (3.8% for CHBe+, n=77, mean follow-up 4.5y; 9.7% for CHBe-, n=30, mean follow-up 3y).[32]

McMahon reported an overall transition probability from CHB to liver cirrhosis of 2 to 3% for clinic-based longitudinal studies, with older age, CHBe+ and high ALT as risk factors.[30] To our knowledge no separate transition rates have been published based on age or ALT. The most detailed data documenting a steep increase of cirrhosis incidence after age 40 were reported for a cohort in Taiwan and obtained during the years following spontaneous e seroconversion.[33]

Hepatitis B e antigen positivity as a marker for an increased progression rate to liver cirrhosis is supported by some studies[1] but seems to be contradicted by the results of a systematic review.[32]

5.1.2 Aim

The aim of the study was to document the natural disease progression to liver cirrhosis and HCC in patients of European origin with e antigen positive or negative chronic hepatitis B.

5.1.3 Methods

Patient dossiers of the Hepatology department of the University Hospital of Leuven were manually screened for patients chronically infected with HBV.

Baseline data recorded included year of birth, gender, country of origin, year of diagnosis of CHB, ALT levels for the first three years after diagnosis, baseline liver ultrasound and biopsy results (Metavir coding was introduced more recently and was not performed for most, re-analysis is ongoing), HB e antigen status. Viral load and genotype data became available more recently, and these data have not yet been analyzed.

Dossiers of patients without liver cirrhosis at baseline and diagnosed as CHBe+ or CHBe- were checked for the year of occurrence of liver cirrhosis. A subgroup of these CHBe+ patients had normal ALT values for the first three years after diagnosis and was coded as CHBe+ with low activity. The year of start of antiviral treatment, diagnosis of HCC (without cirrhosis), death or lost to follow-up were also recorded as these data are used for censoring. CHBe+ patients who showed spontaneous e seroconversion (and transition to an inactive state) were not included in the dataset currently available for analysis.

Data were entered into Stata for calculation of transition rates. Note that for inclusion into a Markov model the here reported yearly transition rates are converted to yearly transition probabilities, using the following formula: transition probability = 1 – exp(-rate).

Separate analyses were performed for CHBe-, CHBe+ and CHBe+ normal ALT patients, and also based on patient age.

5.1.4 Results

Table 27. Patient characteristics at baseline, by patient group.

Group	Patients (male/ female)	Mean age (y) at CHB diagnosis	Mean calendar year at CHB diagnosis
CHBe+ normal ALT	59 (37/22)	34.5	1993
CHBe+	137(103/34)	41.6	1992
CHBe-	82(58/24)	39.2	1989
All	278 (198/80)	39.4	1991

Table 28. Observation period and cases of liver cirrhosis by patient group.

Group	Patients	Mean follow-up in years for patients	Cases of liver cirrhosis	Mean time from CHB diagnosis to cirrhosis for cases (range)
CHBe+ normal ALT	59	10.2	0	NA
CHBe+	137	6.5	23	7.8
CHBe-	82	8.2	29	7.4
All	278	7.8	52	7.4

Table 29. Reasons for censoring, analysis for progression from CHB to cirrhosis, by patient group.

Group	Patients	Observation period				
		Censored because of				Uncensored
		HCC	Death	Loss of follow-up	Start antiviral	
CHBe+ normal ALT	59	0	0	59	0	0
CHBe+	137	1	0	40	73	23
CHBe-	82	2	0	22	29	29
All	**278**	**3**	**0**	**121**	**102**	**52**

An overall transition rate of 2.4% per year from CHB to cirrhosis was found when all patients were grouped. Major differences are observed in the incidence of cirrhosis between CHBe+ patients with normal ALT (not a single case of progression to cirrhosis was seen) versus the two other 'active' CHB groups, where CHBe+ and CHBe- patients showed highly similar progression rates to liver cirrhosis.

Further analyses were performed based on patient age (below 40y, 40 to 49y, 50y+). For this analysis, transition rates are based on observation periods restricted to the age category being analyzed. A patient followed from age 44 to age 53 will thus contribute 5 observation years to the 40-49y category and 4 years to the 50+ category.

Table 30. Transition rate from CHB to cirrhosis by patient age (active CHBe+/- and normal ALT CHBe+ groups pooled).

Age group in years	Observational periods	Time at risk in median years	Mean hazard rate in % (95% CI)
Below 40	136	6.5	0.95 (0.51; 1.78)
40 to 49	112	4	1.86 (1.00; 3.43)
50 plus	131	4	4.84 (3.46; 6.77)
All	379*	6	2.40 (1.83; 3.13)

Note: *There are 192 patients falling into only one observational period, 71 patients being split into two periods and 15 patients being split into 3 periods. This totals 379 observational periods based on 278 patients.

The analysis clearly shows progression rates to cirrhosis that increase with patient age, and similar but somewhat higher progression rates were obtained when the normal ALT patient group was excluded from the analysis.

Table 31. Transition rates from CHB to cirrhosis by patient age, with or without inclusion of CHBe+ patients with normal ALT.

Age group in years	CHBe+/ CHBe- group to cirrhosis excluding normal ALT patients	CHBe+/ CHBe- and CHBe+ with normal ALT to cirrhosis
	Transition rate (95% CI)	Transition rate (95% CI)
Below 40	1.41% (0.76; 2.62)	0.95% (0.51; 1.78)
40 to 49	2.49% (1.35; 4.58)	1.86% (1.00; 3.43)
50 plus	6.29% (4.49; 8.79)	4.84% (3.46; 6.77)
All	3.32% (2.55; 4.34%)	2.40% (1.83; 3.13)

In addition, using the same data set an overall transition rate of 0.115% (0.037% to 0.355%) per year to HCC was found in CHB patients.

5.1.5 Discussion and Conclusion

To our knowledge this is the largest data set of untreated Caucasian CHB patients monitored for disease progression. The at risk person-years in our data set contributing to the estimation of transition rate to cirrhosis in Caucasians was 2.5 times higher for active CHBe+ patients (890 versus 347 person-years) and 7.5 times higher for CHBe- patients (672 versus 90 person-years) compared with the data sets included in a systematic review on natural disease progression.[32]

We show that 59 CHBe+ patients with normal ALT for at least three years do not show any measurable progression to cirrhosis and HCC within a mean follow-up period of 10 years.

Progression rates in persistent CHBe+ and CHBe- patients with elevated ALT were found to be virtually identical (3.3%) and lower than the rates reported in the systematic review (3.8% for CHBe+, 9.7% for CHBe-) and used in Markov models.

Our results represent however overestimations of the real transition rates as we only start the observation period the moment of the first visit to a university hospital, at a time the CHB was already ongoing for an unknown period. For our CHBe+ dataset patients who showed spontaneous e seroconversion were not included. Inclusion of the CHBe+ period of these patients in the analysis would most probably have resulted in lower transition rates for CHBe+ patients.

Patient age was identified as a major determinant of progression rate to cirrhosis. The effect was nonlinear with a major increase in transition rate after age 50. Based on the results found and best available evidence we included in the model the following transition probabilities to cirrhosis for CHBe+ and CHBe-: 1% (0.5-1.5) per year if age < 40, 2% (1-3) for 40-49y, and 5%(2.5-7.5) for age>=50.

The observed transition rate of 0.115% (0.037% to 0.355%) to HCC in CHB patients was used in the model. It is at the low end of the published transition rates for studies in Europe and the US (0.12% to 0.41% per year). These studies were not restricted to Caucasian patients.[32]

Further analysis of this unique data set based on baseline fibrosis stage, ALT, viral load and genotype could be of help to identify those patients at high risk of disease progression.

5.2 COMPARISON OF PUBLISHED QUALITY OF LIFE DATA

5.2.1 Aims

In the first part of this Hepatitis B project, prospective quality of life (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. Five-hundred and twenty-seven (527) patients completed the EQ-5D QoL questionnaire. About two third of the patients were male and the mean age was 46 years. Half of the patients had a European origin (50.9%), 22.4% originated from Africa, 18.0% from Asia and 8.6% from Turkey.[27]

QoL weights were computed based on social preference data collected in Flanders with the EQ-Visual Analogue Scale.[61] Mean utility scores are reported in Table 32 below:

Table 32. Mean EQ-5D utility scores for CHB infection in Belgium (2009).

Hepatitis B infection phase or complication	Mean utility score (Range 0–1)	95% confidence limit	Number of patients	Mean age (years)
Immune tolerance phase	0.81	0.72 – 0.90	22	36.09
Inactive carrier phase	0.83	0.80 – 0.87	153	40.58
Immune reactive phase (HBeAg+)	0.82	0.77 – 0.87	78	43.10
HBeAg- chronic hepatitis B	0.82	0.78 – 0.86	127	45.70
Resolved phase (HBsAg-)	0.74	0.40 – 1.00	6	53.50
Compensated cirrhosis (CC)	0.78	0.73 – 0.84	69	53.36
Decompensated cirrhosis (DC)	0.70	0.17 – 1.00	2	45.50
Hepatocellular carcinoma (HCC)	0.67	0.44 – 0.90	10	60.60
Post-liver transplant (LT)	0.82	0.75 – 0.88	60	59.10

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. Also patients having received a LT had on average a utility score of 0.82. Average utility scores were slightly lower in CC (0.78), in DC (n=2: 0.66 and 0.75) and in HCC (0.67). The mean utility score was only 0.74 in 6 HBsAg- patients without cirrhosis. It 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.

The aim of this section is to identify QOL weights for different health states associated with CHB in the literature and to compare them with our findings. This comparison should allow to identify the most appropriate and robust QoL data to feed our economic model.

5.2.2 Methods

5.2.2.1 Literature search strategy

Electronic databases were consulted for original publications on the quality of life estimates for each health state associated with chronic hepatitis B. Systematic searches were carried out up to October 2010 in the following databases: Medline(OVID), Embase and PsycINFO. Searches using various qualifier for "quality of life" were used as Subject heading or as text word (See tables below).

Table 33. Search strategy and results for Medline(OVID).

Date	**6/10/2010**		
Database	**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)**		
Date covered	**1950 to Present**		
Search strategy	**#**	**Searches**	**Results**
	1	"Quality of Life"/	85819
	2	"Value of Life"/	5147
	3	Quality-Adjusted Life Years/	4630
	4	qol$.tw.	12361
	5	hrqol$.tw.	4275
	6	qaly$.tw.	3224
	7	(quality adj1 life).tw.	2661
	8	1 or 2 or 3 or 4 or 5 or 6 or 7	98319
	9	exp Hepatitis B/	39236
	10	8 and 9	**114**

Table 34. Search strategy and results for Embase.

Date	**06/10/2010**		
Database	**Embase**		
Date covered	**No restrictions**		
Search strategy	**#**	**Searches**	**Results**
	#1	'quality of life'/exp	159850
	#2	qol$:ab,ti	15854
	#3	qaly$:ab,ti	3241
	#4	hrqol$:ab,ti	5055
	#5	'hepatitis b'/exp/mj	33904
	#6	'hepatitis b virus'/exp/mj	15458
	#7	#1 OR #2 OR #3 OR #4	161906
	#8	#5 OR #6	45353
	#9	#7 AND #8	**173**

Table 35. Search strategy and results for PsycINFO(OVID).

Date	**6/10/2010**		
Database	**PsycINFO**		
Date covered	**1806 to September Week 4 2010**		
Search strategy	**#**	**Searches**	**Results**
	1	"Quality of Life"/	18091
	2	"Value of Life"/	0
	3	Quality-Adjusted Life Years/	0
	4	qol$.tw.	3922
	5	hrqol$.tw.	1324
	6	qaly$.tw.	384
	7	(quality adj1 life).tw.	889
	8	1 or 2 or 3 or 4 or 5 or 6 or 7	18997
	9	exp *hepatitis/	1104
	10	8 and 9	50
	11	(hepatitis adj c).ti.	559
	12	10 NOT 11	**5**

5.2.2.2 Selection criteria

Identified references were assessed against pre-defined selection criteria (in terms of population, intervention, outcome and design - Table 36) 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.

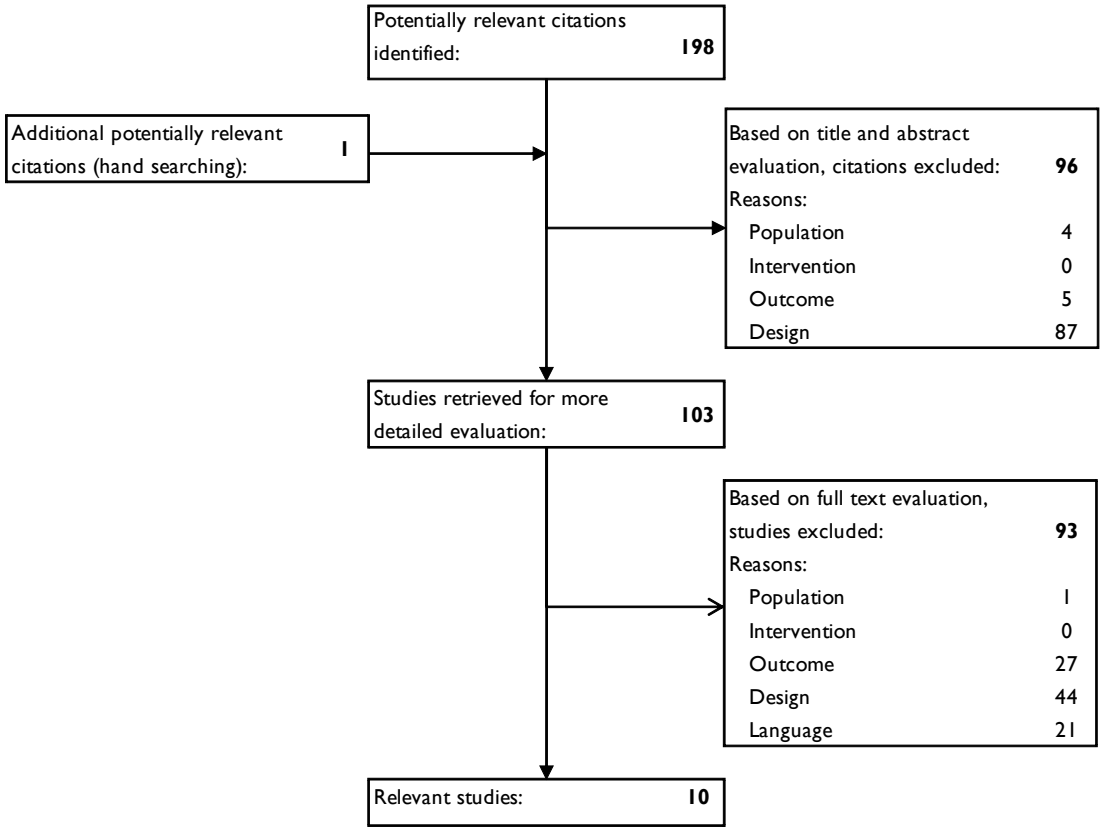
Table 36. Article selection criteria.

	Inclusion criteria	**Exclusion criteria**
Population	Hepatitis B patients	Hepatitis C patients…
Intervention	Medical therapy, vaccination, screening…	Not applicable
Outcome	Unique QoL utility values per health states	Multi-dimensions HRQoL scores, DALYs…
Design	Direct (TTO, SG…) or indirect (generic instruments) valuation methods in primary studies or in cost-utility analyses	Letters…

5.2.2.3 Selection process

The flowchart of the selection process is presented below. The searches on the databases and local HTA websites returned 292 citations. After exclusion of 94 duplicates, 198 unique citations were left. A study identified on the early e-publications of a journal was further added,[53] summing up to a total of 199 unique citations. Ninety-six (96) references were discarded based on their title and abstract, leaving 103 references for full-text evaluations. Another 93 references were excluded at this stage, mostly because the unmet design criteria. Many excluded studies were cost-utility analyses of interventions against hepatitis B (screening, medication, vaccination), in which utility values were not calculated as such but selected from the literature. Ten studies were left that analysed QoL utilities for chronic hepatitis B patients.[43, 62-70]

Figure 20. Flowchart of the selection process for QoL studies.



5.2.3 Results

Utility values computed for different chronic hepatitis B health stages are reported in Table 37 below. There appear to be great diversity in the values reported per health state. The most recent studies derived utilities from the patients themselves.

Table 37. Quality of life of CHB patients: review of the literature (Primary studies).

Study	Country	Tool	Population	Mean age (SD)	N	Value	CHB	CC	DC	HCC	LT	PLT	ICAR
KCE, 2010	Belgium[1]	EQ-5D	CHB patients	46	421	Mean	0.82	0.78	0.70	0.67	-	0.82	0.83
						95% CI	0.78-0.86	0.73-0.84	0.17-1	0.44-0.90	-	0.75-0.88	0.80-0.87
						N	127	69	2	10	-	60	153
Lam et al., 2009[66]	China	SF-6D	CHB patients	50.4 (12.3)	520	Mean	0.75	0.70 [7]		0.72	-	-	0.75
						SD	0.15	0.15 [7]		0.16	-	-	0.14
						N	102	139 [7]		123	-	-	156
Ong et al., 2008[67]	China	EQ-5D	CHB patients	46.2 (12.9)	432	Median	1	1	0.85	0.83	-	0.85	1
						25-75th %	0.85-1	0.85-1	0.76-1	0.73-1	-	0.77-1	1-1
						N	142	66	24	22	-	22	156
Levy et al., 2008[43]	ALL	SG	CHB patients	45.5 (13.1)	534	Mean	0.68	0.69	0.35	0.38	0.57	0.67	-
						95% CI	0.66-0.70	0.66-0.71	0.32-0.37	0.36-0.41	0.54-0.60	0.64-0.69	-
						N	225	98	49	56	50	39	-
	China	SG	CHB patients	-	100	Mean	0.52	0.57	0.26	0.31	0.41	0.55	-
	HK	SG	CHB patients	-	100	Mean	0.60	0.64	0.30	0.38	0.56	0.64	-
	Canada	SG	CHB patients	-	100	Mean	0.66	0.65	0.44	0.46	0.58	0.64	-
	USA	SG	CHB patients	-	56	Mean	0.67	0.66	0.37	0.43	0.57	0.64	-
	UK	SG	CHB patients	-	93	Mean	0.69	0.68	0.35	0.42	0.57	0.66	-
	Spain	SG	CHB patients	-	85	Mean	0.67	0.71	0.44	0.48	0.61	0.70	-
Bondini et al., 2007[63]	USA [2]	HUI Mark-2	CHB patients	44,2 (12.9)	68	Mean	0.78	0.81 [7]		-	-	-	-
						SD	0.20	0.10 [7]		-	-	-	-
						N	48 [3]	20 [3, 7]		-	-	-	-
Pwu et al., 2002[69]	Taiwan	TTO	Clinicians	-	12	Median	0.95	0.90	0.65	0.50	-	-	1
			CHB patients	Not stated	53	Range	0.9-1	0.8-0.95	0.50-0.8	0.33-0.75	-	-	0.95-1
						N	20	20 [7]		1	-	-	12
Aggrawal et al., 2002[62]	India	Expert opinion	Clinicians	-	-	Estimate	0.95	0.90	0.50	0.50	-	-	-
Crowley et al., 2000[64]	Australia	AQOL	Clinicians	-	4	Estimate	0.69	0.56	0.15	0.12	-	-	0.78
Owens et al., 1997[68]	USA	TTO	Clinicians	-	128	Mean	0.812 (SD=0,021) HBV asymptomatic state [4] 0.670 (SD=0,023) HBV mildly symptomatic state [5]						

Study	Country	Tool	Population	Mean age (SD)	N	Value	CHB	CC	DC	HCC	LT	PLT	ICAR
							0.218 (SD=0,021) HBV severely symptomatic state [6]						
Wong et al., 1995[70]	USA	TTO & SG	Clinicians	-	7	Mean	0.94	0.92	0.54	0.49	-	-	0.99
Dusheiko et al., 1995[65]	UK	Expert opinion	Clinicians	-	-	Estimate	0.80	0.50	0.20	0.20	-	-	0.90

CHB=Chronic hepatitis B; CC=Compensated cirrhosis; DC=Decompensated cirrhosis; HCC=Hepatocellular carcinoma; LT=Liver transplant; PLT=Post-liver transplant; ICAR=Inactive carrier; AQOL=Assessment of quality of life; SG=Standard gamble, TTO=Time trade-off.
1=50,9% Europe; 8,6% Turkey; 22,4% Africa; 18% Asia. 2=59% Asian American; 16% White; 25% Other. 3=Self computation. 4=defined as being asymptomatic, but with the potential to transmit the disease. 5=defined as mild fatigue and malaise that did not interfere with work. 6=defined as cirrhosis, ascites and gastrointestinal bleeding. 7= there is no distinction between compensated and decompensated cirrhoses.

5.3 DISEASE MANAGEMENT COSTS

LIST OF ABBREVIATIONS

Abbrevi-ation	Description English	Dutch	Dutch description	French	French description
ATC	Anatomical Therapeutic Chemical Classification System used for the classification of drugs	ATC	Anatomisch Therapeutisch Chemisch Classificatie Systeem voor geneesmiddelen	ATC	Système de Classification Anatomique, Thérapeutique et Chimique
BCPI	Belgian Centre for Pharmaceutical Information	BCFI	Belgisch Centrum voor Farmacotherapeutische Informatie	CBIP	Centre Belge d'Information Pharmacothérapeutique
BFM	Budget Finacial Means (for hospitals)	BFM	Budget Fianciële Middelen voor de ziekenhuizen	BMF	Budget Moyens Financiers des hôpitaux
CBSS	Crossroads Bank for Social Security	KSZ	Kruispunt bank Sociale Zekerheid	BCSS	Banque Carrefour Sécurité Sociale
CNK	National (unique) code for pharmaceuticals	CNK	Nationale (unieke) kode voor geneesmiddelen	CNK	Code national (unique) pour les produits pharmaceutiques
DDD	Defined Daily Dose for an average adult of 70 Kgs.	DDD	Gedefinieerde dagdoses voor een gemiddelde volwassene van 70 Kg.	DDD	Dose quotidienne définie pour un adulte moyen pesant 70 kilos
DPP	DDD per package	DPP	Aantal DDD per farmaceutische verpakking-	DPP	Nombre de DDD par conditionnement pharmaceutique
EF	Extrapolation Factor	EF	Extrapolatie Factor	FE	Facteur d'extrapolation
ETL	Extraction, Transformation and Loading (of data)	ETL	Extractie, transformatie en inladen van database gegevens	ETL	Extraction, transformation et intégration de données dans une base de données commune
EXC	Cost class excluded for cost study	EXC	Kostencategorie uitgesloten voor kostenstudie	EXC	Catégorie de dépenses exclue de l'étude coût
FAMHP	Federal Agency for Medicines and Health Products	FAGG	Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten	AFMPS	Agence Fédérale des Médicaments et des Produits de Santé
FTU	Full Time (personel) Units	VTE	Voltijdse Eenheid	UTP	Unité Temps Plein
GP	General practitioner	HA	Huisarts	MG	Médecin généraliste
HBc	Hepatitis B core antigen	HBc	Hepatitis B kern antigen	HBc	L'antigène du noyau du virus de l'hépatite B
HBe	Hepatitis B e-antigen, associated with the viral nucleocapsid	Hbe	Hepatitis B e-antigeen, geassocieerd met het virale nucleocapside	Hbe	Antigène 'e' de l'hépatite B, associé au nucléocapside viral

Abbrevi-ation	Description English	Dutch	Dutch description	French	French description
HBs	Hepatitis B surface (antigen / antibodies)	HBs	Hepatitis B oppervlakte (virale membraan) antigen	HBs	L'antigène de surface (membrane virale) de l'hépatite B
HBV	Hepatitis B virus related disease	HBV	Hepatitis B virus geassocieerd lijden	VHB	Maladie associée au virus de l'hépatite B
HCC	Hepatocellular Carcinoma	HCC	Hepatocellulair carcinoma	CHC	Carcinome hépatocellulaire
HDI	Health and Disability Insurance	ZIV	Ziekte- en InvaliditeitsVerzekering	AMI	Assurance Maladie Invalidité
HIC	Health insurance companie (7 national)	VI	Verzekeringsinstellingen (7 nationaal)	OA	Organismes assureurs (7 sur le plan national)
HIV	Human Immunodeficiency Virus (associated with AIDS = acquired immuno-deficiency syndrome)	HIV	Humaan Immunodeficiëntie Virus (geassocieerd met AIDS = verworven immunodeficiëntie syndroom)	VIH	Virus de l'immunodéficience humaine (associé au SIDA = syndrome de l'immunodéficience acquise)
IMA	Intermutualistic Agency	IMA	Intermutualistisch agentschap	AIM	Agence Inter mutualiste
MCR	Minimal Clinical records	MKG	Minimale Klinische Gegevens	RCM	Résumé Clinique Minimum
MI	Medical imaging	MBV	Medische BeeldVorming	IM	Imagerie Médicale
nHBV	Not Hepatitis B virus related disease	nHBV	Niet hepatitis B virus geassocieerd lijden	nVHB	Maladie non associée au virus de l'hépatite B
NIHDI	National Institute for Health and Disablility Insurance	RIZIV	Rijksinstituut voor ziekte- en invaliditeitsverzekering	INAMI	Institut National d'Assurance Maladie et Invalidité
PAT	Costs related to 'compulsory patient contribution' regulations (paid by the patient himself)	PAT	Officiële remgelden voor de patiënt	PAT	Coûts patients de ticket modérateur
PH	Pharmanet data	PH	Farmanet gegevens	PH	Données Pharmanet
POP	Population data (demographic and concerning social security status of patients)	POP	Demografische en sociale zekerheidsgegevens van de patiënt	POP	Données démographiques et du statut sécurité sociale du patient
SOC	Social security compensations for families with low tax income	SOC	Compensaties in de sociale zekerheid voor lage gezinsinkomens (MAF)	SOC	Compensations de la sécurité sociale pour familles à bas revenu net imposable (MAF)
SS	Data of health care services delivered to patients (IMA)	SS	Gezondheidszorggegegevens van de patiënt (IMA)	SS	Données des soins de santé du patient (AIM)
SSN	Social security number	INSZ	Inschrijvingsnummer sociale zekerheid	NISS	Numéro d'inscription sécurité sociale

Abbreviation	Description English	Dutch	Dutch description	French	French description
SWOT	Strengths, Weaknesses, Opportunities, Threats	SWOT	Sterkte-zwakteanalyse (een bedrijfskundig model)	AFOM	Atouts, Faiblesses, Opportunités, Menaces
TTP	Trusted Third Party	TTP	Intermediaire vertrouwensorganisatie	TTP	Organisation intermédiaire de confiance
UD	Unit dose (for hospital pharmaceuticals)	UD	Eenheidsdosis (ziekenhuismedicatie)	DU	Dose unité (conditionnements pharmaceutiques en milieu hospitalier)

5.3.1 Data sources

5.3.1.1 Field survey by Belgian hepatologists

Pre-specified data from 554 patients were collected in 18 Belgian hepatology centres, during a routinely planned visit within a six months study period (January 2009 to end of June 2009). Three patients were found to be not eligible and their data were excluded from the study, leaving the remaining 551 patients for inclusion. If available at the centre, the 2006 data were collected from the medical records.

No direct identification data were collected except for the patient's social security number (INSZ-NISS), whenever available. Data, with a unique patient number assigned to each patient, were entered in a MS Access database (Table 38) by the contracted TTP[a] (Trusted Third Party). Social security numbers (INSZ-NISS) were enciphered and a list of the original numbers was transferred to the TTP [b] of the national Intermutualistic Agency (IMA) for linkage to individual healthcare consumption data of 2006 (compulsory health and disability insurance, governed by NIHDI).

Table 38. Layout of VEEDACR database

Field name	Description	Values
ADEF1	Adefovir in 2006	1=ticked
ADEF2	Adefovir in 2009	1=ticked
Age	Age in years	
Antivir06	Antiviral pharmaceuticals in 2006	
Antivir09	Antiviral pharmaceuticals in 2009	
Avir09		
AVMEDO1	Other medication in 2006	
AVMEDO2	Other medication in 2009	
B	Belgian citizenship	
CCIRR1	Compensated cirrhosis in 2006	1=ongoing; 2=new diagnosis
CCIRR2	Compensated cirrhosis in 2009	1=ongoing; 2=new diagnosis
ChepB	Patient_ID	
CHEPB1	Chronic hepatitis B in 2006	1=ongoing; 2=new diagnosis
CHEPB2	Chronic hepatitis B in 2009	1=ongoing; 2=new diagnosis
COUNTRY	Country of origin	
CVIS	Current visit	1=yes; 0=no
DATA1	2006 data available	1=yes;0=no
DBY	Birth year	
DCIRR1	Decompensated cirrhosis in 2006	1=ongoing; 2=new diagnosis
DCIRR2	Decompensated cirrhosis in 2009	1=ongoing; 2=new diagnosis
DCOMPD	IC & QoL completed, day	
DCOMPM	IC & QoL completed, month	
DCOMPY	IC & QoL completed, year	

a VeedaCR nv/sa, Brussels, a contract research organisation
b At that time: IBM Belgium nv/sa

Field name	Description	Values
DFSY	Fibro scan score, year tested	(-1=unknown)
DHBVY	HBV genotype , year tested	(-1=unknown)
DMFSY	Liver biopsy Metavir fibrosis score, year tested	(-1=unknown)
DNA06	DNA quantity in 2006	
DNA09	DNA quantity in 2009	
DNAA1	DNA > 10 000 copies/ml or 2 000 IU/ml in 2006	1=pos;0=negative;-1=unknown
DNAA2	DNA > 10 000 copies/ml or 2 000 IU/ml in 2009	1=pos;0=negative;-1=unknown
DNAB1	DNA > 100 000 copies/ml or 20 000 IU/ml in 2006	1=pos;0=negative;-1=unknown
DNAB2	DNA > 100 000 copies/ml or 20 000 IU/ml in 2009	1=pos;0=negative;-1=unknown
ENTEC1	Entecavir in 2006	1=ticked
ENTEC2	Entecavir in 2009	1=ticked
EU	Other EU citizenship	
flag	VEEDACR internal flag	
FS	Fibroscan score	Range 0-99
GCOM1	General comment1	
GCOM2	General comment2	
GCOM3	General comment3	
HBEAB1	HBE Antibody in 2006	1=pos;0=negative;-1=unknown
HBEAB2	HBE Antibody in 2009	1=pos;0=negative;-1=unknown
HBEAG1	HBE Antigen in 2006	1=pos;0=negative;-1=unknown
HBEAG2	HBE Antigen in 2009	1=pos;0=negative;-1=unknown
HBSAB1	HBS Antibody in 2006	1=pos;0=negative;-1=unknown
HBSAB2	HBS Antibody in 2009	1=pos;0=negative;-1=unknown
HBSAG1	HBS Antigen in 2006	1=pos;0=negative;-1=unknown
HBSAG2	HBS Antigen in 2009	1=pos;0=negative;-1=unknown
HBV	HBV genotype	
HCC1	Hepatocellular CA in 2006	1=ongoing; 2=new diagnosis
HCC2	Hepatocellular CA in 2009	1=ongoing; 2=new diagnosis
IA1	Interferon alpha in 2006	1=ticked
IA2	Interferon alpha in 2009	1=ticked
ICAR1	Inactive carrier in 2006	1=ongoing; 2=new diagnosis
ICAR2	Inactive carrier in 2009	1=ongoing; 2=new diagnosis
INSZ	INSZ / NISS	
ITOL1	Immune intolerance in 2006	1=ongoing; 2=new diagnosis
ITOL2	Immune intolerance in 2009	1=ongoing; 2=new diagnosis
LAMIV1	Lamuvidin in 2006	1=ticked
LAMIV2	Lamuvidin in 2009	1=ticked
LTR1	Liver transplant in 2006	1=ongoing; 2=new diagnosis
LTR2	Liver transplant in 2009	1=ongoing; 2=new diagnosis
MFS	Liver biopsy Metavir fibrosis score	Range 0-4
NOINS	No other insurance	
NONE1	No antiviral medication in 2006	1=ticked
NONE2	No antiviral medication 2009	
NONEU	Non EU citizenship	
OINS	Other insurance	
Orig	Continent of origin	
PEGIA1	PEG Interferon alpha in 2006	1=ticked
PEGIA2	PEG Interferon alpha in 2009	1=ticked
SEX	Sex	1=Male / 2=Female
Sex01	Sex code	0 = female; 1 = male
SexLabel	Label sex code	
SIGN	Signed	1=OK
TENOF1	Tenofovir in 2006	1=ticked
TENOF2	Tenofovir in 2009	1=ticked
VISIT1	Visit number for HBV in 2006	
VISIT2	Visit number in current year, incl. planned	

Field name	Description	Values
VRECID	VEEDACR doc_ID	
Weight2	Body weight in 2009	

5.3.1.2 IMA data

On a sequential base all (new) accountancy data on reimbursements in the field of compulsory health and disability insurance (HDI) are transmitted by the 7 national health insurance companies (HIC) to the legally instituted Intermutualistic Agency (IMA), along with data concerning social security status and population registry characteristics of the patients. This process integrates 3 data collection circuits: health care services (SS), Pharmanet (PH) and population data (POP), the latter from the Crossroads Bank for Social Security (CBSS[c]). From the resulting extensive database only a selection of variables was requested for (Table 39).

Table 39. Specifications of requested IMA data

IMA zone	Description	Field type	Fieldname after ETL	Source (*)
SS00010 PP0010	Patient number (enciphered)	Alphanumeric	Pat_ID	S/F P
SS00015	Start date service delivered	Date	Date_first	S
	Delivery date	Date	Date_first	F
SS00020	NIHDI code	Alphanumeric	NIHDI_code	S
SS00020	Code category	Alphanumeric	Cat_code	F
SS00045	N-group of NIHDI code	Alphanumeric	N_grp	S/F
SS00050	Number of billings	Numeric, integer	N_cases	S
	Quantity	Numeric, decimal	N_units	F
SS00055	Number of days	Numeric, integer	N_days	S
SS00060	Reimbursement amount	Numeric, Euro	N_reimb	S/F
SS00065A	Iidentification health care professional (HCP)	Alphanumeric	Disp_ID	S
SS00065B	Qualification health care professional (HCP)	Alphanumeric	Disp_Q	S
SS00070A	Iidentification health care prescriber (PRESC)	Alphanumeric	Presc_ID	S/F
SS00070B	Qualification health care prescriber (PRESC)	Alphanumeric	Pres_Q	S/F
SS00075	ID number of health care institution (HCI)	Alphanumeric	Inst-ID	S
SS00080	Department of HCI	Alphanumeric	Inst_dept	S
SS00085	ID number of place of service delivered	Alphanumeric	Prest_place	S
SS00110	Admission date	Date	Date_admission	S
SS00115	Discharge date	Date	Date_discharge	S
SS00125	End date prestation (serial services)	Date	Date_last	S/F
SS00130	Related NIHDI code	Alphanumeric	Relative_code	S
SS00135	Number product	Alphanumeric	Prod_ID	S/F
SS00140	Normcode service delivered	Alphanumeric	Norm_prest	S
SS00145	Night/WE-tariff or not	Alphanumeric	N_WE	S
SS00150	Billed NIHDI code	Alphanumeric	Billed_code	S
SS00160	Patient's contribution	Numeric, Euro	QQP	S/F
SS00165	Supplement payed by patient	Numeric, Euro	Suppl	S
SS00170	Number implant	Alphanumeric	Impl_ID	S
SS00180	Reduced reimbursement amount	Numeric, Euro	Red_reimb	F

[c] http://www.ksz-bcss.fgov.be/en/international/home/index.html

IMA zone	Description	Field type	Fieldname after ETL	Source (*)
PP0040A	Year of death	Discriminant	Death_year	P
PP0040B	Month of death	Discriminant	Death_month	P
PP0015	Birth year	Discriminant	Birth_year	P

(*) S: dataset SS = health care services & deliveries for inpatients and outpatients. F: dataset Pharmanet = medical / paramedical prescriptions carried out in 'extra muros' pharmacies (outpatients). P: dataset POP = data concerning social security status and population registry characteristics of all patients

5.3.1.3 Study database

Extensive ETL (Extraction, Transformation and Loading) on VEEDACR and IMA data resulted in the creation of 4 main tables, called matrices, including some newly created variables (Table 40 and 41) Figure 21 represents relationships between main tables.

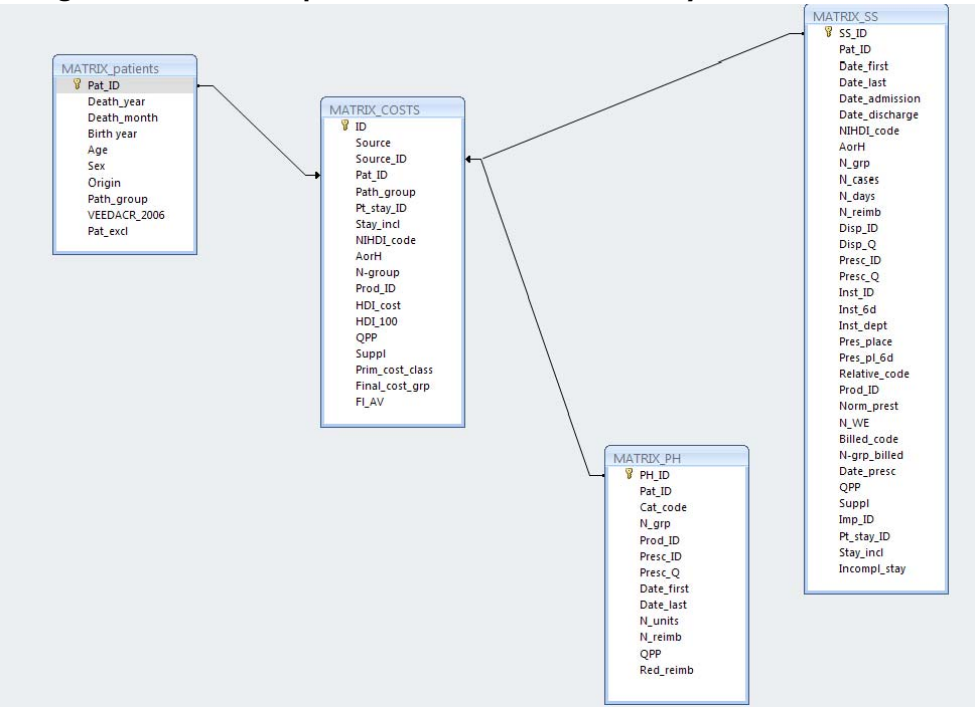
Table 40. Main data matrices in study database

Nr	Matrix Name	Contents
1	Matrix_patients	Patients' characteristics & HBV clinical stage based on VEEDACR data
2	Matrix_SS	HC reimbursement data
3	Matrix_PH	Pharmanet reimbursement data
4	Matrix_costs	2 and 3 integrated with cost sub groupings & extrapolations

Table 41. Newly created variables in study database

New variables	Description	Matrix nr
Origin	Continent of patient's origin	1
Pat_excl	Inclusion (0) or exclusion (1) flag for patient	1
VEEDACR_2006	Flag indicating presence (1) or absence (0) of 2006 data in VEEDACR database	1
AorH	Indicates outpatient (A) or inpatient (H) care or accountancy pseudo code (T)	2/4
InPt_stay_ID	Chronological stay number for inpatient and 'one day' hospital stays	2/4
Inst_6d	ID number of health care institution (HCI) stripped to its leading 6 digit root	2
Pres_pl_6d	ID number of place of service delivered stripped to its leading 6 digit root	2
SS_ID	Unique record number in Matrix_SS	2
PH_ID	Unique record number in Matrix_PH	3
Prim_cost_class	Primary cost sub group of record based on NIHDI billing code	4
Final_cost_grp	Final cost sub group of records (HBV, nHBV, SOC, PAT or EXC) aftre integration	4
Stay_incl	Flag indicating if hospital stay is positively included (value 1); affirmatively excluded (value 0) or not (value -1)	2/4
Fl_AV	Flag indicating HBV antiviral record (for substitution simulations)	4
Source	Indicates source of record (SS = matrix_SS or PH = Matrix_PH)	4
Source_ID	Unique record number of source record (connects Matrix_costs records with their source records in either Matrix_SS or Matrix_PH	4

Figure 21. Relationships between main tables in study database



5.3.2 Primary inclusion counts

Table 42 gives an overview of patient counts in both hepatologists' field survey VEEDACR database and in IMA database after linkage. Not all records in VEEDACR database could be linked to IMA patient records. However, loss was minimal and mainly restricted to the two 'lesser' clinical stages, '10 Not Active' and '11 Active'. Overall linkage percentage was 96.64%.

Two patients labelled <24 HCC> in hepatologists' data turned out to have had a liver transplant in 2006. For this cost study they were transferred to the <26 Liver transplant> group.

For rather obvious reasons (cost heterogeneity) the liver transplant group was subdivided in actual liver transplant in 2006 and post transplantation group (transplantation before 01/01/2006).

Table 42. Patient counts before and after linkage

Hepatologists' field survey		Linkage IMA data for patients 2006	
Clinical stage group	**Patient count**	**Clinical stage group**	**Patient count**
10 Not active	82	10 Not active	76
11 Active	160	11 Active	150
22 Comp. Cirrhosis	53	22 Comp. Cirrhosis	49
23 Decomp. Cirrhosis	5	23 Decomp. Cirrhosis	5
24 HCC	11	24 HCC (*)	6
26 Liver transplant	46	25 Liver transplant	6
		26 Post transpl.	41
2006 data	**357**	**96.64 % linkage**	**345**
No 2006 data	**194**		**173**
Total	**551**		

(*) Two patients (1055 and 1311) labelled <24 HCC> in hepatologists' data had liver transplant in 2006. For this cost study they were transferred to the <26 Liver transplant> group.

5.3.3 Exclusions and sub grouping for cost study

Since HBV infections frequently occur as an epiphenomenon with other pre-existing or concurrent disease(s) or treatment(s) (e.g. coagulation disorders needing multiple blood transfusions, haemodialysis, HIV …) taking 'include-exclude' and 'cost sub grouping' decisions was ineluctable. This process was undertaken in three mutually independent layers: the patient, all his/her hospital stays (inpatient and 'one day') in 2006 and the individual fee-for-service reimbursements in both in- and outpatient settings, services and supplies delivered as well as pharmaceuticals. At the end, integration of all three layers resulted in final cost class aggregations per patient: HBV related (HBV), not HBV related (nHBV) and costs related to social security 'low income compensation' regulations (SOC), permitting a diversified cost balancing.

5.3.3.1 Hospital stays identification

273 hospital stays were identified, 206 inpatient stays and 67 'one day stays'. Their admission and discharge dates were established, as well as their chronology (addendum 1). All billings related to a same stay were bundled by attributing them the unique identification code of the corresponding stay obtained through concatenation of patient number, stay order number and a suffix code indicating "H" for inpatient stay, "O" for 'one day stay', eventually followed by an extra "i" for incomplete (inpatient) stay.

5.3.3.2 High level: patient exclusions

Some, luckily few patients proved having had a discharge in January of the year 2006 with an (irretrievable) admission date in 2005, since IMA data extraction did not retrograde to charges claimed in 2005. Those patients had an incomplete 'stay record' and consequently were discarded for the cost study (Table 43). With two exceptions (a patient with HCC and one with Liver transplant) losses were restricted to the 'lesser HBV stage' and at the same time most numerous patient groups.

One patient in the '11 Active group' proved to have been a psychiatric inpatient with only 134 stay days and no other services whatsoever charged by his hospital. All HBV and other medication were recorded via the outpatient pharmacy's circuit. Consequently, we decided to exclude the inpatient part of his records, but not the medication records.

Table 43. Patient exclusions in IMA data

Clinical stage	Excluded patients (incomplete stay at begin 2006)	Remaining patients
10 Not active	1	78
11 Active	4	151
22 Comp. Cirrhosis	1	50
23 Decomp. Cirrhosis	0	5
24 HCC	1	6
25 Liver transplant	1	6
26 Post transpl.	0	41

5.3.3.3 Medium level: stay exclusions

Since we did not have at our disposal the clinical records[d] of all hospital stays, we had to fall back on an in depth analysis of all billing records in order to indirectly reveal the (main) reason of each admission. Judging was mainly based on 3 axes:

1. the presence of NIHDI billing codes for diagnostic or therapeutic interventions that manifestly had no causal connection whatsoever with HBV infection status (see addendum 2);
2. obviously weighing of exclusion criteria for the other NIHDI codes had to be done separately for each clinical stage group: exclusion criteria were most severely applied to the 'non active' group and they gradually had to become more lenient with increasing severity of illness (SOI): non active' > 'active' > compensated cirrhosis > decompensated cirrhosis > HCC, liver transplant and post transplantation groups, aiming at not to exclude interventions related to HBV clinical stage or treatment complications.
3. Frequency and reimbursement total of a given billing code: the higher the frequency within a given clinical stage group the higher the likeliness of being related to HBV; however - and especially for the low number 'higher SOI' stages - with notorious exceptions (e.g. complications).

A filter was applied eliminating all billing codes not suitable for stay exclusion (e.g. laboratory tests, medical imaging, anaesthesiology…). For this purpose a preparatory 'suitable – not suitable' flagging of the NIHDI N-group classification of billing codes was used (Table 44). **As a consequence, any billing code in any N-group labelled as 'not suitable' could not be eligible for stay exclusion**.

Table 44. Flagging of the N-groups of NIHDI billing codes for stay exclusion exercise

N-group	Label N-group	Filter parameter
N00	Surveillance fees for hospitalized patients	NOT SUITABLE
N01	Consultations, home visits and medical advice	NOT SUITABLE
N02	General procedures (GP level)	NOT SUITABLE
N04	Dental care	SUITABLE
N05	Physical therapy by paramedics ('Kinesitherapy')	NOT SUITABLE
N06	Paramedical care	NOT SUITABLE
N08	Clinical biology - accessible for general practitioners	NOT SUITABLE
N10	Assistance with childbirth	SUITABLE
N11	Gynaecology – obstetrics	NOT SUITABLE
N12	Reanimation	SUITABLE
N13	General procedures and punctions, accessible for all medical specialists	NOT SUITABLE
N14	Anaesthesiology (aspecific coding)	SUITABLE
N15	Operative assistance	NOT SUITABLE
N16	Stomatology	SUITABLE
N18	Ophthalmology	SUITABLE
N19	Urgency surcharges	SUITABLE
N20	General surgery	SUITABLE
N21	Neurosurgery	SUITABLE
N22	Plastic and reconstructive surgery	SUITABLE
N23	Abdominal surgery	SUITABLE
N25	Thoracic surgery	SUITABLE
N26	Vascular surgery	SUITABLE
N28	Otorhinolaryngology	SUITABLE
N30	Urology	SUITABLE
N32	Orthopaedics	SUITABLE

[d] National Minimal Clinical Records (MCR) registry of the Federal Ministry of Health

N-group	Label N-group	Filter parameter
N33	Transplantations	SUITABLE
N40	Internal medicine	SUITABLE
N41	Pneumology	SUITABLE
N42	Gastro-enterology	SUITABLE
N45	Radiation therapy	SUITABLE
N46	Nuclear medicine in vivo	SUITABLE
N47	Nuclear medicine in vitro	NOT SUITABLE
N48	Radio-isotopes	NOT SUITABLE
N50	Roentgen diagnose	NOT SUITABLE
N51	Percutanuous interventions	NOT SUITABLE
N53	Patient's contribution - hospitalized patients	SUITABLE
N54	Paediatrics	SUITABLE
N55	Cardiology	SUITABLE
N56	Neuropsychiatry	NOT SUITABLE
N57	Physical therapy	NOT SUITABLE
N59	Dermato-venereology	SUITABLE
N60	Clinical biology - accessible for medical specialists	NOT SUITABLE
N61	Outpatient lump sum fees - clinical biology	NOT SUITABLE
N62	Inpatient lump sum fees - clinical biology	NOT SUITABLE
N63	Anatomopathology	NOT SUITABLE
N64	Genetic testing	NOT SUITABLE
N70	Devices	SUITABLE
N73	Opticians	SUITABLE
N77	Urostomy, enterostomy and tracheostomy	SUITABLE
N80	Biosynthetics and disposables	NOT SUITABLE
N81	Renal dialysis	SUITABLE
N85	Personal share hospitalization	NOT SUITABLE
N86	Pharmaceuticals	NOT SUITABLE
N87	Hospital nursing	NOT SUITABLE
N88	Revalidation & re-adaptation - patient's contribution	NOT SUITABLE
N89	Placement & travel costs MPC - patient's contribution	NOT SUITABLE
N90	Smoking cessation session codes	NOT SUITABLE
N93	Regularisation codes	NOT SUITABLE
N95 - N96 - N98	Various administrative codes (non relevant for present study)	NOT SUITABLE
N97	Refunding of patient contributions	NOT SUITABLE
N99	Not elsewhere attributable regularisations	NOT SUITABLE

As a result of this scrutiny, approximately 42% of 273 stays were excluded (see addendum 2 for details): 114 stays were definitely excluded and 51 stays were affirmatively included (by finding a HBV specific intervention). However, for the remaining 108 stays no decision could be made in present level. Consequently inclusion-exclusion had to be decided solely on low level NIHDI billing codes criteria (see section below).

Stay inclusion resulted in principal acceptance of all billing records in the corresponding stay, be it with further diversification in separate cost groups (see level 3).

Stay exclusion resulted in total discarding of all billing records in the corresponding stay, exception made HOWEVER of hepatitis B attributable diagnostic testing or subsidiary interventions (Table 45) and hepatitis B specific medication (see section 3.4 beneath).

Table 45. Hepatitis B attributable diagnostic testing or subsidiary interventions

NIHDI_codes	Label	Type
437054_437065	Diagnosis and follow up of HBV : HBe antigen	Test
437091_437102	Diagnosis and follow up of HBV : HBe antibodies	Test
551390_551401	Diagnosis and follow up of HBV: HBs antigen	Test
551412_551423	Diagnosis and follow up of HBV: HBe antigen	Test
551434_551445	Diagnosis and follow up of HBV: anti HBs antibodies	Test
551456_551460	Diagnosis and follow up of HBV: anti HBe antibodies	Test
551471_551482	Diagnosis and follow up of HBV: anti HBc antibodies	Test
355751_355762	Liver punction	Intervention
473395_473406	Percutanuous bile duct or vena portae catheterization	Intervention
473410_473421	Catheterization of the venae suprahepaticae	Intervention
473712_473723	Fibroduodenoscopic placement of a bile duct dilatation prosthesis	Intervention

5.3.3.4 Low level cost sub grouping on NIHDI codes

As argued before, HBV infections frequently occur as an epiphenomenon with other pre-existing or concurrent disease(s) or treatment(s) (e.g. coagulation disorders needing multiple blood transfusions, haemodialysis, HIV …). Therefore it certainly was crucial for this cost study to separate NIHDI code reimbursements in different 'cost sub groups' (Table 46):

1. HBV: costs indisputably or most likely attributable to HBV;
2. nHBV: costs not automatically attributable to HBV diagnosis and/or treatment (see addendum 3);
3. SOC: costs related to social security 'low income compensation' regulations;
4. EXC: cost related to hospital financing by lump sums (laboratory testing, medical imaging, inpatient pharmaceuticals) that were excluded and replaced by 100% extrapolations of fee-for service part of corresponding remunerations (see section 4 beneath);
5. PAT: costs related to 'compulsory patient contribution' regulations (paid by the patient himself).

Table 46. Crude NIHDI cost data 2006 for not excluded patient stays (not extrapolated)

Cost_sub gr	NIHDI reimb (€ × 1000)
HBV	749
nHBV	716
SOC	33
EXC	154

Frequency queries for each NIHDI code per HBV clinical phase group were obtained, including corresponding patient counts and reimbursement totals. Those three elements were considered while scrutinizing all records one by one (be it by means of strategic and consecutive filtering on the N-groups) so that sound decisions could be made on which cost class they should fit in. Results are to be found in addenda 4 to 7.

5.3.3.5 Low level cost sub grouping on pharmaceuticals

Introduction

The Federal Agency for Medicines and Health Products[e] (FAMHP - former Directorate-General for Medicinal Products of the FPS Public Health) is the official authority for medicines and health products in Belgium. The FAMHP ensures, from development to use, the quality, safety and efficacy of medicines for human and veterinary use, including homeopathic medicines, herbal medicines, pharmacy made and officinal preparations. Its authority extends to medical devices and accessories, as well as raw materials for the preparation and production of medicines. It also covers clinical trials registration, marketing authorization procedures in Belgium, pharmacovigilance - control and inspection activities - and advertising regulations.

The FAMHP Marketing Authorisation department is responsible for evaluating and overall managing of requests for marketing authorisation (or their modification) of medicines in Belgium.

Once such authorisation obtained, the Federal Public Service (FPS) Economy[f] sets a maximum price per brand and at the same time the pharmaceutical company can apply for NIHDI refunding[g] at the Commission for Refunding of Medicines[h]. Within a legally fixed delay a motivated proposal on refunding (or not) is handed over to the Minister of Social Affairs, who takes the final decision. If positive, the pharmaceutical brand is added to the 'List of refundable pharmaceuticals', which covers different 'chapters', depending on refundable indications and the pharmaceutical category, resulting sometimes in different reimbursement tariffs. The corresponding database, which is regularly updated, can be consulted online at:

- http://www.riziv.fgov.be/inami_prd/ssp/cns2/pages/SpecialityCns.asp (Dutch) or
- http://www.inami.fgov.be/inami_prd/ssp/cns2/pages/SpecialityCns.asp (French).

Any pharmaceutical authorized for release on the Belgian market is identified by a 7 digit code, called CNK code[i], which is unique for brand name and package. This allows for unequivocal identification, ATC[j]-DDD[k] classification and DPP[l] retrieval. Since hospital pharmaceuticals often are delivered per 'unit dose' (UD), such UD conditionings receive a different CNK code (identifiable by a leading '07' in the CNK code).

Data recordings on delivered pharmaceuticals in Belgium go through two possible channels: one for deliveries by hospital pharmacies (dispensaries accessible to inpatients as well as outpatients) and one by 'extra muros' pharmacies. The former are registered, along with all other charged health care services and medical supplies delivered, through hospital reimbursement claims sent to the health insurance company (HIC) of the patient after his/her discharge[m]. The latter recordings originate in a nationwide, electronic data registry system connecting all 'extra muros' pharmacies with so called legally instituted 'tarification offices', that assemble all individual claims to dispatch them to the corresponding HIC.

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e See http://www.fagg-afmgps.be/en/items-HOME/useful_information/index.jsp and http://www.fagg-afmps.be/en/annual_report/index.jsp

f See: http://economie.fgov.be/en/

g See: http://riziv.fgov.be/drug/nl/drugs/general-information/refunding/index.htm#p2 (Dutch) or http://riziv.fgov.be/drug/fr/drugs/general-information/refunding/index.htm#p2 (French)

h NIHDI Commission for refunding of medicines = Commissie tegemoetkoming geneesmiddelen (CTG) - Commission de remboursement des médicaments (CRM)

i Code National – Nationale Kode

j The Anatomical Therapeutic Chemical (ATC) Classification System used for the classification of drugs is controlled by the WHO Collaborating Centre for Drug Statistics Methodology (WHOCC), and was first published in 1976. See : http://www.whocc.no/atc/structure_and_principles/

k DDD = Defined Daily Dose (for an average adult weighting 70 kg.)

l DPP = Dosis Per Package = package quantity divided by DDD = number of DDD's per package

m Claims remain valid up to 1 year after discharge

For both pathways emphasis should be laid on the fact that prescription registries only contain records on the time points of delivery of drugs and related supplies to individual patients along with information on brand code (CNK code) and amount delivered. However, those sources of data do not provide direct information on the time of initiation and discontinuation of drug treatment. In present study, being a public health cost study, this drawback is of minor importance.

Pharmaceutical deliveries by 'extra muros' pharmacies

Extensive information about the Pharmanet circuit can be found on the official NIHDI web site (downloadable document in English, 80 pages):

http://riziv.fgov.be/drug/nl/statistics-scientific-information/pharmanet/introduction/pdf/analyticalreport_eng.pdf .

Pharmacotherapeutical information (indications, contra-indications, adverse effects, posology…) on outpatient pharmaceuticals can be found at the BCFI – CBIP[n] website at: http://www.bcfi.be/ (Dutch) or http://www.cbip.be/ (French). Although the online consultable database is quite comprehensive, it does not include specific hospital pharmaceuticals.

Pharmaceutical deliveries by hospital pharmacies

Lists of hospital pharmaceuticals and their lump sum ruling inclusion or exclusion are monthly updated and web published (for download by hospital pharmacists) at:

http://riziv.fgov.be/care/nl/hospitals/specific-information/forfaitarisation/index.htm

Inclusion - exclusion tables for pharmaceuticals

All antiviral pharmaceuticals found in the IMA data are listed in Table 47. They were flagged for 'HBV' and 'not HBV' indications i.e. their clinical indication in the present study context (tenofovir, for example, can also be used for treatment of HIV infection, but, since HIV patients were excluded at intake, his indication was not withheld for present study). Based on this table primary inclusion-exclusion decisions were straight forward.

Table 47. Antivirals found in database

CNK-code	ATC5	ATC_label	ATC2_class	Clinical indication (*)
1256072	J05AF05	Lamivudine	Antivirals for systemic use	HBV
1411354	J05AF05	Lamivudine	Antivirals for systemic use	HBV
1411362	J05AF05	Lamivudine	Antivirals for systemic use	HBV
1700608	J05AF05	Lamivudine	Antivirals for systemic use	HBV
1743806	J05AF07	Tenofovir disoproxil	Antivirals for systemic use	HBV
1784032	J05AF08	Adefovir dipivoxil	Antivirals for systemic use	HBV
772483	J06BB04	Hepatitis b immunoglobulin	Immune sera and immuno-globulins	HBV
298398	L03AB04	Interferon alfa-2a	Immunostimulants	HBV
227686	L03AB05	Interferon alfa-2b	Immunostimulants	HBV
1414564	L03AB05	Interferon alfa-2b	Immunostimulants	HBV
458133	J05AB01	Aciclovir	Antivirals for systemic use	Herpes virusses
1663939	J05AB14	Valganciclovir	Antivirals for systemic use	Herpes virusses
1612597	J05AE	Protease inhibitors, rotinavir + lopinavir	Antivirals for systemic use	HIV
1466549	J05AE03	Ritonavir	Antivirals for systemic use	HIV
1612597	J05AE06	Lopinavir	Antivirals for systemic use	HIV
1370659	J05AG01	Nevirapine	Antivirals for systemic use	HIV
760561	J05AR01	Zidovudine and lamivudine	Antivirals for systemic use	HIV
1378280	J05AR01	Zidovudine and lamivudine	Antivirals for systemic use	HIV

(*) Clinical indication used for the purpose for inclusion/exclusion in the study.

[n] BCFI = Belgisch Centrum voor Farmacotherapeutische Informatie, CBIP = Centre Belge d'Information Pharmacothérapeutique

5.3.4 Extrapolations for partial lump sum remunerations

5.3.4.1 Laboratory testing

As elaborated in KCE report 121 "Feasibility study of the introduction of an all-inclusive case-based hospital financing system in Belgium" and its supplement (downloadable at http://www.kce.fgov.be/), financing of laboratory testing in Belgium partly consists of a fee-for-service system and partly of lump sum payments. Codes for billing the latter are to be found in Table 48. Both inpatient and outpatient sectors are involved and related billings are available in the IMA records.

Table 48. Lump sum codes for laboratory tests

Domain	NIHDI code	Specifications - applicability
Inpatient	591102	Lump sum on hospital admission - base sum
	591124	Lump sum on hospital admission - 3 FT
	591146	Lump sum on hospital admission - 2 FT
	591603	Lump sum on hospital admission – accreditation certificate
	592001	Lump sum per hospital stay day – inpatients – acute hospitals
Day care	591091	Lump sum on 'one day' admission - base sum
	591135	Lump sum on 'one day' admission - 2 FT
	591113	Lump sum on 'one day' admission - 3 FT
Outpatient	592874	Lump sum clinical biology art 3 - accreditation certificate - relative cumulative value < B 700
	592830	Lump sum clinical biology art 3 - no accreditation certificate - relative cumulative value < B 700
	592970	Lump sum clinical biology art 3 - accreditation certificate - relative cumulative value B 700 - B 1749
	592933	Lump sum clinical biology art 3 – no accreditation certificate - relative cumulative value B 700 - B 1749
	593073	Lump sum clinical biology art 3 - accreditation certificate - relative cumulative value B 1750 - B 3499
	593036	Lump sum clinical biology art 3 – no accreditation certificate - relative cumulative value B 1750 - B 3499
	593176	Lump sum clinical biology art 3 - accreditation certificate - relative cumulative value > B 3500
	593132	Lump sum clinical biology art 3 - no accreditation certificate - relative cumulative value > B 3500
	592852	Lump sum clinical biology art 18 & 24 - accreditation certificate - relative cumulative value < B 700
	592815	Lump sum clinical biology art 18 & 24 – no accreditation certificate - relative cumulative value < B 700
	592955	Lump sum clinical biology art 18 & 24 - accreditation certificate - relative cumulative value B 700 - B 1749
	592911	Lump sum clinical biology art 18 & 24 – no accreditation certificate - relative cumulative value B 700 - B 1749
	593051	Lump sum clinical biology art 18 & 24 - accreditation certificate - relative cumulative value B 1750 - B 3499
	593014	Lump sum clinical biology art 18 & 24 – no accreditation certificate - relative cumulative value B 1750 - B 3499
	593154	Lump sum clinical biology art 18 & 24 - accreditation certificate - relative cumulative value > B 3500
	593110	Lump sum clinical biology art 18 & 24 - no accreditation certificate - relative cumulative value > B 3500

Inpatients & day care

Hospital lump sum tariffs are dependent on (1) the type of hospital, acute versus rehabilitation hospitals, (2) the hospital case-mix based on previous linked MCR-HBR hospital records, (3) the number of laboratory specialists, counted in full time units (FTU) and (4) whether or not the performing lab physician has a (personal) accreditation certificate[o], which entitles him to charge a higher priced code (591603).

Since hospitals receive lump sums per admission (only acute care hospitals) and per stay day (acute care as well as rehabilitation hospitals) for each inpatient and day care patient whether or not there was any laboratory test performed, lump sum payments to hospitals have little connection with actual services delivered. To restore the link with actual practice for inpatients, lump sum payments were substituted by fee-for-service amounts extrapolated to such an extent that 'theoretical' 100% values were obtained.

Outpatients

For outpatients, lump sum tariffs are dependent on (1) laboratory tests actually performed, i.e. no lump sum is paid without tests, (2) their amount in terms of relative cumulative value, (3) the N-group (N08 versus N47 and N60 – see Table 48) of the laboratory tests performed, and (4) whether or not the clinical biologist has an accreditation certificate. Based on the two first conditions, and unlike inpatients, connection with actual services delivered is in a certain way maintained, albeit with some disproportionality regarding N08 group versus N60 and N47 groups (condition 3).

Calculation of extrapolation factors

Lump sum amounts for laboratory testing were discarded (cost class 'EXC') and each fee-for-service part for laboratory tests (NIHDI N-groups N08, N47 and N60) was extrapolated to its estimated 100% level by multiplying it with a corresponding extrapolation factor (EF) calculated on full NIHDI accountancy records (doc N) for the year 2006 (Table 49). Since the Doc N registry does not include hospital identification, we could not differentiate for the number of laboratory FTU[p].

Table 49. Total NIHDI expenses on inpatient laboratory testing in 2006

Part / Domain	Outpatient & day care	Inpatient
Fee-for-service	362.366.413,42 €	81.239.605,58 €
Lump sums	168.620.963,43 €	314.331.842,06 €
Year total	530.987.376,85 €	395.571.447,64 €
Extrapolation factor	**3,1490**	**4,8692**

For inpatients this method seems quite accurate, at least with reference to NIHDI annual accounts and exception made for the number of laboratory FTU's per hospital.

For day care and outpatients on the other hand we have to accept some more degree of distortion in our extrapolation: since day care services are charged with the same set of fee-for-service billing codes as those used for outpatients we could not fractionate the 2006 total of fee-for-service payments into correct outpatient and day care parts and at the same time separate N08 form N47-N60 reimbursements to calculate different extrapolation factors. This forced us to take all outpatient code reimbursements together for calculation of a common EF, even if lump sum allocation rules are quite different (see Table 48).

o Comparable to the CME certificates in the USA.

p The only way to get to such differentiation would be to calculate EF's on SHA and ADH databases of the NIHDI; unfortunately we did not have those at our disposal.

5.3.4.2 Medical imaging

NIHDI codes for medical imaging (MI) come in two sets: one confined to specialists in radiology (45* codes) and a second for so-called 'connected MI' i.e. allied medical imaging performed by other specialists in the field of their speciality (46* codes, e.g. coronarographies by cardiologists).

As for laboratory testing, financing of medical imaging (MI) consists of partly a fee-for-service system and partly lump sum payments. Billing codes for MI lump sums are listed in Table 50.

Table 50. Lump sum codes for medical imaging

Domain	NIHDI code	Label code
Outpatient	460670	Consultancy fee for specialist in radiology, outpatients (restricted to a specific set of codes – see addendum 10)
	460795	Consultancy fee for specialist in radiology with accreditation certificate, outpatients (restricted to a specific set of codes – see addendum 10)
	460972	Lump sum fee per prescription and per day for outpatient medical imaging listed under art. 17, §1, except if conditions under code 460994 or 461016 are met
	460994	Lump sum fee per prescription and per day for outpatient medical imaging listed under art. 17, §1 with at least one of the codes flagged for this code in addendum 10
	461016	Lump sum fee per prescription and per day for outpatient medical imaging listed under art. 17, §1 with at least one of the codes flagged for this code in addendum 10
Inpatient	460784	Lump sum for medical imaging payable on admission
	460703	Consultancy fee payable on admission in a general hospital (in one or more of following hospital departments: A, C, D, E, G, H, I, K, L, M, NIC , Sp-cardiopulmonary, Sp-neurology or Sp-loco motor rehabilitation)
	460821	Consultancy fee payable to a specialist in radiology with accreditation certificate on admission in a general hospital (in one or more of following hospital departments: A, C, D, E, G, H, I, K, L, M, NIC , Sp-cardiopulmonary, Sp-neurology or Sp-loco motor rehabilitation)

Inpatients and 'one day' admissions

Hospitals receive a lump sum per admission, different for each hospital, and a lump sum per stay day, labelled 'consultancy fee' and meant for remuneration of the 'intellectual' act of the performing radiologist. Lump sums are chargeable whether or not any medical imaging act was performed. Consultancy fees are higher for radiologists with an accreditation certificate. As with laboratory tests, lump sum payments to hospitals have little connection with actual services delivered. To restore the link with actual practice for inpatients, lump sum payments were substituted by fee-for-service amounts extrapolated to such an extent that 'theoretical' 100% values were obtained. Consequently lump sum amounts for medical imaging were discarded (cost class 'EXC').

There is however one group of medical imaging codes that is excluded from this inpatient lump sum ruling: angiocardio- and coronarographies (Table 51). For those billings the full reimbursement amounts are recorded in the IMA data.

Table 51. Medical imaging, inpatient codes excluded from lump sum ruling

NIHDI code	Label code
453084	Angiocardiopneumography, one angle of incidence
464085	Angiocardiopneumography, one angle of incidence
453106	Angiocardiopneumography, two or more angles of incidence
464100	Angiocardiopneumography, two or more angles of incidence
453121	Coronarography, one angle of incidence
464122	Coronarography, one angle of incidence
453143	Coronarography, two or more angles of incidence
464144	Coronarography, two or more angles of incidence

Outpatients

For outpatients a different and more complex lump sum system was developed: there are three different lump sum fees, depending on which (set of) MI investigation(s) is performed (see Table 50 and also addendum 10). No lump sum is chargeable without medical imaging being performed and all three lump sum codes are mutually exclusive (see groups A to C in table 15). Consultancy fees come on top and are higher priced for radiologists with an accreditation certificate, yet they are not always chargeable (group E in Table 52). Moreover, not all NIHDI codes for MI are entitled to a lump sum and/or consultancy fee charging (group n/a in Table 52).

Table 52. Lump sum and/or consultancy fee charging for outpatients

Consultancy_fee	460994	461016	460972	# NIHDI_codes	Extrapolation group
1	1	0	0	23	A
1	0	1	0	31	B
1	0	0	1	5	C
1	0	0	0	32	D
0	0	0	1	48	E
0	0	0	0	107	n/a

This system maintains to some extent connection with actual services delivered. Normally there would be less need for a (rather complex) extrapolation procedure in this sector: provided all MI reimbursements were to be included, we could as well keep the lump sums. However, since we had to sub group MI investigations in 'HBV' and 'nHBV', we were faced to an impossible task to split the corresponding lump sum amounts in proportional fractions, which would be different for each set of services charged per patient and per billing day. The only way to get to a feasible split was to discard the lump sums and extrapolate the fee-for-service amounts.

Calculation of extrapolation factors

'As good as possible' extrapolation factors for inpatient and for outpatient services respectively were calculated based on final NIHDI accountancy records (doc N) for the year 2006 (Table 53). For outpatient services we were able to calculate a separate EF for each extrapolation group (A to E – see Table 52) through a weighing procedure.

Table 53. Total NIHDI expenses (in EURO) on inpatient medical imaging in 2006

Part / Domain	Outpatient					Inpatient
	Group A	Group B	Group C	Group D	Group E	All codes (**)
Fee-for-service (*)	27.535.485	142.387.754	145.665	270.319.534	55.202.561	150.471.341
Lump sums (***)	62.105.197	829.240.836	602.184	507.817.242	124.507.195	97.268.027
Year total	89.640.682	971.628.590	747.849	778.136.776	179.709.757	247.739.368
Extrapolation factor	**3,2555**	**6,8238**	**5,1340**	**2,8786**	**3,2555**	**1,6464**

(*) Calculated for related MI codes. (**) Angiocardiopneumographies and coronarographies excluded. (***) For outpatient lump sums proportionally weighed over the 5 groups.

5.3.4.3 In patient pharmaceuticals

Until 1983 hospital drugs were completely reimbursed on a fee-for-service basis. Since then, several efforts have been taken in order to control escalating expenditures for pharmaceuticals. A first step towards prospective pharmaceutical budgeting for hospitalized patients was made in 1997 for the prophylactic use of antibiotics with surgical interventions. Registration of prophylactic antibiotic deliveries was done by means of newly introduced NIHDI billing codes, accompanied with the recording of the code of the corresponding intervention (in a 'relative code' field). However, track of the delivered antibiotic brand was lost. This system was applied until July 1, 2006.

Since July 1, 2006 a prospective budget for pharmaceuticals delivered to acute hospital inpatients was introduced, disbursed by means of hospital specific lump sum allocations, chargeable under a new NIHDI code 756000 for each (inpatient) admission, regardless presence or absence of any pharmaceutical consumption. Most – but not all – pharmaceuticals are integrated in this budget for approximately 75% of their reimbursement tariff. The remaining 25% of their public reimbursement tariff is still paid through a set of accompanying new codes (see Addendum 11) recorded along with the brand code of the drug. Theoretically this should allow tracking the consumption of hospital pharmaceuticals delivered.

Prospective budgets for inpatient pharmaceuticals are based on hospitals' (retrospective) case-mix data and the national average cost per APR-DRG and severity of illness (SOI), excluding outliers outside the Q3 + 2× (Q3-Q1) limit. Calculations are made on most recent available linked MCD-HBD data[q] (called 'reference year'). This case-mix based 'fine tuning' results in a different lump sum per admission being calculated for each hospital.

However, not all pharmaceuticals were entered in this system. For rather comprehensible reasons special ATC sub groups of pharmaceuticals were excluded:

therapeutically important innovative medication;

particular 'high cost' medication, including orphan drugs, cytostatics, immunoglobulins, immunosuppressors, human albumin, anti-thrombotics and haemostatics, antidotes, somatostatins, direct acting antivirals including HIV antivirals as well as radio-isotopes.

Since all hepatitis B specific medication falls under this last category, full NIHDI cost recordings are still available in the IMA data after June, 30th 2006 and no need for recalculation is present.

[q] Linkage process of MCR (minimal clinical records) with HBD (hospital billing data) takes at least 2 years for completion.

On the other hand, for medication that falls under the lump sum per admission ruling, full cost price calculation, by substituting with exact 100% tariffs valid at time of delivery (direct extrapolation), turns out to fall beyond reach. Indeed, profound validation analyses on remitted hospital data after introduction of this system has revealed major lacunas in the recordings of quantities delivered (confirmed in present study on data 2006), rendering any effort to directly recalculate '100% costs' per brand code (CNK) futile.

Consequently reimbursement amounts for inpatient medication that fall under 'lump sum per admission ruling' were indirectly extrapolated to an estimated 100% value by multiplying them by an overall extrapolation factor calculated on full NIHDI accountancy records (Doc N) of the related NIHDI codes (see see Addendum 11) in the second semester of year 2006. Result of this calculation is presented in Table 54.

Table 54. Pharmaceutical inpatient expenses in 2006, 2nd semester, and all hospitals

Part	Totals
Fee-for-service	35.802.033,65 €
Lump sum	125.395.855,20 €
Total	161.197.888,85 €
Extrapolation factor	**4,5025**

After flagging all IMA inpatient pharmaceuticals records for their eventual entry date in the lump sum per admission ruling, we multiplied the corresponding fee-for-service reimbursement amounts of lump sum regulation subjective pharmaceuticals with above mentioned extrapolation factor.

5.3.4.4 Stay day remunerations

Extrapolation

Since July 2002 refunding of not directly patient imputable hospital costs (capital expenditures for housing and medico-technical facilities, hotel function, nursing care, etc.) chiefly is regulated by the 'Budget of Financial Means' (BFM) allocated to Belgian hospitals per budget year which runs from July 1 to June 30 of the next year.

For stays reimbursed by compulsory health insurance, disbursement of this budget consists of a fixed and a variable part. The variable part of the BFM applies exclusively to subparts B1 and B2 of the BFM, which specifically cover medical hospital activities and together encompass (theoretically) 20% of the total budget. Disbursement of these 20% is done by means of lump sums 'per admission' and/or 'per stay day', both charged with a set of specific NIHDI codesr (grouped in N-group N87) that are recorded in the IMA billing data of the hospitals. Calculation of the variable part share for each hospital and its corresponding lump sum tariffs is based (amongst other complex criteria) on the number of 'justified bed occupation days' and/or the number of hospital admissions in previous year(s), with half yearly revisions. As a result, lump sum allocations vary considerably between hospitals.

The fixed part (approximately 80%) can be attributed to neither an individual stay nor a patient and therefore is disbursed directly to the hospitals through monthly 'twelfths'. This is also why this fixed part is not available in the IMA individual patients' billing records. In cost studies this important lacuna in the data has to be taken into account.

For stays under private insurance covering (including e.g. labour accidents) full stay day prices are charged by the hospitals. For that purpose full stay day prices for each hospital are periodically web published by the NIHDIs . Using those tables direct extrapolation to (official) 100% stay day remunerations is feasible.

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r Lump sums tariffs differ not only per hospital but also per type of bed occupied: acute beds, (chronic) rehabilitation beds, psychiatric beds, beds for severe burns treatment and beds for palliative care. Per admission lump sums apply only to acute beds (including severe burns).

s at: http://riziv.fgov.be/care/nl/hospitals/specific-information/prices-day/index.htm

Standardization

Lump sums for (in)patient stay day's price differently for each hospital: stays in a 'higher priced' hospital induce a higher HDI cost than their equivalents in a 'cheaper priced' hospital. Neutralization comes with standardization of 100% stay day remunerations for all included stays to a common average ('standard') stay day remuneration, and this per type of bed (acute in present study) occupied.

However, since liver transplant surgery is restricted to 'high tech' university hospitals (3 participating in present study) with higher stay day tariffs, standardization for acute bed stay days was confined to this subgroup (standard tariff = 458,20 €), as opposed to the remaining, non university hospitals (standard tariff = 358,28 €).

5.3.4.5 Integrated cost sub grouping per patient

After going independently through the three previous decision levels, an exercise of integration remains to be done: inclusion-exclusion decisions taken in one level can sometimes be overruled by another, 'higher' level.

Global rules applied for separating HBV treatment related health care services (HBV) from others (nHBV and SOC)

1. In first instance, all lump sum remunerations for inpatient and day care hospital laboratory tests and medical imaging were totally discarded and replaced by 100% extrapolated 'à l'acte' remunerations (see section 4).
2. Patients' own 'out-of-pocket' contributions (sub group 'PAT') were discarded since they would only give a partial image of this particular field. Indeed, not all such contributions (only 'official') are registered in the IMA data.
3. All hepatitis B specific laboratory tests and subsidiary hepatobiliary interventions (see Table 8) were included in the 'HBV' group, irrespective of the inclusion-exclusion status of the hospital stays (N = 273), with exception, however of the "10 Not active" stage patients: any such intervention eventually found was to be considered as bearing no relation to HBV infection status.
4. All other health care services and medical supplies delivered were flagged following their primary NIHDI code based sub grouping. However, they were discarded if charged in affirmatively excluded hospital stays.
5. Costs related to social security 'low income compensation' regulations (sub group 'SOC') were separated from the other 2 sub groups, since those costs reflect a global, retro-active mechanism of 'compensatory' patient refunding, depending on his taxable income and the cumulative total of all legally imposed personal contributions in health care costs in the corresponding fiscal year.

Global rules applied for separating HBV treatment related pharmaceutical costs (HBV) from others (nHBV)

1. All hepatitis B specific medication was included in the 'HBV' group (see Table 10 and Addendum 8), irrespective of the inclusion-exclusion status of the hospital stays (N = 273). There is however one exception: for group '01 Non active', any eventual finding of hepatitis B antivirals was considered as not HBV related and therefore labelled as 'nHBV'.
2. All medication under lump sum ruling, in hospital stays affirmatively identified as hepatitis B related (N = 51 included stays, see section 3.1), was also included in the 'HBV' group. In doing so we tried not to exclude medication or interventions related to complications occurred during HBV diagnosis or treatment procedures or its clinical evolution (e.g. metastasis with HCC). There is however one exception for such stays: all specific (and costly) medication or other health care services positively identified as being related to pre-existent or concurrent non HBV pathology was labelled as 'nHBV' (e.g. one case with factor VIII coagulopathy).

3. All other medication under lump sum ruling, in hospital stays not positively identified as hepatitis B related (N= 108), but not excluded was labelled as 'nHBV'.
4. All medication under lump sum ruling, i.e. not HBV related, in hospital stays, affirmatively excluded (N =114), was not withheld for cost calculation.

5.3.5 Results

5.3.5.1 Final patient counts

For various reasons another 23 patients were discarded form the costs calculations: high likeliness for 'missing HBV related data': 7 in the 'Not active' group, 9 in the 'Active group', 3 in the 'Comp Cirrh' group and 2 in the 'HCC group'. Another patient in the Active group was excluded because of the finding of specific HIV anti viral treatment. Finally one liver transplant patient deceased within one month after transplantation and consequently was equally discarded. Final counts are to be found in Table 55.

5.3.5.2 Total HDI costs and Average cost per patient, per clinical stage for one year (2006)

Total HDI costs were calculated per clinical stage and per cost sub group. Dividing those totals by the corresponding overall number of patients in each clinical stage group gives us the average cost per clinical stage and per patient for one year, i.c. 2006.

Table 55. Average cost (in EURO) per clinical stage, per cost sub group and per patient for year 2006

		HBV related w.o HBV antivirals		HBV related withHBV antivirals		Not HBV related		Low income compensations		All HDI costs		Patient's co-payments	
Path_group	N patients	Total (€)	Avg p.p./yr	Total (€)	Avg p.p./yr	Total (€)	Avg p.p./yr	Total (€)	Avg p.p./yr	Total (€)	Avg p.p./ yr	Total (€)	Avg p.p./ yr
Not active	71	7.658	108	7.658	108	164.731	2.320	1.988	28	174.378	2.456	13.830	195
Active	141	78.044	554	329.411	2.336	908.666	6.444	11.244	80	1.249.321	8.860	42.696	303
Comp Cirrh	47	49.104	1.045	112.793	2.400	258.124	5.492	4.494	96	375.411	7.987	16.245	346
Decomp Cirrh	5	31.935	6.387	39.393	7.879	65.598	13.120	986	197	105.977	21.195	1.903	381
HCC	4	34.111	8.528	37.148	9.287	11.451	2.863	921	230	49.520	12.380	3.130	783
Liver transplant	5	468.642	93.728	481.548	96.310	41.546	8.309	2.728	546	525.823	105.165	4.206	841
Post transpl	41	281.864	7.047	328.840	8.020	323.051	7.879	7.379	180	659.270	16.080	16.976	414

(*) calculated on overall sub group patient counts; Avg p.p. / yr: Average per patient per year

5.3.5.3 Cost distributions per clinical stage

For each clinical stage and cost sub group descriptive statistic parameters were calculated (Table 56). Specific HBV anti viral medication costs are included.

Table 56. Descriptive statistics per clinical stage and cost sub group (Euro)

Not Active	**N**	**Min**	**Q1**	**Q2**	**Q3**	**Max**	**Q3+2*(Q3-Q1)**	**Outlier count**
HBV	71	9,23	50,86	78,00	129,16	476,54	285,76	5
nHBV	71	9,85	246,85	632,44	2.493,72	20.203,40	6.987,47	8
SOC	10	5,35	55,48	151,76	314,58	549,60	832,77	0
Active	**N**	**Min**	**Q1**	**Q2**	**Q3**	**Max**	**Q3+2*(Q3-Q1)**	**Outlier count**
HBV	141	18,37	398,40	1.057,59	4.297,27	7.915,28	12.095,01	0
nHBV	141	2,80	311,18	1.041,90	2.481,21	353.279,4*	6.821,27	17
SOC	26	11,19	113,42	195,61	442,65	1.799,64	1.101,12	5
Comp. Cirrhosis	**N**	**Min**	**Q1**	**Q2**	**Q3**	**Max**	**Q3+2*(Q3-Q1)**	**Outlier count**
HBV	47	52,87	1.071,58	1.379,21	3.164,08	7.810,27	7.349,07	2
nHBV	47	11,15	467,81	1.274,01	3.303,79	100.397,16	8.975,75	3
SOC	14	11,83	106,32	238,01	490,06	840,00	1.257,54	0
Decomp. Cirrhosis	**N**	**Min**	**Q1**	**Q2**	**Q3**	**Max**	**Q3+2*(Q3-Q1)**	**Outlier count**
HBV	5	1.341,27	6.040,13	6.767,82	9.846,43	15.397,00	17.459,03	0
nHBV	5	395,85	1.419,00	1.799,81	3.649,41	58.333,98	8.110,23	2
SOC	2	153,35	-	-	-	832,94	-	-
HCC	**N**	**Min**	**Q1**	**Q2**	**Q3**	**Max**	**Q3+2*(Q3-Q1)**	**Outlier count**
HBV	4	272,49	1.959,65	3.904,19	10.387,84	29.066,69	27.244,23	1
nHBV	4	388,70	1.002,70	2.954,49	4.814,48	5.153,09	12.438,04	0
SOC	1	-	-	-	-	-	-	-
Liver transplant	**N**	**Min**	**Q1**	**Q2**	**Q3**	**Max**	**Q3+2*(Q3-Q1)**	**Outlier count**
HBV	5	71.565,72	78.847,33	108.383,04	108.787,40	113.964,82	168.667,54	0
nHBV	5	4.490,41	5.837,61	7.341,79	10.417,41	10.417,41	19.577,02	0
SOC	5	69,56	96,86	154,62	639,33	1.710,14	1.724,27	0
Post transplant	**N**	**Min**	**Q1**	**Q2**	**Q3**	**Max**	**Q3+2*(Q3-Q1)**	**Outlier count**
HBV	40	148,66	5.059,51	6.198,03	7.582,81	34.289,09	12.629,41	5
nHBV	40	1.871,39	4.919,03	7.094,13	8.716,51	41.578,23	16.311,48	1
SOC	15	27,00	174,44	304,26	822,09	1.306,56	2.117,39	0

* Patient with hemphilia, needing huge amounts of factor VIII

The 99% confidence intervals of means for cost sub group HBV are listed in Table 57..

Table 57. 99% confidence intervals of the means (cost sub group HBV – EURO)

		With HBV antivirals				Without HBV antivirals			
Clin. stage	N	Average	SD	Lo 99% CI limit	Up 99% CI limit	Average	SD	Lo 99% CI limit	Up 99% CI limit
Not Active	71	107,9	92,2	79,7	136,0	107,8	92,2	79,7	136,0
Active	141	2.336,3	2559,4	1.781,1	2.891,5	553,5	829,7	373,5	733,5
Comp. Cirrhosis	47	2.399,9	2237,5	1.559,19	3.240,5	1.044,7	1379,4	526,5	1.563,0
Decomp. Cirrhosis	5	7.878,5	4642,2	2.530,9	13.226,1	6.387,1	5168,8	432,8	12.341,3
HCC	4	9.286,9	11517,1	-5.546,2	24.120,0	8.527,6	10620,9	-5.151,2	22.206,7
Liver transplant	5	96.309,6	17494,9	76.156,4	116.462,8	93.728	15846,9	75.473,5	111.983
Post transplant	40	7.759,5	6105,74	5.272,8	10.246,21	7.046,6	6264,2	4.495,3	9.597,8

5.3.5.4 Cost profiles per clinical stage in cost sub group HBV

From a clinicians' point of view it seems interesting to have an overview of the costs' profiles per clinical stage in cost sub group HBV: see Table 58. Costs were aggregated by NIHDI N-groups. Cost groups lower ≤ 500 € total HDI cost were omitted.

Table 58. Cost profiles (in EURO) per clinical stage in cost sub group HBV

Path_ group	N_ group	Label_N-grp_UK	# Patient	HDI_cost (€)	Avg. p.p. (€)
Not active	N01	Outpatient consultations, home visits and medical advice	57	3.987	69,94
	N60	Clinical biology - art. 24§1	68	2.835	41,69
	N08	Clinical biology - accessible for general practitioners (art. 3)	63	679	10,78
Active	N86	Pharmaceutics	14	15.741	1.124,34
	N87	Hospital nursing	6	4.499	749,87
	N50	Röntgendiagnosis	80	14.611	182,63
	N60	Clinical biology - art. 24§1	139	22.966	165,22
	N63	Anatomopathology	3	436	145,28
	N42	Gastro-entereology	17	2.231	131,23
	N00	Surveillance fees for hospitalized patients	41	3.823	93,24
	N01	Outpatient consultations, home visits and medical advice	125	11.610	92,88
	N13	General procedures and punctions, accessible for all medical specialists	27	1.402	51,94
	N80	Biosynthetics and disposables art 35 & 35bis	23	1.186	51,58
	N08	Clinical biology - accessible for general practitioners (art. 3)	126	4.764	37,81
	N04	Dental care	39	1.239	31,76

Path_ group	N_ group	Label_N-grp_UK	# Patient	HDI_cost (€)	Avg. p.p. (€)
Comp Cirrh	N87	Hospital nursing	10	8.416	841,58
	N86	Pharmaceutics	6	4.861	810,22
	N50	Röntgendiagnosis	41	14.475	353,05
	N60	Clinical biology - art. 24§1	47	8.270	175,95
	N42	Gastro-entereology	13	2.223	171,03
	N01	Outpatient consultations, home visits and medical advice	42	4.140	98,56
	N63	Anatomopathology	15	1.366	91,08
	N00	Surveillance fees for hospitalized patients	12	1.016	84,63
	N08	Clinical biology - accessible for general practitioners (art. 3)	44	2.743	62,34
	N80	Biosynthetics and disposables art 35 & 35bis	9	443	49,20
	N04	Dental care	11	263	23,90
Decomp Cirrh	N87	Hospital nursing	3	16.171	5.390,39
	N86	Pharmaceutics	3	3.067	1.022,45
	N60	Clinical biology - art. 24§1	5	4.809	961,82
	N50	Röntgendiagnosis	5	2.553	510,67
	N00	Surveillance fees for hospitalized patients	3	1.173	391,11
	N63	Anatomopathology	2	752	376,18
	N42	Gastro-entereology	4	1.383	345,68
	N08	Clinical biology - accessible for general practitioners (art. 3)	5	1.242	248,34
	N01	Outpatient consultations, home visits and medical advice	5	1.036	207,13
HCC	N87	Hospital nursing	1	12.371	12.371,35
	N86	Pharmaceutics	1	2.321	2.321,04
	N50	Röntgendiagnosis	4	8.442	2.110,57
	N60	Clinical biology - art. 24§1	4	3.127	781,74
	N80	Biosynthetics and disposables art 35 & 35bis	2	1.456	727,95
	N23	Abdominal surgery	1	724	723,93
	N14	Anesthesiology	1	545	544,57
	N42	Gastro-entereology	2	884	442,24
	N19	Surcharges for night / weekend services - Article 26, §1 et 1 ter	1	327	326,74
	N46	Nuclear medicine in vivo	2	494	246,83
	N00	Surveillance fees for hospitalized patients	2	449	224,73
	N13	General procedures and punctions, accessible for all medical specialists	3	560	186,74
	N01	Outpatient consultations, home visits and medical advice	4	571	142,87
	N63	Anatomopathology	3	425	141,79
	N08	Clinical biology - accessible for general practitioners (art. 3)	4	503	125,75
Liver transpl	N86	Pharmaceutics	5	132.481	26.496,29
	N87	Hospital nursing	5	117.924	23.584,78

Path_ group	N_ group	Label_N-grp_UK	# Patient	HDI_cost (€)	Avg. p.p. (€)
	N33	Transplantations	5	99.657	19.931,36
	N60	Clinical biology - art. 24§1	5	43.080	8.615,95
	N50	Röntgendiagnosis	5	19.694	3.938,87
	N14	Anesthesiology	5	8.478	1.695,60
	N08	Clinical biology - accessible for general practitioners (art. 3)	5	7.628	1.525,55
	N12	Reanimation	5	7.462	1.492,32
	N80	Biosynthetics and disposables art 35 & 35bis	5	6.695	1.339,03
	N19	Surcharges for night / weekend services - Article 26, §1 et 1 ter	5	4.436	887,16
	N57	Physical therapy	2	1.446	722,95
	N63	Anatomopathology	5	3.416	683,13
	N01	Outpatient consultations, home visits and medical advice	5	3.068	613,63
	N51	Percutanuous interventions	4	2.030	507,57
	N42	Gastro-entereology	3	1.479	493,08
	N00	Surveillance fees for hospitalized patients	5	2.267	453,49
	N46	Nuclear medicine in vivo	2	753	376,32
	N23	Abdominal surgery	2	676	337,83
	N06	Nursery care	4	930	232,56
	N55	Cardiology	5	1.126	225,23
	N05	Kinesitherapy	4	821	205,31
	N04	Dental care	2	409	204,27
	N82	Implants & disposables art 28 §1	3	568	189,35
	N56	Neuropsychiatry	3	488	162,59
	N13	General procedures and punctions, accessible for all medical specialists	5	769	153,73
Post transpl	N86	Pharmaceutics	36	184.407	5.122,41
	N87	Hospital nursing	10	37.012	3.701,21
	N25	Thoracal surgery	1	1.584	1.584,36
	N50	Röntgendiagnosis	22	18.443	838,34
	N51	Percutanuous interventions	2	1.074	537,10
	N14	Anesthesiology	3	1.572	524,03
	N80	Biosynthetics and disposables art 35 & 35bis	8	4.127	515,93
	N42	Gastro-entereology	10	4.836	483,58
	N60	Clinical biology - art. 24§1	40	15.241	381,03
	N00	Surveillance fees for hospitalized patients	14	3.177	226,93
	N63	Anatomopathology	10	1.595	159,49
	N41	Pneumology	2	300	149,82
	N05	Kinesitherapy	2	254	127,10
	N08	Clinical biology - accessible for general practitioners (art. 3)	40	4.206	105,14
	N01	Outpatient consultations, home visits and medical advice	37	2.986	80,71
	N04	Dental care	10	358	35,83

5.3.6 Discussion

In present study we faced a complex task to calculate health insurance costs for a specific pathology from administrative reimbursement databases. Several aspects of this work need some reflection and elucidation on feasibility, usefulness and validity of available data as well as, last but not least, constraints and their inherent caveats. First of all we should keep in mind that by "costs" we mean the amounts paid by national health insurance (public health and NIHDI), not those paid by the patient him-/herself, nor other societal costs related to sickness leave and incapability to work.

Tracking and segregation of hepatitis B virus related reimbursements

Next, hepatitis B related disease typically emerges as an epiphenomenon with pre-existent and/or concurrent disease. The tables in addenda 2 and 3 perfectly illustrate this: a lot of health care services identified in the data had no bearings with our research focus and approximately 43% of all hospital stays had to be excluded. Only somewhat less than 19% of the stays were affirmatively included by finding a hepatitis B specific diagnostic or therapeutic intervention. For the other near 40% of the admissions as well as all outpatient services we were coerced into a painstaking task of splitting all billing records into at least two categories: those that were related to HBV and those that were not. Indeed, health care insurance databases are about keeping the accounts of health care services' refundings, and patients tend to seek such care for all their sufferings, not only HBV related. Furthermore, NIHDI billing codes usually cover well-defined interventions, but very often they do so regardless clinical indications.

Table 56 as well as the vast listing (data available upon request) of NIHDI billing codes and their frequencies in our study database sheds a more detailed light on the diversity of concomitant disease with hepatitis B infection status: most strikingly, but not exclusively in the 'HBV active' group (the largest group) we found a variety of surgical interventions as well as dialysis for chronic renal failure. After checking as good as possible their clinical context in the data, especially the HBV clinical phase of the patient, the vast majority could be discarded for our cost calculations. However, the more advanced the HBV clinical stage, the more difficult exclusion decisions became. Since we had to consider disease or treatment related complications, some specific (e.g. fibro-endoscopic stenting for bile duct stricture after liver transplant), but most not (e.g. re-operations for post transplant haemorrhage, ICU haemodialysis for acute post transplant renal failure, nosocomial hospital infection …), our exclusion criteria had to become more lenient. In other terms, in more advanced disease stages we allowed more procedures to be included as related to CHB. Possible 'operator' bias was countered by expert group reviews. There remains of course a certain degree of "all experts' opinion" in all this, but that is exactly what medicine is all about: sound clinical judgement and praxis expertise.

Utility of administrative databases for clinical outcomes research and health economic studies

Second, since administrative databases are not meant nor conceived for research purposes, full knowledge of such databases and their SWOT[t] characteristics for research utilization, as well as profound clinical insight in the focused pathology is extremely important.

The use of administrative health care databases for clinical, health services and health economic studies is not a Belgian exclusivity. Indeed, the utility of such administrative data for evaluating the delivery of health services has been well established. As professors Retchin and Ballard listed in their "Commentary: Establishing Standards for the Utility of Administrative Claims Data"[71], the analysis of billing data over the past 20 to 25 years has revealed unexplained practice variations in neighbouring geographic areas[72] and detected opportunities to improve quality of care.[73, 74]

[t] Strengths, Weaknesses, Opportunities, Threats

Furthermore, administrative claims data have also been used to estimate the incidence of disease[75, 76] and the outcomes of surgical procedures.[77-81]

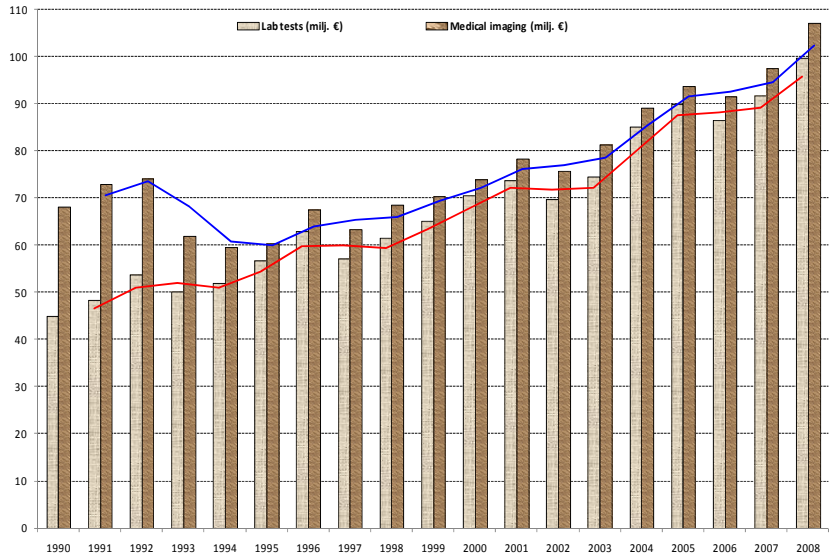
Administrative claims for inpatient as well as outpatient services are collected as a requirement for reimbursement. Since they are so uniformly generated, such registries can offer a relatively unique, population-based health care data source.[82] Another advantage is that the data are relatively inexpensive to gather and frequently present fewer restrictions in terms of sample size than do data from alternative sources. Despite these advantages, there are also problems inherent in the use of information that is collected for purposes other than to support health services research.[83] The information derived from the data may be inaccurate, misleading or even spurious. Moreover, since documentation of care is often nonessential for administrative/reimbursement purposes, some important elements may be incomplete or indistinct. And since the generation of billing data usually follows the utilization patterns of clinical care, disproportionate details are more readily accessible for inpatient episodes than for outpatient care.[71]

All this explains why reimbursement data require scrupulous verification when used to describe and evaluate clinical care and several issues should be considered in substantiating their accuracy.[71]

The case of Belgian reimbursement data

Third, the Belgian reimbursement policy for health care services has gone through drastic reforms in the past 20 years. Historically based on a fee-for-service principle and governed by a national stake holders' consensus model - gathering public health officials with representatives of health insurance companies, hospitals and medical professions - it faced, along with all Western countries, rising expenditures and consequently all kinds of 'bulldozed' budget restraints. Our deeply rooted consensus model not favouring a jump forward into 'all in' pathology or case-mix based refunding, Belgium, rather uniquely, engaged in a step-by-step approach of fractionated and partial lump sum settlements for laboratory tests (started in 1988), medical imaging (in 1992), hospital stay day remuneration (in 2002) and inpatient pharmaceuticals (in 2006). All of them, besides not sustaining their initial budgetary goals (Figure 22), left health care researchers with a major drawback: although individual services still are registered by means of their original fee-for-service codes, lump sum payments have little connection with actual services delivered. The consequences are abundantly elaborated in section 4: complex extrapolation exercises in order to reconnect health insurance costs to actual services delivered.

Figure 22. Total NIHDI expenditures for lab tests and medical imaging, 1990-2008.



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